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Cardiorespiratory fitness and bone turnover markers in adults with metabolic syndrome: the mediator role of inflammation

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ABSTRACT

The relationship between inflammatory markers and bone turnover in adults is well known, whilst a negative association between cardiorespiratory fitness (CRF) and inflammatory markers has also been described. Hence, we tested whether the association between CRF and bone turnover markers is mediated by inflammatory markers in adults with metabolic syndrome. A total of 81 adults (58.5±5.0 yrs, 62.7% women) were included in the analysis. CRF was measured by the six-minute walking test. Serum interleukine (IL)-1β, IL-6, IL-10, tumor necrosis factor alpha, high-sensitivity c-reactive protein (hsCRP) and vascular endothelial growth factor, collagen type I cross-linked C-telopeptide, procollagen type I N-terminal propeptide (P1NP) and total osteocalcin were assessed using a sensitive ELISA kit. Body composition was assessed by dual-energy x-ray absorptiometry. Partial correlation was used to test the relationship between CRF, inflammatory markers and bone turnover markers, controlling for sex, lean mass and fat mass. Boot-strapped mediation procedures were performed and indirect effects with confidence intervals not including zero were interpreted as statistically significant. CRF was positively correlated with P1NP levels (r=0.228, p=0.044) and osteocalcin levels (r=0.296, p=0.009). Furthermore, CRF was positively correlated with IL-1β levels (r=0.340, p=0.002) and negatively correlated with hsCRP levels (r=-0.335, p=0.003), whereas IL-1β levels were positively correlated with P1NP levels (r=0.245, p=0.030) and hsCRP levels were negatively correlated with P1NP levels (r=-0.319, p=0.004). Finally, the association between CRF and P1NP levels was totally mediated by hsCRP (P_M=39.9). Therefore, CRF benefits on bone formation could be dependent on hsCRP concentrations in this population.

INTRODUCTION

Osteoporosis is a major disease affecting ageing populations worldwide (World Health Organization, 2007). Bone loss occurs silently and progressively due to the alteration of bone remodeling cycle, and it is reflected on bone turnover markers (Cooper & Ferrari, 2019). In this regard, the imbalance between the bone formation and resorption processes is influenced by genetics, age, sex hormone deficiency and lifestyle factors, although other metabolic complications (e.g., insulin resistance, chronic inflammation, and the ensuing metabolic syndrome [MetS]) seem to play an important role (Aspray & Hill, 2019).

The excessive fat mass accumulation in individuals with MetS may lead to inflammatory markers secretion such as interleukin (IL)-1β, IL-6, IL-10, tumor necrosis factor alpha (TNF-α), vascular endothelial growth factor (VEGF) and high sensitivity c-reactive protein (hsCRP) (Hanks et al., 2010; Jonas et al., 2015; Nishimura et al., 2009). Overall, the association between inflammatory markers and bone health have been extensively described in different populations (Ding et al., 2008; Gil-Cosano et al., 2020; Hanks et al., 2010; Utsal et al., 2014; Zheng et al., 1997). With regards to bone turnover markers, these inflammatory markers seem to stimulate bone resorption activities while decreasing bone formation in middle-aged and older adults (Chen et al., 2013; Ugurlu et al., 2022) and this may be explained by the differentiation of the stromal cells into adipocytes rather than osteoblasts (Rosen & Bouxsein, 2006). Thus, hsCRP has been negatively associated with osteocalcin and procollagen type I N-terminal propeptide (P1NP) in young, middle-aged and older adults (Andersson et al., 2017; Chen et al., 2013; Ugurlu et al., 2022).

Inflammatory markers have been consistently associated to cardiorespiratory fitness (CRF) in middle-aged adults (Hong et al., 2014; Jae et al., 2008; McGavock et al., 2004). High levels of CRF largely negate the adverse effects of excess adiposity, which is also referred as the ‘fat

and fit' phenomenon (Oktay et al., 2017). Cross-sectional evidence has shown the prognostic role of CRF in relation to bone health status in adult population (DeFina et al., 2016; I. Lee et al., 2020; Ohta et al., 2021; Wainstein et al., 2016), although its association with bone turnover markers has not been investigated yet.

