

Impact of BMI z-score On Left Ventricular Mechanics in a Pediatric Population

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Abstract

Background: Adolescent weight disorders ranging from anorexia nervosa (AN) to obesity (OB) can impact the heart by causing opposite alterations in its morphology, suggesting a direct impact of BMI on the heart. Cardiac function is relatively preserved as assessed by standard ultrasound methods. However, few studies have used speckle-tracking echocardiography (STE), which can detect subtle alterations of left ventricular (LV) function by evaluating deformations. The aim of this study was to assess the link between BMI z-score of female adolescents and myocardial function.

Methods: Ninety-one female adolescents comprising 26 AN patient (age 14.6 ± 1.9 y), 28 OB patients (age 13.2 ± 1.4 y), and 37 controls (age 14.0 ± 2.0 y) underwent STE to assess LV morphology and myocardial regional deformations.

Findings: The BMI z-score of our population ranged from -4.6 to 5.2 . LV morphological remodeling was significantly and positively correlated with BMI z-score ($R^2 = 0.456$, $p < 0.0001$ for LV mass). Global longitudinal strain (LS) and regional LS recorded at the mid and apical levels were significantly correlated with BMI z-score ($R^2 = 0.196$, $p = 0.0001$ and $R^2 = 0.274$, $p < 0.0001$ respectively for apical and medial LS). Circumferential strains and twisting mechanics were not correlated with BMI z-score. Fibrinogen and SBP were the main variables explaining the alteration of longitudinal strains.

Conclusion: A impact of BMI z-score on LV mechanics was observed especially on medial and apical LS. Neither circumferential nor twisting mechanics were altered by BMI z-score in female adolescents.

Introduction

Weight disorders (WDs), ranging from anorexia nervosa (AN) to overweight (OW) and obesity (OB) are extremely common in adolescence [1, 2]. AN, defined by a marked weight loss and low body mass index (BMI), occurs most often in females aged 12–25 years [1]. OB, characterized by excess weight and high BMI, is very common in the pediatric population, with a high prevalence among those aged 15–19 years [2]. These pathologies have numerous impacts on the cardiovascular system, illustrated for example by a decrease in heart rate (HR) and blood pressure (BP) in AN [3] and conversely an increase in these variables in OB [2, 4]. Cardiac remodeling is associated with a decrease in the left ventricular mass (LVM) and in the LV wall thickness in AN [3, 5], and conversely a LV wall thickening and an increase in LVM in OB [2, 4, 6]. In both cases, structural alterations were observed, with presence of myocardial fibrosis [1, 7, 8] probably linked in part to chronic low-grade systemic inflammation [8, 9]. Despite these structural and morphological changes, global cardiac function, assessed by standard ultrasound methods, appears relatively preserved [2–4, 6]. Several recent studies [4, 6, 10–12] assessed regional myocardial strains and twisting mechanics (this latter being an important determinant of LV systolic and diastolic function, [13] by speckle-tracking echocardiography (STE) to characterize their LV function with a greater sensitivity than conventional echocardiography [14]. First findings suggested a decrease in LV longitudinal strains in

OB [4, 6, 11, 12, 15] potentially counterbalanced by an increase in twisting mechanics [15], underlining possible links between WD and cardiac mechanics.

Importantly, the above studies provided very limited data in AN patients [10], or focused on OB patients only [4, 9, 12]. To our knowledge, no study has evaluated the impact of WD on cardiac morphology and regional myocardial function over a broad scale ranging from low BMI in AN to high BMI in OB patients. Interestingly, cardiac mechanics might be altered on a continuum, owing to the opposite changes in loading conditions (i.e., BP) and cardiac morphological remodeling (i.e., cardiac hypotrophy vs. hypertrophy) reported in adolescents with WD, but this remained to be confirmed.

We set out to evaluate cardiac repercussions of WD over a wide range of BMI in female adolescents. We performed linear regression analysis between LV variables (including regional LV strains and twisting mechanics) and BMI z-score, this latter cancelling changes in BMI occurring with advancing age in adolescents [16]. We hypothesized that in female adolescents with WD, (i) there would be a continuum in the adaptation of LV morphology and function, with strong correlations between LV size, myocardial strains, twist and BMI z-score, and (ii) these modifications of strains would be secondary to changes in load conditions, cardiac morphological adaptations, and a particular inflammatory profile.

Method

Study population

This prospective study included female adolescents with AN, normal weight, OW or OB aged 10–18 y to obtain a broad continuous scale of BMI z-scores. The patients had been diagnosed in a pediatric department of a university hospital in France between March 2019 and January 2020. AN patients fulfilled the DSM V criteria for AN (American Psychiatric Association) [17]. OB patients met the IOTF C30 criteria [18]. The adolescents with OB included had primary obesity (i.e., not secondary to any genetic or endocrine pathology) and did not present diabetes or dyslipidemia (verified on the same day as echocardiography by a blood test). The BMI z-score was calculated for all participants. None had congenital heart defects or positive family history of cardiac disease. Written informed consent was obtained from the study participants and their guardians. The Ile-de-France Ethics Committee approved the protocol for this study (18.12.05.66738 CAT 2). Moreover, all methods were carried out in accordance with relevant guidelines and regulations.

