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FEATURED ARTICLE

Prevalence of dementia and mild cognitive impairment in indigenous Bolivian forager-horticulturalists

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Abstract

Introduction: We evaluated the prevalence of dementia and mild cognitive impairment (MCI) in indigenous Tsimane and Moseten, who lead a subsistence lifestyle.

Methods: Participants from population-based samples ≥ 60 years of age ($n = 623$) were assessed using adapted versions of the Modified Mini-Mental State Examination, informant interview, longitudinal cognitive testing and brain computed tomography (CT) scans.

Results: Tsimane exhibited five cases of dementia (among $n = 435$; crude prevalence = 1.2%, 95% confidence interval [CI]: 0.4, 2.7); Moseten exhibited one case (among n = 169; crude prevalence = 0.6%, 95% CI: 0.0, 3.2), all age_≥ 80 years. Age-standardized MCI prevalence was 7.7% (95% CI: 5.2, 10.3) in Tsimane and 9.8% (95% CI: 4.9, 14.6) in Moseten. Cognitive impairment was associated with visuospatial impairments, parkinsonian symptoms, and vascular calcification in the basal ganglia.

Discussion: The prevalence of dementia in this cohort is among the lowest in the world. Widespread intracranial medial arterial calcifications suggest a previously unrecognized, non-Alzheimer's disease (AD) dementia phenotype.

KEYWORDS
cognitive dysfunction, dementia, mental status and dementia tests, Moseten, Tsimane

1 | INTRODUCTION

Of individuals 65 years of age and older living in high-income countries, 8% to 11% have a dementing illness.[1,2] Prevalence increases exponentially with age. The leading cause of dementia is Alzheimer's disease (AD). The most prominent genetic risk factor for AD is the apolipoprotein E (*APOE*) ε4 allele.[1]

We report the prevalence of dementia and mild cognitive impairment (MCI) in Tsimane and Moseten Amerindians of the Bolivian Amazon. The Tsimane are an indigenous population of ≈17,000 who live a physically demanding subsistence lifestyle in small communities located mostly along the Maniqui River, an Amazon tributary. They fish, hunt, and farm with hand tools and gather food from the forest. There is minimal access to electricity, clean water, sewage treatment, or medications[3] (see Figure S1). The Moseten (population ≈3000), although genetically and linguistically related to the Tsimane, are more acculturated into Bolivian society. They live in closer residential proximity to the market economy, have greater Spanish fluency, schooling, and access to clean water, store-bought foods and medical services. Nevertheless, Moseten still reside in rural villages and engage in high subsistence work effort, mainly agricultural.

Studies of other indigenous and rural low-literacy populations have found widely varying prevalence of dementia. A systematic review of 15 studies of indigenous populations in Australia, North America, Guam, and Brazil found dementia prevalence ranging from 0.5% to 20% for age ≥ 60 or 65 years.[4] Where comparator non-indigenous populations were available, indigenous rates tended to be higher than non-indigenous, which the authors attributed to low education levels and a higher prevalence of other risk factors including HIV/AIDS, diabetes, hypertension, alcohol abuse, obesity, cardiovascular disease and mental health disorders.[4]

Evidence is converging as to the major modifiable risk factors for dementia and AD.[5,6] These include low formal education[7]; vascular factors, including midlife hypertension and diabetes[8]; cardiovascular disease other than stroke[9]; physical inactivity[10]; and—a recently recognized addition—air pollution.[6] Higher coronary artery calcium (CAC) scores—a marker of atherosclerosis—is related to increased risk of dementia.[11] Evidence-based dietary recommendations for reducing risk of dementia and AD include regular consumption of fresh vegetables, fruits, and fish.[12] In addition, several microbial pathogens have been associated with AD.[13] The antimicrobial protection hypothesis describes how neuroinflammatory pathways may help fight infection while contributing to AD pathology.[14]

On the basis of this literature, we hypothesized a low prevalence of AD and related dementias among Tsimane and Moseten, due to their low prevalence of CAC[15] and atrial fibrillation[16]; low rates of hypertension[17], type 2 diabetes,[18] obesity, and smoking[15]; high levels of physical activity[19]; and a diet low in processed carbohydrates

and fat.[20] In addition, as most dementia is found among individuals ≥ 75 years of age,[2] the pyramid-shaped age structure of the Tsimane and Moseten populations means that the crude prevalence would be expected to be low. On the other hand, these indigenous populations are subject to high infectious disease burden[21] and systemic inflammation, and the mode with respect to formal schooling for older Tsimane is zero years.[3] Relatively low exposure to traffic and industrial sources of environmental pollution are offset to an unknown extent by cooking fires[22] and biomass burning.[23]

1.1 | Aim of study

To test our hypothesis that Tsimane and Moseten populations will show a low prevalence of AD and related dementias, we undertook a comprehensive assessment of dementia and cognitive impairment among Tsimane and Moseten who were 60 years of age and older. We calculated the prevalence of dementia and MCI. Furthermore, to characterize observed cases, we compared cognitively impaired to not cognitively impaired on neurological symptoms, cognitive test scores, and computed tomography (CT) brain scan images, using a matched case-control sub-sample for the CT analyses.

