



Circulating inflammatory biomarkers in adolescents: evidence of interactions between chronic pain and obesity

Keri R. Hainsworth^{a,b,*}, Pippa M. Simpson^{c,d}, Hershel Raff^{e,f}, Mitchell H. Grayson^{c,g}, Liyun Zhang^{c,d}, Steven J. Weisman^{a,b,c}

Abstract

Introduction: The negative effects of chronic pain and obesity are compounded in those with both conditions. Despite this, little research has focused on the pathophysiology in pediatric samples.

Objective: To examine the effects of comorbid chronic pain and obesity on the concentration of circulating inflammatory biomarkers.

Methods: We used a multiple-cohort observational design, with 4 groups defined by the presence or absence of obesity and chronic pain: healthy controls, chronic pain alone, obesity alone, as well as chronic pain and obesity. Biomarkers measured were leptin, adiponectin, leptin/adiponectin ratio (primary outcome), tumor necrosis factor- α , interleukin 6, and C-reactive protein (CRP).

Results: Data on 125 adolescents (13–17 years) were analyzed. In females, there was an interaction between chronic pain and obesity such that leptin and CRP were higher in the chronic pain and obesity group than in chronic pain or obesity alone. Within the chronic pain and obesity group, biomarkers were correlated with worsened pain attributes, and females reported worse pain than males. The highest levels of interleukin 6 and CRP were found in youth with elevated weight and functional disability. We conclude that in adolescents, chronic pain and obesity interact to cause dysregulation of the inflammatory system, and this effect is more pronounced in females.

Conclusion: The augmented levels of inflammatory biomarkers are associated with pain and functional disability, and may be an early marker of future pain and disability.

Keywords: Pediatric, Chronic pain, Obesity, Leptin, C-reactive protein

1. Introduction

Chronic pain and obesity have negative effects on health when experienced alone.^{14,15,66} Unsurprisingly, negative effects increase when these chronic conditions co-occur.⁴⁷ In adults, a cycle of disability occurs, increasing the risk for depression and behaviors that undermine treatment success.^{5,11,31,58,65} Although it is appreciated that obesity increases the risk of chronic pain^{4,10,23,53,69} and pain increases the risk of obesity,^{32,45,48} few studies have focused on children—a large portion of the pain

population. The number of youth seen in pediatric pain clinics who are either at-risk of, or have obesity, ranges from 34% to 68%.^{26,27,79} In children, obesity is a risk factor for chronic pain conditions^{13,17,55,78} and is associated with pain treatment failure.⁷⁰ It is critical to understand the pathophysiology of co-occurring chronic pain and obesity in pediatrics so that appropriate treatments can be offered.

Inflammation has been proposed as a key link in the association between chronic pain and obesity.^{9,47} Adipocytes

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^a Department of Anesthesiology, Medical College of Wisconsin, Milwaukee, WI, USA, ^b Jane B. Pettit Pain and Headache Center, Children's Wisconsin, Milwaukee, WI, USA, ^c Department of Pediatrics, Medical College of Wisconsin, Milwaukee, WI, USA, ^d Quantitative Health Sciences, Children's Wisconsin and Medical College of Wisconsin, Milwaukee, WI, USA, ^e Departments of Medicine, Surgery, and Physiology, Medical College of Wisconsin, Milwaukee, WI, USA, ^f Endocrine Research Laboratory, Aurora St. Luke's Medical Center, Advocate Aurora Research Institute, Milwaukee, WI, USA, ^g Division of Allergy and Immunology, Medical College of Wisconsin, Milwaukee, WI, USA. Dr. Grayson is now with the Division of Allergy and Immunology, Department of Pediatrics, Nationwide Children's Hospital, The Ohio State University College of Medicine, Columbus, OH, USA

*Corresponding author. Address: Medical College of Wisconsin, Department of Anesthesiology, 9000 W. Wisconsin Ave., Milwaukee, WI, 53226. Tel.: 414-266-6306; fax: 414-266-1761. E-mail address: khainswo@mcw.edu (K.R. Hainsworth).

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secrete hormones that affect inflammatory cytokines (“adipocytokines”).⁷ These factors are important in metabolic homeostasis, reproduction, immunity, and inflammatory processes.^{7,28} Furthermore, augmented production is responsible for the low-grade systemic inflammation characterizing obesity and is a critical pathophysiological component linking obesity and related sequelae.²⁸ Chronic pain and obesity may interact by obesity-induced changes in adipocytokines^{60,74}; these detrimental effects may be potentiated by the proinflammatory environment.⁶⁰ These adipocytokines include leptin, adiponectin, tumor necrosis factor-alpha (TNF-alpha), interleukin 6 (IL-6), and C-reactive protein (CRP)^{24,50} and are associated with increased pain intensity,^{21,22,42} and the etiology and progression of pain-related disease states, such as migraines,⁵² osteoarthritis (OA),^{41,76} and low back pain.^{6,33,55}

We examined the effects of comorbid chronic pain and obesity (CPO) on the circulating inflammatory biomarkers (leptin, adiponectin, TNF-alpha, IL-6, and CRP), relative to both conditions alone (chronic pain [CP] and obesity [O]) and to healthy controls (HCs). We hypothesized that proinflammatory biomarkers (leptin, TNF-alpha, IL-6, and CRP) would be increased and adiponectin (anti-inflammatory) decreased in the CPO group. The leptin/adiponectin (L/A) ratio was the primary outcome, as this index of proinflammatory to anti-inflammatory activity may be more sensitive to obesity-related comorbidities than either marker alone.¹⁹ The prevalence of chronic pain and obesity is higher in females,⁶⁷ with some evidence pointing to a greater risk of pain in females with obesity.⁴⁷ Ergo, we hypothesized that these effects would be more pronounced in females. Secondary aims were to examine relationships between biomarkers and pain attributes (groups with chronic pain), and to explore interrelationships between groups, demographics, and clinical factors important to pediatric chronic pain (functional disability, anxiety, depression, and physical activity) as predictors of systemic biomarkers.^{25,29,34,35,40,56}

2. Methods

2.1. Design and participants

We used a multiple-cohort observational design. Four groups were recruited defined by the presence/absence of obesity and chronic pain. A healthy control group (HC) and an obesity-only (O) group were recruited from well-child checkups at a pediatric clinic (from the same health system as the pain clinic) and through advertisements on the hospital Facebook page and the affiliated medical college intranet. Chronic pain healthy weight (CPHW) and chronic pain and obesity (CPO) groups were recruited from intake appointments in our multidisciplinary pediatric pain clinic. The CPO group was also recruited from well-child checkups at the pediatric clinic. Data were collected from February 2015 through November 2016. This study was approved by the Children’s Wisconsin Institutional Review Board. Participants and parents gave written assent or consent, respectively. Participants received a gift card as compensation.

2.2. Screening criteria

2.2.1. Eligibility

2.2.1.1. Weight criteria

The HC and CPHW groups had a healthy weight (a body mass index [BMI] between the 5th and 85th percentile, based on age and sex³⁹). The O and CPO groups had a BMI in the obese range (≥ 95 th percentile, based on age and sex³⁹).