Anthropometric and clinical assessments

Body height and body mass were measured. BMI was calculated as $\text{body mass} / \text{body height}^2$. Body surface area (BSA) was calculated according to Boyd [19]. BP was measured using an automatic device (General Electric, Dynamap PRO 300 V2, Boston). The average resting HR was recorded at night, using a validated HR monitor (Polar V800, Polar, Finland) [20] and a chest strap (Polar H10, Polar, Finland).

Echocardiographic recordings

Echocardiography was carried out with the subject in the left lateral decubitus position, with Vivid ultrasound systems (GE Healthcare, Horten, Norway) using a 3-5 MHz transducer (M4S probe). Cine loops were recorded in parasternal long axis and apical (5, 4, 3 and 2 chamber) views and saved for blinded offline analysis (EchoPac, BT203 version, GE Healthcare). Grayscale images were saved at a frame rate of 80–90 frames/sec and color tissue velocity images at a frame rate of 120–140 frames/sec. 2D echocardiographic measurements were performed in accordance with the guidelines of the American Society of Echocardiography [21]. All echocardiographic data were averaged from measurements obtained on 3–5 cardiac cycles.

Cardiac morphology

LV diameters and myocardial thickness were measured from the parasternal long axis view. LV mass was estimated using the Devereux formula and indexed to height^{2.7} as recommended in the pediatric population [22]. LV volumes were assessed using Simpson's biplane method. Epicardial fat thickness (EFT) was measured according to recommendations suggested by Iacobellis [23]. EFT was identified as the relatively echo-free space between the outer wall of the myocardium and the visceral layer of pericardium, and measured perpendicularly on the free wall of the right ventricle at end-systole [23].

LV systolic and diastolic functions

LV diastolic function was assessed from peak early (E wave) and atrial (A wave) transmitral flow velocities. EF was assessed using Simpson's biplane method. GLS, circumferential (CS), and twisting mechanics (apical and basal rotations, peak twist and untwisting rate) were obtained as previously detailed [24]. LV twist was calculated as the difference between apical and basal rotations at each percentage of systolic duration. We considered GLS, CS, LV rotations and peak twist as indices of myocardial systolic function. A regional analysis was carried out at the level of the longitudinal strains (basal, median, apical LS) and circumferential (basal and apical CS).

Biological data

A fasting venous blood sample was taken for biochemical determinations with in particular automated immunoassay of fibrinogen.

Statistical analyses

Statistical analyses were performed using SPSS 25 statistical software. All values were expressed as mean \pm SD. One-way analysis of variance (ANOVA) was used to compare groups, after checking the normality of distribution of each variable by a Shapiro-Wilk test. In the absence of normal distribution, the nonparametric Kruskal-Wallis test was used. Correlations were determined between BMI z-score and hemodynamic, biological, and cardiac ultrasound variables by linear regression analysis and Pearson correlation coefficient. R^2 was calculated to assess the proportion of variance explained. Stepwise

regressions were then carried out, including hemodynamic, cardiac morphology and biological variables. Statistical significance for all analyses was assumed at $p < 0.05$.

Results

Population characteristics and resting echocardiography

Ninety-one female adolescents with BMI z-scores ranging from -4.6 to 5.2 comprising 26 AN, 33 normal-weighted, four OW and 28 OB patients were included. **Table 1** shows the anthropometric characteristics and the standard echocardiographic variables of our populations. LV wall thicknesses and mass were higher in OB. EF was similar between groups. The diastolic function of AN patients was characterized by a lower A wave, whereas that of OB patients was characterized by a higher E wave.

Correlations between BP, HR, fibrinogen and BMI z-score

Figure 1 shows correlations between BP, HR and BMI z-score. Significant correlations were observed between systolic BP, HR and BMI z-score, but not with diastolic BP. **Figure 2** represents the positive correlation between fibrinogen and BMI z-score.

Correlations between LV morphological and function variables and BMI z-score

The measurements of the LV and EFT were significantly correlated with BMI z-score (**Figure 3**). Significant correlations were found between GLS and BMI z-score, the highest values being observed for the lowest values of BMI z-score. Interestingly, correlations were obtained between BMI z-score and longitudinal strains at the apical and medial levels, but not at the base. No significant correlations were observed between BMI z-score and circumferential strains (**Figure 4**). Similarly, no significant correlations were observed between the LV basal and apical rotations, twist and untwisting rate, and the BMI z-score (**Figure 5**).

Univariate and stepwise regression analyses

In univariate regression analyses, SBP, HR, LV mass, EFT, fibrinogen and NT-proBNP were significantly correlated with median LS. EFT, fibrinogen and NT-proBNP were significantly correlated with apical LS.

In stepwise regression analyses, fibrinogen and SBP could explain the changes in median LS, and fibrinogen alone the changes in apical LS.

