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Brain volume, energy balance, and cardiovascular health in two nonindustrial South American populations

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Little is known about brain aging or dementia in nonindustrialized environments that are similar to how humans lived throughout evolutionary history. This paper examines brain volume (BV) in middle and old age among two indigenous South American populations, the Tsimane and Moseten, whose lifestyles and environments diverge from those in high-income nations. With a sample of 1,165 individuals aged 40 to 94, we analyze population differences in cross-sectional rates of decline in BV with age. We also assess the relationships of BV with energy biomarkers and arterial disease and compare them against findings in industrialized contexts. The analyses test three hypotheses derived from an evolutionary model of brain health, which we call the embarrassment of riches (EOR). The model hypothesizes that food energy was positively associated with late life BV in the physically active, food-limited past, but excess body mass and adiposity are now associated with reduced BV in industrialized societies in middle and older ages. We find that the relationship of BV with both non-HDL cholesterol and body mass index is curvilinear, positive from the lowest values to 1.4 to 1.6 SDs above the mean, and negative from that value to the highest values. The more acculturated Moseten exhibit a steeper decrease in BV with age than Tsimane, but still shallower than US and European populations. Lastly, aortic arteriosclerosis is associated with lower BV. Complemented by findings from the United States and Europe, our results are consistent with the EOR model, with implications for interventions to improve brain health.

brain volume | mismatch | Tsimane | evolutionary medicine

Significance

This article explores brain volume and aging in two indigenous societies. Whereas brain volume is lower with greater body mass index (BMI) in industrialized populations, the association of BMI and non-HDL cholesterol with brain volume is largely positive, only declining with high BMI and cholesterol. This discrepancy represents a form of evolutionary mismatch we call an "embarrassment of riches" due to recent changes in diet, activity, and other environmental exposures. The minimal dementia and coronary artery disease in Tsimane and Moseten, combined with these findings, imply that aging outcomes are optimized at intermediate lifestyle values. Future research should focus on how our evolved biology interacts with conscious goals in relation to eating, exercise, and physiology.

Age-related declines in brain volume (BV) due to tissue loss appear to be a fundamental feature of human brain aging (1–6). In industrialized populations, brain tissue loss typically becomes noticeable by the fifth decade of life (7–9). Both whole-brain and regional volume declines are associated with cognitive impairment and dementia, and are direct correlates of functional decline (10–12). Nevertheless, rates of brain tissue loss vary among individuals and populations (13–16). Recent studies also suggest that previously identified risk factors may operate differently across populations and environments (17–20). There is thus growing interest in understanding brain aging among diverse populations and environments (17, 18).

Here, we present analyses of brain volume (BV) in middle and old age among two indigenous South American populations, the Tsimane and Moseten. These two populations are of particular interest because their lifestyles and environments contrast significantly with those in developed nations where the majority of research on brain aging is conducted. They have experienced distinct lifetime exposomes, the term employed in aging research that encompasses external environmental exposures (e.g., pathogens and other chemical exposures), internal exposures (e.g., metabolic factors and oxidative stress), and lifestyle factors (e.g., physical activity and diet) (21–24).

The Tsimane are an indigenous population of ~17,000 individuals inhabiting the tropical forests of lowland Bolivia. Their lifestyle (reviewed in ref. 25) is characterized by a heavy reliance on physically demanding subsistence labor in the form of hunting, fishing, gathering, and slash-and-burn horticulture without the assistance of motorized equipment or animals. Recurring infection with intestinal parasites [70% carry helminths (26)] and frequent bouts of respiratory and skin infections result in immune activation profiles characterized by elevated white blood cell counts, C-reactive protein (CRP) levels, and erythrocyte sedimentation rates (ESR) (see ref. 26). The majority of deaths are attributable to infections (27). While the Tsimane are not isolated from world-wide economic and cultural influences, their high levels of physical activity to obtain food, pathogen burden,

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and fertility rates are more representative of past preindustrial environments compared with industrialized societies. Notably, they have low rates of obesity, hypertension, diabetes, and coronary atherosclerosis (28–31). Cross-sectional analysis of BV with age reveals slower age-related trajectories compared with the United States and Europe (6); the prevalence of dementia among Tsimane is also among the lowest reported (32).

The Moseten (population ~3,000) are a "sister" population to the Tsimane in that they share mutually intelligible languages, and their ethnohistory suggests that they may have belonged to the same ethnic group several 100 y ago (33). The composition of Moseten villages, however, is more socioeconomically and ethnically diverse than Tsimane villages, and not all adults are directly involved in horticultural labor. The Moseten live a relatively more globally integrated, acculturated lifestyle compared with the Tsimane, in the sense that they have greater proximity to the market, Spanish fluency, schooling, and access to medical and public services (e.g., health posts in villages, running water, electricity) (34). Because most Moseten still engage in high levels of physically intensive subsistence work and exhibit significant infectious burdens, the Moseten exposome can be considered intermediate between the Tsimane and industrialized populations, but more similar to the Tsimane.

There are three related goals motivating this study. The first is to identify population differences in the cross-sectional rate of decline in BV with age. The second is to investigate the relationship of BV with biomarkers of energy stores and flows—particularly body mass index (BMI) and non-HDL cholesterol (non-HDL-C)—and arterial disease. We assess whether those relationships differ among the Tsimane and Moseten compared with industrialized contexts. The third goal is to test three hypotheses derived from an evolutionary model of population and individual differences in brain health, which we term the embarrassment of riches (EOR) model of brain aging.

The Evolutionary Framework and Hypotheses to Be Tested

The basic reasoning underlying the EOR model is that increased access to food, less energy expended in work, and fewer metabolic demands from pathogen defense were beneficial to, and positively associated with brain health and function in past exposomes. However, in industrialized settings, those factors have now become sufficiently extreme to be detrimental and negatively associated with brain health. The oversupply of nutrients [a "mismatch of too much" sensu Lieberman (35)], combined with low levels of physical activity and exposure to infection ("mismatches of too little") together form an embarrassment of riches that has negative consequences for brain health and function at older ages. The EOR model is built on four conceptual foundations: (1) the theory on the coevolution of diet, intelligence, and lifespan in humans proposed by Kaplan et al. (36, 37); (2) empirical findings of low prevalence of cardiovascular disease and dementia among the Tsimane (31, 32); (3) concepts of human "niche construction" (38, 39); and IV) the evolutionary mismatch framework (35, 40).

