

Ectopic adipose tissue in subsistence populations with minimal coronary disease, large left atria, and very low rates of atrial fibrillation

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ABSTRACT

Background: Greater deposits of epicardial adipose tissue are associated with atrial fibrillation and coronary disease, but have not been studied in subsistence populations.

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Hepatic steatosis
Subsistence population

Methods: We performed CT imaging to measure coronary artery and thoracic aortic calcium (CAC, TAC), epicardial fat thickness (EFT), liver density, and left atrial (LA) anteroposterior diameter and, using a deep learning-enabled software program, epicardial and thoracic fat volume (EFV, TFV), in two remote Amerindian subsistence populations with minimal coronary artery calcification and virtually no atrial fibrillation. We compared 893 adult Tsimane (mean age 58.3±10.5 y, 51.6% male), 440 Moseten (55.9±10.4 y, 53.6% male) to 955 U.S. (56.8±10.8 y, 51.6% male) subjects.

Results: Tsimane and Moseten had 43%-52% lower EFT, EFV, TFV, and 48-92% less CAC and TAC, respectively than the U.S. cohort. Mean liver measurements were 14-22% denser and LA diameters 10-14% larger (≈ 40% larger by volume). For EFV, Tsimane, Moseten, and U.S. cohorts averaged 54.2±25.6, 60.3±35.1, and 106±53.5 cc, respectively (p< 0.05 for all comparisons). EFV remained significantly smaller after adjustment for age, BMI, and other characteristics. For all CT metrics, the more acculturated Moseten measures were intermediate between Tsimane and the U.S. cohort.

Conclusions: Tsimane mean EFV was the lowest of any population ever reported in the literature, achieving a new population standard. The low levels of EFV in the Tsimane and Moseten add to the body of evidence linking ectopic fat and atherosclerosis and further confirm (in the negative) the association, and likely causative role, of epicardial fat and atrial fibrillation.

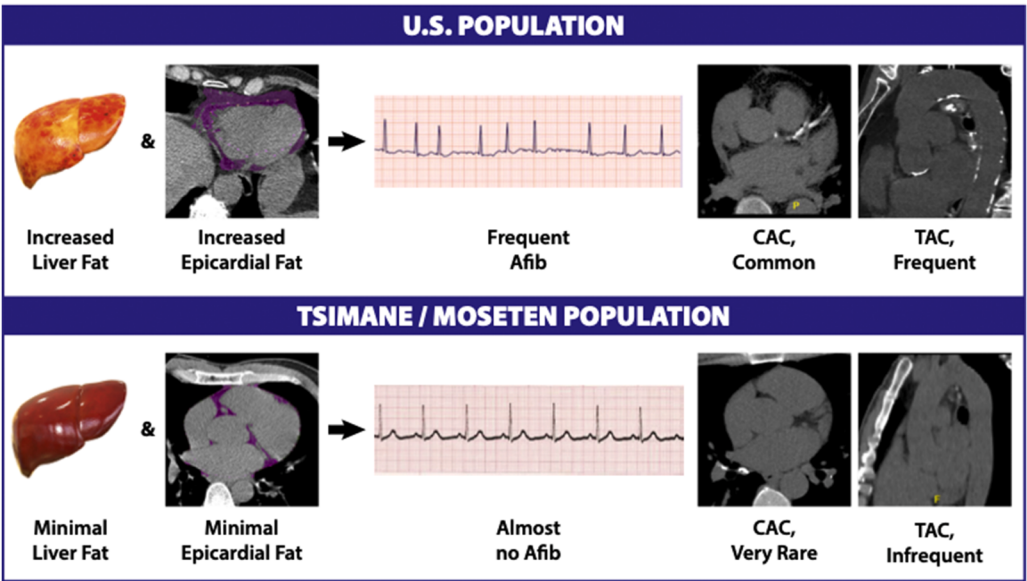
1. Introduction

Ectopic adipose tissue, the fat stored around the heart and in the liver, is distinct from other fat deposits in the body and is known to have significant endocrine and paracrine activity [1]. In particular, epicardial adipose tissue (EAT), the fat between the myocardium and the visceral pericardium, has many know functions: secrete hormones analogous to an endocrine organ, secrete cytokines and apidokines, modulate inflammation and cardiac structure remodeling, store lipids, and metabolize free fatty acids providing heat directly to the adjacent myocardium [2,3]. Among the potentially modifiable risk factors for atrial fibrillation, EAT has gained considerable attention in recent years [2,4-6]. Increased EAT is associated with atrial fibrillation as well as with the prevalence of atherosclerosis. Increased epicardial fat thickness (EFT) and epicardial fat volume (EFV) are more strongly associated with atrial fibrillation than general adiposity [4-7]. For example, EFT on echocardiography predicts rates of unsuccessful electrical cardioversion and recurrence of atrial fibrillation [8]. In addition, success of ablation procedures for atrial fibrillation shows negative correlation for patients with increased EAT [9,10]. EAT is also an independent predictor of stroke in patients diagnosed with atrial fibrillation [11]. The nature of

epicardial fat determined by CT Hounsfield Unit (HU) density has also been reported to be predictive of post-ablation recurrence of atrial fibrillation [12]. Given the strength of these associations and the potential mechanisms, increased EAT is thought to be causally related to atrial fibrillation [13].

Increased EFV and thoracic fat volume (TFV) are associated with metabolic syndrome, coronary artery disease (CAD), and heart failure [14-20]. Epicardial fat is independently associated with major adverse cardiac events, high risk coronary obstructive artery disease and abnormal coronary flow reserve [21-23]. Fatty liver disease, especially metabolic dysfunction-associated steatotic hepatitis, is strongly associated with increased risk of cardiovascular disease [24,25]. Pertinently, Hideo-Kajita *et al.* showed that CT measures of hepatic-spleen CT attenuation predict high and low risk of CAD burden as assessed by the coronary CT angiography-derived Leaman score [26]. Fatty liver disease has primarily been associated with preclinical CAD; a causal association has not yet been clarified. Possible pathogenic mechanisms to explain the complex relationship between cardiovascular disease and fatty liver include insulin resistance, systemic inflammation, cytokines, hepatokines, oxidative stress, genetics, and other factors [26,27].

