

Nickel hypersensitivity and orthodontic treatment: a systematic review and meta-analysis

Lina Gözl¹, Spyridon N. Papageorgiou^{1,2} and Andreas Jäger¹

¹Department of Orthodontics, School of Dentistry, University of Bonn, 53111 Bonn, Germany and ²Department of Oral Technology, School of Dentistry, University of Bonn, 53111 Bonn, Germany

doi:10.1111/cod.12392

Summary

Nickel-containing alloys are widely used in orthodontic appliances, even though nickel is by far the most common contact allergen. However, the scientific evidence concerning allergic reactions to nickel in orthodontic patients has not been evaluated systematically. The objective of this study was to investigate whether the prevalence of nickel hypersensitivity is affected by orthodontic treatment. Unrestricted electronic and manual searches were performed until July 2013 for human clinical studies assessing orthodontic treatment and nickel hypersensitivity. Methodological limitations were evaluated with the Downs and Black tool. Crude and adjusted odds ratios (ORs) with their 95% confidence intervals (CIs) were calculated from random-effects meta-analyses, followed by subgroup and sensitivity analyses. Thirty studies were included in the review, and 24 datasets with 10 184 patients in the meta-analyses. Orthodontic treatment had no significant effect on nickel hypersensitivity ($n = 11$; crude OR 0.99; 95%CI: 0.78–1.25; $p = 0.914$). However, when confounding from factors such as sex and piercings was taken into account, orthodontic treatment was associated with a lower risk of hypersensitivity ($n = 1$; adjusted OR 0.60; 95%CI: 0.40–0.80; $p < 0.001$). This was even more pronounced when orthodontic treatment was performed prior to piercing ($n = 7$; crude OR 0.35; 95%CI: 0.24–0.50; $p < 0.001$). Orthodontic treatment seems to have a protective role against nickel hypersensitivity, especially when it precedes piercings.

Key words: contact dermatitis; meta-analysis; nickel allergy; nickel hypersensitivity; orthodontics; piercing.

Nickel allergy is by far the most common contact allergy in the industrial world, with a prevalence of up to 30%, depending on age, sex, and ethnicity (1, 2). Possible sources for nickel sensitization include jewellery, clothing fasteners, mobile phones, and, in particular, (ear) piercings. The last of these contributes to female patients being affected twice as often as men (3). Because of

the increasing rate of nickel sensitization, the Danish Ministry of Environment mandated in 1992 that release from nickel-containing products in prolonged contact with the skin should be $<0.5 \mu\text{g}/\text{cm}^2$, which subsequently decreased the prevalence of nickel allergy (4, 5). The EU followed its example with similar legislation in 1994 (6), which led to other reports of reduced nickel sensitization (25.8% as compared with 36.7%) (7). In contrast, the rate of nickel hypersensitivity has steadily increased in North America, where such regulatory mechanisms against nickel are lacking (1).

Nickel-containing alloys exist in a wide variety of appliances and auxiliary devices used in orthodontics, with a content of up to 55% by weight. Likewise, the *in vivo* release of nickel ions varies greatly, from 0.5

Correspondence: Lina Gözl, Department of Orthodontics, School of Dentistry, University of Bonn, Welschonnenstr. 17, Bonn DE-53111, Germany. Tel: +49 0228 287 22433; Fax: +49 0228 287 22588. E-mail: Lina.Goelz@ukb.uni-bonn.de

Registration: PROSPERO CRD42013004710.

Accepted for publication 24 February 2015

to 105.7 µg/l, according to the alloy type, body fluid, temperature, mechanical stress, or pH (8, 9). In general, orthodontic materials are considered to be highly biocompatible (10). However, a number of adverse effects have been reported in the literature, including inflammatory and allergic reactions, and cytotoxicity and mutagenicity (11, 12). Allergic reactions are the predominant adverse effects, owing to the inevitable release of nickel ions as a consequence of intraoral corrosion (10). This has caused concerns among orthodontic patients, their parents, and orthodontists, owing to the possible association of orthodontic treatment with the prevalence of nickel hypersensitivity. However, previous *in vitro* and *in vivo* evidence indicates that oral nickel intake, especially prior to cutaneous sensitization, may favour the induction of oral tolerance to nickel (13–15).

The primary objective of this study was therefore to assess the existing evidence and investigate whether the prevalence of nickel hypersensitivity, as assessed with nickel patch tests, is affected by orthodontic treatment. As a secondary objective, the influence of orthodontic treatment was adjusted, if possible, for other known confounding factors that might influence nickel hypersensitivity.

Materials and Methods

Protocol and registration

The protocol for this systematic review was created *a priori*, on the basis of the Cochrane Handbook (16), and was registered prospectively in PROSPERO (CRD42013004710). This systematic review is reported according to the PRISMA statement (17) and its extension for abstracts (18); the MOOSE statement was also considered (19).

Information sources and search

Electronic databases were systematically searched up to July 2013 independently by two authors (L.G. and S.N.P.) (Appendix S1). No limitations were applied regarding publication year, publication status, or publication language. The reference lists of included articles and relevant reviews were checked. Grey literature was searched through appropriate databases and registers. Authors were contacted when necessary for additional data or clarifications.

Eligibility criteria and study selection

As the primary outcome of this review pertained to adverse effects, both randomized and non-randomized

trials were considered (20). Inclusion and exclusion criteria were determined *a priori* (Appendix S2). After removal of duplicates, articles were screened on the basis of title, abstract and full text by the same two review authors. When the decision made on the basis of title and abstract was inconclusive, the full-text article was acquired. Additional reports of the same trial were grouped together; when a study was published in more than one language, the English publication was considered.

Data collection process and data items

Data extraction was performed independently by the same two review authors with a predetermined and piloted collection form. Any disagreement was resolved by discussion with the last author (A.J.). In order to evaluate the effect of orthodontic treatment on nickel hypersensitivity, the results of patch tests performed according to the International Contact Dermatitis Research Group (ICDRG) criteria were considered to constitute a valid outcome for the meta-analysis (21). Reported outcomes were classified according to the timing of assessment regarding orthodontic treatment (i.e. before or after orthodontic treatment), if possible. The factors for the subgroup analyses were selected *a priori* to examine their possible influence on the results, if five or more eligible studies could contribute to the analysis of this factor.

