

## ***Men's skin may be more sensitive than previously thought***

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### **1. Introduction**

Since its first description almost 60 years ago [1], sensitive skin has been the subject of many scientific publications and some handbooks [2]. It received this consensual definition by a group of dermatologists only just recently [3]: “a syndrome defined by the occurrence of unpleasant sensations (stinging, burning, pain, pruritus, and tingling sensations) in response to stimuli that normally should not provoke such sensations. These unpleasant sensations cannot be explained by lesions attributable to any skin disease. The skin can appear normal or be accompanied by erythema. Sensitive skin can affect all body locations, especially the face”. As illustrated by its definition, sensitive skin is not a disease but a syndrome characterized above all by self-declared unpleasant sensations not systematically associated with visible signs such as erythema. They appear on seemingly normal looking skin and are induced by triggering factors such as topical applications or environmental factors [4].

Epidemiological studies using various methodologies (mail, telephone and online questionnaires) [5-9] report a high prevalence of sensitive skin, affecting up to 71% of adults, 40% of whom have moderate to severe symptoms according to a meta-analysis representing more than 50,000 individuals in 18 countries [10]. Subjects are generally asked if they consider themselves as having a sensitive skin, if so, how severe it is, what are the symptoms they feel and what factors trigger them. Epidemiological surveys reveal a wide variety of triggers for sensitive skin, primarily environmental (cold, sun, wind, soaps) [4]. Stress, fatigue, and sleep

disturbances are also frequently cited [4,10]. Sensitive skin can affect the quality of life and psychological well-being [11].

The diagnosis of sensitive skin remains difficult, as its symptoms, mainly sensations of discomfort, are subjective and not always accompanied by visible or measurable signs [3,12]. Psychophysical tests have been developed, including the lactic acid sting test (LAST) [13], used by cosmetic manufacturers to select sensitive skin individuals to test new products suitable for them [3]. The relevance of the LAST has been confirmed by fMRI [14], objectifying the reality of sensitive skin. However, the implication of a subjective pain scale to assess the intensity of stinging during LAST and sometimes too painful sensations can be problematic [15]. An alternative, the capsaicin detection threshold (CDT) test [16], uses capsaicin, a natural agonist of TRPV1, a receptor involved in the detection of noxious stimuli [17,18]. The CDT determines detection thresholds for topically applied capsaicin well correlated with self-reported sensitive skin in women [16,19].

Epidemiological surveys show a higher prevalence of sensitive skin in women than in men, with geographical variations [7, 8, 10]. However, few experimental results corroborate this observation, apart from a study on LAST [20]. Despite its age, a CDT study provides relevant comparative data between men and women given the lack of experimental data on the subject.

## **2. Patients, Materials, and Methods**

### *Study population*

One hundred healthy volunteers (50 women, 50 men) participated in this single-center study conducted between December 2003 and March 2004 in Lyon (France). The two groups were of entirely comparable ages (women:  $22 \pm 4$  y.o., men:  $27 \pm 4$  y.o.) and ethnic background (White European type). No inclusion criteria related to skin sensitivity were used. The main exclusion criteria were: suspected or known allergy to capsaicin or chili pepper, any dermatological, neurological, or vascular condition in the study areas, the use of any topical or systemic treatment likely to modify the test results. The clinical study was conducted in accordance with

the 1975 Declaration of Helsinki, revised in 1983. The protocol received ethical approval from the Consultative Committee for the Protection of Persons in Biomedical Research (CCPPRB) of the Leon Berard Center (Lyon). All volunteers provided written informed consent after being thoroughly informed about the study objectives and procedures. Subjects were also informed that they were free to withdraw from the study at any time.

#### *Sensitive skin questionnaire and score*

Each subject completed a sensitive skin questionnaire (Table 1). This 20-item questionnaire aimed to provide specific information on self-reported facial skin sensitivity (existence, symptomatology, skin reactivity factors). From the questionnaire responses, a sensitive skin score was derived for each subject after normalization of their coordinates on the horizontal axis of a principal component analysis (PCA) of the questionnaire responses.