Virtually all previous studies of the health effects of ectopic adipose tissue have been in sedentary populations from industrialized populations. To evaluate deposits of ectopic adipose tissue in physically active subsistence populations with little coronary atherosclerosis and



Central illustration.

virtually no atrial fibrillation, we worked with the Tsimane Amerindian people of lowland Bolivia [28,29], as well as the geographically-adjacent Moseten people of Bolivia who are small-scale farmers and genetically related to the Tsimane, but are more acculturated into Bolivian society [30,31]. The Tsimane and Moseten offer a unique opportunity to evaluate the extent to which lifestyle and environment may affect ectopic fat deposits in the liver and epicardium and the relationships with cardiovascular health. This study investigates the link between epicardial and liver fat deposits with atrial fibrillation in these people, especially in the absence of atherosclerotic calcifications, compared with U.S. groups of similar age and sex distribution. We hypothesized that Moseten, having intermediate levels of acculturation, would also have intermediate levels of atherosclerosis and ectopic adipose tissue.

2. Methods

2.1. Study population

The Tsimane are an indigenous population of approximately 17,000 who reside primarily in villages along the Maniqui River of the Amazon basin in the Beni Department of Bolivia [29]. The Tsimane are physically active and eat a lean diet derived from gathering, slash-and-burn farming, fishing, and hunting [32]. They also have minimal access to electricity, sanitation, and clean water [33]. They have high rates of infection and inflammation, but have the lowest levels of coronary artery CAC of any population ever reported [29,34]. Tsimane exhibit few of the atherosclerotic risk factors found in industrialized nations, with minimal obesity, hypertension, diabetes, tobacco consumption, and hyperlipidemia and consume a lean diet rich in polyunsaturated fatty acids [29,31,35,36]. They are also physically active. For example, both men and women average over 16,000 step equivalents per day, greater than twice the average count in the US NHANES dataset [37].

The Moseten are an indigenous Bolivian population of approximately 3000 who live in the Beni and La Paz Departments. Moseten 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. Moseten are genetically and ethno-linguistically related to Tsimane, but Moseten began acculturation into broader Bolivian society several decades earlier [30]. Compared to the Tsimane, the Moseten have higher rates of diabetes and obesity, and consume more market goods including processed foods [30]. Moseten lifestyle is also more acculturated with more schooling (averaging about 4.3 years of schooling compared to 1 year for Tsimane) and greater access to electricity and sanitation. The Moseten are also more actively engaged in cash crop farming. Nevertheless, compared to modern industrialized countries, the Moseten lifestyle is much more physically active and closer to that of the Tsimane.

2.2. CT scanning and measurements

Tsimane and Moseten traveled from their homes to the regional capital city of Trinidad, El Beni, Bolivia for medical examinations and non-contrast x-ray CT scanning at the Germán Busch Hospital as has been previously described [29]. ECG-gated CT scans of the heart were performed on a General Electric (Milwaukee, WI, USA) Lightspeed 16 detector scanner between July 2014 and October 2018. Image reconstructions were reviewed, and specific measurements obtained by the core laboratory at St. Luke's Mid America Heart Institute (MAHI) in Kansas City. Calcium scoring, hepatic density, epicardial fat thickness and anteroposterior measurements of the left atrial diameter were performed on a Siemens syngo.via workstation (Erlangen, Germany). CAC scoring was obtained using Siemens calcium scoring software according to the method of Agatston et al. [38]. Calcifications in the wall of the ascending and descending thoracic aorta (TAC) between the carina and the inferior surface of the heart were similarly measured with Siemens

calcium scoring software according to the method of Budoff et al. [39]. Liver density measurements were obtained by placing an elliptical region of interest over the liver on axial CT images as described by Chhabra et al., Patil et al., and Hideo-Kahita et al. [15,24,26]. EFT was measured in the axial projection near the inferior edge of the heart and in the sagittal CT projection anterior to the right ventricle in a manner previously described by Alam et al. and Patil et al. [15,40]. Three adjacent measurements were obtained in each of the two projections and values were averaged. Measurements were obtained in an identical manner on the Tsimane and Moseten subjects and the U.S. comparator subjects. (See supplemental Figure 1.)

Both EFV and TFV were measured from the chest CT scans of the Tsimane, Moseten and 485 MAHI subjects using the deep learning-enabled QFATsoftware program (version 2; Cedars Sinai, Los Angeles, CA) employing a method which has been previously described [14,41]. In brief, the pericardium was automatically segmented from the non-contrast CT datasets. The limits of the heart were automatically defined as the pulmonary artery bifurcation (superior limit) to the posterior descending artery (inferior limit). Epicardial fat volume (reported in cm^3) and mean attenuation (reported in HU) were automatically calculated from 3-dimensional fat voxels between the HU limits of $([-190, -30] \text{ HU})$ enclosed by the visceral pericardium [14,41]. See Fig. 1.

2.3. U.S. comparator samples: MAHI and EISNER study cohort

A comparator sample was drawn from patients who had undergone screening ECG-gated chest CT scanning for CAC at MAHI. The MAHI database of coronary calcium scores is large, containing over 150,000 individuals. The average coronary calcium score as a function of age closely mirrors those results in cross sectional population studies including MESA and the Heinz Nixdorf RECALL study [29,42,43]. Patients in this database did not have known clinical CAD and had self-referred for screening coronary calcium score because of cardiac concerns such as a positive family history. CT scans from patients in the MAHI database were randomly selected to obtain a similar age and sex match relative to Tsimane and Moseten subjects. The comparator CT scans were scored by the core laboratory in an identical manner and on the same CT workstation as the Bolivian study populations.

To evaluate epicardial and thoracic fat volumes against a cross-sectional western population, we also compared the results from the Tsimane and Moseten to measurements from a previously published group with a similar age distribution measured in an identical manner using the same QFAT program, the EISNER Trial (Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research) cohort [14]. In this cohort ($n = 2068$ asymptomatic subjects without known cardiovascular disease, mean age 56 ± 9 y), individuals were followed for a mean of 14 ± 3 years after measurement of CT coronary calcium score, epicardial fat volume and epicardial fat attenuation. EVF was associated with increased risk of major adverse cardiac events. In addition, MACE risk progressively increased with $\text{EFV} \geq 113 \text{ cm}^2$ and coronary artery calcium $\geq 100 \text{ AU}$ and was highest in subjects with both [14].

2.4. Statistical analysis

Mean $\pm$ SD for the CT-based measurements of axial and sagittal epicardial fat thickness, epicardial and thoracic fat volume, epicardial fat density, hepatic density, left atrial anteroposterior diameter, CAC, and TAC for the Tsimane, Moseten, and the US comparator group were calculated.

