American Journal of Preventive Cardiology 23 (2025) 101271

Contents lists available at ScienceDirect

American Journal of Preventive Cardiology

journal homepage: www.journals.elsevier.com/american-journal-of-preventive-cardiology

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

Randall C. Thompson [a,b,*], Benjamin C. Trumble [c,d], Daniel K. Cummings [d,e], Angela D. Neunuebel [a,f], Paul L. Hooper [d,g], Samuel Wann [h], Adel H. Allam [i], Frances Neunuebel [a,j], Benjamin D. Gans [a], Samantha I. King [a,k], Edmond Seabright [d,l], Caleb E. Finch [m], Margaret Gatz [n], Kenneth Buetow [o], Michael I. Miyamoto [p], Guido P. Lombardi [q], M. Linda Sutherland [r], James D. Sutherland [r], Christopher Ward [a], Madeleine J. Lee [a], Ashna Mahadev [a,s], Daniel Eid Rodriguez [b,t], David E. Michalik [u,v], Chris J. Rowan [w], Tianyu Cao [x], Jonathan Stieglitz [y], Cameron M. Quick [a,b], Gregory S. Thomas [r,z], Jagat Narula [aa], Damini Dey [ab], Michael Gurven [x], Hillard Kaplan [d,e]

[a] St Luke's Mid-America Heart Institute of Kansas City, Kansas City, MO, USA
[b] University of Missouri – Kansas City, Kansas City, MO, USA
[c] Arizona State University, School of Human Evolution and Social Change, Center for Evolution and Medicine, Institute of Human Origins, Tempe, AZ, USA
[d] Tsimane Health and Life History Project, San Borja, Bolivia
[e] Economic Science Institute, Chapman University, Orange, CA, USA
[f] Emory University School of Medicine, Atlanta, GA, USA
[g] Department of Anthropology, University of New Mexico, Albuquerque, NM, USA
[h] University of New Mexico School of Medicine, Albuquerque, NM, USA
[i] Department of Cardiology, Al Azhar University, Cairo, Egypt
[j] School of Public Health, Emory University, Atlanta, GA, USA
[k] Department of Medicine, University of Colorado Denver, Denver, CO, USA
[l] School of Collective Intelligence, Université Mohamed VI Polytechnique, Rabat, Morocco
[m] University of Southern California Leonard Davis School of Gerontology, Los Angeles, CA, USA
[n] Center for Economic and Social Research, University of Southern California, Los Angeles, CA, USA
[o] School of Life Sciences, School of Complex Adaptive Systems, Center for Evolution and Medicine, Arizona State University, Tempe, Az, USA
[p] Mission Heritage Medical Group, Providence Health, Mission Viejo, CA, USA
[q] Laboratorio de Paleopatologia, Catedra Pedro Weiss, Universidad Peruana Cayetano Heredia, Lima, Peru
[r] MemorialCare Health System, Fountain Valley, CA, USA
[s] Department of Medicine, Saint Louis University-SSM Health System, St. Louis, MO, USA
[t] Institute of Biomedical Research, Faculty of Medicine, Universidad Mayor de San Simon, Cochabamba, Bolivia
[u] Division of Infectious Diseases, University of California, Irvine School of Medicine, Irvine, CA, USA
[v] MemorialCare Miller Children's & Women's Hospital, Long Beach, CA, USA
[w] University of Nevada, Reno, NV, USA
[x] Department of Anthropology, University of California, Santa Barbara, CA, USA
[y] Toulouse School of Economics, Toulouse, France
[z] Division of Cardiology, University of California, Irvine, CA, USA
[aa] University of Texas Health Houston, Houston, TX, USA
[ab] Cedars Sinai Medical Center, Los Angeles, CA, USA

ARTICLE INFO

Keywords:
Epicardial fat
Atrial fibrillation

ABSTRACT

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

* Corresponding author at: Saint Luke's Cardiovascular Consultants, 4330 Wornall Rd, Suite 2000, Kansas City, MO 64112.
E-mail address: rthompson@saint-lukes.org (R.C. Thompson).

https://doi.org/10.1016/j.ajpc.2025.101271
Received 14 April 2025; Received in revised form 30 July 2025; Accepted 21 August 2025
Available online 22 August 2025
2666-6677/© 2025 Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Hepatic steatosis
Subsistance population

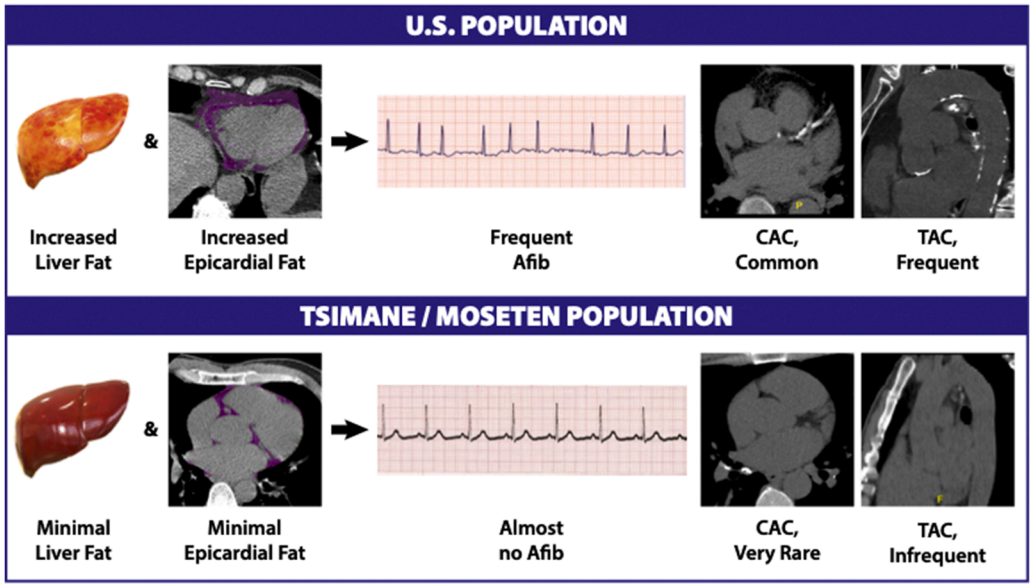
Methods: We performed CT imaging to measure coronary artery and thoracic aortic calcium (CAC, TAC), epicardial fat thickness (EFT), liver density, and left atrial (LA) anteroposterior diameter and, using a deep learning-enabled software program, epicardial and thoracic fat volume (EFV, TFV), in two remote 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 illustraion.