#### *Capsaicin Detection Thresholds*

The test procedures are those used previously [19]. Five solutions with different concentrations of pure-grade capsaicin powder ( $\geq 98.0\%$ , Fluka®) were prepared : C1 =  $3.16 \times 10^{-5} \%$ ; C2 =  $1 \times 10^{-4} \%$ ; C3 =  $3.16 \times 10^{-4} \%$ ; C4 =  $1 \times 10^{-3} \%$ ; C5 =  $3.16 \times 10^{-3} \%$  (w/w). Vehicle used as a control was a 10% absolute ethanol (99.85%, Merck Eurolab®) / 90% distilled water (v/v) solution. The solutions were applied at ambient temperature by an experimenter using a single-use cotton tipped applicator (Société Industrielle du Bois®) and then rubbed twice on nasolabial folds. The test consists of single-blind, split-face applications of increasing concentrations of capsaicin parallel to the vehicle. Sides of capsaicin and control application were randomized. The test started with the lowest concentration of C1 and continued with increasingly concentrated solutions applied every 2 minutes until the subject detected a capsaicin solution. The last applied concentration was considered as the detection threshold for the subject. Five sub-groups were thus defined based on threshold (i.e. sub-groups C1, C2, C3, C4, C5). If no reaction was reported at the highest concentration C5, the subject was considered as “non responder” (sub-group “none”).

### *Statistical analysis*

A PCA was carried out on the 20-item questionnaire to summarize the 20 items as a global sensitive skin score. A biplot was performed to visualize both individuals and items in the first factorial plan. Gender difference was tested for each of the 20 questions using a Fisher's Exact Test. A Student t-test was carried out to test for gender difference in the sensitive skin score. A Chi<sup>2</sup> test was performed to test for gender association in capsaicin detection thresholds. A Jonckheere-Terpstra trend test was carried out to test for association between sensitive skin score and capsaicin detection threshold. The significant statistical threshold was set at 5%. All analyses were performed using SAS 9.4, SIMCA 18 and JASP 0.16 statistical softwares.

## **3. Results**

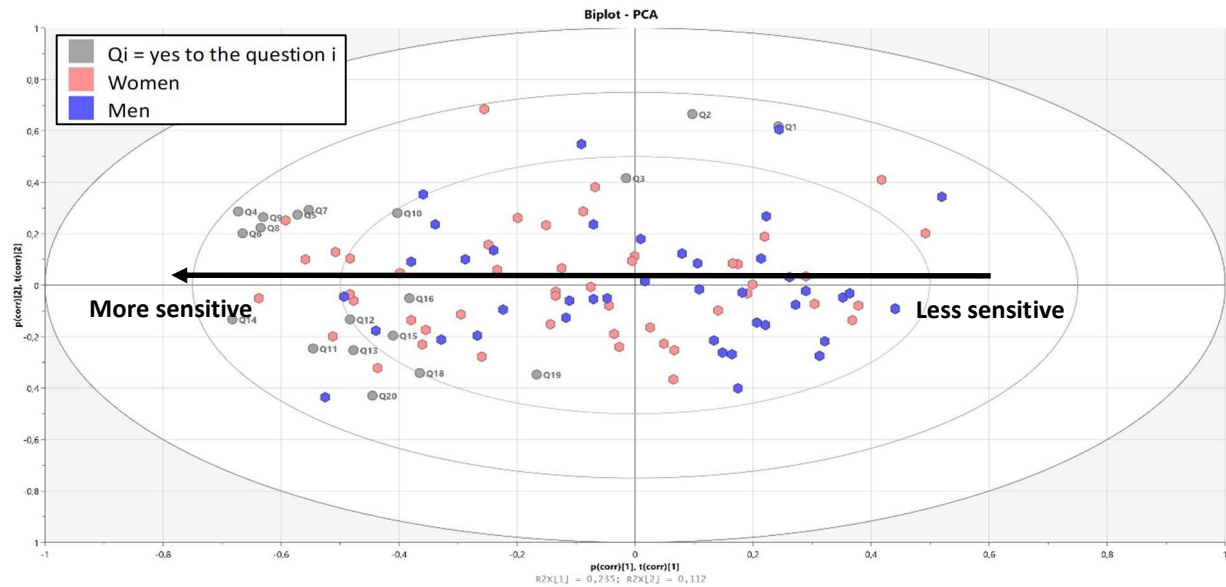
### *Sensitive skin questionnaire and score*

