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Correlation between Obesity and Epicardial Fat Volume in Patients With Coronary Artery Disease: From the Alternative Cardiovascular Bio-Imaging Markers Registry

Background	The primary objective was to investigate the relationship between and obesity and epicardial fat volume (EFV) in individuals diagnosed with coronary artery disease (CAD), with the aim of determining whether a consistent linear relationship exists among these factors.
Material and methods	This cross-sectional study involved a total of 510 participants. To explore the relationship between EFV and obesity in CAD patients, we controlled for potential confounding variables, including age, sex, diabetes mellitus, smoking history, arterial hypertension, hypercholesterolemia, hypertriglyceridemia, statin use, vasculopathy, and prior acute myocardial infarction.
Results	After adjusting for confounding factors, a non-linear relationship was observed between obesity and EFV, with an inflection point identified at 200 ml. The effect sizes and their respective confidence intervals were 1.02 (CI: 1.02–1.03) and 0.99 (CI: 0.98–1.00) on either side of this inflection point. Below a EFV of 200 ml, a positive correlation between obesity and EFV was apparent.
Conclusion	The relationship between obesity and EFV in CAD patients is non-linear, and this should be considered when developing prognostic models for CAD. The findings suggest that the relationship between EFV and obesity is more complex than previously thought and warrants further investigation to better understand its implications for both CAD and obesity risk assessment and management.

Keywords	Epicardial fat volume; obesity; coronary artery disease
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Introduction

Coronary artery disease (CAD) and its associated complications are major factors in human mortality. Globally, approximately 20% of deaths are attributed to CAD-related illnesses each year. Epicardial adipose tissue (EAT) refers to the fat tissue located between the myocardium and the outer layer of the heart, representing approximately 80% of typical heart tissue [1]. This tissue is largely found in the grooves between the ventricles and atria and is mainly made up of adipocytes, alongside with a notable amount of nerve cells that are involved in regulating cardiac function and with immune cells that contribute to immune modulation [2]. EAT acts as an endocrine organ with vital functions, sharing both the blood supply and drainage pathways with the heart, without a fascial barrier separating it from the coronary vessels and the myocardium. EAT releases inflammatory mediators through paracrine mechanisms or into the bloodstream, thus affecting the coronary vessels and contributing to the development of CAD.

Under normal physiological conditions, EAT aids in cardiac energy metabolism, immune modulation, and provides physical support to coronary blood vessels. In contrast, during pathological states, EAT augments inflammatory responses, oxidative damage, and fibrosis. The development of CAD is affected by many factors, with inflammation identified as a crucial element in the atherosclerosis process. While the ways in which EAT interacts with coronary atherosclerosis are intricate, inflammation continues to be a key feature of EAT in individuals suffering from CAD. In patients with CAD, EAT shows reduced concentrations of adiponectin and increased concentrations of leptin, which exacerbates inflammation and oxidative stress, thus speeding up the atherosclerosis process. Studies have shown that the inflammatory profile of EAT is evident in CAD patients, regardless of the concentrations of plasma inflammatory biomarkers [3].

Both obesity and the volume of epicardial fat (EFV) are significant risk factors for the onset of CAD [4–9].

