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Itch sensitization? A systematic review of studies using quantitative sensory testing in patients with chronic itch

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Abstract

As well-established for patients with chronic pain, patients suffering from chronic itch also exhibit signs of peripheral and central sensitization. This has been linked to parallel neuroplastic sensitization processes. However, for chronic itch, sensitization has not yet been systematically assessed, studied, and hence validated. This review (Prospero CRD42016043002) summarizes and meta-analytically evaluates whether sensory aberrations including sensitization for itch occur in chronic itch.

Databases PubMed, Embase, and Cochrane Library were searched for studies investigating somatosensory sensitivity assessment by quantitative sensory testing stimuli, including experimental cutaneous chemical pruritic provocations, in patients with chronic itch from skin-/neurological conditions and compared with healthy controls. Outcomes were extracted for lesional

and non-lesional skin and risk of biases were assessed. Meta-analyses were performed when sufficient quantitative data were available.

Of 4,667 identified papers, 46 were included and 25 were eligible for meta-analyses. Patients (66% atopic dermatitis) were found more sensitive than the controls to histamine-evoked itch in lesional skin (SMD: 0.66 [CI: 0.16,1.15]), but not non-lesionally (SMD: -0.26 [CI: -0.58;0.06]). Cowhage did not evoke more itch in non-lesional skin of patients as compared to the controls (SMD: 0.38 [CI: -0.04,0.81]). For numerous other chemical provocations as well as for mechanical, thermal, and electrical stimulation paradigms, results were ambiguous or based on few studies.

Patients with chronic itch are only robustly sensitized to various chemical pruritic stimuli when applied lesionally. More studies on somatosensory aberrations in chronic itch conditions other than atopic dermatitis are needed to establish whether sensitization is robustly present across chronic itch conditions.

Key words: Pruritus; hyperknesis; alloknesis; pain; central sensitization; peripheral sensitization; neuroplasticity; quantitative sensory testing

1. Introduction

Itch is an unpleasant sensation, distinct from pain, characterized by evoking a desire to scratch the affected area. Most individuals experience occasional acute episodic itch, which usually resolves spontaneously within hours or days.[27,82,105] However, chronic itch (defined as lasting more than 6 weeks[108]) is also associated with cutaneous pain and dysesthesias, and profoundly impacts quality of life e.g., by interfering with sleep, attention, and affective functions.[51,82] Chronic itch is the primary sensory symptom in a wide range of skin, neuropathic , systemic and drug-induced conditions.[108,125] With a point prevalence of chronic itch estimated between ≈5-15%, and largely suboptimal treatment options, chronic itch represents a significant socioeconomic burden.[82]

Notably, the pathomechanisms driving chronic itch in prevalent skin conditions, such as atopic dermatitis, and itch of neurological origin, remain largely unknown. Neuronal sensitization occurring both in the periphery and in the central nervous system has been suggested to play a role as has been established for pain.[14,15,26,67,114]

While pain sensitization has been extensively studied in animals, human surrogate models and patients,[4,99] sensitization for itch has only been sparsely investigated. This is somewhat surprising given that the first attempts to study histamine skin responses were early in the 20th century and, while signs of itch sensitization in patients were studied for the first time some decennia thereafter.[21,22,30] Cormia *et al.* (1952 and 1953) meticulously investigated differences in "itch threshold" by serial diluted intradermal histamine injections in patients with chronic itch of various origins versus healthy controls.[21,22] Additionally, Shelley and Arthur (1955) used various modalities, including mucunain from cowhage spicules and trypsin, to probe itch sensitivity in various pruritic conditions and as well as during extensive array of experimental manipulations.[104] The recent discovery of: parallel afferent itch pathways[50,74] (the neuronal encoding remains enigmatic[52,63]), endogenous receptors of mucunain-induced itch,[87,88] spinal circuitry involved in itch transmission/modulation[2,16,90,110] as well as several novel molecular substrates involved in pruritic signaling[42,73,87,127] has spawned renewed interest in studying whether patients suffering from chronic itch become sensitized akin to what has been shown in chronic pain patients.[5,8,99,128]

1.1. Defining sensitization

Sensitization in the context of pain as well as itch refers to a state of increased responsiveness of nociceptive and pruriceptive neurons, respectively, to their normal or subthreshold afferent input.[34,98,112] In the field of pain research, the molecular mechanisms and behavioral as well as psychophysical manifestations of sensitization have been intensively studied.[64,98,128] Sensitization is usually classified as being either *peripheral* (affecting primary afferent nociceptors) or *central* (affecting nociceptors in the central nervous system), and often both may play a role in chronic itch and pain conditions. Particularly the denotation of central sensitization is associated with ongoing definitional contention,[20,55,98] in part because the underlying pathophysiology is currently not fully understood.[128] Central sensitization may also be aggravated by biopsychosocial factors, such as anxiety, increased attention, and negative expectations.[1,97,117] For the present paper, the term sensitization is used in the broadest sense. As a proxy of sensitization, an increased psychophysical sensitivity in patients compared to that of healthy controls in response to a controlled somatosensory stimulus (often designed to evoke itch) has often been studied. While an increased psychophysical sensitivity is plausibly a reflection of increased responsiveness of peripheral and/or central pruriceptive nociceptors, direct evidence hereof is seldomly present in human studies.[34,98] Nevertheless, it can often be inferred whether underlying processes are likely to be manifesting at a peripheral or central level (e.g. when stimulating on lesional or non-lesional skin, respectively). While much is known about mechanisms of pain sensitization, relatively little is known about the mechanisms causing sensitization specifically for itch. They appear to largely, if not entirely, overlap with the processes leading to sensitization for pain.[46,95] A thorough recapitulation of the mechanisms

behind neuronal sensitization is beyond the scope of the present study and we instead refer to previous excellent reviews.[8,98,102,128]

1.2. Probing sensitization for itch and pain

Not only are the underlying mechanisms of sensitization for itch and pain thought to be largely shared, but painful and pruritic stimuli also induce strikingly similar dysesthesic manifestations.[5,99,107] Within and immediately surrounding the area of painful stimuli, allodynia and hyperalgesia may develop.[69,98] Completely analogue hereto but occurring in the context of itch, are *alloknesis*, describing the state in which an otherwise non-pruritic stimulus, such as light tactile stimuli, provoke a sensation of itch (similar to *allodynia*),[12,106] and *hyperknesis*, describing an increased itch response elicited upon a normally pruritic stimulus, e.g. by means of mechanical probing or a chemical itch provocation (similar to *hyperalgesia*).[10,17,44] These dysesthesias, suggested constitute signs of sensitization, are not only experimental phenomena – they also occur in (and can be highly bothersome for) patients with acute and chronic itch or pain.[7,44,120] Quantitative sensory testing (QST) for experimental itch and pain sensitivity assessment is multimodal, i.e. include thermal, mechanical, electrical, and chemical stimuli. These can be applied to various tissues including muscles, viscera, and skin, with the latter naturally being the most commonly used substrate for QST in chronic itch patients given that itch exclusively arises from the skin and certain mucosal tissues.[9,108,116] Standardized stimuli can be delivered to assess detection thresholds, itch/pain thresholds and supra-threshold reactivity corresponding to different transduction receptors, primary afferent populations and CNS pathways.[29,31] With this approach, specific localized or systemic sensory aberrations (e.g., reduced thermal detection thresholds in small fiber neuropathy or increased itch responses to

mechanical stimuli), can be identified, linked to, and act as proxy measures of an ongoing pathophysiological process.[43,44,66]

While there is a substantial volume of literature on the study of QST methodology and sensory aberrations occurring in pain patients,[8,9,18,66] QST studies in the field of itch research are rather scarce and often more methodologically heterogeneous. Numerous recent studies have investigated somatosensory sensitivity in patients with chronic itch versus healthy controls. This first systematic review in the field comprehensively summarizes and meta-analytically evaluates if, and the degree to which, aberrations including sensitization for itch occur in response to somatosensory stimuli in conditions characterized by chronic itch resulting from skin or neurological conditions as opposed to healthy controls.

2. Methods

2.1. Protocol and registration

This review was performed in accordance with the PRISMA Statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses; see Suppl. Table 1 for the PRISMA Checklist, available at http://links.lww.com/PAIN/A858) and the recommendations of the Cochrane Collaboration (www.cochrane-handbook.org) where applicable.[40,65] The study protocol was prospectively published in the Prospero registry under the no.: CRD42016043002.

2.2. Information sources and searches

The electronic databases PubMed, Embase, and the Cochrane Library were searched from inception until 7 March 2018 by one reviewer using terms related to itch conditions (e.g., chronic

prurit*) and quantitative sensory testing (QST) stimuli (e.g., QST and mechanic*). It was chosen to explicitly search for all kinds of somatosensory stimuli, because most of the studies do not explicitly use the term "quantitative sensory testing" or a comparable term covering the field. No limits to the search terms were applied with regard to publication date, language, or article type. Within the search, all papers that were classified as animal studies without the classification of "human study" were excluded. The PubMed search strategy has been added as Suppl. Table 2 (available at http://links.lww.com/PAIN/A858). For the other databases, comparable terms, e.g., MeSH and EMTREE, were used.

2.3. Eligibility criteria

Studies were included when fulfilling the following criteria: experimental/observational study in which somatosensory sensitivity was quantified by means of QST in patients with a dermatological or neurological condition (classified in accordance with the International Forum for the Study on itch (IFSI) etiological subgrouping of chronic pruritus, category I and III[108]) and healthy controls (the inclusion of healthy controls is essential because cutaneous and sensory changes may occur in patients even in non-lesional skin). Studies were excluded when the majority of the patients had another primary condition than outlined above, such as pruritus associated with a systemic disorder, when lacking a control group, and when itch was not induced by somatosensory stimuli (e.g., by use of visual or auditory stimuli) or not quantified by common psychophysical techniques, such as thresholds or numerical ratings for itch.[103] Only full-text studies displaying previously unpublished data in English peer-reviewed journals, published after 1980 were included.

2.4. Study selection

The titles and abstracts obtained in the searches were screened by one reviewer according to the eligibility criteria. Of potentially eligible studies, including those for which there was any doubt about their eligibility based on the abstract, the full text articles were retrieved via university libraries (Aalborg and Leiden University) or by requesting the article from the study authors. The eligibility of all full-text articles was evaluated using a pre-piloted standardized sheet by two reviewers. A third reviewer was involved if there was doubt or disagreement about article eligibility. Studies that fulfilled the criteria for inclusion were included in the systematic review.

