Blood pressure-related hypoalgesia: a systematic review and meta-analysis

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Objective: Spontaneous or experimentally induced high blood pressure (BP) is associated with reduced pain perception, known as BP-related hypoalgesia. Despite its clinical implications, such as the interference with early detection of myocardial infarction in 'at risk' groups, the size of the association between high BP and pain has not yet been quantified. Moreover, the distinct association between high BP and physiological or psychological components of pain has not yet been considered so far. The aim of this study was to overcome this gap by performing separate meta-analyses on nociceptive response versus quantifiable perceptual measures of pain in relation to high BP.

Methods: PubMed and Web of Knowledge databases were searched for English language studies conducted in humans. Fifty-nine studies were eligible for the analyses. Pooled effect sizes (Hedges' g) were compared. Random effect models were used. Results show that higher BP is significantly associated with lower nociceptive response ($g = 0.38$; $k = 6$) and reduced pain perception, assessed by quantifiable measures ($g = 0.48$; $k = 59$).

Results: The association between BP and pain perception, derived from highly heterogeneous studies, was characterized by significant publication bias. BP assessment, pain assessment, site of pain stimulation, percentage of female participants in the sample, and control for potential confounders were significant moderators.

Conclusion: Current meta-analytic results confirm the presence of BP-related hypoalgesia and point towards the need for a better understanding of its underlying mechanisms.

Keywords: blood pressure, hypertension, hypoalgesia, meta-analysis, pain

Abbreviations: BP, blood pressure; CI, confidence interval; EEG, electroencephalogram; g, Hedges' g; NFR, nociceptive flexion reflex; NRS, Numeric Rating Scale; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; VAS, Visual-Analog Scale; VRS, Verbal Rating Scale

INTRODUCTION

Numerous studies suggest that blood pressure (BP) elevation is associated with decreased pain perception, leading to the concept of BP-related hypoalgesia. This phenomenon has been first observed in preclinical studies, which suggested that it was possible to induce hypoalgesia in rats by experimentally (e.g. pharmacologically) increasing their BP [1,2]. In humans, a reduction in pain perception has been reported in normotensives during spontaneous [3] or experimentally induced high BP [4] as well as in unmedicated hypertensive patients [5] and individuals with a family history of hypertension [6]. Considering that pain is a warning signal in several medical conditions, and vital in the case of cardioischemic disease onset (e.g. heart pain), BP-related hypoalgesia makes the 'at risk' group of hypertensive patients less aware of initial warning symptoms. Reduced pain perception interferes with the early detection of the so-called silent (asymptomatic) myocardial ischemia and infarction [7], conditions that are nearly twice as common in hypertensive patients than in normotensives [7,8]. Indeed, in patients with coronary diseases, an inverse relation between chest pain and BP both at rest [9,10] and during physical activity [11] has been documented. Moreover, longitudinal studies suggest a pathophysiological link between BP-related hypoalgesia and hypertension [12], indicating that reduced pain perception may be a contributing factor rather than a consequence of elevated BP, thus leading to the development of hypertension [13]. The theory of learned hypertension postulates that BP-mediated hypoalgesia is a causal factor in the development of clinical hypertension via a reward mechanism [14]. Here, pain reduction following phasic BP increases might act as a negative reinforcement of this 'coping mechanism', which on a long run might result in the stabilization of high tonic BP [15,16].

Despite such accumulating evidence on the relation between high BP and diminished pain perception, the size of such association has not yet been systematically quantified. To date, only narrative and systematic reviews have been conducted on the topic, all highlighting the heterogeneity of included studies and the impossibility to draw conclusive evidence [5,13,17–20]. In fact, not all studies

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were able to reproduce BP-related hypoalgesia neither in animals nor in humans [21–23]. To make the picture even more complicated, the relationship between hypertension and pain becomes completely reversed in patients with chronic pain [24–28].

To overcome these gaps, we conducted a meta-analysis to provide estimates of the magnitude and generalizability of BP-related hypoalgesia, the association between BP and nociceptive or quantifiable perceptual components of the pain response. In recent years, enough data on the association between BP and pain perception has been accumulated to urge the identification of sources of variation (i.e. heterogeneity) and potential moderators so that a more in-depth understanding of BP-related hypoalgesia as a risk factor for health can be reached.

The identification of potential moderators of the BP–pain association is particularly needed considering that the mechanisms underlying BP-related hypoalgesia have not yet been fully clarified. Data point to the role of arterial baroreceptors, the mechanoreceptors located in the aortic arch and carotid sinus that are involved in the regulation of BP [13]. First, carotid baroreceptors stimulation results in a reduction of pain perception in both hypertensive patients and normotensives [29]. Second, stimulation of baroreceptors by natural increases in BP during the systolic phase of the cardiac cycle is associated with dampened nociception [30–32]. Third, preclinical studies confirm that the association between BP and pain disappears when baroreceptor activity is suppressed by pharmacological denervation [1]. Interestingly, shared brain areas (periaqueductal gray, amygdala, and insula) exist for the regulation of both baroreceptor functioning and pain [33], pointing towards the possibility that both BP elevations and pain modulation depend on a common central mechanism. The nucleus raphe magnus in the rostral medulla, for example, is a crucial hub of the endogenous opioid system [34], which also receives afferent baroreceptor information [35]. Further, the activity of the nociception-suppressive and nociception-facilitative cells on the nucleus raphe magnus (the so-called ON and OFF cells) is temporally associated to spontaneous fluctuations of BP [36]. Stimulation on such cells in rats (via the vagal nerve) has shown to have an effect on both nociception and BP [37]. Lastly, alterations of the afferent sensory pathway cannot be excluded as a contributing factor to dampened pain perception, mostly in patients with persistent hypertension [38].

Given that hypertension is a leading cause of death worldwide, and that meta-analyses have enormous potential value for the development of guidelines for future research or clinical trials, here we quantified existing evidence supporting the association between high BP and pain. The role of potential moderators of such association was examined by considering both the features of the sample and the methodology used to assess BP and pain.

METHODS

Literature search and studies selection

Two search strategies were used to systematically collect empirical studies of the effects of BP on pain perception. First, PubMed (http://www.pubmed.com) and Web of Knowledge (http://apps.webofknowledge.com) databases were searched for English-language publications through 7 January 2019. The following keywords have been used: Blood pressure AND (Hypoalgesia OR Pain stimul* (stimulation, stimulus, stimuli) OR Pain threshold OR Pain tolerance) NOT Animal.

Second, the reference lists of previous systematic reviews were searched for relevant studies.

The search was limited to English-language publications and human samples. Inclusion criteria for our analysis were as follows: BP assessment; painful stimuli administration; pain assessment; and a design suitable for calculating an effect size. Reasons for exclusion were review articles; case reports; conference proceedings, abstracts, and books; studies conducted only on clinical populations with disorders affecting the cardiovascular system (e.g. diabetes, coronary disease) or with chronic pain syndromes (e.g. fibromyalgia).

A total of 5179 results were retrieved. Comparison of the retrieved titles identified 1781 studies that were duplicates, thus leaving 3398 abstracts for further evaluation (see Fig. 1 for the literature search flowchart). The current meta-analysis is based on data extracted from 63 studies that met the inclusion criteria (see Table 1) and had pain perception as outcome (6 for the meta-analysis on nociceptive response and 61 for the meta-analysis on quantifiable perceptual measures of pain). Among the 61 studies having quantifiable perceptual measures of pain as outcome, additional data (not published in the reviewed article but needed to calculate effect sizes or to run moderator analyses) were received for 7 studies [6,25,39–43].

Coding

A standardized data coding form was developed to extract the following information from each study: authors and publication year; study design; characteristics of the study sample (age, percent women, size, subgroups); method that has been used to induce pain (type, site of stimulation, and its duration); BP assessment (type of device and protocol); pain assessment (nociceptive response, quantifiable perceptual measures, and exact method); adjusted covariates; and brief results. Each study (and each participant) was included only once in one of our meta-analyses [44].

Each research article was read and analysed by at least two members of the research team (E.M., C.O.). Disagreements were resolved through group discussion. Intercoder reliabilities were established for 20% of the studies with satisfactory results: Cohen's $k = 0.96$; $r > 0.99$.

