What Is Sensitive Skin? A Systematic Literature Review of Objective Measurements

Renée Richters^a Denise Falcone^a Natallia Uzunbajakava^b Willem Verkruijsse^b
Piet van Erp^a Peter van de Kerkhof^a

^aDepartment of Dermatology, Radboud University Medical Center (Radboudumc), Nijmegen, and ^bPhilips Research, Eindhoven, The Netherlands

Key Words

Sensitive skin · Biophysical measurements · Multifactorial questionnaires

Abstract

Despite sensitive skin being highly prevalent, no consensus on the definition and pathomechanism of sensitive skin exists. Here we report the results of a systematic literature review of diagnostic methods for sensitive skin at clinical, histological and biophysical levels. A systematic search revealed 27 out of 1,701 articles which we appraised in detail. Impaired skin barrier function and increased vascular reactivity are most often associated with sensitive skin. We identified key reasons causing an ambiguity around the sensitive skin phenomenon. We propose using standardized selection methods of subjects by a multifactorial questionnaire spanning a range of provocations, including those of chemical, mechanical and environmental origin, followed by clinical, histological and top-notch biophysical measurements. This could lead to a breakthrough in the understanding of the sensitive skin phenomenon, fueling advances of biomedical and dermatological science.

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Introduction

In the previous century, sensitive skin was rarely reported in the scientific literature and its existence was questioned by biomedical scientists. Various imprecisely defined terms have been proposed to characterize susceptible skin, emphasizing its heterogeneous presentation, and only few research groups have focused on objective approaches to identify differences in sensitive skin [1–10].

In the past years, the view on sensitive skin has changed dramatically. Large epidemiological studies on the prevalence of sensitive skin have been conducted, concluding that the percentage of self-reported sensitive skin is as high as 50–61% among women [11–15] and 30–44% among men [11–14]. Since the prevalence of sensitive skin proves to be high across industrialized countries and to have considerable impact on quality of life [16], unraveling clinical, biophysical and histological characteristics of sensitive skin has become a significant topic of research for cosmetic and pharmaceutical industries and for biomedical researchers.

People classifying themselves as having sensitive skin perceive skin discomfort, particularly characterized by stinging, burning or itching sensations [16–18]. Remark-

ably, visible signs of skin irritation are frequently absent [14, 17–20]. To define the symptom profile and to address exogenous and endogenous factors which may elicit skin reactions, nonuniform questionnaires have been conducted in different populations [12–14]. Furthermore, various chemical and electrical provocations followed by noninvasive measurements of biophysical parameters of the skin have been widely appraised in persons having sensitive skin perceptions to quantify sensory irritation and to reveal the underlying mechanisms of sensitive skin [9, 19, 21–23]. Various exogenous factors such as cosmetic ingredients and environmental conditions have been indicated to trigger sensitive skin reactions. Many provocations used in experiments resulted in sensory skin reactions [19, 21, 22, 24]. However, susceptibility to one provocative agent does not predict susceptibility to another [25–28].

Despite extensive research, a consensus on the definition of sensitive skin has not been reached and attempts to develop a valid diagnostic test to objectively identify the complete profile of sensitive skin have failed. Factors that impede the detection of sensitive skin are the heterogeneity of symptoms [17], the subjectivity of sensory discomfort [29] and the absence of visible clinical features [17, 21]. Updates have been published recently, but a systematic approach and a critical appraisal of published studies is still lacking [19, 22, 30, 31].

Objectives

The aim of this review is to shape a different perspective on research in the area of sensitive skin by relating perceptions, quantitative sensory measurements and objective biophysical and morphological aspects of this phenomenon. We include the following objectives:

- (1) to create an overview of the morphological, physiological and biophysical characteristics of sensitive skin;
- (2) to critically appraise the quality and reliability of diagnostic tests for sensitive skin;
- (3) to identify gaps in the knowledge of sensitive skin;
- (4) to formulate recommendations for future research directions.

This systematic review may be particularly interesting both for innovators working in the area of skin irritation research and experimental dermatology, who aspire to look beyond the solely cosmetic perspective and embrace objective measurements of sensitive skin, and clinicians, who are seeking evidence on the pathomechanical background of sensitive skin to address solutions for individual differences in skin reactions.

Fig. 1. Article selection process.

