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Association of body shape phenotypes and body fat distribution indexes with inflammatory biomarkers in the European Prospective Investigation into Cancer and Nutrition (EPIC) and UK Biobank

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Abstract

Background The allometric body shape index (ABSI) and hip index (HI), as well as multi-trait body shape phenotypes, have not yet been compared in their associations with inflammatory markers. The aim of this study was to examine the relationship between novel and traditional anthropometric indexes with inflammation using data from the European Prospective Investigation into Cancer and Nutrition (EPIC) and UK Biobank cohorts.

Methods Participants from EPIC ($n = 17,943$, 69.1% women) and UK Biobank ($n = 426,223$, 53.2% women) with data on anthropometric indexes and C-reactive protein (CRP) were included in this cross-sectional analysis. A subset of women in EPIC also had at least one measurement for interleukins, tumour necrosis factor alpha, interferon gamma, leptin, and adiponectin. Four distinct body shape phenotypes were derived by a principal component (PC) analysis on height, weight, body mass index (BMI), waist (WC) and hip circumferences (HC), and waist-to-hip ratio (WHR). PC1 described overall adiposity, PC2 tall with low WHR, PC3 tall and centrally obese, and PC4 high BMI and weight with low WC and HC, suggesting an athletic phenotype. ABSI, HI, waist-to-height ratio and waist-to-hip index (WHI) were also calculated. Linear regression models were carried out separately in EPIC and UK Biobank stratified by sex and adjusted for age, smoking status, education, and physical activity. Results were additionally combined in a random-effects meta-analysis.

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Results Traditional anthropometric indexes, particularly BMI, WC, and weight were positively associated with CRP levels, in men and women. Body shape phenotypes also showed distinct associations with CRP. Specifically, PC2 showed inverse associations with CRP in EPIC and UK Biobank in both sexes, similarly to height. PC3 was inversely associated with CRP among women, whereas positive associations were observed among men.

Conclusions Specific indexes of body size and body fat distribution showed differential associations with inflammation in adults. Notably, our results suggest that in women, height may mitigate the impact of a higher WC and HC on inflammation. This suggests that subtypes of adiposity exhibit substantial variation in their inflammatory potential, which may have implications for inflammation-related chronic diseases.

Keywords Body shape, Height, Anthropometric indicators, Inflammation, C-reactive protein

Background

Body fatness has been associated with various comorbidities and cardiometabolic risk [1]. Several studies suggested that abdominal obesity is more strongly associated with cardiovascular risk factors than general obesity usually proxied by body mass index (BMI) [2, 3]. Additionally, waist circumference (WC) is a proxy of abdominal obesity positively associated with body size (mainly weight and BMI, but also height). Thus, the measurement of WC may not provide information on the abdominal deposition of fat beyond BMI.

To overcome the limitations of traditional anthropometric indexes, the allometric body shape index (ABSI) and hip index (HI) [4, 5] were developed to reflect WC and hip circumference (HC) among individuals with the same weight and height [6]. Thus, information on body size is reflected in BMI and height and information on body shape and fat distribution is reflected in ABSI and HI [7]. Alternatively, data-driven body shape phenotypes have been proposed to capture body size and body fat distribution holistically [8]. These phenotypes were derived by a principal component (PC) analysis (PCA) of six anthropometric traits [height, weight, BMI, WC, HC, and waist-to-hip ratio (WHR)] [8]. Four body shape phenotypes were previously identified in the European Prospective Investigation into Cancer and Nutrition (EPIC) study [9] and UK Biobank [10] characterizing overall adiposity (PC1), tall stature with low WHR (PC2), tall stature with central obesity (PC3), and high BMI and weight with low WC and HC likely defining an athletic phenotype (PC4). Previous findings suggested that these complex anthropometric indexes (ABSI, HI, and body shape phenotypes) may be more accurate than traditional anthropometric indexes at capturing information on cardiometabolic and metabolic health [8], cancer risk assessment [9], and mortality risk stratification [11]. However, there is a limited number of studies on the association of these anthropometric indexes or body shape phenotypes with inflammatory biomarkers.

Inflammation has been proposed as a potential biological mechanism linking body fatness to cardiometabolic

diseases and cancer [12, 13]. A previous study using data from UK Biobank reported positive associations of ABSI and BMI with inflammatory biomarkers such as C-reactive protein (CRP), neutrophil, monocyte, and lymphocyte counts, while HI was only inversely associated with lymphocyte count [14]. Additionally, it has been observed that a high ABSI value is an independent predictor of endothelial dysfunction in both sexes [15], suggesting its association with inflammatory processes.

Therefore, we used data from EPIC and UK Biobank cohorts to examine cross-sectionally the associations of the traditional anthropometric indexes, ABSI, HI, WHR, waist-to-height ratio (WHtR), waist-to-hip index (WHI), and four body shape phenotypes (PC1-4), with circulating inflammatory biomarkers.

Methods

Study population: EPIC and UK Biobank

EPIC is a multicentre cohort study that included ~520,000 participants, aged mainly between 35 and 65 years, recruited from 1992 to 2000 across ten European countries (Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the UK). Socio-demographic, dietary, lifestyle, anthropometric, and medical data were collected at recruitment from all participants by country-specific questionnaires. Further details have previously been described elsewhere [16]. Data from Greece were not available for this analysis.

Approximately 386,000 EPIC participants provided a blood sample at recruitment [16]. All participants provided written informed consent and ethical approval for the study was obtained from the International Agency for Research on Cancer (IARC) ethics review panel (No. 20–34) and from all recruiting centres [16].

The UK Biobank is a prospective cohort study with over 500,000 individuals registered with the National Health Service of the United Kingdom [17]. Participants were recruited between 2006 and 2010, aged 40 to 70, and from across 22 study centres in England, Scotland, and

Wales. The study collected a wide range of data, including anthropometric measurements, lifestyle, health-related indexes, and biological samples.

Study population

In EPIC, participants were controls (i.e. cancer-free participants at blood collection) from nested case–control or case-cohort sub-studies conducted on associations between inflammation and cancer [18–28]. All included participants had CRP measured as it was the main inclusion criteria and, some women among the included participants also had additional inflammatory biomarkers measured including interleukin-6 (IL6), IL8, IL10, IL17d, interleukin 1 receptor antagonist (IL1ra), tumour necrosis factor alpha (TNF- α), Interferon-gamma (IFN- γ), leptin, and adiponectin. In total, 17,943 (69.1% women) EPIC participants were included. However, the number of participants included for the analysis of each biomarker was variable due to data availability (Additional file 1: Fig. S1).

The initial UK Biobank study sample included 503,386 individuals. After exclusion of participants with prevalent cancer at baseline and individuals lacking anthropometric measurements, 426,223 UK Biobank participants (53.2% women) who had values for CRP were included (Additional file 1: Fig. S1).