Patients’ medical records were screened for exclusion criteria to ensure that patients in the O and the HC groups did not have chronic pain or any pain-related conditions. Furthermore, the participant and their parent were required to answer 2 screening questions at the time of consent: (1) “do you have any chronic illness?” Those responding “yes” were excluded; (2) “over the past 3 months, have you had pain?” Response options included “not at all,” “rarely,” “sometimes,” “frequently,” and “all the time.” Patients were excluded if they responded “sometimes,” “frequently,” or “all the time.” Patients screened for the O group were included in the CPO group if they presented with pain ≥ 3 months and if they indicated that pain occurred sometimes, frequently, or all the time in the past 3 months. In addition, each of these cases was reviewed by an MD with >30 years’ experience as the medical director of the pediatric pain clinic (S.W.) before inclusion in the CPO group.

Exclusion criteria for all groups included current use of the following: metformin, long-acting analgesics, corticosteroids, and antidepressant or anxiolytic medication(s). In addition, patients were excluded if they used any nonsteroidal anti-inflammatory medication within the past 8 hours, allergy medications or an inhaler on a regular basis (defined as daily use within the past 2 weeks or as ≥ 12 times in the past month), or if either of the latter were used within 48 hours before the blood draw. Diagnostic exclusions included hypertension, postural orthostatic tachycardia syndrome, diabetes mellitus, small fiber neuropathies, autonomic dysfunction, or diagnoses associated with an inflammatory state (other than pain or obesity), including celiac disease, irritable bowel disease, and any form of arthritis.

2.3. Measures

2.3.1. Demographics

Age, sex, and pain location (CPHW and CPO groups) were extracted from the electronic medical record. Pain location was categorized as head, back, musculoskeletal, or others. Height, weight, and waist circumference (as the minimum circumference between the 10th rib and the top of the iliac crest) were measured at the medical appointment. Central adiposity was defined as having a waist to height ratio >0.5 .⁴⁴ An online calculator was used to determine patients’ BMI percentile based on Centers for Disease Control growth charts (<https://zscore.research.chop.edu>). Patients self-reported race and ethnicity.

2.4. Patient-reported outcomes

2.4.1. Pain frequency-severity-Duration scale

Assesses pain attributes in children and adolescents. Participants reported the number of days with pain over the past 2 weeks (0–14 days). The pain intensity (0 = no pain to 10 = worst pain) and average duration (1–2, 3–5, 6–8, 9–12, 12–18, or 18–24 hours) of both usual and worst pain over the past 2 weeks were also reported. Initial validation showed good construct validity in a pediatric chronic pain population.⁶²

2.4.2. Child Activity Limitations Questionnaire

Self-report of functional disability consisting of a list of 21 activities. Respondents indicated the degree to which pain affected the activities in the past month (0 = not at all difficult–5 = extremely difficult). Scores range from 0–105 (higher scores indicating greater functional disability). The Child Activity

Limitations Questionnaire has good construct validity and reliability.²⁵ Internal reliability for the current sample was 0.97.

2.4.3. Patient-Reported Outcomes Measurement Information System self-report child Anxiety and child depression (short forms, version 1.0)

For both, participants rated 8 items on a 5-point Likert scale indicating how frequently they experienced symptoms (0 = never–4 = almost always), such as feeling scared or worried (anxiety) or sadness (depression). Raw scores were converted to T-scores. These measures have been validated in a large population of children and adolescents.³⁰ Internal reliability for the current sample was 0.91 (anxiety) and 0.94 (depression).

2.4.4. Patient-Reported Outcomes Measurement Information System self-report physical activity (short form, version 1.0)

Participants rated 8 items on a 5-point Likert scale indicating how frequently they performed physical activities ranging from minimal activity to greater effort (0 = no days; 4 = 6–7 days), eg, “how many days did you exercise or play so hard that your body got tired?” Raw scores were converted to T-scores. This measure has been validated in a large population of children and adolescents.⁷³ Internal reliability for the current sample was 0.93.

2.4.5. Pubertal Development Scale

A brief self-report measure used to assess pubertal development.⁵⁴ Participants reported growth in height and body hair, and skin changes. Males were asked about facial hair growth and voice changes. Females were asked about breast growth and menstruation age and onset. Scores were categorized as 1 of 5 stages of pubertal development (from prepubertal to postpubertal).⁸

2.5. Procedures

Questionnaires were completed at the time of the blood draw (in the pediatric translational research unit or a laboratory colocated with the pediatric clinic). Blood (8 mL) was drawn into an SST tube, allowed to clot at room temperature for 30 to 60 minutes, and centrifuged (4° C) for 15 minutes at 1000×g. Serum was stored at –80° C.

2.6. Measurement of serum biomarkers

Serum markers were measured by enzyme-linked immunoassays (ELISA) from R&D Systems (Minneapolis, MN). The leptin ELISA has a sensitivity of 7.8 pg/mL, an intra-assay CV of 3.0% to 3.2% and interassay CV of 3.5% to 5.4%. The total adiponectin ELISA has a sensitivity of 0.3 ng/mL, an intra-assay CV of 2.5% to 4.7%, and interassay CV of 5.8% to 6.9%. The high-sensitivity C-reactive protein (CRP) ELISA has a sensitivity of 0.01 ng/mL, an intra-assay CV of 4% to 8%, and an interassay CV of 6% to 7%. The high-sensitivity IL-6 assay has a sensitivity of 0.04 pg/mL, an intra-assay CV of 7% to 8%, and an interassay CV of 7% to 10%. The high-sensitivity TNF-α ELISA has a sensitivity of 0.1 pg/mL, intra-assay CV of 3% to 9%, and an interassay CV of 7% to 10%.

2.7. A priori sample size analysis

This was based on the expected difference between the CPO and O groups on the primary outcome (L/A ratio). Using data from Diamond et al.⁴⁶ and after taking square roots to normalize the data, the mean difference between normal and obese youth on the L/A ratio was 1.4 (SD 1.2). Thus, power was 80% to detect a difference of ~0.78 with 30 participants in each group (Pass 11, Power Analysis and Sample Size Software).

Table 1
Patient demographics by groups.