Various R and R studio packages were used for statistical analysis [44–48]. A Welch's two sample *t*-test with adjustments for unequal variance was used to compare statistical differences between populations for continuous variables. Pearson Chi-square was used to compare differences of proportions. Age-dependent variables were

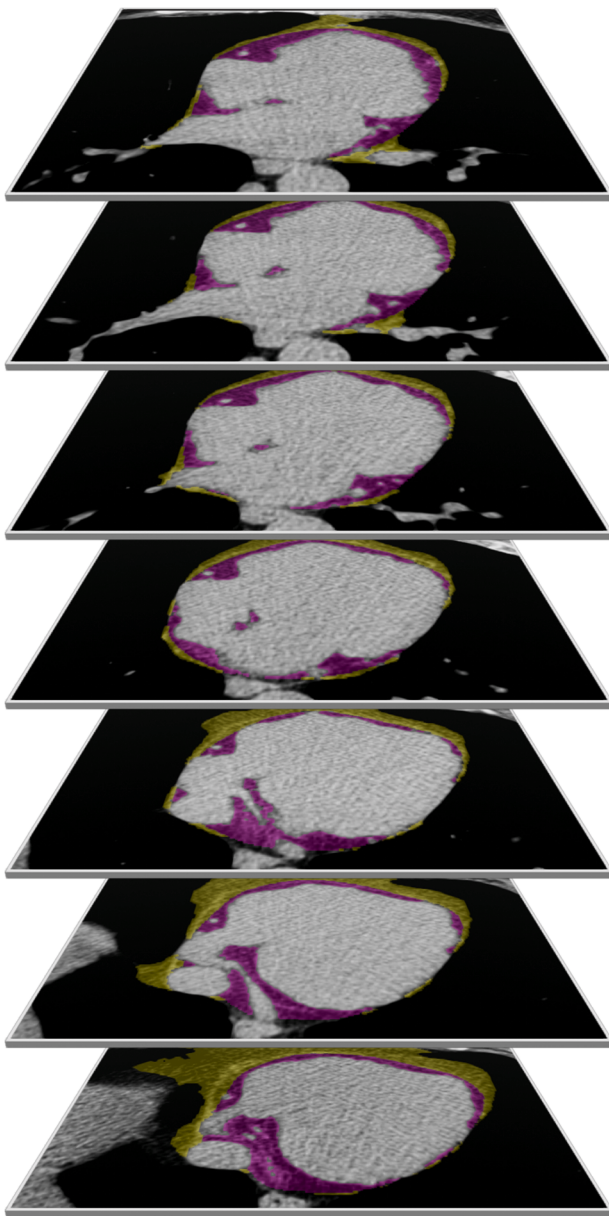


Fig. 1. Axial view CT scans through the heart showing shading of epicardial fat (purple) and thoracic fat (gold) in a United States MAHI comparator subject using the QFAT software program for quantification of epicardial and thoracic fat volume.

plotted using the Loess regression method with 95 % confidence intervals against age. Hazard ratios for a CAC of ≥ 10 AU's were derived using a Cox Proportional Hazard model of the population, including EFV, EFT, epicardial fat density, TAC, body mass index (BMI), and left atrial diameter as covariates. A Schoenfeld Global Test of Residuals was used to validate proportional hazard assumptions. Additionally, we performed multiple linear regression models for epicardial fat volume in all three populations, correcting for age, body mass index, and other standard cardiac risk factors to evaluate whether known risk factors could explain the observed differences. Comparison with a previously published cohort was carried out on the summary statistics of the EISNER Study to our cohorts [14]. This was done using a metanalytic technique considering generic inverse variance and reporting ratios of means [48]. Concordance between epicardial and thoracic fat measurements were compared between two researchers.

Descriptive statistics, Welch's T test, Spearman correlations, Pearson

correlations, density plots, and Loess age distributions were run in R studio.

2.5. Ethics

All phases of the study were approved by the Institutional Review Boards of the University of New Mexico, The University of California, Santa Barbara and the Universidad San Simon, Cochabamba, Bolivia. Additionally, the Gran Consejo Tsimane and Organización del Pueblo Indígena Mosen (the governmental bodies of the Tsimane and Mosen), village leaders, and study participants approved all protocols. Written informed consent was provided by each participant. The study was also reviewed by the St. Luke's Hospital of Kansas City Institutional Review Board which approved the retrospective review of existing CT scans of the MAHI patients.

2.6. Data availability statement

Please see online supplement, Data Availability Statement.

3. Results

3.1. Demographics and comparison between groups

Baseline demographic characteristics and results of the CT scan measurements of the Tsimane, Mosen, and U.S. comparator group are shown in Table 1. The three groups have comparable sex and age distribution. The U.S. comparator group has a higher average BMI (29.5 kg/m^2) than the Mosen (25.5 kg/m^2) and Tsimane (24 kg/m^2). Measures of epicardial and thoracic fat volume are lowest in the Tsimane with the more acculturated Mosen intermediate, and the U.S. comparator group the highest, while epicardial fat thickness is similar between Tsimane and Mosen (Table 1, Fig. 2). Hepatic fat deposits are indicated by lower liver density: Tsimane have the highest liver density with the Mosen intermediate, and the U.S. MAHI comparator group the lowest (Fig. 3).

Mean left atrial diameter is largest in the Tsimane with the Mosen intermediate and the U.S. group the smallest (Table 1 and Fig. 4). Consistent with the known low level of cardiovascular disease in this group, atherosclerotic CAC and TAC are much lower in the Tsimane than in the U.S. comparator group (Table 1, Fig. 5 and Online Supplement Figs. 2–5), especially with advanced age. Atherosclerotic calcifications in the Mosen are intermediate between the Tsimane and U.S. comparator group (Table 1, Fig. 5, Online Supplement Figs. 2–5).

Epicardial fat deposits have a non-linear association with generalized obesity [49].

