OBES SURG (2016) 26:631–639
DOI 10.1007/s11695-015-2008-9

REVIEW ARTICLE

Pain Experience and Perception in the Obese Subject Systematic Review (Revised Version)

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Published online: 12 December 2015

Abstract Pain is an integral part of life and has an important protective function. Pain perception has been shown to differ between subjects and changes with gender, race, and culture. In addition, it has been suggested that obesity influences pain perception and that obesity can be a risk factor for increased pain thresholds. The aim of this systematic review was to examine pain thresholds in obese subjects compared to non-obese subjects. The electronic databases of the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, and EMBASE were searched using combinations of terms for obese, pain measurement, visual analog scale, quantitative sensory testing, and pain perception. Studies without comparison as well as cross-sectional studies, case series, and case reports were excluded. The search was conducted without restrictions on language or date of publication. From a total of 1818 identified studies, seven studies fulfilled the inclusion criteria, whereby only one study tested the pain threshold difference between obese and non-obese and also before and after body weight loss surgery. Two studies showed a lower pain threshold and four studies a higher pain threshold in obese subjects compared to non-obese subjects. Two studies showed no difference in pain threshold before and after substantial body weight loss due to surgery. Weight loss after surgery was not identified as a factor for higher pain thresholds in obese subjects. In view of the heterogeneity of the studies, the variability of the subjects and differences in methodological quality, a meta-analysis could not be performed. From the available literature, there is a tendency towards higher pain thresholds in obese subjects. Neither substantial weight loss, nor gender, were factors explaining difference in threshold. Future randomized, controlled trials should explore demographic variables that could influence pain perception or pain thresholds in obese individuals, and multimodal pain testing is necessary for better understanding of the apparent differences in pain thresholds in obese individuals.

Keywords Obese · Pain measurement · Visual analog scale · Quantitative sensory testing · Pain perception

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Introduction

Pain is an integral part of life and has an important protective function. It is the primary symptom that prompts people to seek medical attention. Pain perception has been shown to vary between patients of different gender, race, and culture. Moreover, it has been suggested that obesity influences pain perception and that obesity early in life can be a risk factor for increased pain perception later in life [1, 2]. Pain perception is related to pain threshold (the stimulus intensity at which pain is first experienced), pain tolerance (the maximum tolerable noxious stimulus), and pain sensitivity (the link between a noxious stimulus and the patient's response). In obesity, all three indices of pain perception may be altered. For example,

when pain threshold increases the stimulus intensity at which pain is perceived shifts to higher intensities, or when pain sensitivity increases a specific noxious stimulus is perceived as more painful [3]. In this report, we will discuss pain threshold as this seems the common measurement in relevant studies.

Obesity is defined as a body mass index (BMI) ≥30 kg/m^2. Obesity is the result of a multisystem chronic pro-inflammatory disorder that is associated with increased mortality and morbidity [4]. Adipocytes, which are known as lipid storage cells, have additional purposes, such as the secretion of adipokines that lead to inflammation, vascular and cardiac remodeling, airway inflammation, and altered microvascular flow patterns. Adipokines contribute to conditions such as insulin resistance and the metabolic syndrome and attract and activate inflammatory cells such as macrophages. This can ultimately lead to organ dysfunction like cardiovascular and pulmonary disease. Hence, obese subjects are at increased risk of diabetes, hypertension, dyslipidemia, breathlessness, sleep apnea, gallbladder disease, and coronary heart disease [4–7].

It has been suggested that obese subjects may have a different pain perception and may react differently to analgesics [8]. Since approximately 15 % of the Dutch population and 36 % of the American population are overweight, this could significantly impact treatment in general, but in particular when undergoing painful interventions or surgery [7, 9–11]. Acute and severe perioperative pain is commonly treated with potent opioids, which in plasma bind to the transporter protein alpha-1-acid glycoprotein. The concentration of this protein is usually higher in patients with a chronic inflammatory state such as obesity. Since the free fraction of the drug is expected to be lower with consequently a reduced effect of opioids, obese patients likely need higher dosages to achieve similar effects [8, 12, 13]. Additionally, obese patients are prone to sleep-disordered breathing, which exacerbates by opioid administration [14].