When studies had more than one measure of pain and/or BP, a hierarchical inclusion method was implemented to prevent conflation of effect size estimates. Our choices were motivated by both theoretical assumptions and the need to reduce heterogeneity, therefore, opting for the most frequently used option. Considering that almost all studies had more than one measure of pain perception, the hierarchical inclusion rule was as follows: for nociceptive response, flexion reflex (NFR), then wind-up, and lastly EEG responses; for quantifiable perceptual measures, pain threshold, next pain tolerance, next Visual-Analog Scale (VAS) or Numeric Rating Scale (NRS), or Verbal Rating Scale (VRS) responses, or else the Mc Gill Pain Questionnaire (if

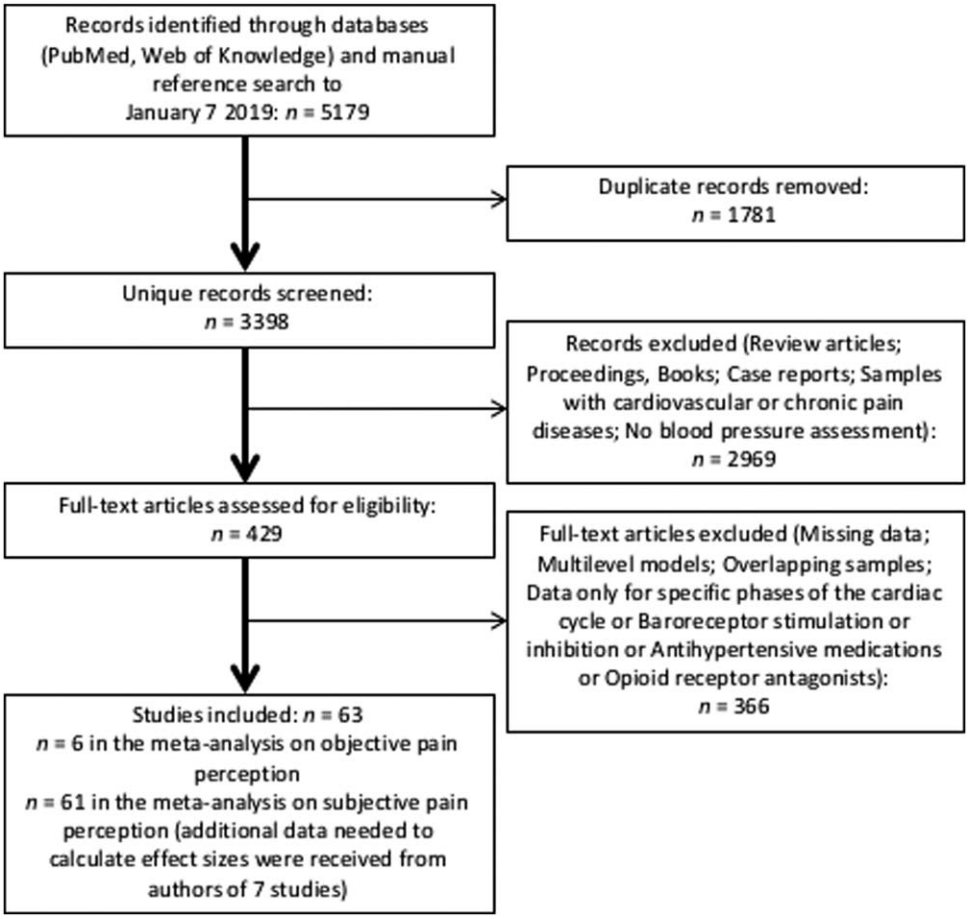

FIGURE 1 Flow chart showing study selection for the meta-analysis.

only subscales, sensory first otherwise total score). When studies assessed both pain intensity and pain unpleasantness, pain intensity was the preferred choice.

When studies had more than one type of pain stimulus, the hierarchical inclusion rule was based on the most frequently used: electrical (intracutaneous first, then extracutaneous), ischemic, CPT, thermal (heat), other (i.e. Forgione–Barber finger pressure, muscle pain, tooth extraction, puncture, surgical operation).

In line with the current guidelines for the assessment of BP [45], which consider 24 h the golden standard, when studies had more than one type of BP assessment (i.e. resting BP and BP reactivity to a task), resting BP has been chosen, with 24-h BP as a preferred choice compared with laboratory BP.

When an article reported overall pain and pain peak [46], overall pain was used in the analysis.

When studies had experimental manipulations, such as pharmacological manipulations [4,47,48], transcutaneous electrical nerve stimulation [49], administration of pain in determined phases of the cardiac cycle [30] or during baroreceptors manipulation, such as neck suction [50,51], only the control/placebo condition or – when reported – the result irrespective of the cardiac phase were included in the analysis. When no difference emerged between these conditions, we first contacted the authors to obtain data for the control/placebo condition, then, if such data was not available, we used the average of the two conditions reported in the article [47].

For studies reporting on medically ill samples (i.e. with a diagnosis of diabetes, coronary disease, psychopathological disorder, chronic pain, etc.), we included only data related to the healthy controls, when it was possible to obtain it either from the article or by contacting the authors [52,53].

Data analysis

Two separate meta-analyses were conducted on nociceptive response and quantifiable perceptual measures of pain, respectively. Calculation of effect sizes and pooled effect sizes were obtained using ProMeta Version 2.0 (Internovi). All the analyses were performed using random-effects models as they account for the amount of variance caused by differences between associations as well as differences among participants within associations. For each study (or subsample of a study), we calculated a Hedges' *g* effect size, and considered *g* equal to 0.20, 0.50, and 0.80 as small, medium, and large effects, respectively [54]. Effect sizes indicating lower pain perception associated with higher BP got a positive sign [55]. Calculation of effect sizes was based on means, standard deviations, *P* values, and sample sizes of the groups. Whenever studies did not provide raw data to

TABLE 1. Studies included in the meta-analysis and conditions/comparisons used to derive effect sizes

Studies (author group, year [ref. no.])	*n*	Percent women	Age	Exp. group	Pain type	Stimulus duration (ms)	Site of stimulation	Pain assessment	BP device	BP protocol	Covariates	Contrast	MA (Hedges' *g*)
Al'Absi *et al.*, 2006 [47]	99	40.4	19.5[1]	At risk	Elect (extra)	17[2]	Sural nerve	Tolerance	Automatic	Rest	Yes[3]	Correlation between BP and pain tolerance irrespective of drug condition	Pain perception (0.51)[4]
Angrilli *et al.*, 1997 [50]	39	0	25.3	Hypo	Elect (intra)	10	Hand	Threshold[5]	Automatic	Rest	No	Correlation between BP and sensory threshold[5]	Pain perception (0.54)[6]
Bruehl *et al.*, 2002 [25]	29	60.8	32.7	Normo	Ischem	300 000[7]	Arm	NRS	Automatic	Rest	Yes[9]	Mean intratask NRS for the high and low resting BP tertiles in pain free subsample	Pain perception (0.48)
Bruehl *et al.*, 2010 [39]	79	50.6	27.5	Normo[10]	Ischem	300 000[7]	Arm	VAS	Automatic	Rest	Yes[11]	Correlation between BP and VAS intensity[12]	Pain perception (−0.19)
Bruehl *et al.*, 2010 [73]	55	65.5	17.1	Normo	Heat	1000[13]	Arm	Threshold	Automatic	Rest	No	Correlation between SBP and acute pain threshold	Pain perception (1.08)
Campbell and Ditto 2002 [49]	45	0	22	At risk	Elect (extra)	5	Arm	VAS	Automatic	Rest	No	Correlation between casual BP and pain in the entire sample	Pain perception (1.29)
Campbell *et al.*, 2003 [12]	110	0	22[14]	Normo[15]	Other[16]	180 000[7]	Hand	Tolerance	Automatic	24h	No	Correlation between pain tolerance at age 14 and SBP at age 22	Pain perception (0.79)
Campbell *et al.*, 2004 [74]	135	43.7	33.4[1]	Normo	Ischem	5000[17]	Arm	VRS	Automatic	24h	No	Correlation between SBP and intensity	Pain perception (0.47)
Chalaye *et al.*, 2013 [75]	26	50	26	Normo	Heat	–[18]	Arm	Threshold	Beat-to-beat	Rest	Yes[19]	Correlation between pain threshold and SBP	Pain perception (0.26)
Chung and Bruehl, 2008 [76]	30	46.7	35	Normo	Heat[20]	15	Arm	Wind up	Beat-to-beat	Rest	Yes[21]	Association between resting BP and thermal wind-up	Nociception (0.77)
Cook *et al.*, 2004 [77]	34	100	19[1]	At risk	Other[22]	–[23]	Leg	NRS	Beat-to-beat	Rest	Yes[24]	Pain intensity during maximal exercise in FH+ versus FH-	Pain perception (0.16)
Cotton *et al.*, 2018 [40]	15[25]	–	/	Normo	Thermal	6000	Leg	VAS	Beat-to-beat	Rest	Yes[26]	Correlation between SBP at baseline and pain intensity ratings[27]	Pain perception (1.21)
de la Coba *et al.*, 2018 [78]	27	100	51.4	Normo[28]	Other[29]	5000	Finger	Threshold	Beat-to-beat	Rest	No[30]	Correlation between SBP and pain threshold	Pain perception (1.18)
de la Coba *et al.*, 2018 [79]	99	58.6	20.7	Normo[31]	Thermal	–	Arm	Threshold	Automatic	Rest	No[32]	Correlation between SBP and pain threshold	Pain perception (0.49)
Deschaumes *et al.*, 2014 [80]	293	46.1	42	Normo[33]	Other[34]	–	Mouth	VAS	Automatic	Rest	No	Correlation between SBP before surgery and postoperative pain[35]	Pain perception (0.05)
Devoize *et al.*, 2016 [81]	26	50	26	Normo	CPT	300 000[7]	Hand	VAS	Beat-to-beat	React	Yes[36]	Correlation between the BP variation and average pain sensation	Pain perception (−0.10)
Ditto *et al.*, 1997 [82]	24[37]	100	19.3	At risk	Elect (extra)[38]	1	Arm	VAS	Beat-to-beat	React	Yes[39]	Maximum pain reported (videogame day) by FH+ versus FH− high MAP reactors	Pain perception (1.48)
Ditto *et al.*, 2009 [41]	40	0	30.1[1]	At risk	Thermal	1000[40]	Arm[41]	VAS	Automatic	24h	No	Pain unpleasantness rating in hypertensive patients and normotensives	Pain perception (0.47)
Drouin and McGrath 2013 [83]	307	43.3	12.4[1]	Normo[42]	Other[43]	/	Hand	VAS	Automatic	Rest	Yes[44]	Correlation between pain ratings and SBP	Pain perception (0.30)
Duschek *et al.*, 2007 [84]	60	53.3	25	Normo	CPT	60 000	Hand	VAS	Beat-to-beat	Rest	Yes[45]	Correlation between pain intensity and SBP	Pain perception (0.58)
Duschek *et al.*, 2008 [85]	60	100	24.5[1]	Hypo	CPT	180 000[7]	Hand	VAS	Beat-to-beat	React	Yes[46]	Correlation between pain threshold and SBP[47]	Pain perception (0.53)

