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Research Article

Physical activity mediates age differences in cognition among Tsimane forager-horticulturalists

Phoebe Imms, PhD[1], Nikhil N. Chaudhari, MS[1,2], Daniel Cummings, PhD[3,4], Daniel Eid Rodriguez, MD[5], Giuseppe Barisano, MD, PhD[6], Paul L. Hooper, PhD[3], M. Katherine Sayre, PhD[7], Edmond Seabright, PhD[3], Randall C. Thompson, MD[8], M. Linda Sutherland, MD[9], James D. Sutherland, MD[9], Benjamin C. Trumble, PhD[10], Michael Gurven, PhD[7], Jonathan Stieglitz, PhD[11], Caleb E. Finch, PhD[1,12], Hillard S. Kaplan, PhD[4], Wendy J. Mack, PhD[13], Margaret Gatz, PhD[14], Andrei Irimia, PhD[1,15,*]

[1]Ethel Percy Andrus Gerontology Center, Leonard Davis School of Gerontology, University of Southern California, Los Angeles, California, United States
[2]Department of Biomedical Engineering, Viterbi School of Engineering, University of Southern California, Los Angeles, California, United States
[3]Department of Anthropology, University of New Mexico, Albuquerque, New Mexico, United States
[4]Economic Science Institute, Argyros School of Business and Economics, Chapman University, Orange, California, United States
[5]Institute of Biomedical Research, Universidad Mayor de San Simon, Cochabamba, Bolivia
[6]Department of Neurosurgery, Stanford University, Stanford, California, United States
[7]Department of Anthropology, University of California, Santa Barbara, California, United States
[8]Saint Luke's Mid America Heart Institute, University of Missouri, Kansas City, Missouri, United States
[9]Department of Radiology, MemorialCare Health Systems, Fountain Valley, California, United States
[10]Center for Evolution & Medicine, School of Human Evolution and Social Change, Arizona State University, Tempe, Arizona, United States
[11]Institute for Advanced Study in Toulouse, Toulouse, France
[12]Department of Biological Sciences, Anthropology and Psychology, Dana and David Dornsife College of Letters, Arts and Sciences, University of Southern California, Los Angeles, California, United States
[13]Department of Population and Public Health Sciences, Keck School of Medicine, University of Southern California, Los Angeles, California, United States
[14]Center for Economic and Social Research, Dana and David Dornsife College of Letters, Arts and Sciences, University of Southern California, Los Angeles, California, United States
[15]Departments of Biomedical Engineering & Quantitative/Computational Biology, University of Southern California, Los Angeles, California, United States

*Address correspondence to: Andrei Irimia, PhD. E-mail: irimia@usc.edu

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Abstract

Background: The Tsimane and Moseten of the Bolivian Amazon are highly physically active and exhibit low rates of cognitive impairment and brain atrophy.

Methods: We use structural equation modelling to examine how their physical activity levels mediate the relationship between (1) age and cognition, and (2) age and cognition via brain volume (BV).

Results: Tsimane males ($n = 305$, mean ± SD age = 59.94 ± 9.68) and Tsimane females ($n = 265$, mean ± SD age = 59.28 ± 9.79) exhibit significantly higher levels of physical activity than Moseten males ($n = 106$, mean ± SD age = 58.15 ± 9.93) and Moseten females ($n = 96$, mean ± SD age = 56.63 ± 9.69). Physical activity significantly mediates the relationship between age and cognition in Tsimane males (indirect effect estimate $\beta = -0.01$, $P < .01$) and Tsimane females (indirect effect estimate $\beta = -0.04$, $P = .01$), but not in Moseten males or females.

Conclusions: Among Tsimane males, who are more physically active than Tsimane females, the association between age and cognition via BV is significantly mediated by physical activity. Among Tsimane females, mediation occurs directly via physical activity, bypassing BV. These results suggest that mechanisms of cognitive differences across ages differ by sex and population. Studying the relationship between brain atrophy and lifestyle in nonindustrialized populations elucidates biological and environmental correlates of brain health.

Keywords: Tsimane and Moseten, exercise, brain atrophy, cognitive decline, novel aging population

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Background

Indigenous to the Bolivian Amazon, the Tsimane and Moseten populations are highly active forager-horticulturalists[1] who live a largely subsistence lifestyle in rural villages.[2] While the majority of US adults do not meet minimum physical activity guidelines (≥150 min of weekly moderate to vigorous physical activity),[3] Tsimane and Moseten consistently meet this benchmark through daily farming, fishing or hunting, visiting others, and other activities.[1] The Tsimane and Moseten have among the lowest prevalence of dementia worldwide.[2,4–6] Cognitive impairment (CI) is highly prevalent in industrialized populations; in 2020, census-adjusted mild cognitive impairment (MCI) prevalence was estimated at 22.7% of US adults over 65 years of age, and dementia prevalence was estimated at 11.3%.[7] By contrast, among Tsimane, the prevalence (standardized to the age distribution of the US 2002 population) of MCI is 12.0%, and dementia is 2.7%; among the Moseten, MCI is 10.0% and dementia 0.9%.[4] A causal link between the Tsimane and Moseten's physically active lifestyle and low rates of CI has been posited but remains speculative.[4,8,9]

Tsimane and Moseten exhibit smaller age differences in brain volume (BV) compared to industrialized populations.[9] Among Tsimane and Moseten males, but not females, some parietal and occipital structures that mediate visuospatial abilities[10,11]—important for navigating Amazonian rainforests—have higher volume in older subjects.[8] The finding that BV of certain brain regions is higher with age for males but not females implies that BV differences across ages may be impacted by sex-specific aspects of nonindustrialization, such as type of physical activity. For example, males are more involved in fishing and hunting that require impressive spatial navigation abilities, which might provide a cognitive advantage over females' domestic activities. It is important to note that previously estimated BV differences across ages in Tsimane and Moseten are not based on longitudinal data, and thus, may be confounded by cohort effects or survivor biases. However, previous work found that the effect of mortality on BV differences with age are small in magnitude, suggesting that mortality selection is unlikely to drive these population differences.[9]

