



# Patterns of progression of cerebral small vessel disease markers in older adults of Amerindian ancestry: a population-based, longitudinal prospective cohort study

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## Abstract

**Background** Progression of cerebral small vessel disease (cSVD) markers has been studied in different races/ethnic groups. However, information from individuals of Amerindian ancestry is lacking. We sought to evaluate progression patterns of cSVD markers in community-dwelling older adults of Amerindian ancestry.

**Methods** Following a longitudinal prospective study design, participants of the Atahualpa Project Cohort aged  $\geq 60$  years received a baseline brain MRI and clinical interviews. Those who also received a brain MRI at the end of the study were included. Poisson regression models were fitted to assess cSVD markers progression according to their baseline load after a median follow-up of  $6.5 \pm 1.4$  years. Logistic regression models were fitted to assess interrelations in the progression of the different cSVD markers at the end of the study.

**Results** The study included 263 individuals (mean age:  $65.7 \pm 6.2$  years). Progression of white matter hyperintensities (WMH) was noticed in 103 (39%) subjects, cerebral microbleeds in 25 (12%), lacunes in 12 (5%), and enlarged basal ganglia-perivascular spaces (BG-PVS) in 56 (21%). Bivariate Poisson regression models showed significant associations between WMH severity at baseline and progression of WMH and enlarged BG-PVS. These associations became non-significant in multivariate models adjusted for clinical covariates. Logistic regression models showed interrelated progressions of WMH, cerebral microbleeds and enlarged BG-PVS. The progression of lacunes was independent.

**Conclusions** Patterns of cSVD marker progression in this population of Amerindians are different than those reported in other races/ethnic groups. The independent progression of lacunes suggests different pathogenic mechanisms with other cSVD markers.

**Keywords** Cerebral small vessel disease · White matter hyperintensities · Cerebral microbleeds · Lacunes · Enlarged basal ganglia-perivascular spaces · Amerindians

## Introduction

Frequency and progression patterns of sporadic cerebral small vessel disease (cSVD) have extensively been studied in White and Asian populations, and to a lesser degree in Blacks [1–12]. However, information from persons of Amerindian ancestry is lacking. The World Bank estimates that 42 million indigenous people (Amerindians) live in Latin America, accounting for about 8% of the region's population [13]. Many of these individuals are settled in rural areas, and about 40% of them live in poverty with limited access to technology needed to diagnose cSVD. Moreover, cSVD is often unrecognized in these settings because many affected individuals remain asymptomatic for years and restricted

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healthcare resources preclude early recognition of neuroimaging markers that preceded the onset of subsequent clinical consequences such as overt strokes and vascular dementia.

During the past decade, a population of older adults of Amerindian ancestry living in rural Ecuador has comprehensively been investigated to assess the prevalence and correlates of the different cSVD markers in this ethnic group. Overall, these studies have documented a high frequency of cSVD markers in this population [14–17], as well as a significant association between non-traditional risk factors—high social risk, sympathetic overactivity—and progression of white matter hyperintensities (WMH) of presumed vascular origin (a reliable marker of cSVD) [18, 19]. However, little is known on whether the different cSVD markers in Amerindians progress independently or interrelated or if this progression is different than that reported in other races/ethnic groups. This knowledge can provide clues on mechanisms involved in their pathogenesis.

Seizing on this population-based prospective cohort, the present study aims to assess patterns and interrelations of the progression of the different cSVD markers as well as their relationships with demographics, level of education, and traditional cardiovascular risk factors.

## Methods

### Study population

Atahualpa is a rural village located in coastal Ecuador. As previously detailed, the population is homogeneous regarding race/ethnicity, levels of education, socio-economic status, and dietary habits [14–17]. Phenotypic characteristics of the population provide support for their Amerindian ancestry. These include olive-moderate brown skin (Type IV in the Fitzpatrick scale), dark brown eyes and hair, short stature, and a predominantly elliptic hard palate [20].

### Study design

Following a longitudinal prospective study design, Atahualpa residents aged  $\geq 60$  years were identified by means of door-to-door surveys, and those who had a baseline brain MRI between 2012 and 2019, and were actively participating in the Atahualpa Project Cohort as of May 2021, were invited to receive a follow-up brain MRI. Characteristics of individuals who did not receive MRIs were compared to those who completed the study. The study followed the STROBE checklist (The Strengthening the Reporting of Observational Studies in Epidemiology) [21]. We explored the pattern of progression of the different cSVD markers after taking into account the relevance of covariates of interest. Participants were followed starting at baseline MRI. The

study design contemplated follow-up MRIs with sufficient exposure time that allowed enough statistical power to detect the hypothesized difference. The achieved sample of this prospective study has adequate power to detect planned differences.