After correcting for age and BMI, the Tsimane and Mosen still have significantly less epicardial fat than the U.S. comparator population (Fig. 6). Also, a regression model of epicardial fat volume with population, age, body mass index, diabetes, HDL cholesterol and triglycerides had almost no effect on the estimated population differences (Online Supplemental Figure 6). This indicates that differences in epicardial fat are not just due to the greater overall adiposity or other measured variables of the U.S. population. Additionally, sex differences in epicardial fat are opposite to what has been previously reported [50]. U.S. men typically have much more epicardial fat than women. This is not the case for the Tsimane and Mosen, with women tending to have more than men (Fig. 6, online supplemental figure 7). In regards to hepatic fat, men in the U.S. comparator population have substantially lower liver density than women, whereas in the Mosen and Tsimane, the differences between men and women is not significant (Online Supplemental Figure 8). Men also tend to have larger left atrial diameters than women in all three study groups (Online Supplemental figure 9).

Table 1
Demographics and key measurements of the United States comparator population, the Tsimane, and the Moseten.

	United States (N = 935)	Moseten (N = 423)	Tsimane (N = 886)	Overall (N = 2244)	p Values* United States vs Tsimane	United States vs Moseten	Tsimani vs Moseten
Sex†					0.988	0.391	0.388
Female	455 (48.7 %)	195 (46.1 %)	431 (48.6 %)	1081 (48.2 %)			
Male	480 (51.3 %)	228 (53.9 %)	455 (51.4 %)	1163 (51.8 %)			
Age					0.012	0.176	< 0.001
Mean (SD)	57.1 (10.6)	56.3 (10.2)	58.4 (10.4)	57.5 (10.5)			
Median [Min, Max]	55.0 [41.0, 92.0]	55.0 [41.0, 85.0]	57.0 [41.0, 94.0]	56.0 [41.0, 94.0]			
Body Mass Index (BMI)					< 0.001	< 0.001	< 0.001
Mean (SD)	29.1 (6.92)	25.5 (4.65)	24.0 (3.48)	25.8 (5.37)			
Median [Min, Max]	28.1 [0, 53.1]	25.0 [12.7, 43.5]	23.6 [13.5, 39.9]	24.7 [0, 53.1]			
Missing	8 (0.9 %)	0 (0 %)	0 (0 %)	8 (0.4 %)			
Average Epicardial Fat Thickness (mm)					< 0.001	< 0.001	0.578
Mean (SD)	4.49 (1.79)	2.28 (1.19)	2.24 (1.34)	3.18 (1.88)			
Median [Min, Max]	4.23 [1.55, 13.1]	1.98 [0.593, 7.83]	1.93 [0.318, 19.9]	2.81 [0.318, 19.9]			
Missing	4 (0.4 %)	0 (0 %)	8 (0.9 %)	12 (0.5 %)			
Epicardial Fat Volume (mL)					< 0.001	< 0.001	< 0.001
Mean (SD)	106 (53.8)	60.5 (34.9)	54.2 (25.7)	69.4 (43.3)			
Median [Min, Max]	100 [7.50, 457]	55.6 [1.70, 194]	50.6 [0.407, 164]	58.9 [0.407, 457]			
Missing	467 (49.9 %)	0 (0 %)	0 (0 %)	467 (20.8 %)			
Total Thoracic Fat Volume (mL)					< 0.001	< 0.001	< 0.001
Mean (SD)	188 (138)	110 (66.6)	90.9 (48.2)	120 (93.4)			
Median [Min, Max]	164 [0.700, 1570]	96.2 [5.93, 387]	81.2 [0.407, 346]	96.2 [0.407, 1570]			
Missing	481 (51.4 %)	0 (0 %)	0 (0 %)	481 (21.4 %)			
Average Epicardial Fat Density (HU)					< 0.001	< 0.001	< 0.001
Mean (SD)	-76.1 (4.88)	-73.9 (5.20)	-71.9 (4.28)	-73.5 (4.99)			
Median [Min, Max]	-76.6 [-87.9, -57.6]	-73.9 [-87.4, -60.4]	-71.9 [-85.6, -55.6]	-73.4 [-87.9, -55.6]			
Missing	495 (51.8 %)	0 (0 %)	0 (0 %)	495 (21.6 %)			
Left Atrial Diameter (cm)					< 0.001	< 0.001	< 0.001
Mean (SD)	3.43 (0.590)	3.78 (0.567)	3.92 (0.625)	3.74 (0.637)			
Median [Min, Max]	3.40 [2.10, 5.60]	3.70 [2.50, 5.80]	3.90 [0, 6.80]	3.70 [0, 6.80]			
Missing	383 (40.9 %)	0 (0 %)	2 (0.2 %)	385 (17.1 %)			
Coronary Aortic Calcium Score(AU)					< 0.001	< 0.001	0.016
Mean (SD)	120 (379)	27.3 (141)	10.2 (52.7)	59.5 (260)			
Median [Min, Max]	0.850 [0, 5670]	0 [0, 1590]	0 [0, 997]	0 [0, 5670]			
Missing	0 (0 %)	1 (0.2 %)	5 (0.6 %)	6 (0.3 %)			
Thoracic Aortic Calcium Score(AU)					< 0.001	< 0.001	0.236
Mean (SD)	207 (834)	111 (963)	54.7 (221)	113 (666)			
Median [Min, Max]	0 [0, 8920]	0 [0, 18,600]	0 [0, 2660]	0 [0, 18,600]			
Missing	383 (40.9 %)	0 (0 %)	2 (0.2 %)	385 (17.1 %)			
Liver Density (HU)					< 0.001	< 0.001	< 0.001
Mean (SD)	55.8 (13.0)	63.5 (9.87)	68.3 (7.68)	63.5 (11.4)			
Median [Min, Max]	57.0 [3.00, 89.0]	65.0 [31.0, 91.0]	69.0 [38.0, 91.0]	66.0 [3.00, 91.0]			
Missing	383 (40.9 %)	0 (0 %)	10 (1.1 %)	393 (17.5 %)			

* - †-Adjusted(Pearson's) Chi-Square Test, otherwise **Welch's T Test**(two-tailed T-Test of independence with correction for unequal variance),.

3.2. Comparison with the EISNER study group

Fig. 7 shows the comparison of the three cohorts with the published results of the EISNER study participants who underwent thoracic fat measurements in an identical manner using the QFAT program [14]. The Tsimane and Moseten have significantly less epicardial and thoracic fat volume, and the Tsimane have greater epicardial fat density than the EISNER participants (Fig. 7). The U.S. comparator population (mean BMI from the Kansas City metropolitan area = 29.5 ± 5.6 kg/m²) has more generalized obesity and greater mean epicardial and thoracic fat volume than the EISNER participants (mean BMI = 26.6 ± 4.9 kg/m²) who were largely drawn from the Los Angeles metropolitan area.