Despite the relationship between CRF and inflammatory markers has been extensively described (Hong et al., 2014; Jae et al., 2008; McGavock et al., 2004), no study has jointly investigated the association of these predictors with bone turnover markers. Assessment of bone turnover together with different inflammatory markers through mediation analysis (Baron & Kenny, David, 1986) may increase our understanding on the mechanism responsible for CRF-related changes in bone mass. Therefore, the aim of this study was to investigate whether the association between CRF and bone turnover markers in adults with MetS is mediated by inflammatory markers.

METHODS

Design and participants

This cross-sectional study was conducted using baseline measurements of the RESOLVE project (REverse metabolic SyndrOme by Lifestyle and Various Exercises, registered at Clinicaltrials.gov, number NCT00917917). An extended description of the study was published elsewhere (Dutheil et al., 2013). Briefly, the RESOLVE project measured 100 overweight/obese adults with metabolic syndrome, according to the International Diabetes Federation definition (Alberti et al., 2006), aged between 50 and 70 years, with a sedentary lifestyle, stable body mass and stable treatment over the previous six months, post-menopausal for women, no hepatic, renal or psychiatric diseases, nor cardiovascular or endocrine diseases except those defining metabolic syndrome, no HIV infection, no use of medications altering

body weight, no restricted diet in the previous year, and with a satisfactory completion of a maximal exercise tolerance test.

A total of 81 participants (58.5±5.0 years old, 43% men) with valid data on CRF, inflammatory markers, bone metabolism markers, lean mass and fat mass were included in this study. Participants were recruited via advertisements and after signing the informed consent. The study was reviewed and approved by the human ethics committees from St Etienne, France.

Anthropometrics and body composition

Body height was measured with a standard stadiometer to the nearest 0.1cm (Holtain, Ltd., Crymych, UK) and body weight was recorded to the nearest 0.1 kg using a digital scale (Seca, Les Mureaux, France). Body mass index was calculated as weight (kg) divided by height squared (m^2). Waist circumference was assessed at midabdominal midpoint between subcostal and supra-iliac landmarks using a tape measure to the nearest 0.1cm. Fat mass and lean mass were measured by Dual-Energy X-ray absorptiometry (Hologic QDR 4500 series; Waltham, USA), with respective in vivo coefficient of variation (CV) of 4.2 and 0.4%. Visceral adipose tissue was assessed from DXA scans, as described by Kamel et al (1999). We determined a CV of 1.6% in the visceral adipose tissue measurements.

Cardiorespiratory fitness and blood pressure

CRF was assessed in field-based conditions using the six-minute walk test. In a nutshell, the participants walked back and forth between cones separated by 30 m, and a length mark was put throughout the hallway every 3 m. Individuals were instructed to walk as far as they could within the 6-minute time period and verbal encouragement was commonly used according to standardized guidelines (Agarwala & Salzman, 2020). Walk distance was measured by counting the number of full laps and rounding to the nearest meter for the partial final lap (ATS, 2002).

Biochemical measurements

Fasting blood samples were drawn between 7.00 and 7.30 a.m., aliquoted and stored at -80°C until analysis. Basic biological assays were performed in the biochemistry laboratory of the University Hospital of Clermont-Ferrand, France. Inflammatory markers (i.e., IL-1β, IL-6, IL-10, TNF-α, hsCRP and VEGF) were assayed by ELISA using commercial kits (Millipore, Billerica, MA, USA). Sensitivity, intra- and inter-assay CVs were 1.3 pg/mL, 9.0% and 9.0% for IL-1β; 1.3 pg/mL, 7.0% and 10.0% for IL-6; 1.6 pg/mL, 4.3% and 4.5% for IL-10; 0.7 pg/mL, 6.0% and 9.0%, for TNF-α; 0.1 mg/mL, <8% and <10% for hsCRP; and <5 pg/mL, 4.7% and 8.1% for VEGF.

Bone turnover markers included the serum concentration of total osteocalcin, which was assayed by ELISA (N-MID Osteocalcin ELISA, Nordic Bioscience Diagnostics A/S, Denmark). Intra- and inter-assay CVs were 2.6% and 4.7%, respectively, with a sensitivity of 0.5 ng/ml. Other bone metabolism markers such as P1NP and CTX-I were assayed using Cobas 6000 (Roche Diagnostic, Mannheim, Germany) with intra- and inter-assay CVs lower than 7%.

