BJD
British Journal of Dermatology

Short contact with nickel causes allergic contact dermatitis: an experimental study

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Summary

Background Knowledge about the required duration of exposure for elicitation of allergic nickel dermatitis in nickel-allergic individuals is limited. However, it often has been proposed that short skin contact is safe.
Objectives To examine whether repeated skin contact with nickel over short time periods (3 × 10 min) can elicit allergic nickel dermatitis.
Methods Sixteen nickel-allergic adults and 10 controls were exposed to, respectively, nickel- and aluminium-containing discs on each volar forearm and on each earlobe for 3 × 10 min. One arm was pretreated for 24 h with sodium lauryl sulfate (SLS) 0·5% under occlusion before exposure. One aluminium and one nickel exposure site were clinically evaluated, and blood flow was measured with laser Doppler flowmetry at day 2 and day 4.
Results Ten of 16 (63%) nickel-allergic participants developed allergic nickel dermatitis on SLS-pretreated arm skin and three of 16 (19%) developed it on normal skin on the earlobe. On the SLS-pretreated arms of nickel-allergic participants, blood flow increased significantly more on the nickel-exposed skin than on the aluminium-exposed skin on days 2 and 4. No change in clinical reactivity or blood flow was found on normal forearm skin in nickel-allergic participants or on any skin in controls.
Conclusions This experimental study showed that relatively short repeated skin contact (3 × 10 min) with metallic nickel elicits allergic nickel dermatitis in irritated skin and at sites with previous dermatitis. The results support the restrictions in current nickel regulation.

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Accepted for publication
27 June 2018

Funding sources
M.G.A. and J.D.J. were financially supported by an unrestricted grant from the Danish Environmental Protection Agency. This study was supported by the Aage Bangs Foundation. The funding sources did not play any role in the study design or the preparation of the manuscript.

Conflicts of interest
None to declare.

DOI 10.1111/bjd.16935

What's already known about this topic?

- Repeated low-dose nickel exposure may be a more potent trigger of allergic nickel dermatitis than less frequent exposure to a higher single dose.
- High nickel deposition onto skin can be measured after only seconds of direct skin contact.
- An impaired skin barrier may increase the risk of allergic nickel dermatitis.

What does this study add?

- Relatively short repeated skin contact (3 × 10 min) with nickel has the potential to provoke allergic nickel dermatitis in irritated skin and at sites with previous dermatitis.

Skin contact with nickel-releasing items can lead to nickel allergy and dermatitis if the duration of exposure is sufficient. Due to a high prevalence of nickel allergy in Europe, nickel release from some consumer items became regulated in European Union (EU) member countries in 2000. Since then, the prevalence of nickel allergy has been reduced in some EU countries, but nickel is still the leading cause of contact allergy.[1] The regulation stated that items intended for 'direct and prolonged contact with the skin' were included, although no exact duration of exposure was determined. In 2014, 'prolonged contact with the skin' was defined by the European Chemicals Agency (ECHA) as being 'more than 10 minutes on three or more occasions within two weeks, or 30 minutes on one or more occasions within two weeks'.[2] Although it is well accepted that long-term skin contact can cause nickel allergy and dermatitis, the significance of relatively short and repeated nickel exposure in relation to induction and elicitation of nickel allergy has been less explored.

To evaluate the regulatory protection against nickel allergy and dermatitis in the EU, improved understanding of the association between short repeated skin contact and nickel allergy and dermatitis is needed. We examined whether relatively short skin contact (3 × 10 min) with metallic nickel has the potential to elicit allergic nickel dermatitis on normal and irritated skin in nickel-allergic individuals.

Materials and methods

Study population

We enrolled 16 current nickel-allergic adult participants and 10 control volunteers with no history of contact allergy. The median age of the nickel-allergic participants (13 women and three men) was 55·5 years (interquartile range 44–63·5) and of the controls (nine women and one man) 34·0 years (interquartile range 25–58). Nickel-allergic participants had previously been diagnosed by patch testing with nickel sulfate 5% in petrolatum (Almirall Hermal, Reinbek, Germany) in Finn Chambers in the time period 2015–2017 at the Department of Dermatology and Allergy, Herlev and Gentofte Hospital.