Discussion

Our study set out to assess the link between BMI z-score of female adolescents with WD and myocardial function. Our main results were that (i) LV morphological remodeling was significantly and positively correlated with BMI z-score, (ii) GLS and longitudinal strains recorded at the apical and medial levels but not at the base were significantly correlated with BMI z-score, the highest strains being observed in adolescents with the lowest BMI z-scores, (iii) from short-axis planes, both circumferential strains and rotations, and so twist and untwisting rates were not correlated with BMI z-score, and (iv) from a multivariate stepwise regression analysis, fibrinogen and SBP were the main variables explaining the alteration of regional longitudinal strains with BMI z-score.

Cardiac remodeling and BMI z-score

We found a positive correlation between the BMI z-score and the LV mass. These results are in agreement with current knowledge on the cardiac remodeling induced by WD, namely a decrease in measurements in AN [3, 25, 26] and conversely an increase in OB [2, 6]. These morphological adaptations are linked not only to the nutritional state itself but also to the load conditions [27], which vary with BMI, as demonstrated in our study by positive correlation between BMI z-score and clinical variables of HR and BP. In AN, possible causes of hypotrophy therefore include decreased afterload from relative hypotension leading to down-regulation of the LV mass [27], reduced preload leading to ventricular remodeling and a direct effect of malnutrition as for skeletal musculature [27]. By contrast, in OB, the excess adipose tissue is responsible for insulin resistance with deleterious effects on the heart: insulin may aggravate hypervolemia through salt and water retention, act as a myocardial growth factor, activate the sympathetic nervous system, and therefore ultimately increase the size of the heart [6]. On the other hand, the increase in preload and afterload (linked to arterial stiffness) also seems to be involved in the morphological changes [2]. Moreover, in line with the literature [23], we showed that these morphological changes were associated with thickening of epicardial fat, which is closely correlated with the BMI z-score. Interestingly, this epicardial fat is considered as a marker of cardiovascular risk [23], in particular because in excess it has direct effects on coronary atherosclerosis and causes fatty infiltration, inflammation and myocardial fibrosis [8, 23].

Regional myocardial function and BMI z-score

The EF, assessed from conventional echocardiographic variables, remained unchanged whatever the BMI z-score. The strength of our study was to evaluate systolic function from the GLS measured by STE. Interestingly, GLS was negatively correlated with the BMI z-score (i.e., lower strains with higher BMI z-score). Moreover, the regional assessment of LV longitudinal strains gave additional information by demonstrating that these correlations were observed only at the mid and apical levels, but not at the base. Our results thus robustly demonstrate a continuum of adaptation of longitudinal strains at mid and apical levels in a population of adolescents from very low to high BMI z-score. In AN patients, only one study used STE and found no alteration in GLS compared with controls, except in a very small subgroup

of patients with purging behavior in whom apical longitudinal strains were reduced. They demonstrated that the only predictor of the apical strains was the BMI z-score [10]. In adolescents with obesity, it is well-established that GLS is lower than in controls [4, 6, 11, 12]. Of note, from regional analysis of longitudinal strains, Binnetoglu et al. (2015) [11] also recently reported a more pronounced decrease in strains at the mid and apical segments compared to the base.

To gain insight into the underlying mechanisms of these alterations, we performed multivariate stepwise regression analyses and observed that fibrinogen and SBP were the two main independent predictors of LV mid or apical strains. Fibrinogen was considered to be a high-risk marker for developing vascular inflammatory diseases, such as arterial hypertension and atherosclerosis [28]. Our results demonstrated close correlations between fibrinogen and not only the BMI z-score but also the SBP. A chronic inflammatory state may therefore appear with increasing BMI z-score mediated in particular by fibrinogen, this latter promoting the appearance of higher SBP, afterload, and *in fine* reduction in strains. It has been recently demonstrated that longitudinal strains are heavily influenced by afterload [29]. The inflammatory state could also induce an adverse effect on strains via an occurrence of myocardial fibrosis, well-established in OB [8].

Twisting mechanics and BMI z-score

For a comprehensive evaluation of the impact of BMI z-score on the myocardial mechanics, we also assessed circumferential strains and rotations. Another important (and unexpected) finding was that both circumferential strains and rotations (and so twist) [13] were normal regardless of the BMI z-score. Interestingly, the discrepancies between findings obtained on longitudinal and circumferential strains suggested a specific impact of BMI z-score on the longitudinal deformations. The greater vulnerability of longitudinally orientated myocardial fibers may be explained by their major distribution in the subendocardium, leading them to be more susceptible to wall stress, ischemia and fibrosis [30].

