General Section
Research Paper

OPEN

PAIN REPORTS

Pain sensitivity does not differ between obese and healthy weight individuals

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Abstract

Introduction: There is emerging evidence suggesting a relationship between obesity and chronic pain.

Objectives: The aim of this study was to determine whether pain-free obese individuals display altered pain responses to acute noxious stimuli, thus raising the possibility of greater pain sensitivity and potential susceptibility for chronic pain development.

Methods: Psychophysical and anthropometric data were collected from 38 individuals with an obese body mass index (BMI) classification (BMI $\geq$ 30) and 41 age/sex-matched individuals of a healthy BMI (BMI $<$ 24.9). Because BMI may be an inaccurate index of obesity, additional anthropometric parameters of central adiposity and percent body fat were examined. Pain responses to suprathreshold noxious heat and cold stimuli were examined. Subjects provided pain intensity and unpleasantness ratings to noxious heat (49°C) applied at varying durations and locations (ventral forearm/lower leg). Cold pain ratings, thresholds, and tolerances were obtained after immersion of the hand in a cold-water bath (0–2°C). Between-group differences in pain responses, as well as relationships between pain responses and obesity parameters, were examined. Importantly, confounds that may influence pain such as anxiety, depression, impulsivity, sleepiness, and quality of life were assessed.

Results: No between-group differences in pain sensitivity to noxious heat and cold stimuli were found. No relationships were found between central adiposity or body fat (percentage or distribution) and pain responses to noxious heat or cold stimuli.

Conclusions: Obesity has minimal influence on pain sensitivity. Accordingly, it is unlikely that obesity alone increases susceptibility for chronic pain development through amplification of nociceptive processes.

Keywords: Heat pain, Cold pain, Obesity, Quantitative sensory testing, Healthy controls, Tolerance

1. Introduction

Obesity and chronic pain are 2 separate, yet intricately intertwined conditions that are currently major U.S. public health concerns. The prevalence of obesity is at epidemic levels with more than 35% of adults being classified as obese.[42] Similarly, about 30% of the population currently suffer from chronic pain conditions.[56] Both obesity and chronic pain decrease quality of life and are often comorbid with additional conditions such as depression, anxiety, and/or poor sleep quality.[1,10,14,24,25,36,57,61,70]

Previous studies have shown that chronic pain and obesity are related, such that obese individuals have an increased risk of developing chronic pain and individuals with chronic pain have an increased risk of being obese.[29,40,46,48,60] Chronic pain conditions relating to obesity are not limited to load-bearing conditions such as chronic low back pain, musculoskeletal pain, or knee osteoarthritis, although these are quite common.[3,12,15,16,28,29,44,47,55,59,74] Obesity has been linked to increased odds of chronic migraine, fibromyalgia, neck pain, abdominal pain, and chronic widespread pain.[16,74] In addition, Stone and Broderick found that obese individuals were 68% more likely to experience pain than healthy weight individuals.[65] Recently, a correlation between body mass index (BMI) and prescription opioids was found, demonstrating that the risk of receiving prescription opioids increased progressively with BMI.[64]

Although obesity and chronic pain are related, it is unclear whether obese individuals, who are otherwise healthy, are more sensitive to experimental pain and might be primed to develop chronic pain conditions. Studies have demonstrated conflicting results regarding whether sensitivity to experimental pain is

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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PR9 6 (2021) e942

http://dx.doi.org/10.1097/PR9.0000000000000942

altered in obese individuals.[9,22,30,33,49,52,79] These conflicting results across studies are likely due to differences in methodologies. Importantly, a critical limitation of the majority of these studies is the use of only BMI to assess obesity. Although BMI is a widely used and acceptable measure for obesity, it has major limitations. Most notably, BMI cannot differentiate between fat mass and lean muscle mass.[41] Thus, individuals with low body fat, but high muscle mass, could be identified as obese. On the other hand, individuals with a high body fat could have a healthy BMI (termed "normal weight obesity" or "skinny fat"[43]). In addition, the outcome measure of pain sensitivity has been most often defined using pain thresholds, and there is a need to assess other measurements such as suprathreshold pain ratings of pain intensity and unpleasantness.[68] Finally, psychological comorbidities such as anxiety, depression, and sleep are common in obese individuals and may influence pain sensitivity. However, these comorbidities are not often adequately addressed.

This study aimed to evaluate differences in pain sensitivity between healthy weight and obese individuals using several measures of obesity (BMI, central adiposity, and percent body fat [BF%]), as well as multiple types, locations, and durations of suprathreshold nociceptive stimuli. Importantly, variability associated with obesity-related comorbidities was removed by controlling for confounding factors in the study design and data analyses.

2. Materials and methods

2.1. Subjects

Study recruitment separately targeted healthy weight and obese participants, with healthy participants' age and sex matched to obese participants. Enrollment of both groups proceeded in parallel through the duration of the study. In general, recruitment was interleaved—an obese participant was enrolled, and then, an age/sex-matching healthy weight participant was enrolled. Assessment for eligibility occurred in 99 subjects, in which 20 were excluded for not meeting the enrollment criteria. Exclusion criteria included BMIs between 25 and 29.9 kg/m^2, a history of chronic pain conditions, chronic disease conditions, psychiatric disorders, neurological disorders, diabetes, and current medication use. Psychophysical and anthropometric data were collected from a total of 79 healthy volunteers (40 females and 39 males) ranging in age from 18 to 66 years with a mean age of 30 $\pm$ 9 years. The distributions of race/ethnicity included 58 Whites, 13 African Americans, 4 Asians, 2 Hispanics, 1 Indian, and 1 multiracial. Subjects were placed into age/sex-matched groups based on having a healthy BMI (n = 41, BMI = 18.5–25 kg/m^2) or an obese BMI (n = 38, BMI $\geq$ 30 kg/m^2). Subjects gave written informed consent stating they understood that they would experience painful thermal stimulation, that the experimental procedures were clearly explained, and that they could withdraw at any time without prejudice. The Wake Forest University School of Medicine Institutional Review Board approved all study procedures.