HIGHLIGHTS

- Indigenous Tsimane and Moseten have a low prevalence of Alzheimer's disease (AD) and related dementias.
- The subsistence lifestyle is physically demanding, with a diet low in saturated fats.
- Low dementia prevalence parallels low prevalence of coronary artery calcification (CAC).
- Mild cognitive impairment (MCI) has prevalence comparable to other populations.

RESEARCH IN CONTEXT

1. **Systematic Review**: The authors reviewed literature on dementia in indigenous, rural, and low-literacy populations using traditional (eg, PubMed) sources and meeting abstracts and presentations. There are almost no other reports on dementia in a subsistence-based population; we cite the most relevant prior studies.
2. **Interpretation**: Our data indicated that the prevalence of dementia, especially Alzheimer's disease (AD), is among the lowest in the world, although we observed prevalent mild cognitive impairment (MCI) similar to other populations. Cases of cognitive impairment among Tsimane were characterized by visuospatial impairments, parkinsonian symptoms, and vascular calcification of the lenticulostriate arteries supplying the basal ganglia.
3. **Future Directions**: Findings are consistent with the Tsimane having the lowest reported levels of coronary artery calcification (CAC) of any population recorded to date. An incidence phase will clarify the role of mortality in creating low prevalence rates and will enable testing predictors of disease risk and protection.

2 | METHODS

2.1 | Participants

The Tsimane Health and Life History Project (THLHP) has been studying the Tsimane population since 2002, focusing on health and aging, and in 2011 expanded its coverage to ≈100 Tsimane villages, where residents were enumerated and tracked. All individuals ≥60 years of age were invited to enroll; individuals age 40 to 59 were recruited by a random sample stratified by community.[15] Beginning in 2015, a total of 10 Moseten villages were added to the project. Ongoing assessment by THLHP physicians and Tsimane anthropologists includes medical evaluations with brief neurological exams, hearing and vision tests, blood panels, and cognitive testing, at ≈2-year intervals. THLHP anthropologists update village censuses biennially to identify anyone who had moved from the village or had died and to establish cause of death based on indirect reports and medical histories. The census has 95% coverage among participating villages.

The sample for the present study was drawn in 2017, comprising every living THLHP participant ≥60 years of age in the participating Tsimane and Moseten territorial village censuses. Participants were visited for a dementia assessment between July 2017 and December 2019. This visit constitutes the baseline dementia evaluation, although we had the advantage of prior waves of cognitive tests as part of earlier THLHP data collection.

All phases of the study were approved by the ethics committee of the San Simon University School of Medicine (Cochabamba, Bolivia), the institutional review board (IRB) of the University of New Mexico Health Sciences Center (which serves as the designated IRB) and the University of California, Santa Barbara. The Tsimane and Moseten governments, village leaders, and study participants approved all protocols. All participants provided informed consent in their native language. When incidental findings arose during brain and chest CT scans, participants were advised and supported to receive medical treatment.

2.2 | Procedures

Dementia assessments were performed by an experienced Bolivian physician (RQG) who had repeatedly examined each participant in the past as part of the ongoing THLHP. Tsimane were interviewed in the Tsimane language; Moseten were interviewed in Spanish.

In designing our protocols, we drew on the Kimberly Indigenous Cognitive Assessment (KICA)[24]; the Indo-US Cross-National Dementia Epidemiology Study[25]; and the Indianapolis-Ibadan Dementia Project.[26]

2.2.1 | Clinical interview

The clinical interview began with self-reported evaluation of vision, hearing, memory, and thinking abilities. Next, we administered the Modified Mini-Mental State Examination (3MS)[27] that we further modified for illiteracy and lack of ability to count by substituting tasks from the same domain (see Supplement A.) We iteratively consulted with Tsimane anthropologists on the team and piloted adjustments. Training and quality control included direct observation of Bolivian physicians in the field and by video. The 3MS score ranges from 0 to 100. A subset of the 3MS items also provide a score for the Mini-Mental State Examination (MMSE).[28]

2.2.2 | Informant interview

A family informant was interviewed for all participants. The informant interview combines a modified caregiver interview from the KICA tool and questions from the Peruvian Spanish translation of the Clinical Dementia Rating scale[29] (see Supplement B.) The interview provides scores for both the KICA[30] and the Blessed Dementia Scale.[31]

2.2.3 | Cognitive battery

The cognitive battery is largely adapted from the Mexican Health and Aging Study.[32] The battery includes Visual Scan (searching for a target symbol amongst distractor symbols), Digit Span Forward, Immediate and Delayed Word Recall, Semantic Fluency (naming animals and fish), Spatial Span (a variation of the Corsi block tapping task), and Stick Design Test[33] (a measure of visuo-constructional ability). For all tasks, we derived population-specific norms for age ≥60 years using cognitive scores from 2008 with cut-offs corresponding to −1 SD, −1.5 SD, and −2 SD from the mean.[34] Longitudinal cognitive profiles with two to four times of testing separated by ≈2 years between assessments were available for over 75% of participants, enabling us to determine whether there had been cognitive decline.

