

Research Paper

Sex-specific Associations of Body Mass Index With Inflammatory Biomarkers (Interleukin-1 Beta and C-reactive Protein) in Healthy Adults

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ABSTRACT

Background: Obesity-related inflammation may exhibit sex-specific patterns due to differences in adipose tissue distribution and immune regulation. This study investigated sex-specific associations between body mass index (BMI) and circulating interleukin-1 β (IL-1 β) and C-reactive protein (CRP) levels in healthy adults.

Materials and Methods: This cross-sectional study included 119 healthy adults (49 females and 70 males). Serum IL-1 β and CRP concentrations were measured using ELISA. BMI was analyzed as a continuous variable and categorized as normal, overweight, or obese. Age-adjusted multiple linear regression and analysis of covariance were performed to examine sex-specific associations.

Results: IL-1 β levels increased progressively across normal, overweight, and obese BMI categories in males ($P < 0.05$), whereas females showed no significant variation in IL-1 β levels across BMI subgroups ($P > 0.05$). BMI was positively associated with IL-1 β in the overall population ($R^2 = 0.105$; $P = 0.039$), males ($R^2 = 0.142$; $P = 0.018$), and females ($R^2 = 0.115$; $P = 0.041$), with stronger effects in males. No significant BMI-CRP associations were found in either sex. Females had significantly higher IL-1 β levels than males, particularly in normal and overweight subgroups, but this difference disappeared in obesity. No sex differences in CRP were observed across BMI subgroups.

Conclusion: BMI was positively associated with IL-1 β in healthy adults, with stronger effects in males, while no significant BMI-CRP associations were found. These findings highlight sex-specific obesity-related inflammation patterns and suggest IL-1 β may be a more sensitive biomarker for adiposity-related inflammation in healthy populations.

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Introduction

Obesity is a major global health problem associated with an increased risk of type 2 diabetes, cardiovascular diseases, and other chronic disorders. Chronic, low-grade systemic inflammation is considered one of the principal mechanisms linking excess adiposity to these adverse health outcomes [1]. As adipose tissue expands, it undergoes hypertrophy, hypoxia, extracellular-matrix remodeling, and infiltration by immune cells [2, 3]. These processes alter the local adipose-tissue environment and promote the production of pro-inflammatory cytokines and adipokines [3]. The resulting inflammatory state may contribute to impaired insulin signaling, metabolic dysfunction, and vascular injury [4].

Interleukin-1 β (IL-1 β) and C-reactive protein (CRP) are crucial inflammatory biomarkers. IL-1 β is a potent pro-inflammatory cytokine whose maturation and secretion are regulated, in part, by the NOD-like receptor family pyrin domain containing 3 inflammasome. Sustained IL-1 β activity may adversely affect pancreatic β -cell function and insulin signaling, thereby contributing to glucose intolerance and insulin resistance [5]. CRP is an acute-phase protein primarily produced by hepatocytes in response to inflammatory stimulation, particularly through interleukin-6-dependent pathways [6].

The relationship between adiposity and inflammation may differ between men and women. This sexual dimorphism may result from differences in sex chromosomes, gonadal hormones, immune regulation, and body-fat distribution [7]. In general, women, particularly before menopause, tend to have a greater proportion of subcutaneous adipose tissue (SAT), whereas men are more likely to accumulate visceral adipose tissue (VAT) [8]. VAT is metabolically active and is associated with increased production of pro-inflammatory mediators, altered free-fatty-acid metabolism, and adverse effects on hepatic insulin sensitivity [9]. Sex hormones may further influence immune-cell activity, cytokine production, and adipose-tissue function [10]. Therefore, an equivalent increase in body mass index (BMI) may not be associated with the same degree of systemic inflammation in men and women.

Although previous studies have examined the association between BMI and inflammatory biomarkers, findings regarding sex-specific effects have been inconsistent. The strength and direction of these associations may vary according to the biomarkers evaluated, characteris-

tics of the study population, and presence of potential confounding factors. In particular, the independent relationships between BMI and IL-1 β and CRP levels remain insufficiently characterized in healthy adults. Studying these associations in individuals without chronic disease, acute infection, or medication use may provide a clearer assessment of the relationship between body mass and inflammation while reducing the influence of disease-related and treatment-related confounding.