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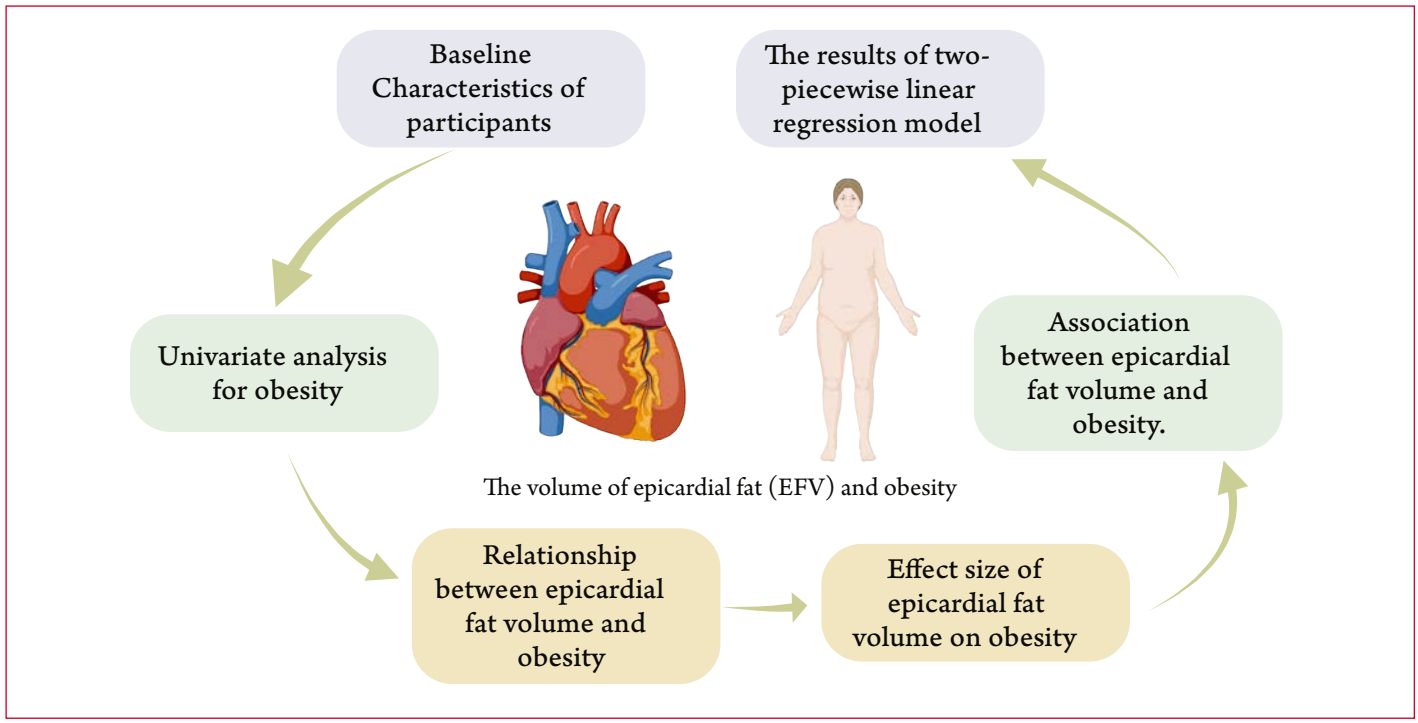
Central illustration. Correlation between Obesity and Epicardial Fat Volume in Patients with Coronary Artery Disease: From the Alternative Cardiovascular Bio-Imaging Markers Registry



EFV reflects the accumulation of visceral fat, and EFV also the cardiovascular problems associated with obesity [10–13], and EAT can be evaluated by conventional imaging techniques [14, 15]. Although there has been a growing focus on EFV for risk evaluation, research examining the connection between obesity and EFV remains sparse. As a result, this study investigated whether an increase in EFV, as associated with obesity, is related to the presence of CAD in patients who show symptoms that could suggest underlying cardiovascular disease (CVD).

Material and methods

Data source

This post-hoc analysis employed data from the Italian ALTER-BIO (Alternative Cardiovascular Bio-Imaging markers) registry, which included 1379 patients who underwent semi-automatically quantified cardiac CT angiography [16]. Clinical variables were evaluated between diabetic and nondiabetic patients to identify potential differences in EFV and adipose CT density.

The Institutional Review Board of the University Hospital of Parma approved the study. All patients had provided written informed consent before data collection, and due to the retrospective nature of the study, the need for further informed consent was waived.

Study population

The primary results and methodologies of the ALTER-BIO study have been previously detailed [16, 17]. The ALTER-BIO is a registry conducted in a hospital setting, which includes patients referred to the Radiology Department at the University Hospital of Parma for cardiac computed tomography angiography (CCTA) from October 2006 to November 2010, due to suspected obstructive cardiovascular disease. This suspicion was based on clinical indicators (symptoms such as typical and atypical chest pain, fatigue, palpitations, arrhythmias, syncope, and neurological symptoms like transient ischemic attacks) and instrumental findings [17]. Body mass index (BMI) was used as an index of obesity, and individuals with a body mass index (\BMI of 30 kg/m^2 or greater were classified as obese [18]. For the assessment of EFV, specialized quantitative software from Siemens Healthineers was utilized, with the detailed methodology described earlier. The evaluation of CAD was performed using multiplanar CT reconstructions, and all coronary segments were examined according to the classification established by the American Heart Association [19].