	HC (n = 31)	CPHW (n = 30)	O (n = 35)	CPO (n = 29)	P
Age, y					0.87
Median (IQR)	15.0 (14.0–16.0)	15.5 (14.0–16.0)	15.0 (14.0–17.0)	15.0 (13.5–16.5)	
Sex					<0.001*
Female, n (%)	23 (74.2)	24 (80.0)	10 (28.6)	15 (51.7)	
Race, n (%)					0.031†
Anglo-American	26 (83.9)	25 (83.3)	33 (94.3)	21 (72.4)	
AA	2 (6.5)	4 (13.3)	1 (2.9)	8 (27.6)	
Others	3 (9.7)	1 (3.3)	1 (2.9)	0 (0)	
Ethnicity					0.29
Not Hispanic, n (%)	31 (100.0)	25 (83.3)	33 (94.3)	26 (89.7)	
BMI %ile					<0.001‡
Median (IQR)	66.0 (43.0–77.0)	59.5 (42.5–73.0)	98.0 (97.0–99.0)	98.0 (97.0–99.0)	
Central adiposity§, (n, %)	1 (3.3)	1 (3.4)	27 (81.8)	26 (92.9)	<0.001
Pubertal stage¶, (n, %)					0.092
Prepubertal	1 (3.2)	0 (0.0)	0 (0.0)	2 (7.1)	
Early pubertal	0 (0.0)	0 (0.0)	4 (11.4)	4 (14.3)	
Midpubertal	5 (16.1)	2 (6.9)	6 (17.1)	3 (10.7)	
Late pubertal	5 (16.1)	7 (24.1)	13 (37.1)	6 (21.4)	
Postpubertal	20 (64.5)	20 (69.0)	12 (34.3)	13 (46.4)	

* Higher frequency of males in the O group (*std resid* = 2.6); lower frequency of females in the O group (*std resid* = –2.3).

† Higher frequency of African Americans in the CPO group (*std resid* = 2.4).

‡ BMI percentile distributed as expected: HC *ns* CPHW < O *ns* CPO.

|| Higher frequency of central adiposity in the CPO (*std resid* = 3.7) and O (*std resid* = 3.1) groups; lower frequency of central adiposity in the CPHW (*std resid* = –3.4) and HC groups (*std resid* = –3.4).

¶ Missing data for 1 CPHW and 1 CPO participant.

§ Missing data for 1 HC, 1 CPHW, 2 O, and 1 CPO participant.

CPHW, chronic pain and healthy weight; CPO, chronic pain and obesity; O, obesity; HC, healthy controls; IQR, interquartile range.

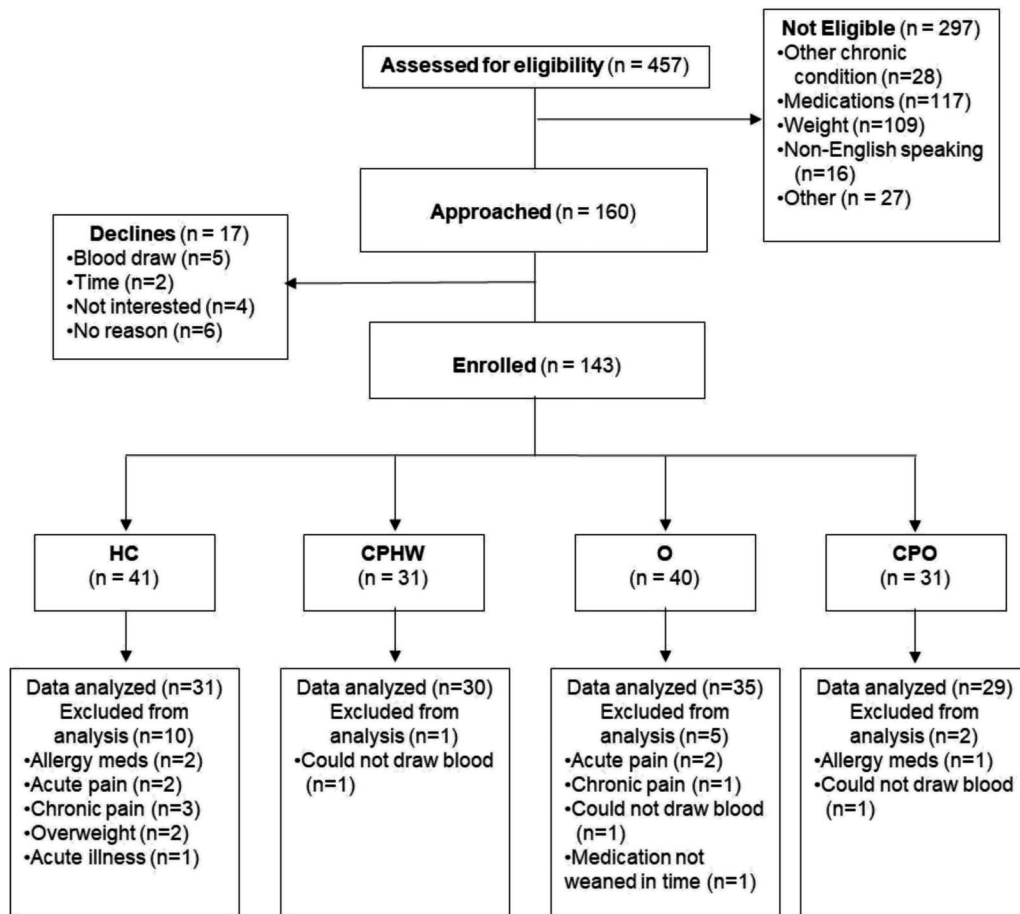


Figure 1. Flow diagram. CPHW, chronic pain and healthy weight; CPO, chronic pain and obesity; O, obesity; HC, healthy controls.

2.8. Statistical methods

Continuous variables are reported as median (interquartile range) and categorical variables as n (%). To compare differences between groups, a Kruskal–Wallis test or a Mann–Whitney test was used for continuous, and a χ^2 test or a Fisher’s exact test for categorical

variables. Minimal missing data are noted in **Table 1**. Spearman correlation tests examined relationships between biomarkers and pain attributes for the 2 groups with chronic pain. A 2-sided P -value of <0.05 (not adjusted for multiple comparisons) was considered statistically significant. Classification and Regression Trees (CART) (nonparametric models) were used to explore which combinations of

Table 2
Pain characteristics of the CPHW and CPO groups.

	CPHW n = 30	CPO n = 29	<i>P</i>
Primary pain location, n (%)			0.67
Head	17 (56.7)	18 (62.1)	
Back	3 (10.0)	2 (6.9)	
Musculoskeletal	0	1 (3.4)	
Others	10 (33.3)	8 (27.6)	
Primary diagnosis for head pain, n (%)			0.69
Chronic daily headache	6 (20.0)	6 (20.7)	
Migraine w and w/o aura	6 (20.0)	7 (24.1)	
Tension headache	5 (16.7)	4 (13.8)	
Unspecified chronicity pattern	0	1 (3.4)	
Duration of chronic pain, <i>mo</i>			0.21
Median (IQR)	28.0 (12.0–84.0)	21.0 (12.0–36.0)	
Pain in the last 14 d			0.061
Median (IQR)	12.0 (5.0–14.0)	8.0 (3.0–12.5)	
Usual pain intensity			0.84
Median (IQR)	5.5 (4.0–7.0)	6.0 (3.0–8.0)	
Worst pain intensity			0.31
Median (IQR)	8.0 (6.0–9.0)	8.0 (6.0–9.0)	

CPHW, chronic pain and healthy weight; CPO, chronic pain and obesity; O, obesity; HC, healthy controls; IQR, interquartile range.