Accordingly, the present study investigated sex-specific associations between BMI and circulating concentrations of IL-1 β and CRP in a well-characterized cohort of healthy adults. We hypothesized that BMI would be positively associated with inflammatory biomarkers in both men and women, but that the strength of these associations would differ according to sex. This difference may reflect sex-related variation in adipose-tissue distribution, adipokine secretion, hormonal regulation, and immune responsiveness. These findings may improve the understanding of sex-specific patterns of obesity-related inflammation and contribute to more individualized approaches to cardiometabolic risk assessment and prevention.

Materials and Methods

Study population

This study was a secondary analysis of data obtained from the control group of a larger comprehensive research initiative. Participants were recruited from the existing research based on convenience, and the final sample size was established by the number of eligible participants available. No official *a priori* calculation of sample size was conducted.

This cross-sectional study included 119 healthy adults (49 females and 70 males). Participants were eligible for inclusion if they were aged ≥ 18 years and had no known history of chronic diseases, including cardiovascular disease, diabetes mellitus, hypertension, chronic kidney disease, or hepatic disorders. Additional exclusion criteria were the presence of acute infection, fever, or systemic inflammatory disease within the past 4 weeks; current use of anti-inflammatory medications, immunosuppressants, or lipid-lowering agents (including statins); pregnancy or lactation in females; use of hormone replacement therapy or oral contraceptives; current or previous diagnosis of malignant disease; and BMI < 18.5 kg/m ^{2} (underweight), to minimize the confounding influence of low body weight on inflammatory marker levels. All participants provided written informed consent prior to

enrollment. The final study sample comprised 119 participants, with a mean age of 46.38 ± 14.07 years overall (45.12 ± 13.77 years in females and 47.26 ± 14.31 years in males). According to BMI classification, 50 participants (42.0%) were normal weight, 51 (42.9%) were overweight, and 18 (15.1%) were obese. Table 1 presents sex-specific distributions.

BMI measurement

Body weight and height were measured using standardized protocols. Body weight was measured to the nearest 0.1 kg using a calibrated digital scale, with participants wearing light indoor clothing and no shoes. Height was measured to the nearest 0.1 cm using a wall-mounted stadiometer, with participants standing upright, heels together, and the head positioned in the Frankfort horizontal plane. BMI was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). BMI was analyzed both as a continuous variable and categorized according to the World Health Organization (WHO) criteria: Normal ($18.5\text{--}24.9 \text{ kg}/\text{m}^2$), overweight ($25.0\text{--}29.9 \text{ kg}/\text{m}^2$), and obese ($\geq 30.0 \text{ kg}/\text{m}^2$). Underweight individuals ($\text{BMI} < 18.5 \text{ kg}/\text{m}^2$) were excluded from the present analysis to minimize the influence of low body weight on inflammatory marker levels.

Blood sampling

Venous blood samples were collected from all the participants after overnight fasting for at least 8 h. A volume of 5 mL of whole blood was drawn into plain serum separator tubes and allowed to clot at room temperature for 30 minutes. Samples were then centrifuged at $1,500 \times g$ for 15 minutes at 4°C , and the separated serum was aliquoted into sterile microcentrifuge tubes and stored at -80°C until analysis.

CRP measurement

Serum CRP concentrations were measured using a turbidimetric assay on a Hitachi 912 auto-analyzer (Roche Diagnostics, Hitachi, Japan) following the manufacturer's instructions.

IL-1 β measurement

Serum concentrations of IL-1 β were measured using a commercially available high-sensitivity ELISA kit (R&D Systems, Wiesbaden-Nordstadt, Germany) following the manufacturer's protocol. In brief, 96-well microplates coated with a murine monoclonal antibody specific for human IL-1 β were incubated with serum