As shown in Table 1, more women (76%) than men (64%) considered that they had sensitive facial skin (Q4), although this difference was not significant ( $p=0.2752$ ). We also did not observe any significant difference with the similar questions: reactive skin (Q6) and prone to irritation (Q5), the latter seeming to speak more to men. However, significant differences between men and women were observed regarding several triggering factors. More women than men reported discomfort (Q9) and adverse reactions (Q10) to cosmetics or toiletries and avoided some as a result (Q7). Facial skin of women was also significantly reported to be more sensitive to cold (Q11), wind (Q14), and air pollution (Q16). A tendency towards greater skin reactivity was also observed in women towards a hot environment (Q12), the sun (Q15), rapid temperature changes (Q13) and stress (Q20).

Question	Percentage of "yes" responses (%)	
	Women (n=50)	Men (n=50)
Q1. Have you ever suffered from <b>eczema or dermatitis</b> ?	14	10
Q2. Did you suffer from <b>eczema or dermatitis as a child</b> ?	8	8
Q3. Have you ever suffered from <b>asthma or hayfever</b> ?	20	24
Q4. Do you regard yourself as having a <b>sensitive</b> facial skin?	76	64
Q5. Do you consider yourself as having a facial skin <b>prone to irritation</b> ?	52	62
Q6. Do you regard yourself as having a <b>reactive*</b> facial skin?	52	46
Q7. Do you <b>avoid certain cosmetics</b> that you feel may cause your facial skin to react*?	<b>30</b>	<b>8</b>
Q8. Do you consider that your facial skin <b>reacts* readily to cosmetics</b> or toiletries?	36	36
Q9. Do some <b>cosmetics</b> or toiletry products make your facial skin <b>itch, sting, or burn</b> ?	<b>52</b>	<b>28</b>
Q10. Have you ever experienced an <b>adverse reaction</b> on your face to a <b>cosmetic</b> or toiletry product?	<b>26</b>	<b>8</b>
Q11. Does the expression "does not tolerate <b>cold weather or a cold environment</b> " apply to your facial skin?	<b>60</b>	<b>20</b>
Q12. Does the expression "does not tolerate <b>hot weather or a hot environment</b> " apply to your facial skin?	22	8
Q13. Does the expression "does not tolerate <b>fast changes in temperature</b> " apply to your facial skin?	40	28
Q14. Does going out in the <b>wind</b> cause your facial skin to itch, burn, or sting?	<b>62</b>	<b>28</b>
Q15. Does going out in the <b>sun</b> cause your facial skin to itch, burn, or sting?	40	30
Q16. Does your facial skin react* to <b>air pollution</b> ?	<b>22</b>	<b>6</b>
Q17. Does your facial skin react* to <b>your monthly cycle</b> ?	54	Non applicable
Q18. Does your facial skin react* to <b>alcoholic drinks</b> ?	18	14
Q19. Does your facial skin react* to <b>spicy food</b> ?	4	6
Q20. Does your facial skin react* to <b>emotion and/or stress</b> ?	56	46

Table 1. Percentages of positive 'yes' responses to the 20 items per gender.

The 20-item questionnaire can be best summarized by a latent variable, a hypothetical and non-observable construct, corresponding to the first factorial axis of a PCA performed on the 20 items. Figure 1 shows the biplot representation of the first factorial PCA plane, with both individuals and variables projected. The horizontal axis mainly characterized by questions Q4 to Q9 and Q14 constitutes an axis of increasing sensitivity. The second axis is mainly defined



by the questions related to atopy (Q1 to Q3). Figure 1 shows that men were associated with lower skin sensitivity than women.

*Fig. 1.* Sensitive skin questionnaire PCA. Biplot representation of the first factorial PCA plane with both individuals and variables projected. The horizontal axis constitutes an axis of increasing sensitivity from right to left. Males, noticeably more present on the right side of the graph, are associated with lower skin sensitivity, while females, more present on the left side, are associated with higher sensitivity.