### Neuroimaging protocol

Both baseline and follow-up MRIs were performed with the same equipment (Philips Intera 1.5 T; Philips Medical Systems, Eindhoven, the Netherlands), following protocols that represented standards for research on cSVD at the time of baseline MRIs [22]. Imaging studies included two-dimensional multi-slice turbo spin-echo T1-weighted (TR 594, TE 15), fluid-attenuated inversion recovery (FLAIR) (TR 9000, TE 120, TI 2500), T2-weighted (TR 4500, TE 100), and T2\*-weighted gradient-recalled echo (TR 686, TE 23) sequences in the axial plane, as well as a FLAIR sequence in the sagittal plane. The pre-established brain imaging package delivered by the manufacturer was used to standardize applicability by technicians.

MRI readings focused on WMH of presumed vascular origin, cerebral microbleeds (CMB), lacunes of presumed vascular origin, and enlarged basal ganglia-perivascular spaces (BG-PVS).<sup>22</sup> WMH were defined as lesions appearing hyperintense on the T2-weighted sequence that remained bright on FLAIR (without cavitation). These lesions were graded according to the modified Fazekas scale, which recognizes three degrees of severity of WMH: mild, moderate and severe [23]. Mild WMH refers to the imaging of periventricular caps or thin lesions and punctate hyperintensities in the subcortical white matter. Moderate WMH is characterized by a smooth periventricular halo and subcortical foci begin to merge. In severe WMH, there is extension of periventricular lesions into the subcortical white matter and large confluent subcortical foci are observed. CMB were identified and rated according to the microbleed anatomical rating scale; only definite CMB were included (well-defined, small, rounded or circular, hypointense lesions located in deep cerebral structures) [24]. Lacunes of presumed vascular origin were defined as fluid-filled cavities measuring  $> 3$  mm but  $< 20$  mm located in the territory of a perforating arteriole [25]. Enlarged BG-PVS were defined as small ( $< 3$  mm) structures of CSF intensity that followed the orientation of perforating arteries [26]. Enlarged BG-PVS were assessed in the single slice with the highest number of these structures on one side, and were rated according to a widely used quantitative scale [27]. Consequently, from 1 to 10 enlarged BG-PVS generated a score of 1, 11–20 a score of 2, 21–40 a score of 3, and  $> 40$  a score of 4.

WMH progression was defined as the increase in at least one grade in the Fazekas scale in the follow-up MRI. CMB and lacunes progression were defined as the appearance of

new CMB or lacunes in the follow-up, respectively (either in subjects who were free of these lesions at baseline or in those who developed additional lesions). Enlarged BG-PVS progression was defined as the increase in one grade in the enlarged BG-PVS scale (Fig. 1).

Both, baseline and follow-up MRIs were independently read by one neuroradiologist and one neurologist blinded to clinical information. Kappa coefficients for interrater agreement for the different cSVD markers at baseline and follow-up were 0.91 and 0.93 for WMH, 0.82 and 0.80 for CMB, 0.88 and 0.92 for lacunes, and 0.84 and 0.78 for enlarged BG-PVS. Discrepancies were resolved by consensus.

### Covariate investigated

Demographics, level of education, and cardiovascular health metrics proposed by the American Heart Association were assessed at the time of baseline MRI and were selected as potential confounders. Cardiovascular health metrics in the poor range were assigned to current smokers, to individuals with a body mass index  $\geq 30$  kg/m<sup>2</sup>, and to those with no moderate or vigorous activity,  $\leq 1$  component of the American Heart Association's healthy diet, blood pressure  $\geq 140/90$  mmHg, fasting glucose  $\geq 126$  mg/dL, and total cholesterol blood levels  $\geq 240$  mg/dL [28]. Less than 15% of the population with vascular risk factors received proper therapy during the study years.