samples (diluted 1:2 in assay diluent) or serial dilutions of recombinant IL-1 β standards at room temperature for 2 h. After washing to remove unbound materials, a biotinylated polyclonal antibody specific for IL-1 β was added to each well and incubated for 2 h at room temperature. Following additional washing steps, streptavidin-horseradish peroxidase conjugate was applied and incubated for 20 minutes in the dark. TMB substrate solution was then added, and the plates were incubated for 15–30 minutes depending on color development. The reaction was stopped by the addition of 2 N H_2SO_4 , and the optical density was measured at 450 nm using a BioTek ELISA reader with wavelength correction set at 540 nm. IL-1 β concentrations were determined by interpolating absorbance values against a standard curve generated using four-parameter logistic regression. The lower limit of detection for the IL-1 β assay was 0.5 pg/mL. All samples were assayed in duplicate, and the mean concentration was used for subsequent analyses. The intra-assay and inter-assay coefficients of variation were $<10\%$, indicating good assay precision. Samples with values below the detection limit were assigned a minimum detectable concentration for statistical purposes.

Statistical analysis

Statistical analysis was performed using SPSS software, version 27.0 (IBM Corp., Armonk, NY, USA). Data distribution was assessed using the Shapiro-Wilk normality test. Variables that deviated from normality were winsorized at the 5th and 95th percentiles and subsequently log-transformed to improve normality and stabilize variance. Comparisons of CRP and IL-1 β levels across BMI categories (normal, overweight, and obese) within each sex were performed using analysis of covariance, with age included as a covariate. Multiple linear regression analyses were performed to evaluate the association between BMI (as a continuous variable) and circulating levels of CRP and IL-1 β , after adjustment for age. Regression models were fitted for the overall population and separately for males and females to examine sex-specific associations. A two-tailed $P < 0.05$ was considered statistically significant for all analyses.

Results

Comparison of serum CRP and IL-1 β levels between BMI subgroups in each sex

Figure 1 shows the comparison of serum CRP and IL-1 β levels between normal, overweight, and obese subgroups within each sex after adjustment for age. The IL-1 β levels demonstrated a graded increase across BMI