2.5. Data collection and extraction

Using pre-piloted forms, the following data were extracted from the included studies by one reviewer and checked by a second reviewer: population characteristics (e.g., diagnosis, sample sizes, demographics), details on the QST stimuli and their application sites (including application on lesional or non-lesional skin), and relevant data on the somatosensory outcome measures. For the latter, the direction of a potential difference along with the significance levels when comparing the patient and control group were collected. The following was considered: 1) for similar provocations, different modes of application, concentrations, or current intensities were pooled across studies; 2) if a study used multiple measurement sites, the results from the most commonly used location was taken (e.g., the forearm) 3) data obtained from lesional or non-lesional skin of patients with itch were preferably compared to those of corresponding areas in the healthy controls (data from lesional and non-lesional skin were never pooled); 4) if a study used multiple concentrations of a compound or multiple stimulus intensities (e.g., electrical current), the highest concentration/intensity of the stimulation was included; 5) if different

subgroups of patients were included (e.g. acutely exacerbated vs. latent AD) and the study authors made separate statistical comparisons, the comparison between healthy controls and the most severely affected subgroup was extracted; 6) outcomes related to the duration of the itch sensation were not included as barely any study recorded the time point of complete abolishment of the itch sensation; 7) data on wheal size were not included since wheal is an entirely non-neuronal response[13]; 8) for patients with sensitive skin symptomatic versus asymptomatic skin areas were referred to as lesional versus non-lesional, respectively. When data of one somatosensory outcome were available from at least five studies, mean and standard deviation (SD)/standard error of the mean (SEM) of the somatosensory outcome measures were extracted for the quantitative meta-analysis from text, tables, figures, or by contacting the study authors. Consensus about ambiguities between the first and second reviewer in relation to any variable within the forms was reached by discussion and potential involvement of a third reviewer. In the case data of one or more studies were missing (and could not be retrieved via contact with the study authors) while there were in total sufficient studies to perform a meta-analysis on the respective outcome, these studies were neither included in the meta-analysis nor in the semi-quantitative overview to avoid presenting the same outcome twice.

2.6. Risk of bias assessments

The risk of bias (RoB) assessment tool developed by Marcuzzi and colleagues[68] specifically for assessment of RoB in QST studies was adjusted. In the original tool, the word “pain” was substituted for “itch” and the criterion of ‘blinding of assessments’ was omitted as blinding with respect to skin conditions is unfeasible, particularly when testing on lesional skin. The adjusted tool took the following criteria into account: 1) clarity of sample description with regard to 1a)

addressing inclusion and exclusion criteria (e.g., cutoffs for participants' age, description of the diagnostic criteria), 1b) demographic characteristics (e.g., sample size, gender percentages, mean clinical itch duration and intensity), 1c) the recruitment procedure (e.g., how participants were recruited); 2) quality of somatosensory assessments with regard to 2a) whether somatosensory assessments were following a standardized or validated procedure, 2b) the comprehensiveness of somatosensory assessment description (e.g., whether the equipment, the number of assessments and the measurement sites had been described as well as reporting on whether stimuli were applied at lesional or non-lesional skin); 3) whether factors known to influence itch perception and assessment of neurogenic inflammation were evaluated and controlled for (e.g., medication intake, age, gender, room temperature, and humidity). Using this adjusted tool, the RoB for all included studies was scored independently by two reviewers. Discrepancies in scoring were identified and resolved through discussion, with potential involvement of a third reviewer. Each criterion was scored as satisfied ('low RoB') when the majority of the items within that criterion were fulfilled, not satisfied when the majority of the items within the criterion was not fulfilled ('high RoB') or partially satisfied when aforementioned information was unclearly presented ('unclear RoB'). Individual studies were given an overall score for RoB by summing the scores for the seven criteria. A score of 1, 0.5, and 0 was given for high, moderate ('unclear'), and low RoB, respectively. Studies with an overall score >3 were judged as *high*, between 2 and 3 as *moderate*, and <2 as *low* RoB. In order to assess the RoB across studies included in the quantitative meta-analyses, funnel plots were created.

2.7. Data synthesis and analyses

For outcomes described in at least five included studies with similar provocations, the standardized mean differences (SMDs) were calculated based on available means and SDs (with SEMs being transformed to SDs) of the patient and control condition for the quantitative meta-analysis. Sufficient data were available for the following stimulus modalities: 1) histamine-induced itch (pooled AUC/mean and peak; applied at non-lesional and lesional skin of patients in comparison to healthy controls), 2) non-histaminergic induced itch (pooled AUC/mean; on non-lesional skin in comparison to healthy controls), and 3) histamine-induced neurogenic flare reactions on non-lesional skin in comparison to healthy controls. For each meta-analysis, a study was only included once (see considerations in paragraph 2.5), except for when results were presented per patient group, in which case the data for each patient group were taken into account. Random effects models were used to statically pool the data and Forest plots were made. A priori planned secondary subset analyses for the different itch conditions were not feasible since the vast majority of studies involved patients with AD. For the meta-analytic outcomes an overall effect size was calculated across all included conditions. However, due to the distinct pathoetiologies involved in different chronic itch conditions such estimates should be interpreted with caution. Sensitivity analyses were planned by performing the same random-effects meta-analysis after excluding studies with an overall high RoB score. Heterogeneity of effects was assessed by I^2 statistics, with 25%, 50% and 75% indicating low, moderate, and high degrees of heterogeneity, respectively.[19] Visually, heterogeneity (e.g., due to reporting bias) was inspected using funnel plots when at least 10 studies were included for the respective quantitative outcome. For somatosensory outcomes described in less than five studies, data were aggregated to display whether the patients showed a significant ($p < 0.05$) increase, decrease, or was not

significantly different ($p > 0.05$) from the healthy control group for semi-quantitative analyses. Review Manager Version 5.3 (RevMan; Copenhagen: The Nordic Cochrane Centre, the Cochrane Collaboration, 2014) was used to conduct the statistical analyses and display the RoB assessments.

3. Results

3.1. Study characteristics

3.1.1. Study selection

From the search strategy, 4,667 articles were retrieved. After screening the titles and abstracts of 3,769 articles, 66 full text articles were screened, of which 20 were excluded (see flow diagram in Figure 1). The reasons for exclusion were that the study did not include either patients (n=6) or healthy controls (n=3), that there was no direct comparison between the patients and control (n=2), that there was no somatosensory provocation (n=3), that stimulation methodology differed across both groups (n=1), that itch was modulated, but a baseline rating was missing (n=1), or that itch was not assessed or not in a standard manner (n=4). Of the remaining 46 studies that were included in the review based on the inclusion criteria, 25 could be included in the quantitative meta-analysis.

3.1.2. Study characteristics

Of the included studies (see Table 1 for the study characteristics), the majority studied patients with AD (n=32), followed by 'mixed' patient populations with chronic itch due to skin conditions (n= 6), psoriasis (n= 2), prurigo nodularis (n=2), chronic post-burn itch, sensitive skin, primary localized cutaneous amyloidosis, and central centrifugal cicatricial alopecia (all

n=1). In total, 932 patients (n= 612 patients with AD) and 822 healthy controls had been included. Note that due to the overrepresentation of included studies conducted in patients with AD, it is important to keep in mind that many of derived results may predominantly apply to this specific chronic itch condition. Chemical stimuli had been applied in 38 studies, mechanical stimuli in 15 studies, thermal stimuli in 12 studies, and electrical stimuli in 11 studies (Table 1). Whereas in most studies patients were tested only on non-lesional skin (n=23), 9 studies tested patients on both lesional and non-lesional skin, 5 studies tested only on lesional skin, and for 4 studies this is unknown. Neurogenic inflammatory responses appear to have been systematically characterized across multiple studies in response to chemical provocations only.

3.1.3. Risk of bias assessment

Of the 46 included studies, 14 were judged as having overall low RoB (i.e. RoB score <2), 32 studies were judged as having overall moderate RoB (i.e. RoB score 2-3), and no studies were considered as having overall high RoB (i.e. RoB score >3). For this reason, sensitivity analyses were not conducted for the quantitative analyses.

Per criterion (see Figure 2 for an overview; and Suppl. Fig. 1 for the RoB scores per study, available at http://links.lww.com/PAIN/A858), particularly the recruitment procedure (criterion 1c) was not (n= 38 high RoB), or inadequately described (n=1 moderate RoB). Also, the in- and exclusion criteria (criterion 1a) were often not reported (n=17 high RoB) or poorly described (n=6 moderate RoB). The demographics and sample characteristics (criterion 1b) were generally well described (n=20 low RoB, n=3 moderate RoB), and were characterized as high RoB in three studies, for instance when both the gender distribution and the intensity and duration of patients'

clinical itch were not reported. All studies described the somatosensory assessment methodology (criterion 2b) adequately (n=44 low RoB and n=2 moderate RoB). Somatosensory assessments rarely followed a standardized or validated procedure (criterion 2a) for itch provocations and QST stimuli were rarely designed specifically to probe the pruriceptive system, because of the novelty of the field and the lack of a "gold standard" to probe itch sensitization. Therefore, this criterion was evaluated as 'low' RoB in only 3 studies and 'moderate' RoB for the remaining 43 studies. Half of the studies described and controlled for factors that may influence the somatosensory assessment/outcomes (criterion 3) and were judged 'low' RoB (n=23), whereas the other half was judged 'moderate' RoB.

Across the studies included in the quantitative meta-analyses, statistical heterogeneity was moderate for two outcomes (i.e. an I^2 statistic of 50% for non-histaminergic evoked mean itch on non-lesional skin and 66% for histamine evoked mean itch on lesional skin) and high for the other 4 outcomes (76% for histamine-evoked mean itch on non-lesional skin, 77% and 75% for histamine evoked peak itch on lesional and non lesional skin respectively, and 89% for histamine flare reactions on non-lesional skin). Inspection of the funnel plots that included at least 10 studies mainly indicates heterogeneity for the outcomes of histamine-evoked peak itch and histamine-induced flare both when comparing the non-lesional skin of patients with the controls. This is mainly due to two studies, which deviate from the symmetry in the direction of less sensitivity of the patients compared to the controls.[37,94] In relation to the overall publication diversity, a few research groups have published more than two papers eligible for inclusion in the quantitative analyses.

3.2 Chemical stimuli

The majority of the included studies applied chemical provocation to elicit both sensory responses, i.e. itch and/or pain, as well as neurogenic inflammatory responses. Most studies used well-known pruritogens or algogens applied either by intradermal injection, iontophoresis or skin prick/puncture. The most frequently studied substance is by far histamine followed by agonists of the PAR2/4 and/or the MRGPRX1/2[86,89] (i.e. cowhage and SLIKGV). No other chemical provocations have been performed in at least 5 studies on patient populations with chronic itch. Cutaneous chemical provocations using 14 distinct chemicals were identified in the literature.

3.2.1. Histamine-induced itch

Results from chronic itch patients suggest that histamine provocations do not evoke increased itch responses (AUC/mean) in non-lesional skin (Fig. 3) but rather a trend towards decreased itch sensitivity is evident (k = 20, SMD: -0.26 [CI: -0.58;0.06]). The outcome is characterized by substantial heterogeneity including a single outlying study in the AD subgroup.[37] For the outcome of peak itch intensity similar results were observed (k = 11, SMD: -0.29 [CI: -0.72;0.14]) substantiating the lack of robust sensitivity alterations for histamine in non-lesional skin (Suppl. Fig. 2, available at http://links.lww.com/PAIN/A858). Oppositely, histamine evokes significantly more itch in lesional skin of chronic itch patients compared to healthy controls (Fig. 4), indicating intra-lesional sensitization to histamine. This effect is driven solely by studies on AD (k = 5, SMD: 0.92 [CI: 0.32;1.53]) and no increased sensitivity is apparent for PSO or CCCA. This observation is also consistent with data extracted for the outcome peak itch where increased responses to histamine were observed in lesional skin only in the AD patients (k = 3,

SMD: 1.07 [CI: 0.56;1.57]), and not overall (k = 5, SMD: 0.58 [CI: -0.10;1.25]), see Suppl. Fig. 3 (available at http://links.lww.com/PAIN/A858).