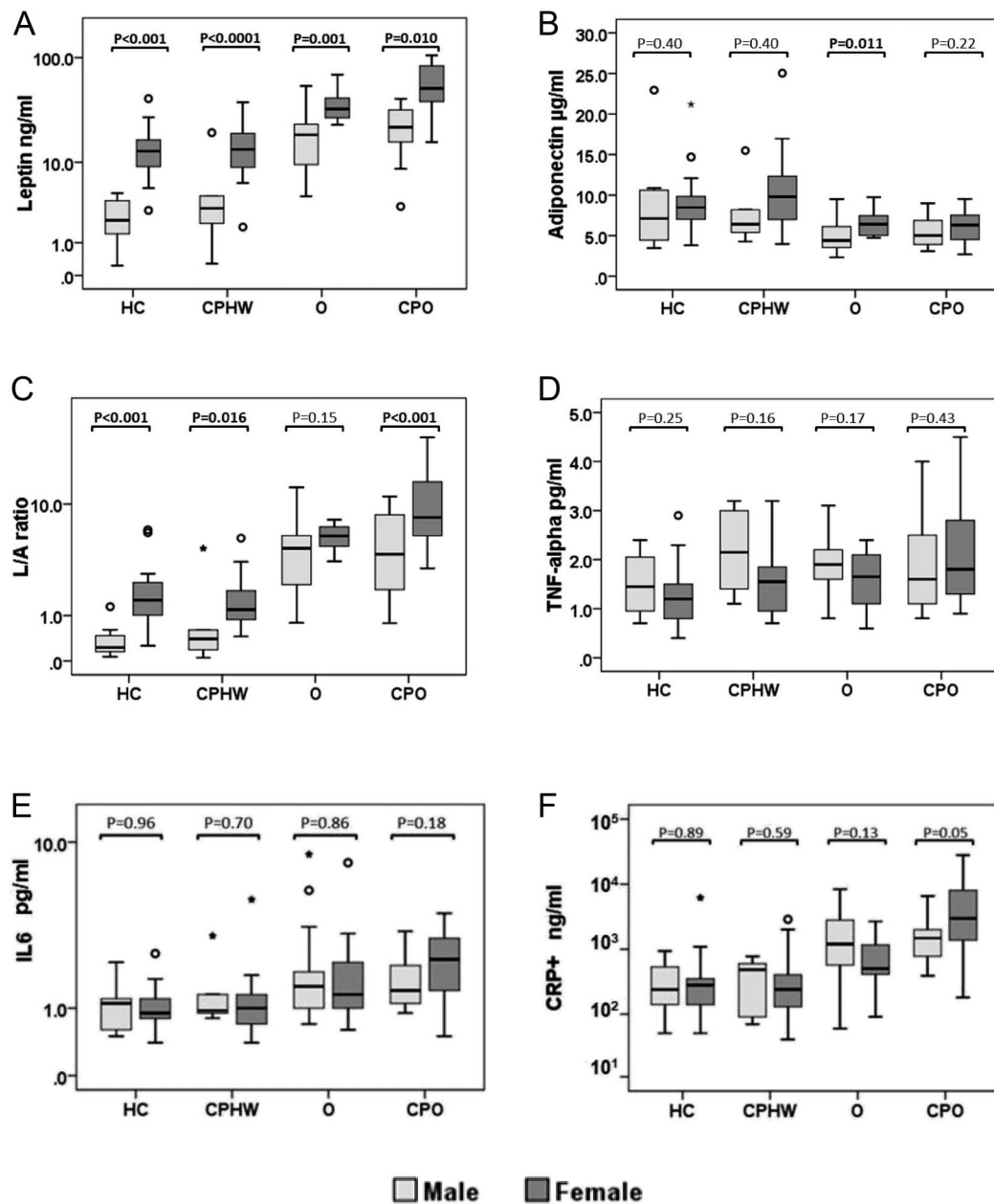


Figure 2. Systemic biomarker concentrations by group and sex. Biomarkers include (A) leptin, (B) adiponectin, (C) L/A ratio, (D) TNF- α , (E) IL-6, and (F) CRP. For right-skewed biomarkers in (A), (C), and (E), a log scale was used for the Y-axis. CRP, C-reactive protein.; CPHW, chronic pain and healthy weight; CPO, chronic pain and obesity; O, obesity; HC, healthy controls; IL-6, interleukin 6.

factors had the strongest associations with each biomarker. CART analysis has the advantage that it is transparent and objective, enables investigation of interrelationships between many variables, and provides thresholds for further investigation. For the 6 multivariable CART analyses, the outcomes were the individual biomarkers (leptin, adiponectin, L/A ratio, TNF- α , IL-6, and CRP). Considered factors included groups (HC, CP, O, and CPO), demographics (age, sex, and Pubertal Development Scale), and clinical factors important to pediatric chronic pain (functional disability, anxiety, depression, and physical activity). Trees were optimized by the least absolute deviation with 10-fold cross validation and split criteria of 10 for the parent node and 5 minima for the terminal node. Data were analyzed using SAS 9.4, SPSS 24.0 (IBM), and Salford Systems CART (Classification and Regression Trees) Software.

3. Results

3.1. Sample characteristics

Figure 1 shows the participant flow. The primary reason for ineligibility was the use of excluded medications. After enrollment, the primary exclusions were self-reports of acute pain (pain intensity $\geq 3/10$) or chronic pain (all were responses of “sometimes” on the screener) in the HC or O groups. Ultimately, the data on 125 adolescents (13–17 years) were analyzed. Demographics are in **Table 1**. Groups did not differ in age, ethnicity, or pubertal stage ($P > 0.05$). However, the O group had more male participants ($P < 0.001$); CPO group had more African Americans ($P = 0.031$). Between-group differences in BMI percentile and central adiposity were consistent and expected based on the inclusion criteria.

Table 3**Between-group differences in systemic biomarker concentrations (shown in Fig. 3) by sex.**