Sedentarism is associated with faster brain atrophy[12] and higher risk of dementia[13] in mid-life and older adults living in industrialized societies. Tsimane men consistently engage in high levels of physical activity,[1,10] beginning at an early age. Total energy expenditure is 264 kcal/day higher in Tsimane compared to industrialized populations,[14] especially among males.[11] In industrialized populations, long-term, regular physical activity is shown to be neuroprotective, improving neurocognitive performance[15] and attenuating age-related declines in cognition.[16] In humans, numerous meta-analyses have strongly linked physical activity to decreased risk of cognitive decline and dementia.[17–21]

This cross-sectional study examines the association of age with physical activity, BV, and cognitive abilities in the Tsimane and Moseten, using structural equation modelling (SEM). We examine whether: (1) physical activity mediates the relationship between age and cognitive scores, and (2) physical activity's mediation of age on cognitive scores acts *via* BV. We hypothesized that physical activity partially explains the relationship between age and cognition, via its impact on BV. The direct and indirect effects of the model are compared across Tsimane males, Tsimane females, Moseten males, and Moseten females, given previously observed age differences in BV and physical activity levels across both sexes and populations.[8]

Methods

Participants

Participants were 1146 Tsimane and Moseten from the Bolivian Amazon who were scanned and neurocognitively assessed between 2015 and 2018 (Table 1). Every Tsimane and Moseten person over the age of 60 was offered the opportunity to participate in CT scanning and cognitive assessment, and a randomly selected, representative sample of subjects between 40 and 60 were also invited. Ethical approval was obtained from the Institutional Review Board of University of California Santa Barbara (IRB #15–133), Universidad Mayor de San Simon, Cochabamba Bolivia, and from the local ethical boards of all other institutions where research was performed. Ethical approval was also obtained from Indigenous governments (Gran Consejo Tsimane, Consejo Regional Tsimane y Moseten, Organización del Pueblo Indigena Moseten), from community leaders, and consent was obtained from all study participants. Of the total sample, 374 individuals (21.59% of Tsimane males, 21.60% of Tsimane females, 53.71% of Moseten males, and 49.57% of Moseten females) did not participate in accelerometry and were removed from subsequent analysis. The final sample consists of 772 individuals (305 Tsimane males, 265 Tsimane females, 106 Moseten males, 96 Moseten females; aged 59.06 ± 9.80 yrs).

Clinical variables

Cognitive scores

The cognitive battery was adapted from the Mexican Health and Aging study.[22] Description of the full battery has been published elsewhere.[2,4,5] CI (encompassing dementia and mild cognitive impairment) was diagnosed according to DSM-V criteria in a complete clinical work-up (see Ref. [4] for more details). Memory and attention were assessed by immediate and delayed word recall,[23] and verbal and tactile digit span forward tasks, respectively. All scores were converted to *z*-scores (standardized to the total sample of combined Tsimane and Moseten) prior to inclusion in the structural equation model (SEM). The average interval from the cognitive testing before CT scan was 77 days ± 271 days (95% CI = [58, 96] days, median = 58 days).

Immediate and delayed word recall

Participants were read a list of eight Tsimane (Spanish for Moseten) nouns three times. Each time they were asked to repeat the list immediately, in any order. Short-term recall (STR) is the average number of correctly recalled words across three trials. After 10 minutes, participants were asked to recall the eight words in any order; the average number of words correctly recalled is their long-term recall (LTR).

Digit span

A standard digit span forward test was adapted to Tsimane (for Tsimane participants) and Spanish (for Tsimane and Moseten participants). A series of numbers were read aloud to participants, beginning with two numbers, and increasing in length by one (after two repetitions) up to a maximum length of nine

Table 1. Descriptive statistics and group comparisons for demographics, cognition, physical activity, and brain volume across populations and sexes

	Mean (SD)				ANOVA *P*	Sig. post hoc comparisons[a]
	TsiM (n=305)	TsiF (n=265)	MosM (n=106)	MosF (n=96)		
Demographics						
Age (yrs)	59.94 (9.68)	59.28 (9.79)	58.15 (9.93)	56.63 (9.69)	**.02**	TsiM > MosF
Education (yrs)	1.65 (3.02)	0.49 (1.13)	2.08 (2.55)	1.10 (2.08)	**<.01**	MosM > MosF MosM > TsiF TsiM > TsiF MosF > TsiF
Cognitive scores						
Long term recall (count)	3.30 (2.22)	3.23 (2.31)	3.29 (1.67)	3.69 (1.95)	.35	
Short term recall (count)	4.13 (0.87)	4.12 (0.93)	4.14 (0.9)	4.16 (0.95)	.99	
Digits forward (count)	3.22 (0.93)	2.78 (0.9)	3.96 (0.94)	3.59 (0.89)	**<.01**	MosM > MosF MosM > TsiM MosM > TsiF MosF > TsiM MosF > TsiF TsiM > TsiF
Tactile digits forward (count)	3.68 (1.41)	3.25 (1.58)	3.88 (0.89)	3.51 (0.82)	**<.01**	MosM > MosF MosM > TsiF TsiM > TsiF
Physical activity						
Physical activity[b] (%)	18.33 (7.81)	16.65 (7.15)	13.72 (7.38)	12.76 (7.44)	**<.01**	TsiM > TsiF TsiM > MosM TsiM > MosF TsiF > MosM TsiF > MosF
No activity (mins)	675.72 (136.10)	625.85 (127.26)	771.94 (152.52)	739.67 (189.78)	**<.01**	MosM > TsiM MosM > TsiF MosF > TsiM MosF > TsiF TsiM > TsiF
Light-intensity activity (mins)	232.31 (53.23)	274.96 (54.17)	221.53 (81.88)	249.21 (75.68)	**<.01**	TsiF > MosF TsiF > TsiM TsiF > MosM
Moderate-intensity activity (mins)	172.35 (73.26)	162.35 (66.18)	143.33 (77.7)	131.27 (72.65)	**<.01**	TsiM > MosM TsiM > MosF TsiF > MosF
Vigorous-intensity activity (mins)	30.13 (32.14)	16.66 (18.98)	15.32 (25.23)	9.06 (12.82)	**<.01**	TsiM > TsiF TsiM > MosM TsiM > MosF TsiF > MosF
Daily steps (count)	16 401.43 (5315.57)	16 283.1 (5039.81)	14 443.59 (6043.95)	14 327.79 (5992.08)	**<.01**	TsiM > MosM TsiM > MosF TsiF > MosM TsiF > MosF
Sleep (mins)	329.58 (97.67)	360.29 (88.75)	287.88 (127.51)	310.79 (146.44)	**<.01**	TsiF > TsiM TsiF > MosF TsiF > MosM TsiM > MosM
Brain volumes						
Percentage brain volume	85.42 (3.91)	85.6 (3.5)	85.89 (4.51)	85.45 (4.17)	.74	

No variables (such as age) were controlled for in any comparisons. Values in bold are significant at $p < .05$.
[a]Games–Howell post hoc comparisons are significant at $P < .05$, adjusted for Type I error, equal variances not assumed.
[b]Physical activity is the percentage of awake time spent moderately or vigorously active.
Abbreviations: MosF, Moseten females; MosM, Moseten males; TsiF, Tsimane females; TsiM, Tsimane males.

numbers. The longest sequence of digits correctly recalled was scored as the digit forward (DF) score. Tactile digit forward (TDF) was tested by pointing to a series of numbered boxes on a poster, beginning with two boxes, and increasing in length to seven boxes. The participant was asked to point to the boxes in the same order as shown by the tester.

