

Does airborne nickel exposure induce nickel sensitization?

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Background and objective: Nickel is one of the most prevalent causes of contact allergy in the general population. This study focuses on human exposure to airborne nickel and its potential to induce allergic sensitization.

Materials and methods: The study group consisted of 309 children at school-starter age living in the West of Germany in the vicinity of two industrial sources and in a rural town without nearby point sources of nickel. An exposure assessment of nickel in ambient air was available for children in the Ruhr district using routinely monitored ambient air quality data and dispersion modelling. Internal nickel exposure was assessed by nickel concentrations in morning urine samples of the children.

Results: The observed nickel sensitization prevalence rates varied between 12.6% and 30.7%. Statistically significant associations were showed between exposure to nickel in ambient air and urinary nickel concentration as well as between urinary nickel concentration and nickel sensitization. Furthermore, an elevated prevalence of nickel sensitization was associated with exposure to increased nickel concentrations in ambient air.

Conclusion: The observed associations support the assumption that inhaled nickel in ambient air might be a risk factor for nickel sensitization; further studies in larger collectives are necessary.

Key words: ambient air; exposure; nickel; nickel in urine; nickel sensitization. © John Wiley & Sons A/S, 2010.

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Nickel, a metal widely distributed in the environment and as a constituent of many alloys, is one of the most prevalent causes of contact allergy in the general population. Median nickel contact allergy prevalence from studies mainly performed in North America and Western Europe between 1966 and 2007 amounted to 8.6% (range 0.7–27.8%) (1). Nickel allergy is primarily induced by skin exposure to nickel ions. Other routes of nickel exposure in relation to nickel sensitization are considered to be

of lower importance. However, there is increasing evidence that oral intake of nickel via food and drinking water can exacerbate nickel dermatitis in nickel-sensitive individuals (2). Airborne nickel dermatitis (3, 4) and asthma (5) have been reported in a few case studies, mainly from occupationally exposed individuals.

To date, few studies have focused on airborne nickel exposure of humans and its possible health effects associated with industrial pollution.

In particular, there is very little information in the literature as to whether nickel in ambient air might be able to induce allergic sensitization in humans (6).

In recent years, we have performed several studies on the influence of industrial pollution on children's health in North Rhine Westphalia, Germany. This area is important for coal mining, steel production, and other heavy industries. In 2000, two industrial 'hot spots' were identified. These areas were characterized by increased total suspended particulate (TSP) levels in the ambient air and site-specific air pollutants, such as nickel and chromium. In a cross-sectional study, the health outcome of children of school-starter age in relation to this exposure has been evaluated. An overview on the first results has been given elsewhere (7). A striking finding was the high prevalence of nickel sensitization in children living close to a steel mill. Here, we present details on the part of the study that is related to airborne nickel exposure as a possible source of nickel sensitization.

Materials and Methods

Study areas and study groups

The cross-sectional study consisting of two 'hot spots' and one reference area in North Rhine Westphalia was conducted during spring/early summer 2000 by following a common protocol. All school starters (1325) in the year 2000 living in the proximity of a coking plant, a steel mill, a sintering plant, and a blast furnace in Duisburg ($n = 620$); in the vicinity of a steel mill in Dortmund ($n = 390$); and in the rural town of Borken ($n = 315$) were asked to participate. Of these children, 1079 were attended for routine examination at the Sanitary Board and 696 children (response rate 64.5%) took part in this study. Only 309 children who had a valid result for the nickel sensitization test and had lived >2 years at their actual home address (therefore exposed $>1/3$ of their life to the assessed nickel in ambient air) were included in the analyses, which are as follows.

Ambient air nickel exposure

Using routinely monitored ambient air quality data of the State Environment Agency of North Rhine Westphalia (www.lanuv.nrw.de) and by means of Lagrange dispersion modelling, an individual annual average concentration was obtained and attributed to each dwelling site of the participants within the city. The reference area of Borken had only one air quality monitoring station and this provided a single background exposure level for the children living in this area.