### Statistical analysis

Data analysis was carried out by the use of STATA version 17 (College Station, TX, USA). Univariate comparisons for either continuous or categorical variables utilized linear models, except when non-parametric models were

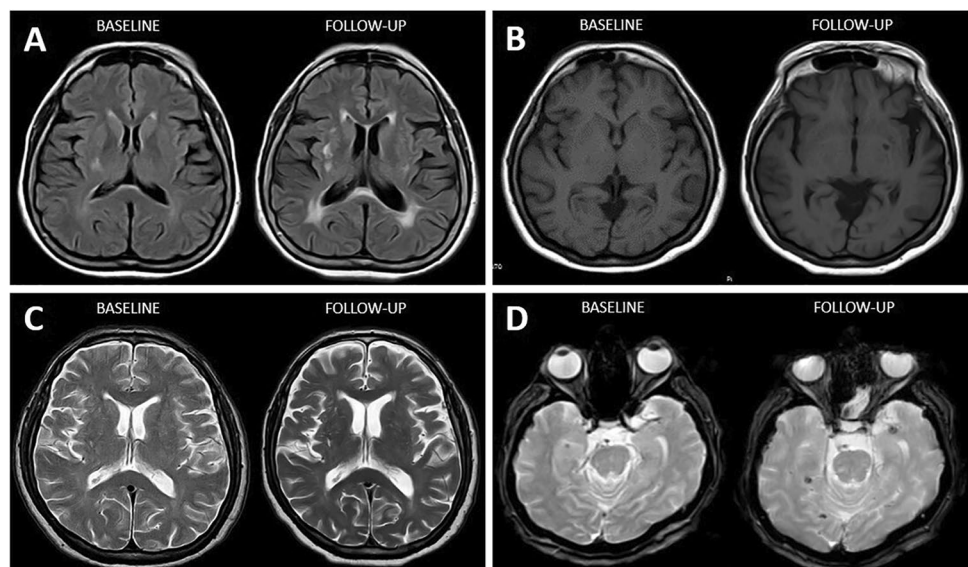
warranted. To calculate person-years of follow-up, we considered the time from baseline to follow-up MRIs. Poisson regression models were fitted to estimate the rate of progression of cSVD markers after taking into account cSVD markers load at baseline as well as clinical covariates, and the time between both MRIs. We used the goodness of fit chi-squared test for Poisson regression, which corroborated the fit of Poisson models to the data. Logistic regression models were fitted to estimate interrelations in the progression of the different cSVD markers. Smoking was not included in any model due to collinearity with other predictors.

## Results

### Recruitment process

A total of 478 individuals aged  $\geq 60$  were enrolled in the Atahualpa Project Cohort between 2012 and 2019. Of them, 403 (84%) received a baseline MRI of the brain and clinical interviews. Among the 75 non-eligible individuals, 36 died or emigrated before the MRI, 19 declined consent, 17 were severely disabled or had contraindications for MRI, and three had missing clinical information. Of 403 subjects that started the study, 263 (65%) had a follow-up MRI and were included in final analyses. Ninety of the 140 excluded study participants died, and the remaining 50 either declined further consent, became disabled, or emigrated between baseline and follow-up MRI. Follow-up time between baseline and follow-up brain MRIs was 1711 person-years (95% CI 1665–1757 years), and the mean follow-up was  $6.5 \pm 1.4$  years (range 2.2–9.1 years).

**Fig. 1** Neuroimaging markers of cerebral small vessel disease. Panel **A** progression of white matter hyperintensities of presumed vascular origin (fluid-attenuated inversion recovery); Panel **B** presence of a new lacune of presumed vascular origin in the left basal ganglia (T1-weighted); Panel **C** progression of enlarged basal-ganglia perivascular spaces in the right basal ganglia (T2-weighted); and Panel **D** appearance of new cerebral microbleeds (T2\*-weighted gradient-recalled echo)



## Baseline characteristics of study participants

The mean ( $\pm$  SD) age of 263 participants at the time of baseline MRI was  $65.7 \pm 6.2$  years (median age: 63.9 years; age range: 60–91 years), 149 (57%) were women, and 192 (73%) had primary school education only. Individual cardiovascular health 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 blood levels: 41 (16%). On baseline MRI, 131 individuals (50%) had mild, 33 (13%) had moderate, and nine (3%) had severe WMH (the remaining 90 [34%] did not have WMH). CMB were present in 22 (8%) and lacunes in 21 (8%) subjects. Abnormally enlarged BG-PVS were documented in 56 (21%) individuals (46 had grade 2 and 10 had grades 3–4); the remaining 207 participants had grade 1 enlarged BG-PVS, which is considered normal.

## Differences across included and non-included individuals

As mentioned, 75 individuals were excluded for not receiving a baseline MRI and 140 did not receive a follow-up MRI ( $n = 215$ ). Table 1 shows differences across excluded and included individuals, which were expected since most of the former died or became disabled during the follow-up. For the subset of 140 individuals who had a baseline—but not a follow-up—MRI, all cSVD markers were significantly more frequent when compared to the analyzed population.