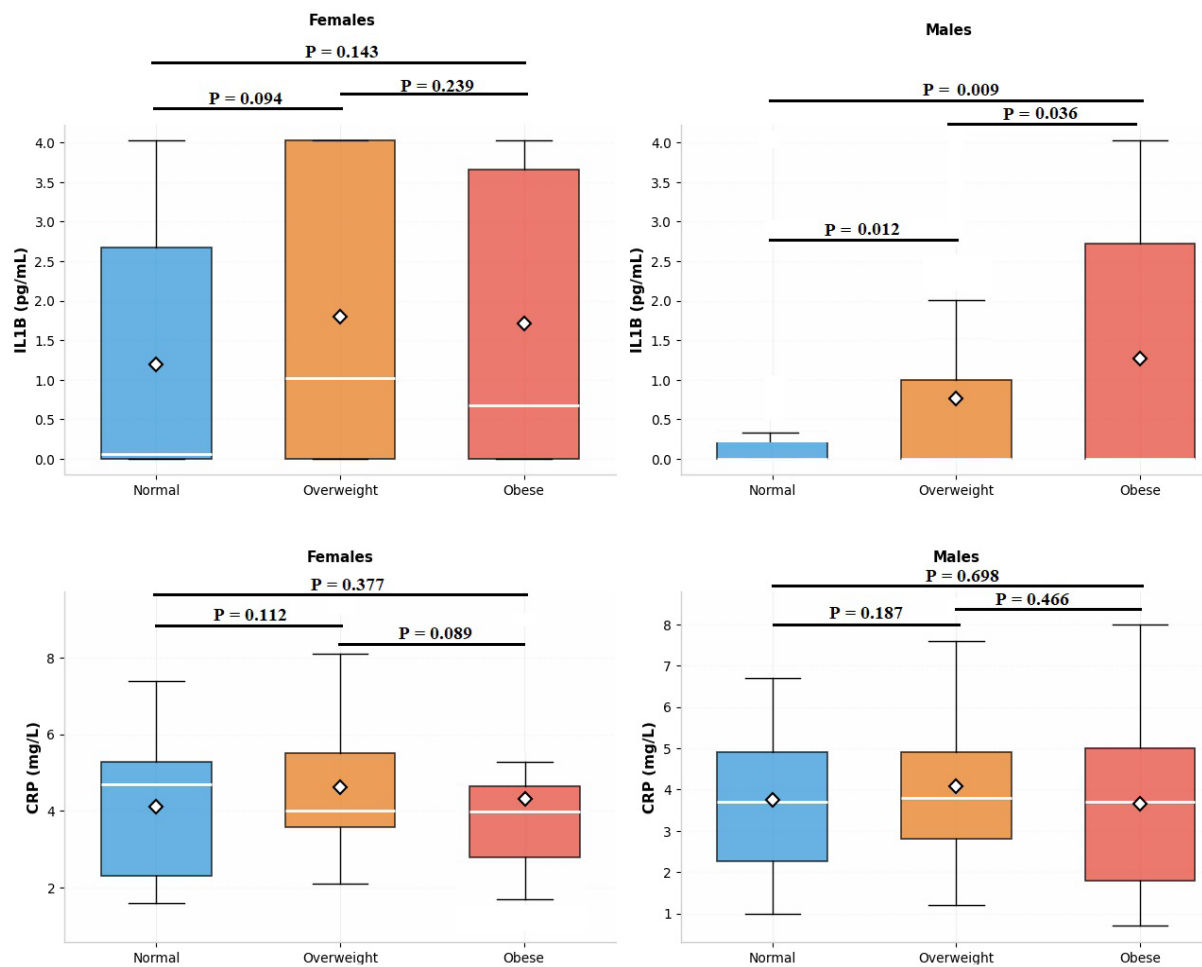


Figure 1. Comparison of serum CRP and IL-1 β levels between normal, overweight, and obese subgroups within each sex, after adjustment for age

Note: $P < 0.05$ is statistically considered significant.

categories in males: levels were significantly higher in the obese subgroup than in both the normal and overweight subgroups, and were also significantly higher in the overweight subgroup than in the normal subgroup ($P < 0.05$). In contrast, the IL-1 β levels did not change between BMI subgroups in females ($P > 0.05$). No significant differences in CRP levels were observed across BMI subgroups in either sex ($P > 0.05$).

Regression analysis between serum CRP/IL-1 β and BMI levels in each sex

Figure 2 shows the age-adjusted linear regression analysis of serum CRP and IL-1 β levels against BMI in the overall population stratified by sex. Significant positive associations were observed between IL-1 β and BMI in the overall population ($R^2 = 0.105$; $P = 0.039$), males ($R^2 = 0.142$; $P = 0.018$), and females ($R^2 = 0.115$; $P = 0.041$). In contrast, no significant associations were

found between CRP and BMI in the overall population ($R^2 = 0.057$; $P = 0.332$), males ($R^2 = 0.147$; $P = 0.166$), or females ($R^2 = 0.007$; $P = 0.145$).

Comparison of serum CRP and IL-1 β levels between sexes

Figure 3 shows the age-adjusted comparison of serum CRP and IL-1 β levels between females and males. The IL-1 β levels were significantly higher in females than in males ($P < 0.05$). In contrast, no significant differences were observed in CRP levels between males and females ($P > 0.05$).

Comparison of CRP and IL-1 β levels between sexes within each BMI subgroup

Figure 4 presents the age-adjusted comparison of serum CRP and IL-1 β levels between females and males