Materials and Methods

To collect data on sensitive skin, an extensive literature search was performed for articles published from January 2000 to July 2012 in the following electronic bibliographic indexes: PubMed, EMBASE, BIOSIS, KOSMET, PASCAL, LIFESCI, HCAPlus, Inspec and Compendex (online suppl. table S1; for all online suppl. material, see www.karger.com/doi/10.1159/000363149). The path towards an understanding of sensitive skin was paved by several research groups previously and served as a basis to trigger a new generation of experimental studies after 2000. The first search strategy contained all possible synonyms for sensitive skin: 'sensitive', 'sensitivity', 'hypersensitive', 'hyperreactive', 'irritation', 'irritated', 'susceptibility', 'sensibility', 'intolerance', and 'cutaneous sensitivity'. The second search strategy contained specific and general terms on diagnostics and physiology. Third, symptoms and sensations were included, being the phenomenon of sensitive skin based on perceptions. The three searches were crossed and restricted to publications on humans, English language and articles which were published after January 1, 2000.

Study Selection Criteria

A total of 3,267 citations were identified by the search strategy. Duplicate citations were removed. Relevant articles were selected by a four-stage process (fig. 1). First, a selection of 1,701 articles (R.R.) was made using a checklist containing four items: descriptions of definition, epidemiology, demography (e.g. age, gender, ethnicity, skin type), and diagnostics on sensitive skin and skin irritation. The presence of at least one of these items was mandatory for an article to be included in the next steps of the analysis. Second, abstracts of selected titles were assessed independently by two reviewers (R.R. and P.v.E.) using a more detailed checklist to select articles considered to be relevant. The main reason for exclusion

was when testing the irritation potential of substances was addressed or when perceptions of individuals were lacking. Consensus was reached by discussion on inclusion; 93 abstracts were eligible for detailed full-text assessment.

Article Screening

After critical assessment of full texts in the third stage, 24 articles were included. The main reason for exclusion was the absence of descriptions or evaluation of perceptions of sensitive skin, e.g. burning feeling, stinging feeling, discomfort, etc. Finally, to ensure that all relevant studies were included, reference lists of literature reviews and included full-text articles were additionally scanned, resulting in the inclusion of 3 articles.

Quality Assessment

The STROBE method (Strengthening the Reporting of Observational Studies in Epidemiology) was used in the assessment of the quality of studies as this tool comprises a level of evidence determination according to the study design of observational studies [32]. Each study received a score of 0–22, expressed as a percentage of the maximum score, by two independent reviewers (D.F. and R.R.), relating to three grades of recommendation based on the fulfillment of quality criteria. When scores differed by more than 1.5, consensus was reached by discussion. Quality assessment and data extraction tables are included in online supplementary table S2.

Results

Article Quality

Overall, 5 articles were classified in category C (score <60%) and the remaining 22 articles were classified in category B (score 60–80%). The mean score of the articles was $63.4 \pm 5.6\%$. Shortcomings mainly refer to (1) poor or absent explanation of the choice of study design and population size, (2) addressing bias and limitations of the study and (3) indication of the number of participants included at each stage.

Definition of Sensitive Skin

Our review confirmed that there is no consensus on the definition and the symptom profile of sensitive skin. The condition has been characterized by solely neurosensory discomfort in 8 studies, while 9 studies suggest that these perceptions may be accompanied by visible skin irritation such as erythema and dryness.

Study Sample Characteristics

All studies included are observational studies in adults. The majority ($n = 16$) included both sexes, nearly all with a higher proportion of women ($n = 13$). Out of 20 studies that appointed the mean age of subjects, 14 addressed a mean age between 25 and 40 years. A total of 8 studies addressed the ethnicity of subjects: 5 studies included Cau-

casian subjects, 3 included Asian subjects; 1 study compared these two skin types. Studies comparing a predetermined population with sensitive skin with a control group included small groups (4–36 subjects). The most frequently investigated body sites were the nasolabial fold ($n = 12$), the volar forearm ($n = 10$), the cheek ($n = 5$), other facial areas ($n = 6$), and the hands ($n = 4$).