Exclusion criteria for all participants were active dermatitis, scar tissue or tattoos on areas to be exposed, generalized dermatitis, pregnancy, breastfeeding, treatment with topical corticosteroids or other topical immunosuppressants on or near exposure areas within four weeks, use of systemic immunomodulatory treatment within 4 weeks, extensive exposure to ultraviolet radiation within 3 weeks (solarium, sunbathing) and participation in other clinical studies within 4 weeks. Recruitment followed approval from the local ethics committee (H-16050296) and the Danish Data Protection Agency. All participants gave written informed consent before the start of the study. The study was registered at ClinicalTrials.gov (NCT03309215).

Restrictions

During the study period, showers and use of emollients in the skin areas undergoing exposure were not allowed. Participants were not allowed to eat, drink coffee or tea, smoke or do physical exercise for 2 h before blood flow measurements, or to use analgesics 24 h before blood flow measurements.

Metallic discs and preparation

The metallic discs used in the study were composed of > 99 wt.% nickel and > 99 wt.% aluminium (active and negative control discs, respectively) and were manufactured by the Technical University of Denmark, Kongens Lyngby, Denmark. The metallic discs had a diameter of 3 cm (area 7·02 cm^2) (back and forearm exposure) and 1 cm (area 0·79 cm^2) (earlobe exposure). In total, 100 metallic discs were used in the study, and the discs were reused for the participants. Nickel release under various conditions was quantified and will be reported separately (manuscript in preparation). To enable reproducible exposure conditions, one side of all discs was prepared in the same manner 1 day before use (Appendix S1; see Supporting Information).

Exposure area

Four exposure areas of 3·5 × 3·5 cm^2 on the mid volar forearms were marked (Richard-Allan® Regular Tip Skin Marker; Aspen Surgical, Caledonia, MI, U.S.A.). The exposure areas on the arms were 'mirrored' and the set-up was identical in all participants (Fig. 1). The exposure areas were slightly adjusted if a local naevus, large vein or haematoma was present. On the earlobes, the metallic discs were placed centrally and no marking of the skin was made (Fig. S1; see Supporting Information). Only the most distal aluminium and nickel areas (3 and 4) of each arm were used for the repeated evaluation of clinical reactivity and blood flow on all study days. The other exposure areas were used to measure nickel penetration over time, and the data will be presented elsewhere (manuscript in preparation).

Pretreatment with sodium lauryl sulfate

A solution of high-purity sodium lauryl sulfate (SLS) (99% purity; Sigma-Aldrich, St Louis, MO, U.S.A.) was prepared in distilled water to a concentration of 0·5% (w/v). A 200-μL aliquot of the solution was applied on a filter paper disc and fitted into an extra-large (18 mm Ø) Finn Chamber on Scanpor Tape (SmartPractice, Phoenix, AZ, U.S.A.), as recommended.[3] Four chambers were applied to one randomized forearm within 1 min after preparation,[4] and occlusive pretreatment was performed during 24 h. The SLS solution was stored in a refrigerator at 4 °C between use.[4]

Pilot study

A pilot study with three nickel-allergic participants preceded the study. The main purpose was to test the logistics and suitability of the equipment and procedures, resulting in changes of the protocol: the method for preparation of discs was