TABLE 1 (*Continued*)

Studies (author group, year [ref. no.])	*n*	Percent women	Age	Exp. group	Pain type	Stimulus duration (ms)	Site of stimulation	Pain assessment	BP device	BP protocol	Covariates	Contrast	MA (Hedges' *g*)
Duschek *et al.*, 2009 [86]	80	80	27.8[1]	Hypo	Thermal	60 000	Arm	Threshold	Automatic	Rest	Yes[48]	Pain threshold in hypotensive patients versus controls	Pain perception (0.45)
Edwards *et al.*, 2002 [30]	36	44.4	23.3	Normo	Elect (extra)	1[49]	Sural nerve	NFR, NRS	Automatic	Rest	Yes[50]	Correlation between SBP and NFR and NRS	Nociception (0.00); Pain perception (0.00)
Fechir *et al.*, 2012 [87]	14	28.6	24.3	Normo	Elect (intra)	0.5	Leg	VAS	Beat-to-beat	React	Yes[51]	Correlation between SBP and analgesia	Pain perception (0.62)
Fillingim *et al.*, 1998 [88]	21	100	23	Normo	Thermal	/[52]	Arm[53]	Threshold	Automatic	Rest	No	Pain onset in high and low BP groups[54]	Pain perception (0.69)
France and Stuart, 1995 [89]	80	0	19.7	At risk	Ischemic	300 000	Hand	NRS	Beat-to-beat	React	No	Correlation between total pain rating index scores and parental history	Pain perception (0.49)
France and Suchowiecki, 2001 [90]	113	52.2	18.9	At risk	Elect (extra)[55]	1[2]	Sural nerve	NFR	Automatic	Rest	Yes[56]	Intensity of stimulation needed to elicit NFR in FH+ and FH−	Nociception (0.58)
France *et al.*, 1991 [51]	45	0	22[1]	At risk	Ischemic	60 000[7]	Leg	Threshold	Automatic	Rest	No	Pain threshold for FH+ and FH−	Pain perception (1.85)
France *et al.*, 2002 [91]	102	46.1	19.1[1]	At risk	Elect (extra)	1[2]	Sural nerve	NFR, threshold	Automatic	Rest	Yes[57]	NFR threshold in FH+ and FH- across periods; pain threshold in FH+ and FH− during the initial premath assessment	Nociception (0.58); Pain perception (0.62)
France *et al.*, 2005 [4]	158	46.2	19.3	At risk	Elect (extra)	1[2]	Sural nerve	NFR, NRS	Automatic	Rest	Yes[58]	NFR threshold and electrocutaneous pain threshold in FH+ versus FH-[59]	Nociception (0.00); Pain perception (0.26)
Frew and Drummond, 2009 [52]	17	54.5[1]	35.8[1]	Normo[60]	CPT[61]	240 000	Foot	VRS	Automatic	React	Yes[62]	Correlation between pain tolerance and SBP during the first CPT in controls	Pain perception (1.13)
Ghione *et al.*, 1988 [92]	156	32.1	32.4[1]	Hyper	Elect (intra)	–	Tooth	Threshold	Automatic	Rest	No	Correlation between mean MAP and pain threshold	Pain perception (0.56)
Girdler *et al.*, 1998 [53]	14	100	24.4	Normo[63]	Ischemic[64]	2000[65]	Arm	Threshold	Automatic	React	Yes[66]	Correlation between mean task SBP and pain threshold	Pain perception (0.13)
Guasti *et al.*, 1995 [93]	67	0	42	Hyper	Elect (intra)	200[67]	Tooth	Threshold	Automatic	24h	Yes[68]	Correlation between 24 h SBP and pain threshold	Pain perception (0.74)
Guasti *et al.*, 1996 [94]	72	0	42.5[1]	Hyper	Elect (intra)	200[67]	Tooth	Threshold	Automatic	24h	Yes[68]	Correlation between 24 h SBP and pain threshold	Pain perception (0.79)
Guasti *et al.*, 1998 [95]	39	0	43	Hyper	Elect (intra)	200[67]	Tooth	Threshold	Automatic	24h	Yes[68]	Pain threshold in hyper versus normo	Pain perception (0.80)
Guasti *et al.*, 1999 [96]	146	0	41.5[1]	Hyper	Elect (intra)	200[67]	Tooth	Threshold	Automatic	24h	Yes[68]	Pain threshold in hyper versus normo	Pain perception (0.46)
Guasti *et al.*, 1999 [97]	181	0	42.5[1]	Hyper	Elect (intra)	200[67]	Tooth	Threshold	Automatic	24h	Yes[68]	Correlation between 24 h SBP and pain threshold	Pain perception (0.65)
Guasti *et al.*, 2002 [98]	73	0	40.5[1]	Hyper	Elect (intra)	200[67]	Tooth	Threshold	Automatic	24h	Yes[68]	Pain threshold in hyper versus normo	Pain perception (0.47)
Horing *et al.*, 2016 [99]	33	63.6	20.1	Normo	Thermal[69]	60 000[70]	Hand	VAS	Automatic	Rest	Yes[71]	Correlation between resting SBP and pain rating during the first trial of the first sequence	Pain perception (0.75)
Keogh and Witt, 2001 [100]	50	50	24.2	Normo	CPT	120 000[7]	Hand	Threshold	Automatic	Rest	Yes[72]	Correlation between changes in SBP and in pain tolerance after caffeine[73]	Pain perception (0.55)

TABLE 1 (*Continued*)