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 syngio.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] 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 ± 9y), 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 EFV ≥113 cm2 and coronary artery calcium ≥ 100 AU and was highest in subjects with both [14].

2.4. Statistical analysis

Mean ± 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 *C*hi-square was used to compare differences of proportions. Age-dependent variables were

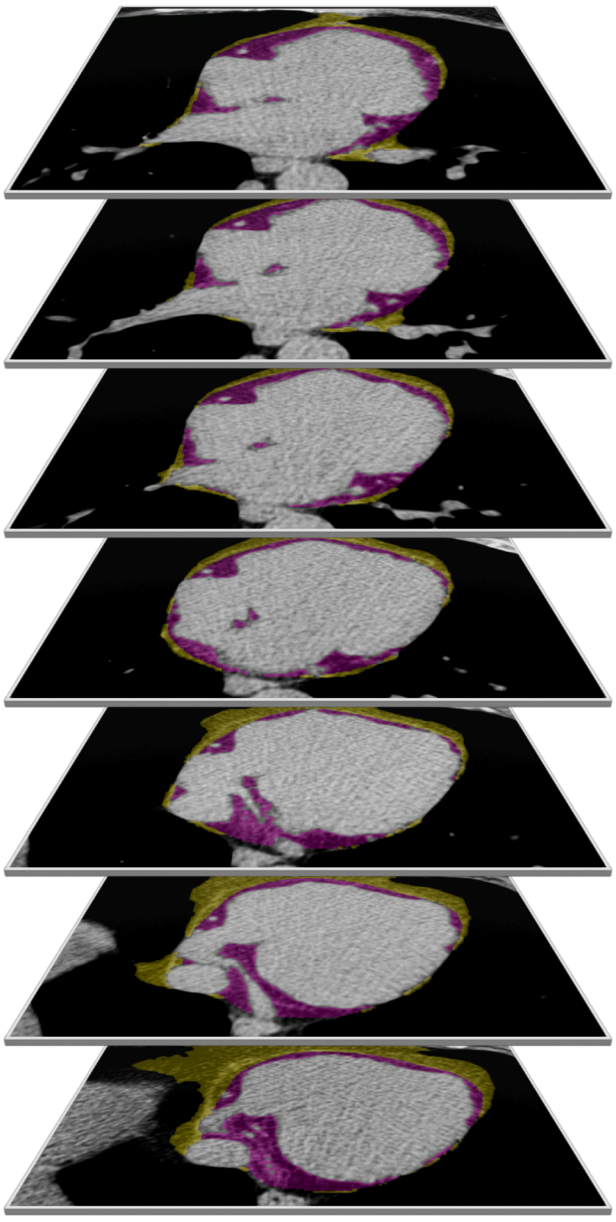


Fig. 1. Axial view CT scans through the heart showing shading of epicardial fat (purple) and thoracic fat (gold) in a United States MAHI comparator subject using the QFAT software program for quantification of epicardial and thoracic fat volume.

plotted using the Loess regression method with 95 % confidence intervals against age. Hazard ratios for a CAC of $\geq$ 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 Moseten (the governmental bodies of the Tsimane and Moseten), 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, Moseten, 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 Moseten (25.5 kg/m) and Tsimane (24 kg/m). Measures of epicardial and thoracic fat volume are lowest in the Tsimane with the more acculturated Moseten intermediate, and the U.S. comparator group the highest, while epicardial fat thickness is similar between Tsimane and Moseten (Table 1, Fig. 2). Hepatic fat deposits are indicated by lower liver density: Tsimane have the highest liver density with the Moseten intermediate, and the U.S. MAHI comparator group the lowest (Fig. 3).

Mean left atrial diameter is largest in the Tsimane with the Moseten 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 Moseten 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 Moseten 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 Moseten, 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 Moseten 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/m^2) has more generalized obesity and greater mean epicardial and thoracic fat volume than the EISNER participants (mean BMI = 26.6 ± 4.9 kg/m^2) 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 cm^3) was even lower than select subgroups such as lean patients from Pakistan who had normal coronary angiograms (mean EFV = 56.6 cm^3) and a select control group of non-obese U.S. women with no CAC and normal EFV (defined as ≤ 95 cm^3; mean EFV = 72 cm^3) [51,52]. Table 2 [14,17,18,22,51–56].