2.2. Anthropometric data collection

Measurements of height, weight, waist circumference (WC), and skinfold thickness were obtained. Subjects were weighed using an electronic scale. Heights were collected using a standard wall-mounted stadiometer. To assess central adiposity, WC was obtained by measuring the distance around the waist at the umbilicus. Waist circumference/height was used to calculate the waist/height ratio (WHR) and indicates on the distribution of body fat. For BF%, skinfold measurements were obtained on the direct skin of the left tricep, bicep, subscapular, and suprailiac regions in accordance with a standard protocol, using a Lange skinfold caliper (Beta Technology, Watertown, WI).[8] The sum of skinfold measurements was used to calculate the BF%.[8]

2.3. Self-report questionnaires

To identify potential confounding factors influencing pain perception and exhibiting relationships with obesity, subjects completed the Spielberger State-Trait Anxiety Inventory,[63] Beck Depression Inventory-II,[2] Epworth Sleepiness Scale,[18] Barratt Impulsiveness Scale-11,[45] and Short-Form 36 Health Survey (quality of life).[71] Questionnaires were completed before sensory testing.

2.4. Psychophysical data collection overview

Subjects underwent a brief sensory training session before sensory testing. Sensory testing included stimulation with short- and long-duration heat stimuli and the cold-pressor test. Heat stimuli were applied using a 16 $\times$ 16-mm TSA II thermal stimulator (Medoc, Ramat Yishai, Israel), with 35°C serving as baseline. To prevent sensitization/habituation, the thermal probe was moved to a different location at the termination of each stimulus (ie, hand and leg). Participants rested their hand/leg on the probe. The thermal probe was not strapped for safety reasons, which allowed participants to stop the stimulation by moving their hand/leg away from the probe. The cold-pressor test was delivered through an ice-water bath kept between 0 and 2°C. Subjects rated pain intensity and unpleasantness using a visual analogue scale (VAS; Parisian Novelty, Chicago, IL) anchored at 0 (no pain and not at all unpleasant) and 10 (most intense pain imaginable or most unpleasant imaginable).[50,51] Subjects were instructed to only provide a rating for painful stimuli and thus provided pain intensity and unpleasantness ratings of zero if no pain was perceived.

2.4.1. Sensory training

To familiarize subjects with heat stimuli and use of the VAS, a sensory training session occurred before testing. During training, heat stimuli (35°C, 43-49°C) were applied to the left ventral forearm with rise and fall rates of 6°C/s, a baseline temperature of 35°C, a plateau duration of 5 seconds, and an interstimulus interval of 30 seconds. Each stimulus temperature was delivered 4 times for a total of 32 stimuli. Subjects provided VAS pain intensity and unpleasantness ratings at the termination of each stimulus.

2.4.2. Sensory testing

The experience of pain can vary based on stimulus duration[19] because of both physical and neurophysiological factors. Brief heat stimuli will produce limited heating of deeper portions of the skin and will recruit populations of nociceptors with terminals in the superficial aspects of the skin.[76] By contrast, intermediate duration stimuli may also be perceived as more painful because of deeper diffusion of heat into the skin and subsequent recruitment of deeper primary afferents.[11] In addition, long-duration high-intensity stimulation may result in increased pain intensity and unpleasantness, as well as changes in primary afferent and dorsal horn mechanisms that reflect temporal summation in addition to deeper diffusion of heat into the skin.[4,19,32,38] To fully assess differences in pain sensitivity that may emerge only in long-duration stimuli, 3 different stimulus durations were used.

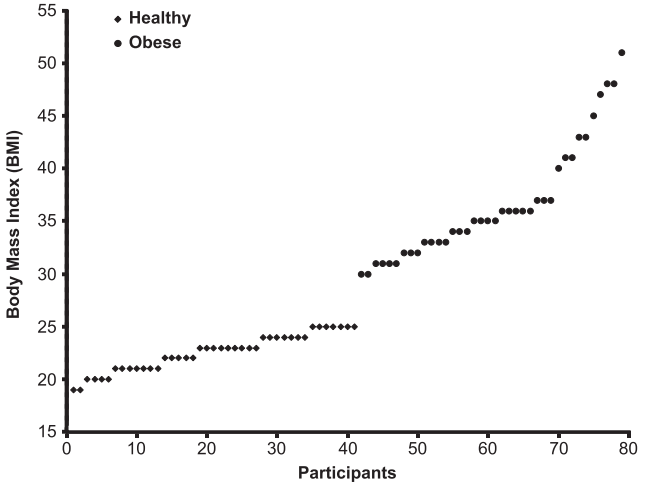

Figure 1. Distribution of body mass index of all participants. Body mass index range for healthy participants was 19 to 25, and body mass index range for obese participants was 30 to 51.

2.4.2.1. Short-duration heat stimuli (5 seconds)

Short-duration (5 seconds) heat stimuli (35, 43, 45, 47, and 49°C) were applied to the right ventral forearm with rise and fall rates of 6°C/s, a plateau duration of 5 seconds, and an interstimulus interval of 30 seconds. Each stimulus was randomly delivered 3 times for a total of 15 stimuli. Subjects provided VAS pain intensity and unpleasantness ratings at the termination of each stimulus. The mean ratings to the three 49°C stimuli were used for analyses to enable comparisons with stimuli of other durations. The ventral forearm was chosen as the site of stimulation to parallel other quantitative sensory testing studies in healthy participants.

2.4.2.2. Cyclic intermediate duration heat stimuli (12 seconds)

Ten intermediate duration (12 seconds) heat stimuli (49°C) were applied to the left lower leg and interleaved with eleven 35°C stimuli in a 6.8-minute series with rise and fall rates of 6°C/s, plateau durations of 12 seconds, and interstimulus intervals of 12 seconds. Subjects provided a VAS pain intensity and unpleasantness rating at the termination of the series. One subject did not complete this stimulation because of the presence of scar tissue on the left calf stimulation site. The stimulus pattern and location was chosen to be comparable with stimuli used in magnetic resonance imaging studies using arterial spin labeling.

2.4.2.3. Cyclic long-duration heat stimuli (30 seconds)

Four long-duration (30 seconds) heat stimuli (49°C) were applied to the right lower leg and interleaved with five 35°C stimuli in a 4.8-minute series with rise and fall rates of 6°C/s, plateau durations of 30 seconds, and interstimulus intervals of 30 seconds. Subjects provided a VAS intensity and unpleasantness rating at the termination of the series. The stimulus pattern and location was chosen to be comparable with stimuli used in BOLD functional magnetic resonance imaging studies.

2.4.2.4. Cold-pressor test

Noxious cold is processed differentially from noxious heat, both peripherally and centrally.[6,20,35,39] Diverse processing of noxious cold yields differences in the subjective experience of pain, both in pain ratings and qualitative descriptors.[35,54] Noxious cold is often delivered through the cold-pressor test, which evokes higher ratings of pain unpleasantness compared with noxious heat pain in healthy individuals and may better represent mechanisms of chronic pain.[54] Accordingly, the cold-pressor task was used to examine sensitivity differences to cold pain between healthy BMI and obese BMI individuals. The cold-pressor test was performed

Table 1

Differences in anthropometric measurements between healthy body mass index and obese body mass index groups.