Assessment of anthropometric measurements

All anthropometric measurements included in EPIC followed standardized protocols, apart from Oxford (UK), where body weight and height were self-reported. However, these self-reported data were improved via prediction equations in Oxford and the self-reported data was considered valid for identifying associations [29]. Weight was measured barefoot and rounded to the nearest 0.1 kg whereas height was measured to the nearest 0.1 cm or 0.5 cm. WC was measured either between the lowest rib and the iliac crest or at the narrowest circumference of the torso. HC was horizontally determined at the wider point of the hip or above the buttocks. Additionally, weight, WC and HC measurements were corrected for clothing differences among centres [29]. When certain anthropometric data were missing like the weight, height, WC, and HC, they were imputed for some individuals using centre-, age-, and sex-specific mean values.

In the UK Biobank, trained personnel collected anthropometric measurements, where Seca 202 stadiometer and Tanita BC-418 body composition analyser were utilized to measure height and weight, respectively. WC was assessed at the point of natural indentation or the umbilicus, while HC was gauged at the widest part of the participants' hips.

Anthropometric indexes and body shape phenotypes

BMI was computed as: weight in kg divided by height in squared metres. WHR was determined by dividing WC by HC, both in centimeters. Additionally, other common indexes were computed, including WHtR and WHI [14].

ABSI was calculated as $WC/(BMI^{2/3}height^{1/2})$ [30] while HI was defined as $HC(height/[height])^{0.310}(weight/[weight])^{-0.482}$ with squared brackets indicating the mean values of the sample [31]. The mean value for height in EPIC was 164.9 cm while for weight was 70.9 kg whereas in the UK Biobank mean height was 168.6 cm and weight was 78.2 kg. Body shape phenotypes were previously derived in EPIC and in UK Biobank [9, 10]. Body shape phenotypes were derived through PCA performed on the standardized residuals of six anthropometric traits: height, weight, BMI, WC, HC, and WHR. For each single anthropometric trait, residuals were derived from a linear regression model of the anthropometric trait onto age, sex, and study centre [8–10]. This further adjustment was performed to remove the additional variability introduced by both age and sex making those traits more comparable across populations. Six PCs were created where each component represented a weighted sum of the six transformed traits and was independent of the other components. Out of the six PCs created, the first four PCs collectively explained 99.8% of the total variation of the six anthropometric variables and were selected for the subsequent analysis. Each of the four identified PCs described a specific body morphology type: PC1, overall adiposity, PC2, tall stature with low WHR, PC3, tall stature with large WHR, and PC4 characterized by high BMI and weight with low WC and HC. Body shape phenotypes showed similar loadings between the two study samples (Additional file 1: Table S1). To facilitate the interpretation of the body shape phenotypes, arithmetic means and SD of age and the six anthropometric traits building the PCs for each study participant in the 5 and 95% of each PC are presented in Additional file 1: Table S2 and S3.

Laboratory measurements

EPIC blood samples were collected (in fasting status in a small proportion of the participants) and stored in liquid nitrogen (-196°C) in a centralized biobank. For laboratory analysis, serum was used for most centres except for Norway and Umea (Sweden) where citrated plasma and heparin plasma were used, respectively. Laboratory procedures for assessing inflammatory biomarkers in EPIC have been already described in detail [18–28]. Values that fell below LOD (Limit of Detection), below LLOQ (Lower Limit of Quantification), or above ULOQ (Upper Limit of Quantification) were set to LOD/2, LLOQ/2 and ULOQ,

respectively. In the EPIC cohort, some biomarkers were measured more than once in different nested case–control or case-cohort studies; in these instances, only data from the study with the highest number of quantified values for that biomarker were retained.

Within the UK Biobank, blood samples [32] were procured throughout the day (from 8 AM to 9 PM), devoid of any stipulated fasting prerequisites. CRP serum biomarker concentrations were quantified using the Beckman Coulter AU5800 analyser.

Statistical analysis

Concentrations of the biomarkers were transformed logarithmically to approximate a normal distribution. We implemented a normalization step of the EPIC data as described in a previously published pipeline [33]. Briefly, linear mixed effect models were used for each biomarker. Models corrected for unwanted random effects like variation due to analytical method and analytical batch and fixed effects such as study centre, fasting status (no, in between, yes) and time of blood draw (≤ 8 h, (8–12 h), (12–16 h), > 16 h), while fixed effects of interest such as anthropometric indexes, sex, and age at recruitment (years; continuous) were preserved. Linear regression models were used to confirm that normalization removed unwanted sources of variation. All the normalized data were then standardized (mean = 0 and standard deviation = 1) to rescale the concentration of the inflammatory biomarkers to enhance comparison.

The characteristics of participants were summarized using percentages for categorical variables and mean and standard deviation for continuous variables. Mann–Whitney tests were used to evaluate differences by sex in both cohorts. Spearman correlation coefficients between anthropometric indexes and CRP were calculated separately for each sex in both studies.

We assessed associations of body shape phenotypes and body fat distribution indexes with inflammatory biomarkers for both sexes in EPIC and UK Biobank using linear regression models adjusted for age at recruitment (years, continuous), smoking status (never, current, former, or unknown), education (primary education, secondary/tech school, university degree or higher, unknown) and physical activity (inactive, moderately inactive, moderately active, active, and unknown in EPIC; MET/week in UK Biobank). Results were combined separately for each sex through random-effects meta-analysis [34]. I^2 was used to assess the proportion of total variability attributable to between-study heterogeneity.

We evaluated interactions of the body shape phenotypes and body fat distribution indexes with age (above vs. below sex-specific median age) and smoking status (never vs. ever smoker), respectively, separately in men

and women. Likelihood ratio tests were used to compare models with and without multiplicative interaction terms. P values were reported non-adjusted and adjusted for Bonferroni correction.

Sensitivity analyses among women were performed with further adjustment for menopausal status (premenopausal or postmenopausal) and use of menopausal hormonal treatment as well as stratification by menopausal status. Additionally, we performed sensitivity analyses excluding participants with cardiovascular diseases (myocardial infarction, stroke, or hypertension), and those with diabetes at baseline in both study samples. Further sensitivity analyses fitting regressions by sex between anthropometric indexes and CRP levels additionally adjusting by ethnicity (White/mixed/Asian/black/other/prefer not to answer) were performed to account for the potential variation introduced by the difference in anthropometric indexes across ethnic groups. These analyses were restricted in UK Biobank given the lack of ethnicity information in EPIC. Finally, associations between obesity categories [obesity class I (BMI 30– < 35 kg/m²), obesity class II (BMI 35– < 40 kg/m²), and obesity class III (BMI ≥ 40 kg/m²)] and CRP levels were further investigated.