Changes in pain perception as well as changes in opioid requirements may cause undertreatment or overtreatment of obese patients when considering perioperative pain; both of which may cause serious complications. Therefore, the apparent association between obesity and pain is the focus of a growing body of research. This systematic review aims to evaluate the differences in pain thresholds in obese subjects and non-obese subjects and to explore if demographic variables could predict pain thresholds in obese subjects.

Subjects and Methods

This systematic review has been conducted in accordance with the PRISMA guidelines for systematic reviews and meta-analyses of Moher at al. [15].

Search Strategy

The Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, and EMBASE were searched from their inception to February 2015. We used the following terms and their synonyms, truncated where necessary: obese, pain measurement, visual analog scale, quantitative sensory testing, and pain threshold. Grey literature was also searched, and a reference crosscheck was performed to detect eligible articles that were not identified through prior searches. The search was conducted without restrictions on language or publication date.

Study Eligibility Criteria

Types of Studies

Included We included randomized, controlled trials (RCTs), prospective and retrospective cohort studies, and case-control studies. RCTs and non-randomized studies directly compared the interventions of interest. For non-randomized studies, we included prospective as well as retrospective studies.

Excluded We excluded descriptive studies, cross-sectional studies, case series, and case reports because of the lower level of evidence.

Types of Participants

Studies on participants between 18 and 65 years old, who underwent a pain test intervention, were included. We examined two types of groups of participants. The first group compared obese subjects to non-obese subjects whose pain thresholds were tested. The second group consisted of obese subjects before and after weight loss surgery who underwent a pain intervention test.

Weight Indicators

Body Mass Index (BMI) BMI was calculated by dividing the present body weight by squared body height (m^2). BMI classification is done according to the World Health Organization; BMI<18.5 kg/m^2 underweight; BMI 18.5–25 kg/m^2 normal weight; BMI≥25 kg/m^2 overweight, BMI 25–30 kg/m^2 pre-obese; BMI≥30 kg/m^2 obesity; and BMI≥35 kg/m^2 morbid obesity.

Ideal Body Weight Ideal body weight in kilograms is defined as follows: height in centimeters minus 100 for men and height in centimeters minus 105 for women [9, 11].

Types of Pain Measurements

Pain is quantified using the visual analog scale (VAS) score (range 0 to 100 mm) or Numerical Rating Scale (NRS) (range 0 to 10), where 0 is no pain and 100 or 10 corresponds to the worst pain imaginable, respectively. The VAS or NRS is frequently used to quantify spontaneous pain or pain intensity in response to noxious stimuli [16].

Studies were included when a test was used with regard to pain threshold comprising at least one of the following: cold detection threshold, warm detection threshold, cold pain threshold, heat pain threshold, mechanical detection and/or mechanical pain thresholds and/ or mechanical pain sensitivity.

Study Selection and Data Extraction

Two reviewers (BT and IT) independently screened titles and abstracts of studies based on inclusion and exclusion criteria. Subsequently, the same reviewers independently checked the remaining full-text reports for eligibility. Data from full-text articles were extracted independently. In all stages, disagreements were solved by discussion or by consulting an independent third reviewer (BV). Data on outcomes were collected and divided into separate groups for analyses. Studies were stratified either based on obesity vs non-obesity or on obese subjects before and after weight loss surgery.

Assessment of Risk of Bias

Two reviewers (BT, IT) independently assessed the risk of bias for methodological quality of each included study, using the Cochrane Collaboration's Risk of Bias (RoB) tool in order to assess the quality of non-randomized studies including cohort and case-control studies. Each study was judged based on selection bias, performance bias, detection bias, attrition bias, reporting bias, and confounding.