## cSVD markers at follow-up

At follow-up, 112 (43%) individuals had mild, 67 (25%) had moderate, and 32 (12%) had severe WMH (the remaining 52 subjects [20%] did not have WMH). A total of 103 (39%) individuals had MRI evidence of WMH progression. Progression from none-to-mild WMH was observed in 33 cases, from none-to-moderate in five, from mild-to-moderate in 42, from mild-to-severe in 10, and from moderate-to-severe

**Table 1** Clinical (upper panel) and neuroimaging (lower panel) differences across individuals excluded because baseline or follow-up MRI were not performed and those who completed the study (unadjusted analysis)

| Clinical characteristics                                   | Excluded individuals ( $n = 215$ ) | Finished the study ( $n = 263$ ) | <i>p</i> value       |
|--|------------------------------------|----------------------------------|----------------------|
| Age at baseline, mean $\pm$ SD                             | 75.4 $\pm$ 9.9                     | 65.7 $\pm$ 6.2                   | < 0.001 <sup>a</sup> |
| Women, <i>n</i> (%)  | 114 (53)                           | 149 (57)                         | 0.427                |
| Primary school education, <i>n</i> (%)                     | 179 (83)                           | 192 (73)                         | 0.007 <sup>a</sup>   |
| Current smoker, <i>n</i> (%)                               | 4 (2)                              | 11 (4)                           | 0.147                |
| Body mass index $\geq 30$ kg/m <sup>2</sup> , <i>n</i> (%) | 45 (21)                            | 63 (24)                          | 0.432                |
| Poor physical activity, <i>n</i> (%)                       | 45 (21)                            | 12 (5)                           | < 0.001 <sup>a</sup> |
| Poor diet, <i>n</i> (%)                                    | 13 (6)                             | 11 (4)                           | 0.353                |
| Blood pressure $\geq 140/90$ mmHg, <i>n</i> (%)            | 113 (53)                           | 104 (40)                         | 0.004 <sup>a</sup>   |
| Fasting glucose $\geq 126$ mg/dL, <i>n</i> (%)             | 84 (39)                            | 72 (27)                          | 0.007 <sup>a</sup>   |
| Total cholesterol $\geq 240$ mg/dL, <i>n</i> (%)           | 15 (7)                             | 41 (16)                          | 0.004 <sup>a</sup>   |
| Cerebral small vessel disease biomarkers                   | Only baseline MRI ( $n = 140$ )    | Finished the study ( $n = 263$ ) | <i>p</i> value       |
| White matter hyperintensities                              |                                    |                                  |                      |
| None, <i>n</i> (%)   | 23 (16)                            | 90 (34)                          | < 0.001 <sup>a</sup> |
| Mild, <i>n</i> (%)   | 59 (42)                            | 131 (50)                         | 0.142                |
| Moderate, <i>n</i> (%)                                     | 33 (24)                            | 33 (13)                          | 0.004 <sup>a</sup>   |
| Severe, <i>n</i> (%)                                       | 25 (18)                            | 9 (3)                            | < 0.001 <sup>a</sup> |
| Cerebral microbleeds (CMB)                                 |                                    |                                  |                      |
| CMB present  | 27 (19)                            | 22 (8)                           | 0.001 <sup>a</sup>   |
| Lacunes of presumed vascular origin                        |                                    |                                  |                      |
| Lacunes present  | 29 (21)                            | 21 (8)                           | < 0.001 <sup>a</sup> |
| Enlarged basal ganglia-perivascular spaces (BG-PVS)        |                                    |                                  |                      |
| BG-PVS Grade 1 (normal)                                    | 85 (61)                            | 207 (79)                         | < 0.001 <sup>a</sup> |
| BG-PVS Grade 2   | 25 (18)                            | 46 (17)                          | 0.927                |
| BG-PVS Grades 3–4  | 30 (21)                            | 10 (4)                           | < 0.001 <sup>a</sup> |

<sup>a</sup>Statistically significant result

in 13. Also at follow-up MRI, 47 (18%) individuals had CMB and 33 (13%) had lacunes. CMB progression was noticed in 25 (10%) individuals, and lacunes progression in 12 (5%). Abnormally enlarged BG-PVS were recognized in 99 (38%) individuals (77 had grade 2 and 22 had grades 3–4). The remaining 164 individuals (62%) had enlarged BG-PVS grade 1 (normal). Overall, 56 (21%) individuals had evidence of enlarged BG-PVS progression. Progression from grade 1 to 2 was observed in 41 cases, from grade 2 to grades 3–4 in 14, and from grade 1 to grades 3–4 in one.