Sensory Hyperreactivity

Population Selection Methods. Different methods are applied to enable the assessment of sensitive skin behavior, including provocations with chemical substances and selection by self-reported perceptions obtained by questionnaire. Studies addressing individual differences in skin reactions elicited sensations by different agents: lactic acid (LA), sodium lauryl sulfate (SLS) and various other topical agents such as capsaicin, menthol, benzoic acid, transcinamic acid, octane, cumene, methyl nicotinate and acetyl-b-methylcholine chloride (vasodilators), ethanol, allergens, occlusion, cocamidopropyl betaine and benzalkonium chloride (surfactants), and balsam of Peru; 1 study selected subjects by determining the current perception threshold in the neck [33] and 12 studies selected subjects based on self-assessment by questionnaire.

The lactic acid stinging test (LAST), first developed to appraise the stinging capacity of topically applied substances [34], is proposed as the best predictor available for sensitive skin and is widely used to select volunteers for clinical studies [3]. We also confirm that the LAST identifies ‘stingers’ – subjects perceiving stinging sensations when LA is applied on the nasolabial fold – assuming to correspond to sensitive skin and was most frequently used to categorize subjects on skin sensitivity ($n = 9$). A detailed evaluation of the articles included in this review reveals that, in sensitive skin, the time to onset of stinging and time to peak are shorter, higher peak amplitudes are observed [35] and mean overall stinging scores are higher in response to LA [36, 37]. However, the test lacks objectivity, sensitivity and specificity for sensitive skin. In fact, 59.9% [15] and 64% [35] of subjects with self-reported sensitive skin report a positive reaction to the LAST. A study by Cho et al. [38] found that 80% of sensitive subjects report stinging following the LAST. However, 66.7% of nonsensitive subjects also experience this reaction. Moreover, several studies have shown that sensitivity to one substance seems not to predict sensitivity to another [28, 35, 39], questioning the validity of the LAST as a reliable diagnostic test for sensitive skin.

Only 2 studies using the LAST as an indicator of sensitive skin found significant differences in biophysical measurements in stingers, namely, a higher transepidermal

water loss (TEWL) on the nasolabial fold ($p = 0.03$) and on the right ($p = 0.05$) and left cheek ($p = 0.03$) [40, 41]. Important to note here is that Distant et al. [41] (2002) included subjects who also met the criteria of self-reported sensitive skin and who had specific skin reactions besides a positive LAST. Differences in skin reactions could barely be enhanced by physical irritants such as SLS [42]. In the past, the enhancement of differences in skin reactions between stingers and nonstingers also failed [25, 27]. In 2011, Schliemann et al. [51] observed that after only 5 days stingers showed significantly higher skin irritation following repetitive cumene and octane application. However, differences in biophysical measurements do not ensure differences in skin sensitivity since these parameters have high interindividual variability in the general population.

As stated earlier, besides the LAST, 12 studies selected sensitive and nonsensitive skin subjects using either extended nonuniform questionnaires, including sensory perceptions, visible symptoms and environmental and endogenous factors, or asking whether an individual had sensitive skin or not. In particular, 1 study used a labeled magnitude scale permitting both semantic descriptors and a continuum of intensity rankings to compare individuals [43].

When sensitive and nonsensitive subjects were selected by questionnaire, few studies found significant differences in biophysical parameters between sensitive and nonsensitive subjects. An inverse correlation was shown between the detection thresholds of capsaicin and sensitive skin indexed by questionnaire [44], suggesting that these methods could be more specific than the LAST in detecting sensitive skin. It is known that whenever skin is challenged by capsaicin, noxious heat or low pH, transient receptor potential vanilloid 1 (TRPV1) is activated [45, 46], resulting in nociceptor-mediated burning pain. An overexpression of this ion channel could play a key role in the pathophysiology of sensitive skin, as its inhibition results in reduced burning sensation following capsaicin application [47]. Differences in pain perceptions were also observed in subjects with sensitive skin by fMRI. Subjects with sensitive skin indexed by questionnaire showed activity in both hemispheres when stimulated with LA on the right nasolabial fold, whereas only the left primary sensorimotor area was active in subjects with nonsensitive skin [36].