Statistical Analysis

Methodological heterogeneity was investigated by the RoB assessment. We used the GRADE [17, 18] approach to rate the overall quality of the evidence per outcome indicating high, moderate, low, or very low, with RCTs starting as high quality of evidence and non-randomized studies as low quality evidence. For each main comparison, a Summary of Findings table was added to present the results on each outcome and quality of evidence.

Results

Literature Search and Study Selection

The initial database search and additional records search yielded 1818 records, and after removing duplicates, 786 articles remained. After screening titles and abstracts, thirteen full-text articles were evaluated. Six were excluded since no obese subjects were described or the analysis for pain threshold was not described. The process of selecting studies and the database keywords strategy is outlined in Fig. 1 and Appendix Table 4.

Study Characteristics of Included Studies

Seven studies, including 380 participants, were included in this systematic review. Two studies were performed in France [19, 26], two in Italy [27, 28], one in the USA [29], one in Poland [30], and one in Israel [31]. Six studies were published in English [19, 27–31] and one in the French language [26].

Six out of seven studies compared obese with non-obese subjects [19, 26–30], and two out of seven studies compared subjects before and after weight loss surgery [19, 31]. The primary hypothesis of the six out of seven studies referred to difference in pain thresholds between obese- and non-obese subjects [19, 26, 28–30], or before and after weight loss surgery [19, 31]. One study [27] used sensory testing between obese and non-obese subjects. Five out of seven studies tested the upper extremities of the body for pain sensitivity and pain threshold [19, 26, 28–30]. One study tested the lower extremities [30], and one study tested 18 pre-defined tender points for pain sensitivity and pain threshold [31].

Characteristics of Subjects in the Individual Studies

Characteristics of the included studies, including test areas and outcomes relevant for this review, are presented in Tables 1 and 2. Studies describe results from 130 women and 31 men. In 41 patients, the gender was not described [28, 30]. With regard to control, non-obese subjects, 129 women, 51 men and 40 gender-undefined subjects were tested [28, 30]. In two studies, only women were tested [26, 31].

Different definitions with regard to BMI and obesity were used. BMI was expressed as mean kg/m^2 (± SD) and ranged between 41.06 (±4.50) kg/m^2 and 45.7 (±6.80) kg/m^2, [19, 27, 28, 31] as single BMI expressed in kg/m^2 [26, 30] and as a BMI in kg/m^2 >130 % of ideal body weight [29].

Age was expressed as mean in years (± SD) [19, 26, 27, 29, 31] or as a median in years (range min–max) [28, 30]. In obese subjects, the age range was 40.26 (±21.8) years to 50.00 (±12.00) years, and the median age was 33.60 (range 16–52) years [30] and 38.95 (29–48) years [28]. In non-obese subjects, the mean age in years ranged between 41.65 (±15.98)