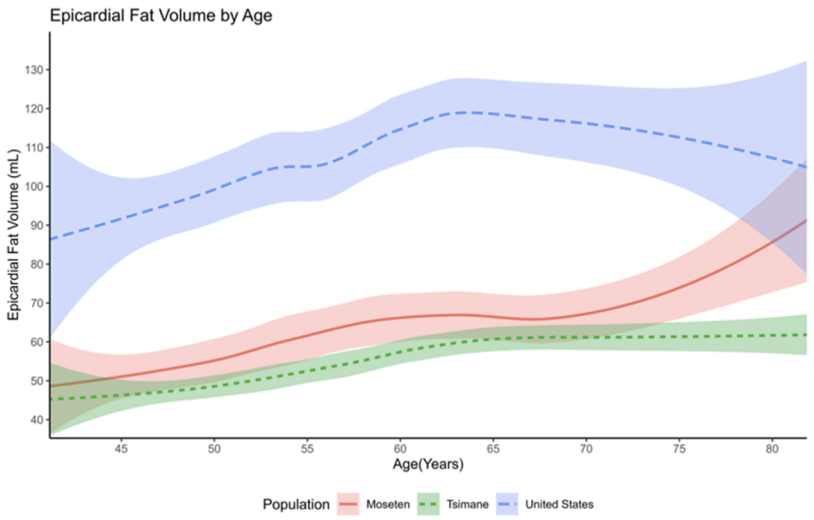


Fig. 2. Epicardial fat volume of the Tsimane, Moseten, and U.S. comparator group by age Loess method, shaded area = 95 % confidence interval).

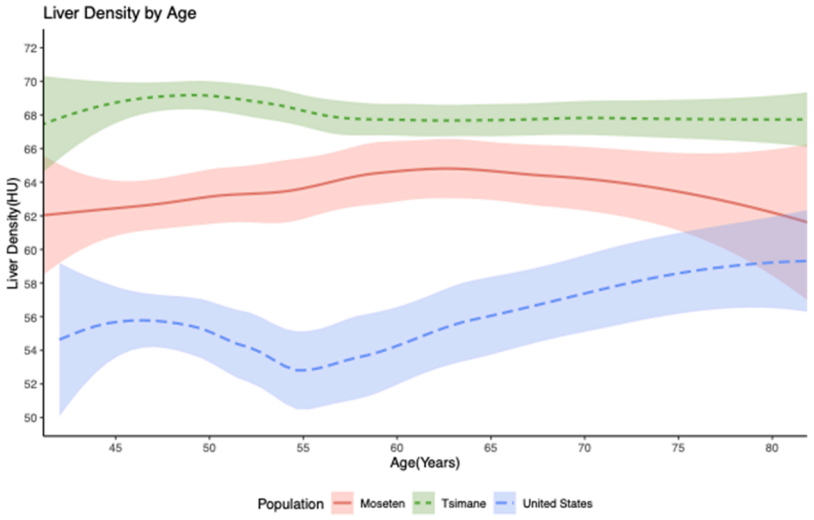


Fig. 3. Hepatic CT scan density Tsimane, Moseten, and the U.S. comparator groups by age (Loess method, shaded area = 95 % confidence interval). The Tsimane and Moseten have less liver fat and therefore greater hepatic density than the U.S. cohort.

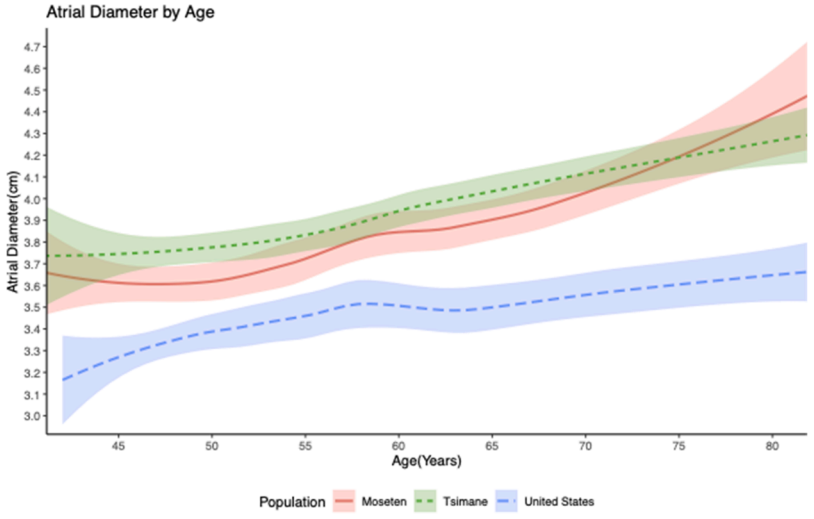


Fig. 4. Left atrial AP diameter of the Tsimane, Moseten, and the U.S. comparator groups by age, (Loess method, shaded area = 95 % confidence interval).

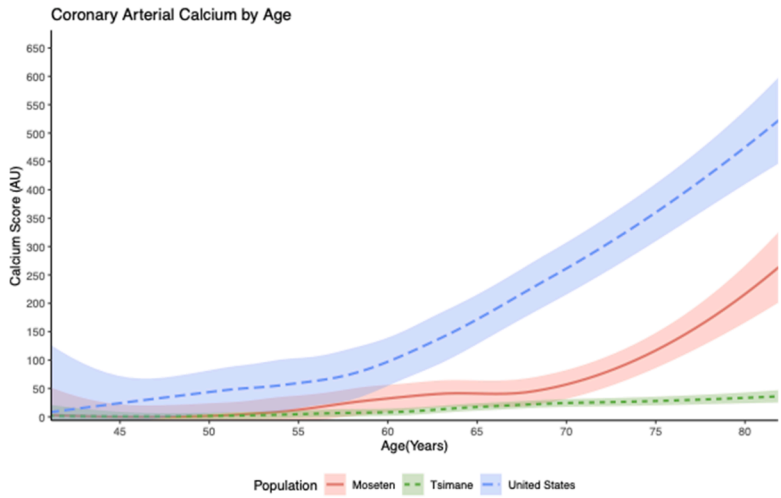


Fig. 5. Mean coronary artery calcium score by age, (Loess method, shaded area = 95 % confidence interval). The Tsimane and Moseten have much less coronary artery calcium than the U.S. comparator group.