Risk of bias in individual studies

The risk of bias of the included non-randomized studies was assessed with a modified Downs and Black checklist (22). In general, the criteria were grouped in five main domains: (i) reporting, (ii) external validity, (iii) internal validity – bias, (iv) internal validity – confounding, and (v) power. All items were given one point when the respective criterion was fulfilled, except for the ‘power’ domain, where up to five points could be given, summing up to a maximum of 30 points per article. Serious methodological limitations were judged to exist when a trial collected <17 points on the checklist. Risk of bias assessment was conducted without blinding.

Risk of bias across studies

If >10 studies were identified for a comparison (16), reporting biases (‘small-study effects’ and/or publication bias) were assessed through inspection of a contour-enhanced funnel plot and tests for funnel plot asymmetry. Harbord’s test was used, whenever possible, instead of Egger’s test, as it outperforms the latter. If the tests hinted at the existence of publication bias, sensitivity analyses were planned.

The overall quality of evidence (confidence in effect estimates) for each of the main outcomes was rated by using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach (23), based on the following interpretations: 'high quality' – further research is very unlikely to change our confidence in the estimate of effect; 'moderate quality' – further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; 'low quality' – further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; and 'very low quality' – very uncertain about the estimate.

Large effects were defined as odds ratios (ORs) > 2 or ORs < 0.5 , and very large effects were defined as ORs > 5 or ORs < 0.2 . The optimal information size (i.e. required meta-analysis sample size) was calculated for each outcome independently, in order to enable identification of a minimal clinically important effect with an average variance (based on this review's study sample): α at 5%, and β at 80%.

The risk of bias within studies was assessed independently by two review authors (L.G. and S.N.P.), and the risk of bias across studies was assessed by one author (S.N.P.). Any disagreement was resolved by discussion with the last author (A.J.). Inter-reviewer agreement for all three stages (study selection, data extraction, and risk of bias assessment) was evaluated with the unweighted Cohen's kappa.

Summary measures and synthesis of results

Data were summarized and considered to be suitable for pooling if similar assessments of nickel hypersensitivity were conducted. In cases of inadequate reporting, the missing data were calculated or requested from the authors.

ORs with 95% confidence intervals (CIs) were selected for the meta-analysis, as many studies reported raw or adjusted ORs from multivariable regression analyses (24). However, the number needed to treat (NNT) was chosen to clinically translate significant findings (25), as it is easily comprehensible. A random-effects model as proposed by DerSimonian and Laird (26) was chosen *a priori* as the primary method for estimating all pooled estimates, as nickel hypersensitivity was expected to differ across studies, owing to differences in the sample (i.e. patient's previous contact with allergens, patient's immunological response, or patient sex) and implementation (i.e. various clinical setting and differences in patch testing). This model takes into account existing unexplained heterogeneity, and can be considered to be more conservative

than a fixed-effect model in the presence of heterogeneity. The extent and impact of between-study heterogeneity were assessed by inspecting the forest plots and by calculating the τ^2 and the I^2 statistics, respectively. The 95% CIs around I^2 were calculated according to the non-central χ^2 approximation of Q . In cases of great unexplained heterogeneity ($I^2 > 75\%$), individual studies were omitted to achieve homogeneity. If homogeneity could not be achieved by excluding one or two trials, and unexplained heterogeneity remained, data were not pooled. For meta-analyses with three or more studies, 95% prediction intervals (PIs) (27) were calculated to predict the results in a future setting, while incorporating existing heterogeneity.

Additional analyses

Possible sources of heterogeneity were sought through prespecified mixed-effects subgroup analyses and random-effects meta-regression with the Knapp–Hartung adjustment for the factors patient age, country of origin, and continent of origin. In order to minimize the risk of multiple testing, the above-mentioned analyses were performed only for meta-analyses with five or more trials.

The robustness of the results was *a priori* to be checked with sensitivity analyses for meta-analyses with ≥ 10 trials, according to the improvement of the GRADE classification by omitting trials.

All analyses were performed in STATA™ version 10 (StataCorp LP, College Station, TX, USA) with the macros *metan*, *metaprop*, *metabias*, *heterogi*, and *confunnel*. All *p*-values were two-sided with a level of significance at 5%, except for the tests of between-study or between-subgroup heterogeneity (10%).

Results

Study selection

From the initially identified 1576 records, 1054 records remained after exclusion of duplicates, to which two additional manually identified articles were added (Fig. 1). A total of 937 records were excluded on the basis of screening. The full texts of 119 articles were obtained and assessed for eligibility, and 89 articles were excluded for various reasons (Appendix S3), leaving 30 articles for further evaluation (Appendix S4). After grouping together of multiple publications from the same study cohort, a total of 24 datasets remained for final evaluation (Table 1).

In total, eight authors were contacted, with various questions regarding included articles, and four of them

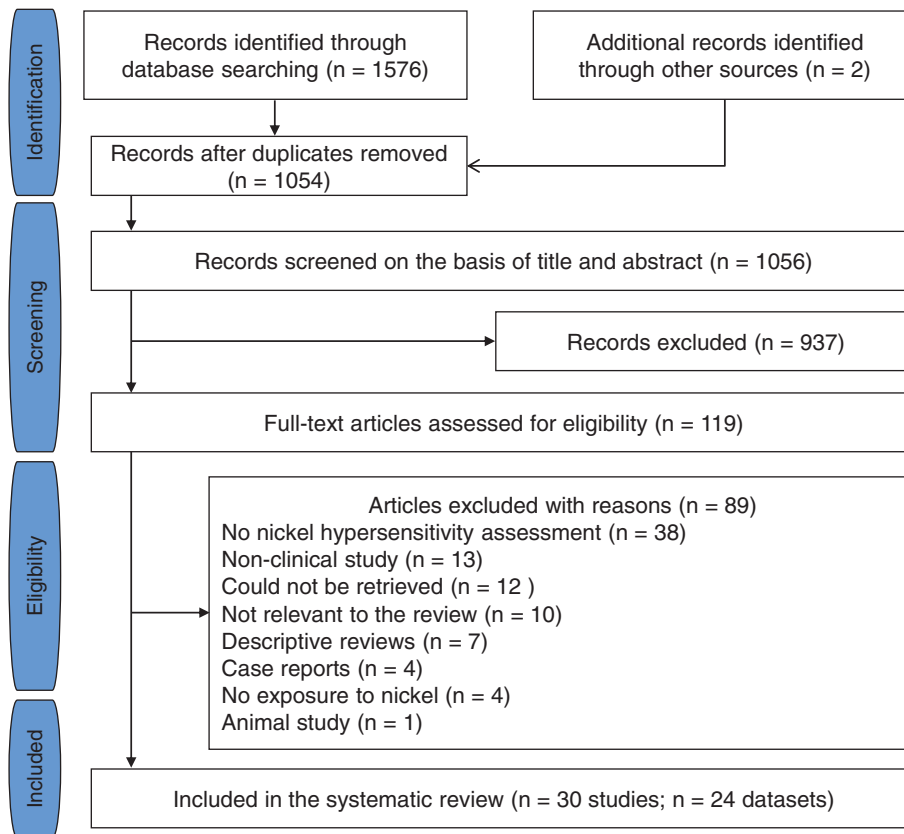


Fig. 1. PRISMA flow diagram for the selection of studies.

