



Longitudinal association of adiposity and high-sensitivity C-reactive protein from adolescence into early adulthood

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Abstract *Background and aims:* Longitudinal studies relating adiposity with low-grade inflammation are scarce. We aimed to examine the longitudinal association between the cumulative exposure to adiposity and low-grade inflammation from adolescence into early adulthood.

Methods and results: Data from a population-based cohort (EPITeen) (n = 1147) was analyzed. Body mass index (BMI), body fat percentage (BF%), waist circumference (WC), and waist-to-height ratio (WHtR) and high-sensitivity C-reactive protein (hsCRP) were ascertained at 13, 17 and 21 years of age and standardized for each wave. Generalized least squares models with a compound symmetry correlation structure were fitted to estimate the longitudinal effect of adiposity on hsCRP and results were presented as linear regression coefficients and 95% confidence intervals [β (95%CI)]. The final model estimated the association between the difference in adiposity between two consecutive evaluations (13–17 and 17 to 21-years-old), adjusted for previous adiposity and hsCRP levels, sex, parental education, leisure-time physical activity and fruits and vegetables intake. A positive association between the cumulative exposure to adiposity and final hsCRP was observed, in which the difference between adiposity indicators of two consecutive study waves was independently associated with hsCRP: 0.382 (0.299; 0.465) for BMI, 0.234 (0.164; 0.304) for WC, 0.395 (0.314; 0.477) for BF% and 0.195 (0.133; 0.258) for WHtR.

Conclusion: A significant longitudinal effect of the accumulation of adiposity on low-grade inflammation was observed. The change in adiposity from consecutive study waves was shown to have a stronger effect on final hsCRP concentrations than both previous adiposity and hsCRP levels.

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Introduction

Obesity prevalence has continuously increased worldwide over the last decades, contributing more progressively to morbidity and mortality [1–3]. This rise in adiposity levels is increasingly observed at early ages [3], with an alarming percentage of adolescents meeting the modified criteria for metabolic syndrome [4]. More ominously, it is well established that adiposity tracks from childhood to adulthood [5].

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Adipose tissue is an active endocrine and paracrine organ that releases a large number of bioactive mediators that contribute towards a low-grade inflammatory state – levels of inflammation previously thought to be inconsequential – that has been suggested to increase cardiovascular risk throughout life [6–9]. Understanding how early life exposure to adiposity triggers low-grade inflammation, and the potential mechanisms by which inflammation and metabolism interact over the lifespan are key to improving metabolic disease treatment and prevention in the near future [10,11].

Among all circulating inflammatory markers of the atherosclerotic process, C-reactive protein (CRP) has received the greatest attention mostly because of its analytical properties [12]. This marker has been used to measure low-grade inflammation through high-sensitivity assays (hsCRP) in order to detect elevated vascular risk in primary settings [13], and previous studies have used hsCRP to assess the relationship between adiposity and low-grade inflammation [14–16].

Adolescence is a dynamic maturational period during which there are major changes in development, namely in body composition [17]. By studying the longitudinal effect of adiposity and low-grade inflammation from adolescence, inferences could be drawn on whether there is a cumulative effect of adiposity on low-grade inflammation, along with whether there is a tracking of the inflammatory state from early ages. However, few longitudinal studies have assessed the tracking of inflammation, particularly in young populations.

Therefore, we aimed to examine the relationship of the dynamics of adiposity, measured by body mass index (BMI), body fat percentage (BF%), waist circumference (WC), and waist-to-height ratio (WHtR), with hsCRP from adolescence into early adulthood in a population-based cohort.

Methods

Subjects

Participants were adolescents, members of the Epidemiological Health Investigation of Teenagers in Porto (EPI-Teen). As reported elsewhere [18] we evaluated adolescents born in 1990, who were enrolled at public and private schools in Porto, Portugal, during the 2003/2004 school year. A second evaluation (17-years-old) took place in 2007–2008 and a third evaluation (21-years-old) in 2011–2013. In the first and second study waves, participants were evaluated at schools, and in the third study wave, participants were invited to complete the evaluation at our University department. Procedures for data collection, namely the anthropometric measurements and blood sample collection, were standardized in all study waves and performed by a team of trained health professionals.