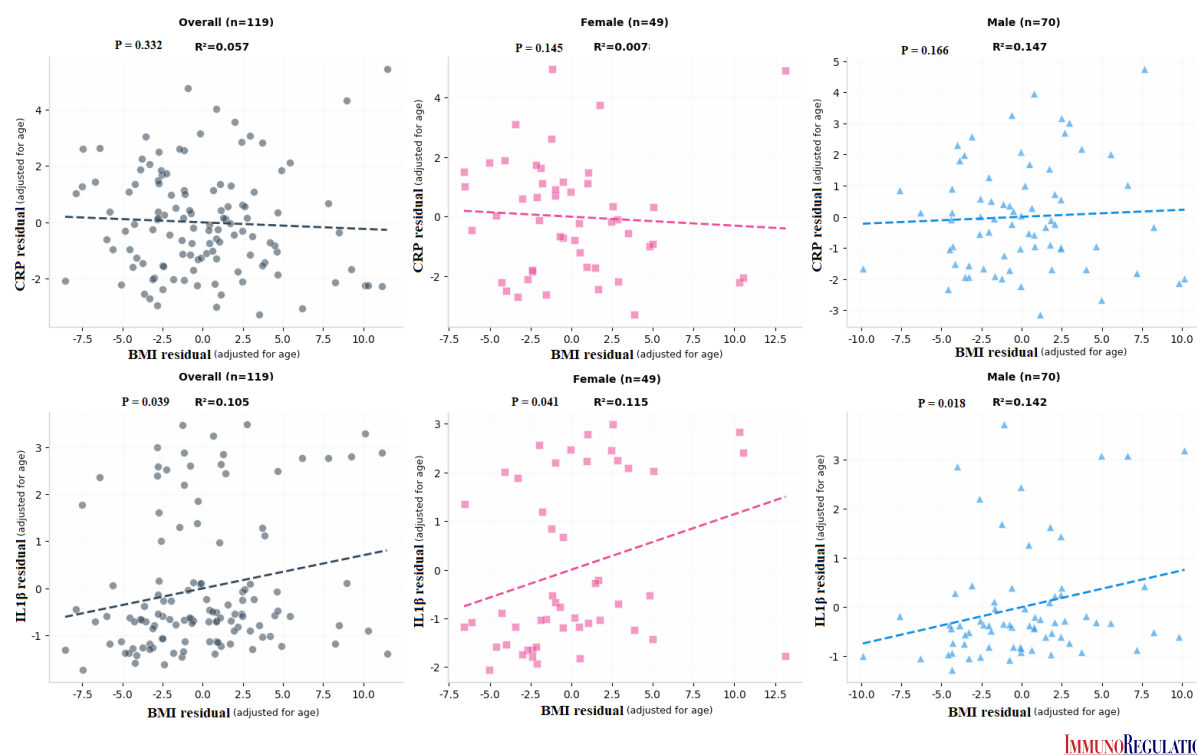


Figure 2. Age-adjusted linear regression analysis of serum CRP and IL-1 β levels against bmi levels in the overall population and stratified by sex

Note: $P < 0.05$ is statistically considered significant.

within each BMI subgroup (normal, overweight, and obese). The IL-1 β levels were significantly higher in females than in males within the normal and overweight subgroups ($P < 0.05$). However, no significant sex differences in IL-1 β levels were observed within the obese subgroup ($P > 0.05$). For CRP, no significant sex differences were detected in any of the BMI subgroups ($P > 0.05$).

Discussion

The present study investigated sex-specific associations between BMI and circulating IL-1 β and CRP levels in a well-characterized cohort of healthy adults. Our findings demonstrate that BMI is positively associated with IL-

1 β levels in both men and women, with a stronger effect observed in males. However, no significant associations were found between BMI and CRP in either sex. Additionally, we observed that females had significantly higher IL-1 β concentrations than males, particularly in the normal and overweight BMI categories; however, this sex difference diminished in the obese subgroup.

The positive association between BMI and IL-1 β observed in our study aligns with the established paradigm that excess adiposity promotes a pro-inflammatory state through activation of the NLRP3 inflammasome and subsequent IL-1 β maturation [11, 12]. Adipose tissue expansion in obesity is accompanied by macrophage infiltration, particularly of the M1 phenotype, which is

Table 1. Characteristics of participants

Characteristic	Mean $\pm$ SD/No. (%)		
	Overall (n=119)	Female (n=49)	Male (n=70)
Age (y)	46.38 $\pm$ 14.07	45.12 $\pm$ 13.77	47.26 $\pm$ 14.31
Normal BMI (18.5–24.9)	50(42.0)	26(53.1)	24(34.3)
Overweight BMI (25.0–29.9)	51(42.9)	16(32.7)	35(50.0)
Obese BMI ($\geq$ 30.0)	18(15.1)	7(14.3)	11(15.7)