3.3. Concordance test for the QFATt measurements

For the 160 subjects who underwent repeat measurement by a second observer, the concordance was high with Spearman rho(p) = 0.96, 0.97, and 0.98 for epicardial fat volume, thoracic fat volume, and

epicardial fat density, respectively. By Kendall's W, the relative concordance measures were 0.98, 0.99, and 0.99.

4. Discussion

This is the first study to evaluate the effect of ectopic adipose tissue on health and disease in a rural subsistence population living a pre-industrial lifestyle. The primary finding of the study was that both the Tsimane and the more acculturated Moseten have lower mean ectopic fat than an age and sex-matched U.S. comparator group. The mean EFV was also substantially less than a cross sectional U.S. population measured in an identical way in the EISNER Study. In fact, the Tsimane had the lowest mean EFV of any population ever reported in the literature. Their value (54.2 cm³) was even lower than select subgroups such as lean patients from Pakistan who had normal coronary angiograms (mean EFV = 56.6 cm³) and a select control group of non-obese U.S. women with no CAC and normal EFV (defined as ≤ 95 cm³; mean EFV = 72 cm³) [51,52]. Table 2 [14,17,18,22,51–56].

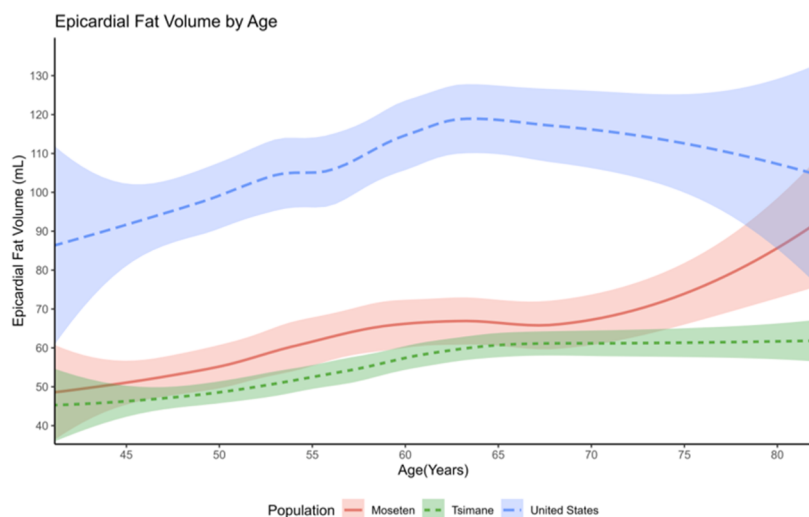


Fig. 2. Epicardial fat volume of the Tsimane, Moseten, and U.S. comparator group by age (Loess method, shaded area = 95 % confidence interval).

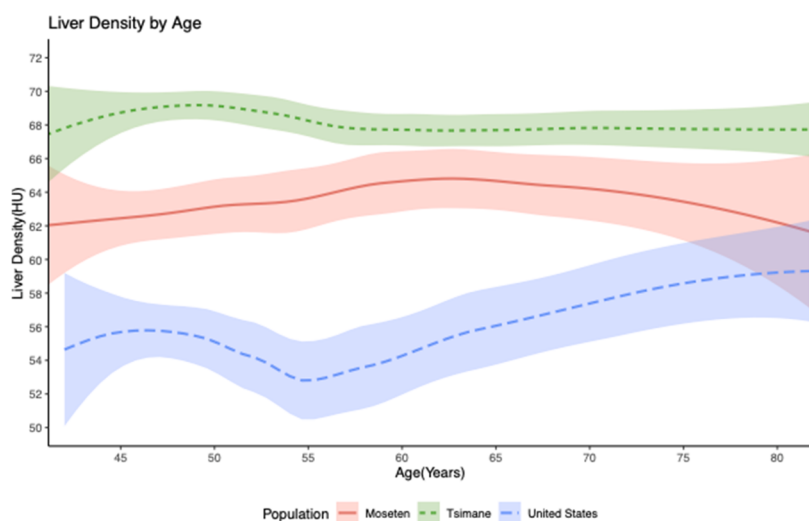


Fig. 3. Hepatic CT scan density Tsimane, Moseten, and the U.S. comparator groups by age (Loess method, shaded area = 95 % confidence interval). The Tsimane and Moseten have less liver fat and therefore greater hepatic density than the U.S. cohort.

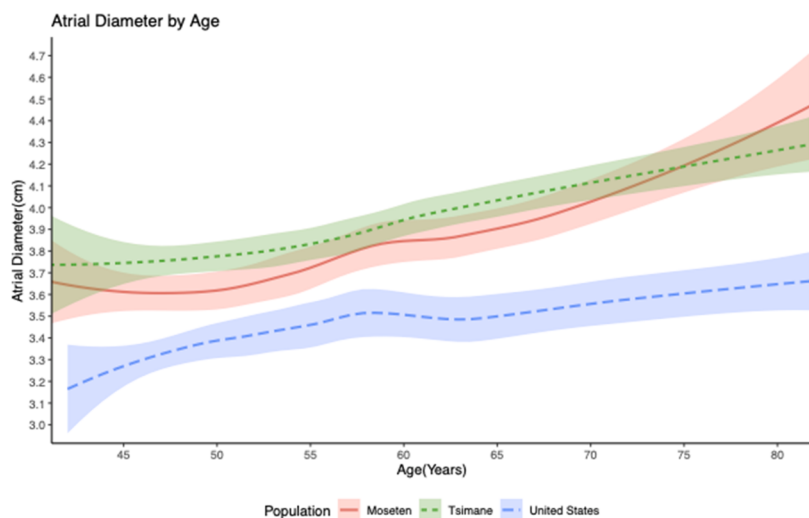


Fig. 4. Left atrial AP diameter of the Tsimane, Moseten, and the U.S. comparator groups by age, (Loess method, shaded area = 95 % confidence interval).