Studies (author group, year [ref. no.])	*n*	Percent women	Age	Exp. group	Pain type	Stimulus duration (ms)	Site of stimulation	Pain assessment	BP device	BP protocol	Covariates	Contrast	MA (Hedges' *g*)
King *et al.*, 2012 [101]	60	64	46	Normo[74]	Other[29]	–	Tooth	VAS	Automatic	Rest	Yes[75]	Correlation between preoperative SBP and pain on the first postoperative day	Pain perception (0.49)
Koenig *et al.*, 2017 [42]	30	100	15.27	Normo[76]	CPT	24 000[7]	Hand	Threshold	Manual	Rest	Yes[77]	Correlation between baseline SBP and pain threshold	Pain perception (0.00)
Luo *et al.*, 2013 [102]	60	51.7	55.6	Hyper[78]	Other[79]	–	Abdomen	VRS	Manual	Rest	No	Pain intensity scores in hypertensive patients versus normotensives	Pain perception (1.06)
McCubbin *et al.*, 2006 [103]	125	60.8	19.5[1]	At risk	CPT	120 000[7]	Hand	MPQ	Automatic	Rest	Yes[80]	Correlation between the total score on the MPQ and resting SBP on the placebo day	Pain perception (0.43)
Myers *et al.*, 2001 [104]	104	48.1	22.4	Normo	CPT	300 000[7]	Hand	Threshold	Automatic	Rest	Yes[81]	Correlation between pain threshold and resting SBP	Pain perception (0.45)
Nahman-Averbuch *et al.*, 2016 [43]	40	50	26.45	Normo	Thermal	–[82]	Arm	Threshold	Manual	Rest	Yes[83]	Correlation between SBP and pain thresholds at baseline	Pain perception (0.24)
Nyklicek *et al.*, 1999 [105]	63	46.6[1]	44.1[1]	Hyper	Elect (extra)	160 000[7]	Arm	Threshold	Automatic	Rest	Yes[84]	Differences in pain threshold in hyper and normo	Pain perception (0.21)
O'Connor *et al.*, 2004 [23]	12	0	22.2	Normo	Other[85]	–[86]	Leg	VRS	Manual	Rest	Yes[87]	Correlation between preexercise SBP and mean pain intensity ratings in the placebo condition	Pain perception (−0.67)
Olsen *et al.*, 2013 [5]	6914	47.3	56.3	Hyper[88]	CPT	106 000	Hand	NRS	Automatic	Rest	No[89]	Correlation between SBP and acute pain ratings in individuals free of chronic pain	Pain perception (0.20)
Ottaviani *et al.*, 2018 [106]	18	55.5	32.7	Normo	Elect (extra)	5	Arm	Threshold	Automatic	24h	Yes[90]	Correlation between home SBP and pain threshold	Pain perception (2.45)
Page and France, 1997 [107]	116	48.3	19.4[1]	At risk	Elect (extra)	1[2]	Sural nerve	NFR, threshold	Automatic	Rest	Yes[91]	Correlation between SBP and NFR and pain threshold	Nociception (0.48); Pain perception (0.24)
Papageorgiou *et al.*, 2017 [108]	40	52.5	51.2	Hyper	CPT	–[92]	Hand	Tolerance[93]	Automatic	24h	No	Tolerance in hyper versus normo	Pain perception (0.61)
Nascimento Rebelatto *et al.*, 2017 [109]	72	55.5	71.4	Hyper	Other[16]	–[94]	Leg[95]	Threshold (PPT)	–[96]	Rest	No	Differences in pressure pain threshold between normo e hyper	Pain perception (0.43)
del Paso *et al.*, 2011 [110]	29	93.1	49.4	Normo[97]	CPT	180000[7]	Hand[98]	Threshold	Beat-to-beat	Rest	Yes[99]	Correlations between baseline SBP and pain threshold in the healthy subgroup	Pain perception (0.79)
Ring *et al.*, 2008 [46]	63	47.6	42.3[1]	Hyper	Elect (extra)	1[2]	Sural nerve	Threshold	Automatic	24h	Yes[100]	Pain threshold in hyper versus normo in the placebo condition	Pain perception (0.17)
Scheuren *et al.*, 2016 [111]	32	50	24.2	Normo	Thermal	60 000	Hand	NRS	Beat-to-beat	Rest	No	Correlation between baseline SBP and NRS sensory	Pain perception (0.12)
Schobel *et al.*, 1998 [48]	21	0	25[1]	At risk	Other[101]	120 000	Hand[102]	NRS	Beat-to-beat	Rest	No	Correlation between resting SBP and pain perception	Pain perception (1.37)
Sheffield *et al.*, 2000 [112]	51	49	38	Normo	Thermal	5000	Arm	VAS	Manual	Rest	No	Correlation between SBP and pain intensity rating	Pain perception (0.60)
Stewart and France, 1996 [113]	82	0	19.7	At risk	Ischemic[103]	420 000[7]	Arm	NRS	Automatic	Rest	No[104]	Ratings of intensity of ischemic pain in FH+ versus FH− at minute 5	Pain perception (0.52)
Umeda *et al.*, 2009 [114]	23	100	20	Normo	Other[105]	120 000[7]	Hand	Threshold	Beat-to-beat	Rest	No	Correlation between resting SBP and pain threshold	Pain perception (−0.14)

TABLE 1 (*Continued*)

Studies (author group, year [ref. no.])	*n*	Percent women	Age	Exp. group	Pain type	Stimulus duration (ms)	Site of stimulation	Pain assessment	BP device	BP protocol	Covariates	Contrast	MA (Hedges' *g*)
Umeda *et al.*, 2010 [115]	50	50	29[1]	Normo	Other[106]	120 000[7]	Hand	Threshold	Beat-to-beat	Rest	Yes	Correlation between resting MAP and threshold across conditions	Pain perception (0.00)
Vassend and Knardahl, 2004 [116]	58	100	35.9	Normo	Electr (ext)[107]	50[108]	Hand	Threshold	Beat-to-beat	React	Yes[109]	Correlation between pain-induced MAP and mean pain threshold	Pain perception (0.76)

The measures reported in the table do not represent the only available variables in the examined studies but those that were used in the current meta-analysis for the computation of the ES and for moderator analysis. [1] Estimated value; [2] duration of each stimulation trial consisting of five 1-ms rectangular pulses with a 3-ms interpulse interval; [3] control for circadian rhythm and menstrual cycle, no alcohol or analgesic medication for 24 h and narcotic medication for 3 days; [4] the study included an NFR assessment, but the provided data was insufficient to derive the ES; [5] without the most extreme point; [6] the study included a EEG measure but given the need to exclude the neck suction manipulation condition, the available information were not sufficient to allow the computation of the ES; [7] maximum duration; [8] for ischemic pain the pharmacological manipulation did not yield any effect, thus, we have considered the average and not only the placebo condition; [9] control for circadian rhythm, no analgesic or anti-inflammatory medications for 24 h prior to study participation; [10] history of abdominal pain during childhood; [11] no caffeine for 3 h prior to the appointment, analgesics or medications potentially affecting blood pressure (e.g. pseudoephedrine) for 12 h prior to the appointment; [12] combines those who were harassed and those who were not; [13] temperature increasing at a ramp rate of 0.5 °C/s; [14] same subjects tested at the age of 14 (longitudinal design); [15] 11 participants had a history of hypertension (at risk); [16] Forgione and Barber's pressure; [17] 10 min of BP cuff inflation, during which subjects contracted their hand for 5 s every 30 s; [18] temperature increasing at a ramp rate of 0.3 °C/s; [19] no analgesic or anti-inflammatory medication at least 24 h prior to testing; [20] also ischemic; [21] no analgesics, nonsteroidal anti-inflammatory drugs, or any medications potentially affecting BP for 12 h prior to and caffeine 3 h prior to study participation; [22] muscle pain (insufficient data on CPT to derive the ES); [23] after a 4-min warm-up at 25 W, resistance increased up to 50W and then at a rate of 24 W/min until participants reached volitional exhaustion; [24] control for menstrual cycle; [25] group of yoga practitioners not included in the analysis; [26] refrain from exercising or consuming caffeinated products for 2 h before testing, and refrain from drinking alcohol or taking any medications outside the usual regimen for 24 h prior. Regularly cycling women (including those using hormonal contraceptives) were always tested in the first 12 days of their menstrual cycle, unless they were on monophasic hormonal contraception; [27] average of certain and uncertain ratings; [28] the study included a group of patients with fibromyalgia that was not considered in the analysis; [29] oral postsurgical pain; [30] medication use (antidepressants, anxiolytics, analgesics and opioids); [31] The group with unresolved chronic pain was not considered in the analysis; [32] no analgesic medications for 12 h prior to the scheduled study session; [33] some had history of cardiovascular problems; [34] spontaneous pain during the first 6 h after the end of surgery in the hospital; [35] composite score taking into account the degree of spontaneous pain reported by the patient during the first 6 h and the amount of analgesic drug intake during the first 3 days; [36] control for menstrual cycle, no smoking and/or drinking coffee 1 h before testing; [37] the sample was constituted by 48 individuals but only high MAP reactors were included in the analysis; [38] also Cold Pressure Test (CPT, 4 °C). Both tasks administered after performance at a videogame; [39] control for menstrual cycle; [40] 10 low-heat and 10 high heat presented at 30-s interval; [41] participants tested with legs up and legs down in counterbalanced order; [42] 16% of parents and 11.3% of biological mothers met criteria for hypertension; [43] child's nondominant ring finger was pierced with a 21-gauge safety lancet for a standardized blood draw; [44] no nonprescription medication and caffeine for 24 h prior to the laboratory visit; [45] no alcohol or beverages containing caffeine for 3 h prior to experimental session; [46] no caffeine and alcohol; [47] controlling for BMI; [48] no smoking, alcohol, and caffeine for 3 h prior to the screening and experimental sessions; [49] five rectangular-wave pulses of 1-ms duration followed by a 4-ms interstimulus interval; [50] no caffeine, alcohol, and vigorous exercise for 2 h, and analgesic medication for 24 h before testing; [51] no smoking and drinking coffee on the day of investigation; [52] staircase ramp of 0.5 C every 5 s; [53] and ipsilateral cheek; [54] thermal pain onset in °C, high versus low BP based on the median split; [55] the study included an ischemic condition; [56] no caffeine, nicotine, alcohol, pain medication, and strenuous exercise for at least 4 h before their arrival at the laboratory; [57] refrain from caffeine, nicotine, alcohol, medications, and strenuous exercise for at least 4 h before their arrival at the laboratory; [58] control for menstrual cycle, no caffeine, nicotine, alcohol, and strenuous exercise for at least 4 h before their arrival at the laboratory, and from analgesic medication for 24 h prior to testing; [59] includes a naloxone condition as data were not presented separately; [60] the study included a sample of MDD that was not considered in the analysis; [61] the study included an arithmetic task with electric shock and both stressors are performed twice; [62] smokers excluded, no alcohol intake for 1 week, no alcoholic or caffeinated beverages for 12 h, no food for 2 h, and no opiate analgesics for 24 h before the experiment; [63] the study included a sample with bulimia nervosa that was not included in the analysis; [64] handgrip during tourniquet cuff inflation; [65] approximate time at which participants had to squeeze and release (handgrip exercise); [66] control for circadian variations, no over-the-counter medications, including analgesics for 24 h and caffeine on the day of testing; [67] burst frequency at 5 Hz; [68] control for circadian rhythms, no medications or washout 3 weeks before the study, no smoking, caffeine, tea, chocolate, cola or alcohol 12 h before the experiment; [69] hand immersion in hot (47 °C) water; [70] 5 trials of 1-min immersion time and 30-s pause, totaling 7.5 min per sequence; [71] abstinence from pain medication and recreational drugs for at least 24 h before the lab visit; [72] no alcohol and caffeine-containing products for 12 h, and food and or cigarettes for 2 h; [73] no association with resting SBP in the placebo condition; [74] endodontic patients; [75] no analgesics up to 6 h prior to clinical assessment; [76] the sample with nonsuicidal self-injuries was not included in the analysis; [77] BMI (continuous), use of medication (yes/no), use of contraceptive pill (yes/no), number of cigarettes smoked per day (categorical), alcohol consumption (yes/no) and drugs taken during the 30 days preceding the study (yes/no); [78] some patients had diabetes mellitus, fatty liver/hepatitis B, cholecystitis/cholecystolithiasis, gastric ulcer, premature ventricular contractions, anemia; [79] major abdominal surgery; [80] nonsmokers, not consuming more than three alcoholic beverages per week, not currently taking any opioid or nonopioid pain medication, tested if menstrual cycle phase had any effect on pain reports; [81] nonsmokers, abstain from caffeine for the 2 h before their appointment; [82] baseline temperature was set at 32.0 °C and was increased or decreased at a rate of 1 °C/s; [83] women who were not on contraception were tested during the follicular phase; those on contraception were tested at days 2–20 after menstruation end. None of the subjects took any analgesic medication for 24 h before the testing; [84] refrain from using alcohol on the day of the experiment, from caffeine consumption for at least 3 h and from smoking for at least 2 h prior to the laboratory session; [85] muscle pain; [86] exercise bouts; [87] nonsmoking and low-caffeine consumers; [88] the study included a sample with chronic pain that was not considered in the analysis; [89] no caffeine consumption for 1 week; alcohol consumption for 24 h; and eating and exercising for 12 h before the experimental testing; [90] participants were asked to refrain from alcohol and use of analgesic or anti-inflammatory medications for 24 h before the study and from caffeine, alcohol, and vigorous exercise for 2 h before the experiment. To avoid circadian influences, all sessions were scheduled in the afternoon; [91] results did not change when the analysis was re-done controlling for analgesic or antihypertensive medications; [92] until retracted; [93] the study included an EEG assessment that was not incorporated in the meta-analysis because of the paucity of studies with this specific type of physiological measures; [94] until the pressure sensation changed into pain; [95] seven anatomical points examined, the left tibia was chosen as it was the most comparable with sites from other studies; [96] doctor diagnosis of hypertension; [97] group with fibromyalgia not included; [98] also arm; [99] excluded those regularly taking prescription or over-the-counter medications; control for circadian rhythm variation; no caffeine and nicotine for at least 2 h preceding their arrival at the laboratory; [100] to refrain from caffeine, alcohol, and vigorous exercise for 2 h, and analgesic medication for 24 h prior to testing; [101] noxious mechano-stimulation: skin fold pinching; [102] also feet and lobe; [103] also CPT; [104] only refrain from smoking 2 h before the session; [105] Forgione–Barber pressure after isometric exercise; [106] caffeine and physical exercise; [107] also pressure pain (not examined); [108] four pulses per second, each pulse with a duration of 50 ms; [109] refrain from vigorous physical activity, drinking tea or coffee, smoking, and having large meals during the last 4 h before. Alcohol was not allowed the last 12 h before the experiment. CPT, Cold Pressor Task; Elect, electrocutaneous stimulation; ES, effect size; Extra, extracutaneous; FH−, without a family history of hypertension; FH+, with a family history of hypertension; Hyper, hypertensive patients; Hypo, hypotensive patients; Intra, intracutaneous; Ischem, ischemic; MA, meta-analysis; MAP, mean arterial pressure; MPQ, McGill Pain Questionnaire; NFR, Nociceptive Flexion Reflex; Normo, normotensives; NRS, Numeric Rating Scale; React, Reactivity; VAS, Visual Analog Scale, VRS, Verbal Rating Scale.