Brain volumes

CT image acquisition and processing

A 16-detector row CT scanner (General Electric BrightSpeed, Milwaukee, WI) was used to acquire images clockwise, in helical mode, with a standard convolution kernel. There were two reconstructions: one with voxels 1.25 mm^3 and another with voxels 0.625 mm^3. Kilovoltage peaks were 120 kV, data collection diameter was 25 cm, mean exposure time was 1.417 s, X-ray tube current was 140 mA, and focal spot was 0.70 mm. Probabilistic classification of voxel intensities segmented the brain into GM, WM, CSF, scalp, and skull.[24] GM and WM were segmented using a CT segmentation approach described elsewhere[8] and summed to obtain BV.

Allometric scaling

Brain structures scale nonproportionally to total intracranial volume TICV[25]; Therefore, raw BV (*r*BV) was allometrically (rather than linearly) scaled to TICV. The natural logarithm of *r*BV was regressed on age, sex, and the natural logarithm of the TICV to produce the allometric scaling coefficient β (ie, the regression coefficient associated with the natural logarithm of TICV). This coefficient was used in the following equation from Kaplan et al.[26] to compute the normalized percentage of BV (hereinafter referred to simply as BV) in subject *i*:

$$\mathrm{BV}_i = r\mathrm{BV}_i \times \frac{\left[\mu\left(\mathrm{TICV}\right)\right]^{\beta-1}}{\mathrm{TICV}_i^{\beta}}.$$

Above, mean $\mu\left(\mathrm{TICV}\right)$ is the mean TICV over participants.

Physical activity

The number of minutes (across 24 h) of inactivity (0 metabolic equivalents, "METs"), light physical activity (0.10 to 2.90 METs), moderate physical activity (3.00 to 5.90 METS), vigorous physical activity (>6.00 METs), and sleep was measured using wrist-worn ActiGraph GT3X accelerometers. Daily measurements were averaged across multiple days controlled for wear-time duration, and accelerometers were worn, on average, for 4.43 days (range 1 to 12 days). Thresholds separating light, moderate, and vigorous activity were determined according to previously identified cutoffs.[27,28] The average interval from the CT scan before accelerometry data acquisition was 1389 ± 526 days (95% CI = [1351, 1426] days, median = 1391 days). "Physical activity" was estimated as the percent of awake time spent in moderate or vigorous physical activity (MVPA), thus: $\left(\text{moderate} + \text{vigorous}\right) / \left(\text{inactivity} + \text{light} + \text{moderate} + \text{vigorous}\right) \times 100$.

Statistical analysis

Descriptives and population and sex comparisons

All statistical analyses were performed in SPSS v29.0.1. Age, years of schooling, cognitive scores, physical activity, and BV were compared across populations and sexes, using one-way ANOVAs with post hoc *t*-tests. Sex and population differences in the percentage of CI diagnoses were tested using χ^2 tests. Of note, only individuals over the age of 60 were assessed for CI. Spearman's correlations between all variables included in the SEM were examined in populations and sexes separately, and FDR-corrected for 112 comparisons (unique correlations between 8 variables) using the Benjamini–Hochberg method.[29] General linear models were used to examine the effect of age (as a categorical predictor: <50 yrs, 50 to 59 yrs, 60 to 69 yrs, 70 to 79 yrs, and ≥80 yrs, to facilitate interpretation and clarity in figures), population, and sex on cognitive scores, physical activity, and BV. To ensure that discretizing age did not lead to a loss of precision we also performed a general linear model with age as a continuous variable.

Structural equation modelling

Prior to SEM, missing cognitive data (<5% for all variables) were replaced by the average of five imputations. Missing data were judged to be missing at random and were imputed using the Markov chain Monte Carlo method based on nonmissing variables (ie, age, sex, population, and years of education). Data were assessed for multivariate outliers and multivariate normality. Confirmatory factor analysis was used to examine factor loadings of LTR, STR, DF, and TDF onto the latent variable of "cognition." Power analysis determined minimum sample size required for detecting a moderate mediation effect (ie, standardized β = 0.30) to be 752 (alpha = 0.05, power (1–β) = 0.80).

Maximum likelihood SEM was performed in SPSS AMOS v29. Model fit was assessed using absolute fit, incremental fit, and parsimonious fit indices (see Supplementary Table S5). Endogenous variables included physical activity, BV, and the latent variable "cognition"—variables included age, STR, LTR, DF, and TDF. The direct effect of age on cognition after accounting for the influence of the mediating variables (physical activity and BV) was defined as *c′*. One-way pathways were drawn from age to physical activity (*a*), physical activity to cognition (*b*), age to BV (*x*), BV to cognition (*y*), and physical activity to BV (*j*). Indirect effects between age and cognition were calculated via physical activity ($a \times b$), BV ($x \times y$), and physical activity via BV ($a \times j \times y$). Where modification indices were greater than 4, the model was re-specified. Path coefficients were reported as standardized values, and their *P*-values and 95% confidence intervals were obtained from bootstrapping with 5000 subsamples.

Multigroup analysis was used to investigate the consistency of effects of physical activity and BV on cognitive scores across sexes and populations. The same analysis as previously described was performed in each stratified subgroup (Tsimane males vs Tsimane females vs Moseten males vs Moseten females). To test if paths differed across these subgroups, we constrained each path to be equal across all subgroup pairings and used χ^2 difference tests to compare the fit of constrained and unconstrained models. We also compared the standardized coefficients and their 95% confidence intervals (obtained through bootstrapping) of the indirect effects.