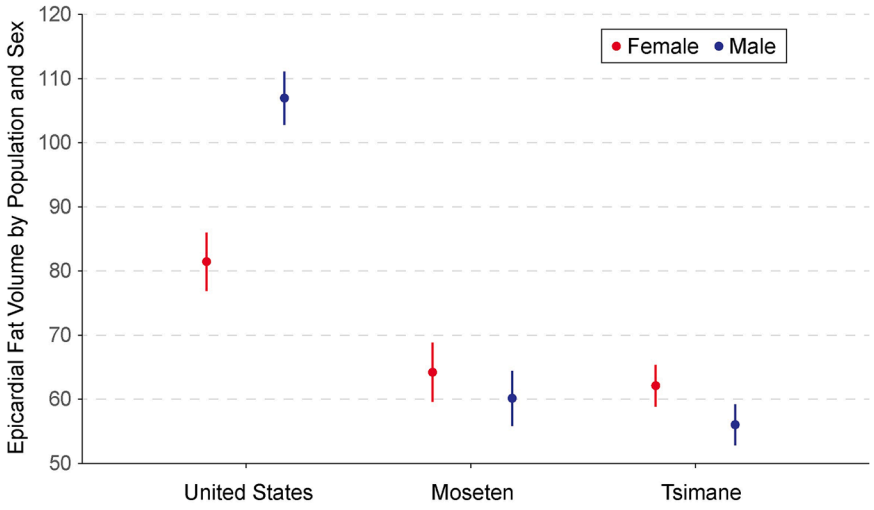


Fig. 6. Comparison of epicardial fat volume for the United States MAHI comparator population, the Moseten, and the Tsimane - expected values for each group corrected for age and BMI. Of note, United States men have greater epicardial fat volume than women, although this is not true for the Tsimane and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

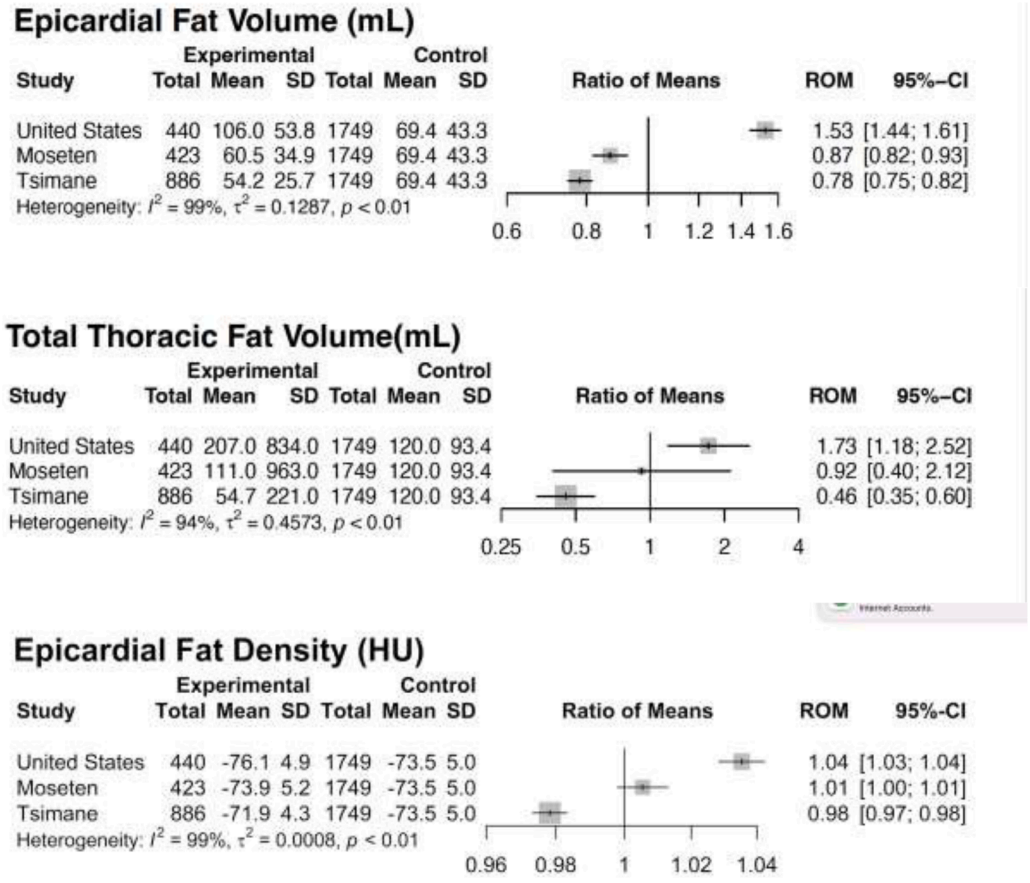


Fig. 7. Comparison of epicardial fat volume, thoracic fat volume, and epicardial fat density, for the U.S. comparator group, the Moseten, and the Tsimane with the published results of the Eisner Study group (Eisenberg citation) using a Ratio of Means approach. 1= the Eisner study mean. The Tsimane and 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 composistion 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/m^2 with an obesity (BMI $\geq$30 kg/m^2) 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 inbitors, 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 overestimatation 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 cardiovascualare events.