Statistical analysis

All the analyses were performed using the IBM SPSS Statistics for Windows version 20.0 (IBM Corp: Armonk, NY, USA), and the level of significance was set to $p < 0.05$. Descriptive characteristics of the participants are presented as mean ± standard deviation (SD) for normally distributed variables or median [interquartile range] for non-normally distributed variables. All variables were checked for normality using Kolmogorov-Smirnov test and visual check of histograms, Q-Q and box plots.

Partial correlation analysis was performed to examine the relationship between CRF, inflammatory markers and bone turnover markers controlling for covariates. We included covariates that were selected in a stepwise hierarchical regression to identify the best predictors

for bone turnover markers (data not shown). Sex, age, body mass index, fat mass, lean mass, waist circumference and visceral adipose tissue were considered for the stepwise method, but only sex, lean mass and fat mass were included.

Then, we performed simple mediation analysis to investigate whether the association between CRF and bone turnover markers was mediated by inflammatory markers, and controlling for sex, lean mass and fat mass. PROCESS macro version 3.1, model 4, with 10,000 bias-corrected bootstrap samples and 95% confidence intervals was used for these analyses. In a nutshell, the mediation analysis is composed of ordinary least squared regression-based equations (paths) that allow us to answer the question of how a predictor transmits its effect (total effect) on an outcome being partitioned into direct (c' path) and indirect effect (a × b path). Most contemporary analysts focus on the indirect effect by stating 2 steps in establishing mediation (Hayes, 2013): (1) show that the causal variable is correlated with the mediator (path a); (2) show that the mediator affects the outcome variable controlling for the predictor (path b). Thus, mediation is assessed by the indirect effect of the CRF (predictor) on bone turnover markers (outcome) through inflammatory markers (mediator). The total (c path), direct (c′ path), and indirect effects (a × b paths) are presented (Figure 1). Indirect effects with confidence intervals not including zero were interpreted as statistically significant (Hayes, 2013) regardless of the significance of the total effect (the effect of CRF on bone turnover markers) and the direct effect (the effect on bone turnover markers when both CRF and inflammatory markers are included as independent variables). The percentage of mediation (PM) was calculated as "(indirect effect/total effect) × 100" to know how much of the total effect was explained by the mediation when the following assumptions were achieved: the total effect is larger than the indirect effect and of the same sign.

RESULTS

Table 1 shows the descriptive characteristics of the overweight/obese adults with metabolic syndrome by sex. Interaction analyses were performed for sex (data not shown) and since no significant interactions were found ($p \leq 0.382$), analyses were performed for men and women together.

INSERT TABLE 1

Partial correlations between CRF, inflammatory markers and bone turnover markers after adjustment by sex, lean mass and fat mass are presented in Table 2. CRF was positively correlated with P1NP and osteocalcin (r=0.228 and r=0.296, respectively). Likewise, CRF was positively correlated with IL-1β (r=0.340) and negatively correlated with hsCRP (r=-0.355). Finally, IL-1β was positively correlated with P1NP (r=0.245) and hsCRP was negatively correlated with CTX and P1NP (r=-0.233 and r=-0.319, respectively). Additionally, IL-6 was positively correlated with IL-1β, IL-10 and TNF-α (r=0.537, r=0.491 and r=0.338, respectively), TNF-α was positively correlated with IL-10 (r=0.487) and VEGF was negatively correlated with P1NP (r=-0.275).

INSERT TABLE 2

Simple mediation analysis models controlling for sex, lean mass and fat mass are depicted in Figure 2. CRF was positively associated with P1NP (Figure 2B and 2E, c=3.394, p=0.044) and osteocalcin (Figure 2C and 2F, c=4.228, p=0.009). With regards to path a, CRF was positively associated with IL-1β (Figure 2A, 2B and 2C, a=4.224, p=0.002) and negatively associated with hsCRP (Figure 2D, 2E and 2F, a=-4.363, p=0.003). In path b, IL-1β was not associated with bone turnover markers, whereas hsCRP was negatively associated with P1NP (Figure 2E, b=-0.311, p=0.020). Finally, when CRF and IL-1β / hsCRP were included as independent variables (c', direct effect), osteocalcin was predicted and P1NP was not. There was a

significant mediating effect of hsCRP on the relationship between CRF and P1NP (IE=1.356, 95%CI=0.269-2.582, P_M=39.9%).