A. Descriptive	Obese BMI		Healthy BMI	
	Males	Females	Males	Females
WC	112.19 ± 14.50	101.17 ± 11.94	77.34 ± 5.88	71.98 ± 6.24
WHR	64.03 ± 8.83	61.84 ± 7.80	44.35 ± 3.29	43.64 ± 3.80
BF%	29.53 ± 5.52	38.66 ± 3.46	14.50 ± 5.39	25.26 ± 4.94

B. Statistics	Estimate	SE	Estimate/SE	Uncorrected *P*	FDR threshold	Exceeded FDR threshold
WC						
Group	−32.778	2.890	−11.341	<0.001	0.006	Yes
Sex	−9.431	2.989	−3.155	0.002	0.050	No
Group × sex	3.537	4.160	0.850	0.395	0.028	No
Age	0.361	0.107	3.379	0.001		
Race	−4.308	2.290	−1.881	0.060		
WHR						
Group	−18.220	1.738	−10.480	<0.001	0.017	Yes
Sex	−1.194	1.798	−0.664	0.507	0.039	No
Group × sex	0.186	2.503	0.074	0.941	0.044	No
Age	0.273	0.064	4.238	<0.001		
Race	−2.289	1.377	−1.662	0.096		
BF%						
Group	−13.874	1.236	−11.225	<0.001	0.011	Yes
Sex	9.428	1.278	7.377	<0.001	0.022	Yes
Group × sex	1.421	1.779	0.799	0.425	0.033	No
Age	0.291	0.046	6.354	<0.001		
Race	1.230	0.979	1.256	0.209		

BF%, body fat percentage; BMI, body mass index; FDR, false-discovery rate; WC, waist circumference; WHR, WC/height ratio.

Table 2

Differences in self-report variables between healthy body mass index and obese body mass index groups.

A. Descriptive	Obese BMI		Healthy BMI	
	Males	Females	Males	Females
Anxiety state	31.89 ± 7.37	30.26 ± 7.65	32.45 ± 8.72	29.89 ± 5.30
Anxiety trait	35.32 ± 8.59	32.21 ± 6.21	33.68 ± 7.79	31.00 ± 8.28
Depression	6.47 ± 7.86	4.32 ± 4.37	4.55 ± 5.34	2.53 ± 2.52
Sleepiness	7.42 ± 5.00	7.63 ± 3.35	6.64 ± 2.46	6.47 ± 2.22
Impulsivity	49.00 ± 7.62	43.93 ± 4.79	46.15 ± 5.57	45.09 ± 5.76
Quality of life	80.32 ± 17.76	82.46 ± 9.27	85.76 ± 10.80	89.24 ± 7.89

B. Statistics	Estimate	SE	Estimate/SE	*P*	FDR threshold	Exceeded FDR threshold
Anxiety state						
Group	0.482	2.296	0.210	0.834	0.042	No
Sex	−1.498	2.374	−0.631	0.528	0.031	No
Group × sex	−1.164	3.305	−0.352	0.725	0.033	No
Age	−0.042	0.085	−0.496	0.620		
Race	−1.013	1.819	−0.557	0.577		
Anxiety trait						
Group	−2.477	2.354	−1.052	0.293	0.022	No
Sex	−3.647	2.434	−1.498	0.134	0.014	No
Group × sex	1.113	3.389	0.328	0.743	0.036	No
Age	−0.163	0.087	−1.873	0.061		
Race	1.106	1.865	0.593	0.553		
Depression						
Group	−2.018	1.651	−1.222	0.222	0.019	No
Sex	−2.478	1.707	−1.451	0.147	0.017	No
Group × sex	0.639	2.377	0.269	0.788	0.039	No
Age	0.021	0.061	0.348	0.728		
Race	1.711	1.308	1.308	0.191		
Sleepiness						
Group	−0.849	1.055	−0.805	0.421	0.025	No
Sex	0.132	1.091	0.121	0.903	0.050	No
Group × sex	−0.261	1.519	−0.172	0.864	0.044	No
Age	−0.007	0.039	−0.182	0.855		
Race	0.307	0.836	0.368	0.713		
Impulsivity						
Group	−2.952	1.863	−1.585	0.113	0.008	No
Sex	−5.122	1.926	−2.659	0.008	0.003	No
Group × sex	4.071	2.682	1.518	0.129	0.011	No
Age	−0.022	0.069	−0.326	0.744		
Race	0.057	1.476	0.039	0.969		
Quality of life						
Group	5.945	3.710	1.602	0.109	0.006	No
Sex	2.605	3.837	0.679	0.497	0.028	No
Group × sex	0.708	5.341	0.132	0.895	0.047	No
Age	0.078	0.137	0.568	0.570		
Race	−1.493	2.939	−0.508	0.611		

BMI, body mass index; FDR, false-discovery rate.

once per subject. Subjects submerged their left hands in an ice-water bath (0–2°C) up to the wrist level for 120 seconds or until pain tolerance occurred. To promote circulation and prevent a boundary layer of warmth from forming around the hand, subjects were instructed to continuously open and close their hands for the duration of the test. In addition, subjects were instructed to notify the experimenter when they first felt pain and to remove their hand when they could no longer tolerate the pain. The duration of submersion until pain presented was recorded as threshold. The duration of submersion before the subject removed their hand was recorded as tolerance. Visual analogue scale ratings of pain intensity and unpleasantness were taken every 30 seconds and at the termination of the test. In the results, only the pain intensity and unpleasantness ratings at the termination of the cold-pressor test (tolerance) are presented because of the relatively short duration of pain tolerance.

2.5. Statistical analyses

Statistical analyses were conducted using *Mplus* (version 8.6). The default parameter estimation algorithm is robust maximum likelihood using the assumption that response variable data will be non-normally distributed, and that parameter estimate SEs will need to be corrected upward to avoid type 1 inferential errors. One participant had missing values for intermediate pain ratings (intensity and unpleasantness); these missing data were handled through maximum likelihood estimation.

After recruitment, BMI was used to divide the participants into healthy BMI and obese BMI groups. Pain ratings, BF%, and WC can differ based on sex[13,34,73]; thus, in the statistical models, sex was also included as a main effect.