Male	Female
Leptin	
CPO > CPHW, <i>P</i>-value = 0.006	CPO > CPHW, <i>P</i>-value<0.0001
CPO vs O, <i>P</i> -value = 0.313	CPO > O, <i>P</i>-value = 0.028
CPO > HC, <i>P</i>-value<0.001	CPO > HC, <i>P</i>-value<0.0001
O > CPHW, <i>P</i>-value = 0.003	O > CPHW, <i>P</i>-value<0.0001
O > HC, <i>P</i>-value<0.0001	O > HC, <i>P</i>-value<0.0001
CPHW vs HC, <i>P</i> -value = 0.477	CPHW vs HC, <i>P</i> -value = 0.832
Adiponectin	
No differences	CPO < CPHW, <i>P</i>-value = 0.002
	CPO vs O, <i>P</i> -value = 0.698
	CPO < HC, <i>P</i>-value = 0.003
	O < CPHW, <i>P</i>-value = 0.018
	O < HC, <i>P</i>-value = 0.014
	CPHW vs HC, <i>P</i> -value = 0.383
Leptin/adiponectin ratio	
CPO > CPHW, <i>P</i>-value = 0.004	CPO > CPHW, <i>P</i>-value<0.0001
CPO vs O, <i>P</i> -value = 0.872	CPO vs O, <i>P</i> -value = 0.056
CPO > HC, <i>P</i>-value <0.001	CPO > HC, <i>P</i>-value <0.0001
O > CPHW, <i>P</i>-value = 0.002	O > CPHW, <i>P</i>-value<0.0001
O > HC, <i>P</i>-value<0.0001	O > HC, <i>P</i>-value<0.0001
CPHW vs HC, <i>P</i> -value = 0.651	CPHW vs HC, <i>P</i> -value = 0.587
TNF-alpha	
No differences	CPO vs CPHW, <i>P</i> -value = 0.111
	CPO vs O, <i>P</i> -value = 0.317
	CPO > HC, <i>P</i>-value = 0.005
	O Vs CPHW, <i>P</i> -value = 0.747
	O Vs HC, <i>P</i> -value = 0.216
	CPHW vs HC, <i>P</i> -value = 0.121
IL-6	
No differences	CPO > CPHW, <i>P</i>-value = 0.002
	CPO > O, <i>P</i> -value = 0.254
	CPO > HC, <i>P</i>-value = 0.001
	O Vs CPHW, <i>P</i> -value = 0.063
	O > HC, <i>P</i>-value = 0.037
	CPHW vs HC, <i>P</i> -value = 0.949
C-reactive protein	
CPO > CPHW, <i>P</i>-value = 0.007	CPO > CPHW, <i>P</i>-value<0.0001
CPO vs O, <i>P</i> -value = 0.977	CPO > O, <i>P</i>-value = 0.031
CPO > HC, <i>P</i>-value = 0.002	CPO > HC, <i>P</i>-value <0.0001
O > CPHW, <i>P</i>-value = 0.021	O > CPHW, <i>P</i>-value = 0.034
O > HC, <i>P</i>-value = 0.004	O > HC, <i>P</i>-value = 0.024
CPHW vs HC, <i>P</i> -value = 0.847	CPHW vs HC, <i>P</i> -value = 0.932

CPHW, chronic pain and healthy weight; CPO, chronic pain and obesity; O, obesity; HC, healthy controls. Bold print indicates significant differences.

Pain characteristics for the CPHW and CPO groups are in **Table 2**. There were no between-group differences on pain-related variables, but there were several sex differences (not shown in **Table 2**) in the CPO group alone. Within the CPO group: females (8.0, 8.0–9.0) reported a significantly higher level of worst pain than males (6.5, 4.0–8.0) ($P = 0.032$), and a longer duration for usual pain (3.0, 1.0–4.0 hours) than males (0.0, 0.0–2.0 hours) ($P = 0.043$).

3.2. Serum biomarkers

Serum biomarkers and their within-group sex differences are shown in **Figure 2**. Between-group sex differences are shown in **Table 3**. Leptin (panel A) was dramatically increased in the groups with obesity (O and CPO) in males and females. In every

group, leptin was significantly higher in females ($P < 0.010$ to <0.0001). In all except the O group, females had 2-fold higher circulating leptin levels. Of note, the highest levels of leptin were found in females with CPO ($P 0.028$ to <0.0001). There was a 4-fold difference between the HC group and the CPO group. **Adiponectin** (panel B) was lower in the 2 groups with obesity (O and CPO). The only sex difference was found in the O group, with adiponectin levels higher in females ($P = 0.011$). The **L/A ratio** (panel C) mirrored between-group and within-group differences found for leptin. Although a sex difference was found in the O group for both leptin and adiponectin, that effect was lost in the L/A ratio results. The only between-group difference in **TNF-alpha** (panel D) was in females. Females with CPO had higher levels of TNF-alpha than females in the HC group. The only between-group differences in **IL-6** (panel E) was in females. Females with CPO had higher IL-6 compared with HC (more than double) and CPHW (almost double). In addition, females in the O group had a higher IL-6 than those in the HC group. Several important findings are apparent in **CRP** (panel F). CRP was dramatically higher in the O and CPO groups, such that overall, median CRP concentration was almost 2-fold increased over the HC and CPHW groups. Compared with leptin, CRP was significantly higher in females in the CPO group alone. Most apparent is that in females, the CPO group had higher levels than all other groups, including the O group, and the difference was >10-fold between the HC and CPHW groups and the CPO group.

3.3. Relationships between inflammatory biomarkers and pain attributes and functional disability

Table 4 shows data for clinical factors. Functional disability was higher in both chronic pain groups for both females and males. Among males, depression was highest in those with CPHW. Among females, depression was highest in the groups with chronic pain. Within the CPO group, females reported greater anxiety and lower physical activity. No other within-group sex differences were found.

We then examined relationships between biomarkers and pain attributes (usual and worst pain intensity, days with pain in the last 14, and duration of chronic pain). As leptin increased, so did usual ($r_s = 0.39$, $P = 0.047$) and worst ($r_s = 0.50$, $P = 0.008$) pain intensity, as well as number of days with pain in the last 14 days ($r_s = 0.40$, $P = 0.034$) in the CPO group; however, leptin was not correlated with any pain parameters in the CPHW group. As CRP increased, usual ($r_s = 0.62$, $P = 0.001$) and worst ($r_s = 0.51$, $P = 0.006$) pain intensity and the number of days with pain in last 14 days ($r_s = 0.40$, $P = 0.036$) increased in the CPO group, but CRP was not correlated with any pain parameters in the CPHW group. Finally, as IL-6 increased, worst pain intensity increased ($r_s = 0.40$, $P = 0.041$) in the CPO group. By contrast, as IL-6 increased in the CPHW group, usual ($r_s = -0.42$, $P = 0.021$) and worst ($r_s = -0.40$, $P = 0.027$) pain intensity decreased, whereas the duration of chronic pain increased ($r_s = 0.49$, $P = 0.006$).

3.4. Regression trees

Figures 3–8 depict regression trees and significant factors for branch points within each tree. Central adiposity and sex were important predictors of leptin, such that females with central adiposity had 2.5× more leptin than the sample median (**Fig. 3**). BMI percentile was the most important predictor of adiponectin (**Fig. 4**). The highest levels were found in White participants with a BMI <90th percentile. Females with central adiposity had a

Table 4
Between-group differences on clinical factors by sex.

	Male					P	Female				
	HC	CPHW	O	CPO	P		HC	CPHW	O	CPO	P
Functional disability		*†		*†	<0.001		‡§		‡§	<0.001	
Median (IQR)	0.00 (0.00–6.00)	34.50 (26.00–39.00)	3.00 (0.00–4.00)	19.50 (6.00–47.25)		1.00 (0.00–2.00)	41.69 (27.71–56.85)	1.50 (0.00–8.00)	32.00 (14.00–57.00)		
Anxiety		¶¶		44.85#	0.014				48.30#	0.066	
Median (IQR)	38.00 (33.50–43.95)	49.80 (48.30–49.80)	40.60 (33.50–44.90)	44.85# (40.60–46.70)		44.90 (38.00–48.30)	47.50 (44.90–59.30)	43.00 (40.60–51.20)	48.30# (46.70–58.70)		
Depression					0.21		***††		††	0.009	
Median (IQR)	35.20§§ (35.20–37.80)	42.95 (35.20–52.00)	40.40 (35.20–43.20)	40.40 (35.20–43.20)		40.40§§ (35.20–45.50)	51.30 (37.80–61.10)	35.20 (35.20–40.40)	48.25 (40.40–60.00)		
Physical activity					0.66					0.97	
Median (IQR)	53.10 (45.20–60.15)	46.45 (39.40–56.30)	51.40 (46.10–57.30)	52.35 (49.20–55.30)		47.80 (41.40–54.30)	45.20 (42.40–53.30)	50.05 (38.90–54.80)	48.70 (42.40–50.50)		

Patient-Reported Outcomes Measurement Information System anxiety, depression, and physical activity are reported as T-scores. Bold print indicates significant differences.

