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Clinical and neuroimaging risk factors for cognitive decline in community-dwelling older adults living in rural Ecuador. A population-based prospective cohort study.

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Abstract

Objective: There is limited information on factors influencing cognitive decline in rural settings from low and middle income countries. Using the Atahualpa Project cohort, we aimed to assess the burden of cognitive decline in older adults living in a rural Ecuadorian village.

Methods: The study included Atahualpa residents aged ≥ 60 years who had a follow-up Montreal Cognitive Assessment (MoCA) repeated at least one year after baseline. MoCA decline was assessed by multivariable longitudinal linear models, adjusted for demographics, days between MoCA tests, cardiovascular risk factors and neuroimaging signatures of structural brain damage.

Results: We included 252 individuals who contributed 923.7 person-years of follow-up (mean: 3.7±0.7 years). The mean baseline MoCA was 19.5±4.5 points and the follow-up MoCA was 18.1±4.9 points ($p=0.001$). Overall, 154 individuals (61%) had lower MoCA scores at follow-up. The best fitted longitudinal linear model showed a decline of follow-up MoCA from baseline (β : 0.14; 95% C.I.: 0.07 – 0.21; $p<0.001$). High glucose levels, global cortical atrophy and white matter hyperintensities were independently and significantly associated with greater MoCA decline.

Conclusion: This study provides evidence of cognitive decline in older adults living in a rural setting. Main targets for prevention should include glucose control, and the control of factors that are deleterious for the development of cortical atrophy and white matter hyperintensities.

Keywords

Cognitive decline; Montreal Cognitive Assessment; Population-based cohort; Rural settings

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INTRODUCTION

Longitudinal studies of cognitive decline in remote rural setting in low- and middle-income countries (LMIC) are sparse and limited by illiteracy, cross-cultural factors, restricted availability of sophisticated diagnostic tools, and a lack of research funding.¹ Indeed, only a few such studies have been conducted and few if any have done neuroimaging to better understand correlates of cognitive decline.^{2–5} In addition, clinical risk factors found to influence cognitive decline have varied across studies, probably due to differences in study design, characteristics of enrolled participants, or time elapsed between baseline and follow-up evaluations.

Increasing incidence of cognitive impairment is a major concern in rural areas of LMIC because of greater life expectancy and changes in lifestyle. Knowledge of region-specific risk factors influencing cognitive decline are urgently needed to implement measures to reduce its burden in rural settings.⁶ Using the Atahualpa Project cohort, this study aimed to assess clinical and neuroimaging risk factors influencing cognitive decline in community-dwelling older adults living in a rural Ecuadorian community.

METHODS

Study population:

The study was conducted in Atahualpa, a rural village of about 2,500 inhabitants located in coastal Ecuador. Atahualpa residents are homogeneous regarding race/ethnicity (Amerindians), living characteristics, dietary habits and socio-economic status. Migration of villagers is limited, making Atahualpa an ideal setting for the conduct of prospective cohort studies.⁷ Community-dwelling individuals identified during door-to-door surveys who signed the informed consent form were enrolled and prospectively followed by means of annual surveys and other overlapping sources. The Institutional Review Board of Hospital-Clinica Kennedy, Guayaquil, Ecuador (FWA 00006867) approved the study.

Inclusion criteria:

Individuals enrolled in the Atahualpa Project meeting the following criteria were included in this study: 1) age ≥ 60 years at the time of the baseline MoCA, 2) having a complete set of baseline interviews assessing covariates of interest (see below), and 3) having a head CT scan and a brain MRI within the first six months after the baseline MoCA. Those who had a follow-up MoCA at least 12 months after the baseline MoCA, were considered for analyses.