Sensitivity analyses also included regressions between body shape phenotypes and CRP levels without adjusting by age, a variable already included in the construction of the PCs. Additionally, correlations between the PCs and age have also been performed. These two analyses were reported to further check of potential bias due to overadjustment and collinearity.

Statistical analyses were performed using R 4.1.3. All tests were two-sided and P value < 0.05 was considered statistically significant. P values were adjusted by Bonferroni correction.

Results

The main characteristics of the study population are presented in Table 1. In EPIC, 69.1% of the participants were women, whereas in UK Biobank women represented 53.2% of the study sample. Additionally, women in both cohorts were generally younger than men. When it comes to anthropometric indexes, men in both EPIC and UK Biobank had higher values compared to women, except for HC and HI, where no such differences were observed and where women had higher values, respectively. Additionally, a higher percentage of men were in the obesity class I whereas a higher percentage of women were found in the obesity classes II and III (Additional file 1: Table S4 and S5). In both study samples, a greater proportion of men were current smokers, had attained higher levels of education, and were more physically active.

Table 1 Main characteristics of the study populations: EPIC and UK Biobank

	EPIC (n = 17,943)			UK Biobank (n = 426,223)		
	Men	Women	P value	Men	Women	P value
	Mean (SD) or n %	Mean (SD) or n %		Mean (SD) or n %	Mean (SD) or n %	
Sex	5546 (30.9%)	12,397 (69.1%)	< 0.001	199,506 (46.8%)	226,717 (53.2%)	< 0.001
Age (years)	53.1 (8.3)	52.5 (8.8)	< 0.001	56.4 (8.2)	56.1 (8.0)	< 0.001
Height (cm)	173.7 (7.3)	161.1 (6.7)	< 0.001	175.7 (6.8)	162.5 (6.3)	< 0.001
Weight (kg)	80.8 (11.6)	66.6 (11.5)	< 0.001	85.9 (14.3)	71.4 (14.1)	< 0.001
BMI (kg/m²)	26.8 (3.6)	25.7 (4.5)	< 0.001	27.8 (4.2)	27.1 (5.2)	< 0.001
< 25 kg/m²	1787 (32.2%)	6221 (50.2%)		50,170 (25.1%)	90,233 (39.8%)	
25–30 kg/m²	2812 (50.7%)	4233 (34.1%)		98,707 (49.5%)	83,154 (36.7%)	
> 30 kg/m²	947 (17.1%)	1943 (15.7%)		50,629 (25.4%)	53,330 (23.5%)	
Waist circumference (cm)	95.1 (10.1)	81.2 (11.2)	< 0.001	96.9 (11.3)	84.6 (12.5)	< 0.001
Waist to Height ratio	0.5 (0.07)	0.6 (0.06)	< 0.001	0.6 (0.1)	0.5 (0.1)	< 0.001
Hip circumference (cm)	101.0 (6.9)	101.6 (9.1)	< 0.001	103.4 (7.6)	103.3 (10.4)	< 0.001
Waist-to-hip ratio	0.9 (0.1)	0.8 (0.1)	< 0.001	0.9 (0.1)	0.8 (0.1)	< 0.001
Waist-to-hip index	4.1 (0.2)	3.6 (0.3)	< 0.001	4.1 (0.2)	3.6 (0.3)	< 0.001
ABSI	80.7 (4.3)	73.6 (5.0)	< 0.001	79.8 (4.2)	73.9 (5.0)	< 0.001
Hip index	96.7 (3.8)	104.3 (4.3)	< 0.001	100.5 (3.7)	107.2 (4.2)	< 0.001
Inflammatory biomarkers^a						
CRP (µg/mL)	2.1 (3.07)	2.2 (35.8)	0.3	2.4 (4.2)	2.6 (4.3)	< 0.001
Interleukin 6 (pg/ml)	-	1.1 (1.5)		-	-	
Interleukin 8 (pg/ml)	-	6.9 (65.6)		-	-	
Interleukin 10 (pg/ml)	-	0.2 (0.4)		-	-	
Interleukin 17d (pg/ml)	-	8.5 (15.6)		-	-	
IL1ra (pg/ml)	-	162.9 (266.7)		-	-	
TNF-α (pg/ml)	-	1.4 (2.1)		-	-	
IFN-γ (pg/ml)	-	4.5 (10.4)		-	-	
Leptin (ng/ml)	-	16.6 (14.2)		-	-	
Adiponectin (µg/ml)	-	10.7 (5.2)		-	-	
Cambridge physical activity index (EPIC)			< 0.001			
Inactive	970 (17.5%)	3199 (25.8%)		-	-	
Moderately inactive	1734 (31.3%)	4508 (36.4%)		-	-	
Moderately active	1330 (24.0%)	2490 (20.1%)		-	-	
Active	1423 (25.7%)	2069 (16.7%)		-	-	
Unknown	89 (1.6%)	131 (1.1%)		-	-	
Physical activity (MET-minutes/week) (UK Biobank)	-	-		2821 (2963.2)	2516 (2467.5)	< 0.001
Smoking status			< 0.001			< 0.001
Never	1676 (30.2%)	7143 (57.6%)		97,847 (49.1%)	135,953 (60.0%)	
Former	2114 (38.1%)	2623 (21.2%)		75,634 (37.9%)	69,904 (30.9%)	
Current	1692 (30.5%)	2517 (20.3%)		25,015 (12.6%)	19,768 (8.7%)	
Unknown (EPIC)/prefer not to answer (UK Biobank)	64 (1.2%)	114 (0.9%)		1010 (0.4%)	1092 (0.4%)	
Education			< 0.001			< 0.001
None/primary education	2164 (39.0%)	5114 (41.3%)		33,638 (16.9%)	37,380 (16.5%)	
Secondary/Tech school	1862 (33.6%)	4839 (39.0%)		48,209 (24.2%)	65,004 (28.7%)	
University degree or higher	1420 (25.6%)	2184 (17.6%)		115,212 (57.7%)	121,780 (53.7%)	
Unknown (EPIC)/prefer not to answer (UK Biobank)	100 (1.8%)	260 (2.1%)		2447 (1.2%)	2553 (1.1%)	

BMI Body mass index, **ABSI** A body shape index, **CRP** C-reactive protein, **IL1ra** Interleukin-1 receptor antagonist, **TNF-α** Tumour necrosis factor alpha, **IFN-γ** Interferon-gamma

Mann–Whitney tests were used to evaluate differences by sex in both cohorts. Significant when *P* value < 0.05

^a All inflammatory biomarkers, except CRP, have missing values. See Additional file 1: Fig. 1

Crude correlations between CRP and all the anthropometric indexes were similar in men and women in both EPIC (Additional file 1: Fig. S2a) and UK Biobank (Additional file 1: Fig. S2b), being Bonferroni-adjusted. Specifically, weight, BMI, WC, WHR, WHI, HC, WHtR, and ABSI showed positive correlations with CRP, whereas height was inversely correlated with CRP (P value < 0.005). Additionally, HI showed weak correlations in UK Biobank only. For the body shape phenotypes, PC1 showed positive correlations with CRP, whereas PC2 was inversely correlated with CRP, in both cohorts and both sexes. PC3 and PC4 showed weak or no correlation with CRP.