At the recruitment, we identified 2786 eligible participants, of whom 2159 (77.5%) agreed to participate. In the second wave, we were able to re-evaluate 1716 participants (79.5%) and a new group of 783 adolescents were

integrated in the cohort as they moved to the school areas. Consequently, the cohort included 2942 participants. In the third study wave, 1764 (60%) participants were re-evaluated. From the 2942 cohort participants, we excluded those who did not have measurements in two consecutive moments for BMI ($n = 836$) and for hsCRP ($n = 864$), hsCRP levels above 10 mg/L that could be indicative of acute infection ($n = 92$), and those with missing information on parental education ($n = 3$). Thus, the present analysis was based on 1147 participants (52.0% females).

This study was conducted according to the guidelines laid down in the 1964 Declaration of Helsinki and its later amendments. The Ethics Committee of Hospital S. João and the Ethics Committee of the Institute of Public Health from the University of Porto approved the study and appropriate standard procedures were developed to guarantee data confidentiality and protection. Written consent was obtained from both legal guardians and adolescents in the first and second study waves, and from participants in the third study wave.

Anthropometrics

Weight and height were obtained with the subject in light indoor clothes and no shoes. Weight was measured in kilograms, to the nearest tenth, using a digital scale (Tanita TBF-300, Tanita Corporation of America, Inc., Illinois, USA) and height was measured in centimeters, to the nearest tenth, using a portable stadiometer (Seca Deutschland, Hamburg, Germany). Waist and hip circumferences were measured to the nearest 0.1 cm with a flexible and non-distensible tape, avoiding exertion of pressure on the tissues and with the subject standing. Waist circumference was measured midway between the lower limit of the rib cage and the iliac crest, at the end of gentle expiration, and hip circumference was measured on the maximum circumference over the femoral trochanters. BF% was estimated by foot-to-foot bioelectrical impedance (Tanita TBF-300, Tanita Corporation of America, Inc., Illinois, USA).

BMI [weight (kg)/height (m)²] was computed. At 13 and 17 participants were classified according to age-specific and sex-specific BMI z-scores developed by the World Health Organization [19]. At 21 BMI z-scores, with a Box-Cox transformation, were computed based on the sample distribution.

High sensitivity C reactive protein

A venous blood sample was drawn after an overnight fast at each study wave. All the samples were analysed at the central laboratory of the Centro Hospitalar São João. HsCRP serum values were determined through particle-enhanced immunonephelometry using an auto-analyser Behring, Nephelometer II, BN II® (Siemens, Lisboa, Portugal). The detection limit was 0.2 mg/L.

In order to achieve a normal distribution, a Box-Cox transformation was performed for hsCRP, and the z-score for age of each wave was used in the analysis.

Covariates

Data on covariates was collected using self-reported questionnaires. Parental educational level was defined as the number of successfully completed years of formal schooling and adolescents were classified according to the parent with the higher education level. This information was used as a proxy of social status [20]. Leisure-time physical activity was evaluated at 21 years-old according to a previously validated closed four-choice question of subjective intensity categories (sitting, standing and/or walking, and very active) [21]. Fruit and vegetable intake were used as a proxy indicator of diet quality [22]. Food intake was assessed at 21 years-old, using an 82-item semi-quantitative food frequency questionnaire. Each participant was asked about the mean frequency of consumption (nine categories ranging from 'never or less than once a month' to '6 or more times a day'), the mean portion consumed (lower, equal or higher than the mean portion size) and the seasonal variation of consumption [23].

Statistical analysis

Continuous variables were presented as median (25–75th percentiles) and Mann-Whitney U test was used for independent group comparison. Proportions were compared using chi-square tests.