Baseline data collection:

Baseline interviews and procedures assessed demographics, years of education, symptoms of depression (by the use of the depression axis of the depression-anxiety-stress scale-21),⁸ sleep quality (by the use of the Pittsburgh sleep quality index),⁹ cardiovascular risk factors (according to criteria and cutoffs proposed by the American Heart Association),¹⁰ and dietary oily fish intake (calculated as servings per week).¹¹ A rural dentist performed a dental exam to assess the number of teeth, and those with less than 10 remaining teeth were considered to have severe edentulism (non-traumatic edentulism was used as a proxy of

chronic inflammatory periodontitis). All subjects with a suspected diagnosis of stroke (on field interviews) were examined by a senior neurologist to confirm the diagnosis. These covariates were included for analysis, as they have shown to modify cognitive performance in Atahualpa residents.⁷

Neuroimaging protocols used in the Atahualpa Project have been detailed elsewhere.¹² In brief, exams were performed by the use of a Philips Brilliance 64 CT scanner and a Philips Intera 1.5T MRI scanner (Philips Medical Systems, Eindhoven, the Netherlands). All exams were independently reviewed by a neurologist and a neuroradiologist, with adequate kappa coefficients for inter-rater agreement for lesions of interest.¹²

CT digital images were viewed on Osirix Medical Imaging software (Pixmeo, Geneva, Switzerland) using the bone window setting to identify and grade carotid siphon calcifications. Using a previously proposed scoring method, we stratified individuals into those with low and high arterial calcium.¹³ The later was defined as the presence of uni- or bilateral thin confluent or thick – interrupted or continuous – calcifications. Using the brain window setting, the bicaudate index was calculated to assess central atrophy, by dividing the minimal intercaudate distance by the brain width along the same line.¹⁴

On MRI, we assessed global cortical atrophy (GCA), silent neuroimaging signatures of cerebral small vessel disease, and evidence of non-lacunar ischemic or hemorrhagic strokes. In particular, GCA was classified in none-to-mild or moderate-to-severe using the visual scale proposed by Pasquier *et al.*,¹⁵ white matter hyperintensities (WMH) of presumed vascular origin 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,¹⁶ cerebral microbleeds (CMB) were identified and rated according to the microbleed anatomical rating scale,¹⁷ lacunar infarcts were defined as fluid-filled cavities measuring 3–15mm located in the territory of a perforating arteriole,¹⁸ and enlarged perivascular spaces (PVS) were defined as small (<3mm) structures of CSF intensity located in the basal ganglia that followed the orientation of perforating arteries.¹⁹ In addition, MRI findings consistent with non-lacunar cerebral infarcts and old intracranial hemorrhages (visualized in the echo-gradient sequence) were noted.

Cognitive performance:

The Spanish version of the MoCA (www.mocatest.org, © Z. Nasreddine MD, version 07 November 2004) was used to assess cognitive performance at baseline and at the end of the follow-up. Baselines MoCA were performed at the time of enrollment or within the first six months thereafter, and subsequent MoCAs were performed at the last censoring visit. Individuals having a baseline MoCA but not a follow-up MoCA were not included. The MoCA evaluates major cognitive domains: visuospatial-executive, naming (unfamiliar animals), attention and calculation, language, verbal abstraction, delayed recall (short-term memory), and orientation. Maximum MoCA score is 30 points, with an additional point given to persons with 12 years of education.²⁰ We did not use a cutoff score for defining cognitive impairment or decline due to poor validity of established cutoffs in poorly educated populations with low literacy.^{14,21} Both baseline and follow-up MoCAs were performed by the same investigator under similar circumstances (exams were performed in a

comfortable environment at the Community Center of the Atahualpa Project, and all men were breathalyzed before the test to ensure a blood alcohol content reading of 0.0%; those who tested positive were requested to stay sober and were invited again after 72 hours).

Statistical analyses:

Data analyses were carried out by using STATA version 15 (College Station, TX, USA). In unadjusted analyses, continuous variables were compared by linear models and categorical variables by χ^2 or the Fisher exact test as appropriate. Multivariable longitudinal linear models were fitted to assess the differences between baseline and follow-up MoCA after adjusting for baseline values (covariates). We fitted three such models, one adjusted for demographics and all clinical covariates, another adjusted for covariates remaining significant or borderline in the previous model plus neuroimaging signatures of interest, and a final model adjusted for demographics, days between tests, and variables remaining significant in the previous models.

RESULTS

Of 437 individuals aged 60 years enrolled in the Atahualpa Project, 292 (67%) fulfilled baseline inclusion criteria. Of these, 252 (86%) had a follow-up MoCA at least 12 months after the baseline MoCA and were included in the analyses. Reasons for not being included were inability to have the MoCA due to aphasia, blindness, deafness or severe disability (n=8), declining to consent for the follow-up MoCA (n=4), moving out of the village (n=2) or dying before the follow-up MoCA (n=26).