INSERT FIGURE 2

DISCUSSION

The present study quantifies for the first time, to our knowledge, the mediating role of inflammatory markers in the association between CRF and bone turnover markers. Interestingly, the results show that hsCRP levels mediate up to 39.9% of the association between CRF and P1NP levels after controlling for sex, lean mass and fat mass. We did not find a mediating role of inflammation in the associations of CRF with CTX and total osteocalcin levels. These findings show how CRF is related to hsCRP and P1NP levels. However, further studies are needed to elucidate the possible mechanisms behind these relationships.

Several studies have assessed the association between CRF and inflammatory markers (Hong et al., 2014; Jae et al., 2008; McGavock et al., 2004). The results of the present investigation confirm that CRF was negatively associated with hsCRP levels, after controlling for sex, lean mass and fat mass (path a). These results agree with several studies which found a negative association between peak oxygen uptake and hsCRP levels in adults with type 2 diabetes (Jae et al., 2008; McGavock et al., 2004). This fact could be related to the strong link between CRF and the improved endothelial function and body composition, which may reduce the inflammatory response in adults (Lucha-López et al., 2021). On the other hand, our positive association of CRF with IL-1β levels is not supported by Hong et al (2014) who found that peak oxygen uptake and IL-1β levels were negatively associated in obese adults after controlling for age, gender, race and mean arterial pressure. These controversial results could

be explained by fat mass or other adiposity measures not being included as covariates in their study despite the known associations between inflammation and obesity. Of note, many randomized clinical trials have failed to show that training-induced increases in CRF independent of weight loss improve levels of inflammatory markers (Arsenault et al., 2009; M. G. Lee et al., 2012). In contrast, combining an exercise intervention with hypocaloric diet has been shown to be effective to reduce CRP in adults with obesity (Bruun et al., 2006; You et al., 2004). The latter results seem to be explained by the amount of fat loss achieved through the exercise and hypocaloric diet intervention compared to the exercise intervention alone. Moreover, Perissiou et al. (2020) found that the ketogenic state achieved after an 8-week exercise intervention combined with low-carbohydrate diet was associated with higher fat loss and lower CRP levels in adults with obesity, suggesting carbohydrate restriction as a key element to modify inflammatory parameters.

Previous evidence has shown that hsCRP levels reduce bone formation markers such as P1NP and osteocalcin in young, middle-aged and older adults (Andersson et al., 2017; Chen et al., 2013; Ugurlu et al., 2022). Agree with these studies, our findings show that the association of hsCRP with P1NP and total osteocalcin levels was negative in adults with MetS. This might be explained by the fact that the inflammatory status derived from the MetS condition impairs the differentiation of bone-marrow stromal cell into osteoblasts (Rosen & Bouxsein, 2006). With regards to the association between IL-1β and bone turnover markers, we did not find any association. Opposite to our results, Al-Daghri et al. (2017) found a negative correlation between IL-1β and osteocalcin in postmenopausal women. The differences between our results and the results of Al-Daghri et al. may be explained by the lack of cofounders in their correlation analysis. Animal and *in vitro* studies suggests that IL-1β provides an important stimulus for osteoclasts' formation and activity, leading to excessive bone resorption. However, the presence of osteoblasts seems to be crucial in the formation of osteoclasts by IL-

1β (Lee et al., 2010) which could compromise the bone resorption in adults with MetS. The latter may explain the lack of association between IL-1β and CTX levels in our sample.