In order to quantify the effect of adiposity on hsCRP z-score, the difference in the adiposity indicators from consecutive study waves was calculated (by subtracting the adiposity indicator at 17y from the adiposity indicator at 13y, and the adiposity indicator at 21y from the adiposity indicator at 17y) and the association with hsCRP z-score was assessed in the end of each wave (at 17y or at 21y). Generalized least squares models with a compound symmetry correlation structure were used to consider the dependence between repeated measurements.

To test if the association was similar in both periods (from 13y to 17y and 17y to 21y), an interaction term between each exposure and the follow-ups was added. Since no statistically significant interaction term was found, a similar effect throughout time was assumed.

Four models were estimated and results are presented as linear regression coefficients (β) and 95% confidence intervals (95% CI). In the first model only the difference between the adiposity levels of two consecutive study waves was included. In the second model, this difference in adiposity measurements was further adjusted for the previous wave adiposity levels. In the third model, previous wave hsCRP levels were further added to consider the tracking of hsCRP. In the fourth model, variables were further adjusted for sex and parental educational level. In order to test the role of diet and physical activity and additional model was tested with that information at 21y.

Statistical analyses were performed using the Statistical Package for the Social Sciences (IBM® SPSS® Statistics), version 23.0 and the R package, version 3.0.1, and statistical significance was considered with an alpha critical value of 0.05.

Results

Comparison of included and non-included participants is presented in Table 1. In general, included and non-included participants were similar. However, included participants had parents with a higher educational level.

Spearman correlations between adiposity indicators and hsCRP in the three study waves are displayed in Table 2. The strongest correlations were observed between adiposity indicators over the study waves. Correlations between hsCRP throughout the evaluations were also verified, but they were lower than those observed for adiposity. Regarding the relationship between adiposity and hsCRP, the relationship was significant but decreased with age for BMI, WC and WHtR, but not for BF%.

No interaction was observed between the exposures and time of follow-ups. Thus, the estimates were fixed throughout the study waves.

The effect of the longitudinal cumulative exposure of BMI on hsCRP levels is depicted in Table 3. After adjustment for previous BMI and hsCRP, sex, parental education, leisure-time physical activity and fruits and vegetables, a significant positive association was observed between the cumulative exposure of BMI z-score on hsCRP, in which the difference between BMI of two consecutive study waves was independently associated with hsCRP ($\beta = 0.382$; 95% CI 0.299; 0.465 for BMI). This means that hsCRP levels increase 0.382 SD per 1 SD increase in each variation of BMI z-score. Results were similar for BF% ($\beta = 0.395$; 95% CI 0.314; 0.477) as well as for WC and WHtR, although with a weaker magnitude of association ($\beta = 0.195$; 95% CI 0.133; 0.258 for WHtR). Although the adiposity levels from the previous evaluations also showed a significant positive association with hsCRP, the magnitude of the effect was weaker ($\beta = 0.179$; 95% CI 0.128; 0.230 for BMI, $\beta = 0.190$; 95% CI 0.134; 0.245 for WC, $\beta = 0.241$; 95% CI 0.171; 0.312 for BF% and $\beta = 0.187$; 95% CI 0.133; 0.241 for WHtR).

Likewise, the adjustment for hsCRP of the previous evaluations showed a positive association with the final hsCRP values. After adjustment for previous hsCRP concentrations, the correlation between hsCRP measurements consistently decreased ($\tau = -0.019$; $\tau = -0.023$; $\tau = 0.005$ and $\tau = -0.019$).

Discussion

In this population-based cohort study, we observed a significant longitudinal effect of the accumulation of adiposity on low-grade inflammation over time. Interestingly, the magnitude of the association of the change in adiposity from consecutive study waves was shown to be more relevant on hsCRP concentrations than the previous value of hsCRP. This indicates that although there is a tracking of low-grade inflammation over time, these inflammatory levels are more dependent on the evolution of adiposity than on the tracking of inflammation.

Consistent with prior research across a wide range of populations [24], we found a positive association between adiposity and hsCRP levels. Though the bulk of literature

Table 1 Comparison of included and non-included participants.