7. ConclusionsWe report that the remotely-living, physically active Tsimane and the genetically and ethnolinguistically-related, more acculturated Moseten 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

Source of funding

This study was funded by the National Institute of Health, National Institute on Aging (NIH/NIA) R01-AG054442 and R01-AG024119. J.S. acknowledges IAST funding from the French National Research Agency (ANR) under the Investments for the Future (Investissements d'Avenir) program, grant ANR-17-EURE-0010. Damini Dey is funded by grants from the National Heart, Lung, and Blood Institute (1R01HL148787–01A1 and R01HL151266). The funding organizations played no role in the study design, methods, or analyses.

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

Randall C. Thompson: Writing – original draft, Supervision, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Benjamin C. Trumble:** Writing – review & editing, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Daniel K. Cummings:** Supervision, Project administration, Investigation, Formal analysis, Data curation. **Angela D. Neunuebel:** Investigation, Data curation. **Paul L. Hooper:** Investigation, Data curation. **Samuel Wann:** Writing – review & editing, Investigation, Conceptualization. **Adel H. Allam:** Investigation, Conceptualization. **Frances Neunuebel:** Investigation, Data curation. **Benjamin D. Gans:** Investigation, Data curation. **Samantha I. King:** Investigation, Data curation. **Edmond Seabright:** Investigation, Data curation. **Caleb E. Finch:** Writing – review & editing, Investigation. **Margaret Gatz:** Investigation. **Kenneth Buetow:** Investigation. **Michael I. Miyamoto:** Writing – review & editing, Investigation, Data curation. **Guido P. Lombardi:** Supervision, Resources, Investigation. **M. Linda Sutherland:** Writing – review & editing, Methodology, Investigation. **James D. Sutherland:** Methodology, Investigation. **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.

Acknowledgements

We thank the HORUS and THLHP teams and our collaborators at the Hospital Presidente German Busch of Trinidad, Bolivia, including Edila Arteaga and Editha Alpire.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ajpc.2025.101271.

References

[1] Suganami T, Nishida J, Ogawa Y. A paracrine loop between adipocytes and macrophages aggravates inflammatory changes: role of free fatty acids and tumor necrosis factor alpha. Arter Thromb Vasc Biol Oct 2005;25(10):2062–8.
[2] Zhou M, Wang H, Chen J, Zhao L. Epicardial adipose tissue and atrial fibrillation: possible mechanisms, potential therapies, and future directions. Pacing Clin Electrophysiol Jan 2020;43(1):133–45.
[3] Wong CX, Ganesan AN, Selvanayagam JB. Epicardial fat and atrial fibrillation: current evidence, potential mechanisms, clinical implications, and future directions. Eur Heart J 2017 May 1;38(17):1294–302.
[4] Heckbert SR, Wiggins KL, Blackshear C, Yang Y, Ding J, Liu J, et al. Pericardial fat volume and incident atrial fibrillation in the multi-ethnic study of atherosclerosis and Jackson heart study. Obes (Silver Spring) Jun 2017;25(6):1115–21.
[5] Gaeta M, Bandera F, Tassinari F, Capasso L, Cargnelutti M, Pelissero G, et al. Is epicardial fat depot associated with atrial fibrillation? A systematic review and meta-analysis. Europace 2017 May 1;19(5):747–52.
[6] Blum S, Meyre P, Aeschbacher S, Berger S, Auberson C, Briel M, et al. Incidence and predictors of atrial fibrillation progression: a systematic review and meta-analysis. Heart Rhythm Apr 2019;16(4):502–10.
[7] Batal O, Schoenhagen P, Shao M, Ayyad AE, Van Wagoner DR, Halliburton SS, et al. Left atrial epicardial adiposity and atrial fibrillation. Circ Arrhythm Electrophysiol Jun 2010;3(3):230–6.
[8] Dereli S, Bayramoğlu A, Yontar OC, Cerşit S, Gürsoy MO. Epicardial fat thickness: a new predictor of successful electrical cardioversion and atrial fibrillation recurrence. Echocardiography Dec 2018;35(12):1926–31.
[9] Sepehri Shamloo A, Dagres N, Dinov B, Sommer P, Husser-Bollmann D, Bollmann A, et al. Is epicardial fat tissue associated with atrial fibrillation recurrence after ablation? A systematic review and meta-analysis. Int J Cardiol Heart Vasc Mar 2019;22:132–8.
[10] Ju Y, Wang M, Ji Y, Wang Z, Wang W, Liu F, et al. The influence of epicardial adipose tissue on the prognosis of atrial fibrillation patients undergoing radiofrequency ablation combined with left atrial appendage occlusion. Sci Rep 2024 Nov 15;14(1):28164.
[11] Rosa MI, Grande AJ, Lima LD, Dondossola ER, Uggioni MLR, Hernandez AV, et al. Association between epicardial adipose tissue and stroke. Front Cardiovasc Med 2021;8:658445.
[12] Ciuffo L, Nguyen H, Marques MD, Aronis KN, Sivasambu B, de Vasconcelos HD, et al. Periatrial fat quality predicts atrial fibrillation ablation outcome. Circ Cardiovasc Imaging Jun 2019;12(6):e008764.