Statistical analysis

Normally distributed, continuous variables are reported as mean ± standard deviation (SD), and those with a skewed distribution are reported as as median with quartiles. Categorical variables are reported as frequencies or percentages. To assess statistical differences among the means and proportions of the groups, one-way ANOVA (for normal distribution), Kruskal-Wallis H test (for skewed distribution), or chi-square tests (for categorical variables) were applied. A univariate linear regression model was employed to examine the relationships between epicardial

fat volume and obesity. The results from both non-adjusted and multivariate adjusted models are included.

In accordance with the STROBE statement, we have presented findings from unadjusted analyses, minimally adjusted analyses, and those from fully adjusted analyses. The decision to adjust for covariates was guided by the principle that their inclusion altered the matched odds ratio by at least 10% [20]. Furthermore, we utilized a generalized additive model (GAM) to explore any potential non-linear relationship. If a non-linear correlation was detected, a two-piecewise linear regression model was applied to estimate the threshold effect of the odds ratio on obesity, utilizing the smoothed plot. When a clear relationship between obesity and the odds ratio emerged from the smoothed curve, a recursive method was employed to automatically determine the inflection point, which corresponded to the maximum model likelihood [21]. Subgroup analyses were conducted through stratified linear regression models, and the modification and interaction within the sub-performed group were assessed using the likelihood ratio test.

All analyses were performed using the statistical software packages R (http://www.R-project.org, The R Foundation, Version 4.2.0) and EmpowerStats (http://www.empowerstats.com, X&Y Solutions, Inc., Boston, MA). A p-value of less than 0.05 (two-sided) was deemed statistically significant.

Table 1. Baseline characteristics of the patients

Characteristic	No-Obesity	Obesity	p-value
Number of participants	398	112	-
EFV (ml)	100.0 ± 52.5	145.1 ± 61.9	<0.001
Age (yrs)	65.2 ± 11.6	64.8 ± 9.6	0.755
Gender			0.733
Male	303 (76.1)	87 (77.7)	-
Female	95 (23.9)	25 (22.3)	-
Diabetes mellitus			0.011
No	319 (80.2)	77 (68.8)	-
Yes	79 (19.8)	35 (31.2)	-
Smoking history recoded			0.760
No	246 (61.8)	71 (63.4)	-
Yes	152 (38.2)	41 (36.6)	-
Arterial hypertension			0.002
No	88 (22.1)	10 (8.9)	
Yes	310 (77.9)	102 (91.1)	
Hypercholesterolemia			0.045
No	124 (31.2)	24 (21.4)	-
Yes	274 (68.8)	88 (78.6)	-
Hypertriglyceridemia			0.394
No	340 (85.4)	92 (82.1)	-
Yes	58 (14.6)	20 (17.9)	-
Statins			0.154
No	161 (44.0)	52 (52.0)	-
Yes	205 (56.0)	48 (48.0)	-
Vasculopathy			0.518
No	301 (75.6)	88 (78.6)	-
Yes	97 (24.4)	24 (21.4)	-
Previous AMI			0.861
No	263 (66.1)	75 (67.0)	-
Yes	135 (33.9)	37 (33.0)	-

Data are mean ± SD or number (percentage).
AMI, acute myocardial infarction.

Table 2. Univariate analysis for obesity

Covariate	Statistical Data	OR (95% CI)	p-value
Age (yrs)	65.1 ± 11.15	1.00 (0.98, 1.02)	0.754
Gender			
Male	390 (76.47)	Reference	-
Female	120 (23.53)	0.92 (0.56, 1.51)	0.733
Diabetes mellitus			
No	396 (77.65)	Reference	-
Yes	114 (22.35)	1.84 (1.15, 2.93)	0.0112
Smoking history			
No	317 (62.16)	Reference	-
Yes	193 (37.84)	0.93 (0.61, 1.44)	0.7602
Arterial hypertension			
No	98 (19.22)	Reference	-
Yes	412 (80.78)	2.90 (1.45, 5.78)	0.0026
Hypercholesterolemia			
No	148 (29.02)	Reference	-
Yes	362 (70.98)	1.66 (1.01, 2.73)	0.0466
Hypertriglyceridemia			
No	432 (84.71)	Reference	-
Yes	78 (15.29)	1.27 (0.73, 2.23)	0.3944
Statins			
No	213 (45.71)	Reference	-
Yes	253 (54.29)	0.72 (0.47, 1.13)	0.155
Vasculopathy			
No	389 (76.27)	Reference	-
Yes	121 (23.73)	0.85 (0.51, 1.40)	0.518
Previous AMI			
No	338 (66.27)	Reference	-
Yes	172 (33.73)	0.96 (0.62, 1.50)	0.8613

Statistical data are mean ± SD or number (percentage). AMI, acute myocardial infarction; CI, confidence interval; OR, odds ratio.