Nickel concentration in urine

For assessment of internal nickel exposure, morning urine samples were collected. The acidified samples were adjusted to pH 3 and subsequently mixed with 1 ml of an aqueous solution containing 2% ammonium pyrrolidinedithiocarbamate (APDTC; p.a. grade, Merck, Darmstadt, Germany). The formed APDTC complexes were then extracted with 1 ml 4-methyl-2-pentanone (MIBK; p.a. grade, Merck, Darmstadt, Germany) for 1 min. After centrifugation (30 min, 4000 g, 4°C), the organic layer was separated and used for nickel analysis by electro-thermal atomic absorption spectrometry (ET-AAS) using a Perkin-Elmer ET-AAS instrument model 4100 ZL. The limit of quantification (LOQ) of the analytical procedure was 0.3 µg/l. No samples below LOQ were observed. Urine samples with creatinine levels >3.0 and <0.2 g/l were excluded from statistical analysis.

Nickel from drinking water

The nickel content in the drinking water was analysed as a potential confounder. Here, too, the ET-AAS was used for the analysis (for details see Ref. 8). The mothers reported on the average tap water consumption of their children. The measurements of nickel content in drinking water were performed only in the study areas of Borken and Dortmund. The LOQ of the analytical procedure was 2.5 µg/l.

Nickel sensitization test and potential confounders

To assess environmental, hereditary, ethnic and life style factors as potential confounders, a standardized questionnaire was used. Details are given by Sugiri et al. (9). Clinical observations included dermatological examinations and patch testing. The TRUE test® with 24 baseline allergens, among them nickel(II) sulfate (Pharmacia, Uppsala, Sweden) was applied for 2D on the upper back; the readings were performed on D2 and D3 by dermatologically trained physicians who examined the child's skin. Patch tests were performed as recommended by the International Contact Dermatitis Research Group (10). For the final analysis, only definitive positive and negative results were considered, whereas irritant and questionable results were excluded. More details are given by Ring (11).

Statistical analysis

Statistical analysis was performed using SAS version 8.2 (SAS/STAT Software, SAS Institute, Inc., Cary, NC, USA). Nickel levels in tap water less than LOQ were set to two-thirds of LOQ.

For a comparison of groups, Mann–Whitney, Kruskal–Wallis, and χ^2 tests were used. The association between nickel concentrations in urine and nickel concentrations in ambient air was assessed by means of Spearman's correlation coefficient and linear regression. The influence of exposure variables on health outcomes was estimated by means of logistic regression analysis, including potential confounders (such as nationality, sex, age, piercing, nickel uptake by drinking water, parents' educational level, passive smoking, and residential area) as covariates to control for confounding. Adjusted odds ratios (OR) together with their 95% confidence interval were used as measures of association.

Results

Characteristics of the study group

The characteristics of the study group specified by study area and in total are summarized in Table 1. The collective of Dortmund stands out by its strikingly high-prevalence rate of nickel sensitization of 31%. The percentage of children that had ear piercing was relatively high and was strongly related to being female. Further stratification by sex showed a significant association between sex and ear piercing, as 88.5% of pierced children were girls ($P < 0.001$) with 42.6% of children having pierced ears in total. The socio-economic and socio-demographic background of the children in Duisburg differed strongly from the two other areas as only 20% of their parents had more than 10 years of school education in contrast to 34% in Borken and Dortmund and 60% were of non-German nationality (predominantly Turkish nationality) compared with 100% and 81% German nationality in Borken and Dortmund, respectively. Furthermore, the children in Duisburg less frequently had an atopic predisposition (prevalence: 28%) than those in the two other areas (prevalence: 54%) where prevalence of eczema, allergy,

hay fever or asthma in the child's parents ever diagnosed by a physician (lifetime prevalence) was used as an indicator of the child's predisposition. Environmental tobacco smoke exposure was lowest in Borken.