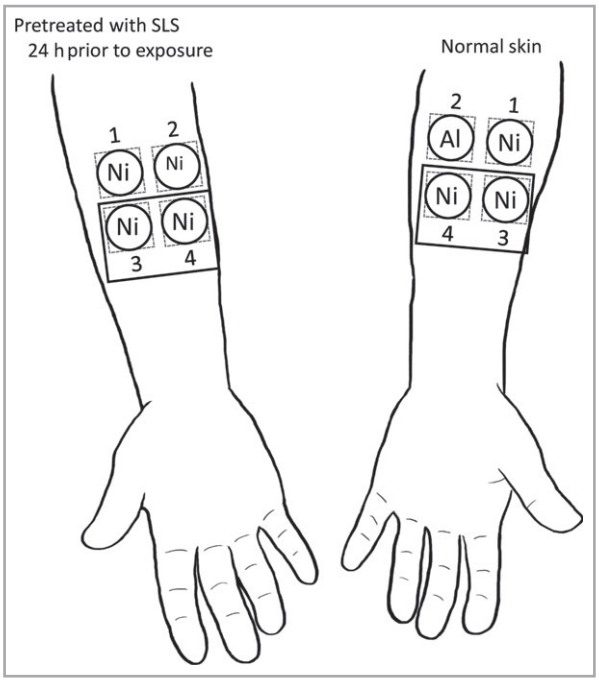

Fig 1. A schematic view of the four exposure areas on each mid volar forearm. The rectangle of each arm marks the two areas (3 and 4) used for all evaluations (clinical and blood flow) during the study. SLS, sodium lauryl sulfate.

changed, points for blood flow measurements were chosen differently, and assessments on day 5 were moved to day 4. More information can be found in Appendix S1.

Experimental study design

The experimental study ran over 12 weeks; the pilot study ran in June 2017 and the main study from September to December 2017. For each participant, the study ran over four study days (Fig. 2) and was conducted at a laboratory and an adjacent exposure chamber located at the Department of Dermatology and Allergy at Herlev and Gentofte Hospital.

On day 0, the four exposure areas on one arm were marked and pretreated with SLS under occlusion (Fig. 1). To verify the nickel allergy status in all participants, patch testing was conducted on the back with nickel sulfate 5% in petrolatum in Finn Chambers. In addition, one prepared disc each of metallic nickel and aluminium was fastened with Scanpor tape on the back. Participants were asked about their previous history of dermatitis on exposure sites and skin diseases in general.

On day 1, the patches with SLS were removed, and the irritant reactions in two areas (3 and 4) were evaluated. The blood flow in the same two areas on the SLS-pretreated arm, on the corresponding two areas on the arm with normal skin and on the skin of both earlobes was measured (Fig. 1) (baseline). On day 1 the participants were acclimatized for 30 min in an exposure chamber with the temperature at 29·2 ± 0·69 °C (range 28·8–29·4) prior to stimulation with the metallic discs, and all metallic disc exposures were performed in the chamber. The exposure chamber (2·1 × 2·2 × 2·3 m), usually used for investigation of airborne allergic reactions, was supplied with fresh air at 0·5 exchange rates per hour and ambient humidity for the season.

Three nickel discs and one aluminium disc were placed centrally in the four premarked exposure areas on each arm. Further, one metallic disc with nickel and one with aluminium were randomly placed centrally on each earlobe. The discs were applied in intervals of 10 min repeated two times with 10-min breaks, thereby being in accordance with the ECHA's definition of prolonged contact.[2] To simulate real-life contact with metallic nickel on both arms and earlobes, friction was created by rotating the metallic discs 90° back and forth two times without lifting the discs from the skin. All discs were applied by the same investigator (M.G.A.); discs were fastened with Scanpor tape and left in place for 10 min. Separate newly prepared discs were used for the three applications at each exposure area.

On the following study days 2 and 4 (24 and 72 h after metallic disc exposure, respectively), clinical evaluation and blood flow measurements were made at the same exposure areas (3 and 4) as on day 1 (Fig. 1). The temperature during measurements of blood flow on days 1, 2 and 4 was kept constant at a mean 23·9 ± 0·78 °C (range 23·3–24·2). The metallic discs and the nickel patch test on the back were removed on day 2 and the clinical evaluations were made on days 2 and 4.

Clinical evaluation

To identify small changes in the exposed forearm skin (irritant and allergic), the exposure areas were evaluated using the modified International Contact Dermatitis Research Group (ICDRG) criteria.[5] Reactions on the earlobes were evaluated as being present or not present. All exposure sites were read by M.G.A. and photos of all exposure sites were subsequently reviewed in a blinded manner by T.M. The clinical evaluation was made and photos were taken 45 min to 1 h after removal of the SLS chambers on day 1 (baseline). Test reactions on the back were photographed and evaluated according to the regular ICDRG criteria approximately 10 min after removal of the chamber and discs.[6]