Linear regression analyses adjusting for age, smoking status, education, and physical activity levels showed that the traditional anthropometric indexes and PC1 (overall adiposity) were all positively associated with

CRP, with stronger estimates than the other body shape indexes in both cohorts (Figs. 1 and 2, Additional file 1: Table S6 and S7) and in both men and women. Height and PC2 (tall stature with low WHR) showed inverse associations with CRP, with similar estimates in both study samples and both sexes. Specifically, estimates for the association between height and CRP in men were -0.12 (95% CI: $-0.15, -0.09$) in EPIC and -0.07 (95% CI: $-0.07, -0.06$) in UK Biobank, whereas in women were -0.10 (95% CI: $-0.13, -0.08$) in EPIC and -0.12 (95% CI: $-0.13, -0.12$) in UK biobank. Estimates for the association between PC2 and CRP in men were -0.09 (95% CI: $-0.12, -0.07$) in EPIC and -0.11 (95% CI: $-0.11, -0.10$) in UK Biobank, while for women they were -0.10 (95% CI: $-0.12, -0.09$) in EPIC and -0.13 (95% CI: $-0.14, -0.13$) in UK Biobank. The other body shape phenotypes, PC3 (tall with high

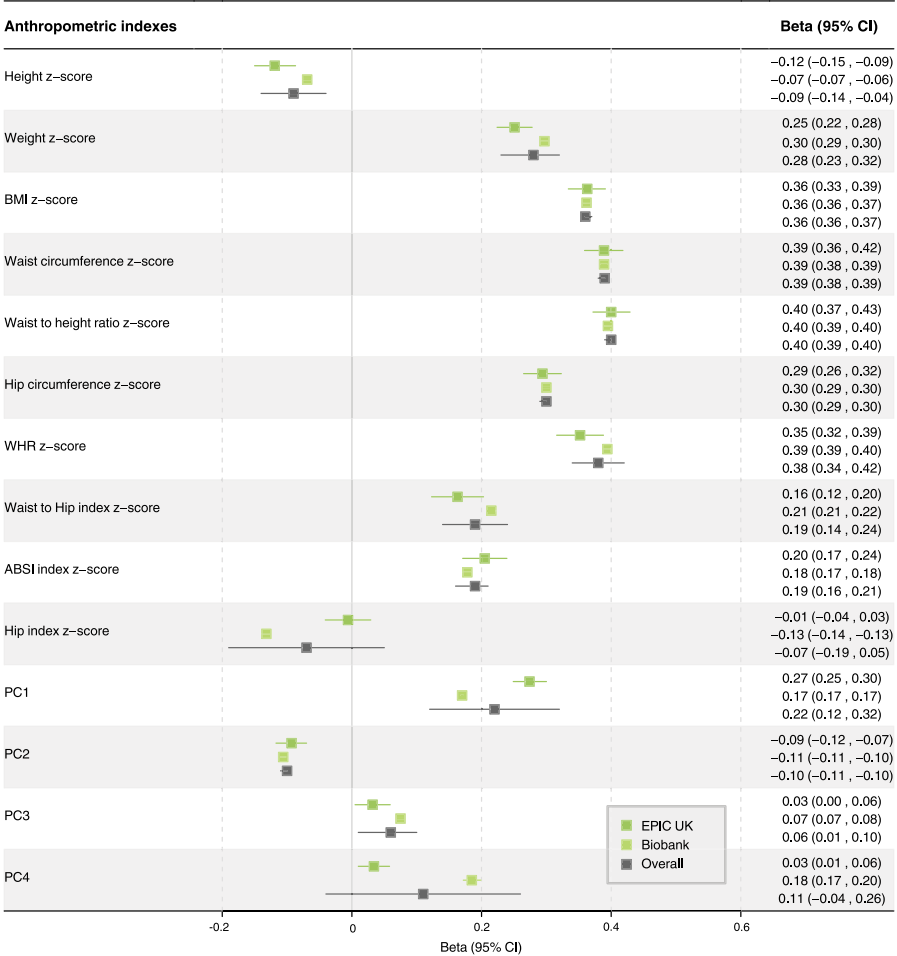


Fig. 1 Associations between anthropometric indexes and C-reactive protein (CRP) among men in the EPIC study and UK Biobank. Adjusted for age at recruitment, smoking status, education, and physical activity. Sample size EPIC: $N = 5546$, sample size UK Biobank: $N = 199,506$. BMI, body mass index; WHR, waist-to-hip ratio; ABSI, allometric body shape index. PC1, overall adiposity; PC2, tall with low waist-to-hip ratio; PC3, tall with high waist-to-hip ratio, PC4, high BMI and weight with low waist circumference and hip circumference. X-axis represents the beta estimates and the 95% confidence intervals (CI).