The mean ($\pm$ SD) age of participants at the time of the baseline MoCA was 67 ± 7 years (median: 66 years; age range: 60 to 90 years), 160 (63%) were women, and 194 (75%) only had a primary school education (mean $\pm$ SD years of education in the entire population were 6.5 ± 2.9). A body mass index 30 kg/m^2 was noted in 57 (23%) persons, blood pressure 140/90 mmHg in 113 (45%), fasting glucose 126 mg/dL in 79 (31%), and total cholesterol levels 240 mg/dL in 35 (14%). Only two (1%) participants were current smokers, 9 (4%) had a poor diet, and 15 (6%) had poor physical activity. The mean number of oily fish servings per week was 9 ± 5.2 . A poor sleep quality was noticed in 74 (29%) of participants, symptoms of depression in 23 (9%) and severe edentulism in 114 (45%).

Using CT, there was evidence of high calcium content in the carotid siphons in 82 (33%) persons, and the mean bicaudate index was 0.12 ± 0.02 . On MRI, 114 individuals (45%) had moderate-to-severe GCA, 47 had moderate-to-severe WMH (19%), 14 had deep CMB (6%), 9 had cortical CMB (4%), 62 had >10 enlarged basal ganglia PVS (25%), 23 had lacunar infarcts (9%; silent in 19 cases), and 11 had other stroke subtypes (4%; ischemic or hemorrhagic).

The mean ($\pm$ SD) age at the time of the follow-up MoCA was 71 ± 7 years (median age: 70 years; age range: 61 to 94 years). The 252 participants with baseline and follow-up MoCA, contributed 923.7 person years of follow-up (mean: 3.7 ± 0.7 years; median: 3.8 years; interquartile range: 1.3 to 4.7 years).

The mean ($\pm$ SD) baseline MoCA score was 19.5 ± 4.5 points (median MoCA: 20 points; range: 6 – 29 points), and that of the follow-up MoCA score was 18.1 ± 4.9 points (median MoCA: 19 points; interquartile range: 6 – 28 points). The decline in MoCA scores between baseline and follow-up was significant in univariate analysis ($p=0.001$). Overall, 154 (61%) individuals had lower MoCA scores in the follow-up, 55 (22%) had the same score, and the remaining 43 (17%) had higher scores. Decline in MoCA scores ranged from 1 to 12 points (mean: 2.7 ± 2.1 points), while increase was only for 1 or 2 points.

As shown in Table 1, factors influencing decline in the follow-up MoCA score in unadjusted analyses were: age at the time of baseline MoCA ($p=0.004$), severe edentulism ($p=0.031$), high calcium content in the carotid siphons ($p=0.029$), the bicaudate index ($p=0.004$), moderate-to-severe GCA ($p<0.001$), moderate-to-severe WMH ($p<0.001$), deep CMB ($p=0.011$), and >10 enlarged basal ganglia PVS ($p=0.002$).

Table 2 shows the results of longitudinal linear models. The first model was adjusted for demographics and clinical covariates and showed a significant decline in the follow-up MoCA scores when compared with baseline MoCAs (β coefficient: 0.11; 95% C.I.: 0.04 – 0.18; $p=0.003$). In this model, covariates remaining significant were age at baseline MoCA and glucose levels ≥ 126 mg/dL. We did not use years of education due to collinearity, since the MoCA gives one extra point for education. A second model, adjusted for covariates remaining significant or borderline in the previous model plus all neuroimaging signatures of interest, also showed a significant decline in follow-up MoCA scores from baseline MoCAs (β coefficient: 0.16; 95% C.I.: 0.09 – 0.23; $p<0.001$). In this model, age was no longer significantly associated with change in MoCA score, but high glucose levels as well as two neuroimaging signatures – moderate-to-severe GCA and moderate-to-severe WMH – remained significantly inversely associated with follow-up MoCA scores. The best fitting model also showed a decline in follow-up MoCA scores from baseline MoCAs (β coefficient: 0.14; 95% C.I.: 0.07 – 0.21; $p<0.001$). Likewise, in this model, high glucose levels, moderate-to-severe GCA and moderate-to-severe WMH remained significant.