responded. Additionally, the corresponding authors of the five studies with the largest sample size (>500 patients) were contacted for raw data or ORs adjusted for confounders, and two responded (in one instance, adjusted ORs were already provided in the article, but were unclear, and in another the raw data were lost). The kappa scores before reconciliation for the selection, data extraction and risk of bias assessment procedures were 0.872, 0.886, and 0.938, respectively, indicating almost perfect agreement.

Study characteristics and risk of bias within studies

The characteristics of the included studies are summarized in Table 1. Most of them were performed in a university setting, and included a total of 10 184 patients with a mean age of 20.4 years. Most of the patients who were treated orthodontically received fixed orthodontic appliances with great variation in their nickel content (Appendix S5). Almost every study provided the assessment of nickel hypersensitivity with nickel patch tests, which were read at various intervals after patch placement, and the ICDRG scale was used for interpretation of results in almost all instances. Eight studies assessed nickel hypersensitivity by using questionnaires, and two

additional articles included only patients with symptoms of nickel allergy, resulting in the exclusion of these studies from the meta-analyses.

Concerning risk bias within studies, the trials scored an average of 16.9 points on the modified Downs and Black tool, with 11 of them showing serious methodological limitations (i.e. <17 points) (Table 1 and Appendix S6).

Results of individual studies, synthesis of results, and risk of bias across studies

The overall prevalence of nickel hypersensitivity in the included studies was 19% (22 studies; 95%CI: 16–22%; $I^2 = 93\%$; 95%CI for I^2 : 91–94%; $p < 0.001$; $\tau^2 = 0.004$). As expected, the pooled prevalence for female patients (15 studies; prevalence = 27%; 95%CI: 22–32%; $I^2 = 94\%$) was much higher than the pooled prevalence for male patients (11 studies; prevalence = 6%; 95%CI: 4–8%; $I^2 = 81\%$). For reporting bias, Egger's test was used, and showed a significant risk of reporting bias (intercept = 2.85; 95%CI: 0.75–4.95; $p = 0.010$).

Primary objective: effect of orthodontic treatment on nickel hypersensitivity. Meta-analyses were performed regarding the prevalence of nickel hypersensitivity in patients

Table 1. Characteristics of the studies included in the current systematic review (abridged form)

No.	Study ^a	Study information (design; setting; country)	Participants (sample size; sex; mean age or range; orthodontic history)	Assessment of nickel hypersensitivity (method; assessor; criteria)	Risk of bias summary
1	Bass et al. 1993	Cross-sectional; university department; United States	29 patients (11/18); mean 20.3 years; no previous ortho-Tx	Ni patch test (nickel sulfate 5% pet.; assessed by 1 orthodontist and 2 dermatologists)	17/30
2	Costa et al. 2003	Cross-sectional; university; Brazil	65 patients (30/35); mean 21 years; indication for orthodontic appliances	Ni patch test (nickel sulfate 5% pet. and control test with pet.; assessed by two observers according to ICDRG criteria)	13/30
3	de Paiva 2005	Cross-sectional; university; Brazil	22 patients (6/16); mean 15.9 years; fixed ortho-appliances for a maximum of 3 years	Ni patch test (5% nickel sulfate; assessed according to ICDRG criteria)	17/30
4	Fors 2008; Fors et al. 2008; Fors et al. 2012a; Fors et al. 2012b; Röhrl and Stenberg 2010	Cross-sectional; secondary schools; Sweden	4376 patients (1400/2976); mean 17.4 years	Ni patch test (patch containing 24 allergens; assessed by a school nurse or 1 dermatologist according to ICDRG criteria) Self-reported questionnaire about nickel sensitivity (results not reported)	26/30
5	Genelhu et al. 2005	Cross-sectional; university; Brazil	48 patients (17/31); mean 17.5 years	Clinical evaluation (gingival hyperplasia; labial desquamation)	15/30
6	Janson et al. 1998	Cross-sectional; university; Brazil	170 patients; range 8–31 years	Ni patch test (nickel sulfate 5% pet. and control; assessed by 2 orthodontists, 2 dermatologists, and 1 pathologist)	17/30
7	Jensen et al. 2002	Cross-sectional; public schools and high schools; Denmark	580 patients (0/580); mean 16.0 years	Ni patch test (three concentrations of nickel sulfate and one control; assessed according to ICDRG criteria)	20/30
8	Johannson et al. 2011	Cross-sectional; schools/university/municipal health centre; Finland	170 patients; mean 13.9 years	Ni patch test (nickel sulfate 5% pet. assessed according to ICDRG criteria by 1 orthodontist trained by 1 dermatologist)	15/30
9	Kalimo et al. 2004	Cross-sectional; university; Finland	153 patients (32/121); mean 22.0 years	Ni patch test (nickel sulfate 5% pet.; assessed according to ICDRG criteria)	15/30
10	Kerosuo et al. 1996	Cross-sectional; university; Finland	700 patients (283/417); range 17–18 years	Ni patch test (nickel sulfate 5% pet; assessed by 1 orthodontist trained by 1 dermatologist)	20/30
11	Koppenburg et al. 1988	Cross-sectional; university; Germany	472 patients undergoing ortho-Tx	Questionnaire	6/30
12	Marigo et al. 2003	Cross-sectional; university; Brazil	35 patients; mean 14.3 years	Ni patch test (nickel sulfate 5% pet. Lymphocyte proliferation test under nickel antigens)	15/30
13	Menezes et al. 2004	Longitudinal; university; Brazil	38 patients (17/21) included; range 9–25 years	Ni patch test (5% nickel sulfate and 7 other allergens; assessed by 1 dermatologist according to ICDRG criteria)	18/30
14	Mortz et al. 2002	Cross-sectional; 40 schools; Denmark	1146 patients	Ni patch test (patch test with nickel sulfate at three different concentrations and a control; assessed by 1 dermatologist)	19/30