Skin blood flow measurements

For a quantitative assessment of inflammation, skin blood flow was measured using laser Doppler flowmetry (moorVMS-LDF1, Moor Instruments Ltd, Axminster, U.K.). Prior to the measurements, the participants were instructed to rest for 15 min in the same position in which the measurements were taken, sitting with the exposure area of the forearms at heart level.[7] During the measurements, participants were asked not to move or talk, and to breathe normally. To secure the same measurement points over the study period, we used a template marking the two most peripheral points corresponding to the area exposed to metallic discs on an imaginary horizontal line through the test centre. Three consecutive

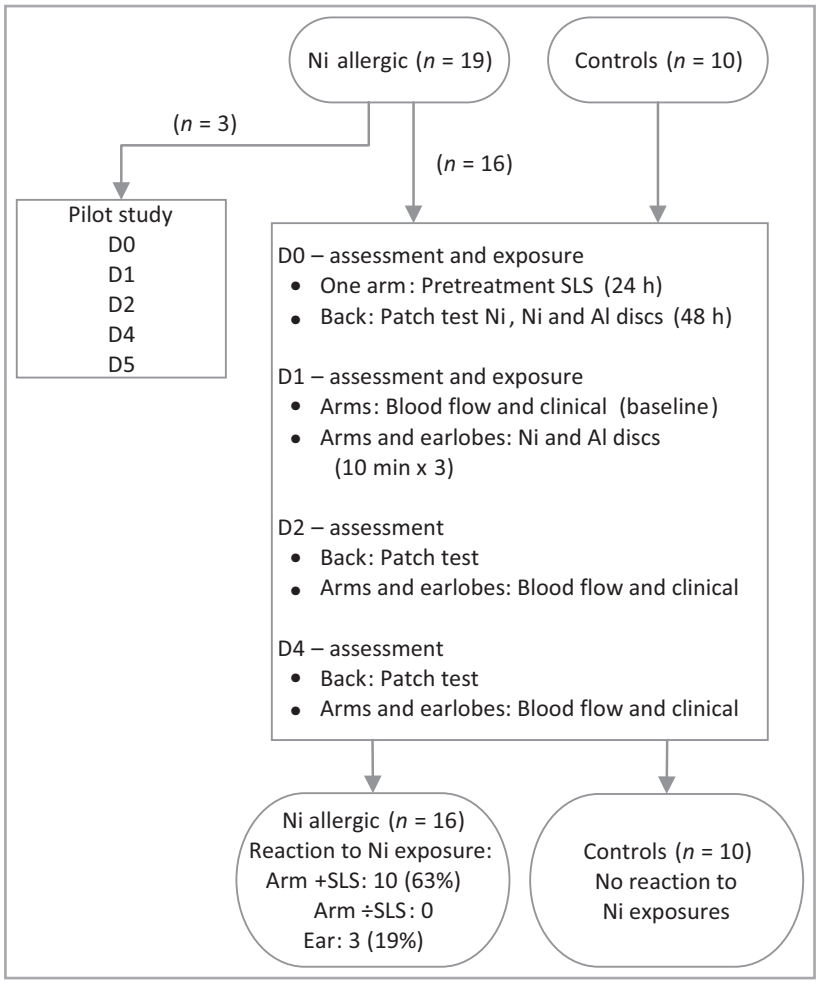

Fig 2. Flowchart of the study including key results. D, day; SLS, sodium lauryl sulfate.

measurements of approximately 20 s were performed, one in the centre of the exposure area and one on either side midway between the centre and the two marked peripheral points. For the earlobes, three consecutive measurements of approximately 20 s were made at the central exposure area.

Statistics

For the statistical analyses, the clinical evaluation scores were transformed to numerical values as follows: ÷ = 0, (+) = 0·5, + = 1·0, +(+) = 1·5, ++ = 2·0, ++(+) = 2·5, +++ = 3·0.[8] For analysis of blood flow measurements, the mean of a steady-state region of interest of each of the three consecutive measurements was used.[7] For monitoring change of the blood flow at one exposure area over time, the baseline values (after SLS occlusion and before nickel or aluminium exposure on day 1) were subtracted from the values at the two different evaluation time points (days 2 and 4).