2.2.4 | Neurological evaluation

A brief neurological assessment evaluated signs associated with parkinsonism or stroke. The Bolivian THLHP physicians received training and supervision at a neurology clinic in the United States and remotely by video.

2.2.5 | Brain CT scan

Between 2015 and 2018, individuals who consented and were able to travel were transported to the German Busch Hospital in Trinidad, Bolivia, for chest and brain CT scans. CT scans were performed by a licensed radiological technician using a 16-detector row multi-slice CT (GE Brightspeed, Milwaukee, WI, USA) under the supervision of project clinicians, using a 0.625-mm slice thickness. Project radiologists (EML, GB, MLS, JDS)—blinded to age, sex, or any clinical information—reviewed CT scans for focal brain lesions (eg, major infarcts, masses, trauma) and visually rated for global cortical atrophy (Pasquier GCA scale), medial temporal atrophy (Scheltens scale), white matter disease/leukoariosis (Fazekas scale), and number of infarcts (see[35]), as well as vascular calcification[36] and basal ganglia calcification.[37] Separately from the diagnostic process, brain volumes were obtained by segmenting CT scans using a probabilistic tissue classification method,[38] with those carrying out the segmentation and quantitative assessment blinded to clinical or demographic information.

2.2.6 | Clinical diagnosis of dementia and MCI

Independent diagnoses were made at separate case conferences by two Bolivian physicians with 15 or more years of experience performing medical exams of Tsimane and Moseten populations and by a USC-based team composed of a clinical psychologist, neurologist, and neuroradiologists. First, each team applied *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) criteria for major and mild neurocognitive disorder,[39] corresponding to dementia and MCI, using the clinical interview including 3MS and MMSE scores; informant interview; and longitudinal cognitive scores from prior data collection occasions by the THLHP. Second, toward specifying an etiologic subtype, if the individual was judged to be demented, each team then applied National Institute on Aging (NIA)/Alzheimer's Association criteria for dementia caused by AD,[40] for which step the USC team viewed the brain CT scans with the preliminary visual ratings. Third, for individuals judged to meet criteria for MCI, we noted which cognitive domains were affected: predominantly or only memory, predominantly one domain other than memory, or multiple domains with none predominant. Once Bolivian and USC teams completed independent diagnoses, disagreements were resolved by discussion to arrive at a final consensus clinical diagnosis.

2.3 | Data analysis

Dementia and MCI prevalence were estimated by population and age groups (60-64, 65-69, 70-74, and ≥75). Denominators for each population and age stratum were the number assessed, minus the number who died during the prevalence period. Age-stratified prevalence estimates are provided with exact binomial confidence limits. To compare age ≥60 years prevalence between the Tsimane and Moseten

populations, directly age-standardized prevalence estimates with confidence limits were computed, using the age distribution of the combined Tsimane plus Moseten population. To account for the different age structure of Tsimane and Moseten compared to Western populations, Tsimane and Moseten age ≥60 prevalence estimates were further directly age- and sex-standardized to the US age ≥60 population structure, using US Census 2002,[41] because it was the year used to calculate the US published rate.[42]

To analyze associations of prevalent cognitive status with CT measures, we constructed a prevalent case-control sample (n = 155) comprising a subset of participants. We individually matched all prevalent cases where CT was available (4 dementia and 39 MCI cases) with up to three controls per case, matched on population, sex, and age (within 3 years). Controls were individuals who had completed the diagnostic protocol and received a consensus diagnosis of cognitively normal. The matched sample optimized statistical power without requiring CT rater assessments of all unimpaired individuals. Raters blind to case ascertainment viewed and rated the brain CT images for this sample. Population estimates of severity of brain calcification from brain CT were obtained using inverse-weighted sampling probabilities among cases and controls. Matched cases and controls were compared on semi-quantitative CT measures using conditional logistic regression, specifying matched case-control sets. Associations of cognitive test scores, neurologic measures, and brain volume from CT were evaluated with logistic regression, using the entire available sample, controlling for age and sex. All association analyses were performed within Tsimane or Moseten population, respectively.

3 | RESULTS

3.1 | Demographic and other characteristics

Visits were completed for 451 Tsimane 60 to 93 years of age and 172 Moseten 60 to 86 years of age (total n = 623; 78.6% of the census population), of whom 534 (85.7%) also participated in CT. See Figure 1 for STROBE sample flow chart showing the sample visited (n = 623) and the sample included in prevalence calculations (n = 604). Table 1 shows the distribution of participants by age and sex. The proportion of men and women did not differ by population. Further description of the population with respect to education, biomarkers, and lifestyle can be found in Table S2,

3.2 | Prevalence

Initial interrater agreement for dementia/MCI/normal cognition was kappa = 0.66. Analyses used the final consensus clinical diagnoses. Table 1 shows crude prevalence rates by age group within each population for consensus clinical diagnoses for dementia and for MCI, and also age-standardized rates for each population standardized to age ≥60 based on a combined Tsimane and Moseten population age distribution. Crude prevalence of dementia for age ≥60 years was 1.2% (exact