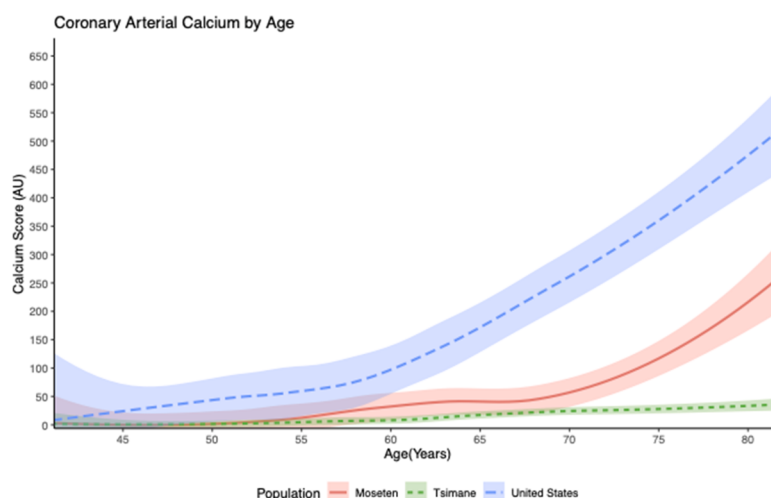


Fig. 5. Mean coronary artery calcium score by age, (Loess method, shaded area = 95 % confidence interval). The Tsimane and Moseten have much less coronary artery calcium than the U.S. comparator group.

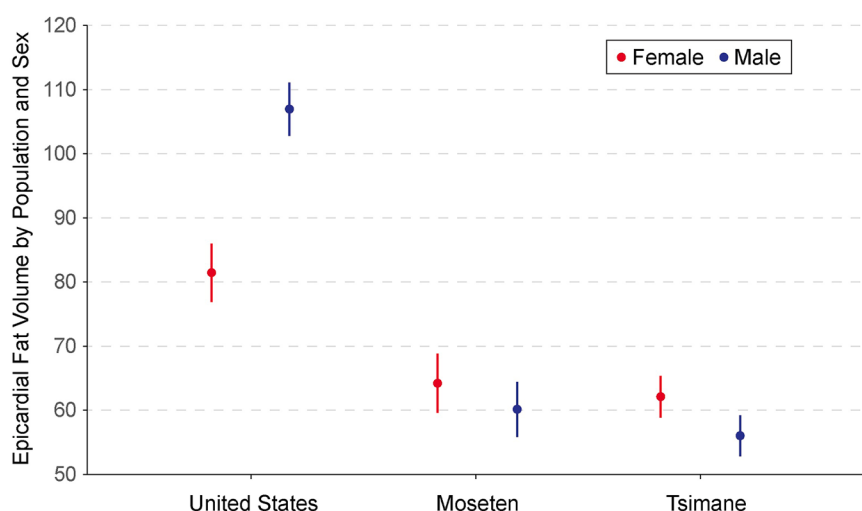


Fig. 6. Comparison of epicardial fat volume for the United States MAHI comparator population, the Moseten, and the Tsimane - expected values for each group corrected for age and BMI. Of note, United States men have greater epicardial fat volume than women, although this is not true for the Tsimane and Moseten.

4.1. Comparative EAT and atrial fibrillation in Amerindians and U.S. population

Rowan *et al.* found that Tsimane and Moseten have almost no atrial fibrillation [28]. Specifically, atrial fibrillation was observed on resting ECG in only one Tsimane subject out of 1314 (0.076 %) and one Moseten subject out of 534 (0.187 %) at baseline. In 1059 adult Tsimane with > 1 ECG, there was only one additional case of atrial fibrillation in the subsequent 7395 risk-year follow up. Among the 542 risk-year follow up in the Moseten, no additional atrial fibrillation cases occurred [28]. Rowan reported that these rates are 1/20th to 1/6th of high-income countries and the lowest levels ever reported [28]. Recent publications have documented that the prevalence of atrial fibrillation in the United States continues to increase and is higher than previously believed, estimated to be 6.8 % of the adult population [57]. Thus, the relative rates of atrial fibrillation in the Tsimane and Moseten are even lower than estimated by Rowan *et al.* The extremely low rates of epicardial fat deposits herein confirm in the negative the previously-described strong direct association between epicardial fat and atrial fibrillation [2,4,5,7–9,12,58]. Other authors have elaborated upon possible mechanisms for a causative link between epicardial fat and atrial fibrillation [4,5,7,16]. The results described in this report, though circumstantial, further

strengthen the likelihood that epicardial fat is mechanistic for atrial fibrillation, particularly since left atrial diameter, considered closely linked to atrial fibrillation, was large in the Tsimane and Moseten. We found both groups had greater left atrial size than the U.S. comparator group. Several recent publications have also demonstrated a possible pathophysiological link between atrial fibrillation and markers of inflammation [59–61]. It should be noted that the Tsimane, who have low levels of sanitation and a high infectious burden, have elevated level of multiple inflammatory markers [28,29,62]. In the Tsimane cohort undergoing ECGs, 42.2 % had an hs-CRP > 3 mg/dl and 56 % had an elevated erythrocyte sedimentation rate. For the Moseten, the values were 47.5 % and 57.8 %, respectively. The relevant tables showing data from the Rowan *et al.* publication are included in the online supplement Tables 1, 2 and 3 [28]. Given the large left atrial diameters and high levels of inflammation, they would have been expected to have high rates of atrial fibrillation.

4.2. Epicardial fat density

Our results demonstrate that Tsimane and Moseten not only had much less EFV than the MAHI comparator cohort or the EISNER study subjects, but also have denser epicardial fat. Lower epicardial fat density