3.2.2. Non-histaminergic itch

For non-histaminergic itch stimuli, induced by cowhage and SLIGKV, only the mean itch outcome was available in the minimally required 5 studies and only for non-lesional skin. Only a single study performed intra-lesional cowhage provocations in AD,[6] and one other study injected SLIGKV; both in AD.[109] Both studies documented significantly increased itch responses in the AD patients. Administration of cowhage in non-lesional skin of chronic itch patients did not evoke significantly more itch than in healthy controls (Fig. 5), although a trend towards increased itch in patients was evident (k = 6, SMD: 0.38 [CI: -0.04, 0.81]). These results were obtained across several different chronic itch conditions. Notably, results of 5 out of 6 studies were well-aligned, showing trending or significant increases in cowhage-induced itch sensitivity in patients, while only Nattkemper *et al.* (2015) found insignificantly reduced responses to cowhage.[75]

3.2.3. Miscellaneous chemical provocations

In the 38 out of 46 studies with chemical provocations, 14 different algogens and pruritogens have been tested in chronic itch patients versus matched healthy controls (Table 1 and 2). Highly varied responses were observed across studies. Several of the chemical provocations were found to induce significantly more itch in patients in single studies and delivered opposite results in others. Many of the applied provocations, which are consistently found to induce similar itch intensities, particularly in non-lesional skin of chronic itch patients versus healthy controls, are

partially or completely histamine-dependent, e.g. compound 44/80 or codeine. Consequently, no sensory sensitization to a particular chemical provocation, aside from histamine, is evident in patients suffering from chronic itch. However, these findings remain to be reproduced. In three studies, a remarkable shift in perception of the sensation quality towards stronger itch and less pain was observed in chronic itch patients when subjected to an intra-lesional cutaneous provocation with an algogen. This phenomenon, tentatively termed '*algoknesis'* (i.e. itch in response to a stimulus which is normally perceived as painful), has been observed in patients with AD, e.g. in response to an acidic provocation,[44] mustard oil,[35] and bradykinin,[43] all of which are normally considered prototypical algogens, which predominantly or exclusively evoke pain in healthy skin.

3.2.4 Neurogenic inflammatory responses

In the present review, only the neurogenic inflammatory responses to histamine were eligible for meta-analysis (Fig. 6). However, numerous chemical provocations capable of evoking neurogenic inflammation have been tested in chronic itch patients (see Table 2). For neurogenic inflammatory responses to histamine, very consistent results are evident. In 11 out of 12 studies in non-lesional skin of AD patients, histamine induced significantly smaller neurogenic flare reactions than in the healthy controls (k = 12, SMD: -1.42 [CI: -1.99, -0.84]). A similarly reduced neurovascular reactivity has been observed in urticaria in a single study,[37] but not in PSO (two studies[3,37]) nor in in patients with sensitive skin (one study[24]). Reduced neurovascular reactivity to chemical provocations in AD is not only observed in response to histamine but has also been reported in response to acetylcholine[91], the mast-cell degranulator compound 48/80,[94,120] IL-2,[122] substance P,[35] and VIP[91] (Table 2). Despite the numerous studies on chemically evoked neurogenic inflammation in patients with chronic itch, increased responses

are never observed irrespective of the applied chemical. Only a few studies have attempted to address alterations in neurogenic inflammatory reactivity intra-lesionally.[6,43] Reliable measurements of neurogenic inflammatory responses in lesional skin is usually unfeasible as most of the studied chronic itch conditions are associated with substantial erythema prior to any chemical provocations.[6] Modern microvascular blood flow imaging techniques enables the assessment of neurogenic flare intensity as opposed to simply the size of the reaction. Such assessments have been performed in a handful of studies with results generally showing no differences or a reduced reaction intensity not only to histamine[6] but also to, e.g. cowhage[32], IL-31[33], mustard oil,[35] substance P,[35] and prostaglandin E2.[76]

3.3. Mechanical stimuli

A diverse range of mechanical probing techniques have been used in patients with chronic itch conditions (Table 3). Most tools, e.g. von Frey or pin prick stimulators, specifically test the sensitivity of the superficial skin fibers, while a more recent study included assessment of the pain sensitivity of deeper tissues. The diversity of assessment approaches is paralleled by diverse results. As for other outcomes the majority of studies are conducted in patients with AD. A couple of notable findings for lesional and non-lesional skin are reproduced in multiple studies; 1) mechanical detection thresholds are increased,[6,101] 2) alloknesis to brush strokes or wool fibers is present[43,120] and 3) hyperknesis to punctate stimuli, e.g., von Frey filaments and pin pricks, is evident.[6,44,60,101] Mechanical and pressure pain thresholds in lesional and non-lesional skin of patients do generally not differ from the healthy controls. Some studies report pinprick hyperalgesia in lesional and non-lesional skin of patients with chronic itch,[6,101] but others found no difference between patients and healthy controls.[44,84]

As opposed to the *in situ* assessment of mechanical sensory sensitivity described above, numerous studies have assessed mechanically evoked itch sensitivity following various types of precipitating itch stimulations. The two techniques commonly used for quantifying the increases in mechanical itch sensitivity perifocally associated with itch provocations involve either quantifying the total extent of the area (e.g. of alloknesis or hyperknesis) or the intensity of these itch dysesthesias.[4] Both techniques have almost exclusively been performed in non-lesional areas, although a few exceptions exist.[6,44] Generally, studies quantifying the extent of the dysesthesic *areas* do not find significant differences between healthy controls and chronic itch patients[45,124] (two studies even found reduced mechanical itch dysesthesias in patients following a histamine provocation[38,126]). Oppositely, when quantifying the *intensity* of the chemically induced itch dysesthesias, more severe dysesthesias appear to develop in chronic itch patients as compared to healthy controls.[6] The literature on occurrence and mechanisms of mechanical itch dysesthesias is extensively summarized elsewhere[4].

3.4. Thermal stimuli

Six studies have performed regular quantitative sensory testing of thermal detection and pain thresholds in lesional and/or non-lesional skin of chronic itch patients (Table 4). For warmth and cold detection thresholds, 4 out of 6 studies found no significant differences,[6,84,96,101] while Yudina et al. (2011) reported significantly increased detection thresholds of approximately 1°C for both warmth and cold detection in AD[130] and Tey et al. (2016) reported increased warmth detection thresholds of 2.7°C in PLCA.[113] Similarly, 3 out of 4 studies investigating cold pain thresholds found no significant changes,[6,84,101] while Yudina et al. (2011) observed decreased

cold pain threshold (i.e. reduced sensitivity for cold).[130] All studies uniformly report that contact heat pain thresholds are unchanged when comparing lesional and/or non-lesional skin of patients with chronic itch to healthy controls, while a single study assessing laser-evoked heat pain in prurigo nodularis found decreased pain threshold to this type of stimulation in both lesional and non-lesional skin.[28] Two studies have specifically assessed warmth- and heat-evoked itch also in AD. Both Ikoma et al. (2004) and Schneider et al. (2018) report significant warmth- and heat-evoked itch in lesional AD skin, even though such stimuli are exclusively perceived as innocuously warm or as burning pain in healthy subjects. Warmth- and heat-evoked itch phenomenologically correspond to warmth alloknesis and heat *algoknesis*, respectively.[4] In non-lesional AD skin, no significant differences were found in heat-evoked itch.[44] Patients with chronic itch subjected to suprathreshold cold pain stimulation by the use of the cold pressor task exhibited either a decreased tolerance,[62] or no difference with the controls.[61]

3.5. Electrical stimuli

Eleven studies applied electrical stimulation for sensory testing purposes in chronic itch patients (Table 5). Widely different stimulation methods, e.g., different electrodes, as well as stimulation paradigms, e.g., to measure itch sensitivity, endogenous itch modulation, or current perception thresholds, have been used. . The results of four studies assessing current perception thresholds are unaligned and show both reduced,[56] unchanged,[72,79] and increased[53] perception thresholds in the patients. Only two of these studies specifically investigated lesional skin areas, which found reduced[56] or unchanged [72] current perception thresholds. Electrical tolerance thresholds were mostly not significantly different [60–62]; only one small study indicated enhanced sensitivity in the patients [60]. Using an electrical stimulation paradigm designed to evoke itch, Ikoma et al. (2004)

found increased itch sensitivity in lesional skin of AD patients but no difference in itch sensitivity in PSO, nor differences in pain sensitivity in these patient groups. In non-lesional skin of AD patients, with the exception of one study showing increased sensitivity in the patients,[79] no changes in electrically evoked itch sensitivity were observed in two studies using similar methodology,[44,45], and another study.[60] Patients with PSO responded less sensitive to non-lesional electrical itch induction,[61] and patients with chronic post-burn itch (CPBP) did not differ from their controls.[62] Pain induced by the electrical inductions was generally not different between the patients (AD, PSO, and CPBP) and controls, but Yudina et al. (2011) found decreased pain thresholds in patients with AD.[130] Of the two studies using electrical stimulation in a paradigm to assess conditioned itch modulation, reduced modulatory efficacy was observed in PSO patients,[61] but not in patients with chronic post-burn itch (CPBP).[62]

4. Discussion

The main findings of the present systematic review and meta-analysis support the notion that patients with chronic itch display alterations in somatosensory sensitivity to a wide range of stimulations in lesional skin, while findings from non-lesional skin are less clear. Studies have predominantly been conducted in patients with AD; the only itch diagnosis for which aggregated meta-analytic evidence was present. Next, studies are characterized by substantial heterogeneity in terms of recruitment criteria, methodology, outcome reporting, and study design.