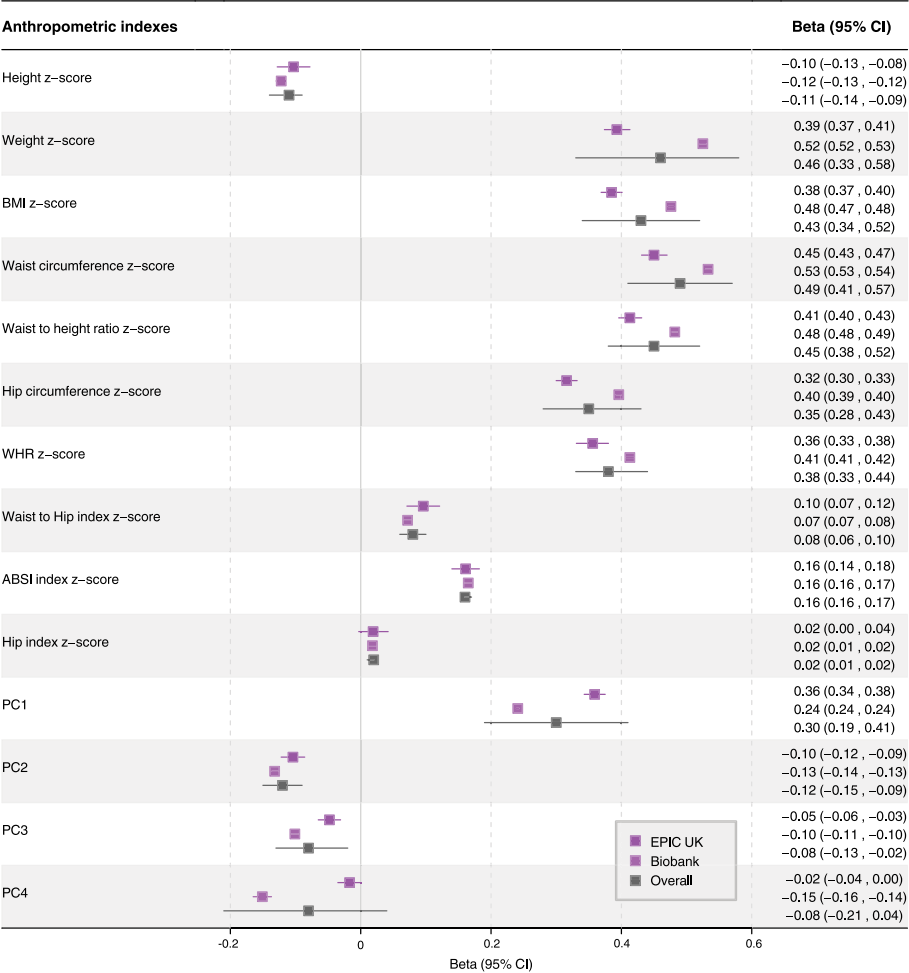


Fig. 2 Associations between anthropometric indexes and C-reactive protein (CRP) among women in the EPIC study and UK Biobank. Adjusted for age at recruitment, smoking status, education, and physical activity. Sample size EPIC: $N = 12,397$, sample size UK Biobank: $N = 226,717$. BMI, body mass index; WHR, waist-to-hip ratio; ABSI, allometric body shape index. PC1, overall adiposity; PC2, tall with low waist-to-hip ratio; PC3, tall with high waist-to-hip ratio; PC4, high BMI and weight with low waist circumference and hip circumference. X-axis represents the beta estimates and the 95% confidence intervals (CI).

WHR) and PC4 (high BMI and weight with low WC and HC) were also inversely associated with CRP in women (PC3: -0.05 ; 95% CI: $-0.06, -0.03$ in EPIC and -0.10 ; 95% CI: $-0.11, -0.10$ in UK Biobank and PC4: -0.02 ; 95% CI: $-0.04, 0.00$ in EPIC and -0.15 ; 95% CI: $-0.16, -0.14$ in UK Biobank). In contrast, positive associations with CRP were observed in men for PC3: 0.03 (95% CI: $0.00, 0.06$) in EPIC and 0.07 (95% CI: $0.07, 0.08$) in UK Biobank and PC4: 0.03 (95% CI: $0.01, 0.06$) in EPIC and 0.18 (95% CI: $0.17, 0.20$) in UK Biobank. On the other hand, HI showed an inverse association with CRP for men and a positive association for women, but only consistent in UK Biobank: -0.13 (95% CI: $-0.14, -0.13$) for men and 0.02 (95% CI: $0.01, 0.02$) for women.

Similar estimates were found in the meta-analysis of both studies for both men and women. However, for HI (in men) and PC4, the meta-analysis showed less robust estimates (Figs. 1 and 2 and Additional file 1: Table S8). In most of the analyses, high heterogeneity was found (Additional file 1: Table S8).

Results for the other inflammatory biomarkers measured only in women from the EPIC study are presented in Figs. 3 and 4 and Additional file 1: Table S9. Traditional anthropometric indexes exhibited a greater number of associations and yielded higher effect estimates compared to the complex anthropometric indexes. Weight, BMI, WC, and HC were positively associated with IL6, IL1ra, TNF- α , and leptin, and inversely associated with IL17d and adiponectin. No associations were found

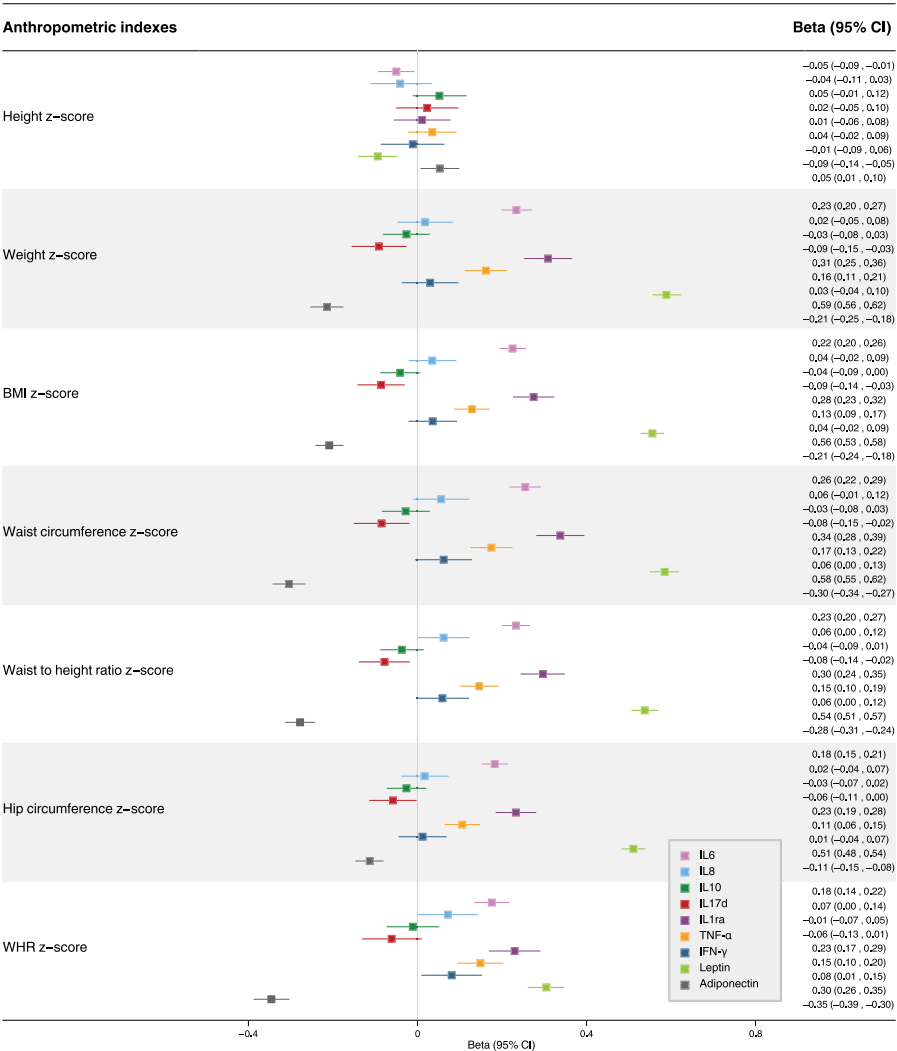


Fig. 3 Associations between simple anthropometric indexes and inflammatory biomarkers among women from the EPIC study. Adjusted for age at recruitment, smoking status, education, and physical activity. BMI, body mass index; WHR, waist-to-hip ratio. X-axis represents the beta estimates and the 95% confidence intervals (CI). IL6 (interleukin 6): *n* = 3315; IL8: *n* = 1415, IL10: *n* = 2036; IL17d: *n* = 1416; IL1ra (interleukin-1 receptor antagonist): *n* = 1803; TNF-α (tumour necrosis factor alpha): *n* = 2425; IFN-γ (interferon-gamma): *n* = 1415; leptin: *n* = 2722; adiponectin: *n* = 3315