Impaired Barrier Function

Transepidermal Water Loss. In total, 11 studies focused on TEWL as a parameter of skin barrier function (table 1). Most studies observed higher TEWL in the unchallenged skin of subjects with sensitive skin compared

to those with nonsensitive skin [20, 41, 48, 49] and in stingers compared to nonstingers [39–41, 50, 51], while only 2 studies identified significantly higher TEWL in sensitive skin [40, 41]. Moreover, higher TEWL at baseline seems to correlate with a stronger TEWL increase following provocation [40]: plastic occlusion resulted in a significantly longer evaporation half-life time in subjects with sensitive skin [49], and a trend to increased recovery time of TEWL following SLS stimulation was also observed [20]. A stronger increase of TEWL was also found following SLS provocation both in sensitive versus nonsensitive atopic skin [52] and in a population of Japanese versus German women [53]. The latter finding is particularly interesting as in general Asian women often report sensitive skin.

Stratum Corneum Hydration. Overall, 10 studies presented data on hydration of the stratum corneum (measured through capacitance, CAP) in sensitive skin (table 1). A significantly lower CAP at facial areas in subjects with sensitive skin [37] and in stingers [40] and a nonsignificantly lower CAP at facial areas in subjects with sensitive skin were found [41]. Challenging the skin with octane or cumene, however, resulted in a significantly lower CAP in stingers compared to nonstingers [51]. A lower CAP at baseline predicted earlier onset of stinging and a weak correlation (Spearman's test: $r = 0.307$, $p = 0.03$), with a higher clinical stinging score identified [39]. On the other hand, other studies found no difference in CAP between stingers and nonstingers [40, 50, 51] or between subjects with sensitive and nonsensitive skin [20, 48], either challenged or unchallenged [20, 48, 51]. The lower CAP is consistent with findings of a clinically dryer skin [15] and a lower facial ceramide content of the stratum corneum found in subjects with sensitive skin ($p = 0.037$) [38]. This implies that an impaired skin barrier and a dryer skin underlie sensitive skin.

Sebum and pH. Previously, a study reported a significantly lower sebum level in subjects with sensitive skin [9]. In studies evaluated in this review, clinically less oily ($p < 0.01$) skin was detected in subjects with sensitive skin [37]. However, objective surface sebum measurements show no differences between subjects with sensitive and nonsensitive skin [37, 54] and between stingers and nonstingers [40]. It is remarkable that Asian people, who more often report sensitive skin [53, 55], have a clinically more oily skin compared to Caucasians (31.9 vs. 24.0%). Aramaki et al. [53] (2002) detected differences in sebum secretion levels between Japanese and Caucasian women following SLS provocation. This indicates that Japanese skin could be more

Table 1. CAP and TEWL in subjects with sensitive versus nonsensitive skin

	Group	Unchallenged skin (baseline)		Challenge	Challenged skin	
		CAP	TEWL		CAP	TEWL
Aramaki et al. [53], 2002	Japanese, German	lower ¹ n.s.	lower ² p < 0.05	SLS	lower ¹ n.s.	lower ² p < 0.05
Cho et al. [38], 2012	SRSS/stingers, non-SRSS/nonstingers	n.a.	lower ² (excluding back) n.s.	SLS	n.a.	unknown ² n.s.
Diogo and Papoila [20], 2010	SRSS, non-SRSS	lower ¹ p = 0.843	higher ² p = 0.478	SLS	lower ¹ p = 0.089	n.a. n.s.
De Jongh et al. [52], 2006	atopy, no atopy	n.a.	higher ³ p = 0.9	single SLS	n.a.	increase, Δ higher ³ p = 0.07
				repeated SLS	n.a.	unknown ³ n.s.
Kim et al. [56], 2008	SS, NSS	higher ¹ n.s.	higher ² n.s.	capsaicin	n.a.	n.a.
Loffler et al. [48], 2001	SRSS, non-SRSS	indistinct ¹ n.s.	indistinct ² n.s.	SLS	unknown ¹ n.s.	unknown ² n.s.
Pinto et al. [49], 2011	SRSS, non-SRSS	n.a.	higher ² p = 0.059	plastic occlusion	n.a.	longer t _{1/2} p = 0.005
Roussaki-Schulze et al. [37], 2005	SRSS, non-SRSS	lower ⁴ p < 0.05	n.a.	acetyl-b-methylcholine chloride NaOH (alkali)	n.a.	n.a.
Schliemann et al. [51], 2011	stingers, nonstingers	higher ¹ n.s.	higher ² n.s.	octane repeated	decrease ¹ higher Δ p < 0.001	indistinct ² n.s.
				cumene repeated	decrease ¹ higher Δ indistinct p < 0.021	indistinct ² n.s.
Wu et al. [39], 2003	stingers, nonstingers	lower ¹ n.s.	higher ² n.s.	LA	n.a.	n.a.
An et al. [40], 2007	stingers, nonstingers	lower ¹ p = 0.77	higher ³ p = 0.03	n.a.	n.a.	n.a.
Distante et al. [41], 2002	SS/stingers, NSS/nonstingers	lower ¹ n.s.	higher ² cheek R: p < 0.05 cheek L: p = 0.03	n.a.	n.a.	n.a.
van de Vijver et al. [54], 2003	SS, NSS	unknown ¹ n.s.	n.a.	n.a.	n.a.	n.a.