Based on what is known about modern foragers, our proposal is that the food niche and pathogen exposomes that are characteristic of human hunter-gatherers led to the evolution of adaptive and coordinated psychological, behavioral, and physiological systems for energy management and pathogen defense. Hunter-gatherer diets were composed of the most nutrient-dense, and largest packages of plant and animal resources in their environment (36, 37). These diets entailed both high physical activity and variability in consumption, consisting of periods of both energy surplus and deficit. Adults typically exhibited low amounts of adipose tissue that varied in relation to temporary energy surpluses, low levels of circulating cholesterol, and insulin-sensitive tissues, phenotypes that are consistent with the context of variable food supply and high demands for physical activity (41–43) (see also ref. 44). Energy surpluses were generally converted into higher fertility, and arterial and cardiovascular health were well-maintained throughout middle and old age (31, 45). In addition, the high and diverse pathogen burden characteristic of past conditions—coupled with energetic limitation—favored immune systems to up- and down-regulate efficiently in response to infectious assaults, with a moderate balance of both T-Helper Type 1 (T_h1) immunity (against intracellular pathogens, bacteria, viruses, and other microorganisms), and T-Helper Type 2 (T_h2) immunity (against extracellular parasites and helminths) (26, 46–49).

We propose that those conditions favored the evolution of the following psychophysiological traits: (1) pleasure in and reinforcement for consumption of foods dense in fats and sugars; (2) appetite regulation that leads to nutrient intake in excess of energy expenditures in times of abundance ensuring storage of fat; (3) responsiveness of the immune system to both pathogen burden and energy stores, with cross-talk between fat stores and the immune system [e.g., adipocyte release of proinflammatory cytokines under conditions of energy surplus (50, 51)]; and (4) linkage of physical activity to acquisition of food and income. Interacting with economic changes in the specialization of labor and mechanized production, these evolved traits impacted the demand and economic incentives for technological advances that increased availability of sugar, oil, and processed foods (52) and reduced physical activity in production and transportation (44, 53–55). Antibiotics, public health infrastructure, and hygiene practices lowered the prevalence of parasitic and bacterial diseases that required energy and nutrients for fever and tissue repair (22, 56–58). In this sense, humans constructed their new environmental niche to generate the exposome shift itself, based on traits that evolved during our species' long-term evolutionary history (38, 39).

The new industrial and postindustrial EOR exposomes include abundant supply of calorie-dense foods, low energetic demands from physical activity or infection, with no fertility outlet for excess calories, harmful products that provide pleasure or other benefits (e.g., cigarette smoking), and other proinflammatory exposures that are byproducts of rich industrial processes (e.g., air pollution from industrial and automotive sources) (22, 44, 53, 54). Increased food consumption and reduced physical activity result in phenotypes with greater adiposity, circulating cholesterol, insulin resistance, and systemic inflammation (35, 40, 59–61), promoting atherosclerotic plaque formation, arterial stiffness, and chronic hypertension (62–65). Immune systems in more hygienic industrialized environments with low helminth burdens are more heavily weighted toward Th1 immunity (26, 46–49), exacerbating the risk of atherosclerosis (66).

The model proposes that BV and other aspects of brain health differ by exposome via differences in system-level states and flows. Though the EOR involves many different aspects of the exposome, we begin by testing a subset of its central hypotheses. The first hypothesis (H1) is that (1) in the food-limited evolutionary past, increases in food energy stores and reductions in pathogen burden would have been positively associated with BV in middle and old age; (2) however, in the energy-abundant EOR exposome, the association between BV and energy stores is negative due to increased atherosclerotic burden, insulin-resistance impairing glucose uptake (67, 68), the inflammatory effects and collateral damage of up-regulated immune activity (58), and promotion of

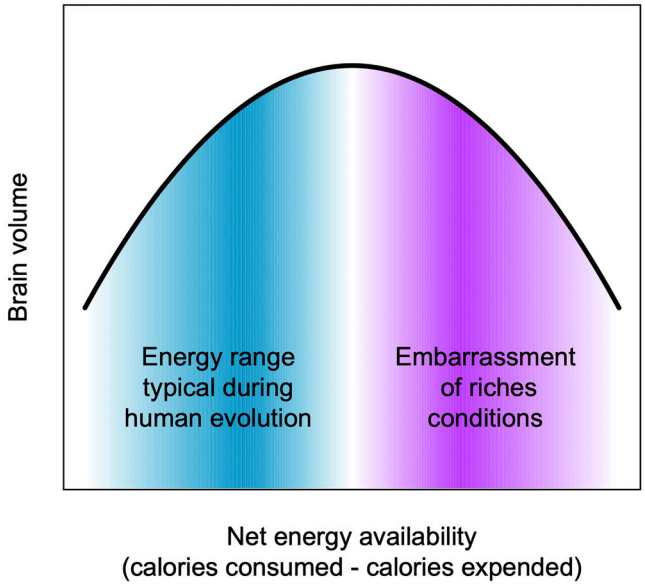

Fig. 1. Hypothesized relationship between net energy availability and BV in middle and old age (H1).

Alzheimer-like changes (69–72). A model for the "rich" transition is from mice with Alzheimer genes, which have greater brain amyloid when fed ad libitum than on caloric restriction (73).

Fig. 1 illustrates this prediction. The x -axis displays net food energy available for all physiological functions after subtracting the energy expended in acquiring and digesting the food. The y -axis displays expected brain health—represented in terms of BV—in middle and old age, the ages at which hunter-gatherers are most productive (37). In the range of net energy availability typical during human evolution, more net food energy would have been associated with larger brain volumes. In industrialized exposomes, the higher availability of net energy interacts with the physiological and psychological control systems that evolved in response to past conditions, and results in a negative relationship between increasing energy and BV. All else held constant, late-life BV is predicted to be largest among individuals with intermediate levels of energy stores, and smallest among both the undernourished and the overnourished. That intermediate sweet spot might be close to or just above the maximum net energy availability experienced during human evolution, perhaps not too distant from the Tsimane and Moseten populations.

The second hypothesis (H2) is that the decrease in BV with age is steepest in populations from industrialized settings with a high prevalence of obesity, or in populations with a relatively large proportion of malnourished individuals. The third hypothesis (H3) is that controlling for age and sex, arteriosclerotic burden is negatively associated with BV in all human populations, since it impairs the supply of glucose and oxygen to the brain.

Results

Potential Correlates of BV by Population, Sex, and Age. Table 1 shows the age–sex distribution of the two populations and compares potential predictors of BV across the Tsimane and Moseten. Both populations share some characteristics which are protective against brain aging. For Tsimane and Moseten, respectively, there is a low prevalence of obesity (4% vs 15%,), diabetes (0.3% vs 1.3%), hypercholesterolemia (0.2% vs 1.3%), and coronary calcium (12% vs 20%).