The LV twist helps to create a uniform distribution of LV fiber stress and fiber shortening across the wall and is essential for the course of systole. Its disappearance has been clearly shown to increase oxygen demand and reduce the efficiency of LV systolic function [13]. LV twist is affected by loading conditions of the heart; an increase in afterload and/or a decrease in preload induce a decrease in twist in animal studies [13]. In physiological states in which pre- and afterload were decreased, twist remained unchanged, or was increased [13]. In our study, the wide range of BMI z-scores, accompanied by changes in SBP, did not impact the twist. We note that other factors could impact the twist and allow its conservation, such as an increase in intrinsic myocardial contractility or an increase in sympathetic activity, which have been suggested to increase the twist [13, 24].

The energy stored during LV twist in elastic components is restored very early in diastole, creating an intraventricular pressure gradient that favours LV filling, thus linking systole to diastole (systolic-diastolic coupling) [13]. Here we observed no significant correlation between peak untwisting rate and BMI z-score, suggesting that this mechanism was preserved over a wide range of WD. Taken together, our results

strongly support that twisting mechanics are unaffected by variation in BMI z-score, probably partly explaining the preservation of systolic and diastolic function in adolescents with WD, regardless of their BMI z-score.

Study limitations

To obtain a broad, continuous scale of BMI z-score, we decided to include AN patients, who were not constitutionally thin. This could therefore introduce bias in our results, linked to the pathophysiology specific to this disease.

Conclusion

WDs ranging from AN to OB are particularly common in adolescents, and result in a broad continuous scale of BMI z-score. Our study showed a positive correlation between this anthropometric marker and the measurements of the LV. Moreover, GLS, apical and mid longitudinal strains were negatively correlated with BMI z-score. Conversely, basal longitudinal strain and other strains occurring during a cardiac cycle were not affected by the BMI z-score. Fibrinogen, and to a lesser extent SBP, could explain the modifications of the longitudinal strains. The importance of inflammatory status, mediated in part by fibrinogen, on LV function awaits confirmation in further studies.

Declarations

Conflict of interest: Nothing to disclose.

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Tables

Table 1. General characteristics and standard ultrasound parameters of our population

	Anorexics (n =26)	Controls (n =37)	Obeses (n =28)
Age (years)	14.6 ± 1.9	14.0 ± 2.0	13.2 ± 1.4 #
<i>Anthropometry</i>			
Height (cm)	159.8 ± 9.1	162.7 ± 9.6	162.9 ± 5.7
Body mass (kg)	40.7 ± 8.2 ***	53.3 ± 11.4	90.4 ± 13 ****###
BMI (kg.m ⁻²)	15,84 ± 2,06 ***	19,98 ± 3,17	34.02 ± 4.10 ****###
BMI z score	-1.8 ± 1.1 ***	0.4 ± 1.3	4.1 ± 0.6 ****###
BSA (m ²)	1.33 ± 0.16 ***	1.55 ± 0.20	2.08 ± 0.17 ****###
<i>Ultrasound parameters</i>			
LV septum thickness (cm)	0.72 ± 0.15	0.76 ± 0.11	0.83 ± 0.18 #
LV posterior wall thickness (cm)	0.67 ± 0.12 ***	0.74 ± 0.11	0.88 ± 0.13 ****###
LV mass (g)	79 ± 26 ***	96 ± 24	128 ± 29 ****###
LV mass ^{2.7} (g.m ^{2.7})	22 ± 6 ***	26 ± 5	34 ± 7 ****###
LV end-diastolic volume (mL)	79 ± 19	90 ± 23	119 ± 27 ****###
LV end-systolic volume (mL)	29 ± 8	33 ± 9	42 ± 11 ****###
Ejection fraction (%)	64 ± 5	64 ± 6	64 ± 6
E wave (cm.s ⁻¹)	84 ± 17	82 ± 14	90 ± 11 *
A wave (cm.s ⁻¹)	30 ± 6 ***	40 ± 8	39 ± 7 ###
E/A	2.9 ± 0.9 ***	2.1 ± 0.5	2.4 ± 0.5 ****###

Values are mean ± SD

: significantly different from controls (: p<0.05; **: p<0.01; *** p<0.001)

#: significantly different from anorexics (#: p<0.05; ##: p<0.01; ###: p < 0.001).

BMI: body mass index. BSA: body surface area. LV: left ventricular.