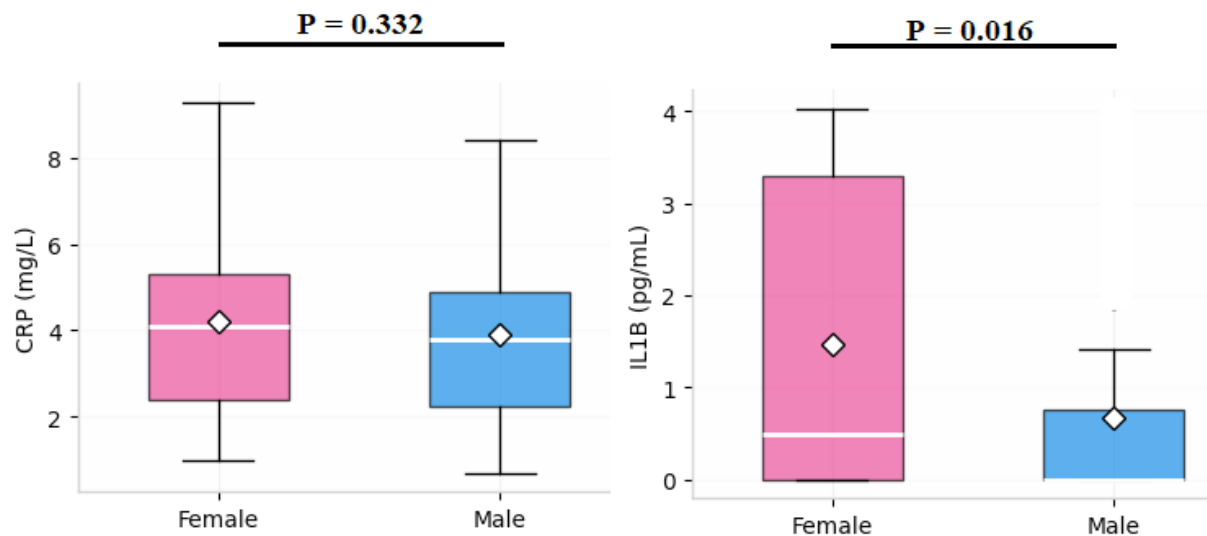


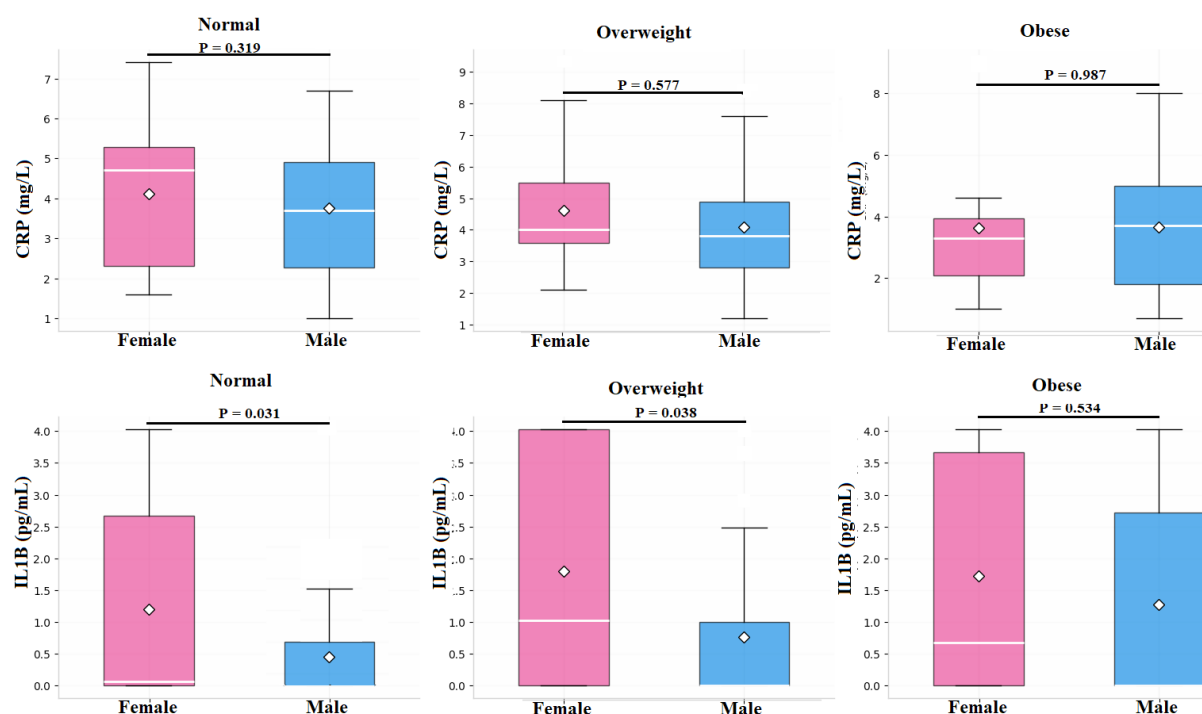
Figure 3. Comparison of serum CRP and IL-1 β levels between females and males, after adjustment for age IMMUNOREGULATION
 Note: $P < 0.05$ is statistically considered significant.