Sensitivity analyses

Sensitivity analyses were performed to assess the effect of (1) data imputation to replace missing cognitive scores, and (2) extreme time intervals between cognitive testing and CT scans on results. For (1), Models 1 and 2 were repeated, excluding subjects with any missing cognitive data on SEM model variables ($n = 745$). The results of these SEMs were compared to the results of those with imputed data. For (2), Models 1 and 2 were performed excluding subjects with extreme time intervals between cognitive testing and CT scans (±1.50 years) were excluded ($n = 727$). Finally, given the notable time interval between accelerometry and CT data collections, Models 1 and 2 were repeated with age at accelerometry replacing the age at CT variable. Additionally, a separate mediation analyses was used to assess whether the time interval between CT scan and accelerometry data collection significantly mediated the relationship between age and MVPA.

Results

Descriptive statistics

Table 1 provides summary statistics by sex and population for demographics, cognitive scores, physical activity measurements, and BVs (see Supplementary Table S1 for detailed ANOVA and post hoc statistics). Males (compared to females) and Moseten (compared to Tsimane) have more years of education and perform better on DF and TDF tasks. Tsimane are significantly more active than Moseten each day, spending 4.29% more of their day in moderate to vigorous physical activity (MVPA). Males are significantly more active than females, spending 1.59% more of their day in MVPA. BV is not significantly different across populations or sexes. The percentage of CI diagnoses (Tsimane males: 3.93%; Tsimane females: 4.15%; Moseten males: 4.72%; Moseten females: 5.21%) is not significantly different across populations or sexes ($\chi^2_{(6)} = 5.77$, $P = .45$).

Spearman correlations between all variables included in the SEM are available in Supplementary Table S2. Multivariable general linear models reveal significant main effects of age (as both a continuous and categorical predictor) on all cognitive scores, BV, and physical activity (Figure 1 and Supplementary Tables S3 and S4). There are significant main effects of population and sex on DF, TDF, and physical activity levels. Significant interaction effects of population and sex by age are observed for LTR and BV. All post hoc population and sex and age comparisons can be found in Supplementary Table S3.

Structural equation modelling

Structural model across all participants

Model fit is compared across both models (see Supplementary Table S5). Model 1 includes all participants without constraining SEM model coefficients across sex and population

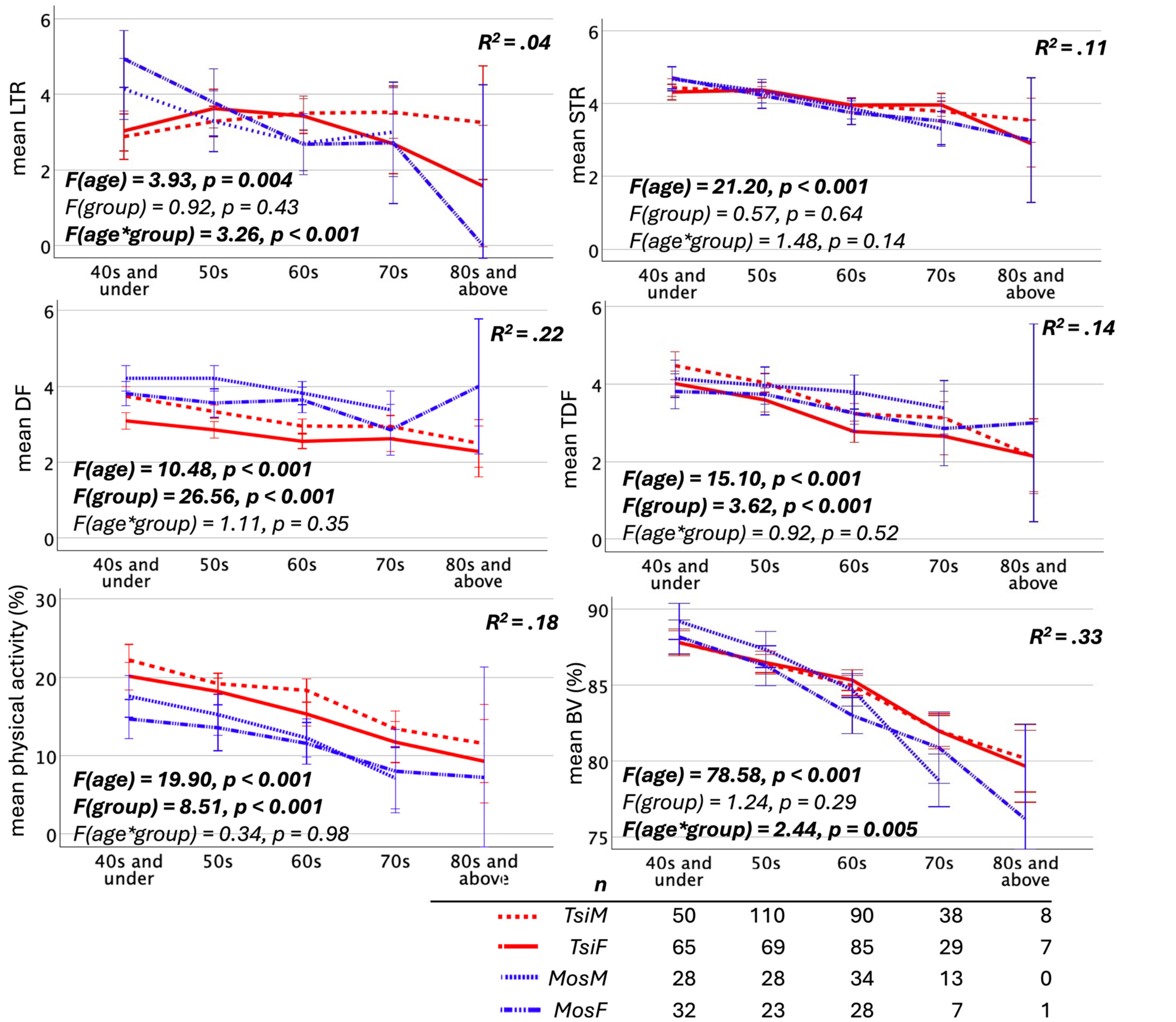

Figure 1. Line graphs of cognitive scores, brain volumes, and physical activity differences across age groups, populations, and sexes. General linear models reveal significant effects of age, population, and sex on all variables, except LTR. *F*-statistics in bold are significant at *P*< .05. Degrees of freedom for *F*-statistics are: age = 4745, population and sex = 3745, and age × population and sex = 11 745. Adjusted R^2 is depicted in the top right of each graph. Results can be found in Supplementary Tables S3 and S4. Bars represent 95% confidence intervals. Abbreviations: BV, brain volume; DF, digit forward; LTR, long term recall; MosF, Moseten females; MosM, Moseten males; STR, short term recall; TDF, tactile digit forward; TsiF, Tsimane female; TsiM, Tsimane male.