Figures

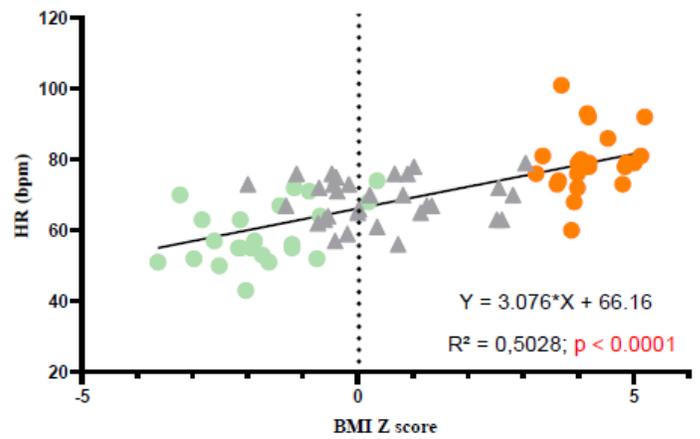
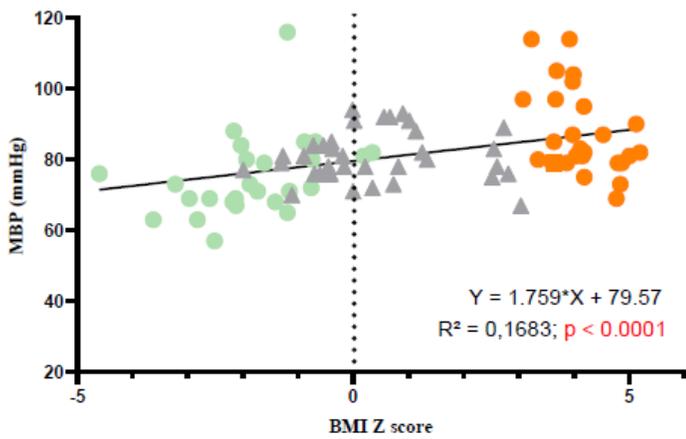
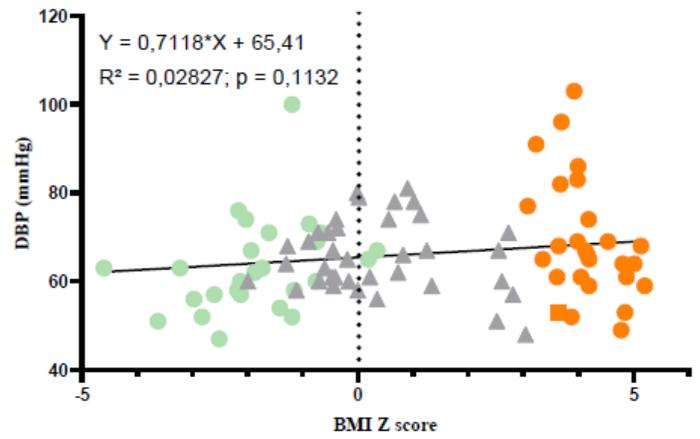
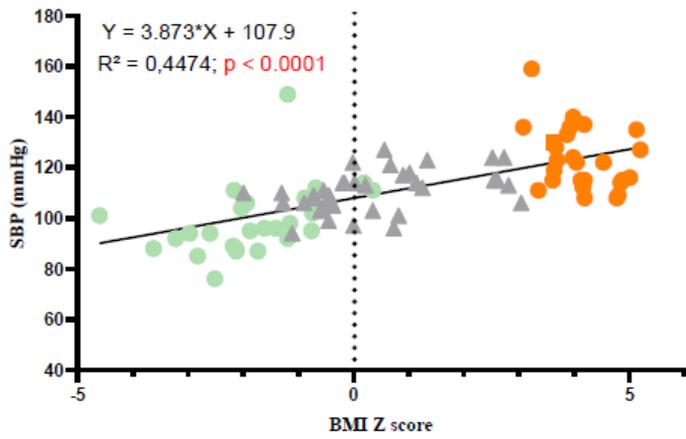