DISCUSSION

Results from this population-based prospective cohort study showed that roughly two thirds of participants decline on the MoCA score after a mean of 3.7 ± 0.7 person-years of follow-up among community-dwelling older adults living in a remote rural setting. High glucose levels and moderate-to-severe GCA and WMH, were consistently associated with MoCA decline in longitudinal linear models. Age at baseline MoCA was associated with MoCA decline in the model adjusted for clinical covariates, but lost significance when neuroimaging signatures were included in subsequent models. In addition, positivity of the β coefficient in longitudinal linear models showed that the higher MoCA score at baseline, more likely MoCA would decline at the follow-up.

Interestingly, the relationship between high glucose levels and cognitive decline did not reach statistical significance in the unadjusted analysis but became highly significant in multivariable models. This may occur due to a number of reasons, including unbalanced sample size, missing data, a large within-group variation, and the presence of suppressor

variables. The latter scenario most likely explains this finding in our cohort, since one or more of the other included variables probably suppressed the true relationship between high glucose levels and cognitive decline, and this relationship only emerged when the other variables were controlled in the multivariate models.²²

During the conduct of the Atahualpa Project, our group performed several cross-sectional studies aimed to assess the independent association between key clinical and neuroimaging variables with cognitive performance. We have reported associations between lower MoCA scores and neuropsychological distress,²³ severe edentulism,²⁴ moderate-to-severe GCA,²⁵ the bicaudate index,¹⁴ severity of carotid siphon calcifications,²⁶ and silent neuroimaging signatures of small vessel disease.²⁷ Most of these associations remained significantly related to cognitive decline in current univariate analyses (Table 1), but lost their significance in multivariate models, suggesting that their effects were attenuated after adjusting for high glucose levels, moderate-to-severe GCA and WMH.

We were unable to find comparable longitudinal studies on cognitive decline conducted in remote rural settings because, as previously noted, none of the studies we found included assessment of the impact of neuroimaging findings on longitudinal cognitive performance, and most of them did not even evaluate the impact of cardiovascular or other clinical risk factors (sleep quality, psychological distress, edentulism) on cognition. From the limited available literature, we found that age at baseline, being female, occupation, a diet poor in vegetables and fish, and less education were often associated with cognitive decline at the follow-up.^{2,4} Some of these variables were investigated in the present study, and some were not because of the homogeneity of the study population. As previously described, almost all men in Atahualpa belong to the blue-collar class and almost all women are homemakers.⁷ In addition, more than 75% of the Atahualpa population have primary school education only (and the MoCA assigns one extra point for people with 12 years of education). Regarding age and sex, we found that age at baseline was significantly associated with decline in the follow-up MoCA in unadjusted analysis and in a model that included clinical covariates, but not after adjusting for neuroimaging signatures of interest. Sex, diet, and physical activity had no effect on outcome in unadjusted or multivariable models. Age may have lost significance after adjusting for moderate-to-severe GCA and WMH because these neuroimaging signatures are on the causal pathway between age-related changes and cognitive performance.

We did not investigate whether the *APOE* ε4 genotype was related to cognitive decline, and this is a limitation of the study. In addition, we relied on a single test to assess cognitive performance. However, the MoCA has proven reliable for assessing cognitive performance in less educated individuals, and has been correlated with structural brain damage documented by MRI in our population.^{14,25–27} While our results are not generalizable to other populations, is important to study rural communities in LMIC because non-communicable diseases are becoming more prevalent as these populations age.

In conclusion, findings that 61% of this community-dwelling older adult sample living in a remote rural setting declined on a global cognitive screen over roughly three years, provides epidemiological evidence of the burden of cognitive decline. The main targets for prevention

identified include glucose control, as well as control of risk factors favoring the development of GCA and WMH of presumed vascular origin.