Table 1. Continued

No.	Study ^a	Study information (design; setting; country)	Participants (sample size; sex; mean age or range; orthodontic history)	Assessment of nickel hypersensitivity (method; assessor; criteria)	Risk of bias summary
15	Pacor et al. 2003	Cross-sectional (for the nickel patch test) and RCT (for the oral nickel challenge); university; Italy	380 patients (176/204); mean 46.0 years	Ni patch test (5% nickel sulfate; assessed according to ICDRG criteria)	15/30
16	Pantuzo et al. 2007	Cross-sectional; university; Brazil	58 patients (28/30); range 11–30 years	VAS scale for subjective symptoms Oral nickel challenge Ni patch test (nickel sulfate 5% pet.; assessed according to ICDRG criteria)	19/30
17	Pazzini et al. 2009; Pazzini et al. 2011	Prospective longitudinal; university; Brazil	96 patients (38/58); range 10–43 years	Cutaneous sensitivity test Ni patch test (nickel sulfate 5% pet.; assessed according to ICDRG criteria)	23/30
18	Saglam et al. 2004	Longitudinal; university; Turkey	82 patients (27/55); mean 14.3 years; no previous ortho-Tx	Ni patch test (5% nickel sulfate and 1% cobalt in pet. and a control; assessed by 2 dermatologists)	20/30
19	Schuster et al. 2004	Cross-sectional survey (questionnaire); orthodontic practices; Germany	Questionnaire sent to 89 orthodontic offices	Questionnaire	9/30
20	Staerkjaer and Mezze 1990	Cross-sectional; private clinics and university clinic; Denmark	1085 patients (0/1085); mean 13.6 years; girls receiving active ortho-Tx	Questionnaire	14/30
21	Todd and Burrows 1989	Questionnaire study; department of dermatology; Northern Ireland	294 patients (26/268)	Ni patch test (nickel sulfate 5% pet.) Ni patch test (nickel sulfate 5% pet.)	14/30
22	van der Burg et al. 1986	Prospective cross-sectional; university; The Netherlands	303 junior hairdressers and junior nurses (41/262); mean 19.1 years	Ni patch test (eight allergens, including 5% nickel sulfate; assessed according to ICDRG criteria)	16/30
23	van Hoogstraten et al. 1991	Questionnaire study; western European dermatology clinics	2176 patients (641/1535); mean 38.4 years	Ni patch test (European standard skin test series; assessed according to ICDRG criteria)	20/30
24	Westphalen 2006; Westphalen et al. 2008	Prospective longitudinal; university; Brazil	20 patients (6/14) about to receive ortho-Tx; mean 16.0 years	Ni patch test (assessed by a dermatologist according to ICDRG criteria) Also measured nickel genotoxicity (not reported here)	19/30

ICDRG, International Contact Dermatitis Research Group; Ni, nickel; RCT, randomized controlled trial; VAS, visual analogue scale; ortho-Tx, orthodontic treatment.

^aA complete reference list is provided in Appendix S4.

Table 2. Results of the meta-analysis regarding the influence of orthodontic treatment and confounding factors on the prevalence of nickel hypersensitivity measured with nickel patch tests

	Analysis	Studies	Null-hypothesis testing			Heterogeneity			Reporting bias	
			OR (95%CI)	<i>p</i>	95%PI	<i>I</i> ² (95%CI), %	<i>p</i>	τ^2	Harbord's intercept	<i>p</i>
Orthodontic treatment	Crude	11	0.99 (0.78–1.25)	0.914	0.50–1.95	56 (0–76)	0.120	0.075	–1.61 (–3.37 to 0.15)	0.068
	Adjusted	1 ^a	0.60 (0.40–0.80)	0.001	–	–	–	–	–	–
Sex	Crude	15	0.21 (0.14–0.30)	<0.001	0.07–0.63	61 (19–76)	0.001	0.228	0.05 (–1.10 to 1.20)	0.925
	Adjusted	1 ^a	0.20 (0.14–0.30)	<0.001	–	–	–	–	–	–
Piercing	Crude	7	7.77 (6.02–10.03)	<0.001	4.53–13.32	24 (0–68)	0.242	0.027	NA	NA
	Adjusted	2	3.53 (2.45–5.08)	<0.001	–	0 (NA)	–	–	–	–
Orthodontic treatment before piercing	Crude	7	0.35 (0.24–0.50)	<0.001	0.16–0.76	23 (0–67)	0.251	0.056	NA	NA
	Adjusted	2	0.39 (0.12–1.29)	0.123	–	61 (NA)	–	–	–	–
Multiple piercings	Crude	2	1.84 (1.52–2.23)	<0.001	NA	0 (NA)	0.353	0.000	NA	NA
	Adjusted	1	1.70 (1.40–2.20)	<0.001	–	–	–	–	–	–
History of allergy	Crude	5 ^b	8.36 (3.99–17.50)	<0.001	0.98–71.18	52 (0–81)	0.078	0.311	NA	NA
	Adjusted	1 ^a	1.00 (0.77–1.30)	1.000	–	–	–	–	–	–
Use of metallic objects	Crude	2	4.10 (1.86–9.00)	<0.001	NA	0 (NA)	0.756	0.000	NA	NA
	Adjusted	0	–	–	–	–	–	–	–	–

CI, confidence interval; NA, not applicable; OR, odds ratio; PI, predictive interval.

^aThe meta-analysis originally included two studies, but the study of Kerosuo et al. was omitted, because extreme inconsistency was found ($I^2 > 75\%$), and the study of Fors et al. 2008 was judged to be less prone to bias.