	Non-included n = 1795	Included n = 1147	p
Sex (%)			
Female	911 (50.8)	596 (52.0)	0.522
Male	884 (49.2)	551 (48.0)	
Parental education, years (%)			<0.001
0–6	414 (30.5)	260 (22.7)	
7–9	346 (20.6)	217 (18.9)	
10–12	427 (25.4)	304 (26.5)	
>12	396 (23.5)	366 (31.9)	
BMI, (Kg/m ²)			
13 years	20.2 (18.3–22.5)	20.2 (18.6–22.7)	0.213
17 years	21.7 (19.9–24.0)	21.7 (20.0–23.9)	0.310
21 years	22.1 (20.3–24.7)	22.4 (20.6–25.0)	0.024
BMI Percentiles at 13y (%) ^a			
Underweight (SD < -2)	21 (1.8)	7 (0.8)	0.145
Normal weight (-2 ≤SD ≤1)	810 (70.2)	614 (69.5)	
Overweight (1 < SD ≤2)	218 (18.9)	187 (21.2)	
Obesity (>2 SD)	105 (9.1)	75 (8.5)	
BMI Percentiles at 17y (%) ^a			
Underweight (SD < -2)	12 (0.9)	7 (0.6)	0.611
Normal weight (-2 ≤SD ≤ 1)	1023 (77.4)	884 (77.1)	
Overweight (1 < SD ≤2)	209 (15.8)	196 (17.1)	
Obesity (>2 SD)	78 (5.9)	60 (5.2)	
BMI Percentiles at 21y (%) ^b			
Underweight	44 (5.7)	58 (5.8)	0.324
Normal weight	534 (69.3)	676 (68.1)	
Overweight	133 (17.3)	198 (19.9)	
Obesity	60 (7.8)	61 (6.1)	
hsCRP, (mg/L)			
13 years	0.3 (0.1–0.9)	0.3 (0.1–0.7)	0.110
17 years	0.5 (0.2–2.1)	0.5 (0.2–1.7)	0.748
21 years	0.8 (0.4–2.0)	0.7 (0.3–1.9)	0.132

Values are expressed as median (25–75th percentiles) or percentages. Total may not add to 2492 due to missing data.

BMI, body mass index; hsCRP, high sensitivity C-reactive protein.

^a Categorized according to WHO growth reference for school-aged children and adolescents [19].

^b Categorized according to WHO classification for adults [39].

on this relationship has been cross-sectional, longitudinal work in UK adults suggests that weight gain can have impact on CRP elevation across all BMI classes [14]. Similar results were found in middle-aged American adults, with a stronger effect observed in those already overweight or obese at baseline. Supporting this relationship weight loss was associated with reduced CRP levels [15]. In a meta-analysis that examined 28 lifestyle interventions aiming to reduce weight, the investigators concluded that weight loss was associated with a decline in CRP values across all types of interventions [25]. Likewise, results from the China Health and Nutrition Survey that identified patterns of weight change across age and sex strata found that steeper weight gain trajectories were associated with elevated hsCRP values, while weight loss showed to be associated with lower risk of inflammation [26].

WC and WHtR showed a weaker magnitude of association with hsCRP than BMI and BF%. Although correlated with total adiposity, when compared to BMI and BF%, WC and WHtR are less indicated to measure overall adiposity levels. These results suggest that total adiposity levels might be more relevant for the development of a low-grade inflammatory state than body fat distribution. In a

previous work [27], we have found that WHR was show to have the least discriminatory ability to correctly identify subjects with elevated hsCRP. Therefore, it was not considered in the present analysis.

In the Bogalusa Heart Study, childhood adiposity was associated with higher hsCRP concentrations in adulthood [28]. Our findings show that the relationship between adiposity and hsCRP is already present in adolescence and also predict inflammation later on. This supports the early induction of low-grade inflammation with the potential for lifelong consequences on metabolic regulation [11]. Additionally, the results show that although there is some tracking of inflammation it is considerably smaller than the effect of adiposity. The fact that this relationship exists well below the levels considered to be at risk for cardiovascular disease, of which events are observed later in life, reflects that there is a continuum obesity-induced inflammatory potential down to very low levels, requiring a life-course approach.