Our results show that the association of CRF with P1NP and total osteocalcin levels was significant after adjusting for sex, lean mass and fat mass (path c, total effect). Moreover, this association became non-significant when hsCRP levels were introduced as covariate (path c', direct effect), suggesting a potential mediating effect of hsCRP levels in its relationship with CRF and P1NP variables. Additionally, the mediation analysis showed that the CRF/P1NP relationship was totally mediated by hsCRP levels, which reinforces the abovementioned protective role of CRF on the adverse effects of adiposity (Oktay et al., 2017). In this sense, Torres-Costoso et al. (2021) have recently shown that fat individuals with high levels of CRF had a good bone health, probably due to its relationship on the decrease in fat mass and the ensuing inflammatory status (Torres-Costoso et al., 2015). Thus, this provides preliminary evidence for the hypothesis that hsCRP levels play an important role in the relationship between CRF and P1NP levels. Hence, our study reveals that, through its effect on hsCRP levels, CRF may reduce the detrimental effects of MetS on bone turnover.

Strengths and limitations

Our study has some limitations. At first, the cross-sectional design rules out the possibility to make cause-effect relationships. Second, the number of participants with complete data in all studied variables is relatively small and thus, caution should be taken when interpreting the results. Third, although 6-minute walk test has been proven to have good validity and reliability, we did not use the gold standard to measure CRF (Mänttäri et al., 2018). The strengths of the study comprise the use of objective measures of inflammatory and bone turnover markers. In addition, our statistical analyses were controlled for sex, lean mass and fat mass which are relevant given their association with bone-related parameters.

To sum up, the present study suggests a mediating effect of hsCRP levels in the association of CRF with P1NP levels. Therefore, if confirmed prospectively, improvements in CRF may reduce hsCRP concentrations with potential benefits in the bone formation processes. Further research should incorporate a broader set of bone metabolism markers (e.g., alkaline phosphatase, sclerostin and irisin) to clarify the role of CRF and inflammatory status on bone remodeling cycle in this population.

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Authorship: JJGC performed the statistical analyses and drafted the manuscript; LGC, DC, FD and EUG made substantial contributions to data interpretations and manuscript drafting; DC, BL, RC, PO, GW, AV and FD conceived of the study, and participated in its design and coordination; DT, MMT, UCU, RB and MZ revised critically the manuscript. all authors have read and approved the final version of the manuscript

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391 **Table 1.** Descriptive characteristics of the study subjects

	All (*n* = 81)	Men (*n* = 35)	Women (*n* = 46)
Age (years)	58.5 ± 5.0	59.2 ± 4.5	59.7 ± 5.4
Anthropometric and body composition			
Body mass (kg)	88.9 ± 13.4	95.6 ± 10.9	83.9 ± 12.9
Height (cm)	165.7 ± 8.8	173.5 ± 6.2	159.7 ± 4.9
BMI (kg/m^2)	32.3 ± 3.8	31.7 ± 3.2	32.8 ± 4.3
Waist circumference (cm)	101.9 ± 9.8	106.9 ± 8.4	98.3 ± 9.2
Lean mass (kg)	58.4 ± 11.1	68.9 ± 6.7	50.5 ± 6.1
Fat mass (kg)	30.4 ± 7.9	26.4 ± 6.1	33.5 ± 7.7
VAT (kg)	3.1 ± 0.7	3.2 ± 0.7	2.9 ± 0.7
Inflammatory markers			
IL-1β (pg/mL)	0.02 [0.02-0.11]	0.04 [0.02-0.25]	0.02 [0.02-0.06]
IL-6 (pg/mL)	2.50 [1.17-4.74]	1.95 [0.82-5.17]	2.64 [1.38-4.68]
IL-10 (pg/mL)	1.30 [0.10-3.41]	2.06 [0.10-5.83]	1.22 [0.10-3.41]
TNF-α (pg/mL)	9.47 [5.36-13.76]	10.72 [6.49-15.45]	8.04 [4.49-12.02]
hsCRP (mg/L)	3.05 [1.58-6.51]	1.68 [0.99-3.58]	4.77 [2.08-8.08]
VEGF (pg/mL)	146.25 [49.8-262.94]	150.06 [74.27-219.38]	142.20 [33.24-276.57]
Cardiorespiratory fitness			
6MWT (m)	581.3 ± 70.6	603.5 ± 74.7	564.5 ± 63.2
Bone turnover markers			
CTX (ng/mL)	0.5 ± 0.3	0.5 ± 0.3	0.6 ± 0.3
P1NP (pg/mL)	43.6 ± 18.7	39.3 ± 15.3	46.9 ± 20.4
Osteocalcin (ng/mL)	14.2 ± 7.8	11.8 ± 4.4	16.1 ± 9.3