Unadjusted analyses showed differences across individuals who had cSVD markers progression compared to those who did not (Table 2). Individuals with WMH progression were older and less often obese than their counterparts without progression. Individuals with enlarged BG-PVS progression were older and more often hypertensive than those who did not have progression of this marker. WMH progression was interrelated with CMB and enlarged BG-PVS progression. Lacunes progressed independently of all other markers of cSVD, and CMB and enlarged BG-PVS also progressed independently of each other.

### cSVD marker severity at baseline and progression

To assess associations between cSVD markers basal loads and their progressions, we fitted separate Poisson regression models using cSVD markers progression as dependent variables. Unadjusted models showed significant associations between WMH basal load and progression (IRR: 1.38; 95% CI 1.19–1.59) and between enlarged BG-PVS basal load and progression (IRR: 1.50; 95% CI 1.11–2.04). However, these associations became non-significant when clinical covariates were taken into account (Table 3). CMB and lacunes basal loads were collinear with CMB and lacunes progression, respectively. Likewise, CMB progression and poor diet, as well as lacunes progression and poor physical activity, were collinear. Age at baseline was the single covariate remaining significant in the model assessing WMH progression. Otherwise, no covariates remained independently significant in these multivariate models.

### Interrelations between cSVD marker progression

Using progression of the different cSVD markers as dependent variables, we fitted logistic regression models to assess interrelations in the progression of these markers. Parsimonious models, adjusted for demographics and removing covariates near to  $p = 1$  in fully adjusted models, showed interrelated progression of WMH with CMB (OR: 2.76; 95% CI 1.07–7.11) and with enlarged BG-PVS (OR: 4.37; 95% CI 2.16–8.83). Lacunes progressed independently to the progression of the other cSVD markers (Table 4).

## Discussion

This longitudinal prospective population-based cohort, conducted in community-dwelling older adults of Amerindian ancestry, shows that the progression of cSVD markers differs from that reported in other races/ethnic groups. WMH, CMB, and enlarged BG-PVS progressions remain interrelated after relevant clinical covariates are taken into account. Lacunes progress independently of the other cSVD markers.

There are no previous reports on the interrelated progression of cSVD markers in Amerindians. However, important pieces of evidence may be gathered from studies conducted in other races/ethnic groups. A longitudinal study conducted in Singapore (346 individuals attending a memory clinic, followed for about 2 years) revealed that arterial hypertension was associated with WMH progression, and age with CMB progression. In the Singapore study, the most important factor for cSVD markers progression was cSVD load at baseline [5]. In the Shanghai Aging Study, WMH severity at baseline predicted progression of all markers of cSVD. However, progression was heterogeneous and interrelations of progression among the different cSVD markers were not estimated [7].

The Rotterdam Scan Study, a population-based cohort that included a White population, followed 668 individuals for three years [29]. This study used WMH and lacunes as cSVD markers of interest, and found that WMH basal load, increasing age, being women, arterial hypertension, smoking, and having lacunes at baseline were associated with increased WMH progression. In the Rotterdam Scan Study, WMH progression was tightly associated with lacunes progression, suggesting a shared pathogenic mechanism. Interrelated progression of WMH and lacunes has also been reported in other studies among White populations [30, 31]. In the Atherosclerosis Risk in Communities Study, including Black and White participants, 901 stroke-free individuals had a follow-up brain MRI about 10 years after baseline [6]. The study only considered progression of WMH and lacunes. It was found that both markers progressed together and this progression was associated with an increased incidence of stroke. Data from the Swedish National Study on Aging and Care in Kungsholmen (325 individuals followed for almost six years) also showed that baseline loads of WMH, lacunes and enlarged BG-PVS predicted interrelated progression of these cSVD markers [8]. In contrast, we did not find such associations, suggesting that—at least in Amerindians—lacunes might be associated to pathogenic mechanisms independent of cSVD such as intracranial atherosclerotic disease or embolism. However, comparisons must be interpreted with caution since not all studies take into account the four cSVD

**Table 2** Characteristics of Atahualpa residents aged  $\geq 60$  years across categories of progression of the different biomarkers of cerebral small vessel disease (unadjusted analyses)