[13] Van Wagoner DR. Paracrine signals modulate atrial epicardial progenitor cells and development of subepicardial adiposity and fibrosis implications for atrial fibrillation. Circ Res 2020 May 8;126(10):1343–5.
[14] Eisenberg E, McElhinney PA, Commandeur F, Chen X, Cadet S, Goeller M, et al. Deep learning-based quantification of epicardial adipose tissue volume and attenuation predicts major adverse cardiovascular events in asymptomatic subjects. Circ Cardiovasc Imaging Feb 2020;13(2):e009829.
[15] Patil HR, Patil NT, King SI, O'Keefe E, Chhabra R, Ansari S, et al. Increased intrathoracic and hepatic visceral adipose tissue independently correlates with coronary artery calcification in asymptomatic patients. J Nucl Cardiol Oct 2014;21(5):880–9.
[16] Zhou J, Chen Y, Zhang Y, Wang H, Tan Y, Liu Y, et al. Epicardial fat volume improves the prediction of obstructive coronary artery disease above traditional risk factors and coronary calcium score. Circ Cardiovasc Imaging Jan 2019;12(1):e008002.
[17] Arshi B, Aliahmad HA, Ikram MA, Bos D, Kavousi M. Epicardial fat volume, cardiac function, and incident heart failure: the Rotterdam study. J Am Heart Assoc 2023 Jan 3;12(1):e026197.
[18] Cosson E, Nguyen MT, Rezgani I, Tatulashvili S, Sal M, Berkane N, et al. Epicardial adipose tissue volume and coronary calcification among people living with diabetes: a cross-sectional study. Cardiovasc Diabetol 2021 Feb 5;20(1):35.
[19] Ritvo PG, Charpentier E, Zeitouni M, Rahoual G, Boussouar S, Croisille C, et al. Epicardial adipose tissue from computed tomography: a missing link in premature coronary artery disease? Eur Heart J Cardiovasc Imaging 2025 Jan 7:jeae335.
[20] Filtz A, Lorenzatti D, Scotti A, Piña P, Fernandez-Hazim C, Huang D, et al. Relationship between epicardial adipose tissue and coronary atherosclerosis by CCTA in young adults (18-45). Am J Prev Cardiol Sep 2024;19:100711.
[21] Atakan A, Macunluoglu B, Kaya Y, Ari E, Demir H, Asicioglu E, et al. Epicardial fat thickness is associated with impaired coronary flow reserve in hemodialysis patients. Hemodial Int Jan 2014;18(1):62–9.
[22] Schlett CL, Ferencik M, Kriegel MF, Bamberg F, Ghoshhajra BB, Joshi SB, et al. Association of pericardial fat and coronary high-risk lesions as determined by cardiac CT. Atherosclerosis May 2012;222(1):129–34.
[23] Yu W, Chen Y, Zhang F, Liu B, Wang J, Shao X, et al. Association of epicardial adipose tissue volume with increased risk of hemodynamically significant coronary artery disease. Quant Imaging Med Surg 2023 Apr 1;13(4):2582–93.
[24] Chhabra R, O'Keefe JH, Patil H, O'Keefe E, Thompson RC, Ansari S, et al. Association of coronary artery calcification with hepatic steatosis in asymptomatic individuals. Mayo Clin Proc Nov 2013;88(11):1259–65.
[25] Stahl EP, Dhindsa DS, Lee SK, Sandesara PB, Chalasani NP, Sperling LS. Nonalcoholic fatty liver disease and the heart: JACC state-of-the-art review. J Am Coll Cardiol 2019 Mar 5;73(8):948–63.
[26] Hideo-Kajita A, Garcia-Garcia HM, Wopperer SB, Freire AFD, Ozaki Y, Cavalcante R, et al. Correlation between computed tomography adapted leaman score and computed tomography liver and spleen attenuation parameters for non-alcoholic fatty liver disease as well as respective inflammatory mediators. Int J Cardiovasc Imaging Dec 2020;36(12):2383–91.
[27] Yudkin JS, Stehouwer CD, Emeis JJ, Coppack SW. C-reactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction: a potential role for cytokines originating from adipose tissue? Arter Thromb Vasc Biol Apr 1999;19(4):972–8.
[28] Rowan CJ, Eskander MA, Seabright E, Rodriguez DE, Linares EC, Gutierrez RQ, et al. Very low prevalence and incidence of atrial fibrillation among Bolivian forager-farmers. Ann Glob Health 2021 Feb 16;87(1):18.
[29] Kaplan H, Thompson RC, Trumble BC, Wann LS, Allam AH, Beheim B, et al. Coronary atherosclerosis in indigenous South American Tsimane: a cross-sectional cohort study. Lancet 2017 Apr 29;389(10080):1730–9.
[30] Kraft TS, Stieglitz J, Trumble BC, Martin M, Kaplan H, Gurven M. Nutrition transition in 2 lowland Bolivian subsistence populations. Am J Clin Nutr 2018 Dec 1;108(6):1183–95.
[31] Lea AJ, Garcia A, Arevalo J, Ayroles JF, Buetow K, Cole SW, et al. Natural selection of immune and metabolic genes associated with health in two lowland Bolivian populations. Proc Natl Acad Sci U S A 2023 Jan 3;120(1):e2207544120.
[32] Gurven M, Jaeggi AV, Kaplan H, Cummings D. Physical activity and modernization among Bolivian Amerindians. PLoS One 2013;8(1):e55679.
[33] Dinkel KA, Costa ME, Kraft TS, Stieglitz J, Cummings DK, Gurven M, et al. Relationship of sanitation, water boiling, and mosquito nets to health biomarkers in a rural subsistence population. Am J Hum Biol Jan 2020;32(1):e23356.
[34] Vasunilashorn S, Crimmins EM, Kim JK, Winking J, Gurven M, Kaplan H, et al. Blood lipids, infection, and inflammatory markers in the Tsimane of Bolivia. Am J Hum Biol Dec 2010;22(6):731–40.
[35] Gurven M, Blackwell AD, Rodríguez DE, Stieglitz J, Kaplan H. Does blood pressure inevitably rise with age?: longitudinal evidence among forager-horticulturalists. Hypertension Jul 2012;60(1):25–33.
[36] Gurven MD, Trumble BC, Stieglitz J, Yetish G, Cummings D, Blackwell AD, et al. High resting metabolic rate among Amazonian forager-horticulturalists experiencing high pathogen burden. Am J Phys Anthr Nov 2016;161(3):414–25.
[37] Cummings DK. Aging and Gender in the Tsimane: Differences in Energy Expenditure, Physical Activity, and Horticultural Work [PhD Thesis]. 2021.
[38] Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol 1990 Mar 15;15(4):827–32.
[39] Budoff MJ, Takasu J, Katz R, Mao S, Shavelle DM, O'Brien KD, et al. Reproducibility of CT measurements of aortic valve calcification, mitral annulus calcification, and aortic wall calcification in the multi-ethnic study of atherosclerosis. Acad Radiol Feb 2006;13(2):166–72.