Specifically, in lesional skin areas, increased itch responses are observed to chemical pruritogens (predominantly histamine, but also cowhage), algogens (e.g., bradykinin), and to mechanical as well as thermal stimuli. The observed sensory alterations predominantly take the form of

increased itch responsivity as opposed to altered detection and pain thresholds. However, meta-analytic evidence is only conclusive for increased lesional histaminergic itch sensitivity in AD. This is mainly due to a low number of studies for other stimulation modalities and populations other than AD. In non-lesional skin of chronic itch patients, several studies indicate that histaminergic sensitivity is unaltered or decreased. Certain non-histaminergic provocations, chiefly cowhage, are found to evoke increased itch in non-lesional skin in some,[6,32] but not all studies.[71,75] Likewise, several studies suggest generalized punctate hyperknesis in non-lesional skin,[60] but this observation is not uniform across studies.[44] Hence, altered somatosensory processing appears to occur in lesional skin of patients with AD suffering from chronic itch, while it remains unclear if and in what way sensory sensitivity is robustly changed in non-lesional skin, in patient groups other than AD, and whether such potential changes correspond to the generalized increased pain sensitivity often reported in chronic pain patients.[8,128]

4.1 Heterogeneity of studies

Surprisingly, little heterogeneity is present in terms the studied conditions. AD is by far the most thoroughly investigated diagnosis with 32 of 46 studies exclusively including AD patients. Other major itchy dermatoses such as PSO and PN have only been investigated with sensory testing in 2 studies each, and patients with urticaria and sensitive skin have only been included in a single study. It is rarely clear whether a convenience, consecutive, or systematic sample of patients is used (Fig. 2, see 'Recruitment procedure'). Studies also differ in terms of diagnostic criteria and the duration of itch at the time of patient enrolment as well as how chronic itch is defined is often not reported (Fig. 2, see 'Inclusion/exclusion criteria'). The latter is unsurprising given that a consensus definition of chronic itch was only proposed by the International Forum for the Study

of itch in 2007.[108] Studies also differ widely in terms of medication allowance, which ranges from complete termination, or partial termination (e.g. for antihistamine or topical corticoids) to no medication changes at all (see Table 1). Sensory testing in chronic itch patients is often heterogeneous in terms of methodology and rarely standardized; there is no gold standard for most stimuli used to test itch sensitization (Fig. 2, see 'Standardization of somatosensory assessment'). In addition, these methods have often been derived from the psychophysical pain research area.[4] As such, the methodology is frequently applied in way which is different from its original intention. For example, multiple studies have assessed heat pain thresholds in lesional skin of chronic itch patients.[6,28,101,130] These all fail to find significant changes relating to the pain threshold. However, studies where heat pain thresholds or suprathreshold stimulations are conducted and patients are specifically asked to rate the associated itch, uniformly show heat hyperknesis in patients with chronic itch when compared to healthy controls.[44,80,101] Nevertheless, in order to draw conclusions in terms of itch sensitization, most important is that stimuli were applied in a similar manner in both the patients and controls (e.g., at the same anatomical location), which seems the case for most studies (also scored under 'Method of somatosensory assessment', Fig. 2). Lastly, heterogeneity across studies is inherent to certain chemical pruritic models. For instance, the use of cowhage is associated with difficulties in controlling administration and potential batch-to-batch variation. Cowhage, nonetheless, remains the 'gold standard' for non-histaminergic itch.[5,50]

4.2 Confounding factors

A previously articulated problem with sensory testing and administration of chemical pruritogens in skin conditions relates to skin barrier alterations, which, unrelated to changes in neuronal

sensitivity, might alter sensory responsivity.[4,6] Decreased skin barrier integrity is well known both in lesional and non-lesional skin of patients with AD.[47,111,123] Responses to chemical provocations, particularly when delivered by iontophoresis, might be exaggerated in such areas. Similarly, skin micro-environment changes can interfere with normal local tissue clearance and might thus alter itch sensitivity to chemical provocations. In contrast, the perception of mechanical or heat stimulations might be reduced in lichenified (i.e. thickened) skin. These factors are rarely considered and may affect both lesional and non-lesional testing results. Moreover, most studies applied the stimuli on a standard anatomical location that is most frequently affected by the itch condition, e.g., the antecubital fossa in AD. Included studies labeled the findings at these locations as 'lesional', without taking into account any individual variations in the exact location of the lesion (e.g., lesionally versus peri-lesionally applied stimuli), the extent of the lesions, and the clinical morphology were not taken into account. Consequently, for this review, data were categorized as 'lesional' and 'non-lesional'. In addition, also individual psychosocial factors, such as anxiety, attention, expectations, and mood, might be associated with itch sensitivity and bias sensory testing results.[11,58,59,97,117]

4.3 Histaminergic or non-histaminergic itch sensitization?

Itch sensitivity to chemical provocations is by far the most thoroughly investigated aspect of the somatosensory status of chronic itch patients (Table 1).[41] Chemical itch provocations are often classified based on their antihistamine-recalcitrance as either histaminergic (e.g. histamine, compound 48/80 or substance P) or non-histaminergic (e.g. cowhage or SLIGKV), but numerous compounds fall somewhere in between (e.g. bradykinin and serotonin).[5,43]

Levels of itch evoked by histamine (the most frequently applied pruritogen, Table 1) are significantly higher in lesional skin of the patients, particularly AD, than in healthy subjects (Fig. 4), but no significant differences are evident for non-lesional skin (Fig. 3). The restriction to lesional areas indicates peripheral sensitization which could involve increased histamine-responsiveness of mechano-insensitive C-fibers in lesional, inflamed skin.[4,6,46] Sensitization of such fibers would also increase pruritic responses to certain peripheral inflammatory mediators, for instance bradykinin, which has indeed been observed.[43] Important drivers of skin inflammation in AD are type-2 cytokines such as IL-4 and IL-13.[123] While these cytokines have not yet been applied as human itch provocations, recent preclinical results show that they act directly on pruriceptive afferents to increase their responsiveness, for instance to histamine.[78] This provides a putative mechanism for the lesional histaminergic sensitization observed in chronic itch patients.[78]

Studies that have attempted to assess itch sensitization in response to purely non-histaminergic itch provocations applied cowhage or SLIGKV (Fig. 5).[109] There is some overlap in the receptors they target, e.g., PAR2/4 and/or certain Mas-related G-protein-coupled receptors .[86,89] In non-lesional AD skin, three of four studies found SMDs of 0.6 to 0.84 in favor of increased itch responses in the patients.[6,32,109] However, the fourth study found an insignificant decrease in cowhage-evoked itch in AD patients,[75] potentially as a consequence of unusually high itch ratings in the control group causing a ceiling effect. In lesional skin of AD patients, two studies found robustly increased itch sensitivity,[6,109], whereas a study in alopecia found no significant alterations in itch sensitivity (Table 2).[96]

Of the 14 additional pruritogenic or algogenic substances, including acetylcholine, bradykinin, citrate buffer (low pH-solution), compound 48/80, IL-31, VIP, substance P, serotonin, mustard oil, and prostaglandin E2, most have been applied only in a couple of studies and often only in non-lesional skin (Table 2). Of the above substances with pruritic properties, most are thought to evoke itch at least partially through histaminergic mechanisms but are less effective and less 'purely' itch-inducing as compared to histamine.[5,41,43] Overall, these studies have yielded negative results or have findings which have not been reproduced. Of note, several studies have shown increased itch responses within lesional skin to common algogens, e.g., bradykinin or citrate buffer, conceivably constituting a modality-switch type of sensitization.[43,44] Analogues observations have been made when applying normally painful heat stimuli (see *4.5*). The mechanism(s) behind this kind of perceptual abnormality is not yet established, but conceivably involves both central and peripheral processes. A recent review further discussing this sensory phenomenon is available.[4]

4.4 Reduced neurogenic inflammatory reactivity

A significantly decreased axon-reflex-flare size on non-lesional skin in response to histamine is clearly evident in AD (i.e. in 11 out of 12 studies), which is corroborated by a single study that included patients with urticaria (Fig. 6). Oppositely, no significant differences are present in PSO or SS. Other substances, such as acetylcholine, substance P, IL-2, VIP and compound 48/80, evoked similarly or less neurogenic flare in non-lesional skin in the patients (almost exclusively AD) when compared to the controls (Table 2). Provocations were mostly done in non-lesional skin due to difficulties associated with standardization, measurement methodology, and potential ceiling effects of neurogenic flare assessment in lesional skin (due to pre-existing skin

inflammation).[6,85] The mechanisms behind this reduced neurogenic inflammatory responsiveness to histamine are unknown but appear to corroborate the subset of studies which find reduced histaminergic itch sensitivity in non-lesional skin.[37,43,46] This may be related to altered biophysical skin properties[4] or medication interference (many antihistamines have long plasma half-lives displaying considerable inter-variability).[129] Other potential mechanisms include adaptive neuronal responses such as receptor downregulation within the microvascular or neuronal component or neuroanatomical changes in epidermal skin innervation,[6,37,46,83,120] but little evidence supports these hypotheses. Either way, the present meta-evidence suggests a robust decrease in axon-reflex-flare responsiveness in AD to histamine and various other chemical provocations but does *not* find significantly reduced accompanying itch. Since the axon-reflex-flare is a proxy measure of activity in primary afferent C-fibers this is a notable mismatch. This can principally be explained by: 1) reduced activity of the receptive primary pruriceptors, after which itch-signaling is amplified in the spinal processing,[46] or 2) decreased secretory capacity of the C-fibers or decreased responsiveness of the micro-vascular component, which is potentially independent of neuronal responses. The robust difference in neurogenic inflammatory capacity between patients with AD and healthy controls might be clinically applicable. A recent experimental study suggested the possibility of using skin responses to diagnose mild or unusual cases of AD.[32] It should be noted that there is little evidence on neurogenic inflammatory reactions in response to provocations specifically activating non-histaminergic pruriceptors.[32] This is likely in part because the predominant human model of non-histaminergic itch relies on cowhage spicules evoking no/or very limited cutaneous erythema in healthy subjects which can only be accurately measure by specialized flowmetric devices.

4.5 Itch sensitization to mechanical, thermal, and electrical stimuli

It was not possible to compile quantitative meta-analytic data on the sensitivity of chronic itch patients to mechanical, thermal, and electrical stimuli, due to the limited studies available that were characterized by substantial heterogeneity (See semi-quantitative overviews; Tables 3-5).

Despite of research showing lowered lesional intra-epidermal nerve-fiber density in chronic itch patients,[48,83], abnormalities in mechanical thresholds have only been sparsely investigated (Table 3). The presently conducted semi-quantitative comparisons build upon the theory outlined in our previous narrative review on mechanical itch dysesthesias.[4] Phenomenologically alloknesis and hyperknesis are analogous to the pain associated phenomena allodynia and hyperalgesia, which are often observed in pain conditions. However, recently the assumption that these sets of sensory phenomena also have analogous underlying mechanisms has been challenged. Two studies have found mechanical detection thresholds (a perceptual correlate of Aβ-fiber function) to be increased (i.e. reduced sensitivity) intra-lesionally in AD,[6,101] but other studies show these thresholds to be decreased or unchanged in lesional skin of PN.[28,84] These findings and their potential implications in the pathoetiology of different itch conditions remains to be further explored. Particularly, one has to consider the possibility that scabbed or lichenified skin might alter the force transduction properties of very low intensity punctate stimulation.[4] On the other hand, reduced Merkel cell density has been implicated in xerotic itch and in the development of mechanical alloknesis through a spinal disinhibition of itch transmission.[16,25] Mechanical hyperknesis to punctate stimuli is documented to occur within lesional skin, but it is unclear whether it exists robustly outside of lesions.[6,44,60,101] Several studies indicate non-lesional hyperknesis,[6,60,101] while others find no significant differences.[44] Notably, allo- and hyperknesis

to mechanical stimuli (and warmth) are commonly reported natural features of AD, even though the well-controlled evidence to support this is seemingly scarce.[6,23,77,120] Alloknesis to brush strokes appears to be restricted to lesional and perilesional skin and likely require more or less ongoing pruriceptive input to a spinal sensitization circuitry.[4,80] However, recent mechanistic evidence suggests that peripheral dysfunction of Aβ-fibers mediating touch might play a role by altering the spinal gating exerted by tactile signaling on pruriceptive transmission.[25] Note that mixed terminology pertaining to allo- and hyperknesis has previously been applied. In this review we apply the terms as defined in Andersen *et al.* 2018.[4]

Warmth alloknesis and heat *algoknesis*[4] appear to exist robustly in lesional AD skin,[44,101] but not in non-lesional skin (Table 4).[101] The detection of sensory aberrations in response to thermal stimulation highlights a problem associated with lesional testing where itch intensity is the outcome. Either a lesion, which prior to the sensory test is completely itch-free is required, or it will inherently be unclear whether the evoked itch is in fact thermally induced versus itch evoked by simply meddling with the lesional skin, e.g. when attaching the thermal probe. While thermal probing appears to cause itch in lesional skin of itch patients, most studies have found that thermal detection and pain thresholds *per se* are not significantly altered (Table 4).