| Variable   | WMH progression      |                       |                     | CMB progression      |                      |                    | Lacunes progression  |                      |                | Enlarged BG-PVS progression |                      |                     |
|--|----------------------|-----------------------|---------------------|----------------------|----------------------|--------------------|----------------------|----------------------|----------------|-----------------------------|----------------------|---------------------|
|  | No ( <i>n</i> = 160) | Yes ( <i>n</i> = 103) | <i>p</i> value      | No ( <i>n</i> = 238) | Yes ( <i>n</i> = 25) | <i>p</i> value     | No ( <i>n</i> = 251) | Yes ( <i>n</i> = 12) | <i>p</i> value | No ( <i>n</i> = 207)        | Yes ( <i>n</i> = 56) | <i>p</i> value      |
| Age at baseline, years (mean $\pm$ SD)           | 64.3 $\pm$ 5.8       | 67.9 $\pm$ 6          | <0.001 <sup>a</sup> | 65.5 $\pm$ 6.1       | 67.1 $\pm$ 6.6       | 0.217              | 65.7 $\pm$ 6.3       | 65 $\pm$ 3.6         | 0.703          | 64.9 $\pm$ 5.5              | 68.9 $\pm$ 7.4       | <0.001 <sup>a</sup> |
| Women, <i>n</i> (%)                              | 91 (57)              | 58 (56)               | 0.928               | 133 (56)             | 16 (64)              | 0.436              | 145 (58)             | 4 (33)               | 0.095          | 117 (57)                    | 32 (57)              | 0.934               |
| Primary school education, <i>n</i> (%)           | 112 (70)             | 80 (78)               | 0.171               | 174 (73)             | 18 (72)              | 0.905              | 182 (73)             | 10 (83)              | 0.409          | 148 (71)                    | 44 (79)              | 0.290               |
| Current smoker, <i>n</i> (%)                     | 11 (7)               | 0                     | ...                 | 10 (4)               | 1 (4)                | 0.962              | 11 (4)               | 0                    | ...            | 11 (5)                      | 0                    | ...                 |
| BMI $\geq 30$ kg/m <sup>2</sup>                  | 46 (29)              | 17 (17)               | 0.023 <sup>a</sup>  | 57 (24)              | 6 (24)               | 0.996              | 62 (25)              | 1 (8)                | 0.194          | 55 (27)                     | 8 (14)               | 0.056               |
| Poor physical activity, <i>n</i> (%)             | 9 (6)                | 3 (3)                 | 0.376               | 10 (4)               | 2 (8)                | 0.319              | 12 (5)               | 0                    | ...            | 7 (3)                       | 5 (9)                | 0.078               |
| Poor diet, <i>n</i> (%)                          | 7 (4)                | 4 (4)                 | 0.846               | 11 (5)               | 0                    | ...                | 9 (4)                | 2 (17)               | 0.084          | 8 (4)                       | 3 (5)                | 0.706               |
| Blood pressure $\geq 140/90$ mmHg, <i>n</i> (%)  | 60 (38)              | 44 (43)               | 0.398               | 90 (38)              | 14 (56)              | 0.077              | 100 (40)             | 4 (33)               | 0.768          | 75 (36)                     | 29 (52)              | 0.035 <sup>a</sup>  |
| Fasting glucose $\geq 126$ mg/dL, <i>n</i> (%)   | 45 (28)              | 27 (26)               | 0.734               | 63 (26)              | 9 (36)               | 0.309              | 68 (27)              | 4 (33)               | 0.741          | 56 (27)                     | 16 (29)              | 0.821               |
| Total cholesterol $\geq 240$ mg/dL, <i>n</i> (%) | 26 (16)              | 15 (15)               | 0.713               | 37 (16)              | 4 (16)               | 0.952              | 38 (15)              | 3 (25)               | 0.407          | 29 (14)                     | 12 (21)              | 0.174               |
| WMH progression, <i>n</i> (%)                    | ...                  | ...                   | ...                 | 87 (31)              | 16 (64)              | 0.007 <sup>a</sup> | 95 (38)              | 8 (32)               | 0.067          | 64 (31)                     | 39 (70)              | <0.001 <sup>a</sup> |
| CMB progression, <i>n</i> (%)                    | 9 (6)                | 16 (16)               | 0.007 <sup>a</sup>  | ...                  | ...                  | ...                | 22 (9)               | 3 (12)               | 0.094          | 17 (8)                      | 8 (14)               | 0.169               |
| Lacunes progression, <i>n</i> (%)                | 4 (3)                | 8 (8)                 | 0.067               | 9 (4)                | 3 (12)               | 0.061              | ...                  | ...                  | ...            | 7 (3)                       | 5 (9)                | 0.078               |
| Enlarged BG-PVS progression, <i>n</i> (%)        | 17 (11)              | 39 (38)               | <0.001 <sup>a</sup> | 48 (20)              | 8 (32)               | 0.169              | 51 (20)              | 5 (20)               | 0.077          | ...                         | ...                  | ...                 |

WMH white matter hyperintensities, CMB cerebral microbleeds, BG-PVS basal ganglia-periventricular spaces