subgroups. Model 2 is the same as Model 1 but includes a multigroup analysis across sexes and populations. Fit scores for Models 1 and 2 are acceptable according to key absolute, incremental, and parsimonious indices. CFA reveals that LTR does not load strongly onto a latent cognitive factor (λ_{LTR} = 0.17, λ_{STR} = 0.56, λ_{DF} = 0.60, and λ_{TDF} = 0.60); LTR is removed from further analysis and factor loadings reassessed. The remaining cognitive score factor loadings after re-specification of the model are all >0.50, and are retained (λ_{STR} = 0.51, λ_{DF} = 0.60, and λ_{TDF} = 0.65). No error terms covary.

Among all participants, the relationship between age and cognition is significantly mediated by physical activity (ie, MVPA) and BV (Figure 2; βs reported are standardized, see Supplementary Table S6 for unstandardized βs, 95% confidence intervals, standard errors, and critical ratios for standardized βs). In both sexes, poorer cognition is significantly associated with older age (β_c = −0.54, $P < .01$). When the indirect paths through physical activity and BV are modeled, the direct effect of age on cognitive score is lessened ($\beta_{c'}$ = −0.23, $P < .01$). Participants spend less time active per year of age (β_a = −0.32, $P < .01$), but physical activity alone does not have a significant association with cognition (β_b = 0.02, $P = .33$), nor does it significantly mediate the relationship between age and cognition ($\beta_{a,b}$ = −0.01, $P = .33$). BV% is lower with older ages (β_x = −0.57, $P < .01$), and higher with more physical activity (awake time spent in MVPA; β_j = 0.07, $P = .02$). Cognition is higher with higher BV (β_y = 0.07, $P = .01$); BV significantly mediates the relationship between age and cognition ($\beta_{x,y}$ = −0.04, $P = .01$). Finally, there is a significant mediation effect of age on cognition by physical activity *via* BV ($\beta_{a,j,y} < -0.01$, $P = .02$).

Sex and population differences in mediation effects of BV and activity

When the SEM is performed on stratified subgroups, significant differences are observed across populations and sexes (CMIN (24) = 58.75, $P < .01$). The direct effect of age on BV (β_x) on the entire structural model is significantly weaker in Tsimane males compared to Moseten males (CMIN (1) = 13.56, $P < .01$). The same effect was also weaker in Tsimane males compared to Moseten females (CMIN (1) = 6.28, $P = .01$), Tsimane females compared to Moseten males (CMIN (1) = 12.29, $P < .01$), and Tsimane females compared to Moseten females (CMIN (1) = 5.35, $P = .02$). The influence of BV on cognition (β_y) on the structural model is significantly stronger in Tsimane males compared to Tsimane females (CMIN (1) = 6.51, $P = .01$).

In Tsimane males but not Tsimane females, BV significantly mediates the effect of age on cognition ($\beta_{x,y}$ = −0.06, $P < .01$; Figure 2 and Table 2; see Supplementary Table S7 for 95% confidence intervals). The effect of age on cognition (via BV) is significantly stronger in Tsimane males compared to Tsimane females (β_{diff} = −0.08, $P = .02$). Physical activity, via BV, significantly mediates the effect of age on cognition in Tsimane males ($\beta_{a,j,y}$ = −0.01, $P < .01$) but not Tsimane females. Physical activity (*not* via BV) mediates the effect of age on cognition in Tsimane females ($\beta_{a,b}$ = −0.04, $P = .01$) but not Tsimane males. No significant mediation effects are observed in Moseten of either sex.

Sensitivity analyses

Sensitivity analysis assessing the effect of data imputation on SEM reveals no meaningful differences in results (Supplementary Table S8). All significant pathways remain significant, all nonsignificant pathways remain nonsignificant, and βs are largely equivalent. The sensitivity analysis assessing the effect of large time intervals between cognitive data collection and CT scan reveals only minor differences with the main analysis (Supplementary Table S9). The effect of MVPA on BV is attenuated ($P = .054$) in Tsimane and Moseten of both sexes, possibly due to the lower sample size. Additionally, there are full mediation effects (rather than partial mediation effects) of MVPA and BV in Moseten males and females. In other words, the direct effect age on cognition is not significant in these populations when MVPA and BV are considered ($P = .09$ and $P = .32$, respectively). All other results are replicated.

The sensitivity analysis in which age at accelerometry (rather than age at CT) is used in the SEM reveals only one minor difference to the originally reported results. When age at accelerometry is used, the direct effect of age on cognition is fully mediated, rather than partially mediated, in Moseten females (Supplementary Table S10). Finally, the time interval between CT scan and accelerometry data collection did not significantly mediate the relationship between age and MVPA (β = .01, $P = .10$, Supplementary Table S11).

Discussion

We examined the impact of physical activity and BV on age differences in cognition in two highly active forager-horticulturist populations with low prevalence of dementia and MCI. As expected, physical activity, BV, and cognitive scores were significantly lower in older adults compared to younger adults. In Tsimane but not Moseten, physical activity mediated the relationship between age and cognition. In Tsimane males, physical activity did not *directly* mediate the relationship between age and cognition, but did so *via* BV, whereby less physical activity was related to lower BVs and subsequently worse cognitive performance. In Tsimane females, physical activity directly mediated the relationship between age and cognition.