Both populations also have high levels of inflammation, reflected in elevated white blood cell counts and high-sensitivity C-reactive protein (hs-CRP), which might render them at greater risk of BV loss. While the Tsimane have higher white blood cell counts than Moseten, the Moseten exhibit significantly higher BMI, higher prevalence of obesity, diabetes, and hypertension, and higher levels of cholesterol, epicardial fat, hs-CRP, and coronary calcium. Moseten metabolic risk biomarkers, however, are significantly lower than in the comparably aged US population of the Multi-Ethnic Study of Atherosclerosis (MESA), of whom 37% were taking antihypertensive medications, 16% were taking cholesterol-lowering medications, and 13% were diabetic (74). Thus, with respect to metabolic risk, the Moseten fall between the low-risk Tsimane and high-risk populations living industrialized lifestyles.

With respect to sex differences, males in both populations are typically taller, heavier, and have greater vascular calcification in the aorta and coronary arteries (see percentages and P-values in Table 1). Table 1 also shows that females in both populations typically have higher levels of obesity, anemia, and epicardial fat. Among the Moseten, females are more likely to have elevated hs-CRP, but this is not the case among the Tsimane. The other variables show no appreciable sex differences. Systolic and diastolic blood pressure, hypertension, anemia, aortic and coronary calcification increase with age in the cross-section (Table 1).

BV Trajectories and Correlates. The cross-sectional relationship between age and BV is significantly negative in both sexes and in both populations (Fig. 2 and Table 2). To examine whether the cross-sectional decline in brain volume steepens with increasing age, we compared the linear age model (see *SI Appendix*, Table S1 for those results) with a polynomial regression of BV on age and age squared (Table 2).

Model 1 in Table 2 shows that the estimates for both age and age-squared are significantly negative, indicating the decrease in BV with age accelerates with advancing age. There are significant differences in age slopes between populations (H2), as shown by the significant interactions of age with population and sex. The linear slope (–0.19%/y) among Tsimane is significantly slightly shallower than among Moseten (–0.26%; $P < 0.001$). The slope among females is also borderline shallower than among males ($P = 0.056$). There were no significant interactions of age squared with population or sex.

Model 2 (Table 2) presents the best-fit (according to Akaike Information Criterion, AIC) regression model of normalized BV on these hypothesized predictors, after controlling for age, sex, population, and their significant interactions. To test H1, we regress BV on the following energetic biomarkers: BMI, serum non-HDL-C, fasting blood sugar, and two measure of excess fat—hepatic steatosis and epicardial fat. We also include height as a measure of both nutritional and health status during development, given the importance of stunting in these environments. Finally, we test for associations of BV with hemoglobin, since anemia is highly prevalent and oxygen transport to the brain is critical for brain function and health. Height, BMI, non-HDL-C, and hemoglobin are positively associated with BV (H1), but one measure of excess fat, epicardial fat, was negatively associated with BV. To test H3, we include atherosclerotic burden in the regression model, as quantified by the extent of calcification along the coronary arteries (coronary arterial calcium, CAC) and thoracic aorta (aortic arch calcification, AAC). Atherosclerosis in the aorta, as measured by calcification of the aortic arch and of the ascending and descending aorta, is negatively associated with BV (H3).

Several other variables, including education, fasting blood sugar, blood pressure, coronary calcium, and liver fat, are not

Table 1. Age distribution and summary of variables by sex and population

Age category	Tsimane sample distribution			Moseten sample distribution			Both pops
	Female	Male	F & M	Female	Male	F & M	F & M
40–49	76	71	147	68	70	138	285
50–59	109	143	252	56	69	125	377
60–69	110	112	222	44	60	104	326
70–79	41	64	105	16	23	39	144
80+	13	10	23	5	5	10	33

	Risk Factors: Means and Percentages				Relationships with age, sex, and pop.			
	Tsimane		Moseten					
Variable	Female	Male	Female	Male	Age slope/ odds	Age slope *P*-value	Sex diff. *P*-value	Pop. diff. *P*-value
Age (yrs)	59.6	59.6	55.5	56.7	1	–	0.320	<0.001
Education (yrs)	1.5	1.5	5.0	2.5	–0.032	<0.001	<0.001	0.104
Weight (kg)	61.8	61.8	57.9	63.5	–0.246	<0.001	<0.001	0.001
Height (cm)	160.2	160.2	149.3	160.1	–0.165	<0.001	<0.001	0.024
BMI	24.0	24.0	26.0	24.7	–0.055	<0.001	0.216	<0.001
Obese (BMI ≥ 30)	4.1%	4.1%	17.5%	12.1%	–0.002	0.010	0.011	<0.001
Cholesterol (mg/dL)	150.3	150.3	163.4	155.9	0.102	0.313	0.051	<0.001
Elevated cholesterol (≥200)	7.8%	7.8%	13.6%	5.4%	1.011	0.350	0.448	0.153
Non-HDL cholesterol (mg/dL)	111.2	111.2	126.5	117.8	0.085	0.415	0.019	<0.001
Elevated non-HDL cholesterol (≥200)	25.8%	25.8%	36.1%	29.5%	1.001	0.854	0.136	0.092
Fasting blood sugar (FBS; mg/dL)	78.7	78.7	77.7	75.4	0.136	0.019	0.218	0.065
FBS elevated (≥125)	0.3%	0.3%	2.0%	1.2%	1.020	0.579	0.584	0.047
Hemoglobin	13.6	13.6	12.3	13.7	–0.031	<0.001	<0.001	0.019
Anemic	0.3	0.3	0.2	0.2	1.048	<0.001	<0.001	0.022
Epicardial fat (mm)	1.9	1.9	2.6	2.0	0.032	<0.001	<0.001	<0.001
Liver density (HU)	68.5	68.5	63.0	64.1	–0.015	0.564	0.245	<0.001
Systolic blood pressure (mmHg)	119.7	119.7	121.9	122.0	0.482	<0.001	0.447	<0.001
Diastolic blood pressure (mmHg)	74.5	74.5	76.6	77.3	0.172	<0.001	0.007	<0.001
Stage 1 hypertensive	23.7%	23.7%	29.8%	28.1%	1.061	<0.001	0.886	<0.001
Stage 2 hypertensive	12.3%	12.3%	17.3%	15.9%	1.068	<0.001	0.686	<0.001
Aortic arch calcification (AAC; AU)	402.1	402.1	434.6	465.4	39.218	<0.001	0.435	<0.001
AAC present (>0)	73.4%	73.4%	68.3%	72.2%	1.149	<0.001	0.025	0.001
Desc. & asc. aortic calcif. (TAC; AU)	52.1	52.1	161.7	75.0	8.508	<0.001	0.310	0.015
TAC present (>0)	33.1%	33.1%	25.4%	26.9%	1.148	<0.001	0.569	0.607
Coronary calcification (CAC; AU)	6.8	15.5	19.4	33.1	1.964	<0.001	0.095	<0.001
CAC present (>0)	10.8%	21.7%	14.8%	26.1%	1.092	<0.001	<0.001	0.001
Leukocytes (WBC; count/ul)	9366.2	9366.2	7846.0	8148.9	6.613	0.465	0.636	<0.001
WBC elevated (≥10,700)	24.3%	24.3%	11.2%	12.6%	0.988	0.123	0.780	<0.001
hs-CRP (mg/dL)	3.6	3.6	4.1	4.1	0.038	0.003	0.234	0.047
hs-CRP elevated (≥3)	43.4%	43.4%	52.2%	46.7%	1.022	0.005	0.970	0.154

significantly associated with total BV, either in the multivariate specification or when added individually to the base model (*SI Appendix*, Table S3). We examined collinearity in the best-fit model and found it to be within acceptable limits (variance-inflation factors <3 for all variables).