Four separate multivariate analyses of variance (MANCOVAs) were performed with age and race included as control covariates. The first MANCOVA tested for IV group (BMI healthy vs BMI obese)

and sex main effects, and a sex-by-group interaction effect, on the 3 anthropometric (BF%, WC, and WHR) response variables. The second MANCOVA tested for the same main and interaction effects (group, sex, and group × sex interaction) on the 6 self-report variables (impulsivity, sleepiness, quality of life, depression, state anxiety, and trait anxiety). The third MANCOVA again tested for the same main and interaction effects (group, sex, and group × sex interaction) on the 10 pain sensitivity variables (cold intensity, cold unpleasantness, cold threshold, cold tolerance, short noxious heat intensity, short noxious heat unpleasantness, intermediate noxious heat intensity, intermediate noxious heat unpleasantness, long noxious heat intensity, and long noxious heat unpleasantness). The fourth MANCOVA examined the 10 pain sensitivity variables (cold intensity, cold unpleasantness, cold threshold, cold tolerance, short noxious heat intensity, short noxious heat unpleasantness, cyclic intermediate noxious heat intensity, cyclic intermediate noxious heat unpleasantness, cyclic long noxious heat intensity, and cyclic long noxious heat unpleasantness) but tested the main effects of the 3 anthropometric (BF%, WC, and WHR) variables and sex, as well as the 3 interaction effects (sex by BF%, sex by WC, and sex by WHR).

The false-discovery rate (FDR) type 1 error correction mechanism was conducted separately for the 4 analyses with the effects for the control covariates excluded.

3. Results

The range for healthy BMI was 19 to 25, and the range for obese BMI was 30 to 51. **Figure 1** presents the distribution of BMI for all participants.

3.1. Differences in anthropometric measurements between healthy body mass index and obese body mass index groups

Groups differ in WC, WHR, and BF%. In addition, significant differences in sex were also found for WC and BF%. No group × sex interactions were found (**Table 1**). After FDR correction, group differences remained significant in addition to the sex effect for BF%.

3.2. Absence of differences in self-report variables between healthy body mass index and obese body mass index groups

Factors such as anxiety, depression, impulsivity, sleepiness, and quality of life can covary with obesity and influence pain sensitivity. However, no significant group differences were found for these variables (**Table 2**). This lack of group differences was found even before FDR type 1 correction.

A significant sex effect was found only for impulsivity, but this was not significant after FDR correction. No group × sex interactions were found for any of the measures before FDR correction.

3.3. Absence of differences in pain sensitivity between healthy body mass index and obese body mass index groups

Pain sensitivity measures were not different between the groups even before FDR correction. For sex effects, before FDR correction, significant effects for sex were found for most of the pain sensitivity measures. However, after FDR correction, no significant sex effect was found.

3.3.1. Noxious heat measures

No group differences were found for the noxious heat measures (pain intensity and unpleasantness ratings for short, cyclic intermediate, and cyclic long noxious heat stimuli, **Table 3** and **Fig. 2**). This lack of significant group differences was evident even before FDR correction for type 1 error.

Sex differences were found for all measures except for pain intensity ratings of short noxious heat, indicating that females had higher pain ratings compared with males. No group × sex interactions were found (**Table 3**). After FDR correction, no sex differences and no group × sex interactions were found (**Table 3**).

3.3.2. Cold measures

No significant differences were found between groups for any of the cold measures (cold pain thresholds, cold pain tolerance, pain intensity, and unpleasantness ratings of cold pain tolerance, **Table 3**, **Fig. 3**). This lack of differences between the groups was found even before FDR type 1 error correction. In addition, no sex differences and no group × sex interactions were found before FDR correction (**Table 3**).

3.4. No relationships between pain sensitivity and anthropometric measures (waist circumference, waist/height ratio, and percent body fat)

Before FDR correction, several significant relationships were found between pain sensitivity measures and anthropometric measures or their interactions with sex. However, after FDR correction, no significant relationships were observed.

3.4.1. Noxious heat measures

For short noxious heat, sex was related to pain intensity and unpleasantness ratings. However, after FDR correction, this was no longer significant. No relationships were found between pain ratings and WC, WHR, BF%, or their interactions with sex (**Table 4**).

For cyclic intermediate noxious heat, pain intensity ratings were related with WC, WHR, and sex. The sex × WC and sex × WHR interactions were also significant. Pain unpleasantness ratings of cyclic intermediate noxious heat were related with WHR and sex (**Table 4**). However, none of these findings remained significant after FDR correction.

For cyclic long noxious heat, pain intensity ratings were related with WC, WHR, and their interactions with sex (sex × WC and sex × WHR). Pain unpleasantness ratings were related with WHR. The sex × WHR and sex × WC interactions were also significant (**Table 4**). None of these findings remained significant after FDR correction.

3.4.2. Cold measures

The anthropometric measures and their interactions with sex were not related to cold pain thresholds or tolerance even before FDR correction (**Table 4**).

Pain intensity ratings of cold pain tolerance were related with the sex × WC and sex × WHR interactions. Pain unpleasantness ratings of cold pain tolerance were related only to sex (**Table 4**). None of these findings remained significant after FDR correction.

4. Discussion

Using noxious heat and cold stimuli across multiple body locations and durations of stimulation, we found no differences in suprathreshold pain intensity or unpleasantness ratings between obese and healthy BMI groups. In addition, no

Table 3

Differences in pain sensitivity between healthy body mass index and obese body mass index groups.

A. Descriptive	Obese BMI		Healthy BMI	
	Males	Females	Males	Females
Short noxious heat—pain intensity	3.09 ± 2.24	4.35 ± 3.19	3.03 ± 2.13	4.82 ± 2.45
Short noxious heat—pain unpleasantness	2.74 ± 2.08	4.69 ± 3.29	2.75 ± 2.06	4.59 ± 2.66
Intermediate noxious heat—pain intensity	4.54 ± 2.62	6.48 ± 2.86	4.98 ± 2.43	6.71 ± 2.39
Intermediate noxious heat—pain unpleasantness	4.40 ± 2.89	7.04 ± 2.45	5.45 ± 2.60	6.43 ± 2.63
Long noxious heat—pain intensity	4.59 ± 2.81	6.63 ± 2.43	4.81 ± 2.55	6.65 ± 2.62
Long noxious heat—pain unpleasantness	4.63 ± 3.12	6.69 ± 2.54	4.79 ± 2.70	6.52 ± 2.87
Cold pain thresholds (s)	15.08 ± 12.71	11.89 ± 9.52	16.18 ± 17.83	11.95 ± 6.52
Cold pain tolerance (s)	76.84 ± 42.45	52.63 ± 33.47	76.86 ± 45.51	56.84 ± 35.64
Cold pain—pain intensity	5.94 ± 2.54	6.82 ± 2.63	5.36 ± 2.68	7.45 ± 2.25
Cold pain—pain unpleasantness	6.16 ± 2.33	7.55 ± 2.18	5.43 ± 2.90	7.83 ± 2.32