392 Data are presented by means ± standard deviation or median [interquartile range].

393 *BMI* body mass index; *VAT* visceral adipose tissue; *HOMA* homeostasis model assessment index-Steady state
394 beta cell function; *HDL*-C high density lipoprotein cholesterol; *LDL-C* low density lipoprotein cholesterol; IL
395 interleukin; *TNF-α* tumor necrosis factor alpha; *hsCRP* high-sensitivity c-reactive protein; *VEGF* vascular
396 endothelial growth factor; *6MWT* six-minute walk test; *CTX* collagen type I cross-linked C-telopeptide; *P1NP*
397 procollagen type I N-terminal propeptide
398

399 **Table 2.** Partial correlations between cardiorespiratory fitness using the 6MWT, inflammatory markers and bone
400 turnover markers adjusting for sex, lean mass and fat mass

	IL-1β	IL-6	IL-10	TNF-α	hsCRP	VEGF	CTX	P1NP	Osteocalcin
6MWT	**0.340***	0.078	-0.007	-0.016	**-0.335***	-0.066	0.194	**0.228***	**0.296***
IL-1β	-	**0.537****	**0.351***	0.166	-0.146	0.061	0.096	**0.245***	0.154
IL-6		-	**0.491****	**0.338***	0.172	0.020	-0.104	-0.006	0.029
IL-10			-	**0.487****	-0.056	0.063	0.014	0.143	0.024
TNF-α				-	0.015	0.183	-0.086	-0.159	-0.062
hsCRP					-	0.185	**-0.233***	**-0.319***	-0.172
VEGF						-	-0.119	**-0.275***	-0.104
CTX							-	**0.699****	**0.743****
P1NP								-	**0.693****

401 Boldface indicates statistical significance. *$P < 0.050$, **$P < 0.001$

402 IL interleukin; *TNF-α* tumor necrosis factor alpha; *hsCRP* high-sensitivity c-reactive protein; *VEGF* vascular
403 endothelial growth factor; *6MWT* six-minute walk test; *CTX* collagen type I cross-linked C-telopeptide; *P1NP*
404 procollagen type I N-terminal propeptide