between the traditional anthropometric indexes and IL8 or IL10. Both WHtR and WHR showed similar associations and were positively associated with IL8. WHR was also positively associated with IFN-γ. Additionally, ABSI was positively associated with IL6, IL1ra, TNF-α, and leptin and inversely associated with adiponectin. HI showed positive associations with leptin and adiponectin. For the body shape phenotypes, PC1 was positively associated with IL6, IL1ra, TNF-α, and leptin, and inversely associated with IL17d and adiponectin. PC2 showed inverse associations with IL6, IL1ra, and leptin and a positive association with adiponectin. PC3 was inversely associated with leptin and adiponectin. PC4 showed no association with any inflammatory biomarker.

In sub-group analyses by age groups and smoking status, estimated associations between anthropometric indexes and CRP were all in the same direction and similar in magnitude (Additional file 1: Table S10–S13). However, several tests for multiplicative interaction may reach statistical significance due to the large sample size, in particular in the UK Biobank. Sensitivity analyses among women stratifying by menopausal status at recruitment showed similar results in both pre and postmenopausal women for the associations between anthropometric indexes and CRP in both EPIC and UK Biobank (Additional file 1: Table S14 and S15). Results were also similar when models were further adjusted for menopausal hormonal treatment

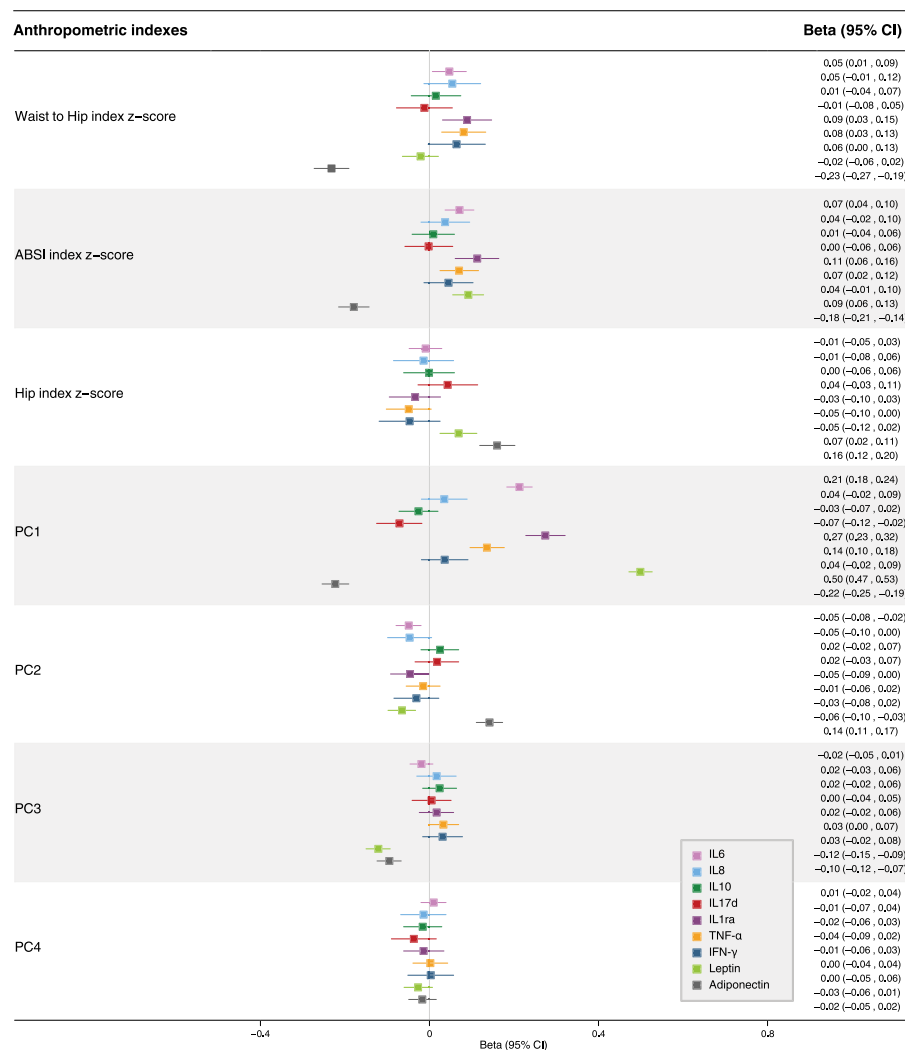


Fig. 4 Associations between complex anthropometric indexes and inflammatory biomarkers among women from the EPIC study. Adjusted for age at recruitment, smoking status, education, and physical activity. ABSI, allometric body shape index. X-axis represents the beta estimates and the 95% confidence intervals (CI). PC1, overall adiposity; PC2, tall with low waist-to-hip ratio; PC3, tall with high waist-to-hip ratio; PC4, high BMI and weight with low waist circumference and hip circumference. IL6 (interleukin 6): $n = 3315$; IL8: $n = 1415$; IL10: $n = 2036$; IL17d: $n = 1416$; IL1ra (interleukin-1 receptor antagonist): $n = 1803$; TNF- α (tumour necrosis factor alpha): $n = 2425$; IFN- γ (interferon-gamma): $n = 1415$; leptin: $n = 2722$; adiponectin: $n = 3315$

(postmenopausal women only). The sensitivity analyses excluding participants with cardiovascular diseases (myocardial infarction, stroke, and hypertension) and diabetes at baseline yielded similar results to those from the main analysis (Additional file 1: Table S16 and S17 for EPIC and Additional file 1: Table S18 and S19 for UK Biobank). No differences in the associations by sex between anthropometric indexes and CRP levels models additionally adjusted by ethnicity were found in UK Biobank (Additional file 1: Table S20).

In an exploratory analysis, associations fitted by obesity class showed similar results in both EPIC

and UK Biobank presenting a higher and increasing estimate as the categories included higher BMI ranges. Associations for all obesity categories were higher in women than men (Additional file 1: Table S4 and S5).

Finally, analyses excluding age as a confounder were not showing differences in the results (Additional file 1: Table S21 and S22). Slight inverse and positive correlations were found between PC1, PC3, and PC4 and age among men and women in both cohorts, respectively (Additional file 1: Fig. S3).