CAP = Capacitance (stratum corneum hydration); n.s. = nonsignificant difference; SRSS = self-reported sensitive skin; n.a. = not applicable; SS = sensitive skin; NSS = nonsensitive skin. Significant p < 0.05.

¹ Measured by Corneometer, C+K Electronics. ² Measured by TEWA meter, C+K Electronics. ³ Measured by VaporMeter, Delfin. ⁴ Ionto-Skin-Diagnose, Ionto Comed GmbH.

susceptible to chemical irritation, possibly due to alterations in sebum secretion levels. The literature is inconclusive with regard to the role of sebum secretion in sensitive skin perceptions.

Recent studies show no significant differences in skin surface pH for subjects with sensitive skin [37, 54] and stingers [40], while previous studies reported significantly higher baseline pH in subjects with sensitive skin [9]

and a significantly stronger increase of pH at 25 min after stimulus among stingers compared to nonstingers [4]. Skincare products of pH 8 affect the impact of SLS, as evidenced by a significant increase of TEWL [56]. It seems reasonable to conclude that there is an impaired barrier function, allowing faster penetration of LA and therefore a faster increase of surface pH after LA [4], enhancing sensitivity to chemical agents [56].

Skin Structure and Viscoelasticity. The skin of stingers with self-reported sensitive skin appears to be rougher since fast Fourier transform evaluation of tapes after tape-stripping the stratum corneum in 243 stingers revealed a lower content of cells. This implies a more irregular and rougher [57], possibly less hydrated, skin. However, objectively measured skin elasticity and distensibility show no correlation with hypersensitivity [54].

Based on these results, we suggest that an impaired skin barrier function plays a role in the pathomechanism of sensitive skin and needs to be investigated in depth.

Inflammatory or Vascular Response

Individuals with sensitive skin frequently report red- dening of their skin [15, 35, 37, 38, 43, 44, 49, 57, 58]. Therefore, the assessment of erythema in skin irritation has been widely investigated, either by visual assessment [28, 37, 41, 59, 60] or by quantitative methods such as tristimulus re- flectance colorimetry (a^* value) [20, 50–52], reflectance spectrophotometry (erythema index) [38, 53, 59] or laser Doppler flowmetry (cutaneous blood flow) [20, 41, 48, 50, 51, 53, 61]. Increased vascular reactivity has been empha- sized in the literature as a key player in sensitive skin patho- physiology. In this review, lower objective values for red- ness were found at baseline: lower a^* values in subjects with sensitive skin [20, 50, 53] and lower erythema index and cutaneous blood flow in stingers [38, 41, 50, 51] and sub- jects with sensitive skin [20, 38, 48] were observed (table 2). Inconclusive evidence was found with respect to enhanced vascular reactivity following provocations (table 2). The ap- plication of LA, SLS, capsaicin or cumene failed to enhance differences in erythema responses [20, 50, 51, 53], while the application of octane, acetyl-b-methylcholine chloride, al- lergen patch testing (European standard and cosmetics), and methyl nicotinate resulted in a stronger erythema re- sponse in stingers and in sensitive skin [37, 51]. Similar re- sults on methyl nicotinate were found in 1991 [1]. Remark- ably, 1 study observed a blanching reaction following me- thyl nicotinate solely in subjects with sensitive skin [37]. Japanese women demonstrate stronger vascular reactions compared to Caucasian women [53]. A proposed explana- tion for vascular reactivity in sensitive skin is a higher con- centration of chemical agents absorbed in the skin, possibly implying an impaired barrier function, which could elicit vascular responses [62]. At a histological level, no differ- ences with respect to endothelium markers were observed [33]. With regard to genetic characteristics, nonatopic sub- jects with a G-to-A transition (TNF- α polymorphism-308) have significantly higher stinging response following the LAST compared to nonatopic subjects with the wild type

($p = 0.03$), suggesting that TNF- α and an increase in NGF play a role in the perception of skin irritation [60].