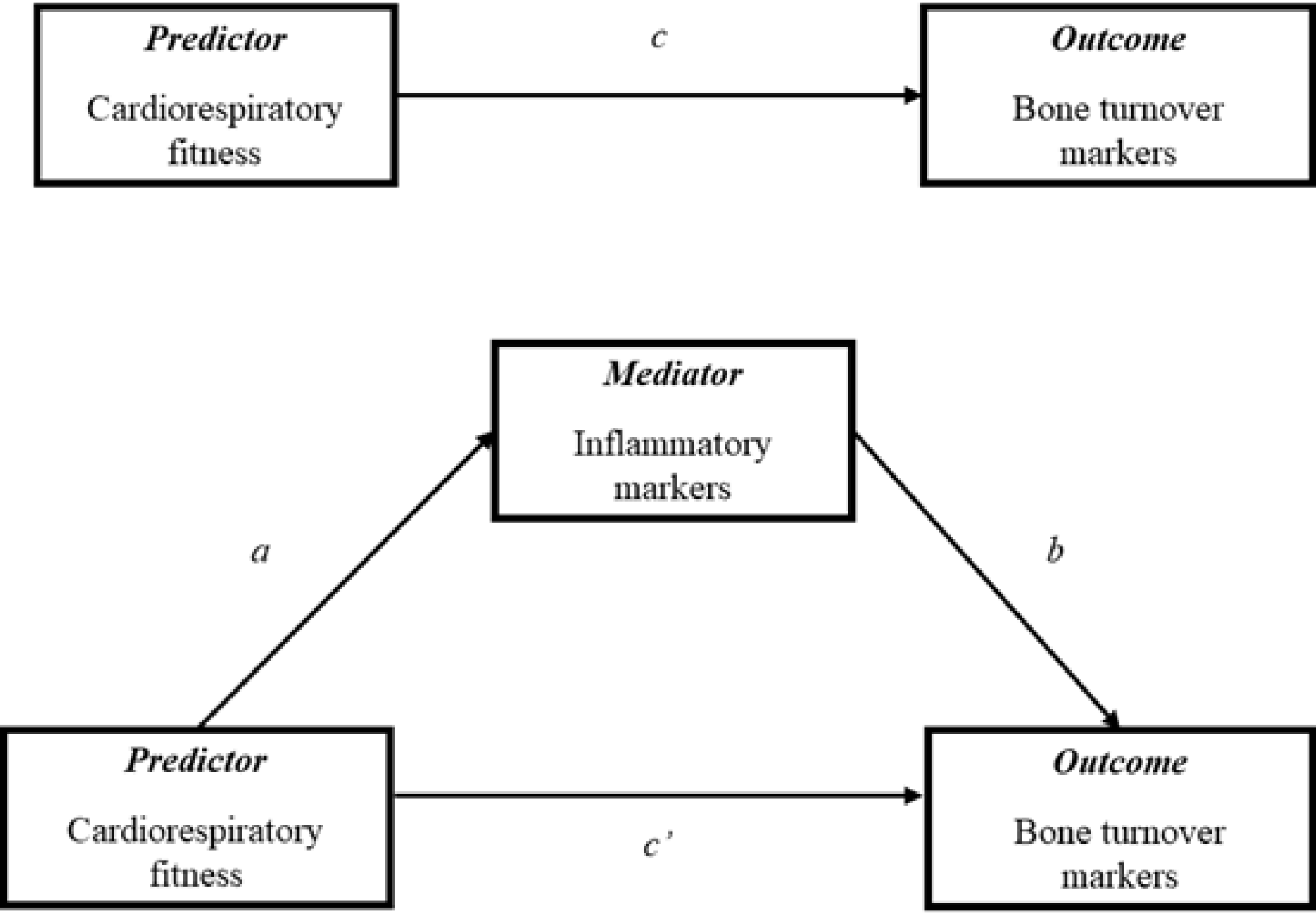
405

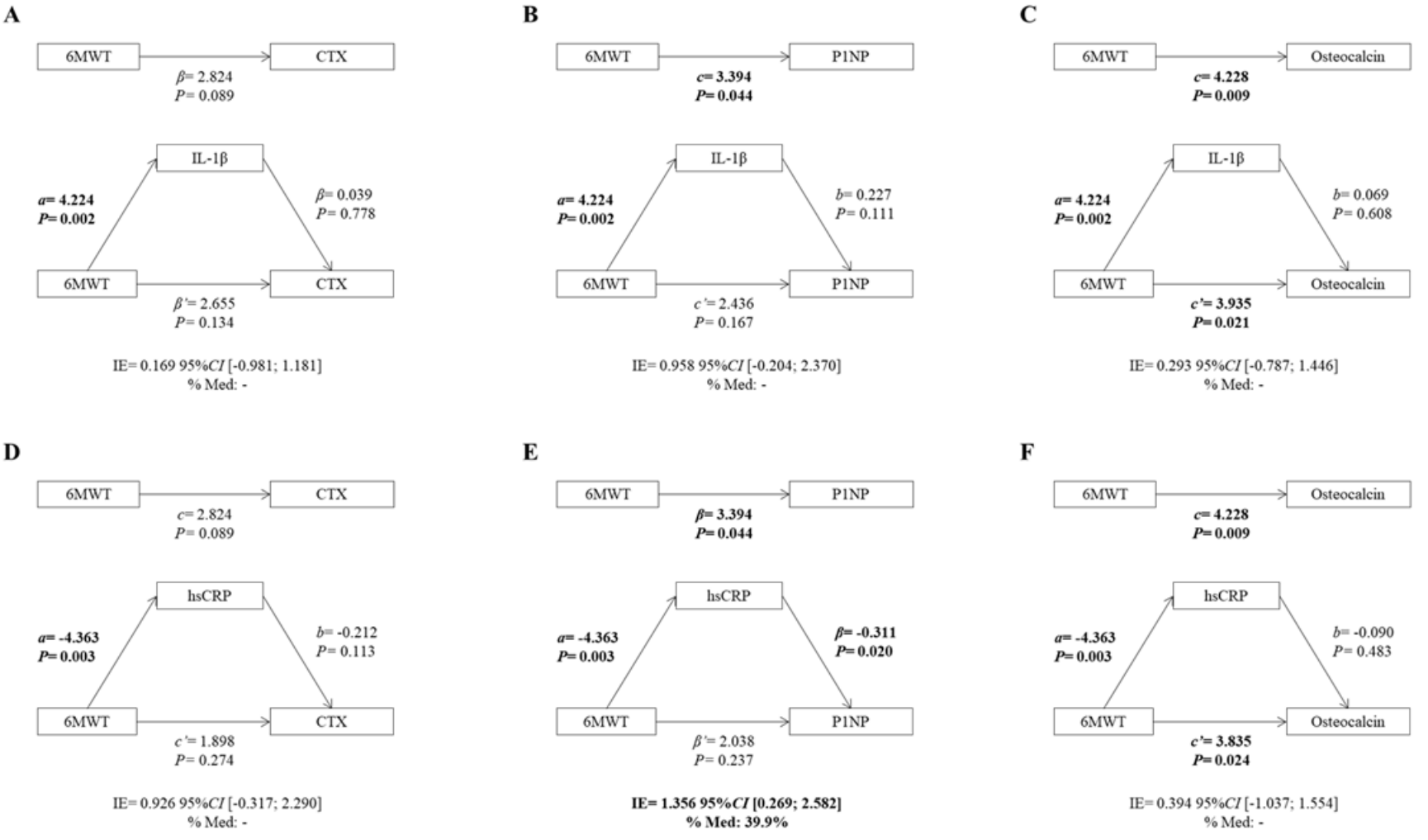
406 ## List of Figures

407 **Figure 1.** Causal diagram reflecting the simple mediation analyses. Path c shows the association
408 between the predictor and the outcome. Arrows a x b show the natural indirect effect pathway, and c'
409 shows the natural direct effect pathway.

410

411 **Figure 2.** Simple mediation models of the relationship between cardiorespiratory fitness using the
412 6MWT and bone turnover markers using IL-β and hsCRP as mediators, controlling for sex, lean mass
413 and fat mass. *IL* interleukin; *hsCRP* high-sensitivity c-reactive protein; *6MWT* six-minute walk test;
414 *CTX* collagen type I cross-linked C-telopeptide; *P1NP* procollagen type I N-terminal propeptide


Predictor
Cardiorespiratory fitness
c
Outcome
Bone turnover markers
Mediator
Inflammatory markers
a
b
Predictor
Cardiorespiratory fitness