calculate effect sizes and instead provided statistics (e.g. *r*, *t*), we applied transformation formulas to convert to *g* [56]. When an article reported *P* less than 0.05 or nonsignificant, we relied on a highly conservative estimate of the effect size and computed Hedges' *g* with *P*-values of 0.045 and 1 (one-tailed), respectively.

When the standard deviation (SD) of the changes was not provided, we imputed a change-from-baseline SD using a correlation coefficient as indicated by Higgins and Green: $SD_{change} = \sqrt{[SD^2_{baseline} + SD^2_{final} - (2 * Corr * SD_{baseline} * SD_{final})]}$ [57]. When only standard errors (SE) were provided, standard deviations were obtained by applying the following formula $SD = SE * \sqrt{n}$ [57].

Cochran's Q and I^2 statistics were used to assess heterogeneity between studies. A statistically significant Q value rejects the null hypothesis of homogeneity of findings among studies, indicating that systematic differences may potentially influence the results. I^2 values of 25, 50, and 75% reflect low, moderate, and high heterogeneity, respectively.

The problem of publication bias or 'file-drawer effect' (i.e. the existence of unpublished studies with null results) was estimated informally by inspecting the funnel plot of effect size against standard error for asymmetry and formally by using Begg and Mazumdar's rank correlations, and Egger's regression intercept test. We did not rely on the popular failsafe *N* as it has been considered a problematic method to assess publication bias [58].

We first run the analyses including the entire set of studies and then subsequently re-run them without some potential outliers, identified based on having statistically significant standardized residuals [59]. Statistics reported in the present meta-analysis conform to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (see supplemental material for PRISMA checklist, http://links.lww.com/HJH/B298) [60].

Moderator analysis

For each outcome, we examined how the size of the association varied as a function of sex (% of women), mean age (years), experimental sample (hypertensive patients, normotensives, at risk), pain type (CPT; electrical, ischemic, thermal, other), painful stimulus duration (min), site of stimulation (arm/hand, foot/leg, sural nerve, tooth/mouth), pain assessment (NFR, EEG, wind-up/threshold, tolerance, VAS/NRS/VRS, McGill Pain Questionnaire), device to assess BP (beat-to-beat versus noncontinuous), protocol to assess BP (rest, reactivity, 24 h), and adjustment for potential confounders (yes, no).

First, sex was examined as a moderator, in light of reported prominent sex differences in the association between pain and cardiovascular activity [61] and in the prevalence of BP-related hypoalgesia [62]. Moreover, prominent sex differences have been reported in pain perception, namely compared with men, women report more pain and have a lower pain threshold and tolerance to experimental pain stimuli [63–65].

BP-related hypoalgesia appears to be independent of age, as there is evidence of reduced pain perception of offspring of hypertensive patients even in newborns [66]. However, age was examined as a moderator because of its known influence on pain perception [67,68].

Third, we wanted to test whether BP-related hypoalgesia is more pronounced in individuals at risk for hypertension (i.e. with borderline hypertension, or family history of hypertension) or with a formal diagnosis of hypertension compared with normotensives. We did so because on one hand, hypoalgesia can be induced in normotensive individuals by experimentally increasing BP [4], and on the other hand, because the putative mechanisms implicated in BP-related hypoalgesia are impaired both in hypertensive individuals and in those who are at risk to develop hypertension [69]. Importantly, all studies conducted on hypertensive individuals either required participants to discontinue drug treatment for at least 2 weeks before the experimental session or recruited unmedicated hypertensive individuals.

Fourth, we examined if specific types of pain induction would evoke more pronounced BP-hypoalgesia; for example, intracutaneous electrical stimulation is considered the most appropriate stimulus, as it is less likely to recruit nonpain fibers [70].

Fifth, painful stimulus duration was examined as a potential moderator of the association between BP and pain perception, given that longer versus brief painful stimulus duration may differently stimulate endogenous opioid responses [71].

Similarly, whereas baroreceptor functioning is thought to play a role in the association between transient phasic BP increases (spontaneous or induced) and hypoalgesia, other key variables may play a role in the association between tonic BP and pain perception, such as neurovascular alterations impairing nociceptive transmission in stable hypertension [72]. Thus, to better understand the pathophysiological mechanism underlying BP-related hypoalgesia, the moderating role of BP assessment (i.e. 24-h, tonic or phasic) was also considered.

Lastly, in order to inform future studies on the best way to elicit BP-related hypoalgesia, body site of pain stimulation, pain assessment, and adjustment for potential confounders were examined as covariates.

A minimum of five studies for each subgroup was required for the moderation analysis. Stimulus duration (continuous moderator) was evaluated using meta-regression, whereas categorical moderators (prevalence of women, experimental sample, pain type, site of stimulation, pain assessment, device to assess BP, protocol to assess BP, and adjustment for potential confounders) were entered as grouping variables in the effect size calculations.

RESULTS

Table 1 discloses the specific contrasts that were used to extract effect sizes in the present meta-analyses. Studies marked with an asterisk in the table and figures indicate potential outliers. Given the small number of studies assessing DBP in association with pain sensitivity [25,47,50], the present meta-analyses focus on SBP only. For this reason, from now on, the acronym BP will be used to refer to SBP.