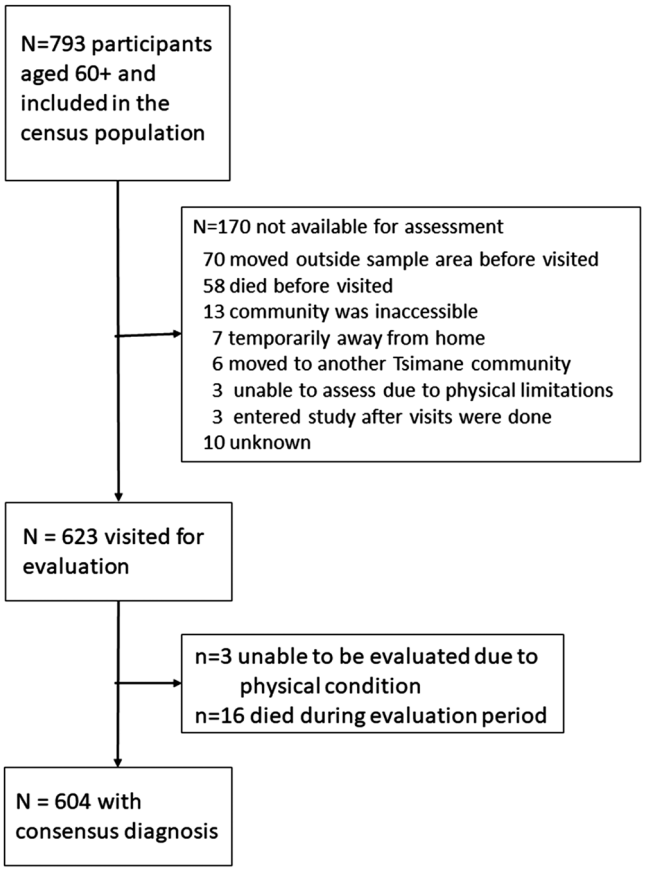

FIGURE 1 Sample flow chart. Notes: Of the 793 individuals identified from the population census as potentially eligible, 170 were not available for assessment, primarily due to moving outside of the area or to death. The absence of refusals reflects the fact that these individuals were already part of the THLHP. Of 623 visited for evaluation, 3 were unable to be assessed due to physical limitations; 16 were excluded from prevalence calculations due to death during the prevalence period. Table S1 compares those who were able to be visited for a dementia evaluation to those who were identified as eligible from the census, but who were unable to participate in a dementia evaluation. Those who did not participate were on average 2 years older, but did not differ from participants on prior waves of cognitive testing

95% confidence interval [CI]: 0.4, 2.7) in Tsimane and 0.6% (95% CI: 0.0, 3.2) in Moseten (P = .73 for age-standardized population difference). All dementia cases were mild and all cases were ≥80 of age when assessed. CT was available for three of the five Tsimane dementia cases; two of these indicated predominantly vascular causes and one followed an AD pattern. When Tsimane and Moseten prevalence was age-standardized to the US 2002 population structure, for Tsimane, dementia prevalence was 2.7% (exact 95% CI: 0.1, 5.4); for Moseten it was 0.9% (95% CI: 0.0, 2.6).

MCI age-standardized prevalence estimates for age ≥60 years were comparable for the two populations: 7.7% (95% CI: 5.2,10.3) in Tsimane and 9.8% (95% CI: 4.9, 14.6) in Moseten (P = .44 for population difference). For Tsimane, 5 of the 35 MCI cases had memory as the predominant cognitive domain affected; 30 cases were either predominantly

TABLE 1 Prevalence of dementia and mild cognitive impairment by population

Age group (in years)	60-64	65-69	70-74	≥75	Age-standardized
TSIMANE					
N	135	139	82	79	435
% Men	44.4%	54.7%	57.3%	48.1%	50.8%
Dementia					
N cases	0	0	0	5	5
Prevalence % (95% CI)	–	–	–	6.3 (2.1, 14.2)	1.2 (0.1, 2.0)
MCI					
N cases	1	13	7	14	35
Prevalence % (95% CI)	0.7 (0.0, 4.1)	9.4 (5.1,15.5)	8.5 (3.5, 16.8)	17.7 (10.0, 27.9)	7.7 (5.2, 10.3)
MOSETEN					
N	68	50	28	23	169
% Men	52.9%	54.0%	50.0%	56.5%	53.2%
Dementia					
N cases	0	0	0	1	1
Prevalence % (95% CI)	–	–	–	4.4 (0.1,22.0)	0.7 (0.0, 2.2)
MCI					
N cases	5	4	4	3	16
Prevalence % (95% CI)	7.4 (2.4, 16.3)	8.0 (2.2, 19.2)	14.3 (4.0, 32.7)	13.0 (2.8, 35.6)	9.8 (4.9, 14.6)

Note: 95% Confidence intervals (CIs) for age-specific estimates are exact binomial. 95% CI for age-standardized estimates are based on normal distribution. If those who died during the prevalence period are not removed, crude prevalence is 1.1% for Tsimane and 1.2% for Moseten (vs crude prevalence of 1.2% and 0.7% with adjustment for deaths during the prevalence period). One Moseten dementia case was among those who died during the prevalence period.

affected in another domain (eg, executive) or in multiple domains. For Moseten, 9 of the 16 MCI cases predominantly involved memory.