c'
Outcome
Bone turnover markers


A
6MWT
CTX
β= 2.824
P= 0.089
IL-1β
a= 4.224
P= 0.002
β= 0.039
P= 0.778
6MWT
CTX
β'= 2.655
P= 0.134
IE= 0.169 95%CI [-0.981; 1.181]
% Med: -
B
6MWT
P1NP
c= 3.394
P= 0.044
IL-1β
a= 4.224
P= 0.002
b= 0.227
P= 0.111
6MWT
P1NP
c'= 2.436
P= 0.167
IE= 0.958 95%CI [-0.204; 2.370]
% Med: -
C
6MWT
Osteocalcin
c= 4.228
P= 0.009
IL-1β
a= 4.224
P= 0.002
b= 0.069
P= 0.608
6MWT
Osteocalcin
c'= 3.935
P= 0.021
IE= 0.293 95%CI [-0.787; 1.446]
% Med: -
D
6MWT
CTX
c= 2.824
P= 0.089
hsCRP
a= -4.363
P= 0.003
b= -0.212
P= 0.113
6MWT
CTX
c'= 1.898
P= 0.274
IE= 0.926 95%CI [-0.317; 2.290]
% Med: -
E
6MWT
P1NP
β= 3.394
P= 0.044
hsCRP
a= -4.363
P= 0.003
β= -0.311
P= 0.020
6MWT
P1NP
β'= 2.038
P= 0.237
IE= 1.356 95%CI [0.269; 2.582]
% Med: 39.9%
F
6MWT
Osteocalcin
c= 4.228
P= 0.009
hsCRP
a= -4.363
P= 0.003
b= -0.090
P= 0.483
6MWT
Osteocalcin
c'= 3.835
P= 0.024
IE= 0.394 95%CI [-1.037; 1.554]
% Med: -