External and internal nickel exposures and their associations

The differences in ambient air quality data specified by area are listed in Table 2. As showed, the children residing in Dortmund had higher values of nickel concentration in ambient air compared with the reference area Borken. The correspondent values in the study area Duisburg were even higher (Mann–Whitney test: $P < 0.001$) then in Dortmund. Because the daily uptake of nickel in tap water has been assessed only in Borken and Dortmund the further analysis of this parameter was restricted to these two areas. As shown in Table 3, the observed differences of distribution parameters between both areas were not significant (Mann–Whitney test: $P = 0.289$). All nickel levels in urine were above the LOQ. The urinary nickel distribution for the three study groups of Borken, Dortmund, and Duisburg is shown in Table 4. Corresponding to the ambient air nickel exposure concentrations, the children living in Duisburg had the highest median nickel concentration in morning urine. The highest urinary nickel concentrations were observed in children living in Dortmund, whereas the median urinary nickel concentration in Dortmund was nearly identical to the median level of the children from the reference area Borken. The comparison of distribution of urinary nickel exposure for the three areas by means of Kruskal–Wallis test showed significant differences ($P < 0.001$), whereas the difference between Dortmund and Borken was not significant (Mann–Whitney test: $P = 0.195$). A weak but significant correlation

Table 1. Characteristics, atopic diseases and symptoms, and allergic test results of the study group of children from Borken, Dortmund and Duisburg, Germany

	Borken ^a	Dortmund ^a	Duisburg ^a	Total ^a	P-value ^b
Age, mean (years)	6.3 (105)	6.2 (101)	6.5 (103)	6.3 (309)	<0.001
Sex (male)	45.7 (105)	42.6 (101)	52.4 (103)	46.9 (309)	0.353
Nationality, German	100.0 (104)	81.2 (101)	40.2 (102)	73.9 (307)	<0.001
Parents' education ^c	33.0 (103)	35.4 (96)	19.8 (96)	29.5 (295)	0.037
Ear piercing	39.1 (105)	41.8 (98)	47.1 (102)	42.6 (305)	0.498
Predisposition ^d	54.3 (105)	53.0 (100)	27.7 (101)	45.1 (306)	<0.001
Passive smoking	19.4 (103)	45.5 (101)	48.0 (100)	37.5 (304)	<0.001
Current allergic eczema ^e	5.8 (104)	8.1 (99)	4.0 (101)	5.9 (304)	0.465
Patch test Ni(II)SO ₄	13.3 (105)	30.7 (101)	12.6 (103)	18.8 (309)	<0.001

^aPercentage and sample size in parentheses.

^bTest of differences between areas: χ^2 -test and Kruskal–Wallis test, respectively.

^cSchool years >10.

^dFather or mother with allergy or eczema or asthma or hay fever.

^ePoint prevalence, day of investigation.

Table 2. Ambient air exposure to nickel in TSP (ng/m³) of children from Borken, Dortmund and Duisburg, Germany

Study area	Borken ^a	Dortmund	Duisburg	Total
<i>n</i>	105	99	99	303
Range	2.5	5.0–16.5	5.5–24.8	2.5–24.8
P25	–	5.0	11.8	2.5
Median	–	5.0	14.9	5.0
P75	–	7.2	18.8	11.8

TSP, total suspended particulate; *n*, sample size; Px, xth percentile.^aBorken had only one ambient air measuring station (background level).**Table 3.** Nickel uptake in drinking water (µg/d) in children from Borken and Dortmund, Germany

Study area	Borken	Dortmund	Total
<i>n</i>	80	92	172
Range	0.00–26.00	0.00–48.10	0.00–48.10
P25	0.52	0.53	0.53
Median	0.90	1.16	1.01
P75	2.08	2.58	2.39

n, sample size; Px, xth percentile.**Table 4.** Nickel in the morning urine (µg/l) of children from Borken, Dortmund and Duisburg, Germany

Study area	Borken	Dortmund	Duisburg	Total
<i>n</i>	78	73	59	210
Range	0.30–15.07	0.39–26.02	0.67–16.00	0.30–26.02
P25	1.53	1.66	3.00	1.83
Median	2.61	2.67	4.60	3.07
P75	4.07	5.79	6.75	5.70

n, sample size; Px, xth percentile.

($r = 0.256$, 95% confidence limits: 0.137–0.375, $P < 0.001$) between nickel concentration in ambient air and urine was observed using Pearson correlation of the log-transformed values (Fig. 1). Because Borken had only one air quality monitoring station the same correlation analysis was repeated without this area. Here too, a weak but significant correlation ($r = 0.195$, 95% confidence limits: 0.029–0.361, $P < 0.025$) between urinary and ambient air nickel levels was found.