Physical activity explains age-related cognitive differences in Tsimane but not Moseten

Physical activity mediated cognitive performance in Tsimane only, suggesting a population-dependent effect of physical activity on brain volume differences across ages. Tsimane, especially males, were significantly more active than Moseten, exhibiting larger quantities of daily moderate- and vigorous-intensity physical activity (MVPA), and fewer minutes of light-intensity activity. Higher amounts of time spent in MVPA may reduce cognitive decline by decreasing levels of β-amyloid in the brain, and by improving blood circulation, antioxidation, and anti-inflammatory processes.[19,30,31] Physical activity can improve neurocognitive function through increasing BDNF (increasing synaptogenesis), increasing hippocampal volume, via cellular and molecular pathways, and socioemotional functions (eg, mood, motivation, sleep) for reviews, see.[32,33] Physical activity mediates the relationship between age and cognitive

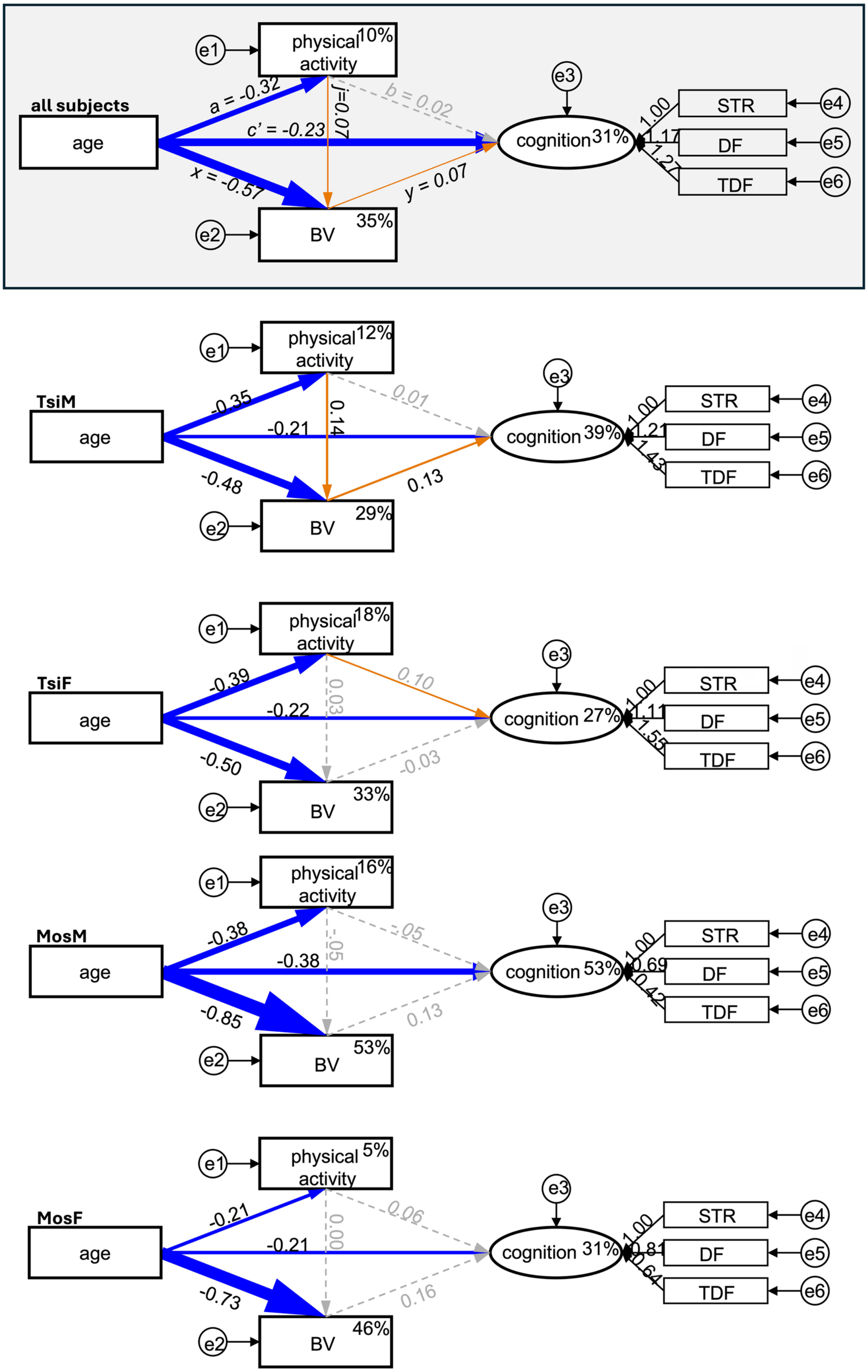

Figure 2. Structural equation models for participants of both sexes and populations combined (top) and for multigroup structural equation models by sex and population. Blue arrows are significant negative direct effects (also indicated by negative signs next to beta values), orange arrows are significant positive direct effects (also indicated by no negative sign next to beta values). Arrow thicknesses scale proportionally to the standardized beta they represent, which are written alongside. Arrows with (grey) dashes represent betas that are not significant. The percentage of variance in each predictor explained by the structural model ($R^2 \times 100$) is described by the value in the top right of each shape. Abbreviations: BV, adjusted percent brain volume; DF, digit forward; e, error; MosF, Moseten female; MosM, Moseten male; STR, short term recall; TDF, tactile digit forward; TsiF, Tsimane female; TsiM, Tsimane male.

Table 2. Pathway and mediation effect estimates in the multigroup structural equation model