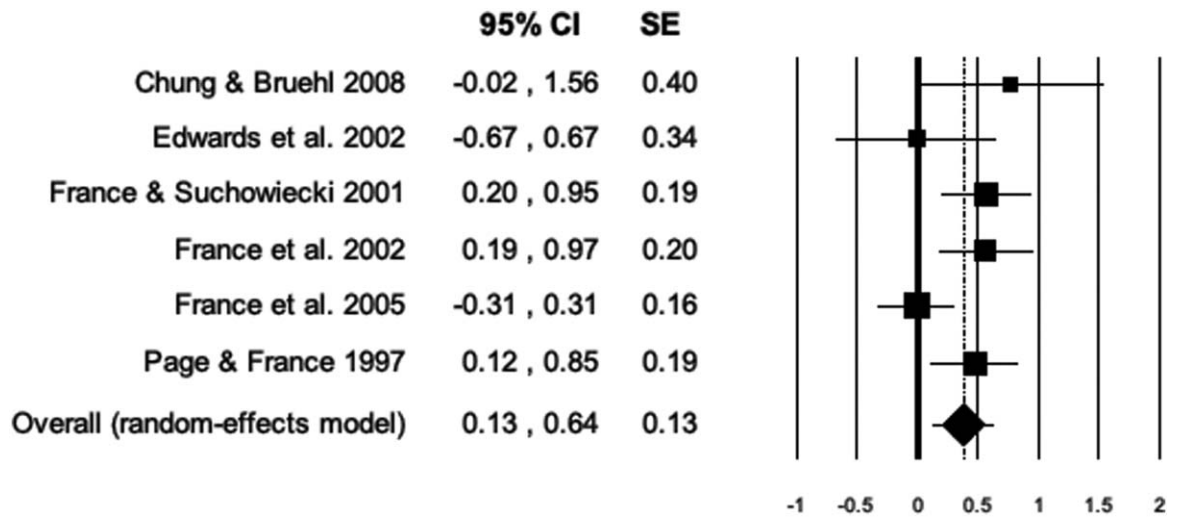

FIGURE 2 Forest plot for meta-analysis on the association between blood pressure and physiological nociceptive response.

Nociceptive response

The meta-analysis of six studies (555 adults) between BP and physiological nociceptive response yielded a statistically significant negative association. As depicted in Fig. 2, the overall effect size for all included studies was low, $g = 0.38$, 95% confidence interval (95% CI 0.13–0.64), $P = 0.003$. Tests of homogeneity reflected relatively low heterogeneity, $Q = 10.25$, $P = 0.069$; $I^2 = 51.2$. Publication bias was not detected by the funnel plot, Egger's test (intercept = 1.17, $t = 0.54$, $P = 0.062$), or Kendall's tau ($Z = 0.56$; $P = 0.57$).

Exclusion of a potential outlier [4] significantly increased the effect size ($g = 0.51$, 95% CI 0.31–0.71, $P < 0.0001$) and reduced heterogeneity ($Q = 2.93$, $P = 0.57$; $I^2 = 0$), without affecting the presence of publication bias. Moderation analysis could not be performed because of the inadequate number of studies in this meta-analysis.

Quantifiable perceptual measures of pain

Analysis of 61 studies (11 126 participants) showed a significant association between high BP and diminished pain perception ($g = 0.48$, 95% CI 0.40–0.57, $P < 0.0001$), which was medium in size. Figure 3 shows the forest plot. Significant heterogeneity was shown by the Q and I^2 statistics, Q (58) = 149.1, $P < 0.0001$; $I^2 = 59.8$. Evidence of publication bias was detected by an asymmetrical funnel plot (see Fig. 4). The bias was confirmed by Egger's regression test (intercept = 1.27, $t = 5.90$, $P < 0.0001$) but not by Kendall's tau ($Z = 0.76$; $P = 0.45$).

Exclusion of extreme outliers [39,51,106] neither changed the effect size ($g = 0.47$, 95% CI 0.39–0.55, $P < 0.0001$) nor heterogeneity, Q (55) = 117.8; $P < 0.0001$; $I^2 = 51.6$.

Results of moderation analysis for quantifiable perceptual measures of pain

As shown in Table 2, contrasting studies having a prevalence of women (≥60%) with studies having less than 60% of women in the sample yielded a significant difference, Q (1) = 4.89, $P = 0.03$, with the latter being more strongly associated with perceptual measures of pain ($g = 0.55$, $k = 16$, $n = 715$ versus $g = 0.33$, $k = 28$, $n = 9239$). Only the second set of studies presented significant heterogeneity, Q (26) = 46.1, $P = 0.01$; $I^2 = 43.6$.

The type of BP assessment emerged as a marginally significant moderator, Q (2) = 5.40, $P = 0.06$, with studies that used 24-h BP assessment ($g = 0.61$, $k = 12$, $n = 1049$) or BP recorded during the painful stimulation ($g = 0.58$, $k = 11$, $n = 442$) being characterized by a stronger association compared with studies assessing resting BP ($g = 0.41$, $k = 36$, $n = 9580$). It has to be noted that only studies assessing resting BP showed substantial heterogeneity, Q (35) = 90.1; $P < 0.0001$; $I^2 = 61.2$.

Studies assessing threshold or tolerance assessment produced a higher overall effect size ($g = 0.56$, $k = 31$, $n = 2182$) than studies using VAS, NRS, VRS, or McGill Pain Questionnaire ($g = 0.38$, $k = 27$, $n = 8764$; Q (1) = 3.89; $P = 0.04$, with both sets of studies being characterized by significant heterogeneity (Q (29) = 55.5; $P = 0.002$; $I^2 = 47.7$ and Q (26) = 56.9; $P < 0.0001$; $I^2 = 54.4$, respectively).

Site of pain stimulation was a marginally significant moderator of the association between BP and pain perception (Q (3) = 8.20; $P = 0.06$), with studies targeting the sural nerve yielding a small effect size and no heterogeneity ($g = 0.30$, $k = 6$, $n = 574$; Q (4) = 4.99; $P = 0.42$; $I^2 = 0$), studies targeting the hand/foot having a small-to-medium effect size and moderate heterogeneity ($g = 0.404$, $k = 21$, $n = 8155$; Q (20) = 37.96; $P = 0.01$; $I^2 = 47.3$), and studies targeting the arm/leg or the mouth/teeth showing medium effect size and significant heterogeneity ($g = 0.56$, $k = 22$, $n = 1117$; Q (21) = 53.4; $P < 0.0001$; $I^2 = 60.7$ and $g = 0.53$, $k = 9$, $n = 1165$; Q (8) = 19.9; $P = 0.01$; $I^2 = 59.8$).

Lastly, mean effect size was lower in studies that did not control for potential confounders ($g = 0.65$, $k = 21$, $n = 8209$) compared with those that did control ($g = 0.42$, $k = 38$, $n = 2862$); Q (1) = 4.40; $P = 0.03$ with only the first set of studies being characterized by significant heterogeneity; Q (20) = 84.8; $P < 0.0001$; $I^2 = 76.4$.

Age, BP device, and pain type did not moderate the association between BP and pain perception. Meta-