Results

Baseline characteristics of participants

A total of 510 patients with coronary artery disease (390 men and 120 women) were collected from the ALTER-BIO registry, with an average participant age of 65.1±11.2 yrs. Among these patients, 398 (78.0%) were classified as non-obese, while 112 (22.0%) were identified as obese. The baseline characteristics can be found in Table 1. No statistically significant differences were observed between the groups for age, gender, recorded smoking history, hypertriglyceridemia, use of statins, presence

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of vasculopathy, or history of previous acute myocardial infarction (AMI). In contrast to the non-obese group, obese patients exhibited significantly greater epicardial fat volume, prevalence of diabetes mellitus, arterial hypertension, and hypercholesterolemia.

Univariate analysis

Table 2 presents the results of the univariate analysis. The findings indicated a positive correlation between obesity and epicardial fat volume, diabetes mellitus, arterial hypertension, and hypercholesterolemia. In contrast, age, gender, recorded smoking history, hypertriglyceridemia, statin use, vasculopathy, and previous AMI did not demonstrate an association with obesity.

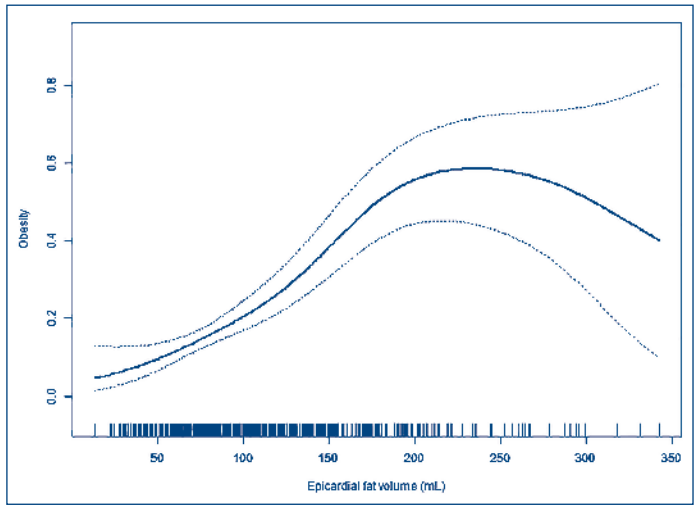
The relationship between epicardial fat volume and obesity

Univariate linear regression models were utilized to assess the relationships between epicardial fat volume and obesity. Additionally, both the non-adjusted and adjusted models are presented in Table 3. In the crude model, a correlation was found between epicardial fat volume and obesity (OR = 1.01, 95% CI: 1.00 to 1.02, p < 0.0001). In the minimally adjusted model, which accounted for age and gender, the effect size indicated a strong correlation (OR = 1.02, 95% CI: 1.01 to 1.02, p<0.0001). Even after adjusting for additional covariates, significance was maintained in the fully adjusted model (OR = 1.02, 95% CI: 1.01 to 1.02, p<0.0001). For sensitivity analysis, we also treated epicardial fat volume as a categorical variable (quartile), revealing a similar trend (p for trend was p<0.001).

The analyses of a non-linear relationship epicardial fat volume and obesity

In this study, we examined the non-linear relationship between epicardial fat volume and obesity, given that epicardial fat volume is a continuous measure (Fig. 1). Our findings indicated that this relationship was indeed non-linear after controlling for factors such as age, sex, diabetes mellitus, smoking history, arterial hypertension, hypercholesterolemia, hypertriglyceridemia, statin use, vasculopathy, and previous AMI. Utilizing a two-piecewise linear regression model, we determined the inflection point to be 203.3. For practical clinical use, we defined the inflection point as 200 ml. To the right of this inflection point, the effect size was 0.99 with a 95% confidence interval of 0.98 to 1.00 and a p-value of 0.1805. Conversely, a positive correlation between epicardial fat volume and obesity was noted to the left of the inflection point (1.02, with a 95% confidence interval of 1.02 to 1.03, p<0.0001) as shown in Table 4.