The additional variables in model 2 change the parameter estimate of age and age-squared terms (for Tsimane females) from –0.193 to –0.149, and from –0.003 to –0.002 (Table 2), suggesting that these variables account for about 25 to 30% of the effect of age on BV. Dividing the estimated effect sizes by the rate of annual decline (0.149), the parameter estimates can be converted to equivalent years of aging. For example, being male (parameter estimate = –1.004) is estimated to be equivalent to 6.7 y of BV loss, while a one-SD increase in aortic arch calcification (parameter estimate = –0.339) is equivalent to 2.3 y of loss. Holding age, sex, and population constant, if an individual were

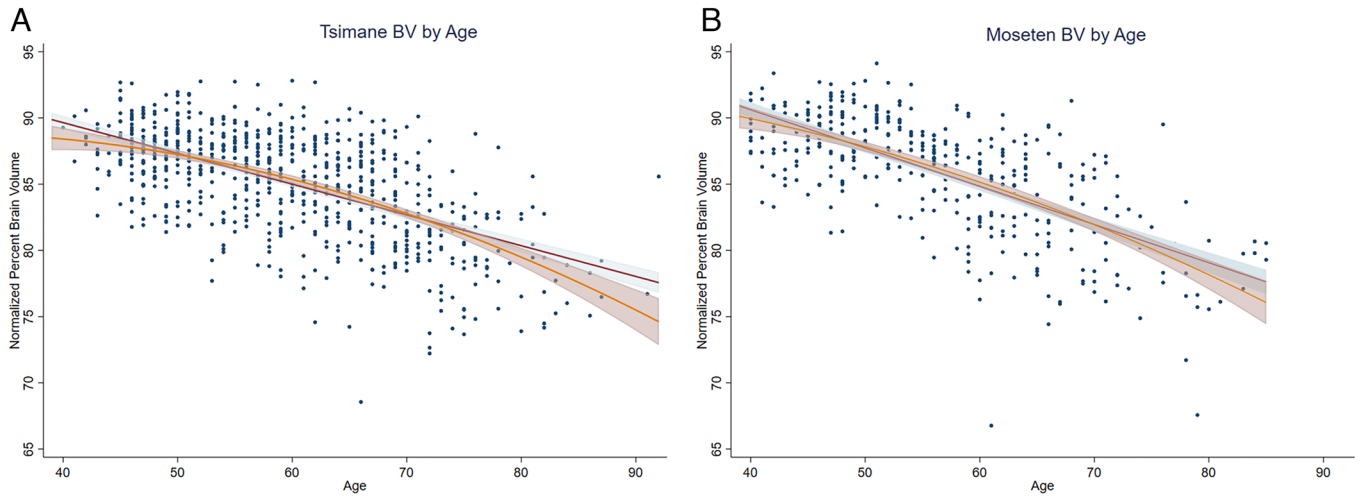

Fig. 2. Normalized percent brain volume by age in the Tsimane (panel A) and Moseten (panel B). The red and orange lines display the linear and quadratic age fits, respectively. The shading is the 95% CI for the polynomial fit.

1 SD above the mean for all protective variables (height, BMI, non-HDL-C, hemoglobin) and 1 SD below the mean for the risk variables (epicardial fat, AAC, TAC) in model 2, the sum of those effects would equate to 16.0 y of slower brain aging.

Model 3 includes the squared terms for BMI and non-HDL-C to test for curvilinear effects, displayed in Fig. 1 and predicted by H1. While we expect that most Tsimane and Moseten will fall on the increasing part of Fig. 1, a small number of Tsimane and Moseten are already displaying EOR phenotypes (Table 1)**.** The linear terms are positive and the squared terms for both BMI and non-HDL-C are significantly negative, the predicted curvilinearity. The model with both squared terms features an improvement over the linear model both by Akaike's Information Criteria (AIC) and Bayesian Information Criteria (BIC). Fig. 3 *A* and *B* display the predicted values and SEs of BV for the range of z -scores of BMI and non-HDL-C, using the parameter estimates (in bold) for the linear and squared terms in model 3 and while holding all other factors at their respective means (i.e., z-score = 0) for the baseline of Tsimane females at age 58 (Margins: Stata 17.0). The curve is increasing until about 1.6 SDs above the mean (accounting for ~95% of the individuals in the two populations), followed by a decreasing segment from that value to the highest values. The small sample sizes in the decreasing segment of the curve generate large SEs.

As a robustness check, we employed the same model but replaced the linear and squared terms for BMI and cholesterol with the standard four BMI categories of underweight (BMI < 18.5), "healthy/normal" (BMI: 18 to 24.9), overweight (BMI:25 to 29.9), and obese (BMI ≥ 30); and four categories of non-HDL-C (<80, 80 to 129, 130 to 159, ≥ 160 mg/dL). We also recoded hemoglobin with the male- and female- defined cutoffs for anemia. Those results are displayed in model 4. Fig. 3 *C* and *D* display the predicted values and SEs of BV from the parameter values in model 4 for the BMI and non-HDL-C categories, respectively, again holding all other factors at their respective means. Model 4 shows that the highest BV is associated with being overweight and having mid-high cholesterol. Postestimation comparisons (pwcompare: Stata 17.0) show that overweight individuals have significantly higher BV than underweight (P = 0.021) or normal weight (P < 0.001), but not significantly higher than obese individuals P = 0.396), again probably the result of small sample size. Similarly, BV among individuals in the two lowest categories of non-HDL-C (<80 and 80 to 129 mg/dL) is significantly lower (P < 0.001 and P = 0.005, respectively) than among those in the mid-high range category (130 to 159 mg/dL), but the high-range category (≥160 mg/dL) is not significantly different from the mid-high range (P = 0.113).

SI Appendix, Table S4 presents a best-fit "full model" that includes the significant interactions of sex and population with the hypothesized variables related to BV. That model shows a marginally significant interaction between height and age (P-value = 0.061) and a significant interaction between male sex and BMI (P-value = 0.036). It also suggests that calcification of the aortic arch is not associated with BV in Moseten females (P-value = 0.034). Those interaction effects are small relative to the main effects. As such, there is a small improvement (decrease) in the AIC, but the BIC favors the simpler model with the curvilinear relationships for BMI and cholesterol.