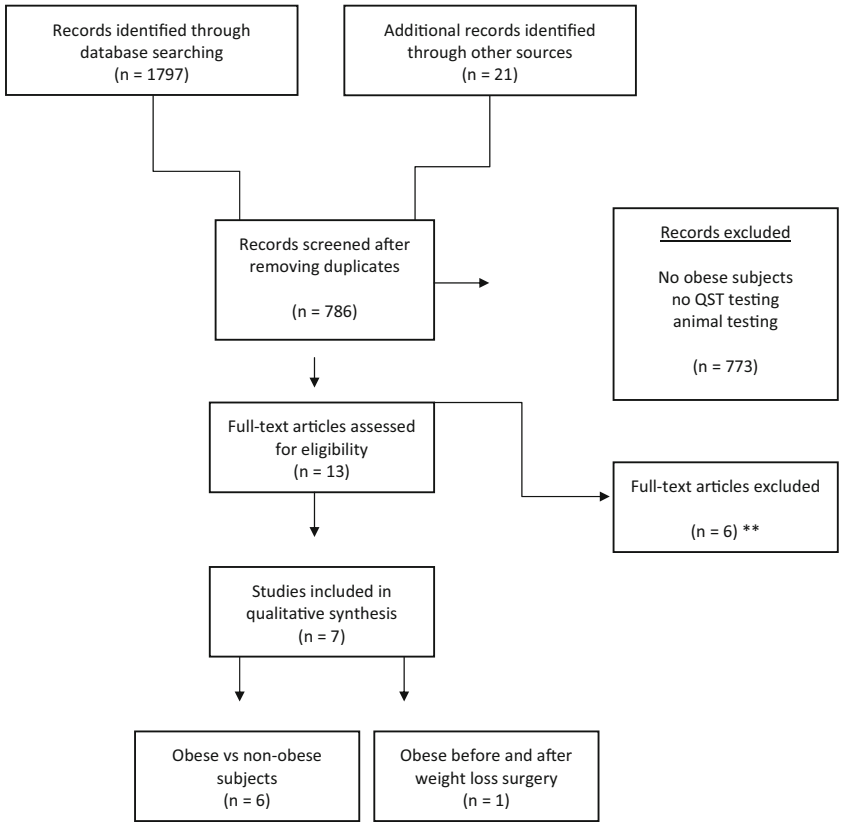

Fig. 1 Flow of information through the different phases of the systematic review. *[19]; **[20–25]

years and 49.0 (±8.0) [19, 26, 27, 29, 31], and their median age ranged from 29.0 (20–50) and 37.95 (29–48) years [28, 30].

Whereby, the mean and median between both groups were tested for normality. The unpaired sample *t* test was performed for the mean and was $t=0.031$ $P=0.98$. And for the median, a Mann-Whitney *U* test was performed with a *P* value of 0.67. Both groups were equally distributed.

Risk of Bias and Methodological Quality

As described in Table 3, four studies had a high-quality rating score result in the GRADE approach [19, 27, 29, 31], and three studies scored a moderate quality rating score [26, 28, 30]. Considering methodological quality, all studies were assessed as high risk of performance bias because no attempt was made to blind study subjects to the intervention. Also, all studies were assessed as having a low risk of reporting bias. All main outcomes measured were clearly described in the introduction or methods section. Confounding was unclear in five out of seven studies [19, 26, 28–30], and two out of seven had a low risk of bias [27, 31] as they attempted to clearly describe the distributions of principal confounders in each group of subjects. Selection bias was unclear in two out of seven studies [28, 30], risk of selection bias was low in four out of seven studies [19, 26, 27, 29], and high in one study [31] because the latter study recruited different intervention groups from the same population. Risk of detection bias was unclear in three studies [26, 29, 30], and low in four studies [19, 27, 28, 31], as they had made an attempt to blind the researchers. Risk of attrition bias was high in three out of seven studies [26, 29, 30] and low in four out of seven studies [19, 27, 28, 31]. In these studies, the main findings were clearly described.

Heterogeneity between the studies was high due to the different methods used for pain threshold testing. None of the studies described a formal power analysis, and it was therefore not possible to assess whether the number of included subjects were sufficient for a powerful statistical analysis.

Results of the Individual Studies

As demonstrated in Table 2, two studies published in 1982 described lower pain thresholds [26, 29], and four studies published after 1983 described a higher pain threshold in obese subjects compared to non-obese subjects [19, 27, 28, 30].

Maffiuletti et al. [27 tested sensory thresholds in obese subjects and did not specifically describe pain thresholds. The authors showed a higher pain threshold in obese subjects compared to non-obese subjects.

Two studies showed that body weight loss after surgery did not influence pain thresholds within tested groups [19, 31]. Dodet et al. [19] tested the change over time and concluded that higher pain thresholds found in obese subjects did not change after substantial body weight loss.