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REFERENCES

1. Maestre GE. Assessing dementia in resource-poor regions. *Curr Neurol Neurosci Rep.* 2012;12(5): 511–519. [PubMed: 22864986]
2. Chandra V, Pandav R, Dodge HH, et al. Incidence of Alzheimer's disease in a rural community in India. The Indo-US Study. *Neurology.* 2001;57(6):985–989. [PubMed: 11571321]
3. Mejia-Arango S, Gutierrez LM. Prevalence and incidence rates of dementia and cognitive impairment no dementia in the Mexican population: data from the Mexican Health and Aging Study. *J Aging Health.* 2011;23(7):1050–1074. [PubMed: 21948770]
4. Prince M, Acosta D, Ferri CP, et al. 2012 Dementia incidence and mortality in middle-income countries, and associations with indicators of cognitive reserve: a 10/66 Dementia Research Group population-based cohort study. *Lancet.* 380(9836):50–58. [PubMed: 22626851]
5. Xu H, Dupre NE, Gu D, Wu B. The impact of residential status on cognitive decline among older adults in China: Results from a longitudinal study. *Geriatrics.* 2017;17(1):107. [PubMed: 28506252]
6. Baez S Ibáñez A Dementia in Latin America: an emergent silent Tsunami. *Front Aging Neurosci.* 2016;8:253. [PubMed: 27840605]
7. Del Brutto OH, Mera RM, Castillo PR, Del Brutto VJ. Key findings from the Atahualpa Project: what should we learn? *Expert Rev Neurother.* 2018;18(1):5–8. [PubMed: 29088979]
8. Osman A, Wong JL, Bagge CL, Freedenthal S, Gutierrez PM, Lozano G. The depression anxiety stress scale – 21 (DASS-21): further examination of dimensions, scale reliability, and correlates. *J Clin Psychol.* 2012;68(12):1322–1338. [PubMed: 22930477]
9. Buysee DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. *Psychiatry Res.* 1989;28(2):193–213. [PubMed: 2748771]
10. Lloyd-Jones D, Hong Y, Labarthe D, et al. Defining and setting national goals for cardiovascular health promotion. The American Heart Association's strategic impact goal through 2020 and beyond. *Circulation.* 2010;121(4):586–613. [PubMed: 20089546]
11. Del Brutto OH, Mera RM, Gillman J, Castillo PR, Zambrano M, Ha JE. Dietary oily fish intake and blood pressure levels: a population-based study. *J Clin Hypertens (Greenwich).* 2016;18(4): 337–341. [PubMed: 26395549]
12. Del Brutto OH, Del Brutto VJ, Lama J. Sub-estudio de neuroimagen del Proyecto Atahualpa. *Rev Ecuat Neurol.* 2017;26(2):111–127.
13. Woodcock RJ, Jr, Goldstein JH, Kallmes DF, Cloft HJ, Phillips CD. Angiographic correlation of CT calcification in the carotid siphon. *AJNR Am J Neuroradiol.* 1999;20(3):495–499. [PubMed: 10219418]
14. Del Brutto OH, Mera RM, Del Brutto VJ, Sedler MJ. The bicaudate index inversely associates with performance in the Montreal Cognitive Assessment (MoCA) in older adults living in rural Ecuador. The Atahualpa Project. *Int J Geriatr Psychiatry.* 2016;31(8):944–950. [PubMed: 26833914]
15. Pasquier F, Leys D, Weerts JG, Mounier-Vehier F, Barkhof F, Scheltens P. Inter- and intraobserver reproducibility of cerebral atrophy assessment on MRI scans with hemispheric infarcts. *Eur Neurol.* 1996;36(5):268–272. [PubMed: 8864706]
16. Pantoni L, Basile AM, Pracucci G, et al. Impact of age-related cerebral white matter changes on the transition to disability: the LADIS study: rationale, design and methodology. *Neuroepidemiology.* 2005;24(1–2):51–62. [PubMed: 15459510]