* P = 0.003 vs HC.

† P < 0.001 vs O.

‡ P < 0.0001 vs HC.

§ P < 0.001 vs HC.

¶ P = 0.006 vs HC.

¶¶ P = 0.012 vs O.

Within the CPO group, females > males (P = 0.035).

** P = 0.021 vs HC.

†† P = 0.010 vs O.

††† P = 0.016 vs O.

§§ Within the HC group, females > males (P = 0.038).

|| Within the CPO group, males > females (P = 0.036).

CPHW, chronic pain and healthy weight; CPO, chronic pain and obesity; O, obesity; HC, healthy controls; IQR, interquartile range.

high L/A ratio (2.8× higher than sample median) (Fig. 5). Furthermore, the highest L/A ratio was found in the youngest males with central adiposity. The highest TNF-alpha was found in youth with obesity (Fig. 6). Among those without obesity, lower levels of TNF-alpha were found in those with higher levels (T scores >50.5) of anxiety. IL-6 is 1 of 2 biomarkers that was significantly predicted by a clinical outcome, namely, functional disability (Fig. 7). IL-6 was best predicted by youth with the

highest levels of functional disability (>30) and a BMI percentile >80. For these youth, the median level of IL-6 was almost 2× more than the sample median. Those with central adiposity had 3× more CRP than the sample median (Fig. 8). Of note, the highest CRP was found in those with both central adiposity and the greatest functional disability (>30; all in this subgroup had CPO), such that CRP concentration almost 5-fold higher than the sample median.

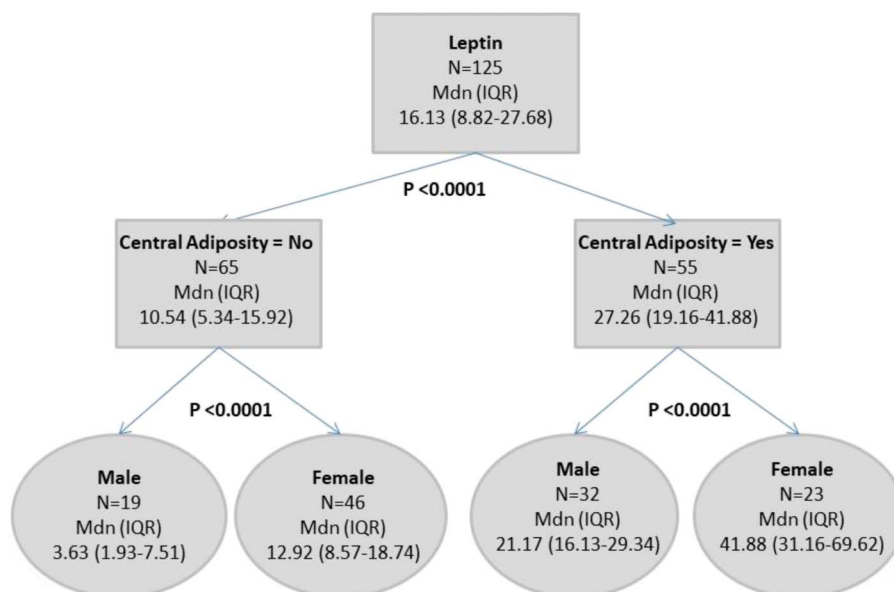


Figure 3. Regression tree: leptin. Regression tree analysis representing the significant predictors of systemic levels of leptin (ng/mL). Central adiposity is the most important independent variable, higher leptin is associated with central adiposity. Sex is also an important independent variable, it shows that females have a higher leptin level than males, particularly so for youth with (P < 0.0001) central adiposity.

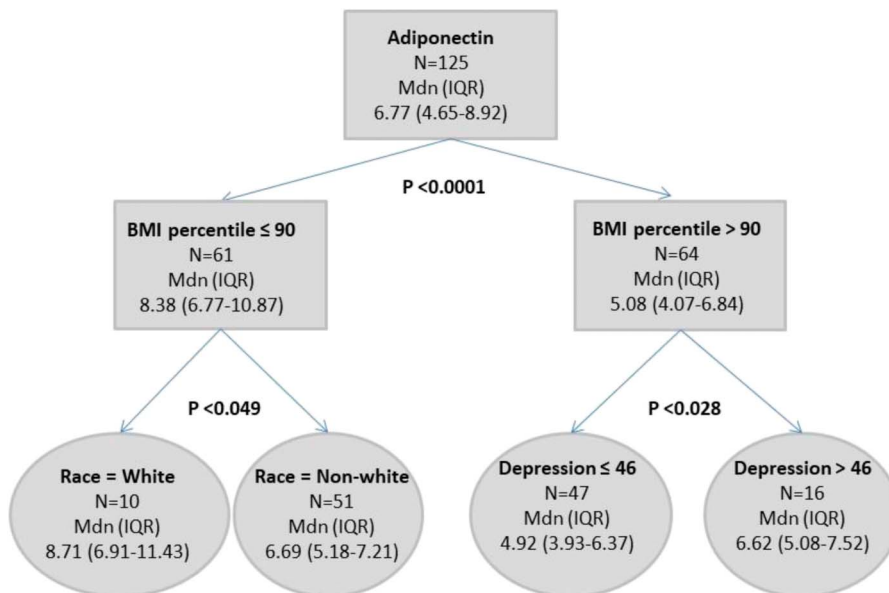


Figure 4. Regression tree: adiponectin. Regression tree analysis representing the significant predictors of systemic levels of adiponectin ($\mu\text{g/mL}$). Body mass index percentile is the most important predictor. Other important predictors include race ($P < 0.049$) and the depression T-score ($P < 0.028$). IQR, interquartile range.