Allergic Predisposition

Epidemiological studies support the association be- tween sensitive skin and atopic diathesis due to a signifi- cantly higher individual manifestation of atopy in the sensi- tive skin group [14]. This indicates that impaired skin bar- rier function and increased mast cell degranulation could be involved in the pathophysiology. One of the included studies showed that atopic predisposition enhances erythe- ma responses ($p = 0.03$) [52]. Although dermographism is comparable between subjects with sensitive and nonsensi- tive skin [37], histologically, increased numbers of CD117+ mast cells ($p < 0.08$) and a larger cross-sectional area of lymphatic vessels identified by LYVE-1 and podoplanin ($p < 0.001$) were seen in individuals with a low current per- ception threshold [33]. Such differences in physiology are possibly responsible for the modulation of the perception threshold of nociceptive stimuli via the release of mast cell mediators. Total IgE in the blood does not differ [33].

Discussion

As sensitive skin is highly prevalent in the Western world, the understanding of the physiological reality of sensitive skin is of high importance. This systematic litera- ture review concludes that potential causal pathways hy- pothesized to lead to a response pattern commonly desig- nated as sensitive skin are the following: (1) sensory hyper- reactivity, (2) impaired barrier function, (3) inflammatory or vascular responsiveness and (4) atopic predisposition.

This review also confirms that the identification of sensitive skin is complex. A single overall definition for sensitive skin is not supported by evidence and no objec- tive diagnostic test has been found to be sensitive and re- producible. Strong evidence on pathways underlying sen- sitive skin is lacking. Only few provocative methods such as SLS, vasodilators and capsaicin possibly trigger the mechanism of sensitive skin, since these agents enhanced differences between subjects with sensitive and nonsensi- tive skin. The strongest evidence refers to an impaired skin barrier function. This impaired barrier may trigger both vascular hyperreactivity and sensory perceptions, suggesting different mechanisms according to different discomfort presentation.

The variety of tests, selection methods and measure- ment methods has potentially led to the large diversity of theories on the mechanism of sensitive skin. First, highly

Table 2. a* values, erythema index and visual erythema assessment in subjects with sensitive versus nonsensitive skin

	Group	Unchallenged skin (baseline)		Challenge	Challenged skin	
		a* value	LDF		a* value	LDF
Aramaki et al. [53], 2002	Japanese, German	lower ¹ n.s.	lower ² n.s.	SLS LA	lower (n.s.) ¹ higher ³	lower (n.s.) ² n.a.
Diogo and Papoila et al. [20], 2010	SRSS, non-SRSS	lower ¹ p = 0.033	lower ² p = 0.143	SLS	higher ¹ p = 0.514	lower ² p = 0.178
Kim et al. [56], 2008	SS, NSS	lower ¹ n.s.	similar ³ n.s.	capsaicin	n.a.	n.a.
Loffler et al. [48], 2001	SRSS, non-SRSS	n.a.	indistinct ² n.s.	SLS	n.a.	unknown ² n.s.
Schliemann et al. [51], 2011	stingers, nonstingers	higher ¹ n.s.	unknown ⁴ n.s.	repeated octane repeated cumene single octane single cumene	higher ¹ day 5 p = 0.002 higher ¹ n.s.; n.a. n.a.	n.a. n.a. unknown ⁴ p = 0.976 unknown ⁴ p = 0.631
Distante et al. [41], 2002	SS/stingers, NSS/nonstingers	n.a.	higher ² (excluding forehead) n.s.	n.a.	n.a.	n.a.
<i>Erythema index</i>						
Cho et al. [38], 2012	SRSS, non-SRSS/ stingers, nonstingers	indistinct ⁵ n.s.	n.a.	n.a.	unknown ⁵ n.s.	n.a.
De Jongh et al. [52], 2006	atopy, no atopy	higher ⁵ n.a.	n.a.	SLS	higher Δ^5 erythema p < 0.05	n.a.
<i>Visual erythema assessment</i>						
Roussaki-Schulze et al. [37], 2005	SRSS, non-SRSS	n.a.	n.a.	acetyl-b-methylcholine chloride NaOH (alkali) European standard, cosmetic patches	higher p < 0.01 higher p < 0.05 higher p < 0.05	n.a.