No definite conclusions can be drawn from the data on electrical stimulation (Table 5). Regardless of whether the applied electrical stimulation paradigm is intended to evoke itch or simply measures the current perception threshold, findings display limited concordance between studies. This may be due to data incongruousness, the low number of studies, and

methodological heterogeneity, e.g., variation in geometry and application of the applied electrodes, the electrical stimulation paradigms applied as well as the body location tested.

4.6 Conclusion

This systematic review and meta-analysis support the notion that somatosensory sensitivity to a wide range of stimulations is present in the lesional skin (probable primary sensitization) of patients with chronic itch (primarily AD). This is in part analogous to the body of evidence suggesting sensitization in chronic pain.[8,128] Unlike for pain conditions, limited evidence favor robust non-lesional sensitization in chronic itch (at least with the current testing paradigms and patient populations). This indicates that sensitization of itch measured by psychophysical assessments might manifest in a less centralized manner, at least in patients with AD, as compared to pain. Moreover, sensory phenotypes with distinct sensitization and loss-of-function profiles have been uncovered in chronic pain disorders, but have not yet been thoroughly assessed in the context of itch.[6]

Evidence in favor of lesional sensitization to histamine provocations in AD is evident. In lesional skin, increased itch responses to other pruritogens, to some algogens, and to mechanical as well as thermal stimuli are semi-quantitatively apparent. Moreover, meta-analytic evidence conclusively shows reduced neurogenic inflammatory responses in patients with AD with data compiled from 12 studies. Based on 18 studies, chronic itch patients in general, and patients with AD in particular, do not have significantly altered sensitivity to histamine provocations in non-lesional skin. Results analogous to those for histamine were found for cowhage/SLIGKV although much fewer studies have been conducted using these non-histaminergic itch stimuli (6

studies in non-lesional skin and only 2 in lesional skin). The semi-quantitative analysis did not provide conclusive results as to the potential sensory aberration occurring in non-lesional skin, but a majority of studies reported punctate hyperknesis. The included studies are cross-sectional, are characterized by heterogeneity in several important domains, rarely investigate correlations between psychophysical findings and clinical characteristics, and have predominantly been conducted in patients with AD.

Measuring itch sensitization could have potential clinical utility, for instance for the purpose of enhancing individualized prognosis and treatment. However, a consolidation of the taxonomy used to describe itch sensitization signs as well as more standardized and uniform psychophysical testing approaches are needed. Moreover, longitudinal studies comparing itch sensitization outcomes with clinical characteristics as well as disease burden in larger and more diverse patient samples are required to adequately elucidate somatosensory changes and their implications in patients suffering from chronic itch.

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Table 1 Characteristics of included studies, including characteristics of the patient and healthy control sample and the somatosensory tests / provocations

Study data		Patient and healthy controls characteristics							Somatosensory tests / provocations				
First author	**Publication year**	**Patient population**	**Sample size patients**	**Sample size HC**	**Medication allowed**	**Mean age patients (y)**	**Mean age HC (y)**	**Sex**	**Lesional skin tested**	**Mechanical**	**Electrical**	**Chemical**	**Thermal**
Amatya et al.[3]	2010	PSO	15	15	0	41.2	39.5	m + f	yes + no	no	no	yes	no
Andersen et al.[6]	2017	AD	25	25	1	25.2	26.3	m + f	yes + no	yes	no	yes	yes
Bin Saif et al.[96]	2013	CCCA	16	15	2	44	39	f	yes + no	no	no	yes	yes
Falcone et al. [24]	2017	SS	9	9	0	21	21	m + f	Yes	no	no	yes	no
Gronroos et al.[28]	1997	PN	5	5	1	40-70 [a]	29-54 [a]	m + f	yes + no	yes	no	yes	yes
Hawro et al.[33]	2014	AD	10	10	1	30.7	31.2	m + f	no	no	no	yes	no
Hawro et al. [32]	2016	AD	22	18	0	30 [b]	29 [b]	m + f	no	no	no	yes	no

Heyer et al. [36]	1989	AD	27	20	1	23.0	28.8	m + f	no	no	no	yes	no
Heyer et al.[35]	1991	AD	20	20	1	26.4	31.8	m + f	no	no	no	yes	no
Heyer et al.[38]	1995	AD	19	20	1	30	26	m + f	no	yes	no	yes	yes
Heyer et al.[39]	1997	AD	15	15	1	24-38 [a]	17-36 [a]	m + f	no	no	no	yes	no
Heyer et al.[37]	1998	Mixed	64	16	0	26 (eczema-free AD); 27 (acute AD); 33 (PSO); 26 (URT)	28	m + f	no	no	no	yes	no
Hosogi et al.[43]	2006	AD	14	15	0	24.5	28.2	m + f	yes + no	yes	no	yes	no
Ikoma et al.[46]	2003	Mixed	18 (AD); 6 (PSO)	15	1	24.5 (AD); 27.5 (PSO)	28.7	m + f	yes + no	no	no	yes	no
Ikoma et	2004	Mixed	34	20	0	25.6 (AD)	29.5	m +	yes +	yes	yes	yes	yes

al.[44]						44.2 (PSO)		f	no				
Ikoma et al.[45]	2005	AD	10	20	0	24.7	33.1	m + f	no	no	yes	yes	no
Ishiuji et al.[48]	2008	AD	16	10	2	34.3	34.3	m + f	yes + no	yes	no	yes	yes
Ishiuji et al.[49]	2009	AD	8	7	2	33.1	34.6	m + f	yes	no	no	yes	no
Kobayashi et al.[53]	2003	AD	25	30	2	23	24	m + f	n.r.	yes	yes	yes	no
Koppert et al.[54]	1996	AD	16	16	2	Entire study population: 29.1		m + f	no	no	no	yes	no
Krzanowska et al.[56]	2015	Mixed	38	49	2	37.8 (AD); 44.6 (PSO)	26.3	m + f	yes + no	no	yes	no	no
Mochizuki et al.[70]	2015	Mixed	10	10	n.r.	37.2	31.4	m + f	no	no	no	yes	no
Mori et al.[72]	2010	AD	32 (extrinsic); 17 (intrinsic)	24	2	30.0 (extrinsic); 33.0 (intrinsic)	28.9	m + f	no	no	yes	no	no
Nattkemper et al.[75]	2015	AD	10	10	0	28	27	m + f	no	no	no	yes	no

Neisius et al.[76]	2002	AD	8	8	1	26	25	m + f	no	no	no	yes	no
Ozawa et al.[79]	2009	AD	24	24	1	22.0	23.5	m + f	no	no	yes	no	no
Papoiu et al.[81]	2011	AD	15	15	1	32.6	30.9	m + f	no	no	no	yes	no
Pereira et al.[84]	2017	PN	12	8	2	50	49	m + f	yes	yes	no	no	yes
Rasul et al.[85]	2013	AD	25	25	1	31.1	30.4	m + f	no	no	no	yes	no
Rukwied & Heyer [92]	1998	AD	24	14	0	26 (acute); 28 (non-acute)	25	m + f	no	no	no	yes	no
Rukwied et al.[91]	1999	AD	14	14	0	31	28	m + f	no	no	no	yes	no
Rukwied et al.[94]	2000	AD	9	9	1	28	27	m + f	no	no	no	yes	no
Schneider et al.[100]	2008	AD	8	6	1	31.4	29	m + f	no	no	no	yes	no
Schneider et al.[101]	2018	Mixed	33	30	0	51	48.6	m + f	yes	yes	no	no	yes
Steinhoff	2003	AD	38	33	1	25.4	26.5	m +	yes +	no	no	yes	no

et al.[109]								f	no				
Tey et al.[113]	2016	PLCA	20	20	2	61.0	59.5	m + f	yes	no	no	no	yes
Tran et al.[115]	2010	AD	21	24	0	31.8	28.9	m + f	n.r.	yes	yes	yes	no
van Laarhoven et al.[60]	2007	AD	15	19	2	33.2	43.3	f	primarily yes	yes	yes	no	no
van Laarhoven et al.[61]	2010	PSO	25	31	2	47	52	f	no	no	yes	yes	yes
van Laarhoven et al.[62]	2016	CPBP	15	15	2	41.6	41	m + f	no	yes	yes	yes	yes
Vogelsang et al.[118]	1995	AD	15	15	0	17-36 [a]	24-38 [a]	m + f	no	no	no	yes	no
Wahlgren & Ekblom[119]	1996	AD	20	20	0	25 [b]	28 [b]	m + f	n.r.	yes	no	yes	no
Wahlgren et al.[120]	1990	AD	32	32	1	24 [b]	22 [b]	m + f	no (yes for wool)	yes	no	yes	no

Wahlgren et al.[122]	1995	AD	8	8	1	24.0	19.5	m + f	no	no	no	yes	no
Weisshaar et al.[126]	1998	AD	12	12	1	27.5	29	m + f	no	yes	no	yes	no
Yudina et al.[130]	2011	AD	38 (electr) ; 22 (therm)	26 (electr) ; 15 (therm)	2	23.5	25	m + f	n.r.	no	yes	no	yes

Legend: [a]range; [b]median

Abbreviations: AD: Atopic Dermatitis; CPBP: chronic post-burn itch; CCCA: Central centrifugal cicatricial Alopecia; HC: healthy controls; PLCA: Primary localized cutaneous amyloidosis; PN: Purigo Nodularis; PSO: Psoriasis; SS: sensitive skin; URT: urticaria; Mixed: various skin diseases; electr: electrical; therm: thermal; f: female; m: male; n.r.: not reported; y: years

Table 2 Semi-quantitative analyses of somatosensory outcomes for chemical provocations which were applied in less than 5 studies (no quantitative meta-analysis was conducted for these outcomes). The table displays whether the patients were significantly ($p<0.05$) more sensitive, significantly ($p<0.05$) less sensitive or not significantly different from the healthy controls. See separate rows for results from lesional and non-lesional skin.