B. Statistics	Estimate	SE	Estimate/SE	*P*	FDR threshold	Exceeded FDR threshold
Short noxious heat—pain intensity						
Group	−0.420	0.737	−0.570	0.568	0.042	No
Sex	0.844	0.762	1.108	0.268	0.015	No
Group × sex	1.122	1.061	1.058	0.290	0.018	No
Age	−0.044	0.027	−1.629	0.103		
Race	1.570	0.584	2.689	0.007		
Short noxious heat—pain unpleasantness						
Group	−0.327	0.753	−0.435	0.664	0.040	No
Sex	1.566	0.778	2.011	0.044	0.007	No
Group × sex	0.435	1.084	0.401	0.688	0.022	No
Age	−0.041	0.028	−1.455	0.146		
Race	1.479	0.596	2.479	0.013		
Intermediate noxious heat—pain intensity						
Group	0.251	0.785	0.320	0.749	0.027	No
Sex	1.610	0.812	1.983	0.047	0.008	No
Group × sex	0.238	1.129	0.211	0.833	0.030	No
Age	0.012	0.029	0.417	0.677		
Race	1.086	0.621	1.750	0.080		
Intermediate noxious heat—pain unpleasantness						
Group	0.856	0.803	1.066	0.286	0.017	No
Sex	2.275	0.830	2.740	0.006	0.002	No
Group × sex	−1.168	1.154	−1.012	0.312	0.048	No
Age	0.016	0.030	0.555	0.579		
Race	1.227	0.635	1.934	0.053		
Long noxious heat—pain intensity						
Group	0.277	0.793	0.350	0.727	0.025	No
Sex	1.918	0.820	2.339	0.019	0.003	No
Group × sex	0.008	1.142	0.007	0.995	0.035	No
Age	0.034	0.029	1.162	0.245		
Race	0.870	0.628	1.384	0.166		
Long noxious heat—pain unpleasantness						
Group	0.249	0.850	0.293	0.770	0.028	No
Sex	1.933	0.879	2.199	0.028	0.005	No
Group × sex	−0.102	1.224	−0.083	0.934	0.038	No
Age	0.045	0.031	1.423	0.155		
Race	1.020	0.674	1.514	0.130		
Cold pain thresholds (s)						
Group	1.384	3.808	0.363	0.716	0.023	No
Sex	−3.941	3.938	−1.001	0.317	0.045	No
Group × sex	0.250	5.482	0.046	0.964	0.033	No
Age	0.193	0.141	1.368	0.171		
Race	5.330	3.017	1.766	0.077		
Cold pain tolerance (s)						
Group	−0.147	12.189	−0.012	0.990	0.037	No
Sex	−22.201	12.605	−1.761	0.078	0.050	No
Group × sex	0.878	17.547	0.050	0.960	0.032	No
Age	−0.345	0.451	−0.765	0.444		
Race	−12.648	9.657	−1.310	0.190		

(*continued on next page*)

Table 3 (*continued*)

Differences in pain sensitivity between healthy body mass index and obese body mass index groups.

B. Statistics	Estimate	SE	Estimate/SE	*P*	FDR threshold	Exceeded FDR threshold
Cold pain—pain intensity						
Group	−0.608	0.783	−0.777	0.437	0.043	No
Sex	0.776	0.810	0.958	0.338	0.020	No
Group × sex	1.368	1.127	1.214	0.225	0.012	No
Age	0.006	0.029	0.202	0.840		
Race	0.567	0.620	0.915	0.360		
Cold pain—pain unpleasantness						
Group	−0.762	0.755	−1.008	0.313	0.047	No
Sex	1.231	0.781	1.576	0.115	0.010	No
Group × sex	1.253	1.087	1.152	0.249	0.013	No
Age	0.014	0.028	0.495	0.620		
Race	0.852	0.598	1.425	0.154		

BMI, body mass index; FDR, false-discovery rate.