Figure 1

Correlations between blood pressures, heart rate and BMI z score

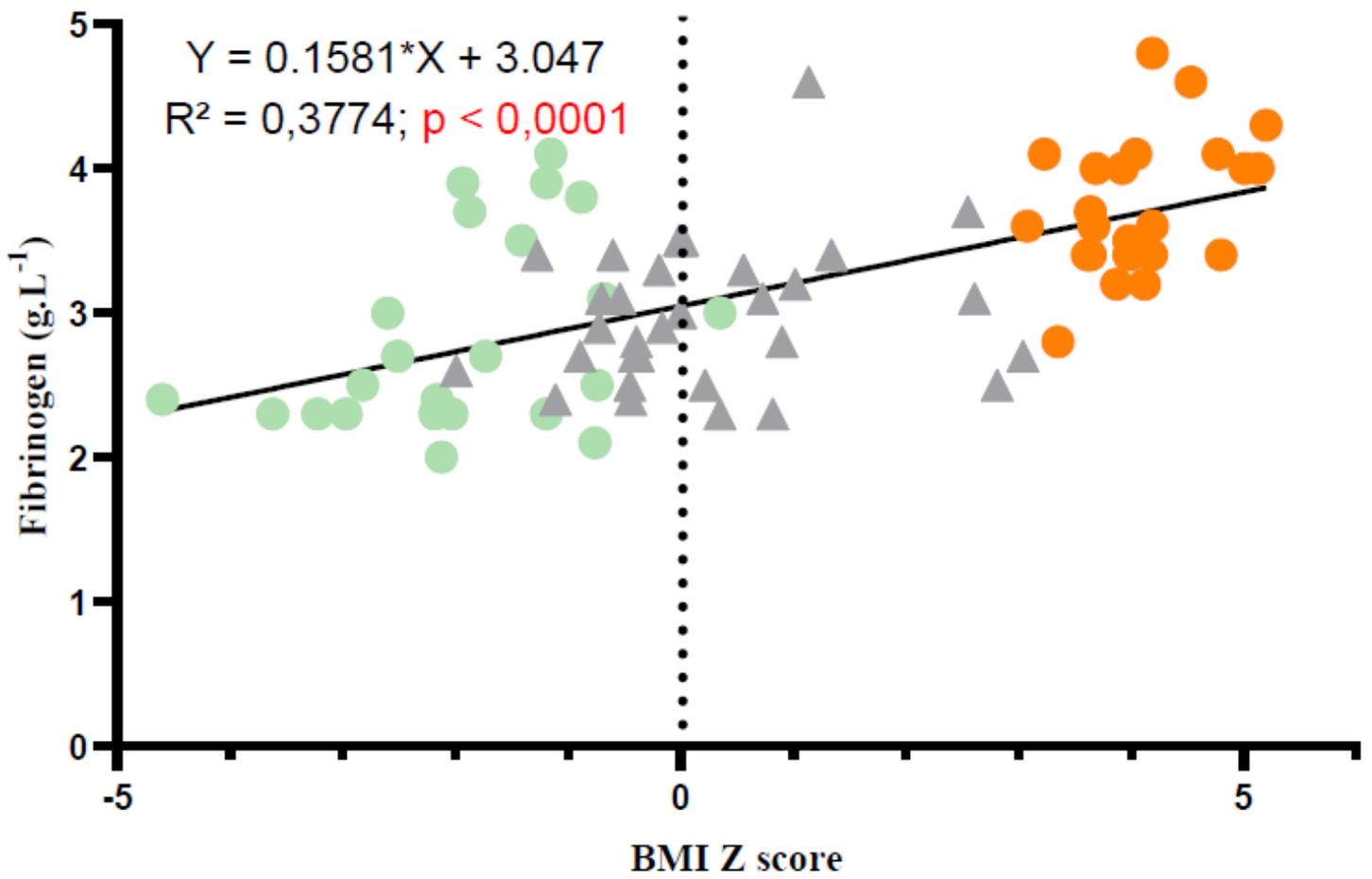


Figure 2