Discussion

Evaluation of the Hypotheses. Table 3 summarizes the results for each hypothesis. H1 predicted that across individuals, BV would be largest at some intermediate "optimal" level of energy balance, and lowest with either undernourishment or obesity. This prediction was supported by the quadratic (model 3) and categorical (model 4) specifications of BMI and serum non-HDL-C, as measures of energy stores and flows, respectively. Adding quadratic terms for BMI and non-HDL-C revealed significant curvilinear relationships with estimated peaks in BV at about 1.6 and 1.4 SD above the mean, respectively—corresponding to a BMI of 30.0 and a non-HDL-C level of 160 mg/dL—as illustrated in Fig. 3 *A* and *B*. Using categorical groupings of BMI and non-HDL-C, analyses revealed stronger positive effects from low levels to intermediate-high levels, but too few individuals were obese or hypercholesterolemic to detect a significant downward trend. However, evidence of smaller BV with greater obesity at later ages is found in most prior studies in industrialized populations (75–80) where there is a high prevalence of obesity and morbid obesity, and a low prevalence of underweight. Thus, our results from the Tsimane and Moseten—in combination with findings from the United States and Europe—provide the strongest support for the inverted U-shaped relationship predicted by H1. To our knowledge, there are no published studies examining whether the relationship of BMI to BV is also curvilinear in industrialized populations, or whether individuals with very low BMIs in these populations also evidence reduced BV.

We utilized BMI as a measure of energy stores, because of its comparability across studies and because it aggregates muscle,

Table 2. Regression models predicting normalized percent brain volume as a function of age, population, sex, energy markers, and aortic calcium

	Model 1 Base age/sex/pop. Model		Model 2 Model 1 + linear predictors		Model 3 Quadratic BMI and nonHDL-C		Model 4 Categorical BMI, nonHDL-C and anemia	
Predictor variable	Parameter estimate	*P*-value	Parameter estimate	*P*-value	Parameter estimate	*P*-value	Parameter estimate	*P*-value
Constant	85.644	<0.001	86.180	<0.001	86.487	<0.001	85.757	0.000
Age (centered on median age)	−0.193	<0.001	−0.149	<0.001	−0.144	<0.001	−0.152	0.000
Age squared	−0.003	<0.001	−0.002	0.010	−0.002	0.008	−0.002	0.010
Male	0.224	0.228	−1.004	0.002	−1.039	0.001	−0.701	0.027
Moseten	0.027	0.892	0.132	0.550	0.205	0.352	0.133	0.549
Male X Age	−0.034	0.056	−0.046	0.021	−0.051	0.010	−0.047	0.020
Moseten X Age	−0.072	<0.001	−0.077	<0.001	−0.078	<0.001	−0.076	0.000
Z-Height	–	–	0.662	<0.001	0.635	<0.001	0.641	<0.001
Z-BMI	–	–	0.370	0.001	0.524	<0.001	–	–
Z-BMI squared	–	–	–	–	−0.174	0.003	–	–
Z-nonHDL-C	–	–	0.310	0.005	0.392	0.001	–	–
Z-nonHDL-C squared	–	–	–	–	−0.140	0.009	–	–
Z-Hemoglobin	–	–	0.263	0.025	0.245	0.036	–	–
Z-Epicardial fat	–	–	−0.279	0.012	−0.282	0.011	−0.239	0.030
Z-Aortic arch calc. (AAC)	–	–	−0.339	0.004	−0.361	0.002	−0.341	0.004
Z-Asc–desc. aortic calc.	–	–	−0.162	0.090	−0.165	0.081	−0.153	0.108
BMI: <18.5	–	–	–	–	–	–	−0.212	0.654
BMI: 18.5–24.9 (baseline)	–	–	–	–	–	–	–	–
BMI: 25–29.9	–	–	–	–	–	–	0.941	<0.001
BMI: ≥30	–	–	–	–	–	–	0.598	0.130
nonHDL-C < 80	–	–	–	–	–	–	−0.814	0.012
nonHDL-C 80–129 (baseline)	–	–	–	–	–	–	–	–
nonHDL-C 130–159	–	–	–	–	–	–	0.731	0.005
nonHDL-C ≥160	–	–	–	–	–	–	0.066	0.864
Anemia	–	–	–	–	–	–	−0.495	0.057

95% CIs are reported in *SI Appendix*, Table S2 in the supplement.

bone and fat. One possible reason why BVs were significantly higher among "overweight" than "healthy weight" individuals is that both the Tsimane and Moseten are, on average, more muscular than individuals living in sedentary populations at the same BMI (90). For example, although we do not have gold-standard measures of body fat, we find that body fat (as estimated by bioimpedance for a BMI of 25) in this sample is 17% and 25% among males and females, respectively, compared with 28% and 40% among Mexican American and non-Hispanic white participants in the Nutritional and Health Evaluation Survey [NHANES (91)]. It is also possible that, in an environment with high demands for physical activity and repeated infections, the higher BMIs may be protective for the brain (92).

The largest BVs were associated with a non-HDL-C of approximately 155 to 160 mg/dL (~92nd percentile in this sample), which is above the upper-limit recommended by the American Heart Association [<130mg/dL (87)] and about 55 to 60 mg/dL higher than the mean Tsimane population values prior to 2014, when lifestyle change began to accelerate (e.g., proliferation of boat motors and introduction of electricity in some villages). In industrialized populations, most studies of BV have examined total serum cholesterol. Some studies report positive (81, 82, 93) while others report negative (83) relationships between serum cholesterol and BV. Notably, U-shaped associations have also been described between cholesterol and cognitive impairment, with stronger associations with both higher and lower cholesterol levels (83). Dementia risk has also been linearly associated with total cholesterol and triglycerides in prospective cohorts (94). Fasting blood sugar and hepatic fat were not significantly associated with BV in either Bolivian population, likely because diabetes and excess liver fat are rare. In industrialized settings, both diabetes (84–86, 88, 89) and nonalcoholic fatty liver disease (95, 96) are negative correlates of BV, consistent with the EOR model.