Figure 1. Association between epicardial fat volume and obesity



A threshold, nonlinear association between epicardial fat volume and obesity was found in a generalized additive model (GAM). Solid red line represents the smooth curve fit between variables. Blue bands represent the 95% of confidence interval from the fit. All adjusted for age, sex, diabetes mellitus, smoking history, arterial hypertension, hypercholesterolemia, hypertriglyceridemia, statins, vasculopathy, previous AMI.

The results of subgroup analyses

According to Table 5, the analysis of interactions revealed that there were no statistically significant findings related to age, gender, diabetes mellitus, smoking history, arterial

Table 3. Relationship between epicardial fat volume and obesity

Outcome	Crude Model		Model I		Model II	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
EFV (ml)	1.01 (1.00, 1.01)	0.0953	1.01 (1.00, 1.01)	0.03	1.01 (1.00, 1.01)	0.0818
EFV (quartile)						
Quartile 1	Reference		Reference		Reference	
Quartile 2	2.04 (0.77, 5.40)	0.1516	2.49 (0.92, 6.74)	0.0722	2.36 (0.83, 6.71)	0.1083
Quartile 3	2.07 (0.73, 5.84)	0.1709	2.93 (0.99, 8.66)	0.0516	3.12 (0.99, 9.90)	0.0529
Quartile 4	4.76 (1.35, 16.86)	0.0155	6.46 (1.75, 23.89)	0.0052	8.59 (2.10, 35.05)	0.0027
p for trend	<0.001	-	< 0.001	-	< 0.001	-

EFV, epicardial fat volume; CI, confidence interval; OR, odds ratio. Crude model, no adjustments of other covariates.
Model I, adjusted for age and sex. Model II, adjusted for age, sex, diabetes mellitus, smoking history, arterial hypertension, hypercholesterolemia, hypertriglyceridemia, statins, vasculopathy, previous AMI.

Table 4. The results of two-piecewise linear regression model

Inflection point of EFV	Effect size (β)	95% CI	p-value
< 203.3	1.02	1.02 to 1.03	<0.0001
≥203.3	0.99	0.98 to 1.00	0.1805

Effect: EFV. Cause: Obesity. EFV, epicardial fat volume; CI, confidence interval. Adjusted: age, sex, diabetes mellitus, smoking history, arterial hypertension, hypercholesterolemia, hypertriglyceridemia, statins, vasculopathy, previous AMI.

Table 5. Effect size of epicardial fat volume on obesity in prespecified and exploratory subgroups in each subgroup

Characteristic	No of participants	OR (95% CI)	p -value	p-value for interaction
Gender				0.9619
Male	390	(1.01, 1.02)	<0.0001	-
Female	120	(1.00, 1.02)	0.0096	-
Age (yrs)				0.88
>=70	194	(1.01, 1.02)	<0.0001	-
<70	316	(1.01, 1.02)	<0.0001	-
Diabetes mellitus				0.1175
No	396	(1.01, 1.02)	<0.0001	-
Yes	114	(1.00, 1.01)	0.0302	-
Smoking history				0.3946
No	317	(1.01, 1.02)	<0.0001	-
Yes	193	(1.01, 1.02)	<0.0001	-
Arterial hypertension				0.2081
No	98	(1.01, 1.04)	0.0062	-
Yes	412	(1.01, 1.02)	<0.0001	-
Hypercholesterolemia				0.3251
No	148	(1.00, 1.02)	0.0226	-
Yes	362	(1.01, 1.02)	<0.0001	-
Hypertriglyceridemia				0.8069
No	432	(1.01, 1.02)	<0.0001	-
Yes	78	(1.00, 1.02)	0.0175	-
Statins				0.9547
No	213	(1.01, 1.02)	<0.0001	-
Yes	253	(1.01, 1.02)	<0.0001	-
Vasculopathy				0.5276
No	389	(1.01, 1.02)	<0.0001	-
Yes	121	(1.01, 1.02)	0.0004	-
Previous AMI				0.3725
No	338	(1.01, 1.02)	<0.0001	-
Yes	172	(1.01, 1.02)	0.0001	-

AMI, acute myocardial infarction; CI, confidence interval; OR, odds ratio. Adjusted for age, sex, diabetes mellitus, smoking history, arterial hypertension, hypercholesterolemia, hypertriglyceridemia, statins, vasculopathy, previous AMI except for the subgroup variable.

hypertension, hypercholesterolemia, hypertriglyceridemia, statins, vasculopathy, or previous AMI.