Table 1 Baseline characteristics of the included studies and differences between obese vs non-obese subjects

Author	Year	Obese *N*	Definition obese	Age obese	Non-obese *N*	Definition non-obese	Age non-obese	Test area	Results in the obese subject
McKendall et al. [29]	1982	*N*=26 18 women 8 men	BMI≥130 % of ideal weight	Women 43.78 (±11.22)[a] Men: 42.92 (±14.67)[a]	*N*=34 14 women 20 men	BMI<130 % of ideal weight	Women 42.12 (±11.62)[a] Men 41.65 (±15.98)[a]	Index finger in pressure device.	Lower pain threshold
Pradelier et al. [26]	1982	*N*=30 30 women 0 men	Single BMI 35.7	40.26 (±21.8)[a]	*N*=20 20 women 0 men	Single BMI 23.0	41.85 (±13.18)[a]	Neurophysiologic biceps reflex device	Lower pain threshold
Zahorska markiewicz et al. [30]	1983	*N*=20 (Undefined gender)	Single BMI 38	33.6 (16-52)[b]	*N*=20	Single BMI 20.6	29.0 (20-50)[b]	Forearm and arm with electrical stimulation device	Higher pain threshold
Maffiuletti et al. [27]	2001	N=32 16 women 16 men	BMI 42.1 (±6.8)[a] 41.9 (±6.0)[a]	Women 50.0 (±12.00)[a] Men: 48.00 (±10.00)[a]	*N*=35 17 women 18 men	BMI 22.0 (±3.2)[a] 24.8 (±2.5)[a]	Women 49.0 (±10.0)[a] Men 49.0 (±8.0)[a]	Quadriceps muscle with electrical stimulation device	Higher pain threshold
Miscio et al. [28]	2005	*N*=21 (Undefined gender)	BMI 41.06 (±4.74)[a]	38.95 (29-48)[b]	*N*=20 (Undefined gender)	BMI 22.71 (±2.88)[a]	37.95 (29-48)[b]	Index, little finger and big toe with vibration and thermal device.	Higher pain threshold
Dodet et al. [19]	2013	*N*=31 24 women 7 men	BMI 45.7 (±6.8)[a]	40.3 (±10.5)[a] (Undefined gender)	*N*=49 36 women 13 men	BMI 22.6 (±2.6)[a]	38.5 (±11.2)[a] (Undefined women or men)	Electrode box between thumb and index finger	Higher pain threshold

BMI body mass index, *SD* standard deviation

[a] Mean (±SD)

[b] Median (range)

Table 2 Baseline characteristics and differences before and after weight loss surgery

Author	Year	Obese *N*	Definition obese	Age	Type of surgery	Weight loss	Test area	Results
Buskila et al. [31]	2005	*N*=42 women	BMI 42.4 (±4.5)*	34.1 (±NA)	Laparoscopic Roux Y Gastric Bypass	Mean weight loss BMI 31.3 (±5.4)*	18 tender points on the site of the body with an algometer[a]	No difference in pain threshold before and after weight loss
Dodet et al. [19]	2013	*N*=31 24 women 7 men	BMI 45.7 (±6.8)*	40.3 (±10.5)* (Undefined gender)	Laparoscopic Roux Y Gastric Bypass	Mean weight loss 32.0 KG (23.9) in 6 months	Electrode box between thumb and index finger	Higher pain threshold not affected by drastic weight loss

[a] Instrument used to measure pressure pain threshold with weight (in Nm) indicator.

None of the included studies described a variable that could predict pain threshold in obese subjects. Gender was described to be a possible predictor; however, no differences in pain thresholds were shown [19, 27, 28].

Discussion

This systematic review aimed to assess the thresholds of pain in obese subjects compared to non-obese subjects and in obese subjects after substantial body weight loss surgery (laparoscopic gastric bypass or sleeve surgery). Of the seven included studies, two studies [26, 29] showed a lower pain threshold, and four studies [19, 27, 28, 30] demonstrated a higher pain threshold in obese subjects compared to non-obese subjects. Furthermore, two studies showed no difference in pain thresholds in obese subjects before and after substantial body weight loss due to surgery [19, 31]. No demographic variables were identified that were likely to influence pain or pain thresholds.