The resulting blood flow changes at days 2 and 4 for the respective exposure area (SLS or non-SLS, nickel or aluminium) were added for the nickel-allergic group and the control group, respectively. A paired t-test was used to compare the change in blood flow between the nickel and the aluminium exposure areas. A same method was used for the numerical values from the clinical evaluation. A positive allergic reaction was defined as a greater increase in the clinical evaluation score at the nickel area compared with the aluminium area at the respective measurement day.

Normality assumptions for the paired t-test were fulfilled. Power analysis to determine the appropriate sample size was done aiming for 80% power and a significance of 5%. The study data were collected and managed using REDCap electronic data capture tools.[9] All statistical analyses were made in SAS, version 9·4 for Windows (SAS Institute Inc., Cary, NC, U.S.A.) and the graphs with GraphPad Prism version 6·07 for Windows (GraphPad Software, La Jolla, CA, U.S.A.).

Results

All 26 included participants completed all study days. One nickel-allergic participant was excluded from the analyses of the arms at day 4 because she developed dermatitis with suspected superinfection at the nickel exposure areas of the SLS-pretreated arm, which impeded further evaluation. The study

characteristics for each participant are shown in Table 1. Previous and current nickel patch test reactivity in the nickel-allergic participants can be found in Table S1 (see Supporting Information).

Ten of the 16 nickel-allergic participants (63%, 95% confidence interval 38·6–81·5) developed allergic nickel dermatitis on the SLS-pretreated skin, and none did on normal skin on the arms. For the nickel-allergic participants, the overall increase in clinical reactivity on the SLS-pretreated skin from baseline to the two measurement days (days 2 and 4) was significantly higher at the nickel vs. the aluminium exposure area (Fig. 3a). The blood flow increased, with 42·0 tissue perfusion units (TPU) more at the nickel- vs. the aluminium-exposed SLS-pretreated skin at day 2, and with 50·2 TPU more at day 4 for nickel-allergic participants (Fig. 3b, Table 2). A small but significant increase in blood flow at the nickel vs. aluminium exposure sites was seen in normal skin of nickel-allergic participants from baseline to day 2, but not to day 4 (Table 2).

Three of the 16 nickel-allergic participants (19%, 95% confidence interval 6·6–43·0) reacted to metallic nickel on the earlobe, one of them at day 4 and the other two after the last study day, namely at day 5. The two allergic reactions that occurred on day 5 were assessed by a description of the reaction and a verifying photo received from the nickel-allergic participants. There was no change in blood flow in the earlobes at the nickel site compared with the aluminium site for nickel-allergic participants at any time point compared with baseline. The three nickel-allergic participants with earlobe reactions in this study (nos. 4, 7 and 15) had reported previous earlobe dermatitis. Two of them reported a history of hand dermatitis and one of atopic dermatitis (Table 1).

No allergic reactions or blood flow changes were seen in the control participants (Table 2). The key results of the study presented for each individual are listed in Table S2 (see Supporting Information). Photos of the exposure areas of one nickel-allergic participant and one control volunteer over the study period can be found in Figure 4.

Discussion

In this experimental study, we found that relatively short repeated skin contact with metallic nickel (3 × 10 min) caused allergic nickel dermatitis in irritated skin in the

Table 1 Characteristics of the study population

				Self-reported			
Participant	Sex	Age (years)	No. of ear piercings	Atopic dermatitis[a]	Hand dermatitis[a]	Hand dermatitis ≤ 3 months[b]	Earlobe dermatitis ever
Nickel							
1	Female	56	2	−	−	−	+
2	Female	48	2	−	−	−	+
3	Male	66	0	−	−	−	−
4	Female	19	≥ 8	+	+	+	+
5	Male	65	0	−	−	+	−
6	Female	20	≥ 8	−	−	−	+
7	Female	69	2	−	−	−	+
8	Female	65	2	−	−	−	+
9	Female	55	2	−	+	+	+
10	Female	61	4–7	−	−	−	+
11	Male	56	0	−	+	+	−
12	Female	48	4–7	−	−	−	−
13	Female	44	2	+	−	−	−
14	Female	44	4–7	−	−	−	+
15	Female	62	2	−	+	+	+
16	Female	42	2	−	−	−	+
Control							
17	Female	63	2	−	−	−	−
18	Female	24	2	−	−	−	−
19	Female	66	2	−	−	−	−
20	Female	34	2	−	−	−	−
21	Female	58	2	−	−	−	−
22	Female	25	3	−	−	−	−
23	Female	27	3	−	−	−	−
24	Female	34	4–7	−	−	−	−
25	Female	57	2	−	−	−	−
26	Male	24	0	−	−	−	−