Association between nickel exposure and nickel sensitization

The comparison of the nickel concentrations in TSP of ambient air between sensitized and non-sensitized children is shown in Fig. 2a and it shows an association of nickel sensitization prevalence with the exposure to nickel in ambient air for the Duisburg area (Mann–Whitney test: $P = 0.094$). A similar association in Dortmund was not observed probably because the nickel concentrations were higher in ambient air registered in

Duisburg than that in Dortmund and so the differences (sensitized/non-sensitized) in Duisburg were more pronounced. Children's urinary nickel concentrations separated by study area and patch-test results are shown in Fig. 2b. Overall, nickel levels of sensitized children were higher in urine than that of non-sensitized children (Mann–Whitney test: $P < 0.001$). Children who had an urinary nickel exposure or an ambient air nickel exposure below the median of the respective exposure showed a higher prevalence of nickel sensitization than those with both levels below median (χ^2 -test: $P = 0.109$).

Logistic regression analysis

Besides nickel in ambient air and internal nickel exposure, the following factors are assumed to affect the prevalence of nickel allergy in children and, therefore, are considered as potential confounders for the association between the external and, respectively, internal exposures of nickel and nickel sensitization: sex, social status, nationality, ear piercing, passive smoking, family predisposition, and nickel uptake in tap water. The social status was assessed by classifying the school grade achieved by the parents. Additionally, the children's area of residence was introduced as an independent determinant in the regression model to cover unknown risk factors specific for the respective area. Borken was used as the reference. Nickel uptake in tap water on the day of examination was only available for Dortmund and Borken. In a subgroup analysis, the daily nickel uptake in tap water showed no influence on the nickel sensitization in the study group with tap measurements available and, therefore, was not considered anymore as a potential confounder. Adjusted OR estimated by logistic regression analysis (Table 5) show the associations of ambient air and internal nickel exposure and other potentially influencing factors with the nickel sensitization prevalence within the study group. Additionally, the raw OR of each influencing factor are also shown in Table 5. The internal nickel exposure assessed by nickel in urine turned out to be an important and significant risk factor for nickel sensitization (Table 5, Model 2). The prevalence of nickel sensitization was about twice as high as in children with nickel urine concentrations above the 75th sample percentile compared with children with concentrations below the 25th percentile. Furthermore, the external nickel exposure assessed by the nickel concentration in TSP of ambient air as well showed a significant influence ($P = 0.062$) on the nickel sensitization prevalence (Table 5, Model 1). As estimated by the regression model, the prevalence of nickel sensitization was about four times as high as in children with an exposure to nickel in ambient air