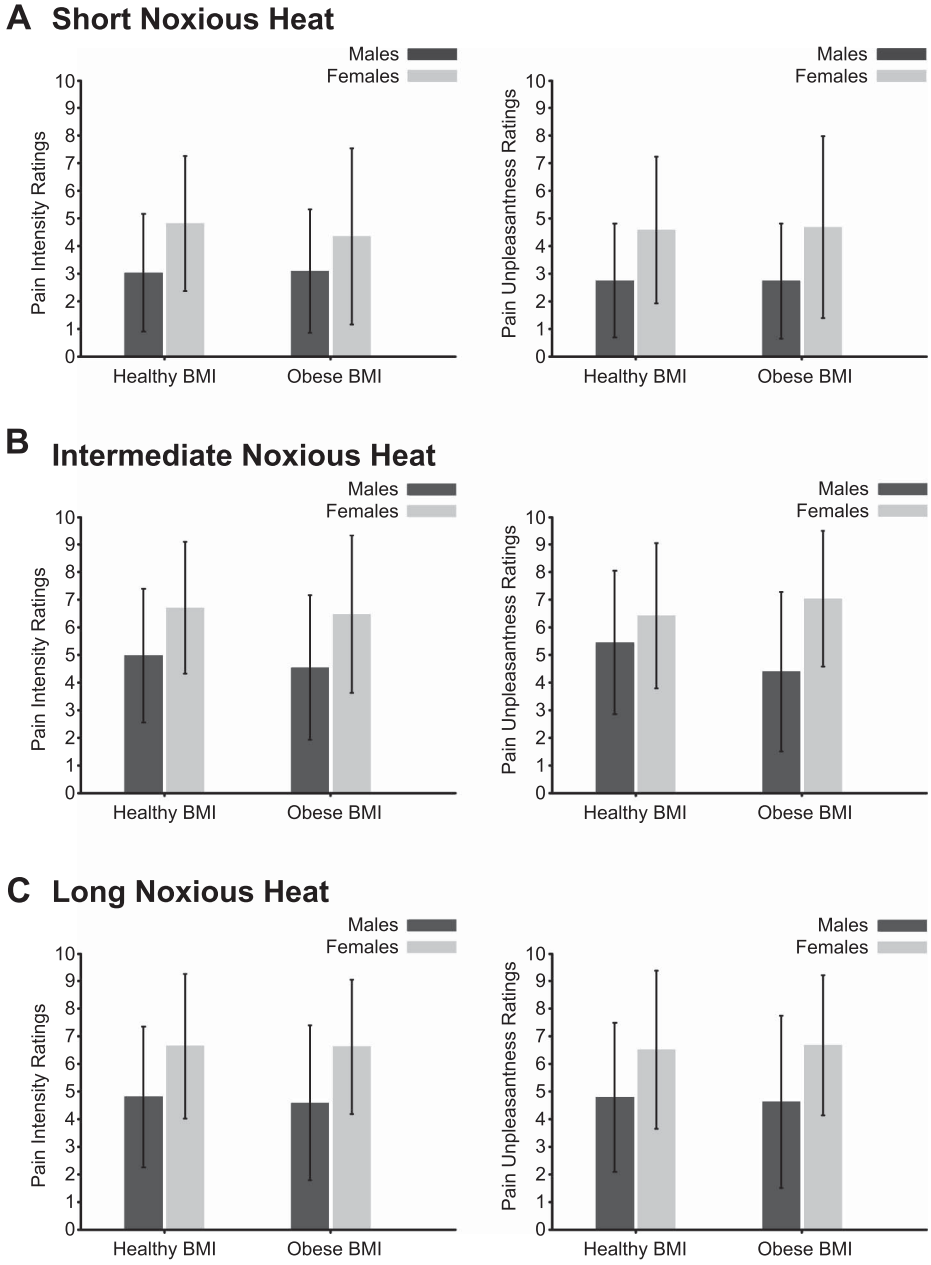

Figure 2. Pain evoked by experimental noxious heat stimuli does not differ between healthy weight and obese individuals. Between-group comparisons of pain intensity and unpleasantness ratings to noxious heat: (A) Short noxious heat: Stimuli were applied for 5 seconds to the right ventral forearm. (B) Intermediate noxious heat: Stimuli were applied to the left calf for 12 seconds. (C) Long noxious heat: Stimuli were applied to the right calf for 30 seconds. BMI, body mass index.

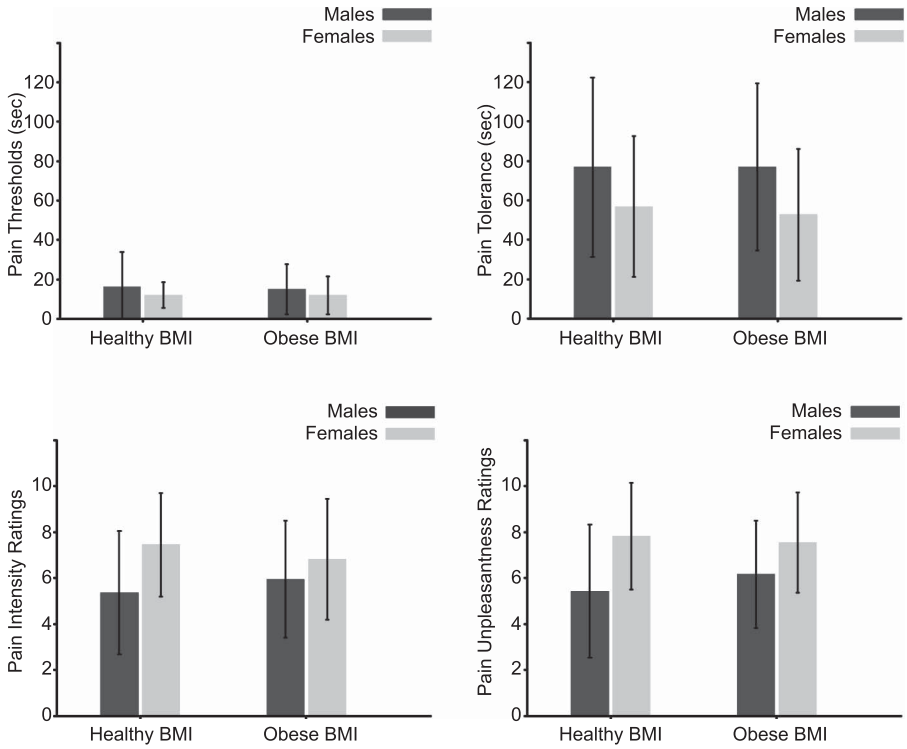

Figure 3. Pain evoked by experimental noxious cold stimuli does not differ between healthy weight and obese individuals. Between-group comparisons of pain thresholds, tolerance, and intensity and unpleasantness ratings to cold stimuli: Cold-pressor threshold was recorded at the time the subject first reported pain. Cold-pressor tolerance was recorded at the time the subject withdrew their hand from the test. Cold pain intensity and unpleasantness ratings were obtained at tolerance-driven termination of the test (0–120 seconds). BMI, body mass index.

between-group differences were found for cold pain thresholds or tolerance. Furthermore, we found no relationships between anthropometric measures of WC, WHR, or BF% and pain sensitivity. These results suggest that for otherwise healthy individuals, pain sensitivity does not differ based on obesity or as a function of central adiposity or body fat (percentage or distribution). Accordingly, our findings indicate that obesity alone has little direct influence on pain sensitivity in healthy obese individuals.

Previous studies have produced conflicting results regarding altered pain sensitivity in obese individuals. Pradalier et al.[49] found decreased nociceptive reflex thresholds (increased sensitivity) to electrical stimuli in obese individuals when compared with healthy weight individuals. Similarly, a study examining pressure pain thresholds found increased sensitivity to mechanical stimuli in obese individuals when compared with healthy weight individuals.[30] Another study found lower pressure pain thresholds in the obese group compared with the healthy weight group, but no differences were found for heat and cold pain thresholds and tolerance.[66] Conversely, obese individuals displayed increased heat and cold pain thresholds (decreased sensitivity) on the fingers but not the toes.[33] Obese individuals also displayed increased pain thresholds and decreased pain ratings to noxious cold stimuli on the abdomen, but not on the forehead or hand.[52] In addition, obese individuals exhibited increased pain thresholds to noxious heat stimuli on the abdomen but no significant differences in pain ratings to a 1-minute 48°C stimulus.[52] Morbidly obese individuals also had higher electrical pain threshold and tolerance than healthy weight individuals but no differences in heat pain threshold and tolerance.[69] Contrary to the above studies that found some differences in pain sensitivity between obese and healthy weight individuals, other studies did not find such differences, which is in agreement with the results of this study. In a large study (n = 300), no relationships were found between BMI and pressure and heat pain thresholds as well as cold pain tolerance using the cold-pressor test.[37] This study also included a thorough examination of covariates such as anxiety, depression, and quality of life. Interestingly, no differences in behavioral factors and quality of life were found between the groups. Quality of life was assessed using the SF-36, a popular survey to examine how physical health affects functioning and well-being.[71] Both chronic pain and BMI can impact the quality of life.[26,58,72,77] In this study, the obese BMI participants were healthy with no chronic pain or other conditions that are associated with obesity, such as diabetes. Thus, the lack of differences between the groups in behavioral factors and quality of life may be due to the relatively healthy obese participants. Our findings are also in agreement with another study that found no difference in electrical pain ratings between obese and healthy weight groups.[22] Although psychological data were not collected for that study, subjects were healthy and without underlying medical conditions or diabetes. Another recent study found no differences in pressure pain thresholds and the conditioned pain modulation response between healthy subjects that have normal BMI and high BMI.[9] In addition, no correlations were found between BMI and pressure pain thresholds.[9] Possible sources for the discordance across studies are differences in psychophysical and anthropometric measures, healthiness of obese subjects, and control of psychological factors that may influence pain.