As both groups are continuously distributed on the first axis, it also illustrates that the condition of sensitive skin is more of a continuum from non-sensitive to very sensitive skin, rather than a binary division between sensitive and non-sensitive skin. The sensitive skin score of each individual was calculated from their y coordinates on the horizontal axis of the PCA as follows:  $10 \cdot (y - \text{min}) / (\text{max} - \text{min})$  where min and max correspond to extreme values. This method of calculation made it possible to establish a sensitive skin score from 0 to 10 for each subject. As illustrated by Table 2, women's group presented a significantly higher score than men's (Student t-test,  $p=0.0048$ ).

	Mean	Std Error	Minimum	Maximum
Women (n=50)	5.23	0.38	0.23	10.00
Men (n=50)	3.74	0.35	0.00	9.03

*Table 2.* Sensitive skin score for both groups.

### Capsaicin detection thresholds

Fig. 2 displays the distribution of both groups according to capsaicin detection threshold. As can be observed, both groups were distributed continuously across all test response modalities. As the dilution factor between the lowest concentration (C1) and the highest concentration (C5) was 100, this continuum of population distribution from C1 to None (= non-perception of C5) reflected the very high intra-group variability in the ability to perceive topically applied capsaicin. The main differences observed between men and women concerned the lowest C1 concentration detected by 20% of men and 6% of women and the “None” modality (28% in men, 36% in women). Although it may appear that men detected lower capsaicin concentrations than women, a Chi-2 test indicates that there was no significant inter-group difference ( $p=0.4476$ ).

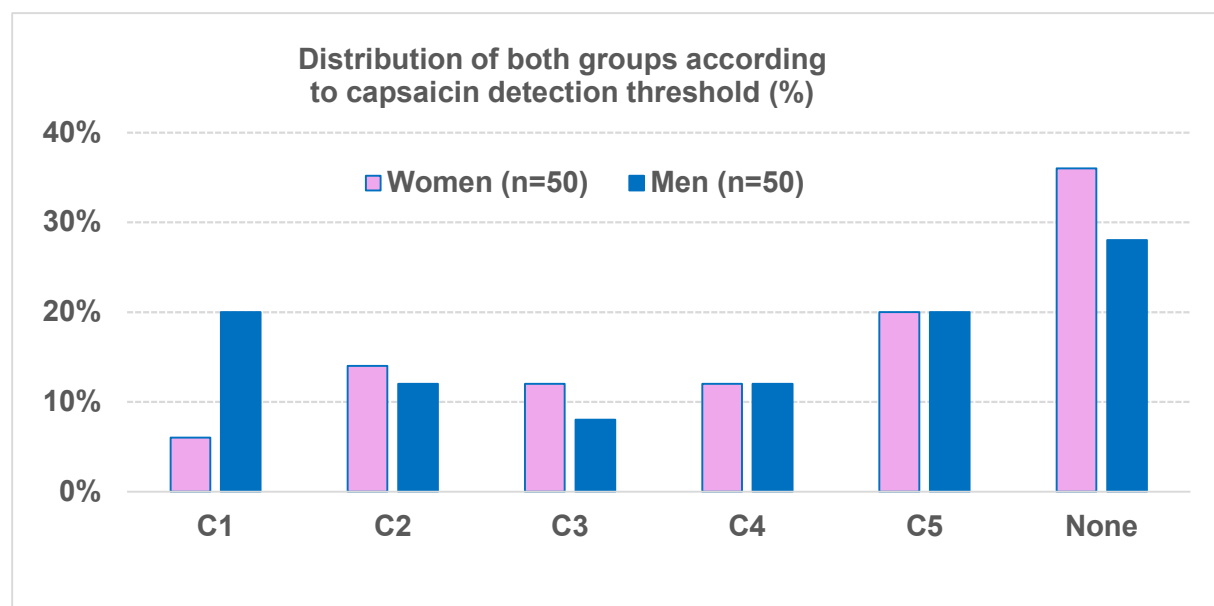


Fig. 2. Capsaicin detection thresholds for both groups (in percentage of the subjects)

### Link between sensitive skin score and capsaicin detection threshold

Figure 3 shows the sensitive skin score (mean with 95% CI) per CDT for both groups. In the female population, a progressive decrease in the sensitive skin score was observed as the detection threshold increased from 6.1 for C1 to 4.3 for None. The only exception corresponded to C3 (mean = 6.9). This link was statistically confirmed using Jonckheere-Terpstra test ( $p=0.0395$ ). This statistical link indicates that the more women reported having sensitive

skin, the lower the concentration of topical capsaicin they perceived. However, this link did not appear in the male population ( $p=0.8036$ ).