<sup>a</sup>Statistically significant result

**Table 3** Poisson regression models showing progression of the different cerebral small vessel disease biomarkers (dependent variables) according to their baseline loads, after adjusting for demographics, level of education, and cardiovascular risk factors

| Variable                           | WMH progression<br>IRR (95% CI) | CMB progression<br>IRR (95% CI) | Lacunes progression<br>IRR (95% CI) | Enlarged BG-<br>PVS progression<br>IRR (95% CI) |
|------------------------------------|---------------------------------|---------------------------------|-------------------------------------|---|
| WMH at baseline                    | 0.74 (0.54–1.01)                | 1.63 (0.96–2.79)                | 2.00 (0.86–4.68)                    | 1.38 (0.94–2.03)                                |
| CMB at baseline                    | 0.91 (0.41–2.03)                | ...                             | 3.38 (0.62–18.5)                    | 1.68 (0.69–4.12)                                |
| Lacunes at baseline                | 1.26 (0.58–2.73)                | 0.94 (0.18–4.85)                | ...                                 | 0.76 (0.26–2.20)                                |
| Enlarged BG-PVS at baseline        | 1.32 (0.90–1.93)                | 0.95 (0.41–2.21)                | 1.04 (0.32–3.44)                    | 0.66 (0.37–1.18)                                |
| Age at baseline                    | 1.04 (1.00–1.07) <sup>a</sup>   | 0.99 (0.93–1.07)                | 0.93 (0.83–1.05)                    | 1.04 (0.99–1.08)                                |
| Being women                        | 1.01 (0.67–1.53)                | 1.19 (0.49–2.89)                | 0.37 (0.99–1.41)                    | 0.85 (0.48–1.50)                                |
| Primary school education           | 1.16 (0.71–1.90)                | 0.82 (0.32–2.11)                | 1.49 (0.30–7.37)                    | 1.00 (0.50–1.99)                                |
| BMI $\geq$ 30 kg/m <sup>2</sup>    | 0.78 (0.44–1.37)                | 0.96 (0.33–2.81)                | 0.36 (0.04–2.95)                    | 0.60 (0.26–1.38)                                |
| Poor physical activity             | 0.68 (0.20–2.31)                | 1.69 (0.32–8.91)                | ...                                 | 2.37 (0.81–6.90)                                |
| Poor diet                          | 1.09 (0.39–3.08)                | ...                             | 4.14 (0.74–23.1)                    | 0.76 (0.21–2.73)                                |
| Blood pressure $\geq$ 140/90 mmHg  | 0.96 (0.63–1.46)                | 1.89 (0.83–4.34)                | 0.80 (0.21–3.02)                    | 1.39 (0.78–2.47)                                |
| Fasting glucose $\geq$ 126 mg/dL   | 0.92 (0.58–1.46)                | 1.49 (0.63–2.54)                | 0.96 (0.25–3.62)                    | 1.09 (0.59–1.99)                                |
| Total cholesterol $\geq$ 240 mg/dL | 0.99 (0.57–1.75)                | 0.82 (0.27–2.54)                | 2.50 (0.57–10.9)                    | 1.27 (0.63–2.54)                                |

Empty cells (...) represent collinearity

WMH white matter hyperintensities, CMB cerebral microbleeds, BG-PVS basal ganglia-periventricular spaces

<sup>a</sup>Statistically significant result

**Table 4** Parsimonious logistic regression models, adjusted for demographics and removing covariates near to  $p=1$  in fully adjusted models, showing interrelated progression of white matter hyperintensities with cerebral microbleeds and enlarged basal ganglia-perivascular

spaces. Lacunes progression is independent to the progression of the other cerebral small vessel disease biomarkers (numbers in cells correspond to odds ratios with 95% confidence intervals)

| Independent variables       | Dependent variables           |                               |                                  |  |
|-----------------------------|-------------------------------|-------------------------------|----------------------------------|--|
|                             | WMH progression <sup>b</sup>  | CMB progression <sup>c</sup>  | Lacunes progression <sup>d</sup> | Enlarged BG-<br>PVS progression <sup>e</sup> |
| WMH progression             | .                             | 2.91 (1.13–7.49) <sup>a</sup> | 3.34 (0.78–14.2)                 | 4.45 (2.21–8.96) <sup>a</sup>                |
| CMB progression             | 2.76 (1.07–7.11) <sup>a</sup> | .                             | 3.79 (0.83–17.4)                 | 1.04 (0.37–2.91)                             |
| Lacunes progression         | 2.73 (0.69–10.8)              | 3.29 (0.75–14.5)              | .                                | 2.34 (0.63–8.64)                             |
| Enlarged BG-PVS progression | 4.37 (2.16–8.83) <sup>a</sup> | 1.02 (0.37–2.77)              | 2.25 (0.58–8.66)                 | .  |