Across populations, the number of dementia cases was the same for men as for women (three in each). MCI was significantly more prevalent among women than among men. In Tsimane, using the combined Tsimane/Moseten population for standardization, the age-standardized prevalence of MCI was 11.1% (95% CI: 6.6, 15.6) in women and 4.7% (95% CI: 1.9, 7.5) in men ($P = .02$ for sex difference). MCI prevalence in Moseten was 10.7 (95% CI: 3.2, 18.3) in women and 8.9% (95% CI: 2.7, 15.1) in men ($P = .71$).

3.3 | Brain calcification

Median interrater reliability of visual CT ratings was kappa = 0.88. Prevalence of intracranial vascular calcifications in both large and small arteries was notable, regardless of cognitive status. Weighting the case-control sample results (which disproportionately represent older participants) to match the entire population using inverse weighting by sampling probability, we estimate that 95.2% (95% CI: 88.7, 98.6) of Tsimane ≥60 years of age have intracranial internal carotid artery (ICA) calcification, 98.2% (95% CI: 90.4, 100.0) have intracranial vertebral artery calcification, and 74.4% (95% CI: 62.2, 84.3) have vascular calcification involving the lenticulostriate arteries (LSAs), representing terminal vessels supplying the basal ganglia and posterior limb of the internal capsule. Calcifications in the ICA appeared in the majority of cases as a continuous rim in the media (rather than the intima) of the arterial wall, in a pattern known as medial arterial calcification.[34] Complete population prevalence figures for all visual rating scales for Tsimane and Moseten are shown in Table S3.

In the subsample of Tsimane comprising cases with cognitive impairment (dementia or MCI) and matched controls, shown in Table 2, there is a general pattern of cases having higher scores than controls on indices of brain calcification, with these differences most notable for calcification of the LSAs.

3.4 | Characterizing observed cases

Table 3 *shows APOE* genotype, brain volumes, cognitive scores, and neurological symptoms for all impaired (dementia and MCI cases) compared to all non-impaired individuals in Tsimane and Moseten. The number of *APOE* ε4 alleles did not significantly distinguish impaired from non-impaired Tsimane or Moseten. However, carrying two *APOE* ε4 alleles was associated with significantly greater odds of cognitive impairment. Total brain volume and white matter volume, but not gray matter volume, were significantly lower for impaired than non-impaired Tsimane (by 3.9% for total brain volume and 9.8% for white matter volume), but did not differ for Moseten. Cognitive test scores were significantly lower for impaired than non-impaired Tsimane. Results were similar for Moseten. Among neurological symptoms, bradykinesia and rigidity were common in these populations,

TABLE 2 Semi-quantitative ratings of CT for Tsimane cases and controls

	Rating scale	Interrater reliability (kappa)	Percentage in cases ($n = 35$)	Percentage in controls ($n = 89$)	Association with cognitive impairment OR (95% CI)
Global cortical atrophy (simplified Pasquier)	0[a]	.83	25.7	46.1	3.70 (0.88, 15.6)
	1[a]		57.1	48.3	
	2		17.1	5.6	
	3		0.0	0.0	
Medial temporal atrophy (Scheltens)	0[a]	.85	37.1	59.6	8.89 (1.85, 42.9)
	1[a]		40.0	36.0	
	2		20.0	3.4	
	3		2.9	1.1	
	4		0.0	0.0	
Internal carotid artery (ICA) calcification extent (Babiarz/ Kockelkoren)	Absent[a]	.87	0.0	1.1	4.06 (0.77, infinity)
	Dots[a]		0.0	6.7	
	<90°		2.9	4.5	
	90-270°		42.9	38.3	
	270-360°		54.3	49.4	
ICA calcification morphology	Indistinguishable[b]	.77	0.0	1.1	6.10 (1.23, 30.4)
	Irregular/patchy[a]		14.3	32.6	
	Continuous		85.7	66.3	
Basal ganglia (BG) calcification	Absent[a]	.97	0.0	10.1	5.27 (1.05, infinity)
	Vascular only		74.3	70.8	
	Parenchymal only		0.0	0.0	
	Both		25.7	19.1	
Lenticulostriate arteries (LSA) calcification	Absent[a]	.93	0.0	10.1	4.77 (1.04, 22.0)
	Dots[a]		5.7	12.4	
	1-2 LSA		57.1	51.7	
	Multiple LSA		37.1	25.8	
LSA calcification diameter	Mean mm	r = .90	Mean = 1.4 SD = 0.3	Mean = 1.2 SD = 0.5	2.36 (0.94, 5.92)
LSA calcification density	Maximum Hounsfield units	r = .98	Mean = 124.7 SD = 34.8	Mean = 103.3 SD = 49.2	1.11 (1.01, 1.23)
Non-ICA vascular calcification	None[b]	.92	0.0	1.1	4.58 (0.57, 36.6)
	LSA only[b]		0.0	0.0	
	Vertebral artery only[a]		2.9	10.1	
	Both		97.1	88.8	
Temporal artery calcification	Absent [a]	.85	77.1	79.8	1.18 (0.42, 3.36)
	Present		22.9	20.2	
Deep white matter disease (WMD) (Fazekas)	0[a]	.91	82.9	89.9	1.62 (0.57, 4.65)
	1		2.9	7.9	
	2		11.4	1.1	
	3		2.9	1.1	