The two studies that showed lower pain thresholds in obese individuals were both published in the year 1982 [26, 29]. All other included studies showed a higher pain threshold. Reasons for the discrepancy in the results between the studies published in 1982 could not be identified. However, different types of tests were performed.

Rolke et al. [3] developed a battery of standardized tests to assess the function of sensory nerves. This multimodal testing method investigates pain thresholds for pressure, heat, and cold. Testing different modalities gives a more complete overview of the function of the nerves and decreases bias. The difficulty with the assessment of quality and implications of the published studies is that they tested only one method, instead of multiple sensory function paradigms. The assessment of multiple sensory pain thresholds using different modalities (pressure, heat, cold) is associated with a more reliable claim on the function of the overall nociceptive system of an individual. Moreover, Rolke et al. developed reference values for this battery of tests, which aid in the comparison of different populations of subjects [3].

There is currently limited evidence demonstrating that body weight is a primary factor affecting pain perception in general. However, there is a tendency towards higher pain thresholds (and consequently a lowered pain sensitivity at low intensity stimuli) in obese subjects. The one study showing that weight loss did not affect pain thresholds suggests that other factors than obesity per se influenced pain perception in the studies presented here. Indeed other unknown factors may influence pain perception in the obese.

According to Miscio et al. [28], and Dodet et al. [19] many physiological changes associated with obesity may affect pain pathways, causing possible altered pain sensitivity. This study suggests that the pain sensitivity threshold may be affected by factors such as cognition (e.g., intelligence level) and social

Table 3 Methodological quality of included studies

Study	Selection bias	Performance bias	Detection bias	Attrition bias	Reporting bias	Confounding	GRADE score
McKendall et al. [29]	−	+	?	+	−	?	High
Pradalier et al. [26]	−	+	?	+	−	?	Moderate
Zahorska markiewicz et al. [30]	?	+	?	+	−	?	Moderate
Maffiuletti et al. [27]	−	+	−	−	−	−	High
Miscio et al. [28]	?	+	−	−	−	?	Moderate
Dodet et al. [19]	−	+	−	−	−	?	High
Buskila et al. [31]	+	+	−	−	−	−	High

− = low risk of bias, + = high risk of bias, ? = unclear risk of bias

GRADE: Grading recommendations assessment development and evaluation

High: true effect lies close to the estimate of the effect

Moderate: true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low: true effect may be substantially different from the estimate of effect

Very low: true effect is likely to be substantially different from the estimate of effect

economic status. Belsky et al. [32] and Tchicaya et al. [33] conclude in their studies that there is a relationship between obesity, lower intelligence level, and lower social economic status. However, none of the included studies in this systematic review evaluated to what point cognition or social economic status may have influenced pain perception. Future studies should therefore evaluate the influence of these variables on pain perception in obese subjects.

Our systematic review has some limitations. The proportion of women in most studies was considerably higher than men [19, 26, 29, 31]. Only one study had a balanced distribution of gender in both groups [27]. The majority of the subjects undergoing body weight loss surgery are women [34]. This skewed distribution may mask influenced pain perception among gender and therefore could have influenced our findings and conclusions. Additionally, none of the studies report on race or ethnicity. Riley et al. [35] showed recently, in a well-conducted study, that race differences in pain perception are present and increase with age. Further studies should address the impact of race and age of pain perception in the obese sub-population. Also, Price et al. [36] did research, which focused on the role of excess subcutaneous fat between obese and non-obese subjects on pain thresholds, this paper also found that obese subjects have a higher pain threshold compared to non-obese subjects, but only on areas with excess subcutaneous fat. On areas with less subcutaneous fat (forehand and hand), there was no significant difference. None of the studies in this review focusses on this issue.