	Unstandardized	Standardized			
	β	β	95% CI		P
			Lower	Upper	
Tsimane males					
age → PA (a)	−0.280	−0.354	−0.453	−0.249	**<.001**
age → BV (x)	−0.192	−0.482	−0.585	−0.382	**<.001**
PA → BV (j)	0.072	0.143	0.040	0.245	**.005**
BV → cog (y)	0.030	0.130	0.057	0.222	**<.001**
age → cog (c')	−0.020	−0.213	−0.310	−0.135	**<.001**
PA → cog (b)	0.001	0.005	−0.049	0.072	.876
age → PA → cog (a,b)	>−0.001	−0.002	−0.026	0.017	.847
age → BV → cog (x,y)	−0.003	−0.063	−0.113	−0.027	**<.001**
age → PA → BV → cog (a,j,y)	−0.002	−0.007	−0.018	−0.002	**.003**
Tsimane females					
age → PA (a)	−0.307	−0.388	−0.484	−0.286	**<.001**
age → BV (x)	−0.201	−0.504	−0.603	−0.413	**<.001**
PA → BV (j)	0.017	0.034	−0.073	0.138	.531
BV → cog (y)	−0.006	−0.027	−0.130	0.075	.580
age → cog (c')	−0.020	−0.219	−0.344	−0.124	**<.001**
PA → cog (b)	0.011	0.096	0.017	0.189	**.029**
age → PA → cog (a,b)	−0.003	−0.037	−0.078	−0.007	**.014**
age → BV cog (x,y)	0.002	0.013	−0.036	0.070	.558
age → PA → BV → cog (a,j,y)	−0.001	0.000	−0.001	0.006	.416
Moseten males					
age → PA (a)	−0.302	−0.382	−0.550	−0.218	**<.001**
age → BV (x)	−0.338	−0.852	−1.047	−0.655	**<.001**
PA → BV (j)	−0.027	−0.053	−0.222	0.105	.548
BV → cog (y)	0.030	0.130	−0.061	0.283	.152
age → cog (c')	−0.035	−0.381	−0.704	−0.051	**.014**
PA → cog (b)	−0.005	−0.046	−0.257	0.122	.580
age → PA → cog (a,b)	0.002	0.017	−0.049	0.099	.571
age → BV cog (x,y)	−0.001	−0.111	−0.237	0.054	.173
age → PA → BV → cog (a,j,y)	0.003	0.003	−0.004	0.021	.316
Moseten females					
age → PA (a)	−0.169	−0.214	−0.373	−0.047	**.027**
age → BV (x)	−0.291	−0.732	−0.890	−0.570	**<.001**
PA → BV (j)	0.002	0.004	−0.155	0.160	.965
BV → cog (y)	0.038	0.164	−0.035	0.444	.082
age → cog (c')	−0.020	−0.212	−0.546	0.028	**.044**
PA → cog (b)	0.007	0.058	−0.108	0.263	.457
age → PA → cog (a,b)	−0.001	−0.012	−0.069	0.019	.375
age → BV cog (x,y)	−0.003	−0.120	−0.326	0.022	.113
age → PA → BV → cog (a,j,y)	0.003	0.000	−0.010	0.006	.793

Letters in brackets (ie, a, x, j, etc.) represent the pathway measured. Values in bold are significant at $p < .05$.
Abbreviations: BV, brain volume; cog = latent cognitive variable; PA, physical activity.

performance for both males and females in industrialized populations and is specifically associated with greater hippocampal and medial temporal lobe thicknesses.[34,35] Studies have shown that higher intensities of physical activity is more important for mediating cognitive function than light physical activity.[36] Our results support this explanation, as Tsimane (particularly males) exhibit larger quantities of MVPA, but not larger quantities of light-intensity physical activity, compared to Moseten.

In Moseten, physical activity did not significantly mediate the association between age and BV or cognitive scores. The Moseten are linguistically and genetically related to the Tsimane but are more acculturated into Bolivian society.[5] The Moseten have a slightly higher rate of CI,[4] are less physically active (although still highly active), and have higher rates of obesity, diabetes, hypertension, and coronary calcium than the Tsimane—although, still substantially lower than industrialized populations.[26] We may not have observed significant mediation effects in the Moseten due to lack of power ($n = 570$ Tsimane, compared to $n = 202$ Moseten) or selection bias (see Limitations). In particular, the estimates linking BVs with cognition are 0.13 for both the Tsimane and Moseten males, but statistical significance is only reached for the Tsimane cohort. The estimate linking BV with cognition in Moseten females is 0.16 but does not reach statistical significance. Confidence intervals around the mediation effects were wider in Moseten (males: $\beta_{a,j,y} < 0.01$, 95% CI = [<−0.01, 0.02]; females: $\beta_{a,j,y} < -0.01$, 95% CI = [−0.01, 0.01]) compared to Tsimane (males: $\beta_{a,j,y}$ =

−0.01, 95% CI = [−0.02, <−0.01]; females: $\beta_{a,j,y} < 0.01$, 95% CI = [<−0.01, 0.01]), suggesting more uncertainty in the estimate due to small sample size. Nonetheless, while sample size may help explain some of the uncertainty in the estimates, the parameter estimates linking MVPA with BV are quite different (and notably larger in Tsimane males), suggesting that, for this pathway, it is more than just sample size explaining inter-cohort differences.

Sex-dependent mediation of cognition by BV

In Tsimane males, the effect of age on cognition was mediated via physical activity acting on BV. By contrast, in Tsimane females, the mediation effect was significant only via physical activity. This suggests that, in Tsimane females, physical activity acts on an unexplored variable to influence cognitive differences with age. Alternative lifestyle and health variables not included in our model may be larger contributors to BV and cognitive differences across ages in Tsimane females. Females in these populations experience greater sex-specific burdens, such as high fertility rate, that could negatively affect BV and cognitive aging.[11,37] While Tsimane and Moseten females exhibit less MVPA than their male counterparts, Tsimane females participate in more light physical activity compared to Tsimane males and Moseten males and females. This finding speaks to sex-based disparities in engagement in different types of physical activity. Females also have fewer years of schooling than male Tsimane (Table 1). However, education levels were extremely low (on average, less than two years) in both sexes and populations. Industrialized population CI rates are higher in females.[38] There were no significant differences in CI prevalence between sexes in this sample, although previous reports on the entire sample have shown that Moseten females have higher prevalence of CI than Moseten males.[4]

Alternative pathways to cognitive impairment

Our hypothesis is based on the idea that physical activity impacts BV, which then subsequently impacts cognition. However, it is also possible that other factors could impact BV first, then, physical activity, and subsequently cognition. Indigenous populations of Australia, North America, Guam, and Brazil exhibit *higher* prevalence of dementing illnesses and cognitive decline than their nonindigenous counterparts.[39] Higher CI prevalences in these populations were tentatively attributed to higher rates of cardiovascular illness and obesity that accompany changes in acculturation in Indigenous groups. By contrast, coronary atherosclerosis in the Tsimane and Moseten is lower than in any other population studied to date.[6] Body mass is negatively associated with BV and overall health in industrialized countries due to poor health in people with very high body mass. In the Tsimane and Moseten, body mass is positively related to BV, possibly due to poor health in those with very low body mass. Future studies may be able to model how these and other measures of physical health mediate the relationship between age and cognition in the context of differing in lifestyle factors due to varying levels of market integration and urbanization.