^bThe meta-analysis originally included six studies, but the study of Fors et al. was omitted, because extreme inconsistency was found ($I^2 > 75\%$), and the study of Fors et al. (13) was less compatible with the others.

treated with orthodontic appliances as compared with untreated patients (Table 2). Eleven studies were eligible for the assessment of the effect of orthodontic treatment on nickel hypersensitivity, and showed that the crude effect of orthodontic treatment on nickel hypersensitivity was not significant (11 studies; crude OR 0.99; 95%CI: 0.78–1.25; $p = 0.914$; $I^2 = 56\%$; Fig. 2) (Table 2). However, when confounding factors such as sex and piercings were taken into account, orthodontic treatment was associated with a significantly lower risk of nickel hypersensitivity than no orthodontic treatment (one study; adjusted OR 0.60; 95%CI: 0.40–0.80; $p < 0.001$) (Table 2 and Fig. 2). This translates clinically to an NNT of 18, meaning that the relative benefit of avoiding an additional nickel hypersensitivity event could be seen for every 18 patients treated orthodontically.

Secondary objectives: confounding factors influencing nickel hypersensitivity. Various factors were assessed regarding their effect on nickel hypersensitivity (Table 2). Fifteen trials provided data about the patient's sex (Table 2 and Fig. 3), with the pooled estimate indicating that male patients have a lower risk of having nickel hypersensitivity than female patients (15 studies; crude OR 0.21; 95%CI: 0.14–0.30; $p < 0.001$; $I^2 = 61\%$). This effect was robust even after adjustment for possible confounders (one study; adjusted OR 0.20; 95%CI: 0.14–0.30; $p < 0.001$).

Regarding piercings, the meta-analysis indicated that piercings were significantly associated with an increased risk of nickel hypersensitivity (seven studies; crude OR

7.77; 95%CI: 6.02–10.03; $p < 0.001$; $I^2 = 24\%$). This effect remained robust after adjustment for confounders, although its magnitude was diminished (two studies; adjusted OR 3.53; 95%CI: 2.45–5.08; $p < 0.001$; $I^2 = 0\%$) (Table 2 and Fig. 4). Additionally, the number of piercings significantly influenced the prevalence of nickel hypersensitivity, indicating a possible dose–response effect. Patients with multiple piercings had a higher risk of having nickel hypersensitivity than patients with a single piercing (two studies; crude OR 1.84; 95%CI: 1.52–2.23; $p < 0.001$; $I^2 = 0\%$), and this effect remained robust after adjustment for confounders (one study; adjusted OR 1.70; 95%CI: 1.40–2.20; $p < 0.001$).

Moreover, consideration of the timing of piercings with reference to orthodontic treatment showed that orthodontic treatment before piercings significantly reduced the risk of nickel hypersensitivity (seven studies; crude OR 0.35; 95%CI: 0.24–0.50; $p < 0.001$; $I^2 = 23\%$). This translates clinically to an NNT of 6, meaning that the relative benefit of avoiding an additional nickel hypersensitivity event could be seen for every 6 patients treated orthodontically before having any piercings. This protective effect of orthodontic treatment before piercing remained robust after adjustment for confounding factors, although it became statistically non-significant, owing to the loss of power (two studies; adjusted OR 0.39; 95%CI: 0.12–1.29; $p = 0.123$; $I^2 = 61\%$; Table 2 and Fig. 5).

Additionally, a positive history of allergy and frequent contact with metallic objects significantly increased the

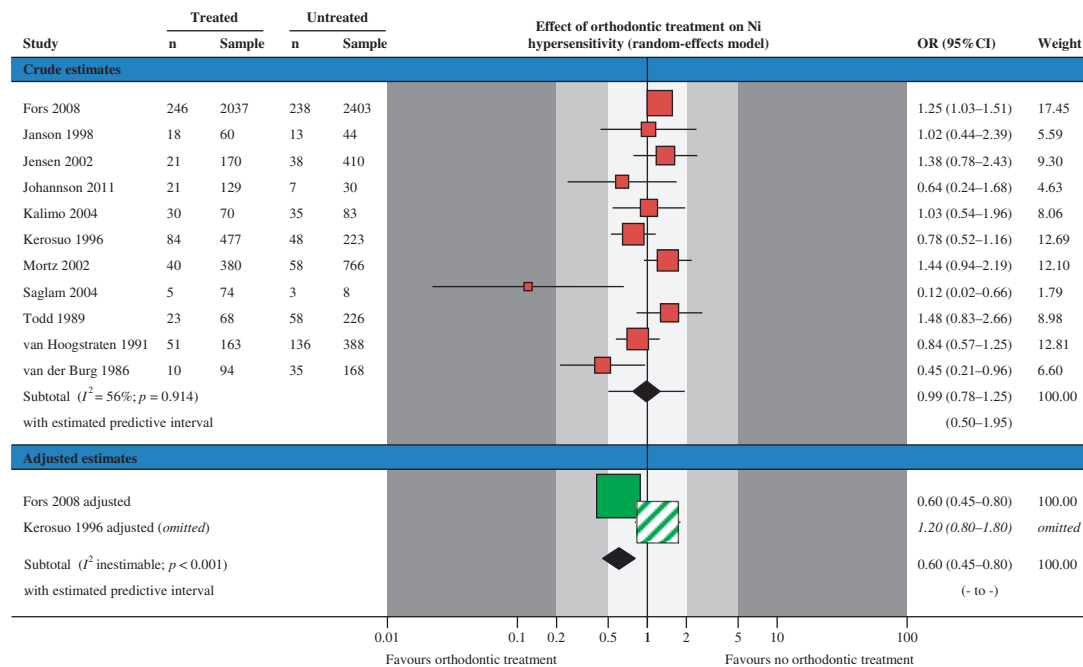


Fig. 2. Forest plot of the effect of orthodontic treatment on nickel hypersensitivity based on the random-effects model, together with the 95% confidence interval (CI) and the 95% prediction interval. The studies on the left indicate that patients treated orthodontically experience nickel hypersensitivity less often, and the studies on the right indicate that patients treated orthodontically experience nickel hypersensitivity more often. OR, odds ratio.