[40] Alam MS, Green R, de Kemp R, Beanlands RS, Chow BJW. Epicardial adipose tissue thickness as a predictor of impaired microvascular function in patients with non-obstructive coronary artery disease. J Nucl Cardiol Oct 2013;20(5):804–12.
[41] Commandeur F, Goeller M, Razipour A, Cadet S, Hell MM, Kwiecinski J, et al. Fully automated CT quantification of epicardial adipose tissue by deep learning: a multicenter study. Radiol Artif Intell 2019 Nov 27;1(6):e190045.
[42] Schmermund A, Möhlenkamp S, Stang A, Grönemeyer D, Seibel R, Hirche H, et al. Assessment of clinically silent atherosclerotic disease and established and novel risk factors for predicting myocardial infarction and cardiac death in healthy middle-aged subjects: rationale and design of the Heinz Nixdorf RECALL study. Risk factors, evaluation of coronary calcium and lifestyle. Am Heart J Aug 2002;144(2):212–8.
[43] Bild DE, Detrano R, Peterson D, Guerci A, Liu K, Shahar E, et al. Ethnic differences in coronary calcification: the multi-ethnic study of atherosclerosis (MESA). Circulation 2005 Mar 15;111(10):1313–20.
[44] R Studio Team. RStudio: integrated development environment for r [internet]. [Internet]. 2020. Boston, MAAvailable from, http://www.rstudio.com/.
[45] Aragon TJ, Fay MP, Wollschlaeger D, Omidpanag A. Package "epitools" [internet]. https://cran.r-project.org/web/packages/epitools/epitools.pdf; 2017.
[46] Auguie B. _gridExtra: miscellaneous functions for "Grid" Graphics_. R package [internet]. Available from: https://CRAN.R-project.org/package=gridExtra; 2020.
[47] Lumley T. Package "rmeta" [internet]. Available from, https://cran.r-project.org/web/packages/rmeta/rmeta.pdf; 2022.
[48] Wickham H. ggplot2: ggplot2. WIREs Comp Stat Mar 2011;3(2):180–5.
[49] Xu C, Wang D. Correlation between obesity and epicardial fat volume in patients with coronary artery disease: from the alternative cardiovascular bio-imaging markers registry. Kardiologiia 2025 Jan 31;65(1):34–40.
[50] Mancio J, Pinheiro M, Ferreira W, Carvalho M, Barros A, Ferreira N, et al. Gender differences in the association of epicardial adipose tissue and coronary artery calcification: EPICHEART study: EAT and coronary calcification by gender. Int J Cardiol 2017 Dec 15;249:419–25.
[51] Subhan S, Sami A, Akhtar W, Jan MU, Ullah A, Malik J. Association of epicardial fat volume with coronary artery ectasia and coronary artery disease. Angiology Jul 2023;74(6):563–8.
[52] El Shahawy M, Tucker S, Izadi L, Sabatini A, Mohan S. Excess epicardial fat volume in women is a novel risk marker for microvascular dysfunction, which may be a contributing factor in the atypical chest pain syndrome. Egypt Heart J 2021 Apr 13;73(1):37.
[53] Yu W, Zhang F, Liu B, Wang J, Shao X, Yang MF, et al. Incremental value of epicardial fat volume to coronary artery calcium score and traditional risk factors for predicting myocardial ischemia in patients with suspected coronary artery disease. J Nucl Cardiol Aug 2022;29(4):1583–92.
[54] Roest S, Budde RPJ, Brugts JJ, von der Thüsen J, van Walsum T, Taverne YJHJ, et al. Epicardial fat volume is related to the degree of cardiac allograft vasculopathy. Eur Radiol Jan 2023;33(1):330–8.
[55] Weferling M, Rolf A, Fischer-Rasokat U, Liebetrau C, Renker M, Choi YH, et al. Epicardial fat volume is associated with preexisting atrioventricular conduction abnormalities and increased pacemaker implantation rate in patients undergoing transcatheter aortic valve implantation. Int J Cardiovasc Imaging 2021 Dec 26.
[56] Kim D, Yu HT, Kwon OS, Kim TH, Uhm JS, Joung B, et al. Effect of epicardial fat volume on outcomes after left atrial posterior wall isolation in addition to pulmonary vein isolation in patients with persistent atrial fibrillation. Front Cardiovasc Med 2022 Oct 26;9:1005760.
[57] Noubiap JJ, Tang JJ, Teraoka JT, Dewland TA, Marcus GM. Minimum national prevalence of diagnosed atrial fibrillation inferred from California acute care facilities. J Am Coll Cardiol 2024 Oct 15;84(16):1501–8.
[58] Wong CX, Sun MT, Odutayo A, Emdin CA, Mahajan R, Lau DH, et al. Associations of epicardial, abdominal, and overall adiposity with atrial fibrillation. Circ Arrhythm Electrophysiol Dec 2016;9(12):e004378.
[59] D'Anna L, Prandin G, Valente M, Zhang L, Malhotra P, Sacco S, et al. C-reactive protein elevation and subsequent atrial fibrillation detection after ischemic stroke treated with mechanical thrombectomy: an inverse probability weighting analysis. Int J Stroke 2025 Mar 28:17474930251332489.
[60] Luo Y, Yang L, Cheng X, Bai Y, Xiao Z. The association between blood count based inflammatory markers and the risk of atrial fibrillation heart failure and cardiovascular mortality. Sci Rep 2025 Mar 24;15(1):10056.
[61] Zhang Z, Li S, Tu T, Liu C, Dai Y, Wang C, et al. Non-linear relationship and predictive value of systemic immune-inflammation index for atrial fibrillation recurrence after catheter ablation in hypertensive patients. Heart Rhythm 2025 Mar 17. S1547-5271(25)02195-2.
[62] Kaplan H, Hooper PL, Gatz M, Mack WJ, Law EM, Chui HC, et al. Brain volume, energy balance, and cardiovascular health in two nonindustrial South American populations. Proc Natl Acad Sci U S A 2023 Mar 28;120(13):e2205448120.
[63] Trumble BC, Negrey J, Koebele SV, Thompson RC, Samuel Wann L, Allam AH, et al. Testosterone is positively associated with coronary artery calcium in a low cardiovascular disease risk population. Evol Med Public Health 2023;11(1):472–84.
[64] Gurven M, Kaplan H, Winking J, Eid Rodriguez D, Vasunilashorn S, Kim JK, et al. Inflammation and infection do not promote arterial aging and cardiovascular disease risk factors among lean horticulturalists. PLoS One 2009 Aug 11;4(8):e6590.
[65] Kaler SN, Ralph-Campbell K, Pohar S, King M, Laboucan CR, Toth EL. High rates of the metabolic syndrome in a first nations community in western Canada: prevalence and determinants in adults and children. Int J Circumpolar Health Dec 2006;65(5):389–402.