Limitations

This study was cross-sectional rather than longitudinal. Repeated measurements within participants would allow direct measures of change in BV, cognition, and physical activity. Some amount of the relationship between these variables and age may not have been due *only* to aging processes, but also to survivorship bias and changing physical, cultural, and social influences experienced by different cohorts and generations of Tsimane and Moseten. Further bias may have been introduced by the fact that participants were excluded if they did not have CT *and* accelerometry data. Participants who were physically (or otherwise) unable to complete these data collections, which included travelling a large distance for scanning, are not represented in our sample. Nonetheless, there were very few individuals who were unable to travel for CT due to injury or illness.[6] A greater percentage of Moseten participants (54% of males and 49% of females) were excluded due to lack of accelerometry data than Tsimane participants (22% of both males and females). Higher exclusion rates in the Moseten due to missing accelerometry data may have caused selection bias by removing a nonrandom subset of participants. Thus, caution should be taken with the validity and generalizability of the observed results in the Moseten. SEM requires complete data: missing cognitive scores were replaced with the average of five imputations, but SEMs were not repeated across each of the imputed datasets. Thus, the imprecision associated with missingness may not be adequately represented. Nonetheless, a sensitivity analysis in which subjects with missing cognitive data were excluded revealed no meaningful changes to results.

Accelerometry was performed, on average, 3.81 years after CT scans were acquired; physical activity levels may have changed by the time when BVs were estimated, due to normal or pathological aging factors. There is a temporal lag in CT scanning and accelerometry because CTs were collected in Trinidad, while accelerometry data were collected during a separate data collection campaign in the field. While physical activity measured across one week may not necessarily be indicative of long-term patterns of activity, it has been shown to be moderately stable over adulthood in industrialized populations.[40] Repeated accelerometry measurement would be useful to examine how stable physical activity patterns are over time in these populations. Additionally, there was variance in the length of accelerometer wear-time: data from subjects with one day of data (6% of the sample) may not be as representative as data from those worn for 12 days. We did not exclude subjects based on wear-time, as we were unwilling to introduce more bias due to differences in compliance. Cross-sectional age differences observed in these data (Figure 1) reveal lower MVPA in older age groups, suggesting that, had the accelerometry been performed at the same time as the CT scans, MVPA levels would have been higher on average. Thus, it is likely that results would have been stronger had the two measures been collected closer together, temporally. Furthermore, thresholds separating light, moderate, and vigorous activity were determined to have a classification accuracy of 87% in laboratory settings with individuals from industrialized populations[27,28]; these cutoffs may not be applicable to Tsimane and Moseten.

In the combined Tsimane and Moseten sample, only 45.34% of participants were over 60 years of age, and 8.72% of participants with neurological assessments had CI (it should be noted that 366 participants were not assessed for CI as they were <60 yrs of age). Prevalence of CI in this sample is similar to the unstandardized proportions reported in Ref. [4], suggesting that our study participants are representative of the whole Tsimane and Moseten sample. Physical activity mediates cognitive performance more among older adults than younger adults in industrialized populations,[41] especially among those with mild cognitive impairment who exhibit low amounts of physical activity.[42] Low levels of daily physical activity predict cognitive decline among older adults (>70 yrs) more so than younger adults.[43] Tsimane and Moseten's physical activity may be a stronger mediator of cognition and BV among their older population who exhibit cognitive symptoms, but the limited size of this sample rendered such analysis unfeasible. Finally, LTR was excluded from SEM due to weak factor loadings on the "cognition" latent variable. This is likely due to inter-tester variability leading to larger amounts of missing data, because the test protocol had not been finalized during this earlier wave of testing.

Conclusion

We find that age differences in cognition reflect sex- and population-specific aspects of nonindustrialization. In Tsimane males, who exhibit higher levels of daily moderate to vigorous physical activity than Moseten and Tsimane females, physical activity mediated the relationship between age and cognition via BV. In Tsimane females, physical activity mediated cognition directly, indicating that physical activity acts on alternative sex-dependent burdens in these forager-horticulturalists. In Moseten, who were the least physically active (although still highly active), there were no significant mediation effects of physical activity on cognition, although lack of power may undercut some of these inter-cohort differences. Our results suggest that physical exercise helps to explain preserved cognition in the most physically active subgroups of this highly active population.

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Author contributions

Phoebe Imms: Conceptualization; Methodology; Formal Analysis; Investigation; Data Curation; Writing—Original Draft; Writing—Review & Editing; Visualization. Nikhil Chaudhari: Formal Analysis; Data Curation; Software; Resources; Writing—Review & Editing. Daniel Cummings: Methodology; Investigation; Resources; Writing—Review & Editing; Project Administration. Daniel Eid Rodriguez: Methodology; Investigation; Resources; Writing—Review & Editing; Project Administration. Paul L. Hooper: Methodology; Investigation; Resources; Writing—Review & Editing; Project Administration. M. Katherine Sayre: Methodology; Investigation; Resources; Writing—Review & Editing; Project Administration. Edmond Seabright: Methodology; Investigation; Resources; Writing—Review & Editing; Project Administration. Randall C. Thompson: Methodology; Investigation; Resources; Writing—Review & Editing; Project Administration. Linda M. Sutherland: Methodology; Investigation; Resources; Writing—Review & Editing; Project Administration. James D. Sutherland: Methodology; Investigation; Resources; Writing—Review & Editing; Project Administration. Benjamin C. Trumble: Methodology; Investigation; Resources; Writing—Review & Editing; Project Administration. Michael D. Gurven: Methodology; Investigation; Resources; Writing—Review & Editing; Project Administration. Jonathan Stieglitz: Methodology; Investigation; Resources; Writing—Review & Editing; Project Administration; Supervision; Funding Acquisition. Caleb E. Finch: Conceptualization; Methodology; Investigation; Resources; Writing—Original Draft; Writing—Review & Editing; Project Administration; Supervision; Funding Acquisition. Hillard Kaplan: Conceptualization; Methodology; Investigation; Resources; Writing—Original Draft; Writing—Review & Editing; Project Administration; Supervision; Funding Acquisition. Wendy J. Mack: Conceptualization; Methodology; Investigation; Resources; Writing—Original Draft; Writing—Review & Editing; Project Administration. Margaret Gatz: Conceptualization; Methodology; Investigation; Resources; Writing—Original Draft; Writing—Review & Editing; Project Administration. Andrei Irimia: Conceptualization; Methodology; Validation; Investigation; Resources; Writing—Original Draft; Writing—Review & Editing; Supervision; Project Administration; Funding Acquisition.

Supplementary material

Supplementary material is available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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Conflicts of interest

None declared.

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