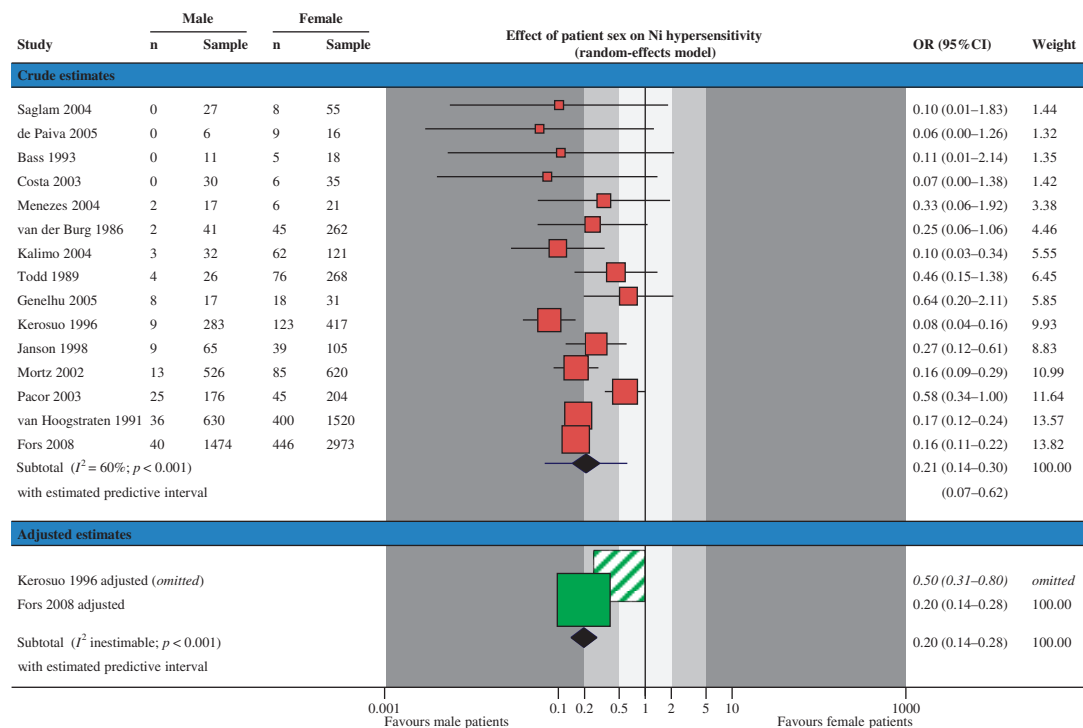


Fig. 3. Forest plot of the effect of patient sex on nickel hypersensitivity based on the random-effects model, together with the 95% confidence interval (CI) and the 95% prediction interval. The studies on the left indicate that male patients experience nickel hypersensitivity less often, and the studies on the right indicate that male patients experience nickel hypersensitivity more often. OR, odds ratio.

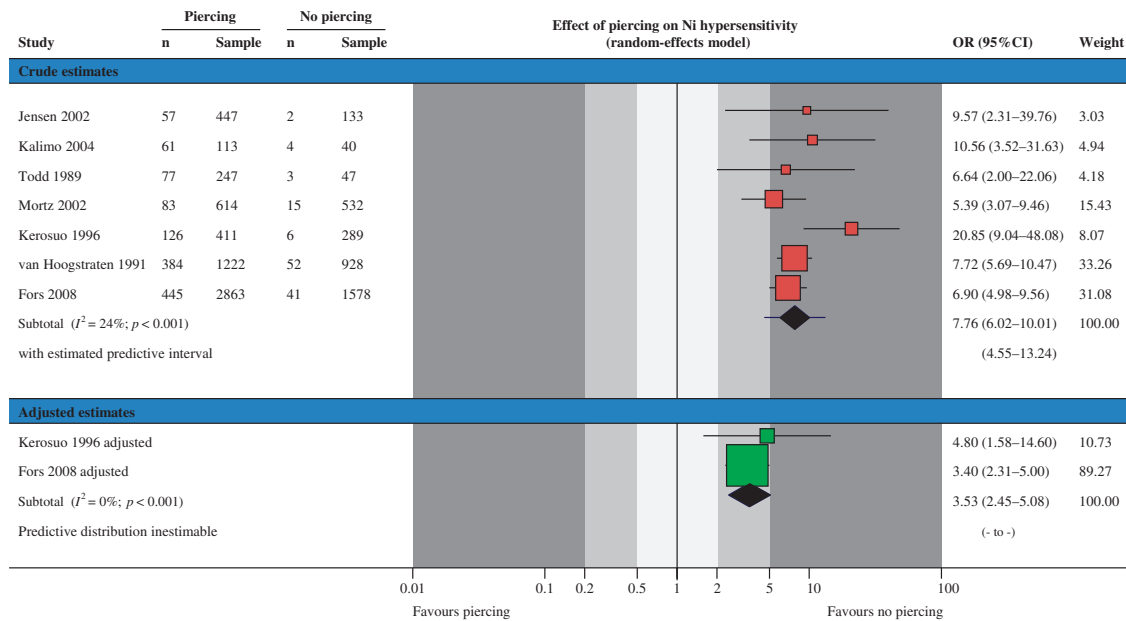


Fig. 4. Forest plot of the effect of piercing on nickel hypersensitivity based on the random-effects model, together with the 95% confidence interval (CI) and the 95% prediction interval. The studies on the left indicate that patients with piercings experience nickel hypersensitivity less often, and the studies on the right indicate that patients with piercings experience nickel hypersensitivity more often. OR, odds ratio.

risk of nickel hypersensitivity (Table 2), although determination of robustness by adjusting for confounders was not possible.

Risk of bias across studies and additional analyses

Reporting bias was evident in the overall prevalence of nickel hypersensitivity according to Egger's test, and was probably accentuated by the imprecision of single-group analyses. In order to account for the small-study effects, the meta-analysis of overall prevalence was divided into two subgroups: the 50% most precise and the 50% least precise of the studies (Appendix S7). It could be concluded that small and imprecise studies tended to exaggerate the prevalence of nickel hypersensitivity (prevalence = 26%; 95%CI: 17–34%) as compared with large and precise studies (prevalence = 15%; 95%CI: 12–18%). Indications of slight funnel plot asymmetry were judged to exist for the factor of orthodontic treatment and patient sex (Fig. 6), but were not affirmed for either of the two factors with the Harbord test ($p > 0.05$).

The GRADE assessments for the main outcomes of the present study ranged from 'very low' to 'high' (Table 3; explained in Appendix S8). The quality of clinical recommendations was upgraded, owing to the magnitude of effect, with regard to patient sex, piercings, and the timing of orthodontic treatment. In addition, upgrading was performed for the factors patient sex and piercings,

owing to the absence of residual confounding. Finally, the quality of clinical recommendations was enhanced as a consequence of dose–response effects. Instead, the GRADE assessment for orthodontic treatment on nickel hypersensitivity was downgraded on the basis of inconsistency. Even though evidence of spurious effects was plausible after removal of confounding factors, we decided not to upgrade, as only one study contributed to the adjusted analysis.