17. Gregoire SM, Chaudhary UJ, Brown MM, et al. The microbleed anatomical rating scale (MARS): reliability of a tool to map brain microbleeds. *Neurology*. 2009;73(21):1759–1766. [PubMed: 19933977]
18. Wardlaw JM, Smith EE, Biessels GJ, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol*. 2013;12(8):822–838. [PubMed: 23867200]
19. Doubal FN, MacLulich AMJ, Ferguson KJ, Dennis MS, Wardlaw JM. Enlarged perivascular spaces on MRI are a feature of cerebral small vessel disease. *Stroke*. 2010;41(3):450–454. [PubMed: 20056930]
20. Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*. 2005;53(4):695–699. [PubMed: 15817019]
21. Gómez F, Zunzunegui M, Lord C, Alvarado B, García A. Applicability of the MoCA-S test in populations with little education in Colombia. *Int J Geriatr Psychiatry*. 2013;28(8):813–820. [PubMed: 22996789]
22. , Ludlow L, Klein K. Suppressor variables: the difference between “is versus “acting as”. *J Stat Education*. 2014;22(2):1–28.
23. Del Brutto OH, Mera RM, Del Brutto VJ, et al. Influence of depression, anxiety and stress on cognitive performance in Community-dwelling older adults living in rural Ecuador: results of the Atahualpa Project. *Geriatr Gerontol Int*. 2015;15(4):508–514. [PubMed: 25155360]
24. Del Brutto OH, Gardener H, Del Brutto VJ, et al. Edentulism associates with worse cognitive performance in community-dwelling elders in rural Ecuador: results of the Atahualpa Project. *J Community Health*. 2014;39(6):1097–1100. [PubMed: 24627152]
25. Del Brutto OH, Mera RM, Zambrano M, Soriano F, Lama J. Global cortical atrophy (GCA) associates with worse performance in the Montreal Cognitive Assessment (MoCA). A population-based study in community-dwelling elders living in rural Ecuador. *Arch Gerontol Geriatr*. 2015;60(1):206–209. [PubMed: 25306507]
26. Del Brutto OH, Mera RM, Sullivan LJ, Zambrano M, King NR. Calcifications in the carotid siphon inversely associate with cognitive performance in stroke-free community-dwellers living in rural Ecuador (the Atahualpa Project). *Int J Stroke*. 2016;11(8):935–937. [PubMed: 27401268]
27. Del Brutto VJ, Ortiz JG, Del Brutto OH, Mera RM, Zambrano M, Biller J. Total cerebral small vessel disease score and cognitive performance in community-dwelling older adults. Results from the Atahualpa Project. *Int J Geriatr Psychiatry*. 2018;33(2):325–331. [PubMed: 28548298]

Key Points:

- There is limited information on factors influencing cognitive decline in remote rural settings.
- Using the Atahualpa Project cohort, we found a significant decline in MoCA score in subjects aged ≥ 60 years, after a mean of 3.7 ± 0.7 person-years of follow-up.
- High glucose levels and the presence of moderate-to-severe GCA and WMH, were associated with MoCA decline. Individuals with higher MoCA scores at baseline were more likely to have declined at the follow-up.
- Our findings provide observational evidence for vascular and imaging correlates of cognitive decline in community-dwelling older adults living in a remote rural setting.

Table 1

– Characteristics of participants included in this study according to whether the follow-up MoCA declined or not with respect to the baseline MoCA (univariate analyses).

	Total series (n=252)	No decline in MoCA follow-up (n=98)	Decline in MoCA follow-up (n=154)	p value
Age at baseline, years (mean±SD)	67 ± 7	66 ± 6	68 ± 7	0.004 *
Days between tests (mean±SD)	1,339 ± 267	1,336 ± 273	1,341 ± 263	0.885
Women, n (%)	160 (63)	64 (65)	96 (62)	0.633
Education, years (mean±SD)	6.5 ± 2.9	6.7 ± 3.1	6.5 ± 2.7	0.662
Current smokers, n (%)	2 (1)	2 (2)	0	0.150
Body mass index 30 Kg/m ² , n (%)	57 (23)	28 (29)	29 (19)	0.072
Poor physical activity, n (%)	15 (6)	5 (5)	10 (7)	0.649
Poor diet, n (%)	9 (4)	3 (3)	6 (4)	0.998
Blood pressure 140/90 mmHg, n (%)	113 (45)	43 (44)	70 (45)	0.806
Fasting glucose levels 126 mg/dL, n (%)	79 (31)	27 (28)	52 (34)	0.299
Total cholesterol 240 mg/dL, n (%)	35 (14)	16 (16)	19 (12)	0.372
Severe edentulism, n (%)	114 (45)	36 (37)	78 (51)	0.031 *
Oily fish intake, servings/week (mean±SD)	9 ± 5.2	8.8 ± 4.4	9.1 ± 5.7	0.658
Poor sleep quality, n (%)	74 (29)	27 (28)	47 (31)	0.614
Symptoms of depression, n (%)	23 (9)	6 (6)	17 (11)	0.186
High calcium content in carotid siphons, n (%)	82 (33)	24 (24)	58 (38)	0.029 *
Bicaudate index (mean±SD)	0.12 ± 0.02	0.12 ± 0.02	0.13 ± 0.03	0.004 *
Moderate-to-severe global cortical atrophy, n (%)	114 (45)	27 (28)	87 (56)	<0.001 *
Moderate-to-severe white matter hyperintensities, n (%)	47 (19)	7 (7)	40 (26)	<0.001 *
Deep cerebral microbleeds, n (%)	14 (6)	1 (1)	13 (8)	0.011 *
Cortical cerebral microbleeds, n (%)	9 (4)	2 (2)	7 (5)	0.489
Overt stroke, n (%)	15 (6)	3 (3)	12 (8)	0.173
Silent stroke (lacunar infarctions), n (%)	19 (8)	5 (5)	14 (9)	0.242
Enlarged basal ganglia perivascular spaces, n (%)	62 (25)	14 (14)	48 (31)	0.002 *