There are several important features of this study. First, this study used a comprehensive exploration of anthropometric

Table 4

Relationships between pain sensitivity and anthropometric measures.

	Estimate	SE	Estimate/SE	*P*	FDR threshold	Exceeded FDR threshold
Short noxious heat—pain intensity						
BF%	−0.082	0.084	−0.980	0.327	0.031	No
WC	0.056	0.100	0.560	0.576	0.038	No
WHR	−0.039	0.180	−0.215	0.830	0.047	No
Sex	2.324	1.066	2.179	0.029	0.008	No
Sex × WC	−0.044	0.157	−0.282	0.778	0.044	No
Sex × WHR	0.038	0.263	0.145	0.885	0.049	No
Sex × BF%	0.033	0.126	0.261	0.794	0.045	No
Age	−0.029	0.032	−0.908	0.364		
Race	1.715	0.615	2.787	0.005		
Short noxious heat—pain unpleasantness						
BF%	−0.090	0.085	−1.060	0.289	0.029	No
WC	0.077	0.101	0.762	0.446	0.032	No
WHR	−0.070	0.182	−0.386	0.700	0.040	No
Sex	2.829	1.079	2.620	0.009	0.001	No
Sex × WC	−0.058	0.159	−0.367	0.713	0.041	No
Sex × WHR	0.081	0.267	0.304	0.761	0.043	No
Sex × BF%	0.039	0.127	0.309	0.757	0.042	No
Age	−0.026	0.032	−0.796	0.426		
Race	1.711	0.623	2.746	0.006		
Intermediate noxious heat—pain intensity						
BF%	−0.103	0.085	−1.217	0.224	0.026	No
WC	0.178	0.102	1.748	0.081	0.017	No
WHR	−0.288	0.184	−1.568	0.117	0.019	No
Sex	2.359	1.082	2.179	0.029	0.009	No
Sex × WC	−0.327	0.159	−2.055	0.040	0.010	No
Sex × WHR	0.534	0.268	1.992	0.046	0.011	No
Sex × BF%	0.095	0.127	0.747	0.455	0.033	No
Age	0.040	0.032	1.232	0.218		
Race	1.300	0.624	2.085	0.037		
Intermediate noxious heat—pain unpleasantness						
BF%	−0.058	0.088	−0.663	0.508	0.036	No
WC	0.122	0.105	1.161	0.245	0.026	No
WHR	−0.237	0.189	−1.249	0.212	0.025	No
Sex	2.401	1.115	2.154	0.031	0.009	No
Sex × WC	−0.243	0.164	−1.482	0.138	0.022	No
Sex × WHR	0.509	0.276	1.843	0.065	0.014	No
Sex × BF%	−0.025	0.131	−0.189	0.850	0.049	No
Age	0.036	0.033	1.084	0.274		
Race	1.433	0.642	2.232	0.026		
Long noxious heat—pain intensity						
BF%	−0.021	0.085	−0.252	0.801	0.046	No
WC	0.224	0.101	2.209	0.027	0.006	No
WHR	−0.423	0.183	−2.317	0.020	0.004	No
Sex	1.936	1.083	1.788	0.074	0.016	No
Sex × WC	−0.408	0.159	−2.569	0.010	0.002	No
Sex × WHR	0.715	0.267	2.675	0.007	0.001	No
Sex × BF%	0.047	0.128	0.367	0.713	0.041	No
Age	0.054	0.032	1.669	0.095		
Race	0.939	0.625	1.503	0.133		
Long noxious heat—pain unpleasantness						
BF%	−0.021	0.093	−0.221	0.825	0.046	No
WC	0.211	0.110	1.916	0.055	0.012	No
WHR	−0.396	0.199	−1.994	0.046	0.011	No
Sex	2.004	1.178	1.702	0.089	0.018	No
Sex × WC	−0.380	0.173	−2.196	0.028	0.007	No
Sex × WHR	0.679	0.291	2.333	0.020	0.004	No
Sex × BF%	0.029	0.139	0.209	0.835	0.048	No
Age	0.062	0.035	1.779	0.075		
Race	1.111	0.680	1.635	0.102		
Cold pain thresholds (s)						
BF%	0.627	0.423	1.481	0.138	0.023	No
WC	−0.577	0.503	−1.149	0.251	0.028	No
WHR	0.459	0.906	0.507	0.612	0.039	No
Sex	−10.264	5.371	−1.911	0.056	0.013	No
Sex × WC	0.575	0.789	0.729	0.466	0.034	No
Sex × WHR	−0.736	1.326	−0.555	0.579	0.039	No
Sex × BF%	−0.368	0.633	−0.581	0.561	0.037	No
Age	0.124	0.160	0.777	0.437		
Race	3.211	3.099	1.036	0.300		

(*continued on next page*)

Table 4 (*continued*)

Relationships between pain sensitivity and anthropometric measures.