		Responses to chemical provocations		
Outcome	**Skin area**	**Patients significantly less sensitive**	**No significant difference**	**Patients significantly more sensitive**
Itch AUC/M	Lesional	Bradykinin in AD*[43]	5-HT in AD[43]; Citrate buffer in PSO[44]; Substance P in AD[43] and in PSO[3]	Citrate buffer in AD[44]; Cowhage in AD[6]; SLIGKV in AD[109]
	Non-lesional	5-HT in AD*[43]; VIP[91]	5-HT in AD[85]; Acetylcholine in AD[39,91,118] Bradykinin in AD[43]; Compound 48/80 in AD[94,120]; IL-2 in AD[122]; IL-31 in AD[33]; Prostaglandin E2 in AD[76], SLIGKV in AD[109]; Substance P in AD[35,43] and PSO[3]; VIP in AD[92]	Citrate buffer in AD[44]; Cowhage in AD [6,32]
Peak itch	Lesional		Substance P in PSO[3]; Cowhage in CCCA[96]	Cowhage in AD[6]
	Non-lesional		5-HT in AD[85]; Codeine in AD[109]; Compound 48/80 in AD[121]; Cowhage in AD[6,32] and CCCA[96]; IL-31 in AD[33]; Substance P in PSO[3]	
Itch peak latency	Lesional		Substance P in PSO[3]	Histamine in PSO[3]
	Non-lesional	Substance P[35]	5-HT in AD[85]; Histamine in AD[85] and PSO[3]; IL-31 in AD[33]; Substance P in PSO[3]	Acetylcholine in AD[39,118]
Pain AUC/M	Lesional		5-HT in AD[43]; Citrate buffer in AD and PSO[44]; Cowhage in AD[6]; Histamine in AD[43]; Substance P in AD[43]	Bradykinin in AD[43]
	Non-		5-HT in AD[43]; Acetylcholine in	

	lesional		AD[91]; Bradykinin in AD[43]; Cowhage in AD[6]; Histamine in AD[43]; Substance P in AD[43]; VIP in AD[91]	
Flare area	Lesional	Histamine in AD[43]	5-HT in AD[43]; Bradykinin in AD[43]; Histamine in AD[46,48]; Substance P in AD[43]	
	Non-lesional	5-HT in AD[85]; Acetylcholine in AD[91]; Compound 48/80 in AD[94,120]; IL-2 in AD[122]; Substance P in AD[35,43] VIP in AD[91,93]	5-HT in AD[43]; Acetylcholine in AD[39,118]; Bradykinin in AD[43]; IL-31 in AD[33]; mustard oil in AD[35]; Prostaglandin E2 in AD[76]; Substance P in PSO[3]	
Flare intensity	Lesional			
	Non-lesional	Substance P in AD[35]; Histamine in AD [6]	Cowhage in AD[32]; Histamine in AD[32,36]; IL-31 in AD[33]; Mustard oil in AD[35]; Prostaglandin E2 in AD[76]	Acetylcholine in AD[39,118]; VIP in AD[93]

Abbreviations: 5-HT: Serotonin; AD: Atopic Dermatitis; AUC: area under the curve; CPBP: chronic post-burn itch; IL: interleukin; M: mean; PLCA: Primary localized cutaneous amyloidosis; PSO: Psoriasis; mixed CP: various skin diseases; VIP: vasoactive intestinal polypeptide. Asterisk (*); not statistically compared in original paper, but assumed based on other reported significant differences.

Table 3 Semi-quantitative analyses of somatosensory outcomes for mechanical stimuli which were applied in less than 5 studies (no quantitative meta-analysis was conducted for these outcomes). The table displays whether the patients were significantly ($p<0.05$) more sensitive, significantly ($p<0.05$) less sensitive or not significantly different from the healthy controls. See separate rows for results from lesional and non-lesional skin.

		Responses to mechanical stimuli		
Outcome	**Skin area**	**Patients significantly less sensitive**	**No significant difference**	**Patients significantly more sensitive**
Mechanical detection threshold	Lesional	AD[6]; Mixed CP[101]	PN[84]	PN[28]
	Non-lesional		AD[6]	
Mechanical pain/pressure pain threshold	Lesional		MPT in AD[6] and in PN[84]; PPT in PN[84]; Von Frey in AD[60]	MPT in mixed CP[101]
	Non-lesional		MPT in AD[6]	Von Frey in AD[60]
Itch AUC/M/Peak (alloknesis/hyperknesis prior to itch provocation)	Lesional		Pin prick in PSO[44]	Pin prick in AD[44] and mixed[101] Von Frey in AD[6,60]; Wool in AD[120]
	Non-lesional		Von Frey in CPBP[57]	Pin prick in AD[44]; Von Frey in AD[6,60]; Wool in AD[120]
Mechanically evoked	Lesional		Pin prick in	Pin prick in AD[6] and

pain/mechanical pain sensitivity			AD and PSO[44] and in PN[84]; Von Frey in AD[60]	in mixed CP[101]
	Non-lesional		Pin prick in AD[44]; Von Frey in AD[60]	Pin prick in AD[6]
Development of mechanical alloknesis/hyperknesis after itch provocation	Lesional		After histamine in AD[6]	After cowhage in AD[6]
	Non-lesional	After histamine in AD[38,126]	After electrical itch in AD[45]; After histamine in AD[6]	After cowhage in AD[6]
Two-point discrimination	Lesional			
	Non-lesional		Discrimination of touch in AD[119]	Discrimination of itch in AD[119]

Abbreviations: AD: Atopic Dermatitis; AUC: area under the curve; CPBP: chronic post-burn itch; M: mean; MPT: mechanical pain threshold; PLCA: Primary localized cutaneous amyloidosis; PN: Purigo Nodularis; PSO: Psoriasis; mixed CP: various skin diseases; PPT: pressure pain threshold

Table 4 Semi-quantitative analyses of somatosensory outcomes for thermal stimuli which were applied in less than 5 studies (no quantitative meta-analysis was conducted for these outcomes). The table displays whether the patients were significantly ($p<0.05$) more sensitive, significantly ($p<0.05$) less sensitive or not significantly different from the healthy controls. See separate rows for results from lesional and non-lesional skin.

		Responses to thermal stimuli		
Outcome	**Skin area**	**Patients significantly less sensitive**	**No significant difference**	**Patients significantly more sensitive**
Warmth detection threshold	Lesional	PLCA[113]	AD[6]; CCCA[96]; PN[84]; Mixed[101]	
	Non-lesional	AD[130]	AD[6]; CCCA[96]	
Heat pain threshold	Lesional		AD[6]; CCCA[96]; PN[84]; PLCA[113]; Mixed[101]	
	Non-lesional		AD[6,130]; CCCA[96]	
Laser pain threshold	Lesional			PN[28]
	Non-lesional			PN[28]
Cold detection threshold	Lesional		AD[6]; PN[84]; Mixed[101]	
	Non-lesional	AD[130]	AD[6]	
Cold pain threshold	Lesional		AD[6]; PN[84]; Mixed[101]	
	Non-lesional	AD[130]	AD[6]	
Cold pain tolerance	Lesional			
	Non-lesional		PSO[61]	CPBP[62]
Itch induced by thermal stimuli	Lesional			Heat in AD[44]; warmth, cold, heat pain, cold pain in mixed CP[101]
	Non-lesional		Heat in AD[44]	
Pain	Lesional		Heat in AD[44]	

induced by thermal stimuli	Non-lesional		Heat in AD[44]	

Abbreviations: AD: Atopic Dermatitis; AUC: area under the curve; CPBP: chronic post-burn itch; M: mean; PLCA: Primary localized cutaneous amyloidosis; PN: Purigo Nodularis; PSO: Psoriasis; mixed: various skin diseases

Table 5 Semi-quantitative analyses of somatosensory outcomes for electrical stimulation which were applied in less than 5 studies (no quantitative meta-analysis was conducted for these outcomes). The table displays whether the patients were significantly ($p<0.05$) more sensitive, significantly ($p<0.05$) less sensitive or not significantly different from the healthy controls. See separate rows for results from lesional and non-lesional skin.

		Responses to electrical stimulation		
Outcome	**Skin area**	**Patients significantly less sensitive**	**No significant difference**	**Patients significantly more sensitive**
Current perception threshold	Lesional	AD[56]; PSO[56]	AD[72]	
	Non-lesional	AD[56]; PSO[56]	AD[72,79]	AD[53]
Conditioned itch modulation	Lesional			
	Non-lesional		CPBP[57]	PSO[61]
Electrical tolerance threshold	Lesional		AD[60]	
	Non-lesional		PSO[61]; CPBP[62]	AD[60]
Electrical pain threshold	Lesional			
	Non-lesional			AD[130]
Electrically induced itch	Lesional		AD[60]; PSO[44]	AD[44]
	Non-lesional	PSO[61]	AD[44,45,60]; CPBP[62]	AD[79]
Electrically induced pain	Lesional	AD[44]	AD[60]; PSO[44]	
	Non-lesional		AD[44,45,60]; PSO[44,61]; CPBP[62]	

Abbreviations: AD: Atopic Dermatitis; CPBP: chronic post-burn itch; PSO: Psoriasis

Figure legends

Fig. 1. Flow diagram of the selection process of studies obtained by the search of the databases PubMed, Embase, and the Cochrane Library, including reasons for exclusion.

Fig. 2.

Risk of bias summary: review authors' judgments about each risk of bias item presented as perce ntages across all studies included.

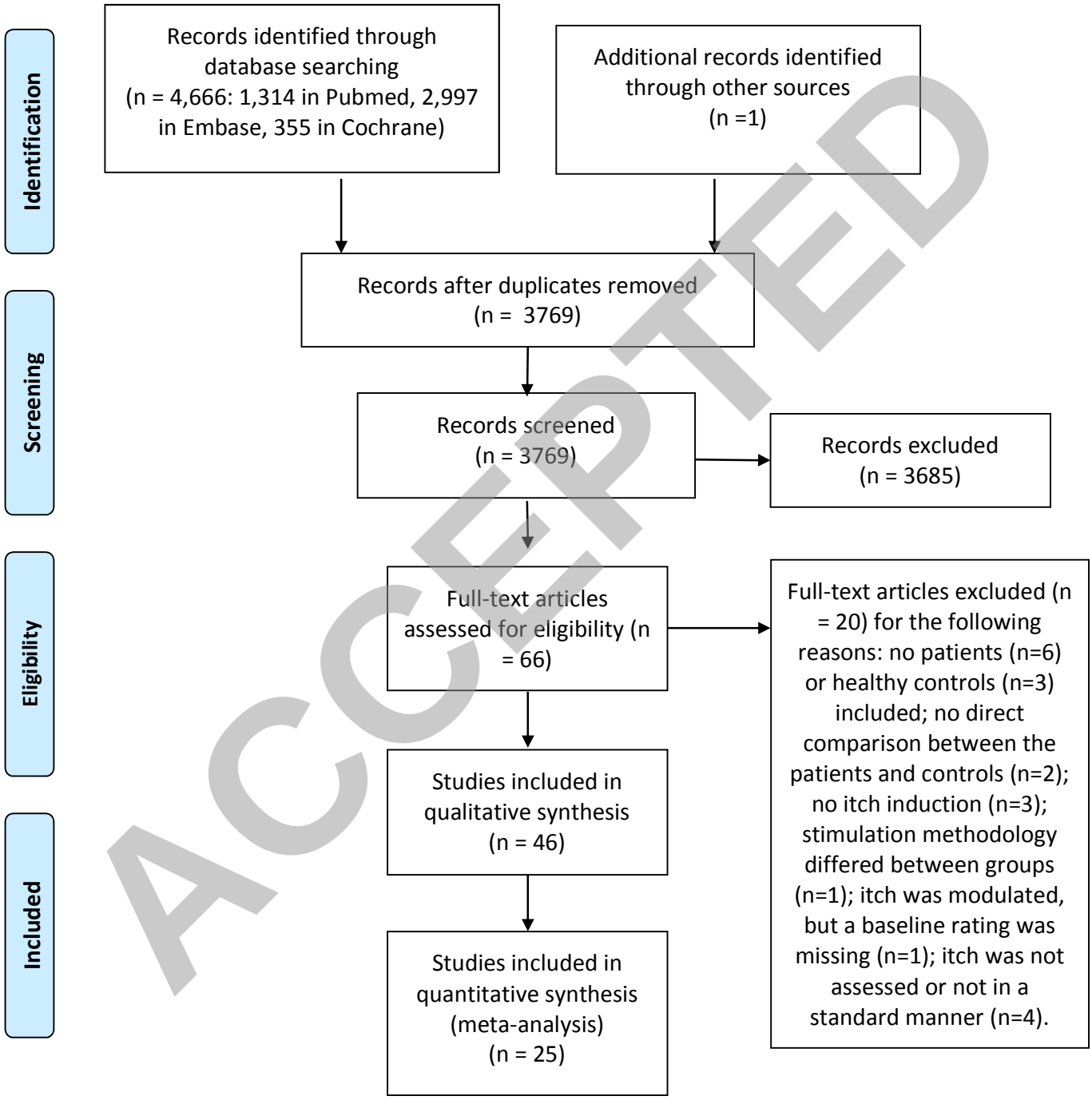
Fig. 3. Forest plot of the random effects meta-analysis for the outcome mean/area under the curve (AUC) itch during histamine provocations on non-lesional skin of patients and healthy controls. *Abbreviations: AD: Atopic Dermatitis; CCCA: Central centrifugal cicatricial Alopecia; CI = confidence interval; PSO: Psoriasis; Std. = standardized.*