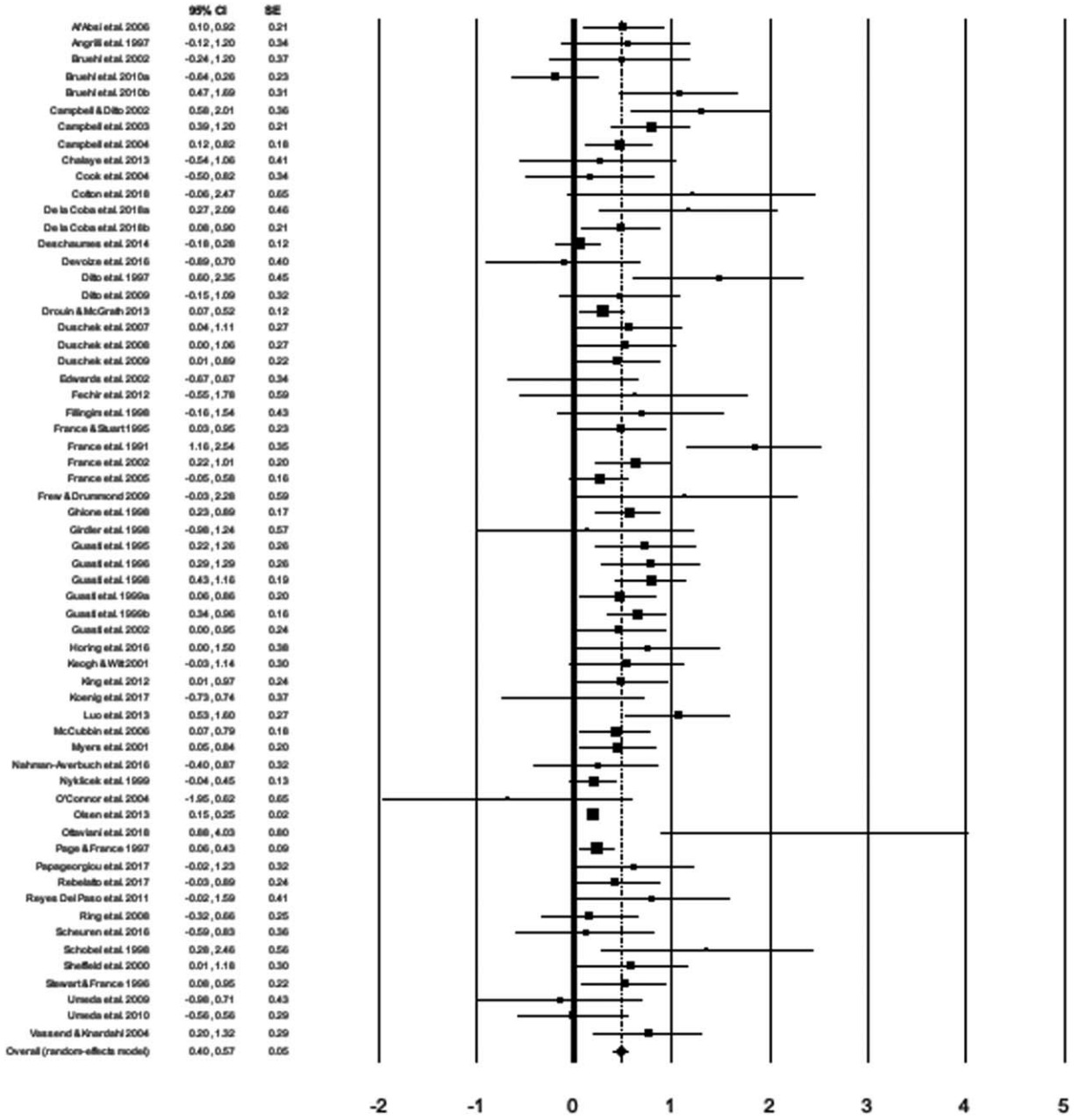

FIGURE 3 Forest plot for meta-analysis on the association between blood pressure and quantifiable perceptual measures of pain.

regression analysis did not show any significant role of painful stimulus duration as moderator.

Overall, results did not change when extreme outliers [39,51,106] were excluded from the analysis, with the following exceptions: after the exclusion, type of BP assessment became significant as a moderator of the association between BP and pain perception, $Q\ (2) = 7.16$; $P = 0.03$, whereas adjustment for potential confounders was no longer a significant moderator of such association, $Q\ (1) = 2.84$; $P = 0.092$.

DISCUSSION

Over the past decades, many experimental studies, conducted both in animals and humans, have investigated the phenomenon of BP-related hypoalgesia. Most of these studies have shown a positive association, but some failed to replicate the effect. This is the first systematic meta-analysis performed on the topic, which also aimed at considering the distinctive effects of high BP on nociceptive and perceptual components of the pain response. Results confirmed the existence of a significant association between BP and pain perception in the expected direction, that is, diminished pain perception in the presence of elevated BP. When the full set of studies was examined, the size of the effect was small for nociceptive response and became medium after exclusion of potential outliers. In the case of quantifiable perceptual measures of pain, the size of the effect was medium.

Despite measuring an inherently different phenomenon, both meta-analyses suggest a significant association between BP and pain responses. However, the meta-

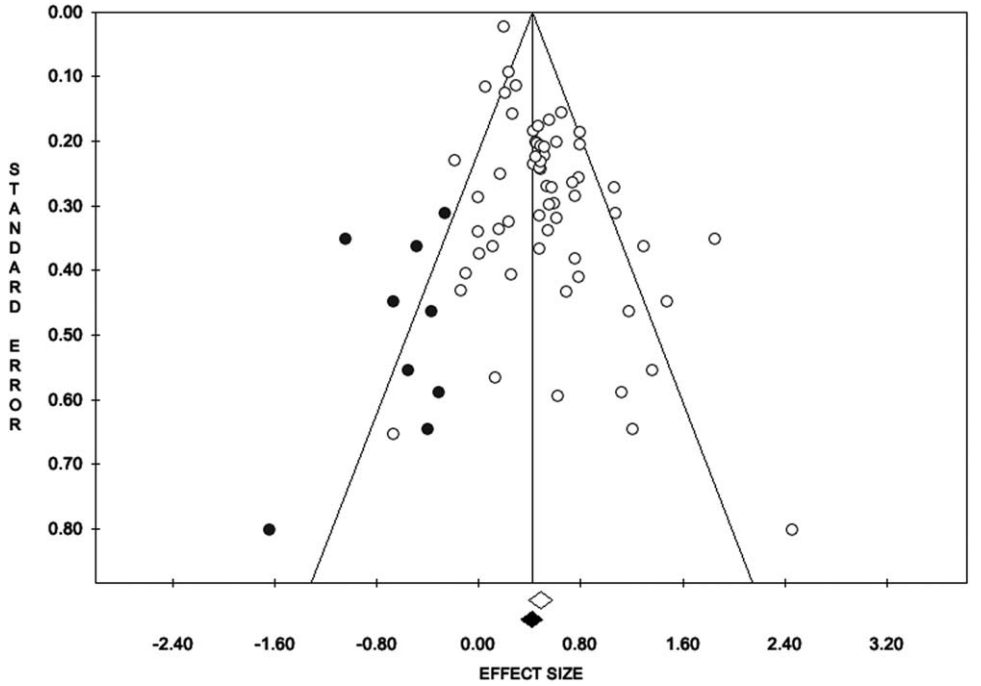

FIGURE 4 Funnel plot for meta-analysis on the association between blood pressure and quantifiable perceptual measures of pain.

analysis conducted on quantifiable perceptual measures of pain was characterized by significant heterogeneity and the presence of publication bias, pointing to the possibility of systematic errors.

By performing additional moderation analysis, we also tried to characterize the association between BP and pain responses by considering both the features of the sample and the methodology used to assess BP and pain. Unfortunately, studies examining nociception did not meet the requirements to be included in subgroup analyses, as they were quite limited ($k = 6$); instead, we were able to perform moderation analysis for studies examining quantifiable perceptual measures of pain. Results showed larger effects in studies that had a prevalence of female individuals in the sample; assessed pain threshold or tolerance (compared with those using VAS, NRS, VRS, or McGill Pain Questionnaire), assessed 24-h ambulatory BP (compared with resting or pain-related BP increases in the laboratory), provided painful stimuli over the arm/leg or the mouth/teeth (compared with the hand/foot or the sural nerve), and did not statistically adjust for potential confounders.

As expected in light of existing studies detecting sex differences in BP-related hypoalgesia [61], the inverse association between BP and perceptual measures of pain was larger in studies that had a prevalence of women in the sample. It has to be noted, however, that this is not a completely predictable result, as some studies arose doubts on the generalizability of BP-related hypoalgesia in women. For example, it has been observed that whereas in men at risk for hypertension the pain sensation following the cold pressor task decreased more rapidly compared with men without a family history of hypertension, in women at risk there was a tendency to report higher pain compared with women who did not carry a risk for hypertension [61].

The best way to assess pain perception is a matter of debate and goes beyond the scope of the present work. However, pain threshold and tolerance (with the majority assessing threshold) and measures of pain intensity appeared to be quantifiable ways to capture the perceptual components of BP-related hypoalgesia compared with self-report on the unpleasantness of pain. Our result is consistent with previous work where higher self-reported pain sensitivity was associated with higher anxiety but not with subjects' actual pain threshold or tolerance [117].

Studies using 24-h ambulatory BP assessment as well as studies assessing BP responses in the laboratory, yielded larger BP–pain perception associations compared with studies relying on resting BP. This result can be explained by the fact that whereas spontaneous or induced transient phasic BP increases are recognized to be linked with baroreceptor functioning, when tonic BP is examined, other key variables may play a role, for example, neurovascular alterations impairing nociceptive transmission in stable hypertension, particularly with comorbid diabetes [72].

Studies stimulating the sural nerve yielded the smaller effect sizes compared with studies stimulating other body regions, such as the arm/leg or the mouth/teeth. However, it has to be noted that only six studies stimulated the sural nerve, and this was the only set of studies that was not characterized by significant heterogeneity. For these reasons, this moderation analysis does not provide conclusive evidence against the use of sural nerve stimulation in future studies.