[a]Participants were asked if a doctor had ever told them that they had hand dermatitis or atopic dermatitis. [b]Participants were asked for presence of dermatitis within the last 3 months; dermatitis was reported only on the hands in this period.

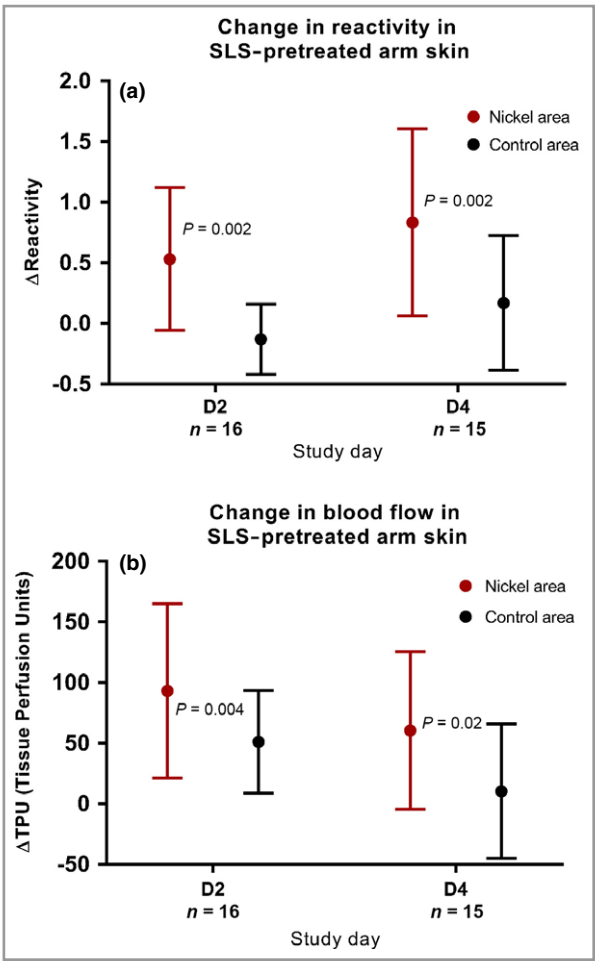

Fig 3. (a) Sodium lauryl sulfate (SLS)-pretreated arm skin in nickel-allergic participants. The change in clinical reactivity is given as a numerical value (mean with 95% confidence interval) from baseline to measurement days (D2, D4) at nickel and aluminium exposure areas. The numerical values were transformed from scores as follows: ÷ = 0, (+) = 0·5, + = 1·0, +(+) = 1·5, ++ = 2·0, ++(+) = 2·5, +++ = 3·0. (b) Change in blood flow on SLS-pretreated arm skin from baseline to the measurement days (D2, D4) at the nickel and aluminium exposure areas (mean with 95% confidence interval). A paired t-test was used to compare the change in clinical reactivity (a) and blood flow (b) between the nickel and aluminium sites.

majority (63%) of nickel-allergic participants. This finding was supported by a statistically significant blood flow increase both 1 and 3 days after exposure to nickel compared with aluminium, and in the absence of clinical reactivity in non-nickel-allergic controls. Furthermore, we showed that some of the nickel-allergic participants (three of 16) developed dermatitis on earlobe skin after nickel exposure.