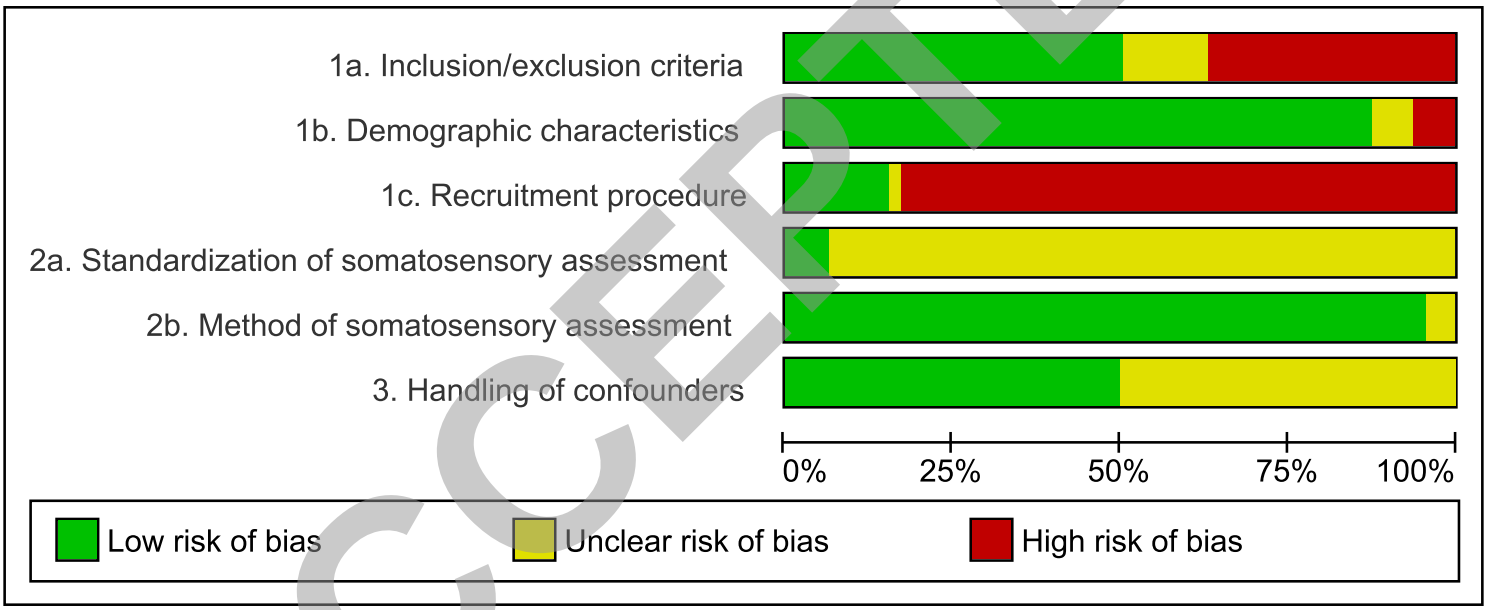
Fig. 4. Forest plot of the random effects meta-analysis for the outcome mean/area under the curve (AUC) itch during histamine provocations on lesional skin of patients and healthy controls. *Abbreviations: AD: Atopic Dermatitis; CCCA: Central centrifugal cicatricial Alopecia; CI = confidence interval; PSO: Psoriasis; Std. = standardized*

Fig. 5. Forest plot of the random effects meta-analysis for the outcome mean/area under the curve (AUC) itch during non-histaminergic itch provocations (cowhage and SLIGKV) on non-lesional skin of patients and healthy controls. *Abbreviations: AD: Atopic Dermatitis; CCCA: Central centrifugal cicatricial alopecia; CI = confidence interval; PSO: Psoriasis; Std. = standardized*

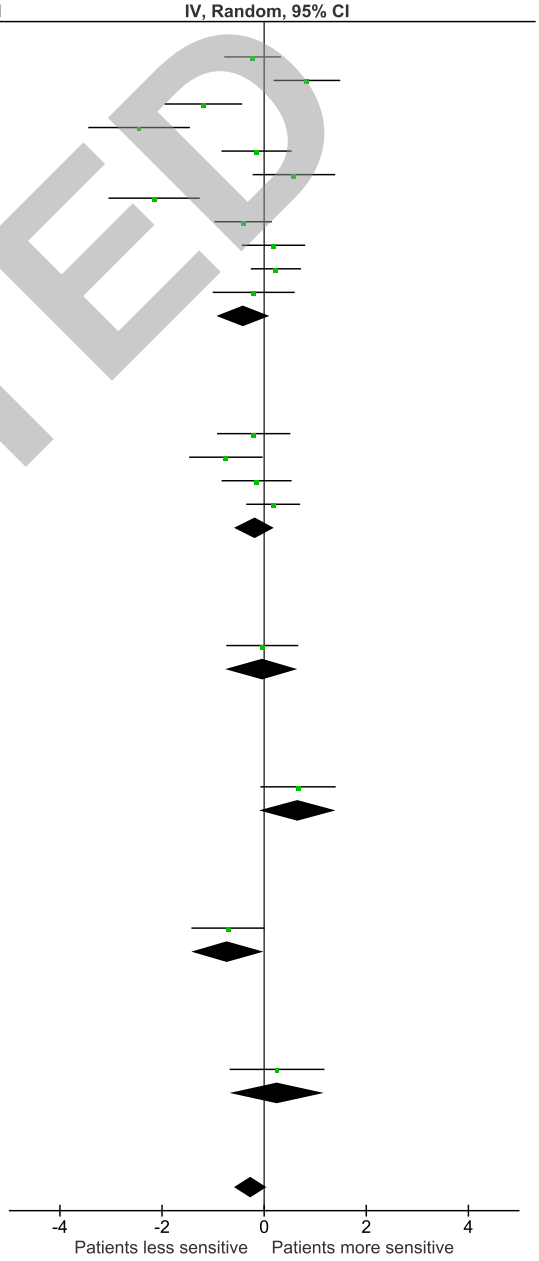
Fig. 6. Forest plot of the random effects meta-analysis for the outcome area of neurogenic inflammation (flare area) following histamine provocations in non-lesional skin of patients and healthy controls. *Abbreviations: AD: Atopic Dermatitis; CCCA: Central centrifugal cicatricial Alopecia; CI = confidence interval; PSO: Psoriasis; Std. = standardized*