We observed that hsCRP values increased with the variation of adiposity. This result underscores the need for early prevention strategies given that in an individual participant meta-analysis, whose participants were on

Table 2 Spearman correlations between adiposity indicators and hsCRP of the three study waves.^a

	BMI 13y	BMI 17y	BMI 21y	WC 13y	WC 17y	WC 21y	BF% 13y	BF% 17y	BF% 21y	WHR 13y	WHR 17y	WHR 21y	WHtR 13y	WHtR 17y	WHtR 21y	hsCRP 13y	hsCRP 17y	hsCRP 21y
BMI 13y	-	0.827	0.694	0.841	0.651	0.536	0.663	0.511	0.497	0.204	0.224	0.199	0.801	0.681	0.613	0.254	0.197	0.195
BMI 17y	-	-	0.767	0.706	0.784	0.601	0.453	0.524	0.438	0.237	0.314	0.310	0.667	0.795	0.674	0.212	0.245	0.154
BMI 21y	-	-	-	0.620	0.668	0.839	0.290	0.273	0.508	0.291	0.342	0.464	0.583	0.604	0.877	0.235	0.240	0.209
WC 13y	-	-	-	-	0.732	0.627	0.540	0.387	0.385	0.526	0.368	0.368	0.876	0.639	0.600	0.291	0.217	0.160
WC 17y	-	-	-	-	-	0.712	0.307	0.349	0.287	0.401	0.690	0.498	0.596	0.836	0.628	0.208	0.220	0.105
WC 21y	-	-	-	-	-	-	0.110	0.062 [†]	0.272	0.448	0.534	0.785	0.503	0.485	0.878	0.220	0.187	0.113
BF% 13y	-	-	-	-	-	-	-	0.810	0.742	-0.048 [†]	-0.092	-0.258	0.590	0.530	0.304	0.142	0.166	0.308
BF% 17y	-	-	-	-	-	-	-	-	0.807	-0.143	-0.101	-0.304	0.409	0.597	0.284	0.065 [†]	0.196	0.313
BF% 21y	-	-	-	-	-	-	-	-	-	-0.119	-0.145	-0.194	0.384	0.481	0.494	0.081 [†]	0.155	0.410
WHR 13y	-	-	-	-	-	-	-	-	-	-	0.546	0.591	0.570	0.269	0.363	0.198	0.091	-0.018 [†]
WHR 17y	-	-	-	-	-	-	-	-	-	-	-	0.665	0.337	0.528	0.413	0.147	0.125	-0.062 [†]
WHR 21y	-	-	-	-	-	-	-	-	-	-	-	-	0.299	0.252	0.622	0.159	0.090	-0.095
WHtR 13y	-	-	-	-	-	-	-	-	-	-	-	-	-	0.687	0.620	0.281	0.204	0.207
WHtR 17y	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0.649	0.180	0.245	0.218
WHtR 21y	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0.213	0.207	0.219
hsCRP 13y	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0.308	0.210
hsCRP 17y	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0.322
hsCRP 21y	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

BMI, body mass index; hsCRP, high sensitivity C-reactive protein; y, years.

^a A p < 0.001 was observed for all the correlations except for those marked with †.

average 60 years-old, every 1-SD increase in CRP was shown to increase vascular risk by more than 60% [29].

In addition to the influence of adiposity on hsCRP values, we also found a tracking of low-grade inflammation itself. Similar results were observed in the Young Finns Study, which determined the correlation between childhood and adulthood hsCRP concentrations and found a significant tracking, reporting childhood hsCRP and childhood BMI as predictors of adulthood hsCRP [30]. However, our results suggest that there is potential to revert these low-grade inflammatory levels, since the association between the dynamics in adiposity levels were more strongly associated with final hsCRP values than the tracking of inflammation itself. This has great relevance from a disease prevention standpoint, given that the attempt to treat established obesity in adulthood may be too late to have a crucial long term impact on health, reinforcing the need for preventive strategies at the onset of disease [31]. By shaping the regulation of adiposity-induced inflammation, early environments moderate responses to inflammatory stimuli later in life, with implications for the association between inflammation and cardiometabolic disease [32]. Moreover, the recent advent of highly sensitive laboratory assays for CRP has led to the discovery that low-grade inflammation may contribute to the pathophysiology of cardiovascular disease at early stages [33]. In fact, current guidelines recommend hsCRP as a reliable, rapid and cheap method for both primary and secondary prevention [13,34,35].