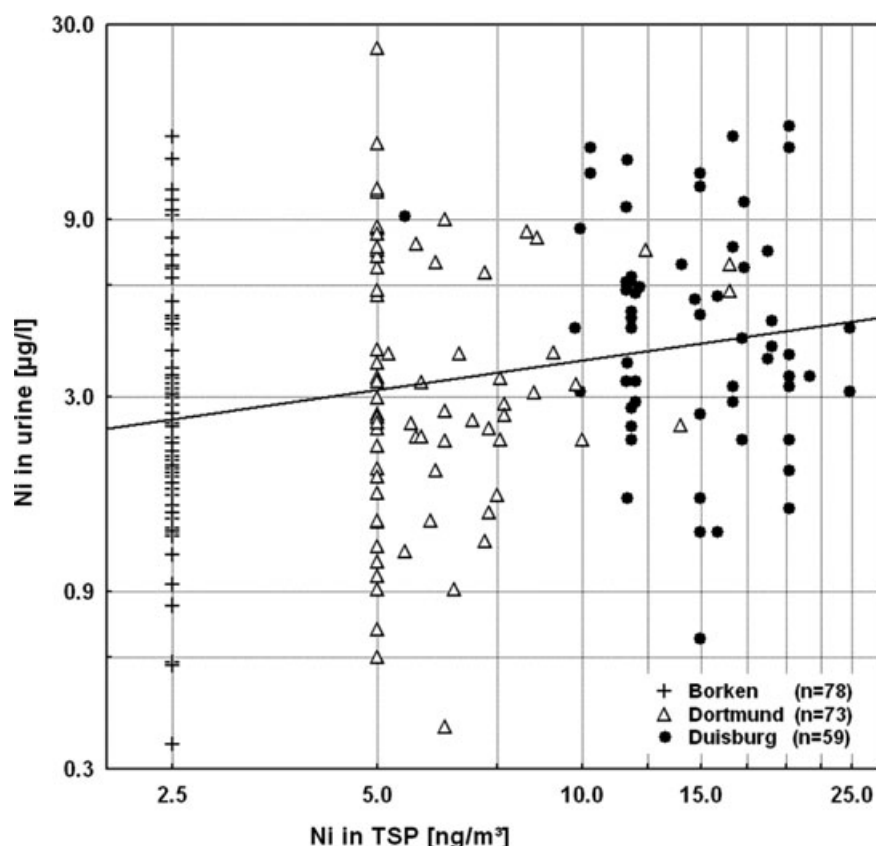


Fig. 1. Association between exposure to nickel in total suspended particulate in ambient air and urinary nickel of children from Borken, Dortmund and Duisburg, Germany, with linear regression in double logarithmic scale. TSP; total suspended particulate.

above a concentration level of 12 ng/m^3 compared with children with concentrations below 2.5 ng/m^3 . Obviously by comparing the raw and adjusted OR, the study area was a strong confounder for the influence of nickel in ambient air on nickel sensitization. Furthermore, the lower prevalence level in Duisburg in comparison with Borken remained unexplained in regression modelling. Higher social status (parents' education level) was a further risk factor of nickel sensitization, but with weak significance. All the other factors considered in the regression analysis were of no significant influence. By comparing the pseudo R^2 of the two regression models, the nickel concentration in urine turned out to have a higher explanatory value than nickel in ambient air.

Discussion

This study shows a statistically significant association between nickel sensitization and internal nickel exposure in the investigated study group of 6-year-old children, as urinary nickel values of sensitized children were significantly higher than that of non-sensitized children. At a weaker significance level, the association between the mean annual exposure to nickel in ambient air and the nickel sensitization

also was obvious in multivariate logistic regression analysis ($P = 0.062$). Furthermore, the assumption that inhaled nickel in ambient air was a risk factor of nickel sensitization is supported by the significant association between urinary nickel concentration and exposure to nickel in ambient air. The otherwise potentially influencing factors such as sex, age, nationality, familial predisposition, environmental tobacco smoke or nickel exposure through skin or through drinking water did not show noticeable associations with the prevalence of nickel sensitization in the study group. The only exception was a higher parental school education which resulted in increased nickel sensitization prevalence. This result of an influence of nickel exposure in ambient air on nickel sensitization in children must be appraised in view of the large variability of nickel sensitization prevalence within the study areas. The sensitization prevalence in the industrialized area of Dortmund was more than twice as high as in the rural area of Borken, but the prevalence in the other industrialized area of Duisburg was even less than in Borken. In the statistical modelling, the environmental nickel exposure was not able to explain the large differences of sensitization prevalence between study areas.