WMH white matter hyperintensities, CMB cerebral microbleeds, BG-PVS basal ganglia-perivascular spaces

<sup>a</sup>Statistical significant result

<sup>b</sup>Adjusted for age, sex, body mass index, physical activity, diet, and total cholesterol blood levels

<sup>c</sup>Adjusted for age, sex, physical activity, blood pressure, and fasting glucose

<sup>d</sup>Adjusted for age, sex, and diet

<sup>e</sup>Adjusted for age, sex, body mass index, physical activity, blood pressure, and total cholesterol blood levels

markers used in the present study and protocols used for assessing progression (particularly WMH progression) are heterogeneous. Moreover, some studies are restricted to patients with stroke or attending a memory clinic, and may not be representative of the population at large.

In the present study of Amerindians, the progression of lacunes occurred independently of WMH, CMB, and BG-PVS progression, suggesting that the former may not be exclusively related to cSVD. In this view, we have recently

reported that lacunes of presumed vascular origin are more frequently associated with intracranial atherosclerotic disease than with cSVD and that only one-fourth of the effect of intracranial atherosclerosis on lacunes was mediated by WMH [32].

The present study has some limitations. Inasmuch as the identification of individuals by means of door-to-door surveys supposes a lack of selection bias, non-included individuals were older, had more cardiovascular risk factors, and

a more severe cSVD burden than those who were included. However, the same differences have been reported in other studies that attempted to differentiate non-included and included individuals [5]. In the present study, differences across excluded and included individuals were likely related to the SARS-CoV-2 pandemic, since old individuals (particularly those who had COVID-19 and remained with respiratory sequelae) did not accept the practice of follow-up MRIs. This was reflected in the rate of declined consent, which increased substantially from the first (baseline) to the second (follow-up) invitation. Another factor that limited the number of individuals included this study was the high mortality rate related to COVID-19 in the village [33], and the fear of older adults to remain in a village with poor sanitary resources, which are evidenced by the excess numbers of deaths and emigration from 2020 to 2021, compared to those occurring from 2012 to 2019. The modified Fazekas scale may be less reliable than volumetry to assess slight changes in WMH severity in the follow-up [34], and this may be perceived as another limitation of this study. It is also possible that some unmeasured confounders may be responsible for at least part of the findings of the present study. Indeed, recent studies showed the importance of non-traditional risk factors (sympathetic overactivity, high social risk) in the progression of WMH in the study population [18, 19]. In addition, the fact that less than 15% of the population with vascular risk factors received proper therapy during the study years precluded assessment of the impact of medications on cSVD markers progression, as has been demonstrated in other studies [35]. The good side of this is that we had the opportunity to assess cSVD progression in a virtually untreated population, which gave us more clear estimates of the natural history of cSVD marker progression.

Despite these limitations, the study has several strengths that include its population-based design, the racial homogeneity of the study population, the systematic assessment of cardiovascular risk factors and cSVD markers by means of uniform and standardized protocols, and the practice of baseline and follow-up MRIs using the same equipment and procedures.

In conclusion, this is the first study showing patterns of cSVD markers progression in Amerindians, which differed with those reported in other races/ethnic groups, mostly by the little contributory role of cardiovascular risk factors on cSVD progression and the fact that lacunes progressed independently to the other cSVD markers. This knowledge may open new avenues of research for comparison of cSVD progression patterns across different races/ethnic groups. This, in turn, will allow a better understanding of the natural history of cSVD markers in these vulnerable populations. Exploring their possible different pathogenic mechanisms, may help implement policies and cost-effective intervention strategies to reduce consequences of covert cSVD.

**Author contributions** OHB: study design, imaging readings, and manuscript drafting; RMM: statistical analysis of data; AFC: data collection and interpretation; DAR: data collection and interpretation; BYR: study coordinator; VJB: imaging readings and significant intellectual contribution to manuscript content. All authors read and approved the final version of the submitted manuscript.

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**Data availability** Aggregated data from this study are available from the corresponding author upon written request.

## Declarations

**Conflict of interest** The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Ethical approval** The Ethics Committee of Hospital–Clínica Kennedy, Guayaquil, Ecuador (FWA 00030727) approved the study.

**Informed consent** Study participants signed comprehensive informed consents at enrollment, as well as before the practice of follow-up MRIs.

**Statement of human and animal rights** All human studies have been approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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