Discussion

In the current investigation, we employed GLM and GAM models to clarify the relationship between obesity and EFV among patients suspected of having obstructive cardiovascular disease. In the non-adjusted model, the minimally adjusted model, and in the fully adjusted model, EFV was significantly correlated with obesity. This association was also evident when epicardial fat volume was treated as a categorical variable. Additionally, we examined the possibility of a curvilinear relationship between obesity and epicardial fat volume, finding a positive correlation ($p<0.0001$). The relationships between EFV and obesity varied across the left and right sides of an inflection point at EFV = 203.3 ml. As stated above, we have designated the inflection point as EFV = 200 ml for clinical convenience.

We performed a PubMed search using, concurrently, the keywords 'epicardial fat volume,' 'obesity,' and 'coronary artery disease'. At the end of February 2023, we retrieved thirteen scholarly articles from PubMed that indicated a positive relationship between EFV and obesity in the context of coronary artery disease. Nevertheless, none quantified the direct link between obesity and EFV. To the best of our knowledge, this represents the first inquiry into the quantitative relationship between these two factors.

Through univariate correlation analysis, Aitken-Buck identified a strong correlation between EAT thickness and BMI, an index of obesity (r=0.56) [22], which aligns with findings from several recent studies [23–25]. Thus, our findings support the conclusion that EAT thickness has a positive and consistent correlation with BMI. Non-invasive imaging techniques assessing both two-dimensional EAT thickness and three-dimensional EAT volume have confirmed a solid positive relationship between EAT deposition and BMI.

Nevertheless, there have been some indirect, contradictory findings. A clinical registration investigation did not observe a statistically significant link between changes in weight and alterations in EAT [26]. Ngo and Gokce found no link found between obesity and cardiovascular risk factors [27]. These discrepancies may have resulted from variations in cohort characteristics, sample sizes, and adjustments for confounding variables.

Our research possesses several advantages compared to earlier studies. We utilized not only a generalized linear model to assess the linear association between EFV and obesity, but we also employed the generalized additive model to explore a possible nonlinear relationship. GAM offers clear benefits for managing non-linear relationships, as it effectively addresses non-parametric smoothing and fits regression splines to the dataset. Employing GAM enabled us to uncover the true connections between exposure and outcome more effectively. This investigation utilized a cross-sectional design that may involve unavoidable confounding variables; therefore, we applied rigorous statistical adjustments to mitigate residual confounding.

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While prior research indicated a linear link between EFV and obesity, MRI results demonstrated a significantly greater accumulation of fat in epicardial adipocytes among individuals with visceral obesity compared to those without it. The thickness measurements of the EAT at the levels of the left ventricle and right ventricle were observed to be 1.43 times and 1.75 times greater, respectively, in individuals with visceral obesity compared to those without [23, 28]. In our analysis, however, we found no evidence supporting this relationship after adjusting for confounding factors not accounted for in the previous study.

Our study does have several limitations. Firstly, being a cross-sectional study, it offers only limited evidence regarding the association between exposure and outcome, making it challenging to discern causality. Secondly, since our sample population consisted solely of Chinese participants, the results may not be applicable to other ethnic groups. Thirdly, due to the limitations of the raw data available, we were unable to explore the relationship between atrial fibrillation and heart rate or mortality. The presence of tachycardic or bradycardic symptoms may result from arrhythmias (either tachycardic or bradycardic), which could either lead to or be a consequence of ischemia, but this connection was not captured in our observational cohort study.

It is important to acknowledge certain other limitations in our research. Firstly, the primary constraint of this investigation was its observational design. Secondly, due to its cross-sectional nature, the study possessed limited ability to draw causal connections between obesity EFV. Additional, prospective follow-up research is required to confirm and extend these results. Thirdly, there may have been an additional selection bias, as participants lacking data on both obesity and EFV were not included. Nevertheless, the baseline characteristics of the excluded group were comparable to those of the participants who were included in the analysis.

Conclusions

The relationship between obesity and EFV in CAD patients is non-linear, and this should be considered when developing prognostic models for treatment CAD and for treatment of obesity. The findings suggest that the relationship between EFV and obesity is more complex than previously thought and warrants further investigation to better understand its implications for CAD risk assessment and management.

No conflict of interest is reported.

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