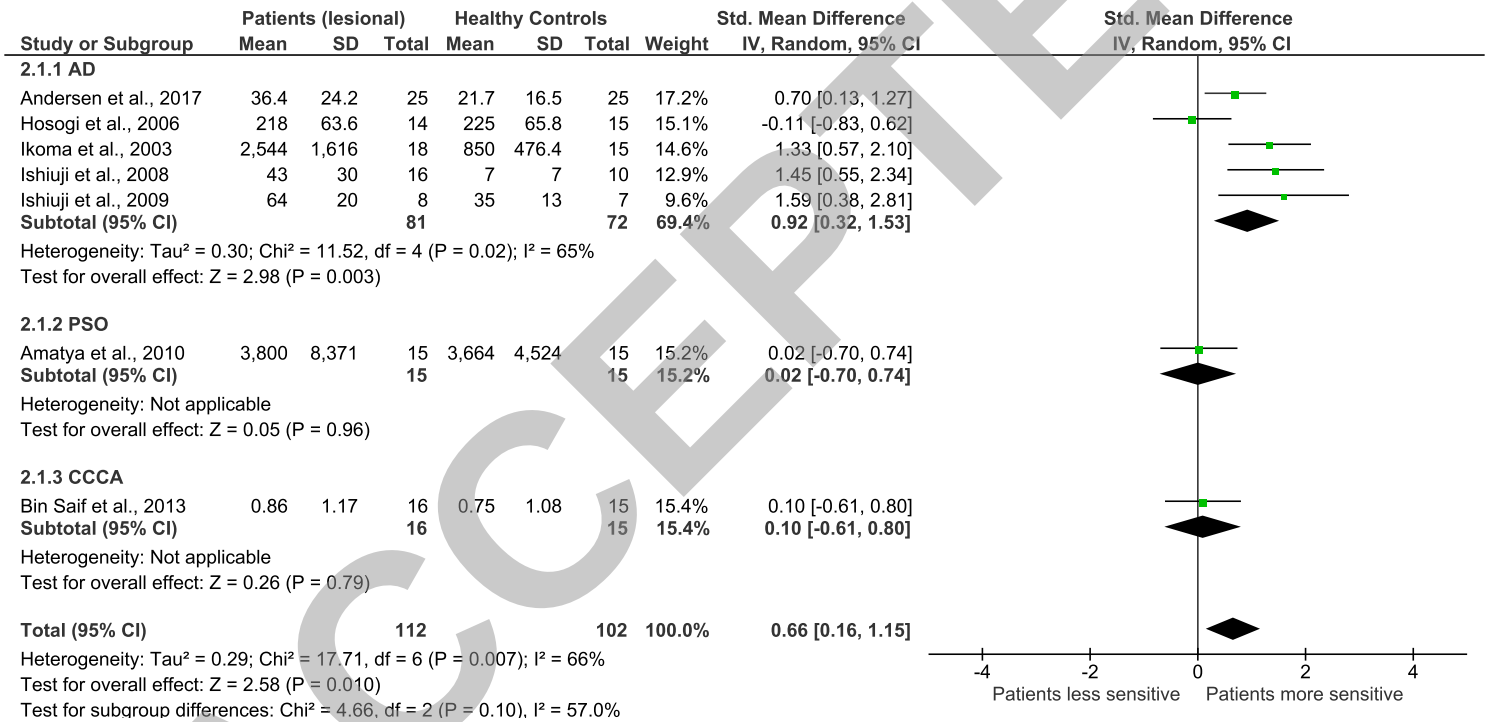
PRISMA 2009 Flow Diagram

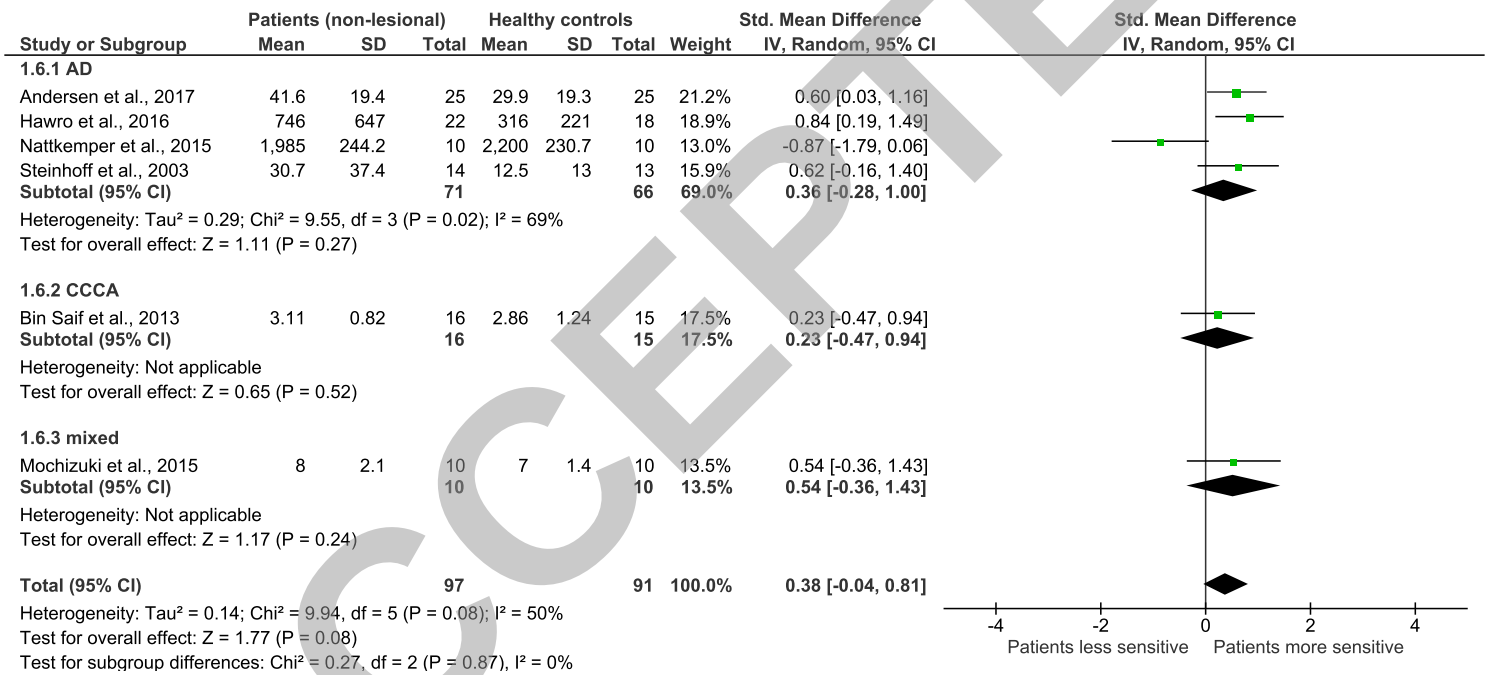




Study or Subgroup	Patients (non-lesional) Mean	SD	Total	Healthy controls Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.1.1 AD								
Andersen et al., 2017	18.1	14.9	25	21.7	16.5	25	5.9%	-0.23 [-0.78, 0.33]
Hawro et al., 2016	746	647	22	316	220.6	18	5.5%	0.84 [0.19, 1.49]
Heyer et al., 1998	14.6	8.8	16	24	6.4	16	5.1%	-1.19 [-1.95, -0.43]
Hosogi et al., 2006	102	16	14	225	66	15	4.2%	-2.45 [-3.44, -1.45]
Ikoma et al., 2003	719	1,078	18	850	476	15	5.4%	-0.15 [-0.83, 0.54]
Ishiuji et al., 2008	16	16	16	7	13	10	4.9%	0.58 [-0.23, 1.39]
Koppert et al., 1996	7.2	9.6	16	38	17.2	16	4.6%	-2.16 [-3.05, -1.26]
Rasul et al., 2013	9,739	9,764	25	15,043	15,000	25	5.8%	-0.41 [-0.97, 0.15]
Wahlgren and Ekblom, 1996	5,077	3,014	20	4,321	4,867	20	5.6%	0.18 [-0.44, 0.80]
Wahlgren et al., 1990	12,588	17,872	32	9,206	10,003	32	6.1%	0.23 [-0.26, 0.72]
Weisshaar et al., 1998	44	23.6	12	49	23.6	12	4.9%	-0.20 [-1.01, 0.60]
Subtotal (95% CI)			**216**			**204**	**58.0%**	**-0.40 [-0.91, 0.11]**
Heterogeneity: Tau² = 0.62; Chi² = 62.81, df = 10 (P < 0.00001); I² = 84%								
Test for overall effect: Z = 1.52 (P = 0.13)								
1.1.2 PSO								
Amatya et al., 2010	2,668	4,918	15	3,664	4,524	15	5.2%	-0.21 [-0.92, 0.51]
Heyer et al., 1998	18.6	7.6	16	24	6.4	16	5.2%	-0.75 [-1.47, -0.03]
Ikoma et al., 2003	719	1,077.6	18	850	476.4	15	5.4%	-0.15 [-0.83, 0.54]
Van Laarhoven et al., 2010	2.9	2.5	25	2.5	2	31	6.0%	0.18 [-0.35, 0.70]
Subtotal (95% CI)			**74**			**77**	**21.8%**	**-0.18 [-0.57, 0.20]**
Heterogeneity: Tau² = 0.04; Chi² = 4.15, df = 3 (P = 0.25); I² = 28%								
Test for overall effect: Z = 0.93 (P = 0.35)								
1.1.3 CCCA								
Bin Saif et al., 2013	2.81	1.89	16	2.88	1.89	15	5.3%	-0.04 [-0.74, 0.67]
Subtotal (95% CI)			**16**			**15**	**5.3%**	**-0.04 [-0.74, 0.67]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.10 (P = 0.92)								
1.1.4 Chronic post-burn itch								
Van Laarhoven et al., 2016	4.2	2.2	15	2.8	1.9	15	5.2%	0.66 [-0.08, 1.40]
Subtotal (95% CI)			**15**			**15**	**5.2%**	**0.66 [-0.08, 1.40]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.76 (P = 0.08)								
1.1.5 Urticaria								
Heyer et al., 1998	18.9	7.6	16	24	6.4	16	5.2%	-0.71 [-1.42, 0.01]
Subtotal (95% CI)			**16**			**16**	**5.2%**	**-0.71 [-1.42, 0.01]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.93 (P = 0.05)								
1.1.6 Sensitive Skin								
Falcone et al., 2017	4.27	1.83	9	3.78	1.87	9	4.5%	0.25 [-0.68, 1.18]
Subtotal (95% CI)			**9**			**9**	**4.5%**	**0.25 [-0.68, 1.18]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.53 (P = 0.59)								
Total (95% CI)			**346**			**336**	**100.0%**	**-0.26 [-0.58, 0.06]**
Heterogeneity: Tau² = 0.38; Chi² = 75.26, df = 18 (P < 0.00001); I² = 76%								
Test for overall effect: Z = 1.58 (P = 0.11)								
Test for subgroup differences: Chi² = 8.74, df = 5 (P = 0.12), I² = 42.8%								







Study or Subgroup	Patients (non-lesional) Mean	SD	Total	Healthy controls Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.4.1 AD								
Andersen et al., 2017	4.3	2.3	25	6.3	2.4	25	7.0%	-0.84 [-1.42, -0.26]
Hawro et al., 2016	215	220.5	22	518	343.7	18	6.8%	-1.05 [-1.72, -0.38]
Heyer et al., 1989	815	639	27	1,754	483	20	6.8%	-1.60 [-2.27, -0.93]
Heyer et al., 1995	1,200	971	19	1,739	499	20	6.9%	-0.69 [-1.34, -0.04]
Heyer et al., 1998	4.8	1.1	16	19.7	1.6	16	2.9%	-10.58 [-13.43, -7.73]
Hosogi et al., 2006	3.3	1.5	14	7	2.7	15	6.5%	-1.63 [-2.49, -0.77]
Ikoma et al., 2003	12.3	8.5	18	25.3	9.7	15	6.7%	-1.40 [-2.17, -0.63]
Ishiuji et al., 2008	1	0.3	16	1.6	0.7	10	6.5%	-1.19 [-2.05, -0.32]
Koppert et al., 1996	3.6	5.6	16	20.2	7.6	16	6.4%	-2.42 [-3.36, -1.48]
Rukwied et al., 2000	9.3	6.3	9	21.4	7.5	9	6.0%	-1.66 [-2.77, -0.55]
Wahlgren et al., 1990	1,211	737	32	1,679	753	32	7.1%	-0.62 [-1.12, -0.12]
Weisshaar et al., 1998	2,370.5	836	12	2,075.2	1,201.6	12	6.6%	0.28 [-0.53, 1.08]
Subtotal (95% CI)			**226**			**208**	**76.3%**	**-1.42 [-1.99, -0.84]**
Heterogeneity: Tau² = 0.82; Chi² = 72.28, df = 11 (P < 0.00001); I² = 85%								
Test for overall effect: Z = 4.84 (P < 0.00001)								
1.4.2 PSO								
Amatya et al., 2010	261.4	401.6	15	198.6	190.8	15	6.8%	0.19 [-0.52, 0.91]
Heyer et al., 1998	13.1	1.6	16	19.7	1.6	16	5.7%	-4.02 [-5.28, -2.76]
Subtotal (95% CI)			**31**			**31**	**12.5%**	**-1.88 [-6.01, 2.25]**
Heterogeneity: Tau² = 8.61; Chi² = 32.48, df = 1 (P < 0.00001); I² = 97%								
Test for overall effect: Z = 0.89 (P = 0.37)								
1.4.3 URT								
Heyer et al., 1998	11.5	1.1	16	19.7	1.6	16	4.9%	-5.82 [-7.50, -4.15]
Subtotal (95% CI)			**16**			**16**	**4.9%**	**-5.82 [-7.50, -4.15]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 6.82 (P < 0.00001)								
1.4.4 Sensitive skin								
Falcone et al., 2017	2,358.62	665.16	9	2,437.59	623.31	9	6.4%	-0.12 [-1.04, 0.81]
Subtotal (95% CI)			**9**			**9**	**6.4%**	**-0.12 [-1.04, 0.81]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.25 (P = 0.80)								
Total (95% CI)			**282**			**264**	**100.0%**	**-1.66 [-2.29, -1.03]**
Heterogeneity: Tau² = 1.38; Chi² = 140.34, df = 15 (P < 0.00001); I² = 89%								
Test for overall effect: Z = 5.19 (P < 0.00001)								
Test for subgroup differences: Chi² = 34.25, df = 3 (P < 0.00001), I² = 91.2%