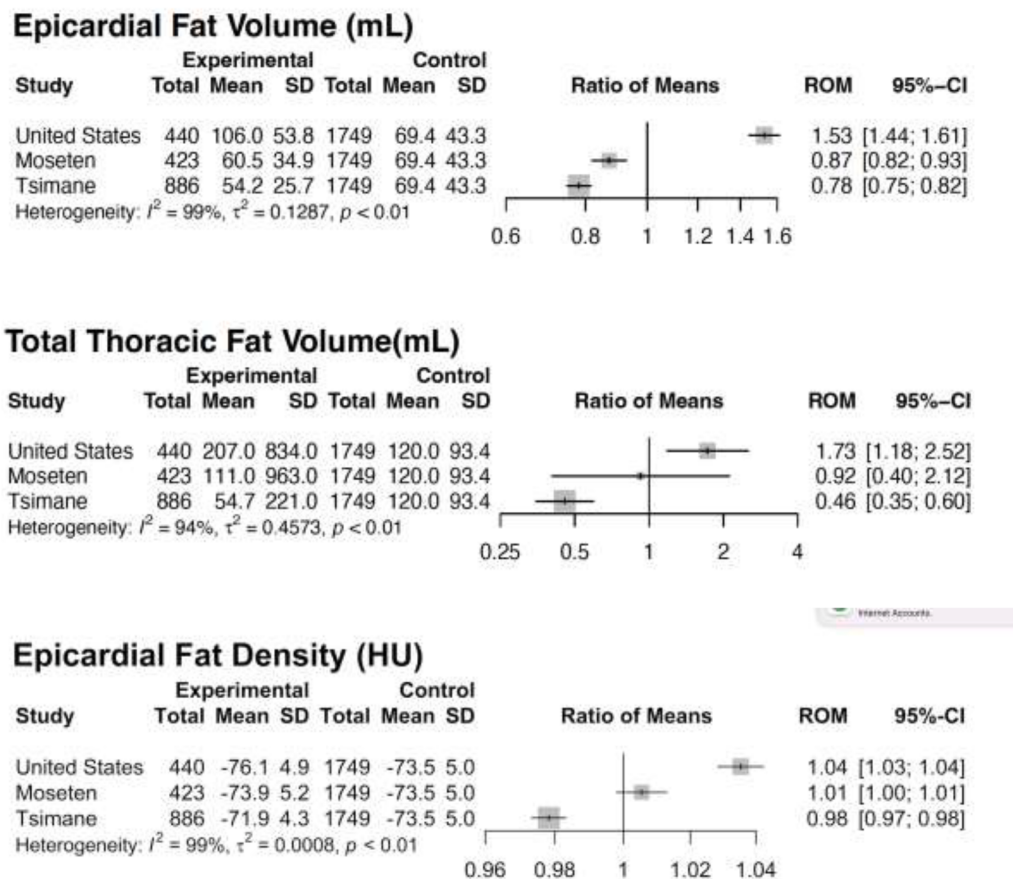


Fig. 7. Comparison of epicardial fat volume, thoracic fat volume, and epicardial fat density, for the U.S. comparator group, the Moseten, and the Tsimane with the published results of the Eisner Study group (Eisenberg citation) using a Ratio of Means approach. 1= the Eisner study mean. The Tsimane and Moseten have significantly less epicardial fat and thoracic fat volume and the Tsimane have lower epicardial fat density than the Eisner participants. The U. S. comparator population (from the Kansas City metropolitan area) has greater mean epicardial and thoracic fat volume than the Eisner participants who were largely drawn from the Los Angeles metropolitan area.

Table 2
Mean epicardial fat volume (EFV) from the current study and previous published studies.

Author	Country	Population	N	Mean Age	Mean BMI	Mean EFV	Citation	Comments
Thompson	Bolivia	Tsimane Cross Sectional	893	58.3	24	54.2	current study	
Thompson	Bolivia	Moseten Cross Sectional	440	55.9	25.5	60.3	current study	
Thompson	United States	Cor Cal Database	485	56.7	29.2	106	current study	
Eisner	United States	Cross Sectional	2068	56.1	26.6	78.5	14	
Arshi	Netherlands	Cross Sectional	2103	68	27.6	105.6	17	
Cosson	France	Diabetic Cross Sectional	409	57	29.1	92	18	
Yu	China	Suspected CAD, no ischemia	109	61	25.6	106.6	23	
Subhan	Pakistan	Normal coronary angiography	500	51.6	24.1	56.6	50	
El Shahawy	United States	No CAC, non-obese, "normal EFV"	16	57	23.5	72	51	Normal EFV defined as < 96 cm ³
Yu	China	MPI patients, Middle Tertile of EFV	55	62.3	24.9	107–128	52	
Kim	Korea	Afib ablation, Median EFV	1187	60	25.3	116	55	Median EFV
Weferling	Germany	TAVR Patients	560	80	26.4	129.5	54	
Roest	Netherlands	Heart Transplant Patients	149	45.5	25.9	208.4	53	EFV correlated with grade of cardiac allograft vasculopathy

was shown to be a predictor of major adverse cardiac events at a mean follow up of 14 ± 3 years in the EISNER study [14], and thus the Tsimane and Moseten composition would be viewed as healthier in this regard as well.

4.3. Lifestyle of the Tsimane and Moseten

The Tsimane and Moseten are physically active and have very low rates of diabetes and metabolic syndrome, conditions that are closely

related to ectopic fat deposition [29]. The Tsimane and Moseten also have lower average BMI than most industrialized populations and are rather muscular [63]. Mean BMI for Tsimane is 24 kg/m² with an obesity (BMI ≥ 30 kg/m²) prevalence of about 5 %. Moseten show greater mean BMI (26.0) with about 18 % prevalence of obesity [28]. Although the Tsimane diet is now changing with acculturation, they traditionally consumed a high energy diet with 64 % derived from complex carbohydrates, and with low fat intake (40–46 g/d) and high protein (119–139 g/d) [30]. There is also very little tobacco consumption with a mean of <0.8 lifetime pack years in all age groups [64]. Although there could be important relevant genetic differences between these indigenous Amerindians and the mostly white MAHI and EISNER Study comparator groups, there are striking differences in diet and lifestyle which play an important role in the deposition of ectopic fat. Also, other Amerindian tribes who live a modern North American lifestyle tend to have particularly high, not low, rates of diabetes and metabolic syndrome [65]. Thus, we posit that the strikingly low rates of measured ectopic fat in the Tsimane and Moseten are primarily related to their healthier lifestyle of diet and physical activity. The Tsimane consume a diet lower in fat than the typical North American diet, with males eating less than half the daily fat intake of U.S. men [30]. More striking is their high level of physical activity and low sedentary time [32]. Prior studies have also shown that the Tsimane have high physical activity levels (PAL). Men display 24-hour PAL of 2.02–2.15 and women 1.73–1.85, both very high by Western standards. They also burn >250 additional calories per day than western populations [32,36,66]. Online supplement Figure 10 illustrates the high level of exercise of the Tsimane compared to the U.S. population. At age 50, the activity level of both men and women approximates the equivalent of 17,500 steps per day [66]. Exercise is frequently prescribed for patients with metabolic syndrome or hepatic steatosis and the near absence of these conditions in the very active Tsimane indirectly support this recommendation and suggests that higher levels of exercise could prevent and/or improve these metabolic dysfunctions [67,68].