Statistically significant result

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Table 2:

Longitudinal linear models fitted to assess factors associated with MoCA decline. Upper panel shows a model adjusted for demographics and clinical covariables. Center panel shows a model adjusted for relevant clinical covariables plus all neuroimaging signatures of interest. Lower panel shows the best model adjusted for demographics, days between tests, and covariables remaining significant in the previous models.

Follow-up MoCA	β coefficient	95% confidence interval	<i>p</i> value
Baseline MoCA	0.11	0.04 to 0.18	0.003 *
Age at baseline MoCA	0.09	0.05 to 0.14	<0.001 *
Sex	0.18	−0.45 to 0.80	0.582
Days between tests	0.01	−0.01 to 0.02	0.355
Smoking	0.85	−2.36 to 4.05	0.604
Body mass index	0.06	−0.65 to 0.77	0.868
Physical activity	0.68	0.58 to 1.95	0.287
Diet	0.76	−0.79 to 2.31	0.338
Blood pressure	0.35	−0.23 to 0.93	0.234
Fasting glucose	0.66	0.04 to 1.28	0.036 *
Total cholesterol	0.13	−0.70 to 0.96	0.759
Severe edentulism	0.53	0.07 to 1.11	0.077
Oily fish intake	0.02	−0.03 to 0.08	0.439
Poor sleep quality	0.08	−0.55 to 0.72	0.797
Symptoms of depression	0.51	−0.48 to 1.51	0.313
Follow-up MoCA	β coefficient	95% confidence interval	<i>p</i> value
Baseline MoCA	0.16	0.09 to 0.23	<0.001 *
Age at baseline MoCA	0.02	−0.04 to 0.08	0.513
Sex	0.48	−0.11 to 1.07	0.112
Days between tests	0.01	−0.01 to 0.02	0.057
Fasting glucose	0.62	0.03 to 1.22	0.040 *
Severe edentulism	0.38	−0.17 to 0.94	0.173
Carotid siphon calcifications	0.44	−0.21 to 1.09	0.186
Bicaudate index	1.38	−11.4 to 14.2	0.832
Global cortical atrophy	1.04	0.38 to 1.71	0.002 *
White matter hyperintensities	1.22	0.37 to 2.07	0.005 *
Deep cerebral microbleeds	0.55	0.73 to 1.83	0.395
Cortical cerebral microbleeds	0.77	−0.74 to 2.29	0.317
Overt stroke	0.75	−0.44 to 1.94	0.214
Silent stroke	0.49	−0.64 to 1.62	0.394
Enlarged perivascular spaces	0.08	−0.65 to 0.81	0.831
Follow-up MoCA	β coefficient	95% confidence interval	<i>p</i> value

Follow-up MoCA	β coefficient	95% confidence interval	<i>p</i> value
Baseline MoCA	0.14	0.07 to 0.21	<0.001 *
Age at baseline MoCA	0.02	−0.03 to 0.07	0.471
Sex	0.40	−0.17 to 0.97	0.165
Days between tests	0.01	−0.01 to 0.01	0.194
Fasting glucose	0.69	0.12 to 1.27	0.018 *
Global cortical atrophy	1.11	0.45 to 1.77	0.001 *
White matter hyperintensities	1.45	0.67 to 2.22	<0.001 *

* Statistically significant result