4. Discussion

We assessed the effects and interactions of chronic pain and obesity on inflammatory biomarkers in adolescents. The major findings were as follows: (1) in females, there was an interaction between chronic

pain and obesity such that leptin and CRP were higher in the CPO group than in chronic pain or obesity alone; (2) within the CPO group, biomarkers were correlated with worsened pain attributes, and females reported worse pain than males; (3) the highest levels of IL-6 and CRP were found in youth with elevated weight and functional

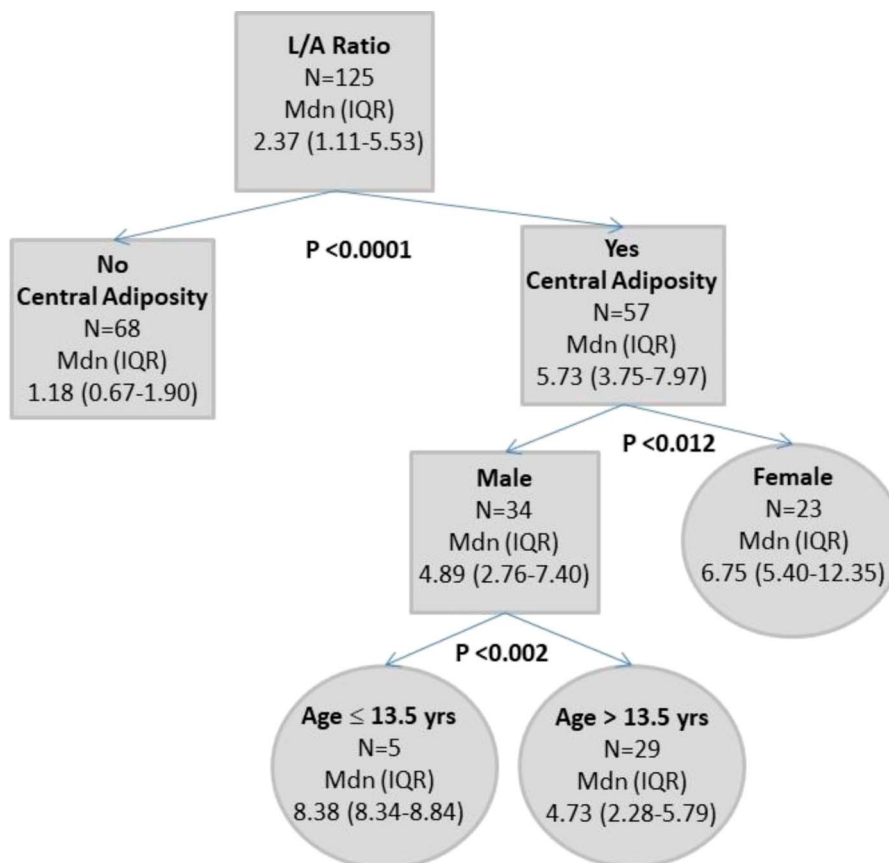


Figure 5. Regression tree: leptin/adiponectin ratio. Regression tree analysis representing the significant predictors of systemic levels of the leptin/adiponectin ratio. Central adiposity is the most important predictor. Other important predictors include sex ($P < 0.012$) and age ($P < 0.002$).

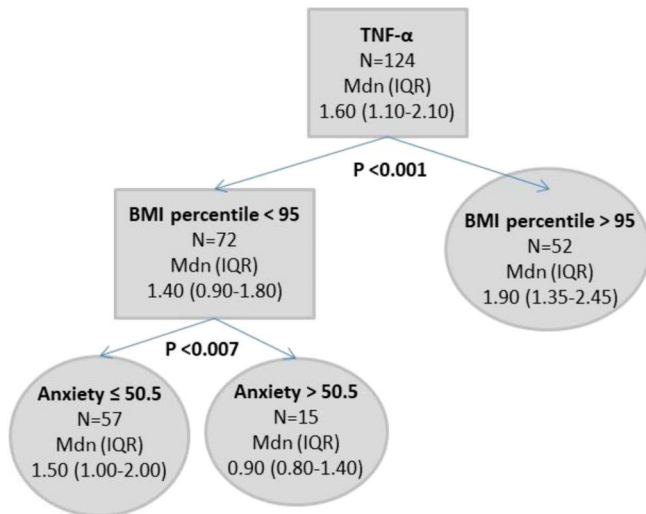


Figure 6. Regression tree: TNF-alpha. Regression tree analysis representing the significant predictors of circulating levels of TNF-alpha (pg/mL). BMI percentile is the most important predictor ($P < 0.001$). Anxiety is another important predictor ($P < 0.007$).

disability. These preliminary findings suggest that chronic pain and obesity interact to cause dysregulation of the inflammatory system, which may increase functional disability.

In males, biomarkers in the CPO and O groups did not differ, suggesting that differences between the CPO and CPHW groups can be explained by obesity. By contrast, females with CPO had higher leptin and CRP than all other groups, suggesting that chronic pain and obesity interact to augment inflammation beyond that associated with obesity. This interaction is consistent with our recent findings on suPAR, a newer index of chronic inflammation.⁵⁷ The current findings of elevated leptin and CRP are concerning, as

both are associated with chronic pain and obesity-related comorbidities.^{3,7,12,42,51,52,60,77} Although leptin is typically elevated in obesity and higher in girls than boys by puberty,⁵² we found a 4-fold increase in females with CPO. With the 10-fold increase in CRP, this suggests dysregulation of the inflammatory system associated with the comorbid state. Although we cannot explain the mechanisms of this, the interaction between chronic pain and obesity may have a biochemical basis, with a number of potential mediating factors, including diet.⁷²

We hypothesized that the effects of CPO on biomarkers would be more pronounced in females.^{18,29,75} Chronic pain is more prevalent in females, and female sex is a risk factor for chronic pain.^{38,67} Worldwide, the prevalence of obesity is greater in adult females.¹ In the United States, although the prevalence of obesity does not differ by sex, the prevalence of severe obesity (9.2%) in adults is higher in women. Our data are consistent with the concept that pediatric pain is greater in females for most pain types,³⁷ and 70 to 85% of patients seen in pediatric pain clinics are females.⁴⁹ Even in the biomarkers with more subtle between-group differences, the effects of comorbid chronic pain and obesity were more pronounced in females. Females with CPO had higher TNF-alpha than HCs, and higher IL-6 than both the HCs and CPHWs. Mechanisms for this greater prevalence of pain in females (including in children) are not well understood.³⁷ Despite the paucity of research on chronic pain and comorbid obesity, it seems that females are also more affected by the co-occurring conditions.^{52,53,55}

Although between-group differences were not found in pain attributes for the 2 pain groups, there were several interesting within-group differences. In the CPO group, leptin and CRP were correlated with several clinical parameters. These correlations were not found in the CPHW group. Interestingly, IL-6 was negatively correlated with usual and worst pain intensity in the CPHW group but positively correlated with worst pain intensity for the CPO group. Although this contrast is difficult to explain, it may be due to the pleiotropic nature of IL-6.²⁰