4.4. Atherosclerosis in Amerindians

The Tsimane and Moseten also had very low rates of coronary artery calcification [28]. Prior studies have demonstrated a possible causative link between EAT and atherosclerotic CAD [15,24,25,40,69]. Both Tsimane and Moseten also had significantly less hepatic fat (i.e. higher liver density) than the U.S. MAHI comparator group (Table 1 and Fig. 3). As hypothesized, the more acculturated Moseten not only had intermediate levels of EAT compared to the Tsimane and the U.S. group, they also had intermediate levels of CAC and TAC, (Fig. 5, Online supplement Figs. 2–5) lending further strength to the association of EAT fat and atherosclerotic disease.

The genetically and linguistically-related, but more acculturated Moseten lived a lifestyle similar to the Tsimane in prior generations, but in the last several decades roads were built that provided them direct access to larger towns where they could sell their crops and purchase food and supplies. As such, their diet contains more store-bought food, resulting in a decrease in their PAL. The EAT levels in the Moseten are intermediate between those of the Tsimane and the Western comparator population, probably reflecting the more recent change in lifeways. The Moseten TAC and CAC is only modestly higher than that of the Tsimane, consistent with a lag between change in lifestyle and the expression of atherosclerosis. The very low CAC rates in the Tsimane people was previously reported [29], but the rates of TAC in this group and both TAC and CAC in the Moseten are novel. Also, while coronary events have been documented to be low in subsistence populations, to our knowledge, TAC has not been previously reported. Thoracic aortic calcifications are a manifestation of atherosclerosis and correlate with CAD, but may have additional risk factors [70–72]. Our findings demonstrate that the Tsimane and Moseten not only have low rates of CAC, but they also have very low rates of TAC, further suggesting that their life-ways are

additionally protective against non-coronary manifestations of atherosclerosis.

5. What are the implications for clinicians and preventive healthcare workers?

The current study adds to the growing body of data regarding the link between increased ectopic fat and cardiovascular diseases [73]. Recently, numerous studies have demonstrated that epicardial fat deposits and hepatic steatosis are modifiable risk factors and that treatment with glucagon-like peptide-1 (GLP-1) analogs and sodium-glucose cotransporter 2 (SGLT2) inhibitors can be effective treatments. For example, two recent meta-analyses have confirmed that epicardial fat can be substantially reduced with both GLP-1 analogs and SGLT2 inhibitors, although it is not yet clear which class of drugs is more effective [74,75]. Meta-analysis level data also demonstrates that hepatic steatosis and even non-alcoholic steatohepatitis is improved with the use of GLP-1 analogs [76,77]. Given the emergence of drug treatments for ectopic epicardial and hepatic fat and the current epidemic of cardiovascular diseases, earlier use of these drugs in patients with these ectopic fat deposits would seem to be warranted [75]. Also, cardiovascular imaging tests including echocardiography, cardiovascular CT scanning, and cardiac magnetic resonance, can detect increased epicardial fat deposits, but in current clinical practice the finding is not usually reported. Given the accumulating evidence, routine reporting of hepatic steatosis and excess epicardial fat on, for example, screening coronary calcium scoring, is warranted. At one of the authors' medical centers, this is already the case.

6. Limitations

The study has several limitations. While the Tsimane, Moseten, and EISNER samples can be considered population-based, the U.S. comparator population CT scans from MAHI were not strictly obtained in such a manner. However, the MAHI coronary calcium scoring database is very large and prior studies have demonstrated that the CAC scores included in it closely track coronary calcium score by age and sex of established population based studies such as the MESA and Heinz Nixdorf RECALL studies [29,42,78]. Also, while the average age of the US population is slightly lower than the Tsimane (56.7 $\pm$ 10.8 y vs 58.3 $\pm$ 10.5 y) and age is an important cardiovascular risk factor, age is only weakly associated with ectopic fat and left atrial diameter (see Figs. 2,3, and 4) and the differences in ectopic fat deposits are large. Also, pertinently, the Tsimane group was on average older than the US group, which would tend to underestimate rather than overestimation these difference. Thus, we believe that this U.S. sample represents a reasonable estimate of the range of epicardial fat thickness and hepatic density in an industrialized population. Also, we further compared epicardial fat with results of prior published studies and the key findings are concordant.

We would note that this study, apart from atrial fibrillation, does not link imaging findings to clinically relevant hard outcomes. Future research should focus on establishing whether improving ectopic fat helps to prevent symptomatic cardiovascular events.

7. Conclusions We report that the remotely-living, physically active Tsimane and the genetically and ethnolinguistically-related, more acculturated Mosen Amerindians of Bolivia, both of whom have minimal coronary and thoracic aortic atherosclerosis and almost no atrial fibrillation despite large left atrial size and high levels of inflammation, have minimal epicardial adipose tissue. These data suggest an achievable lower limit of human visceral fat, add to the body of evidence linking ectopic fat with cardiovascular disease, and confirm in the negative the strong association between epicardial fat and atrial fibrillation.

Non-standard abbreviations

AU	Agatston Units
CAC	Coronary Artery Calcium
EAT	Epicardial Adipose Tissue
EFT	Epicardial Fat Thickness
EFV	Epicardial Fat Volume
LA	Left Atrial
TAC	Thoracic Aorta Calcium
TFV	Thoracic Fat Volume

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Author agreement

The undersigned declare that this manuscript submission is original, has not been published before, and is not currently being considered for publication elsewhere. We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us. We understand that the Corresponding Author is the sole contact for the Editorial process. He/she is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs Signed by all authors as follows:

CRediT authorship contribution statement

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Christopher Ward: Writing – original draft, Resources, Formal analysis. **Madeleine J. Lee:** Investigation, Data curation. **Ashna Mahadev:** Investigation. **Daniel Eid Rodriguez:** Supervision, Project administration, Investigation. **David E. Michalik:** Writing – review & editing, Investigation. **Chris J. Rowan:** Supervision, Investigation. **Tianyu Cao:** Formal analysis, Data curation. **Jonathan Stieglitz:** Project administration, Funding acquisition. **Cameron M. Quick:** Investigation. **Gregory S. Thomas:** Writing – original draft, Supervision, Conceptualization. **Jagat Narula:** Writing – review & editing, Visualization, Conceptualization. **Damini Dey:** Software, Resources. **Michael Gurven:** Writing – review & editing, Supervision, Resources, Methodology. **Hillard Kaplan:** Writing – review & editing, Supervision, Resources, Project administration, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Dey's employer, Cedars Sinai Medical Center, may receive royalties from GFAT. All of the other authors have no conflicts to declare.

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Supplementary materials

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