A second aspect that could affect the outcome of this systematic review is the observation that different cut-off levels for BMI were used in the different studies. For example, McKendall et al. [29] used a BMI ≥130 % of ideal BMI as cut-off point, the study of Pradelier et al. [26] used a single BMI level and the study of Miscio et al. [28] used a mean BMI level. This variation with regard to applied definitions makes comparison of the reported studies difficult. In the future, uniform, international cut-off points with regard to normal body weight, ideal body weight and BMI should be used.

Conclusions

This systematic review included seven studies that showed both lower and higher pain thresholds between obese and non-obese subjects.

There is a tendency towards a higher pain threshold in the obese subjects compared to non-obese subjects. Excess body weight loss did not influence pain threshold in obese subjects, and therefore, other variables likely predict the altered pain threshold in obese subjects.

Methodological well-conducted randomized controlled trials with an expected variability, solid power analyses, and extensive measurements methods are necessary to investigate the pain sensitivity and pain perception in obese subjects versus non-obese subjects. In addition, more research is needed into demographic factors that could influence pain perception in obese individuals.

In the meantime, physicians should recognize the fact that obese patients may have altered pain thresholds leading to different pharmacotherapeutic needs. However, since there are no general established pain strategies for the obese, the pharmacotherapeutic regimen should be titrated based on individual needs. In general, we should retain the current policy of higher opiates dosages in the per-operative phase until more research is produced.

Acknowledgments The authors acknowledge Chantal den Haan from St. Lucas Andreas hospital in Amsterdam for her help and support in database search and Prof Dr. A. Dahan from the Leiden University Medical Center for his critical comments on this systematic review.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no competing interests.

Informed Consent For this type of study, formal consent is not required.

Appendix

Table 4 Database keywords strategy

The Cochrane Library=Total of 252 articles	
	ID
Search	
#1	MeSH descriptor: [Obesity] explode all trees
#2	obes*:ti,ab,kw (Word variations have been searched)
#3	#1 or #2
#4	MeSH descriptor: [Pain Perception] explode all trees
#5	MeSH descriptor: [Pain Measurement] explode all trees
#6	Pain perception or perception of pain or pain measurement* or VAS or visual analog scale* or QST or quantitative sensory test*:ti,ab,kw (Word variations have been searched)
#7	#4 or #5 or #6
#8	#3 and #7
PubMed=Total of 611 articles	
6	Search ((“Obesity”[Mesh] OR obes*[tiab])) AND ((“Pain Perception”[Mesh] OR pain perception[tiab] OR perception of pain[tiab] OR “Pain Measurement”[MeSH Terms] OR pain measurement*[tiab] OR VAS[tiab] OR visual analog scale*[tiab] OR QST[tiab] OR quantitative sensory test*[tiab]))
5	Search “Pain Perception”[Mesh] OR pain perception[tiab] OR perception of pain[tiab] OR “Pain Measurement”[MeSH Terms] OR pain measurement*[tiab] OR VAS[tiab] OR visual analog scale*[tiab] OR QST[tiab] OR quantitative sensory test*[tiab]
4	Search “Pain Measurement”[MeSH Terms] OR pain measurement*[tiab] OR VAS[tiab] OR visual analog scale*[tiab] OR QST[tiab] OR quantitative sensory test*[tiab]
3	Search “Pain Perception”[Mesh] OR pain perception[tiab] OR perception of pain[tiab]
2	Search “Pain Perception”[Mesh]
1	Search “Obesity”[Mesh] OR obes*[tiab]
Embase.com=Total of 934 articles	
	Query
9	#1 AND #7 NOT [medline]/lim
8	#1 AND #7
7	#2 OR #3 OR #4 OR #5 OR #6
6	(“quantitative sensory” NEXT/1 test*):ab,ti
5	(“visual analog” NEXT/1 scale*):ab,ti
4	(pain NEAR/3 measurement*):ab,ti
3	pain AND perception:ab,ti OR perception AND of AND pain:ab,ti OR vas:ab,ti OR qst:ab,ti
2	“nociception”/exp OR “pain assessment”/exp OR “visual analog scale”/exp
1	obesity’/exp OR obes*:ab,ti

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