(Continues)

TABLE 2 (Continued)

	Rating scale	Interrater reliability (kappa)	Percentage in cases ($n = 35$)	Percentage in controls ($n = 89$)	Association with cognitive impairment OR (95% CI)
Periventricular WMD	0[a]	.86	52.2	74.2	2.63 (0.98, 7.05)
	1		26.1	15.7	
	2		21.7	9.0	
	3		0.00	1.1	
Infarcts	Absent[a]	.76	62.9	75.3	1.60 (0.70, 3.66)
	Lacunar		28.6	22.5	
	Cortical		8.6	2.2	

Notes: Semi-quantitative ratings summarized as percentages in each scoring category. Quantitative scores shown as means and standard deviations. Reliability was evaluated for semi-quantitative variables by kappa (or weighted kappa where there were multiple ordinal categories) or by Pearson correlation where there was a quantitative scale. Association with cognitive impairment was evaluated by conditional logistic regression, using the matched case-control sample (where age and sex were matching variables). Case (combining dementia and mild cognitive impairment) versus control status (cognitively non-impaired) is the dichotomous outcome and each rating scale is tested as the predictor. Rating scales were binarized based on neuroanatomical meaningfulness, either whether there was pathology present, or the location of the pathology.

[a]Indicates the codes included in the reference group.

[b]Indicates codes that were excluded from the analysis. Results are reported as an odds ratio (OR) and 95% confidence interval (CI), with exact OR for internal carotid artery (ICA) calcification extent and basal ganglia (BG) calcification. OR >1.00 indicate that cases had greater atrophy, intracranial calcification, or white matter density than controls.

more so for Tsimane than Moseten. Both rigidity and gait abnormalities distinguished impaired from non-impaired Tsimane. Tables S4 and S5 show that poorer cognition was associated with severity of intracranial vascular calcification, greater severity of atrophy, and reduced brain volumes, especially white matter volume.

Post hoc analyses explored the relationship between intracranial and CAC. Although in general, CAC was low and intracranial calcifications were extensive, CAC scores tended to be higher with greater extent of ICA calcification and LSA calcification (linear regressions predicting intracranial calcification by CAC score controlling for age, sex and population, $P = .08$ for ICA, $P = .015$ for LSA).

4 | DISCUSSION

Our results show the expected low prevalence of dementia in Tsimane and Moseten Amerindians. There were no significant overall differences between these two related populations in rates of dementia and cognitive impairment.

We contextualize the results by comparing to published rates of dementia for the United States[42] and Europe[2] (Figure 2A, yellow bars). We also compared Tsimane and Moseten to published prevalence rates in similar groups, including indigenous and illiterate rural populations, selecting studies that applied clinical diagnostic criteria and were not based only on medical record review or mental status screening (Figure 2A, green bars). Rates for Tsimane and Moseten are closest to the lowest rates included in a systematic review of indigenous populations.[4] Highest age-standardized prevalence rates were among Australian Aboriginals[43] and Chamorros on Guam.[44] Rates for Tsimane and Moseten were most analogous to earlier reports from a rural Indian agrarian population[45] and a Cree native population in Manitoba.[46] AD accounted for only 12.5% of Cree dementia cases. Similarly, within Tsimane, the proportion of dementia cases that were clearly AD was low.

We compared Tsimane and Moseten MCI prevalence within age groups to rates of MCI in a published meta-analysis from the American Academy of Neurology (AAN),[47] largely including high-income countries (Figure 2B). The prevalence of MCI for Tsimane and Moseten is generally within the CIs of MCI prevalence in persons 60 to 80 years of age from high-income countries.[47] Rates in the meta-analysis continued to increase after age 80, while rates among Tsimane and Moseten did not.

Low prevalence of dementia in Tsimane and Moseten occurs in populations with a physically active subsistence lifestyle and low rates of cardiovascular disease, diabetes, and obesity, which may protect brain health despite a high load of parasitic and bacterial infections.[15,18–21] In contrast, indigenous populations with high rates of dementia do not practice a subsistence lifestyle and are prone to these other conditions.[4]

Furthermore, we were struck by an unusual phenotype in dementia and MCI cases, associated with prominent medial arterial calcifications affecting the intracranial internal carotid, vertebral, and lenticulostriate arteries. It is notable that greater severity of vascular intracranial calcification was associated with smaller brain volumes and greater risk of cognitive impairment. Consistent with the pattern of calcifications that we observed, dementia and MCI participants frequently displayed parkinsonian symptoms on neurological examination and cognitive deficits in attention, visuospatial, and executive domains.[48]

Although calcifications were more common among the cognitively impaired, we observed high rates of intracranial vascular calcification in both cases and controls. Tsimane rates of calcification of 95.7% in internal carotid and 98.2% in vertebral arteries can be