a major source of IL-1 β production [13]. Our findings extend this understanding by revealing that the BMI-IL-1 β relationship exhibits sexual dimorphism, with a more robust association in males. This observation is consistent with the work of Cartier et al. (2009), who reported stronger correlations between adiposity measures and inflammatory markers in men than in women, and may be explained by the differential distribution of adipose tissue between sexes [14]. Men typically accumulate more VAT, which is metabolically more active and produces greater quantities of pro-inflammatory cytokines than SAT, which predominates in women [15]. Visceral adiposity is associated with increased macrophage infiltration, enhanced inflammasome activation, and elevated IL-1 β secretion [16]. Therefore, the stronger BMI-IL-1 β association in men likely reflects the greater contribution of VAT to systemic inflammation at equivalent BMI levels. Conversely, our finding of no significant association between BMI and CRP in either sex is somewhat unexpected, given the well-documented positive relationship between obesity and CRP in numerous epidemiological studies [17, 18]. The absence of a significant BMI-CRP association in our healthy cohort is notable, given the well-established positive relationship reported in many epidemiological studies. The most likely explanation is our use of a standard CRP assay, which has lower sensitivity in the low-to-normal concentration range typical of healthy adults, whereas most prior studies employed high-sensitivity CRP (hs-CRP) assays [19]. Additionally, CRP levels are influenced by factors not captured in our analysis, such as dietary composition, physical activity, and genetic polymorphisms [20, 21]. Finally, our modest sample size may have limited power to detect small

effect sizes. Notably, our null finding is consistent with those of many studies that reported nonsignificant BMI-CRP associations in healthy populations, suggesting that the CRP response to adiposity may be less pronounced in the absence of obesity-related comorbidities. [22-24].

The observation that females had significantly higher IL-1 β levels than males, particularly in the normal and overweight subgroups, is intriguing and may reflect sex-specific differences in immune regulation. Estrogens have been shown to modulate innate immune responses, with some studies reporting enhanced IL-1 β production in females [25]. However, the disappearance of this sex difference in the obese subgroup suggests that obesity-related factors may override the basal sex differences in IL-1 β production. One possible explanation is that as BMI increases, the pro-inflammatory effects of adipose tissue expansion become dominant in both sexes, diminishing the relative contribution of sex hormones to IL-1 β regulation [26]. Alternatively, the lower frequency of obesity in our female sample may have limited statistical power to detect sex differences within this subgroup. Our findings are partially consistent with those of Cartier et al. (2009), who reported higher IL-1 β levels in healthy women than in men but did not observe significant interactions between sex and adiposity [F4].

The lack of sex differences in CRP levels across all BMI subgroups is consistent with several previous studies that reported similar CRP concentrations in men and women after adjusting for adiposity [27]. This suggests that CRP, as an acute-phase reactant, may be less sensitive to sex-specific immune modulation than IL-1 β . Fur-



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Figure 4. Comparison of serum CRP and IL-1 β levels between females and males within each normal, overweight and obese subgroups, after adjustment for age

Note: $P < 0.05$ is statistically considered significant.

thermore, CRP production is regulated by IL-6, which is influenced by sex hormones to a lesser extent than IL-1 β .

When we stratified participants by BMI category to examine sex differences within each subgroup, we observed that IL-1 β levels were significantly higher in females than in males within the normal and overweight subgroups. However, this sex difference was no longer observed in the obese subgroup. This pattern suggests that the sex-related disparity in IL-1 β is most evident at lower levels of adiposity and becomes attenuated as obesity develops. One plausible explanation is that in normal and overweight individuals, the immunomodulatory effects of sex hormones on IL-1 β production are more apparent, whereas in obesity, the overwhelming pro-inflammatory stimulus from adipose tissue expansion may override these hormonal effects [28]. No significant sex differences were observed in any of the BMI subgroups, reinforcing the conclusion that CRP levels are less sensitive to sex-specific immune modulation.