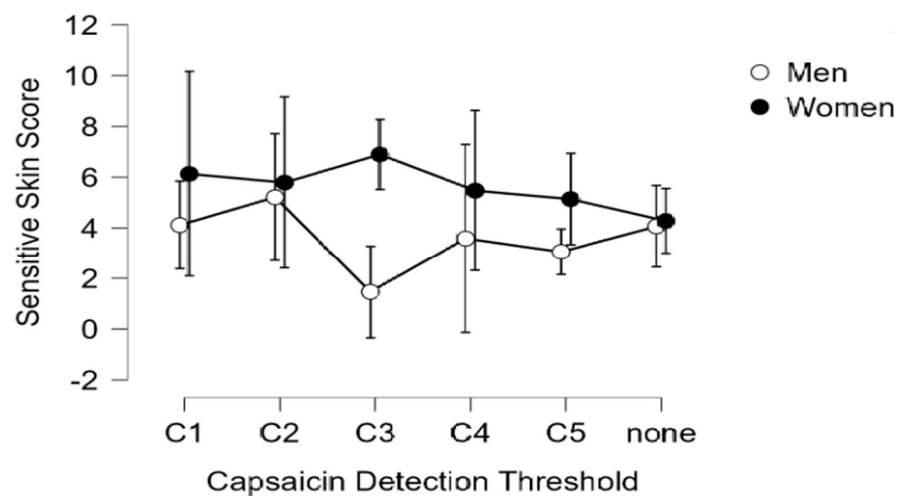


Fig. 3. Representation of sensitive skin score (mean with 95% CI) by capsaicin detection threshold.

#### 4. Conclusion

The study aimed to confirm on 50 men and 50 women of comparable age and ethnic background whether or not men have less sensitive skin than women, as indicated by numerous epidemiological studies [10]. In addition to a questionnaire approach, gender-related differences in facial cutaneous neurosensitivity were explored using the CDT test [16].

The questionnaire in this study confirmed that men generally report less sensitive skin than women. Interestingly, the sensitive skin score summarizing the overall questionnaire response profile showed more inter-group difference than the simple response to the question: "Do you regard yourself as having sensitive facial skin?". In women, is it a greater awareness of this problem, greater exposure to certain triggers such as cosmetics, or a greater ease in recognizing a certain fragility? The question still remains.

The CDT test surprisingly showed that men perceived capsaicin concentrations at least slightly lower than those of women. This result do not correspond to the previous experimental result showing a trend towards a higher sensitivity to LAST in females than males [20]. This apparent difference in results is likely due in part to the different nature of the tests. Unlike the LAST, the CDT does not rely on the individual pain scale. The CDT explores the subject's ability to



perceive the appearance of a subtle stimulus without scoring its intensity. The LAST questions the subject about the severity of the stinging sensations. However, in most published studies women are described as more sensitive to experimental pain than men [21]. CDT results were linked to sensitive skin score in women but not in men. This result would suggest that self-assessment of sensitive skin by women is more relevant than in men.

The present findings confirm in males the main features of the CDT test previously described on women of different populations [16, 17]. Male group as female group was divided into six levels: the five tested capsaicin concentrations and level “none”. The two log unit range of CDT indicates a large inter-individual variability in sensitivity to topically applied capsaicin in men as previously seen in women. This variability at least partially explains the highly variable skin reactivity to external triggers in relation to sensitive skin syndrome. So, it is probably as important to formulate sensitive skin cosmetic products for men as for women, even if men recognize themselves as less affected by this syndrome.

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