Mixed-effects subgroup analysis on the basis of the country or continent of origin of included studies was possible in only a handful of instances. For the overall prevalence, neither the country nor the continent had a significant effect on nickel hypersensitivity ($p = 0.703$ and $p = 0.394$, respectively). For the factor of orthodontic treatment, continent had no significant modifying effect ($p = 0.138$). For the factor of patient sex, country of origin was marginally significant ($p = 0.085$), whereas continent was not ($p = 0.780$). As, however, country had a modifying role in only one instance, and no logical explanation could be found, the credibility of this subgroup analysis is questionable. A meta-regression on the basis of the mean patient age reported in the included studies is presented in Appendix S9. According to the results of meta-regression, there was no significant association between prevalence of nickel hypersensitivity or the ORs for any of the factors and the reported mean patient age ($p > 0.10$).

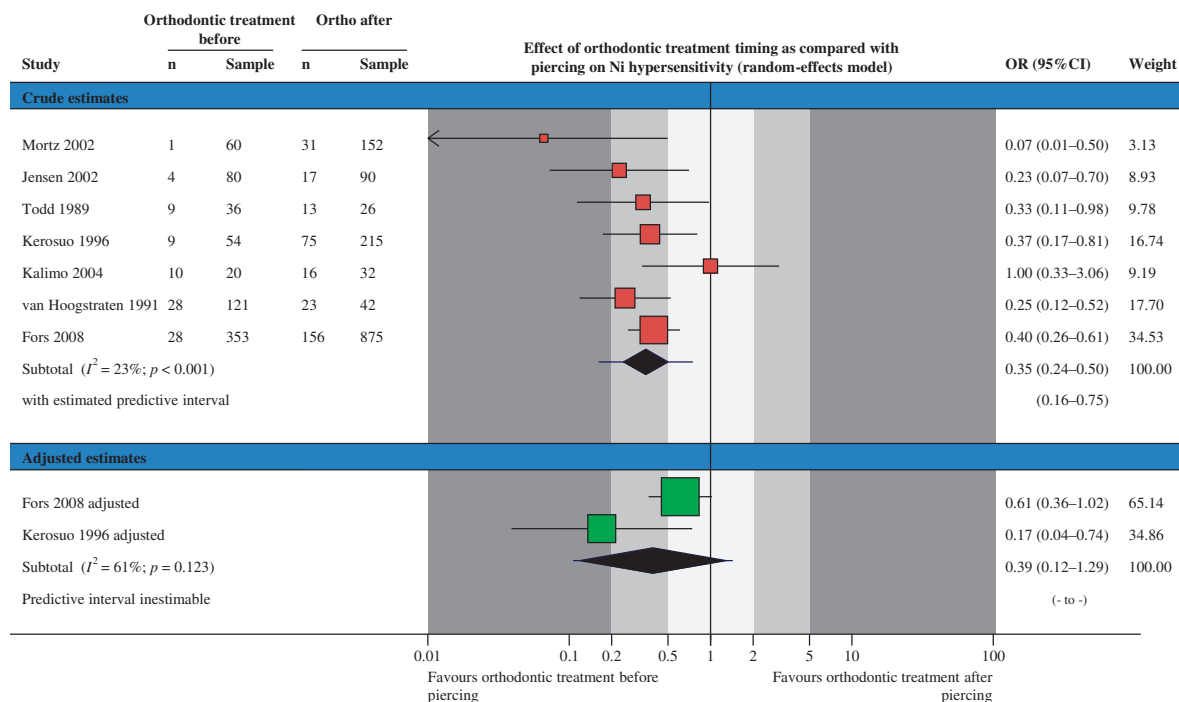


Fig. 5. Forest plot of the effect of orthodontic treatment timing on nickel hypersensitivity based on the random-effects model, together with the 95% confidence interval (CI) and the 95% prediction interval. The studies on the left indicate that patients treated orthodontically before ear piercing experience nickel hypersensitivity less often, and the studies on the right indicate that patients treated orthodontically before ear piercing experience nickel hypersensitivity more often. OR, odds ratio.

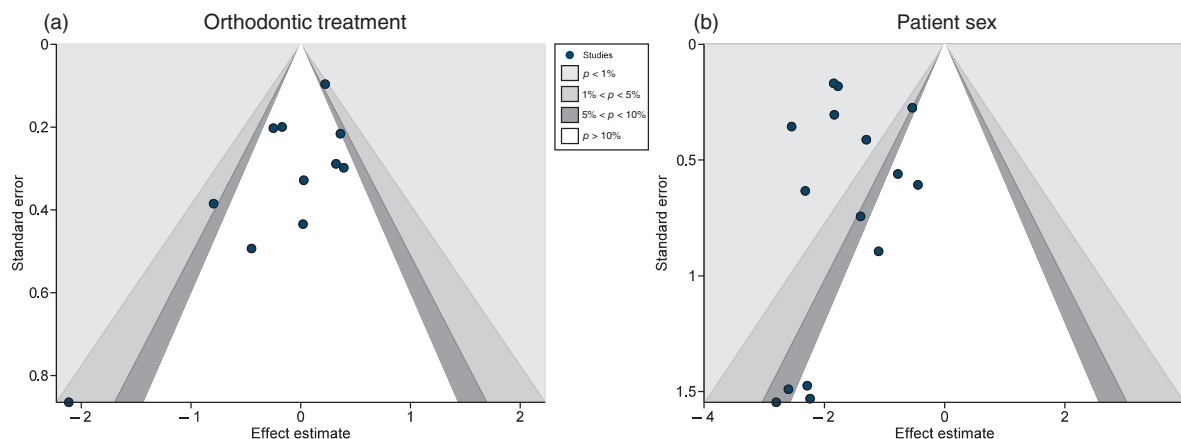


Fig. 6. Contour-enhanced funnel plot of (a) the effect of orthodontic treatment on nickel hypersensitivity, and (b) the effect of patient sex on nickel hypersensitivity, for the studies included in the analysis.