Our study has several limitations that warrant consideration. First, the cross-sectional design precludes causal inferences regarding the direction of associations between BMI and inflammatory biomarkers. Longitudinal studies are needed to establish whether elevated

IL-1 β levels precede or follow increases in BMI and whether these relationships differ by sex. Second, our sample size was relatively modest, particularly in the obese female subgroup ($n=7$), which may have limited statistical power for sex-specific subgroup analyses and increased the risk of type II errors. As this was a secondary analysis of an existing study, no official power calculation was performed prior to the study. Third, we used a standard CRP assay instead of a hs-CRP assay. The standard assay exhibits lower sensitivity in the low-to-normal concentration range commonly found in healthy adults, potentially contributing to the lack of BMI–CRP associations observed in our results. Future research in healthy subjects should use hs-CRP assays to identify minor variations in low-grade inflammation. Fourth, we did not assess or regulate multiple lifestyle factors that are recognized to affect inflammatory status, such as smoking, exercise, nutrition, and alcohol consumption. The lack of this information might have led to residual confounding factors that could have affected the noted associations. Future research should include detailed lifestyle evaluations to more effectively distinguish the link between adiposity and inflammation. Fifth, although we excluded individuals with BMI < 18.5 kg/m ^{2} , our study did not include measures of body composition, such as VAT, SAT, or muscle mass. BMI is an imperfect

proxy for adiposity and does not capture the distribution of adipose tissue, which is critical for sex-specific differences in inflammation. Sixth, we did not measure the concentrations of sex hormones, such as estradiol and testosterone, which could have provided mechanistic insights into the observed sex differences in IL-1 β levels. Seventh, the single time-point measurement of inflammatory biomarkers may not fully capture the dynamic nature of these mediators, and repeated measurements could have provided more stable estimates.

Despite these limitations, our findings have important clinical implications. The observation that BMI is more strongly associated with IL-1 β in men than in women suggests that obesity-related inflammatory risk may be sex-dependent, with men potentially experiencing greater IL-1 β -mediated inflammatory consequences at equivalent BMI levels. This finding supports the concept that sex-specific thresholds for obesity-related inflammation are required in clinical practice. Furthermore, the lack of association between BMI and CRP in healthy adults underscores the importance of selecting appropriate inflammatory biomarkers for assessing obesity-related risk in different populations. IL-1 β may be a more sensitive marker of the early inflammatory response to adiposity in healthy individuals, whereas CRP may better reflect inflammatory activity in the context of established metabolic diseases or other comorbidities.

Conclusion

Our study demonstrates that BMI is positively associated with IL-1 β levels in healthy adults, with a stronger effect in males, while no significant association was observed between BMI and CRP in either sex. These findings highlight the sex-specific nature of obesity-related inflammation and suggest that IL-1 β may be a sensitive biomarker for detecting adiposity-related inflammatory changes in healthy populations. However, the number of obese women in our study was very small ($n=7$), and the apparent disappearance of the sex difference in IL-1 β within this subgroup should be interpreted with caution, as it may reflect limited statistical power rather than a true absence of difference. Future studies with larger sample sizes, longitudinal designs, and comprehensive measures of body composition and sex hormones are needed to further elucidate the mechanisms underlying sex differences in obesity-related inflammation and to inform sex-specific strategies for cardiometabolic risk assessment and prevention.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Research Ethics Committee of [Shahed University](#), Tehran, Iran (Code: IR.SHAHED.REC.1400.046).

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Authors' contributions

Conceptualization, methodology, and formal analysis: Ensie Sadat Mirsharif; Supervision: Tooba Ghazanfari; Investigation: Ensie Sadat Mirsharif and Tooba Ghazanfari; Data curation and visualization: Hossein Hassanpour and Tooba Ghazanfari; Validation: Hossein Hassanpour; Writing: All authors.

Conflicts of interest

The authors declared no conflict of interest.

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