LDF = Laser Doppler flowmetry; n.s. = nonsignificant difference; n.a. = not applicable; SRSS = self-reported sensitive skin; SS = sensitive skin; NSS = nonsensitive skin. Significant p < 0.05.

¹ Measured by Chromameter, Minolta. ² Measured by Peri Flux System, Perimed. ³ Measured by Laser blood flow detector, Moor Instruments. ⁴ Measured by Laser Doppler Imager, Moor Instruments. ⁵ Measured by DermaSpectrometer, Cortex Technology.

heterogeneous methods to measure biophysical characteristics are applied following different provocations at different body sites in different moments in time in order to select subjects with sensitive skin. Even within the LAST method, various concentrations and inclusion criteria are used which are different from the original LAST [34]. Second, some studies did not set the required environmental conditions for biophysical measurements on TEWL and CAP, as recommended in the published guidelines [40]. Also, despite the assumption that various host factors such as allergic predisposition promote sensitive skin [21], many included studies did not take these potential confounders into consideration in selection processes, resulting in different populations, or did not report these confounders. Moreover, useful research data of the cosmetic industry is frequently kept confidential or

published studies have methodological shortcomings and enrolled small subject groups, thus complicating the reliability and completeness of data on sensitive skin.

In order to unravel the pathomechanism and potential triggering pathways of this mechanism, first of all the symptom and perception profile associated with sensitive skin should be identified. A perception-based selection of subjects enables us to investigate the structural and physiological differences of sensitive skin compared to 'normal' skin. This selection could be more specific than the LAST.

Second, an important question is whether sensitive skin is a 'container term' comprising multiple pathways that elicit sensitivity. More specifically, and with relevance for clinical practice, is there a set of triggers that are able to predict a certain proclivity to having sensitive skin? Since

sensitive skin seems not to be a one-dimensional condition, a more specific identification method for sensitive skin compared to provocations with LA or capsaicin may be a questionnaire or a scoring scale for neurosensory perceptions. A questionnaire enables the inclusion of a broader spectrum of triggers and common symptoms of sensitive skin and is applicable for clinical practice in order to predict one's propensity to experience sensitive skin.

We propose that selection methods with higher specificity such as subjective scoring scales could be adequate diagnostic tools to detect subjects with sensitive skin for research purposes and, when combined with consistent biophysical measurements, could possibly highlight significant differences in subjects with sensitive skin with respect to nonsensitive subjects and lead to consistent results. We propose using multifactorial questionnaires spanning a range of provocations, including those of chemical, mechanical and environmental origin, followed by clinical, histological and top-notch biophysical measurements. This could lead to a breakthrough in the understanding of the sensitive skin phenomenon, fueling the advances of biomedical and dermatological science. The next step could be to zoom in on the potential mechanisms involved with advanced techniques. For example, an extended analysis of the skin barrier structure and composition could provide new insights into the pathways involved in the development of the sensitive skin phenomenon.

Born out of clinical practice, it might be that sensitive skin plays a role in interindividual variability in reactivity potential among dermatological patients, as experienced in skin diseases such as psoriasis or acne [6, 63]. This knowledge relates sensitive skin to knowledge on pathology in skin diseases and could be the basis for addressing solutions to differences in individual skin reactions in clinical practice. The ultimate goal of the identification of underlying mechanisms is to develop rational interventions for each individual with sensitive skin, implementing personalized medicine. For the future, we recommend using approaches focused on identifying the pathomechanisms causing perceptions of skin discomfort designated as sensitive skin to propose an evidence-based diagnosis and intervention for patients with sensitive skin.

Disclosure Statement

Prof. Dr. P. van de Kerkhof, the principal investigator of this study, has received reimbursement of the costs made to conduct this review from Philips Electronics Nederland B.V., acting through Philips Research. The authors affiliated to Philips Research are employees of Philips Research and have received a salary for this study. The authors affiliated to Radboudumc are employees of Radboudumc and have also received a salary for this study.

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