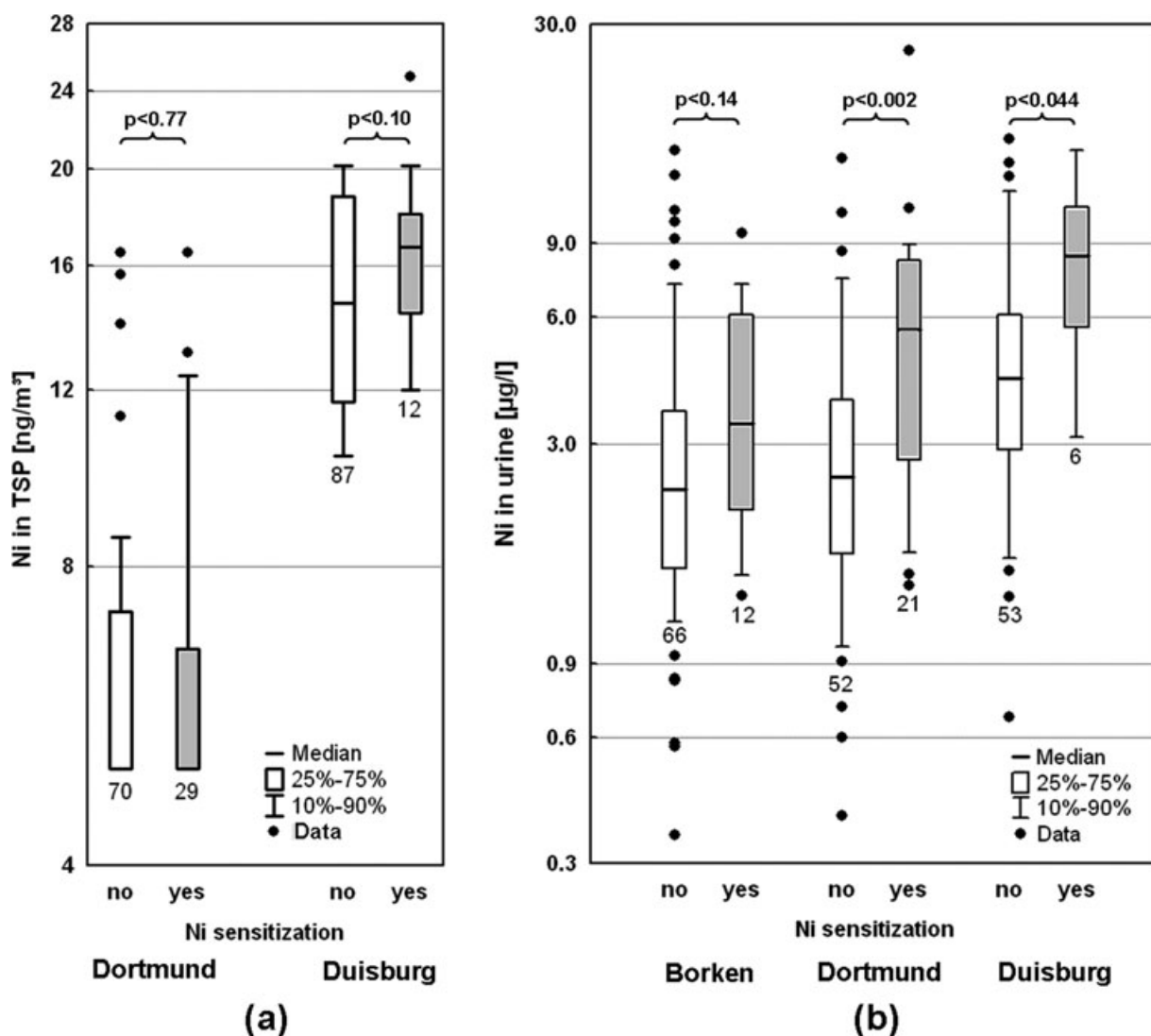


Fig. 2. (a) Exposure to nickel in TSP (total suspended particulate) in ambient air and (b) urinary nickel levels of nickel sensitized and non-sensitized children from Dortmund and Duisburg, Germany; distributions represented by box–whisker plots, Mann-Whitney test for group comparison.

Recent epidemiological studies have showed that the differences in air pollution are associated with allergic symptoms and diseases in the general population (12). These findings are consistent with previous observations showing that the metal composition of ambient particulate matter influences the severity of allergic airway diseases in humans and mice (13, 14). In our study, we observed remarkably high prevalences of allergic symptoms, diseases, and sensitizations in the children from the study area in Dortmund, which was situated in close vicinity to a steel mill (7).

Our findings could have the following potential explanation. Although cutaneous nickel exposure occurs from time to time, airborne exposure is constantly present; hence, even the exposure of the low concentrations of nickel in ambient air may be sufficient to induce sensitization. Furthermore, the

mucosa of the respiratory tract of children is often inflamed or irritated. Recent studies have shown that the metal composition of ambient particulate matter influences the severity of allergic airway diseases in humans and mice (12, 13). Inflammation or irritation causes the creation of an acid milieu that facilitates penetration of particles into the tissue. Nickel present in the inhaled air may be oxidized by oxidative species usually present in inflamed tissue. Nickel in oxidation states III and IV, as previously described by Artik et al. (14), is more potent in inducing nickel sensitization, as it probably causes the enhancement of production of major histocompatibility complex (MHC) and co-stimulatory molecules responsible for priming and cloning of T-cells. The clinical evidence that allergy occurs more readily in inflamed tissue supports this hypothesis.