Discussion

In this study, we identified associations between various body shape phenotypes and body fat distribution indexes and inflammatory biomarkers in both the EPIC and UK Biobank cohorts, revealing significant gender-specific and phenotype-specific associations. Specifically, we found positive associations between the traditional anthropometric indexes (such as BMI, WC, and WHR), ABSI, and PC1 (overall adiposity) and CRP, in both sexes from EPIC and UK Biobank, as well as with IL6, IL1ra, TNF- α , and leptin in women from the EPIC study (no data available for men). On the other hand, height and PC2 (tall with low WHR) showed inverse associations with CRP in both study populations and with IL6, IL1ra, and leptin in EPIC. PC3 (tall with high WHR) was inversely associated with CRP among women but positively associated among men, in both cohorts. PC3 was also inversely associated with leptin and adiponectin in women of the EPIC study. The differential associations of PC3 with CRP in men and women add a valuable layer of understanding that extends beyond traditional measures of adiposity. Additionally, our results suggest an inverse association between height, independent of WC/WHR, and inflammation, especially in women.

The positive associations found between traditional anthropometric indexes and inflammation are in line with existing literature [35]. However, the mechanisms that cause the adipose tissue dysfunction triggering low-grade inflammation are not yet fully understood [36, 37]. In addition, it has been observed that normal weight individuals with abdominal fat accumulation can have metabolic alterations whereas some individuals with obesity can be metabolically healthy [38–40]. However, there is no consensus on the definition of metabolically healthy obesity and further research is needed as literature suggests that the clinical relevance of the associations with metabolic dysfunction is speculative, and mostly based on cross-sectional studies. In this sense, a study using data from the UK Biobank [41] indicated that individuals classified as metabolically healthy obese still face elevated risks of cardiovascular diseases, respiratory disease, diabetes, and all-cause mortality compared to individuals without obesity and without obesity-related risk factors.

Therefore, it would be useful to consider complex anthropometric indexes over single indexes as they may better reflect body fat distribution and could better capture inflammatory status [31]. From the results of our study, BMI, WC, and WHR are interchangeable and do not give additional insight on the association with CRP or IL6.

Two of the most used complex anthropometric indexes, ABSI and HI, have previously shown associations with inflammatory biomarkers [14], endothelial dysfunction

[15], and cardiometabolic risk factors [42]. However, literature examining associations of those indexes and inflammatory markers is scarce and focused exclusively on ABSI, rarely considering HI. Large ABSI has also been associated with higher CRP in previous studies [43, 44], and, in agreement with our findings, BMI has also shown stronger positive associations with CRP in women compared to men [44]. In our study, ABSI showed stronger associations with CRP than HI suggesting that ABSI is more closely linked to inflammatory status. A previous study in UK Biobank [14] found that BMI and ABSI were positively associated with CRP showing similar results to ours. However, no associations were found for HI and CRP in that study. Even if BMI seems to show greater associations with inflammation than ABSI, they are independent by design and should be interpreted as complementary. Thus, our results suggest that using complex anthropometric indexes, beyond traditional metrics like BMI, into clinical practice could improve the identification of individuals at higher risk of inflammation-related conditions. This could lead to earlier interventions and better clinical outcomes.

Among the body shape phenotypes, we found that PC1 (overall adiposity) was the one more correlated with single anthropometric indexes. This is expected as PC1 is constructed based on higher loadings in BMI, weight, HC, and WC. Likewise, PC1 and all these anthropometric indexes showed similar associations with CRP. On the other hand, PC2 (tall stature with low WHR) consistently exhibited inverse associations with CRP across both cohorts and sexes. In this sense, the multivariate approach of a PCA simplifies to holistically account for different traditional anthropometric indexes, like adiposity and height. Thus, body shape phenotypes may better reflect body composition than individual indexes for risk assessment and incorporated into clinical practice could help refine models for inflammation-related diseases, enabling more personalized and effective intervention strategies. Previous findings have suggested that WHR may be positively linked to CRP [45], irrespective of age, sex, metabolic and various lifestyle factors in several studies. However, we showed that PC3 (tall stature with high WHR) was inversely associated with concentrations of CRP in women. Overall, our results for PC2, in both sexes, and PC3, in women, suggest that height mitigates the positive association of abdominal adiposity with CRP, especially in women. Women generally have a higher proportion of body fat compared to men [46], even when matched for BMI, and this physiological difference also could contribute to variations in inflammatory markers. These observed associations highlight the importance of tailored public health initiatives that

address gender-specific risk factors and promote lifestyle modifications to mitigate inflammation and its related conditions.

Evidence suggests that height is positively associated with cancer risk [47–50], but also inversely associated with cardiometabolic risk [51] and diabetes [52], for the latter also when adjusting for WC. Although BMI and WC are established variables with which to assess morbidity and mortality risk, adult height is also associated with mortality independently of adiposity measures [53]. Previous research supports that shorter height is positively associated with cardiovascular risk [54] and that this risk might at least in part be mediated by cardiometabolic risk factors relevant for type 2 diabetes, namely blood pressure, blood lipids, and inflammation [55, 56]. Also, in one analysis that studied a sub-sample of the EPIC study, height appeared to be more strongly correlated with CRP among women, playing a stronger role in the association with diabetes in women than in men [52]. These results suggest taller height in women might have some metabolic implications. This stronger inverse association of taller height and CRP in women could explain the divergent result for PC3 as, for women, height can be a major driver than WHR of the association with CRP. However, more studies in different cohorts are needed to support these findings.

In our study based on two cohorts, height emerged as an indicator inversely associated with CRP in both sexes, even in combination with abdominal adiposity in women from both studies. We found similar results when considering menopausal status or when excluding those with cardiovascular diseases or diabetes. Furthermore, height was inversely associated with IL6 and leptin in women from EPIC. These inverse associations suggest that height could be protective for inflammatory status.

Strengths and limitations

The primary strength of our study is the novel results on anthropometric indexes and inflammation in two large cohort studies: EPIC and UK Biobank. These studies were conducted following standardized procedures. The use of several anthropometric indexes is another major strength as it allows comparison between them. Also, we performed sensitivity analyses, excluding those with diabetes and cardiovascular diseases to detect potential shared molecular pathways with adiposity that could bias our results.

The main limitation of our study is the lack of data for some of the inflammatory biomarkers in UK Biobank and in men in EPIC. Furthermore, we cannot determine subcutaneous adipose tissue from overall adipose tissue as we have no body composition data using objective

techniques. Also, the cross-sectional design of the study does not allow us to establish causal relationships while one-time-point measurements are not ideal to assess temporal relationships. However, this study could be considered a starting point for further longitudinal studies.

Conclusions

This study adds to our understanding of the relationship between body composition and systemic inflammation. Our findings affirm an inverse relationship between height and inflammation. Notably, our results suggest that a taller height may mitigate the impact of a large WC or a large HC on inflammation in women. PC2 (tall stature with low WHR) and PC3 (tall stature with large WHR) were inversely associated with CRP in both the EPIC and UK Biobank studies. These findings underscore the value of body shape phenotypes suggesting that they could serve as additional tools for risk stratification in epidemiological studies as well as to improve personalized approaches to disease prevention and management. Further longitudinal studies that include more inflammatory markers are needed.