[66] Trumble BC, Pontzer H, Stieglitz J, Cummings DK, Wood B, Emery Thompson M, et al. Energetic costs of testosterone in two subsistence populations. Am J Hum Biol Nov 2023;35(11):e23949.
[67] Wan T, Hong KD, Lu SY. Exercise prescription intervention rehabilitation suggestions for fatty liver patients. Evid Based Complement Altern Med 2022;2022: 2506327.
[68] Colonetti T, Grande AJ, Amaral MC, Colonetti L, Uggioni ML, da Rosa MI, et al. Effect of exercise on epicardial adipose tissue in adults: a systematic review and meta-analyses. Heart Fail Rev Nov 2021;26(6):1399–411.
[69] Lu H, Liu H, Hu F, Zou L, Luo S, Sun L. Independent association between nonalcoholic fatty liver disease and cardiovascular disease: a systematic review and meta-analysis. Int J Endocrinol 2013;2013:124958.
[70] Takasu J, Katz R, Nasir K, Carr JJ, Wong N, Detrano R, et al. Relationships of thoracic aortic wall calcification to cardiovascular risk factors: the multi-ethnic study of atherosclerosis (MESA). Am Heart J Apr 2008;155(4):765–71.
[71] Hermann DM, Lehmann N, Gronewold J, Bauer M, Mahabadi AA, Weimar C, et al. Thoracic aortic calcification is associated with incident stroke in the general population in addition to established risk factors. Eur Heart J Cardiovasc Imaging Jun 2015;16(6):684–90.
[72] Desai MY, Cremer PC, Schoenhagen P. Thoracic aortic calcification: diagnostic, prognostic, and management considerations. JACC Cardiovasc Imaging Jul 2018; 11(7):1012–26.
[73] Chong B, Jayabaskaran J, Ruban J, Goh R, Chin YH, Kong G, et al. Epicardial adipose tissue assessed by computed tomography and echocardiography are associated with adverse cardiovascular outcomes: a systematic review and meta-analysis. Circ Cardiovasc Imaging May 2023;16(5):e015159.
[74] Myasoedova VA, Parisi V, Moschetta D, Valerio V, Conte M, Massaiu I, et al. Efficacy of cardiometabolic drugs in reduction of epicardial adipose tissue: a systematic review and meta-analysis. Cardiovasc Diabetol 2023 Jan 31;22(1):23.
[75] Bao Y, Hu Y, Shi M, Zhao Z. SGLT2 inhibitors reduce epicardial adipose tissue more than GLP-1 agonists or exercise interventions in patients with type 2 diabetes mellitus and/or obesity: a systematic review and network meta-analysis. Diabetes Obes Metab Mar 2025;27(3):1096–112.
[76] Potter KJ, Phinney J, Kulai T, Munro V. Effects of GLP-1 receptor agonist therapy on resolution of steatohepatitis in non-alcoholic fatty liver disease: a systematic review and meta-analysis. J Can Assoc Gastroenterol Apr 2025;8(2):47–57.
[77] Ghosal S, Datta D, Sinha B. A meta-analysis of the effects of glucagon-like-peptide 1 receptor agonist (GLP1-RA) in nonalcoholic fatty liver disease (NAFLD) with type 2 diabetes (T2D). Sci Rep 2021 Nov 11;11(1):22063.
[78] Budoff MJ, Young R, Lopez VA, Kronmal RA, Nasir K, Blumenthal RS, et al. Progression of coronary calcium and incident coronary heart disease events: MESA (multi-ethnic study of atherosclerosis). J Am Coll Cardiol 2013 Mar 26;61(12): 1231–9.