We created a theoretical worst-case scenario for provocation of allergic nickel dermatitis: irritated skin,[10,11] restriction of showering and emollients, slightly elevated ambient temperature,[12,13] pure nickel discs with newly prepared and untouched surfaces, and discs manually applied with friction and pressure.[14] Although these conditions are presumed to increase the risk of elicitation, they are not far from the real-life setting. Irritated skin is common in the general population, demonstrated recently by a lifetime prevalence of itchy skin rash and contact dermatitis in 52·3% and 15·5% of people, respectively.[15] Also, pressure and friction are common during skin contact with metallic items. A strength of the present study is that the set-up was controlled and reproducible: the metallic discs had equal surface properties, the temperature during exposures and measurements was uniform, all exposures and assessments were made by the same investigator, and all photos of the exposure areas were subsequently evaluated by a blinded investigator (T.M.).

The elicitation potential of short nickel skin contact has rarely been studied. Most studies on short repeated nickel exposure are repeated open application test studies. Fischer *et al.* found that repeated low-dose nickel exposure may be a more potent trigger of allergic nickel dermatitis than less frequent exposure to a higher single dose.[16,17] The exposures in the present study may more accurately represent most real-life exposures with nickel, as we used metallic nickel instead of nickel solution, and included factors such as pressure and friction. Also, the exposures were made in an exposure chamber with a temperature resembling an average Mediterranean midsummer day. Remarkable differences in the prevalence of nickel allergy have consistently been demonstrated between EU countries.[1] Several factors affecting the exposure to nickel are likely to contribute to the differences. Among them are fashion, compliance with the nickel restriction,[18] and possibly ambient temperature.[13]

The fact that we found enhanced clinical reactivity to nickel only on irritated skin in nickel-allergic participants and on skin with previous earlobe dermatitis (suggestive of allergic nickel dermatitis) is consistent with the current literature in the field. The elicitation threshold by a single occlusive nickel exposure on skin with a defective barrier has generally been found to be reduced compared with an intact barrier.[10,19] Furthermore, skin sites with previous allergic nickel dermatitis have been shown to have a local allergen-specific memory and a reduced threshold for elicitation of dermatitis.[5,20,21] The results of this study are in line with our previous finding that nickel-allergic individuals report dermatitis after relatively short direct contact with metallic items (21·4% after 10 min of contact).[22] Moreover, the increased occurrence of nickel dermatitis in patients with atopic dermatitis may point to the effect of an irritated and impaired skin barrier.[23]

Weaknesses of the study include the following. Firstly, there was no standardization of the pressure on the discs. Secondly, the blood flow measurement points were marked only peripherally on the skin, which increases the risk that the measurements were not made on exactly the same three points over the study days. Using the mean of three measurements reduces the uncertainty regarding this factor. Thirdly, no blinding could be done for the metallic disc exposures, clinical evaluations or blood flow measurements, as the same exposure pattern was used for all participants to avoid confusion. Fourthly, one could argue that the nonacceptance of

Table 2 Blood flow in nickel-allergic and control participants

	Patients	Day	Baseline blood flow (TPU)[a]	Change in blood flow from baseline (TPU) (95% CI)[b]	P-value
SLS-pretreated arm skin					
Nickel-allergic participants	16	2	58·0	42·0 (15·3–68·8)	0·004
	15[c]	4	53·5	50·2 (7·5–93·0)	0·024
Controls	10	2	42·2	−14·3 (−30·5–1·82)	0·076
	10	4	42·2	−3·5 (−23·6–16·6)	0·7
Normal arm skin					
Nickel-allergic participants	16	2	24·2	3·8 (0·82–6·86)	0·016
	15[c]	4	23·7	2·3 (−1·72–6·23)	0·24
Controls	10	2	25·6	−1·1 (−6·43–4·30)	0·66
	10	4	25·6	−2·3 (−9·16–4·63)	0·48

TPU, tissue perfusion units; CI, confidence interval; SLS, sodium lauryl sulfate. [a]The mean of the baseline values of the aluminium and nickel exposure sites. [b]Difference between the nickel and aluminium test sites. [c]One participant was excluded at day 4 due to suspected superinfection.