Table 5. Association between nickel sensitization determined by patch test and exposure to nickel in ambient air and urine, respectively, for children from Borken, Dortmund and Duisburg, Germany, estimated by raw OR and OR adjusted for potential confounders using logistic regression (sample size: 193)

Influencing factors	Model 1				Model 2		
	OR _{raw}	OR _{adj}	95% CI	P	OR _{adj}	95% CI	P
Ni in TSP (9.3 ng/m ³) ^a	0.99	4.23	0.92–19.43	0.062	–	–	–
Ni in urine (3.9 µg/l) ^a	1.80	–	–	–	2.07	1.34–3.19	0.001
Sex (male)	0.71	0.70	0.27–1.80	0.451	0.69	0.26–1.82	0.450
Age (years)	1.17	1.76	0.52–5.89	0.359	2.15	0.59–7.79	0.243
Nationality, German	1.78	1.77	0.48–6.59	0.391	1.64	0.41–6.56	0.480
Parents' education ^b	2.03	2.27	0.99–5.17	0.050	1.84	0.81–4.19	0.141
Predisposition ^c	1.23	0.91	0.40–2.05	0.818	0.91	0.40–2.08	0.818
Ear piercing	1.93	1.13	0.43–2.95	0.804	0.87	0.32–2.36	0.781
Passive smoking	0.84	0.85	0.35–2.03	0.705	0.63	0.25–1.61	0.335
Duisburg	0.76	0.15	0.01–1.82	0.133	0.68	0.16–2.85	0.591
Dortmund	2.35	1.48	0.49–4.53	0.486	2.56	1.00–6.55	0.048
Borken (reference)	1.00	1.00	–	–	1.00	–	–
Pseudo R ²	–	–	8.37%	–	–	13.16%	–

TSP, total suspended particulate in ambient air; OR_{raw}, raw odds ratios; OR_{adj}, adjusted odds ratios; 95% CI, 95 percent confidence interval; P, P-value.

^aFor comparison of continuous influencing factors a rounded quartile range (P₂₅–P₇₅) was used as a unit step.

^bSchool years >10.

^cFather or mother with allergy or eczema or asthma or hay fever.

In contradiction to our results, Smith-Sivertsen et al. (6) conjectured an immuno-tolerance effect in an adult population from the Russian town of Nikel with nickel refineries and extremely elevated nickel concentrations in ambient air. Living in this environment was likely to reduce nickel hypersensitivity, i.e. it contributed to the development of immunological tolerance in non-sensitized people prior to exposure, although, no correlation between nickel in ambient air and nickel in urine was found in this investigation. Several studies argued that a long-term oral nickel exposure, (e.g. dental braces), by previously non-sensitized people might prevent nickel allergy by inducing immunological tolerance (15–18). A possible conclusion of the seemingly contradiction between our results and the above-mentioned in the literature might be that immunological reactions to long-term oral and inhaled nickel uptake follow different pathways and, therefore, that long-term airway exposure in early age could lead to allergy rather than tolerance.

The following limitations that could have influenced the outcome of our study deserve mention. Individual exposure to nickel in ambient air was assessed by estimated annual nickel concentrations in total suspended particles at the children's home addresses. Individual activity profiles were not taken into account. Therefore, the applied exposure estimates were likely to contain large errors which could have biased the estimation of the association between external nickel exposure and the prevalence of nickel sensitization. Internal nickel exposure was assessed by individual urinary nickel concentrations measured in morning urine samples

and collected only once during the investigation phase. Nevertheless, these measurements were used as long-term internal exposure. The patch-test readings in the study groups were performed 2D and 3D after the patch application. Hence, false positive results due to skin irritation were expected to be rare. Only one irritant reaction was excluded in the study group. Furthermore, other possible causes that can provoke false positive patch-test results were not considered in the study.

In conclusion, this study suggests that the elevated nickel concentrations in ambient air might be able to certain extent to induce nickel sensitization in children. Therefore, a similarly designed study with larger collectives and in other areas with known elevated nickel concentrations in ambient air is under way to check the findings of this study.

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