	Estimate	SE	Estimate/SE	*P*	FDR threshold	Exceeded FDR threshold
Cold pain tolerance (s)						
BF%	−1.758	1.352	−1.300	0.194	0.024	No
WC	−1.121	1.607	−0.698	0.485	0.035	No
WHR	3.340	2.895	1.154	0.249	0.027	No
Sex	−16.889	17.165	−0.984	0.325	0.030	No
Sex × WC	1.782	2.521	0.707	0.480	0.034	No
Sex × WHR	−5.516	4.238	−1.301	0.193	0.024	No
Sex × BF%	2.304	2.024	1.138	0.255	0.029	No
Age	−0.141	0.510	−0.276	0.782		
Race	−9.197	9.906	−0.928	0.353		
Cold pain tolerance—pain intensity						
BF%	−0.055	0.087	−0.632	0.527	0.036	No
WC	0.185	0.103	1.798	0.072	0.015	No
WHR	−0.304	0.186	−1.641	0.101	0.019	No
Sex	1.996	1.100	1.814	0.070	0.014	No
Sex × WC	−0.372	0.162	−2.304	0.021	0.005	No
Sex × WHR	0.626	0.272	2.303	0.021	0.006	No
Sex × BF%	0.006	0.130	0.043	0.966	0.050	No
Age	0.029	0.033	0.896	0.370		
Race	0.705	0.635	1.111	0.267		
Cold pain tolerance—pain unpleasantness						
BF%	−0.071	0.085	−0.836	0.403	0.031	No
WC	0.181	0.101	1.798	0.072	0.016	No
WHR	−0.283	0.181	−1.560	0.119	0.020	No
Sex	2.749	1.075	2.558	0.011	0.003	No
Sex × WC	−0.246	0.158	−1.558	0.119	0.021	No
Sex × WHR	0.405	0.265	1.528	0.127	0.021	No
Sex × BF%	0.038	0.127	0.296	0.767	0.044	No
Age	0.040	0.032	1.253	0.210		
Race	1.012	0.620	1.631	0.103		

BF%, body fat percentage; FDR, false-discovery rate; WC, waist circumference; WHR, WC/height ratio.

measures including BMI, central adiposity, BF%, and distribution of BF. The majority of the previous studies relied solely on "% above ideal weight" or BMI as the marker of obesity. These measures have known disadvantages and may misclassify individuals who are athletic or with high muscle mass as obese or vice versa and misclassify individuals with high fat mass as normal weight.[41,43] In addition, this study controlled for comorbidities and psychological factors that may influence pain sensitivity. Subjects in this study were all healthy, without medical conditions, and not taking any medications. Previous findings of altered pain sensitivity in the obese may have been driven by the effects of confounding conditions on pain sensitivity, rather than the obesity itself.[30,33,49] Moreover, this study assessed both pain intensity and unpleasantness ratings. Pain unpleasantness represents the affective component of pain and is distinguished from the sensory component of pain.[31,53] Because pain is a multidimensional experience consisting of sensory, affective, and cognitive components,[31] it is important to assess pain unpleasantness in addition to pain intensity. This study also assessed different stimulus durations that can evoke different experiences of pain,[19] possibly because of recruitment of different nociceptors (nociceptors with terminals in the superficial aspects of the skin vs deeper primary afferents).[11,76] Different distributions of fat in peripheral tissues might contribute to different pain sensitivity; however, this study found no differences between the groups for any stimulus durations.

The mechanisms that link obesity and pain can be mechanical (excess weight on joints that can lead to injury and damage to the joints and, thus, pain), behavioral (lower physical activity and higher rates of sleep disturbance in obese individuals), or physiological (secretion of proinflammatory cytokines).[7] In addition, interference of the nociceptive signal by adipose tissue could also be proposed. However, the lack of differences in pain responses between the obese BMI and healthy BMI groups is consistent with what is known about peripheral nociceptive processes. Afferent fibers terminate in the epidermis, superficial to the subcutaneous hypodermis where adipose tissue is stored.[62,67,80] Therefore, it is unlikely that adipose tissue directly interferes with nociception through a blocking or buffering of nociceptor activation. Thus, no differences in pain sensitivity between healthy weight and obese individuals were found even for the short noxious heat stimuli. Interestingly, Price et al.[52] have proposed that a decrease in afferent fiber density, because of skin stretching, may account for pain sensitivity differences in obese subjects. A between-group analysis found that obese subjects displayed differences in pain thresholds to stimuli delivered to the abdomen, but not the hand or forehead. This study cannot be directly compared with those findings, as pain responses to abdominal stimulation were not measured. However, the finding of only abdominal alterations is consistent with this study, suggesting that pain sensitivity is not systemically altered in obese groups. In addition, and in support of the present findings, it has been shown that pain sensitivity does not change after substantial weight loss following bariatric surgery.[5] Furthermore, a large investigation of pain measures in patients with chronic back pain found no difference in pain severity or frequency between healthy weight, overweight, and obese groups.[23] This collection of evidence, coupled with the results from this study, indicates that increased adiposity alone does not alter pain sensitivity in healthy individuals.

5. Limitations

Because this study was limited to healthy obese subjects, we did not examine whether pain sensitivity is altered in metabolically unhealthy obese individuals. However, these results indicate that if pain

sensitivity is altered in metabolically unhealthy obese individuals, it is most likely a by-product of a covarying underlying condition and not the direct result of increased adiposity. Future studies should aim to delineate differences between obese individuals with and without chronic pain in an effort to uncover factors that may contribute to the increased risk of chronic pain development in obese individuals. In addition, we did not examine mechanical, pressure, or electrical pain and therefore cannot comment on whether participants experiencing those modalities display alterations in pain sensitivity related to obesity. We also did not examine lifestyle habits. Healthy habits of exercising regularly, consumption of alcohol in moderation, no smoking, and eating >5 fruits and vegetables every day reduce the risk of mortality even in obese individuals. Thus, a healthy lifestyle may also impact pain sensitivity in obese individuals.[27] Another limitation of the study is that obesity biochemical indicators, including cytokines and hormones such as leptin and ghrelin, were not examined. Given the limited amount of evidence when this study was designed, potential effect sizes were unknown and, thus, no power calculations were performed for this study. However, the number of participants was larger than that in other published articles.[9,22,52]

6. Summary

Risk of chronic pain development is increased in obese individuals. Experimental pain sensitivity was not altered in obese individuals regardless of testing modality or duration of stimulation. In addition, we found no relationships between experimental pain sensitivity and central adiposity or body fat. These results suggest that increased adiposity does not in-and-of-itself alter nociception. Although experimental pain sensitivity can predict chronic pain development,[17,21,75,78] more research is needed to determine whether experimental pain can predict chronic pain development in obese individuals.

Disclosures

The authors have no conflicts of interest to declare.

This study was funded by grant number R01NS039426 and R01NS085391.

Article history:
Received 29 March 2021
Received in revised form 24 May 2021
Accepted 25 May 2021

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