Correlation between fibrinogen and BMI z score

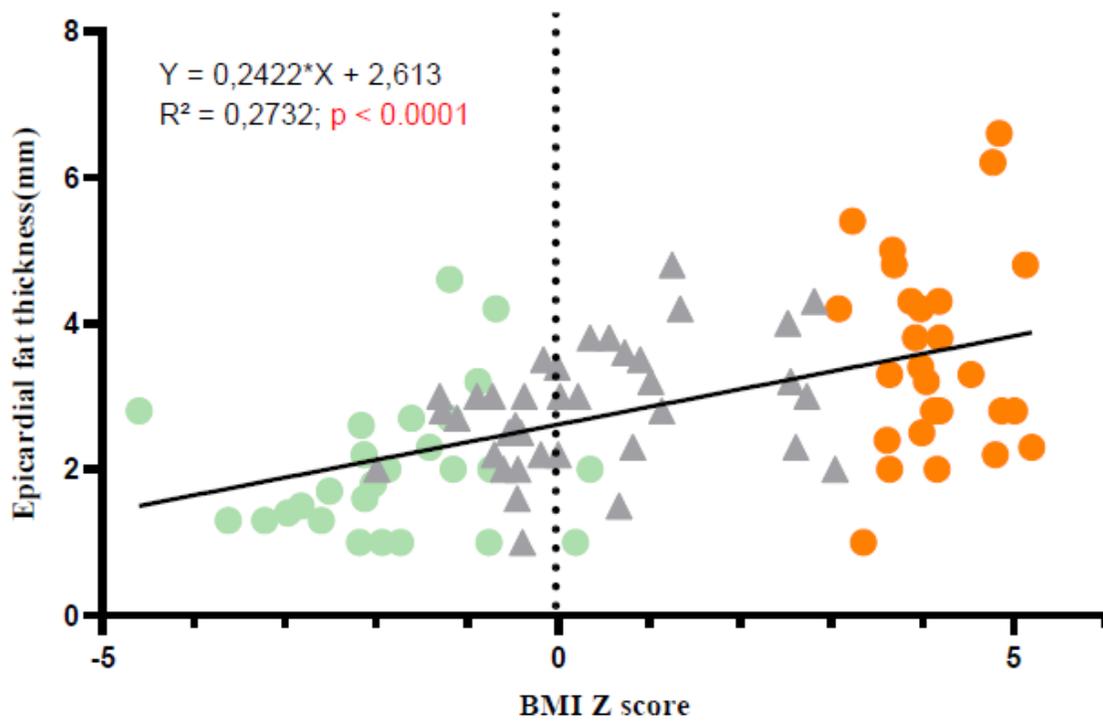
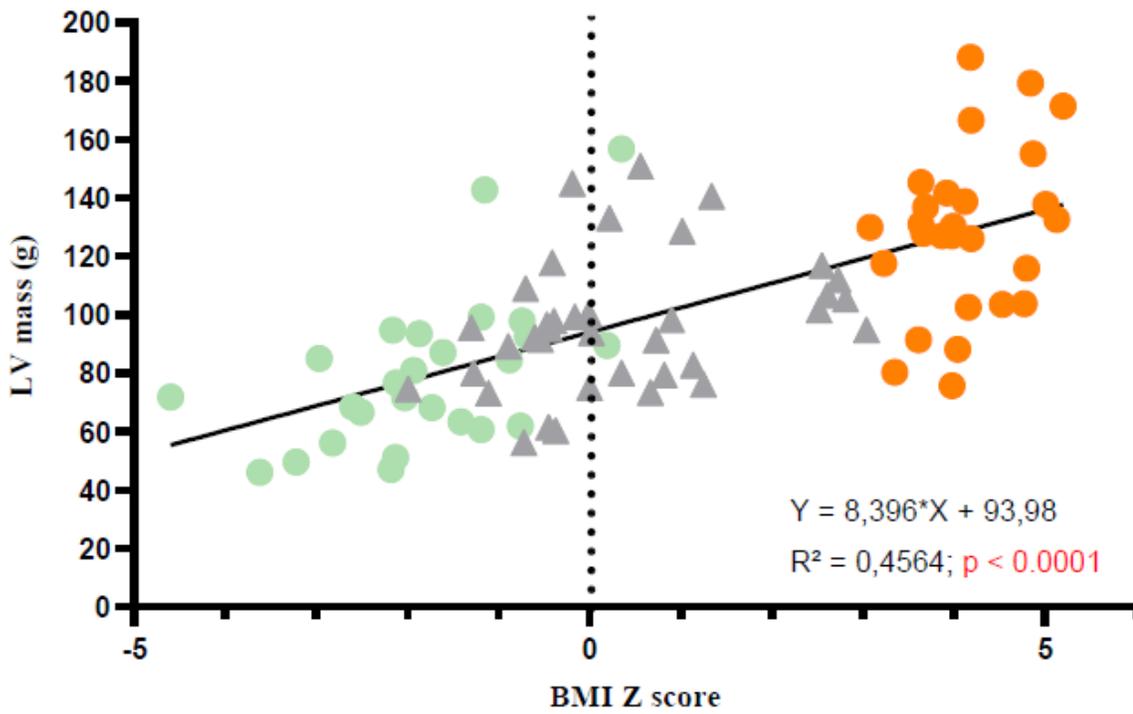