As tests of H2 regarding population acculturation and access to purchasing energy-dense foods, we find that the cross-sectional slope of BV with respect to age was shallower among Tsimane than Moseten (Table 2), and this difference remains even after accounting for the risk factors in the model. Some mix of a more sedentary lifestyle and US/European diet (i.e., more saturated fats and refined sugar, less fiber) may be responsible for the unexplained differences between Moseten and Tsimane (34). The Tsimane age slope is shallower than that found in comparative industrialized populations (6). The Moseten age slope is shallower than that of US and German samples (97, 98), but similar to that of the Rotterdam sample (99). The rank order of age-related decline in BV (1. United States and Europe, 2. Moseten 3. Tsimane) is not likely due to younger age composition of the Tsimane/Moseten sample. The Schippling et al. study of US and

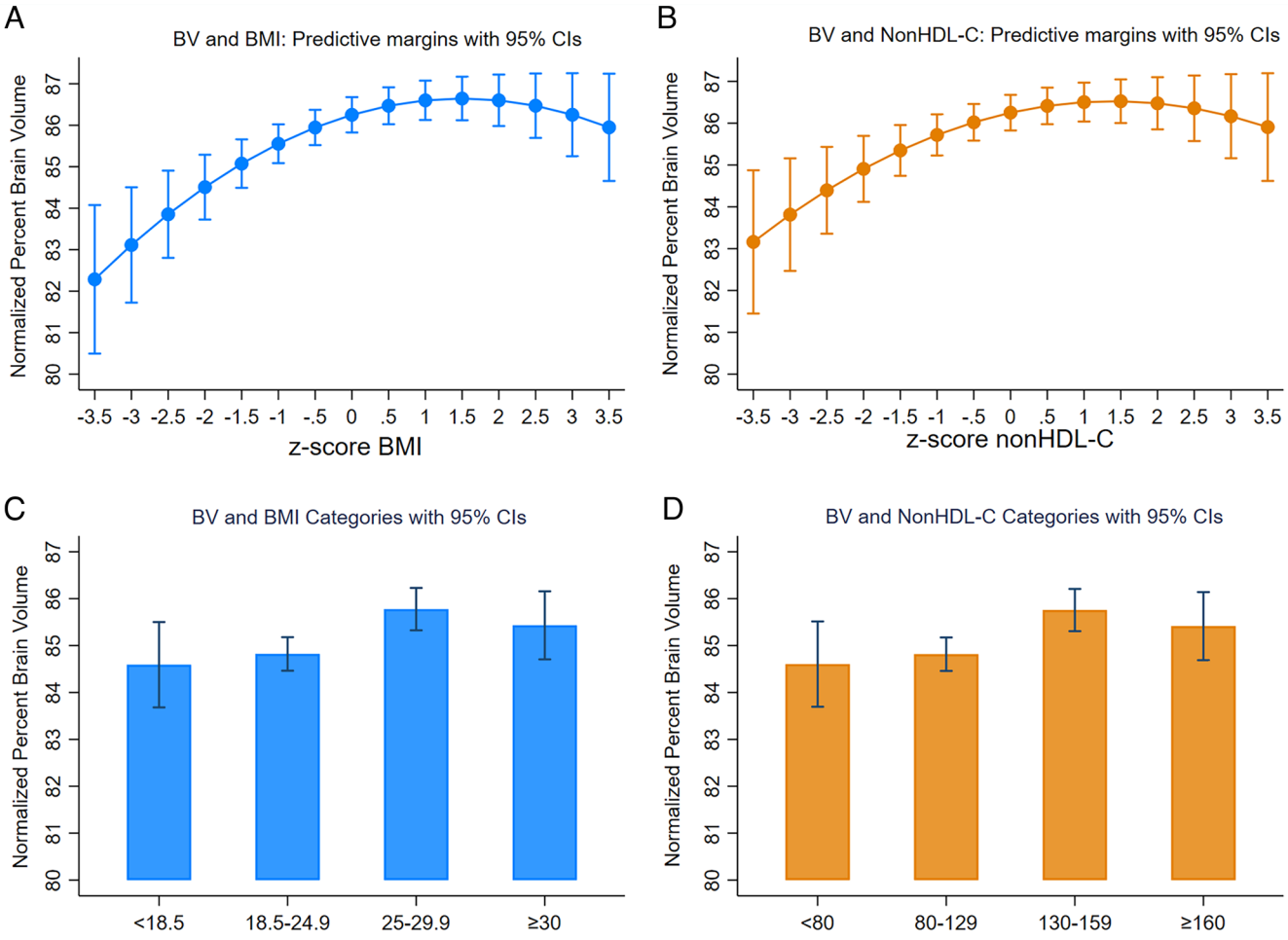

Fig. 3. Normalized percent brain volume as a function of BMI and non-HDL cholesterol. Panels (*A*) and (*B*) shows BV with SE as a function of standardized (*z* -scored) values of BMI and non-HDL-C, based on model 3 in Table 2. Panels (*C*) and (*D*) show BV as a function of BMI and non-HDL-C categories, with the means and CIs estimated based on model 4 in Table 2. The values plotted in the figure reflect the expectation for Tsimane females at the median age of 58 with all other model variables at their mean (z-score = 0).

European participants included only individuals up to age 70 and found a steeper age slope than found for the Tsimane and Moseten (97). The longitudinal slopes found in the Baltimore Longitudinal Study of Aging [(98): Fig. 8*A* and *D*] are also steeper than the Tsimane and Moseten cross-sectional slopes at all ages.

Consistent with H3, arteriosclerosis in the thoracic aorta was associated with lower BV. This is consistent with evidence that atherosclerosis is negatively associated with BV across diverse populations (100–104). One reason that industrialized populations may experience greater brain atrophy with age is the much higher prevalence of clinical atherosclerosis (31). In the case of the Tsimane and Moseten, most (83%) aortic calcification is concentrated in the arch, which has the three branches feeding the carotid and subclavian arteries. This aortic arch calcification shows the strongest negative association with BV. The mechanisms underlying this relationship in these populations requires further investigation. Links between aortic arch calcium and BV loss could arise in the context of atheroembolism, cerebral vascular disease, or subclinical cerebral ischemia. In a smaller Tsimane/Moseten sample of individuals aged 60+, we found high rates of medial arterial calcification in the internal carotid and lenticulostriate arteries of the brain, which is associated with cognitive impairment (32). However, the lack of a significant relationship between arch calcification and BV among Moseten women is puzzling, since it holds for Tsimane men and women and Moseten men (*SI Appendix*, Table S4). We also do not find an association of coronary artery calcification with BV. This may be because very few individuals have any coronary calcium. Alternatively, it may be that that the etiology and downstream consequences of aortic, carotid, and lenticulostriate arteriosclerosis (79) differ from those of coronary atherosclerosis, at least in this sample.

Our theoretical model and empirical findings raise interesting questions, given that compared with other primates, humans are outliers both in terms of brain size and lifespan (36). Studies of nonhuman primates have produced conflicting results regarding the relationship between BV and age, perhaps due to small sample size and captive conditions. For example, one study reports rates of about 0.20 and 0.30 percent per year for chimpanzees and macaques, respectively, apparently similar to those we observed in this study (105). However, another study of adult chimpanzees found no significant decrease in neocortical gray matter and white matter volumes up to age 45 (106). Among chimpanzees, brain aging may only become pronounced after the normal oldest ages at death.