TABLE 3 Associations of cognitive impairment with brain volume, *APOE*, cognitive test scores, and neurological symptoms

	TSIMANE			MOSETEN		
Predictor	Impaired	Non-impaired		Impaired	Non-impaired	
Mean (SD) or %	(*n* = 41)	(*n* = 407)	OR (95% CI)	(*n* = 18)	(*n* = 154)	OR (95% CI)
Volumes, % of intracranial volume						
Total brain volume	80.7 (4.9)	84.0 (3.9)	1.15 (1.04, 1.27)	81.0 (3.5)	82.7 (4.4)	1.06 (0.94, 1.20)
Gray matter volume	46.9 (5.2)	46.6 (6.7)	0.96 (0.90, 1.02)	45.9 (7.5)	46.0 (6.8)	1.00 (0.93, 1.08)
White matter volume	33.7 (7.7)	37.4 (7.3)	1.08 (1.02, 1.14)	35.2 (8.4)	36.6 (6.9)	1.02 (0.94, 1.10)
APOE						
No ε4	75.8% (57.7, 88.9)	80.4% (75.7, 84.5)	Overall effect 1.65 (0.79, 3.44)	60.0% (26.2, 87.8)	69.9% (59.5, 79.0)	Overall effect 2.24 (0.78, 6.40)
One ε4	15.2% (5.1, 31.9)	18.8% (14.7, 23.3)	0 versus 1 allele 0.86 (0.30, 2.51)	20.0% (2.5, 55.6)	28.0% (19.1, 38.2)	0 versus 1 allele 0.81 (0.14, 4.67)
Two ε4	9.1% (1.9, 24.3)	0.9% (0.2, 2.6)	0 versus 2 alleles 10.7 (1.47, 78.6)	20.0% (2.5, 55.6)	2.2% (0.3, 7.6)	0 versus 2 alleles 11.5 (1.28, 102.8)
Cognitive test						
Visual scan	15.1 (6.8)	21.7 (8.8)	1.09 (1.03,1.16)	16.5 (9.1)	21.8 (12.2)	1.04 (0.99,1.10)
Digit span forward	1.5 (1.0)	2.7 (1.0)	1.99 (1.45,2.72)	2.9 (1.2)	3.6 (0.9)	1.96 (1.11, 3.44)
Immediate recall	2.9 (0.8)	4.2 (0.9)	6.81 (3.76,12.4)	3.2 (0.6)	3.9 (0.8)	3.26 (1.50, 7.10)
Delayed recall	1.4 (1.5)	3.8 (1.9)	1.82 (1.48,2.24)	0.9 (1.3)	3.0 (1.8)	2.00 (1.41, 2.83)
Verbal fluency	8.2 (2.2)	11.6 (2.4)	1.91 (1.55, 2.35)	8.6 (2.5)	10.8 (2.6)	1.44 (1.14, 1.83)
Spatial span	0.9 (1.1)	2.6 (1.2)	2.77 (1.98,3.86)	2.8 (0.9)	3.3 (1.0)	1.57 (0.96, 2.57)
Stick design test	5.1 (3.0)	8.7 (2.6)	1.47 (1.27, 1.70)	8.4 (3.0)	10.4 (1.9)	1.63 (1.14, 2.32)
Neurological evaluation						
Tremor at rest	19.4%	8.2%	1.99 (0.67,5.86)	20.0%	2.5%	9.16 (1.47, 57.1)
Bradykinesia	71.0%	47.0%	1.59 (0.65,3.85)	53.3%	24.8%	3.58 (1.07, 12.0)
Facial masking	35.5%	9.5%	2.25 (0.87, 5.83)	0.0%	1.6%	3.32 (0.00, 29.2)
Rigidity	64.5%	35.1%	2.35 (1.02, 5.38)	50.0%	21.5%	3.39 (1.06, 10.8)
Abnormal gait	45.4%	9.0%	4.85 (1.80, 13.1)	0.0%	8.6%	0.42 (0.00, 2.38)

Note: Cognitively impaired includes both those diagnosed with dementia and MCI. Sample sizes: Brain volume *N* = 357 Tsimane; 150 Moseten. *APOE N* = 369 Tsimane; 103 Moseten. Visual scan *N* = 392 Tsimane; 152 Moseten. Digit span *N* = 420 Tsimane; 169 Moseten. Immediate and delayed recall and verbal fluency *N* = 441 Tsimane; 170 Moseten. Spatial span *N* = 432 Tsimane; 166 Moseten. Stick design test *N* = 423 Tsimane; 81 Moseten. Tremor at rest *N* = 349 Tsimane; 136 Moseten. Bradykinesia and facial masking *N* = 346 Tsimane; 136 Moseten. Rigidity *N* = 347 Tsimane; 135 Moseten. Abnormal gait *N* = 322 Tsimane; 130 Moseten. 95% CIs are shown for *APOE* allele frequencies based on exact binomial method. Associations with cognitive impairment were evaluated by logistic regression, adjusting for sex and age at visit. Odds ratios (ORs) are per unit of the continuous variables. Brain volume is shown as percentage of intracranial volume. *APOE* = apolipoprotein E. Number of *APOE* ε4 alleles is shown as 0, 1, or 2. Logistic regression tests the overall effect of number of ε4 alleles, and then compares one or two ε4 alleles to a reference group of no ε4 alleles. For cognitive tests, the unit of measurement is points scored on the respective test. Digits forward was administered in Tsimane for Tsimane, in Spanish for Moseten. Immediate recall is the average of three learning trials. Neurological evaluation is shown as percent manifesting each symptom. Logistic regression tests having the symptom relative to absence of the neurological symptom. OR >1.00 indicates that cognitively impaired individuals scored worse (lower brain volume, presence of ε4, lower cognitive scores, more likely to show neurological symptoms).