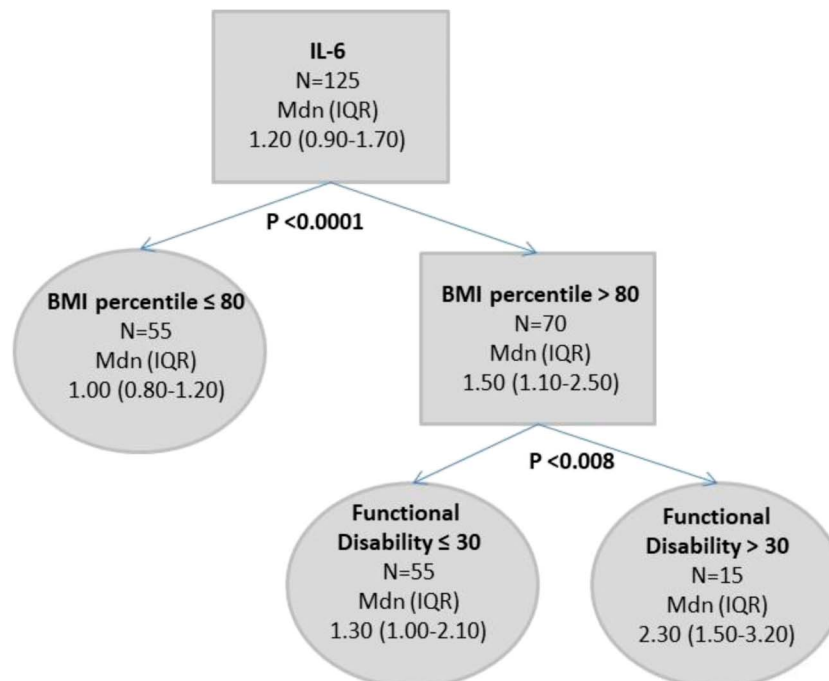


Figure 7. Regression tree: IL-6. Regression tree analysis representing the significant predictors of systemic levels of IL-6 (pg/mL). BMI percentile is the most important predictor. Functional disability is another important predictor ($P < 0.008$).

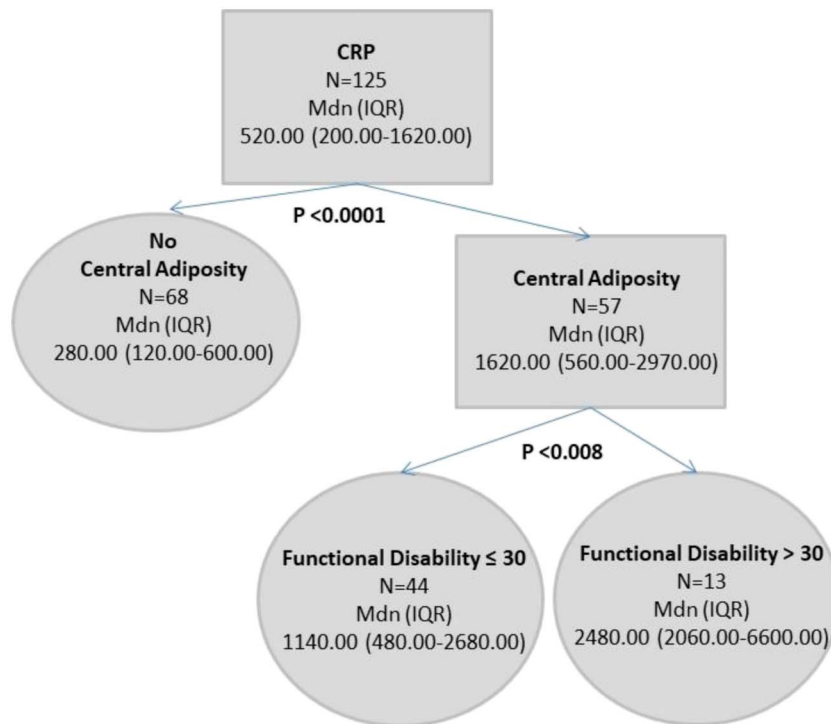


Figure 8. Regression tree: C-reactive protein. Regression tree analysis representing the significant predictors of systemic levels of C-reactive protein (ng/mL). Central adiposity is the most important predictor. Functional disability is another important predictor ($P < 0.008$).

The tree analyses showed that biomarker concentrations were associated with obesity, as expected. However, IL-6 and CRP were also associated with functional disability, a key target in pediatric pain management, and a critical outcome for youth with CPO.^{25,70} Future studies should examine whether the thresholds found in these models are clinically useful.

Overall, we propose that inflammatory processes may increase pain and functional disability in youth with CPO. That biomarkers were related to pain and functional disability for the CPO group, but almost no relationships were found for the CPHW group, suggests a possible threshold effect. Furthermore, although we did not find differences in functional disability between the pain groups, over time, inflammation may take a toll in terms of pain. In one meta-analysis, CRP was associated with pain and decreased function in OA but was not associated with radiographic OA.³³ This suggests that elevated CRP may be an early sign of future damage, long before degeneration is visible.

We propose that elevated inflammation at an early age may increase the risk of exacerbating current pain conditions and the development of new pain conditions across the lifespan. This would be consistent with evidence that a proinflammatory milieu potentiates the negative effects of inflammatory biomarkers, and evidence that elevated biomarkers increase risk of pain and have long-lasting effects.^{60,64,68,77} For example, chronic inflammation triggers irreversible structural and biochemical changes leading to intervertebral disc degeneration (IVDD) and low back pain.⁶⁰ Furthermore, an elevated BMI in early, rather than late adulthood is associated with a higher risk of IVDD.⁷⁷ As another example, baseline CRP, IL-6, and TNF- α predict knee pain in weight-bearing and non-weight-bearing positions over 5 years.⁶⁸

4.1. Limitations

We did not include youth with overweight (BMI 85th–94th percentile), which limited the exploration of relationships between biomarkers and BMI as a continuous variable. We also did not measure body composition. Therefore, we may have missed patients with “normal weight obesity,” who may have elevated proinflammatory biomarkers, despite having a normal BMI percentile.⁵⁹ Results were not adjusted for multiple comparisons. Finally, the obese group data may have been influenced by the greater number of males. This also applies to race, as more African Americans were in the CPO group. Although the consistency of our findings suggests that the results were probably not affected by these factors, future studies should examine a larger and more balanced sample. As we have recommended for serum suPAR, evaluation of biomarker levels in a very large cohort of subjects from different racial and ethnic groups may provide insight into potential mechanisms for the interaction of obesity and pain.⁵⁷

Future research should examine inflammation in children with widespread pain and pain associated with inflammation, to evaluate a possible greater synergistic effect than found here.⁶⁰ Of importance for youth with CPO, novel treatment options such as nutritional interventions should be evaluated.⁴⁶ An 18-month intervention of diet and exercise reduced proinflammatory markers and improved pain and function with knee OA.⁶¹ The change in biomarkers accounted for 15% of the pain reduction independent of BMI and 29% of the improvement in function.⁶¹ It was proposed that interventions to decrease systemic inflammation have the potential to improve pain and function. Future studies should evaluate this potential for youth with CPO. Other possible treatment options include exercise,⁶³ neurostimulation (eg, vagus nerve stimulation),³⁶ nutrition,¹⁶ probiotics,^{43,71} or pharmaceuticals that affect inflammatory systems.²

We conclude that in adolescents with chronic pain and obesity, the inflammatory system is dysregulated, and this effect is more pronounced in females. The increased inflammatory biomarkers were associated with pain and functional disability. With additional studies in more subjects, this augmentation may become a useful, early marker of future pain and disability.

Disclosures

The authors have no conflicts of interest to declare.

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