A major strength of our study is the use of a prospective population-based cohort, with measures of both adiposity and inflammation over time. The assessment of the longitudinal association between adiposity and systemic low-grade inflammation over time in a population-based observational approach is crucial to inform the nature of any temporal associations, which cannot be assessed with a cross-sectional design [36]. Our results are supported by recent reciprocal Mendelian randomization studies which have shown that adiposity causally influences circulating CRP concentrations and not vice versa [37,38]. Nonetheless, some limitations should be considered. Since evaluations at 13 and 17 were performed at school the logistical conditions available did not allow to evaluate the pubertal stage, therefore we were unable to evaluate how the pubertal stage could influence the association between adiposity and hsCRP. Although we relied on a single hsCRP measurement within each wave, this inflammatory marker has shown to be stable with little or no diurnal variation and, even a single measurement, adds prognostic information on cardiovascular risk comparable to blood pressure or cholesterol [13].

In conclusion, we observed a longitudinal effect of the accumulation of adiposity on low-grade inflammation from adolescence into early adulthood. Additionally, the change in adiposity from consecutive study waves showed to be more relevant than previous adiposity and hsCRP levels on final hsCRP concentrations. Our results support the relevance of the prevention of adiposity gain and related low-grade inflammation since early ages, avoiding

Table 3 Generalized least squares models to estimate the longitudinal association of the cumulative effect of adiposity on hsCRP levels.