Lastly, BP-related hypoalgesia appears to be less pronounced when factors that influence both pain and BP are taken into account, such as nicotine, caffeine, analgesics, chocolate, alcohol, and strenuous physical exercise. However, although effect sizes were larger in studies that did not control for such covariates, a significant inverse relation

TABLE 2. Association between blood pressure and quantifiable perceptual measures of pain in different subgroups

	Random-effects model			Heterogeneity		Test of difference
	k	*N*	*g* (95% CI)	*Q*	I^2	*Q*
	58	10 969	0.48 (0.39–0.57)**	144.4**	60.5	
Percent of women						4.89*
<60%	28	9239	0.33 (0.24–43)**	49.5*	45.4	
≥60%	16	715	0.55 (0.38–0.73)**	17.5	14.4	
BP assessment						5.40§
24 h	12	1049	0.61 (0.47–0.75)**	12.6	12.7	
Rest	36	9580	0.41 (0.31–0.52)**	90.1**	61.2	
Task	11	442	0.58 (0.38–0.78)**	8.8	0	
BP device						0
Beat-to-beat	15	564	0.49 (0.27–0.70)**	20.6	31.9	
Sphygmomanometer	43	10 435	0.49 (0.39–0.59)**	121.7**	65.5	
Pain type						2.11
CPT	11	7455	0.37 (0.21–0.53)**	14.1	29.1	
Electrical[a]	11	782	0.49 (0.27–0.71)**	28.9**	65.4	
Ischemic	7	463	0.52 (0.12–0.93)*	24**	75	
Thermal	9	437	0.54 (0.34–0.74)**	5.6	0	
Other	12	1082	0.41 (0.17–0.65)**	30.5**	63.9	
Pain assessment						3.89*
VAS NRS, VRS, MPQ	27	8764	0.38 (0.26–0.51)**	56.9**	54.4	
Threshold/tolerance	31	2182	0.56 (0.44–0.68)**	55.6*	46	
Sample						2.58
At risk	13	971	0.62 (0.40–0.84)**	37.1**	67.7	
Hypertensive patients	13	8011	0.51 (0.34–0.68)**	43.2**	72.2	
Normotensives	33	2089	0.42 (0.29–0.54)**	52.2*	38.7	
Adjustment for covariates						4.40*
No	21	8209	0.65 (0.45–0.84)**	84.8**	76.4	
Yes	38	2862	0.42 (0.33–0.51)**	49.9	25.9	
Pain site						6.40§
Arm/leg	22	1117	0.56 (0.36–0.76)**	53.2.2**	60.5	
Hand/foot	21	8155	0.44 (0.30–0.58)**	37.9*	47.3	
Mouth/tooth	9	1165	0.53 (0.33–0.73)**	19.9*	59.8	
Sural nerve	6	574	0.30 (0.17–0.43)**	4.99	0	
Age						0.96
<21 years	14	1287	0.42 (0.28–0.56)**	20.5	36.7	
≥21 <40 years	29	1507	0.52 (0.36–0.68)**	54*	48.2	
≥40 years	16	8277	0.49 (0.33–0.64)**	49.2**	69.5	

Moderation analyses are presented for the full set of studies including potential outliers (see the Results section for moderation results that changed after outliers' exclusion). CI, confidence interval; CPT, Cold Pressor Task; ES, Hedges' *g* effect size; *k*, number of studies; MPQ, McGill Pain Questionnaire; *n*, number of participants; NRS, Numeric Rating Scale; *Q*, contrast between (sub)sets of studies; *Q*, I^2, heterogeneity statistics; VAS, Visual Analog Scale; VRS, Verbal Rating Scale.
[a]Results did not change when intracutaneous and extracutaneous were considered separately.
*$P < 0.05$.
**$P < 0.0001$.
§$P = 0.06$.

between BP and quantifiable perceptual measures of pain also emerged in the subsample of studies that did control for confounders, somewhat reassuring on the reliability of present results.

As to nonsignificant moderators, the inverse relation between BP and quantifiable perceptual measures of pain does not exclusively regard hypertensive individuals but is also present in normotensives [62]. This finding, already present in the literature on the topic, had never been previously quantified. In the present meta-analytic work, when clinical characteristics of the sample (normotensives, hypertensive individuals, at risk) were considered as a potential moderator, the analysis did not reveal significant differences. In our view, this provides further indirect support to the notion that BP-related hypoalgesia is rather associated with phasic BP changes than with stable BP levels. Unfortunately, the number of studies conducted on hypotensive patients was not sufficient to include this sub-sample in the moderation analysis. The few studies conducted on this population seem to suggest enhanced pain perception in hypotensive patients compared with normotensives [50,86].

Limitations and conclusion

Although results support the existence of BP-related hypoalgesia, several limitations need to be acknowledged. First, we did not include studies published in languages other than English and the so-called grey literature. If on one hand, the choice to include only articles that underwent peer review is a guarantee for higher quality studies, on the other hand, it is associated with an increased likelihood to introduce a confirmatory bias because of the tendency of authors not to report nonsignificant results and editors' tendency to reject articles with many nonsignificant findings. This has the ultimate consequence to artificially inflate the effect size and is particularly relevant for the present meta-analysis, given that publication bias possibly influenced the results.

Second, given the disproportionate number of studies conducted on nociceptive response versus pain perception, separate analyses were mandatory. Also, there was marked heterogeneity across studies investigating quantifiable perceptual measures of pain. This is not surprising if we consider that the examined studies were substantially different in terms of type of induced pain, stimulation site, the instrument and protocol that have been used for BP assessment, and the control of possible confounders (e.g. caffeine, alcohol, and nicotine consumption). To address this limitation, random-effects models were used in all the analyses. Nevertheless, present results claim for the need to establish guideline criteria that, if applied by future studies, could guarantee the replicability of results.

Present results also highlight the need for longitudinal investigations, as they are the only type of studies able to inform on the causal relation between BP and pain perception. Unfortunately, only two longitudinal studies on the topic have been conducted so far [12,83].

A further limitation concerns the plausible existence of that several other important moderators that have not been considered in the present meta-analysis. In this regard, it is important to underline that, because of the limited number of studies, it has not been possible to examine the effect of some plausibly critical moderators, such as the phase of the cardiac cycle in which the pain stimulation occurred [30,75,98], or whether pain stimulation occurred during simultaneous baroreceptor stimulation or inhibition [50,51], or the role of pharmacological manipulation of BP or pain perception by antihypertensive medications or opioid receptor antagonists [43,76,95]. It would be also interesting to explore the notion that BP is associated with impaired interoceptive awareness (i.e. the ability to read physiological signals coming from the body), which in turn leads to reduced pain perception. Indeed, on one hand, hypertensive individuals show poorer interoceptive awareness compared with normotensives and within the hypertensive group, those with low interoceptive awareness have higher BP [118]. On the other hand, individuals with low interoceptive awareness are characterized by higher pain threshold and tolerance compared with those with high interoceptive awareness [119].

Further, the exclusion of studies that reported on the association between BP and pain in samples characterized by diseases, such as diabetes [120], hypothyroidism [121], fibromyalgia [110], and coronary disease [9,122], although motivated by the aim of examining BP-related hypoalgesia in 'normal' conditions, could be viewed as a limitation to the generalizability and clinical relevance of the results. Such limitation concerns also the exclusion of psychiatric conditions, such as anxiety and mood disorders. In fact, dampened emotion has been reported with increasing BP [123], and pain is influenced by affect [124], therefore, exploring the role of affect in BP-related hypoalgesia is warranted. In spite of this, very few of the examined studies included dispositional characteristics or momentary affect ratings in their protocols [43,125].

Considering the higher cardiovascular risk that Afro-American individuals are subjected to, another limit is the lack of studies examining ethnic differences in the relation between BP and pain perception. A rare exception is represented by Reimann *et al.* [126], who found a higher BP reactivity and higher pain perception in response to the cold pressor task in hypertensive Afro-Americans compared with hypertensive European Americans, matched for age and sex. Unfortunately, being the only study examining these associations on the basis of ethnic differences, it had to be excluded from the present meta-analysis.

Lastly, there is a lack of neuroimaging studies conducted on the topic. Preclinical studies suggest the existence of a shared network for pain perception and baroreceptor functioning encompassing the brainstem [17,20] and the insular cortex [127]. In humans, such circuits mainly regard the insular cortex and the anterior cingulate cortex [33,106,128].

Future studies also need to have more age diversity in order to clarify if the association between BP and pain perception remains the same during childhood, adolescence, adulthood, and aging. Unfortunately, there is a paucity of studies conducted in children and adolescents [76,129] and on elderly samples [109]. Plausibly for ethical reasons, the majority of studies have been indeed conducted on young adults, thus limiting the generalizability of results to populations at different development stages. A valuable exception is represented by a study that investigated the association between maternal family history of hypertension and the pain evoked by a vitamin K injection (indirectly assessed by crying duration and facial expression) in 1-h-old newborns [66]. The authors found reduced pain responses in those whose mother had a family history of hypertension, suggesting a family incidence for BP-related hypoalgesia. Unfortunately, this study had to be excluded from the analysis, as it was the only one examining this specific population.

Limitations notwithstanding, the present meta-analysis confirmed the existence of a significant association between elevated BP and reduced pain, measured both at physiological (i.e. nociceptive) and perceptual levels. This result has important clinical implications considering that, although hypoalgesia may be viewed as a 'positive' side effect of high BP [102,130,131], it carries the risk to interfere with the early detection of the so-called silent (asymptomatic) myocardial ischemia and infarction [7], which are nearly twice as common in hypertensive patients than in normotensives [8]. Research that elucidates the causal mechanisms underlying this phenomenon and its role in the pathogenesis of hypertension is highly relevant for the prevention of cardiovascular morbidity, the most widespread and costly health problem facing our nation today.

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Conflicts of interest

There are no conflicts of interest.

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