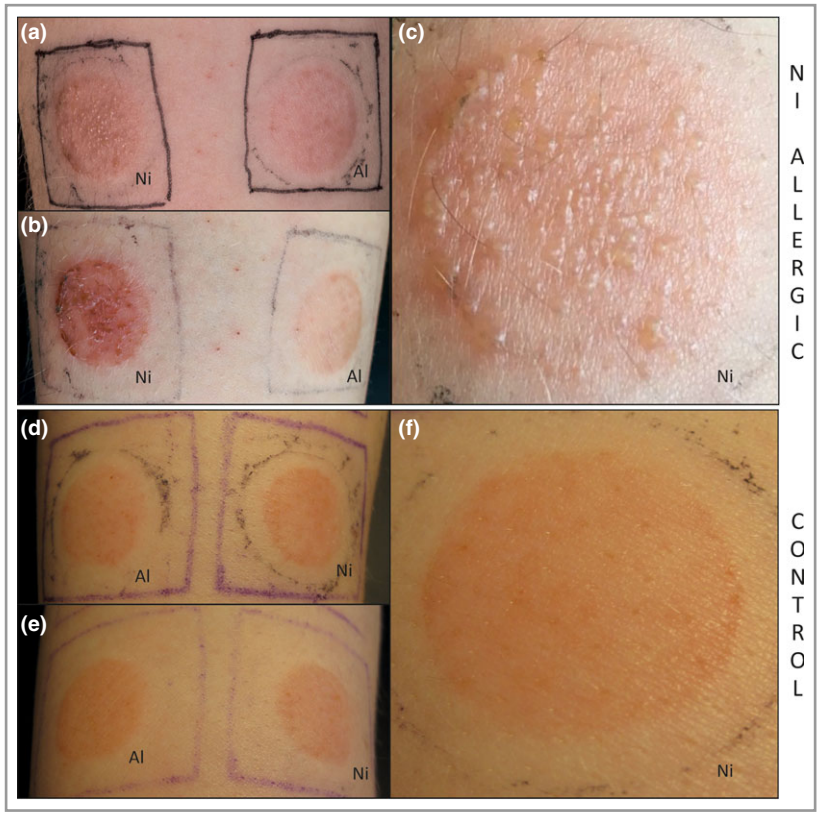

Fig 4. Photos of the reactions of one nickel-allergic participant (no. 4; a–c) and one control participant (no. 20; d–f) at day 2 (a, d) and day 4 (b, e) after exposure to nickel and aluminium discs on the sodium lauryl sulfate-pretreated arm. (c, f) Close-up of the nickel-exposed areas at day 2, corresponding to (a) and (d).

emollients and water on exposure areas is far from the real-life setting. However, this was a compromise to produce a worst-case scenario, to meet the aim of studying the potential of relatively short repeated nickel exposure.

In the present study, we wanted to examine whether relatively short repeated nickel contact can elicit allergic nickel dermatitis. The duration of the exposures fulfilled the definition of prolonged contact according to the ECHA, in an attempt to enhance protection by the nickel regulation. In real life, skin contact with metallic items can be located to sites with previous irritant or allergic contact dermatitis, which may be more susceptible to short-duration nickel contact. From the results we conclude that in skin with low-grade dermatitis, or previous dermatitis, relatively short skin contact with nickel can be sufficient to elicit allergic nickel dermatitis. The results may be valuable for nickel-allergic individuals and dermatologists in order to evaluate the possible risk of allergic nickel dermatitis after short contact with metallic items. From

a regulatory perspective, the results of this study underline the importance of regulating metallic items intended for short direct contact, in order to prevent allergic nickel dermatitis.

In conclusion, this experimental study shows that relatively short repeated skin contact with metallic nickel can elicit allergic contact dermatitis in irritated skin and on sites with previous dermatitis.

Acknowledgments

We are very grateful to Anne Marie Topp, Lene Toft-Jensen and Julie Sølberg for their help during the experiments, and Anna Bünning Olsson for graphics support. Josefine Bandier granted us access to the laser Doppler flowmeter.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Appendix S1 Pilot study and metal disc preparation.

Fig S1. Metallic disc placed centrally on the earlobe without marking of the skin.

Table S1 The reproducibility of nickel allergy in the nickel-allergic participants illustrated by patch test reactivity and reactions to metal discs on the back.

Table S2 Key results for each nickel-allergic participant.

Powerpoint S1 Journal Club Slide Set.