Figure 3

Correlations between LV mass, epicardial fat thickness and BMI z score

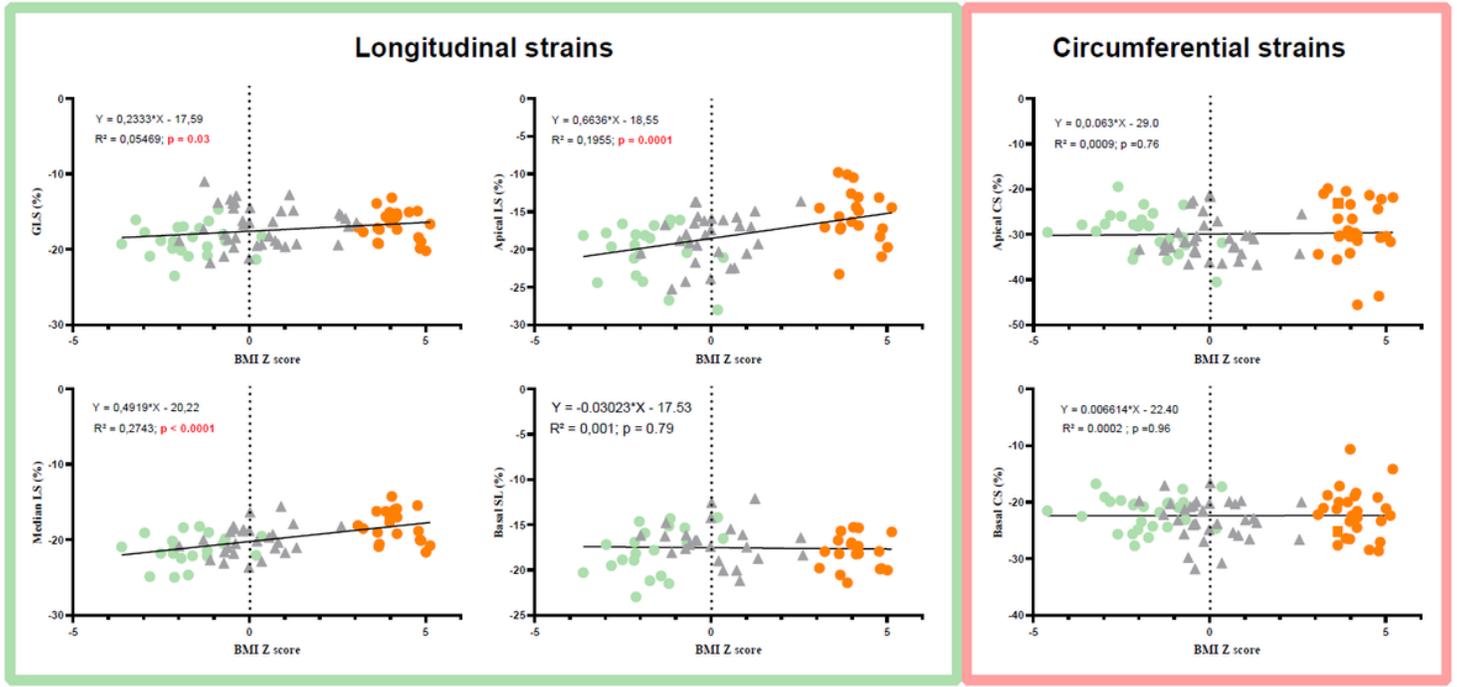


Figure 4

Correlations between LV longitudinal and circumferential strains and BMI z score

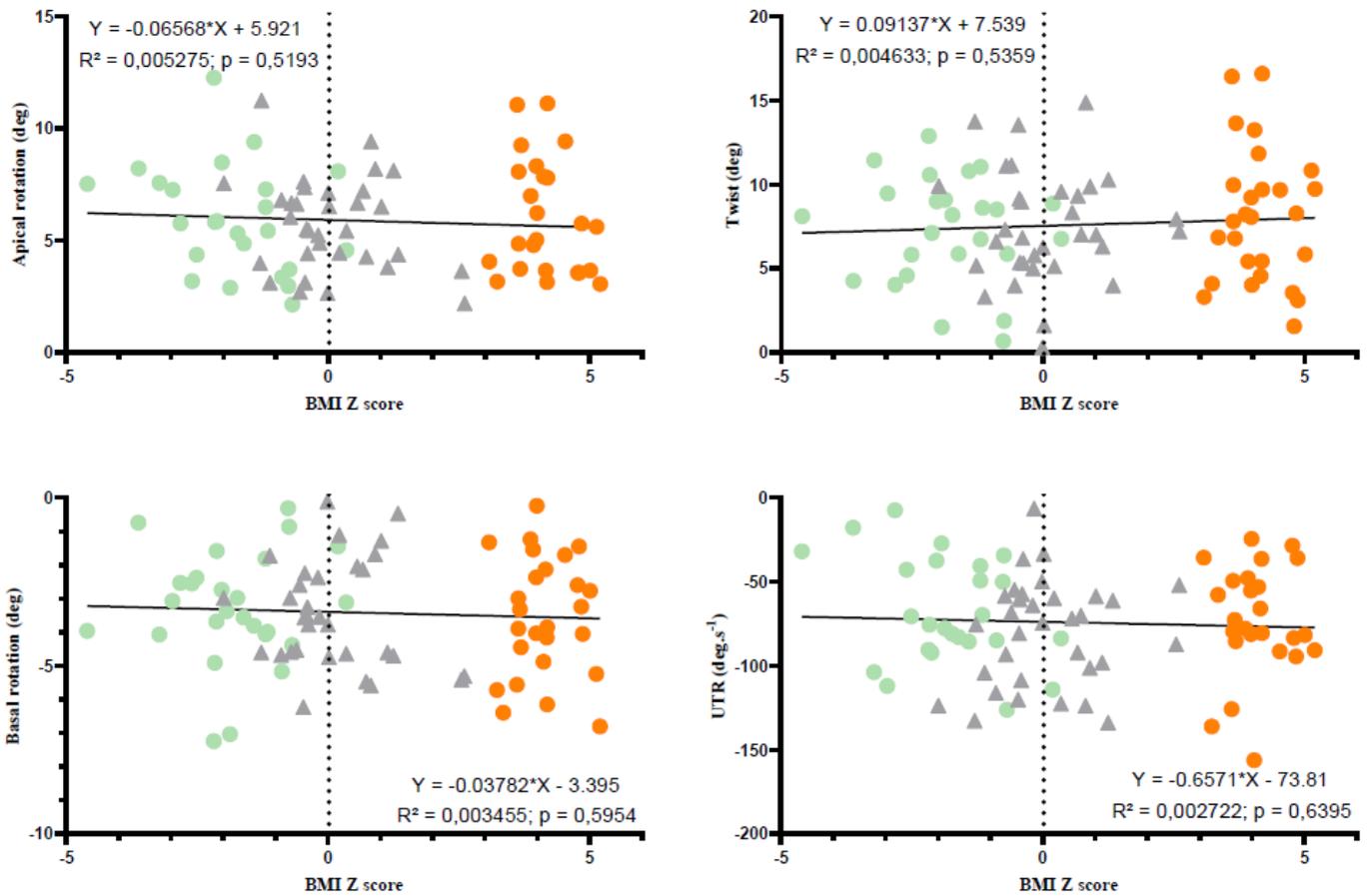


Figure 5

Correlations between twisting mechanics parameters and BMI z score