HsCRP z-score							
BMI		WC		BF%		WHtR	
	β (95% CI)		β (95% CI)		β (95% CI)		β (95% CI)
Model 0		Model 0		Model 0		Model 0	
ΔBMI z-score	0.177 (0.104; 0.250)	ΔWC z-score	0.037 (−0.022; 0.096)	ΔBF% z-score	0.238 (0.161; 0.315)	ΔWHtR z-score	0.029 (−0.024; 0.084)
τ	0.368	τ	0.367	τ	0.371	τ	0.364
Model 1		Model 1		Model 1		Model 1	
ΔBMI z-score	0.295 (0.218; 0.372)	ΔWC z-score	0.114 (0.048; 0.180)	ΔBF% z-score	0.388 (0.309; 0.468)	ΔWHtR z-score	0.162 (0.100; 0.224)
Previous BMI z-score	0.224 (0.172; 0.277)	Previous WC z-score	0.159 (0.099; 0.220)	Previous BF% z-score	0.330 (0.274; 0.386)	Previous WHtR z-score	0.259 (0.199; 0.319)
τ	0.333	τ	0.346	τ	0.327	τ	0.322
Model 2		Model 2		Model 2		Model 2	
ΔBMI z-score	0.293 (0.215; 0.371)	ΔWC z-score	0.100 (0.033; 0.168)	ΔBF% z-score	0.404 (0.324; 0.484)	ΔWHtR z-score	0.157 (0.094; 0.220)
Previous BMI z-score	0.155 (0.106; 0.203)	Previous WC z-score	0.103 (0.047; 0.159)	Previous BF% z-score	0.276 (0.226; 0.326)	Previous WHtR z-score	0.200 (0.144; 0.256)
Previous hsCRP z-score	0.280 (0.233; 0.326)	Previous hsCRP z-score	0.268 (0.218; 0.319)	Previous hsCRP z-score	0.275 (0.227; 0.322)	Previous hsCRP z-score	0.250 (0.200; 0.300)
τ	0.026	τ	0.054	τ	0.013	τ	0.049
Model 3		Model 3		Model 3		Model 3	
ΔBMI z-score	0.358 (0.281; 0.435)	ΔWC z-score	0.232 (0.162; 0.302)	ΔBF% z-score	0.393 (0.312; 0.475)	ΔWHtR z-score	0.195 (0.132; 0.257)
Previous BMI z-score	0.165 (0.119; 0.212)	Previous WC z-score	0.187 (0.132; 0.243)	Previous BF% z-score	0.239 (0.169; 0.310)	Previous WHtR z-score	0.186 (0.132; 0.240)
Previous hsCRP z-score	0.316 (0.271; 0.361)	Previous hsCRP z-score	0.296 (0.247; 0.344)	Previous hsCRP z-score	0.285 (0.237; 0.334)	Previous hsCRP z-score	0.289 (0.240; 0.338)
Sex	−0.432 (−0.518; −0.346)	Sex	−0.537 (−0.638; −0.436)	Sex	−0.093 (−0.223; 0.038)	Sex	−0.400 (−0.494; −0.305)
Parental education	0.001 (−0.009; 0.010)	Parental education	0.001 (−0.010; 0.010)	Parental education	−0.001 (−0.011; 0.009)	Parental education	0.001 (−0.009; 0.011)
τ	−0.052	τ	−0.026	τ	0.002	τ	−0.022
Model 4		Model 4		Model 4		Model 4	
ΔBMI z-score	0.382 (0.299; 0.465)	ΔWC z-score	0.234 (0.164; 0.304)	ΔBF% z-score	0.395 (0.314; 0.477)	ΔWHtR z-score	0.195 (0.133; 0.258)
Previous BMI z-score	0.179 (0.128; 0.230)	Previous WC z-score	0.190 (0.134; 0.245)	Previous BF% z-score	0.241 (0.171; 0.312)	Previous WHtR z-score	0.187 (0.133; 0.241)
Previous hsCRP z-score	0.293 (0.245; 0.341)	Previous hsCRP z-score	0.294 (0.245; 0.343)	Previous hsCRP z-score	0.284 (0.235; 0.332)	Previous hsCRP z-score	0.288 (0.239; 0.336)
Sex	−0.471 (−0.565; −0.378)	Sex	−0.542 (−0.643; −0.440)	Sex	−0.093 (−0.223; 0.037)	Sex	−0.402 (−0.496; −0.307)
Parental education	0.002 (−0.008; 0.012)	Parental education	0.001 (−0.009; 0.012)	Parental education	0.001 (−0.010; 0.011)	Parental education	0.002 (−0.008; 0.013)
Physical Activity	−0.013 (−0.076; 0.050)	Physical Activity	0.001 (−0.063; 0.065)	Physical Activity	0.005 (−0.059; 0.069)	Physical Activity	−0.005 (−0.069; 0.059)
Fruits and vegetables	−0.014 (−0.032; 0.003)	Fruits and vegetables	−0.011 (−0.029; 0.007)	Fruits and vegetables	−0.011 (−0.029; 0.007)	Fruits and vegetables	−0.009 (−0.027; 0.009)
τ	−0.019	τ	−0.023	τ	0.005	τ	−0.019

τ: the residual correlation between hsCRP measurements.

BMI, body mass index; WC, waist circumference, BF%, body fat percentage; WHtR, waist-to-height ratio hsCRP, high sensitivity C-reactive protein.

Δ: change in adiposity indicator z-score from two consecutive study waves (13–17y or 17–21y).

Previous BMI/WC/BF%/WHtR z-score: adiposity indicator z-score from the previous study wave (13y or 17y).

Previous hsCRP z-score: hsCRP z-score from the previous study wave (13y or 17y).

decades of dysfunctional adipose tissue and envisaging long-term cardiovascular health.

Conflicts of interest

The authors declare no conflict of interest.

Contributions

MC performed the statistical analysis and drafted the first version of the manuscript. MS performed the statistical analysis and contributed to the interpretation and discussion of the data. HB and JTG provided significant advice and contributed to the revision and discussion of the manuscript. ER conceived and designed the study, coordinated and supervised data collection, and contributed to the interpretation and discussion of the data. All authors critically reviewed the manuscript and approved the final version.

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