In this regard, brain volume decline appears to accelerate after age 60 in most human samples [Table 2 and refs. 7–9], and it is interesting to consider the evolved "expected use-life" of the human brain. Hunter-gatherers and other subsistence populations show a modal age at adult death of approximately 70 y, with few people living past age 85 (107). At older ages in industrialized populations, the decline in BV occurs in association with other pathological changes in gray and white matter, such as amyloid plaques, p-tau tangles, and blood–brain barrier leakage (108). This

Table 3. Summary of findings regarding brain volume (BV) in relation to the hypotheses

Hypothesis	Latent risk or protective factor	Findings from Tsimane and Moseten	Findings from industrialized countries	References
H1	Energy stores and flows	Relationships to BV: Curvilinear with BMI and cholesterol Positive with height and hemoglobin Negative with epicardial fat None with blood sugar or hepatic fat	Negative relationships between weight, BMI, blood sugar, hepatic fat, and BV Negative and positive relationships between cholesterol and BV	(74–85) (81–83)
H2	Population acculturation	Greater BV decline with age in Moseten relative to Tsimane	Greater BV decline with age relative to Tsimane and Moseten	(6, 31, 84–86)
H3	Atherosclerotic burden	Negative relationship between aortic calcium and BV No relationship between coronary calcium and BV	Negative relationships between coronary and aortic calcium and BV	(87–89)

may be why dementia risk accelerates rapidly with advancing age (108). This may especially be the case in populations with high prevalence of obesity and sedentary behavior, where other metabolically induced pathological changes contribute to functional decline. Consistent with the relatively shallow decrease in BV with age, we found no cases of dementia prior to age 80 among the Tsimane and Moseten (32). The probability of being cognitively impaired or demented was also negatively associated with BV (32).

Implications of the Findings for Clinical Practice. We highlight two implications for medicine. The first is that there may be intermediate ranges of human biology that are "sweet spots" for optimizing certain health outcomes. The present results suggest that lifestyles associated with healthy hearts are also associated with less age-related brain volume decline. It is striking, however, that non-HDL cholesterol, composed of the two elements of supposedly "bad" cholesterol, triglycerides and low-density lipoprotein (LDL), is positively associated with BV in the linear model and through most of the distribution in the curvilinear model. With respect to coronary artery disease, evidence from trials with lipid-lowering drugs suggests that lower levels of LDL may always be better, with no lower limit (109, 110). It is possible that those results are restricted to later age interventions among people with high lifelong levels of circulating LDL. It is also possible that optimal levels may differ with respect to specific chronic diseases of aging. In the case of BV, optimal levels of circulating non-HDL cholesterol may be higher for the lipid-hungry brain than for cardiovascular health. More generally, whereas atherosclerotic stenoses and intimal plaque rupture and erosion may be most relevant to coronary artery disease, other forms of arteriosclerosis—such as distensibility loss due to medial arterial calcification and arterial stiffening of large and small arteries—may be more important to brain aging in the Tsimane and Moseten populations. Furthermore, as mentioned earlier with respect to BMI, optimal levels of non-HDL-C may be higher in the context of high physical activity and pathogen burden.

The second implication for medicine is that interventions to reverse EOR trends could be aided by understanding how evolved biology interacts with conscious decision-making. Sedentary lifestyles, greater adiposity, obesity, and their downstream health consequences are increasingly common world-wide. Globalization of food production and distribution, mechanization, decreased demand for physical labor, and improved transportation systems have the combined effect of increasing the supply of inexpensive, calorie-dense foods and decreasing physical activity. Interacting with evolved human biology, these changes have generated a world-wide trend toward higher obesity, increasing by 340% in men and 230% in women from 1975 to 2016 (111). Until recently, poverty, especially in developing countries, was typically associated with protein-calorie malnutrition. Now, however, an increasing proportion of the world's poor are obese (112), and many countries face a double burden of malnutrition and overweight.

While the transition to the EOR phenotype was a gradual process in the United States and Europe, it may be rapid in developing contexts, and these processes are now at work in both the Tsimane and Moseten populations. Sweetened beverages and corn oil are of growing importance in their diets. Levels of circulating cholesterol have risen in the Tsimane in recent years. Whereas blood samples taken in 2008 to 2010 had mean total cholesterol levels of 138 mg/dL (28), the measures from 2015–2018 show a mean of 151 mg/dL (Table 1). The older Tsimane and Moseten in our sample likely experienced both lower cholesterol and lower blood pressure throughout most of their adult lives than the values reported in Table 1.

Many people under EOR conditions attempt to resist the temptation to be sedentary and consume high-calorie processed foods. In one study, nearly half of US adults (49%) reported having attempted to lose weight in the last 12 mo (113). The conscious desire to exercise more and eat less may be historically novel. Yet, the evolved neurological mechanisms controlling hunger, physical activity, and their relative balance have ancient roots. We need a better understanding of how conscious learning, self-control, and motivations interact with those mechanisms, and of how genetic, epigenetic, developmental, and sociocultural processes modify those behavioral controls (35, 40, 55). Future intervention strategies will need to confront those complex interactions.

Limitations. It is important to highlight two important study limitations. The first is that the analyses are cross-sectional; associations with BV found across individuals of different ages need to be confirmed with longitudinal data. The possibility that some of the associations between BV and age may represent cohort differences requires investigation. Moreover, the associations of BV with the hypothesized risk/protective factors do not necessarily imply that they are causally related. The associations could be spurious, due to common associations with other unobserved factors that may be more important. Our findings are thus preliminary and tentative.

This analysis is also limited in its focus on age-related associations with total BV. While differences in total BV represent a global measure of brain aging, it will be instructive to examine differential rates of volume decline across brain regions, in relationship to population/exposome effects, sex differences, and risk/protective factors. Not all brain regions change volume at the same rate (114, 115). The regions of the brain that exhibit relatively greater loss in industrialized populations compared with the Tsimane may help illuminate mechanisms underlying how sedentary behavior, adiposity, hypertension, atherosclerosis, and poor glucose control affect brain morphology and function.

Finally, we did not assess the relationships of genetic variation, alcohol consumption, or infectious processes with BV, or their potential interactions with the risk and protective factors assessed in this study. These are important next steps for theoretical and empirical advances.