compared to 79.0% intracranial carotid artery calcification and 16.9% vertebrobasilar artery calcification in a population-based European sample ≥60 years of age.[49] Although intracranial vascular calcification was correlated with CAC, the high prevalence of intracranial vascular calcification contrasts with the very low prevalence of CAC found in these populations.[15] Currently, the pathogenic mechanism leading to the observed medial arterial calcification is not known. Future research will investigate not only vascular factors but also infectious and inflammatory disorders—highly prevalent in these populations—as well as metabolic, toxic, dietary, and familial risk factors.[50]

Limitations of this work include the lack of a separate validation for protocols, low power and large confidence intervals resulting from low numbers of cases, and not yet having biomarkers for amyloid beta and tau. We adapted cognitive assessments to minimize biases related to illiteracy, innumeracy, and how the culture understands time. To optimize diagnostic accuracy, we made diagnostic determinations by two independent teams before arriving at a consensus. Finally, because

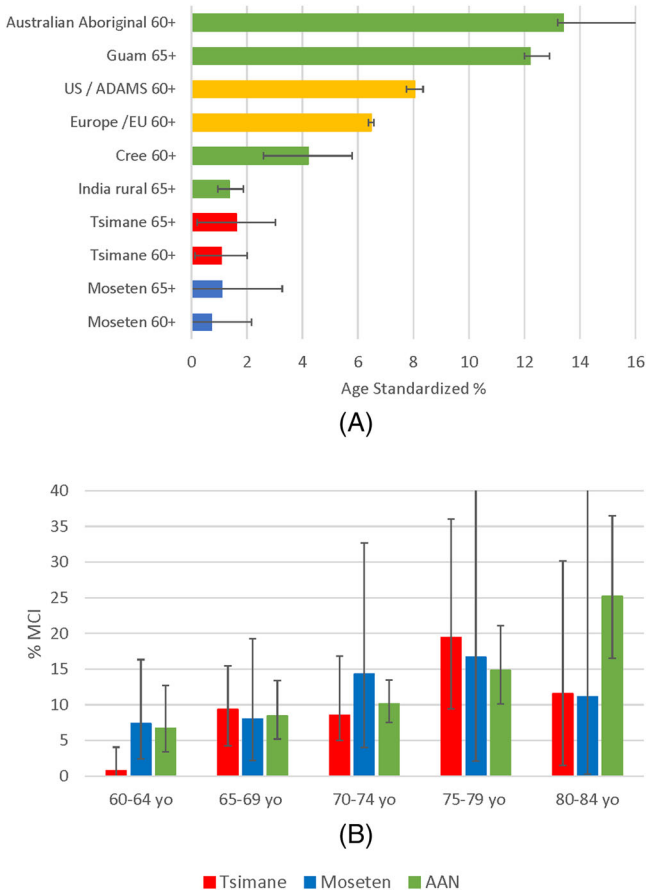

FIGURE 2 (A) age-standardized dementia prevalence and (B) age-specific mild cognitive impairment (MCI) rates among Tsimane and Moseten compared to other populations. Notes: (A) Australian Aboriginal[43]; Guam[44]; US /ADAMS[42]; Europe[2]; Cree[46]; India rural[45](B) AAN = American Academy of Neurology meta-analysis[47]

cognitive test scores were used in establishing cognitive decline, they are thus not independent of the classification of impaired versus non-impaired.

There are three classes of explanation for low disease prevalence: failure to locate cases; selective mortality (both selective survival of those less at risk for dementia and high mortality among cases); and a favorable risk factor profile. Because of the long-term research presence of the THLHP staff and doctors in the Tsimane communities, there are low rates of failure to locate participants. Although the diagnostic protocols required considerable adaptation, the administration of a complete clinical interview and complete informant interview to all participants and family members during a single visit, plus a separate cognitive test battery, makes it unlikely that cognitive impairment was missed.

An incidence phase currently in progress will enable us to identify MCI cases that have progressed sufficiently to meet diagnostic criteria for dementia, to tease apart the contribution of mortality to low prevalence, and to analyze specific risk and protective factors for incident cases. Beyond the exogenous and endogenous exposome, as part of the risk/protection factor profile, we will consider the potential role of protection from AD associated with AmerIndian ancestry.[51] We will also pursue correlates of intracranial calcification in order to further characterize the unusual phenotype of vascular cognitive impairment with medial arterial calcification that we observed.

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CONFLICT OF INTERESTS

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SUPPORTING INFORMATION

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