Abbreviations

ABSI	Allometric body shape index
BMI	Body mass index
CRP	C-reactive protein
EPIC	European Prospective Investigation into Cancer and Nutrition study
HC	Hip circumference
HI	Hip index
IARC	International Agency for Research on Cancer
IFN- γ	Interferon gamma
IL	Interleukin
LLOQ	Lower limit of quantification
LOD	Limit of detection
PC1	Overall adiposity
PC2	Tall stature with low WHR
PC3	Tall and with high WHR
PC4	High BMI and weight with low WC and HC
TNF- α	Tumour necrosis factor alpha
ULOQ	Upper Limit of Quantification
WC	Waist circumference
WHR	Waist-to-hip ratio
WHtR	Waist-to-height ratio

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12916-024-03544-3>.

Additional file 1: Fig. S1. Flowchart with the included number of subjects in EPIC and UK Biobank. IL1ra: Interleukin-1 receptor antagonist; TNF- α : Tumour necrosis factor alpha; IFN- γ : Interferon-gamma. Fig. S2a. Correlations between adiposity and concentration of C-reactive protein in the EPIC study by sex. Fig. S2b. Correlations between adiposity and concentration of C-reactive protein in UK Biobank study by sex. Fig. S3. Correlations between body shape phenotypes and age in the EPIC and UK Biobank study by sex. Table S1. Loadings of the principal components derived in EPIC ($n = 17,943$) and UK Biobank ($n = 426,223$). Table S2. Mean and standard deviations of age and the six anthropometric traits building the body shape phenotypes for individuals included in the top and bottom 5% of each PC in the EPIC study. Table S3. Mean and standard deviations of age and the six anthropometric traits building the body shape phenotypes for

individuals included in the top and bottom 5% of each PC in UK Biobank study. Table S4. Sample size and associations between individuals with obesity and by obesity class and C-reactive protein (CRP) levels in EPIC. Table S5. Sample size and associations between individuals with obesity and by obesity class and C-reactive protein (CRP) levels in UK Biobank. Table S6. Associations between anthropometric indexes and C-reactive protein (CRP) in the EPIC study. Table S7. Associations between anthropometric indexes and C-reactive protein (CRP) in UK Biobank study. Table S8. Meta-analysis results of the associations between anthropometric indexes and C-reactive protein (CRP) in the EPIC and UK Biobank cohorts. Table S9. Associations between anthropometric indexes and all the inflammatory biomarkers analysed in EPIC. Table S10. Associations between anthropometric indexes and C-reactive protein (CRP) stratifying by sex-specific median age and p-values for likelihood ratio test comparing models without and with interactions in the EPIC study. Table S11. Associations between anthropometric indexes and C-reactive protein (CRP) stratifying by smoking status and p-values for likelihood ratio test comparing models without and with interactions in the EPIC study. Table S12. Associations between anthropometric indexes and C-reactive protein (CRP) stratifying by sex-specific median age and p-values for likelihood ratio test comparing models without and with interactions in UK Biobank study. Table S13. Associations between anthropometric indexes and C-reactive protein (CRP) stratifying by smoking status and p-values for likelihood ratio test comparing models without and with interactions in UK Biobank study. Table S14. Associations between anthropometric indexes and C-reactive protein (CRP) in the EPIC study. Data presented for all women and by menopausal status. Table S15. Associations between anthropometric indexes and C-reactive protein (CRP) in UK Biobank study. Data presented for all women and by menopausal status. Table S16. Associations between anthropometric indexes and C-reactive protein (CRP) in the EPIC study excluding 3,643 participants with CVD at baseline defined as myocardial infarction (heart attack), stroke or hypertension. Table S17. Associations between anthropometric indexes and C-reactive protein (CRP) in the EPIC Study excluding 484 participants with diabetes at baseline. Table S18. Associations between anthropometric indexes and C-reactive protein (CRP) in UK Biobank excluding 102,020 participants with CVD at baseline defined as myocardial infarction (heart attack), stroke, or hypertension. Table S19. Associations between anthropometric indexes and C-reactive protein (CRP) in UK Biobank excluding 26,365 participants with diabetes at baseline. Table S20. Associations between anthropometric indexes and C-reactive protein (CRP) in UK Biobank additionally adjusted for ethnicity. Table S21. Associations between body shape phenotypes and C-reactive protein (CRP) in the EPIC study excluding age as a confounder. Table S22. Associations between anthropometric indexes and C-reactive protein (CRP) in UK Biobank study excluding age as a confounder.

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IARC disclaimer

Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy, or views of the International Agency for Research on Cancer/World Health Organization.

Authors' contributions

EMGG, and LPN analysed the data. EMGG, LPN, AS, SC, CB, AN, YMS, RFJ, PAE, HB, MG, MV, JMAB, AO, AT, VS, CCE, DA, AKH, MG, SMCY, NRZ, CCD, ELL, MBS, DP, SS, FR, GM, TK, VV, SR, HF and LD have drafted the manuscript or substantively revised it. LD conceived and designed the work. EMGG, LPN, SC, HF, and LD contributed to the interpretation of the data. All authors have read and approved the submitted manuscript.

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Availability of data and materials

EPIC data are available for investigators who seek to answer important questions on health and disease in the context of research projects that are consistent with the legal and ethical standard practices of IARC/WHO and the EPIC centres. The primary responsibility for accessing the data belongs to IARC and the EPIC centres. For information on how to submit an application for gaining access to EPIC data and/or biospecimens, please follow the instructions at <https://epic.iarc.fr/access/>.

The data that support the findings of this study are available from UK Biobank but restrictions apply to their availability. You could also use this statement: UK Biobank is an open access resource. Bona fide researchers can apply to use the UK Biobank dataset by registering and applying at <http://ukbiobank.ac.uk/register-apply/>. These data were used under licence for the current study, and so are not publicly available. The data are, however, available from the authors upon reasonable request and with permission of UK Biobank.

Declarations

Ethics approval and consent to participate

This study complies with the Declaration of Helsinki. EPIC was approved by the Ethics Committee of the International Agency for Research on Cancer (IARC) (ref IEC 14–02), Lyon, France, as well as the local ethics committees of the study centres. All participants provided written informed consent for data collection and storage as well as individual follow-up.

The UK Biobank study was approved by the Northwest Multi-Centre Research Ethics Committee (reference for UK Biobank is 16/NW/0274) and all participants provided written informed consent to participate in the UK Biobank study. The study protocol is available online (<https://www.ukbiobank.ac.uk/media/gnkeyh2q/study-rationale.pdf>).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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