Conclusions

This paper examined individual and population differences in BV in later adulthood. Building on existing ideas about the "mismatch" between evolved human biology and modern exposomes, we proposed the EOR model to explain both how modern environments and lifestyles have been shaped by evolved human motivations, and how behavior, physiology, and brain aging respond to those environmental shifts. The theory and findings suggest that there may be optimal levels of food intake, physical activity, and adiposity that maximize brain health and minimize the rate of brain tissue loss with age. It is also possible that those optima will vary with the exposome and differ across populations. We hope that this paper stimulates further research and efforts to extend and test the theory.

Methods

Study Populations. The Tsimane sample includes individuals residing in villages in the communal territories under the jurisdiction of two tribal leadership organizations, the Gran Consejo Tsimane and the Consejo Regional Tsimane Moseten. All participants self-identify as Tsimane and are fluent in the Tsimane language; preliminary genetic analyses reveal very little genetic admixture from Europeans (116). The sample includes a small percentage of individuals (<5%) who self-designate as descending from other ethnic groups in addition to Tsimane. Our cohort-based panel design sampled adults aged 40+ from approximately 100 villages in the Beni Department. All individuals aged 60+ were invited to enroll, of which ~80% participated; individuals aged 40 to 59 were recruited by a random sample stratified by community (see ref. 31) for additional details on recruitment and sampling). The Tsimane sample for the present analysis includes 749 individuals over age 40 (47% female; see Table 1 for the age distribution).

The same study design was employed in 10 Moseten communities in the Beni and La Paz Departments. Those villages are predominantly composed of members of the Moseten ethnicity, but also include individuals who identify with other indigenous ethnic groups or who claim mixed Aymara/Quechua/Latin descent (~38%). The sample from the Moseten communities includes 416 individuals over age 40 (45% female; see Table 1). There were two individuals in the Moseten sample and one in the Tsimane sample that were age 39 but included in the 40 to 49-y-old group.

Human subjects approval was granted by the institutional review boards at the University of New Mexico (HRRC # 07–157; #15-133; #17-230) and UC Santa Barbara (HRRC # 28-21-0788). Informed consent was established at three levels for each population: individual, community, and overarching Tsimane and Moseten governing councils.

CT Acquisition and Measurement. Between 2015 and 2018, participants were transported to the CT imaging facility at the German Busch hospital in Trinidad, Bolivia. Although MRI would have been preferable to CT for brain imaging, MRI is not easily accessible in Bolivia. Brain volumes were segmented from CT scans as described in refs. 6 and 117. Measurements of coronary artery calcification (CAC) and thoracic aortic calcium, liver density (which relates inversely to hepatic fat), and epicardial fat thickness were obtained from CT scans of the chest by the Core Laboratory at St. Luke's Mid America Heart Institute in Kansas City (MAHI). Calcifications in the aortic valve, and the walls of the ascending aorta, aortic arch, and descending aorta were measured using the same calcium scoring software and results were expressed in Agatston units (AU) for those locations. Most studies of aortic calcification do not include the aortic arch in their field of view (118, 119), but because the arteries supplying blood to the brain originated in the aortic arch, it was included in our study. For that reason, we divide aortic calcification into two compartments, the descending and ascending aorta (TAC) and the aortic arch (AAC). Maximum epicardial fat thickness was measured anterior to the right ventricle in three places on the axial view of the chest CT scan and three places on the sagittal view with the six measurements then being averaged. See *SI Appendix* for additional details.

Risk Factors. Baseline demographic information was collected by the Tsimane Health and Life History Project mobile medical team along with measurements of the following variables: height, weight, blood lipids from fasting morning blood draws, fasting blood sugar, systolic and diastolic blood pressure, hematocrit, and high-sensitivity C-reactive protein (hs-CRP) (see ref. 31 for laboratory procedures).

Statistical Analyses. Analyses focused on predictors of variation in BV. To account for individual differences in body and head size, BV measurements are typically considered in terms of the percentage of the total intracranial volume (TICV). In the present sample, the scaling relationship between TICV and BV was observed to be significantly nonlinear (*SI Appendix*, Table S5). The scaling exponent β of this nonlinear relationship was estimated using log–log regression to be 0.918 (95% CI 0.889 to 0.946). To reduce the variance across individuals due to this nonlinear scaling, brain volumes as percentages of TICV were normalized using the formula:

$$\text{normalized percent BV} = \text{BV}_i \times \frac{\text{mean(TICV)}^{\beta-1}}{\text{TICV}_i^{\beta}},$$

where BV_i and TICV_i are the unadjusted values of individual i, mean(TICV) is the mean TICV, and β is the observed scaling exponent (see ref. 6 for additional details). Normalized percent brain volume can thus be interpreted as the percent of the total intracranial space occupied by the brain, adjusting for the observed nonlinear relationship that exists between TICV and BV. While the use of the normalized variable improves the precision of model estimates, none of the results are qualitatively different when using unadjusted volumes (*SI Appendix*, Table S6).

Regression models were estimated in STATA 17.0. Best-fit models were identified based on AIC minimization. In these models, continuous variables (except age, which is measured in years from the median age of 58) were transformed into standardized units (z-scores) so that the parameter estimates reflect the difference in normalized percent BV expected from a 1 SD difference in the predictor. To test for curvilinear effects, linear (x_{ij}) and quadratic terms (x_{ij}^2) were employed for BMI and non-HDL-C with the subscripts i and j representing individuals and variables, respectively. As a robustness check and for comparative purposes, we also employed models in which BMI and non-HDL-Cis divided into categories. Sample sizes for each predictor are given in *SI Appendix*, Table S3.

Data, Materials, and Software Availability. All relevant computer code for variable definitions and statistical analysis has been deposited in [Github] (https://github.com/hkaplan/tsimane-brain-volume). Individual-level data are stored in the Tsimane Health and Life History Project (THLHP) Data Repository, and are available through restricted access for ethical reasons. THLHP's highest priority is the safeguarding of human subjects and minimization of risk to study participants. The THLHP adheres to the CARE Principles for Indigenous Data Governance, which assure that the Tsimane and Moseten 1) have sovereignty over how data are shared, 2) are the primary gatekeepers determining ethical use, 3) are actively engaged in the data generation and 4) derive benefit from data generated and shared use whenever possible. The THLHP is also committed to the FAIR Principles to facilitate data use. Requests for individual-level data should take the form of an application that minimally details the exact uses of the data and the research questions to be addressed, procedures that will be employed for data security and individual privacy, potential benefits to the study communities, and procedures for assessing and minimizing stigmatizing interpretations of the research results (see the following webpage for links to the data sharing policy and data request forms: https://tsimane.anth.ucsb.edu/data.html). Requests for individual-level data will require institutional IRB approval (even if exempt) and will be reviewed by an Advisory Council composed of tribal leaders, tribal community members, Bolivian scientists, and the THLHP leadership. A similar structure exists for the Moseten data. The study authors and the Tsimane leadership are committed to open science and are available to assist interested investigators in preparing data access requests.

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