A sensitivity analysis on the basis of the design of the included studies was not possible, as no randomized studies were found. A sensitivity analysis on the basis of the improvement of the GRADE assessment was likewise not possible. Only the factor of orthodontic treatment suffered from a low GRADE score, but omission of single studies was not straightforward and was not conducted.

Discussion

Summary of evidence

In the present systematic review, we identified 30 studies comprising 24 datasets for meta-analyses, including 10 184 patients, that investigated the effect of orthodontic treatment or other factors on nickel hypersensitivity.

Table 3. Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) summary of findings table for the main outcomes of the systematic review

Factor	Illustrative comparative risks (95%CI)		Relative effect (95%CI)	NNT	Patients (studies)	GRADE
	Assumed risk	Corresponding risk				
Patient sex (crude estimates)	Female patients 278 per 1000	Male patients 58 per 1000 (39–83)	OR 0.21 (0.14–0.30)	5	10 027 (15)	⊕⊕⊕⊕ high ^{a,b}
Piercings (crude estimates)	Patients without piercings 28 per 1000	Patients with piercings 219 per 1000 (170–282)	OR 7.76 (6.02–10.01)	5	9470 (7)	⊕⊕⊕⊕ high ^{a–c}
Orthodontic treatment (crude estimates)	Untreated patients 233 per 1000	Patients treated orthodontically 231 per 1000 (182–294)	OR 0.99 (0.78–1.25)	1000	10 184 (11)	⊕⊕⊕⊕ very low ^{d,e}
Timing of the orthodontic treatment relative to piercings (crude estimates)	Patients treated orthodontically after ear piercing 349 per 1000	Patients treated orthodontically before ear piercing 122 per 1000 (84–174)	OR 0.35 (0.24–0.50)	6	9470 (7)	⊕⊕⊕⊕ high ^{b,f}

Patients: Assessed for adverse reactions to nickel with nickel sulfate patch tests applied to the skin. *Settings:* University clinics, schools, municipal health centres, and private clinics (Belgium, Brazil, Denmark, England, Finland, Italy, Northern Ireland, Spain, Sweden, The Netherlands, Turkey, United States). *Exposure:* Positive response to patch test (allergic reaction to nickel). *Comparison:* Negative response to patch test (no allergic reaction to nickel).

CI, confidence interval; NNT, number needed to treat; OR, odds ratio.

All studies start from 'low', owing to the inclusion of non-randomized studies (see Appendix S8 for details).

^aUpgraded by two because of very large effect magnitude.

^bUpgraded by one because of absence of residual confounding.

^cUpgraded by one because of dose–response effect.

^dDowngraded by one because of inconsistency.

^eEvidence of spurious effects after removal of confounding (indication of protective role of orthodontic treatment against nickel hypersensitivity), but we decided not to upgrade, as only one study provided these data.

^fUpgraded by one because of large effect magnitude.

The overall prevalence of nickel hypersensitivity in the included trials was 19%, with high heterogeneity, which agrees with previous epidemiological studies of people with different ethnic backgrounds (14). Women were significantly more affected (27%) than men (6%).

Regarding the primary outcome, the existing evidence indicates that orthodontic treatment is not significantly associated with an increased risk of nickel hypersensitivity. Because of inconsistency among the included studies, the quality of evidence was very low. However, spurious effects resulting from confounding were plausible, as adjustment for confounders in one included study (13) led to a great change in the ORs (crude OR 1.25; adjusted OR 0.60). The present data are in agreement with previous studies reporting that the frequency of allergic reactions during orthodontic treatment is low, ranging between 0.03% and 0.3% (28, 29). On the other hand, Kolokitha et al. (14) found a higher prevalence of nickel hypersensitivity among patients who had received orthodontic treatment. Their meta-analyses included eight studies, most of which evaluated nickel hypersensitivity after orthodontic treatment, and only two of which evaluated

nickel hypersensitivity before treatment. Those two trials detected no significant increase in positive patch test reactions after orthodontic treatment as compared with the results before treatment. Moreover, when they excluded patients with piercings, they could no longer detect a significant increase in nickel hypersensitivity in the orthodontic treatment group. Interestingly, when we took confounding factors such as sex or piercings into account, orthodontic treatment seemed to lower the risk of nickel hypersensitivity. Therefore, various factors seem to play a crucial role in the effect of orthodontic treatment on nickel hypersensitivity. Incomplete study data, however, and the inability to retrieve the requested data after author communications make it difficult to draw a conclusion at the present time.

In this study, male patients were less prone to develop nickel hypersensitivity than female patients (OR 0.21). If this is converted for female patients, we obtain an OR of 4.76, indicating that the odds of nickel hypersensitivity for female patients are increased by 376% as compared with the odds for male patients. These results are in line with other studies showing that girls are more than twice

as often affected as boys (1–3), and might be explained by the frequent use of jewellery and ear piercings. Additionally, hormonal contributions have also been proposed to explain this imbalance between the two sexes (30).

Ear and body piercings constitute one of the main sensitizers for nickel hypersensitivity, as has been already previously shown (31, 32) and was confirmed by our results (OR 7.77). Additionally, a possible dose–response relationship further supports the influence of piercing on nickel hypersensitivity, as the risk of allergic reactions among patients with multiple piercings was significantly higher than that among patients with a single piercing (OR 1.84), underlining the importance of piercing as a confounding factor.

Notably, we showed that orthodontic treatment before piercing might reduce the induction of nickel hypersensitivity (adjusted OR 0.35), possibly via orally induced tolerance. Animal studies provide further evidence for the frequency of nickel allergy being reduced upon oral contact with nickel, probably because of mucosal anergic immune cells (15, 33). Clinical studies are in line with these data, showing that oral administration of nickel improves allergic symptoms, finally leading to a more tolerogenic immune response (34, 35).

Regarding frequent contact with metal objects, we found that this increased the risk of nickel hypersensitivity (OR 4.10), supporting the theory that repeated skin contact with nickel-containing metallic materials favours the induction of nickel allergy. Jewellery, mobile phones, clothing fasteners or coins have been suggested as possible sensitizers (3).

In addition, patients with a positive history of allergy were found to be at risk for an increased prevalence of nickel hypersensitivity. This may be attributable to a genetic predisposition or anatomical differences in the skin, as it has been shown that atopic dermatitis is associated with metal allergy (36). Mutations of the filaggrin gene (skin protein) favour the development of atopic dermatitis, nickel allergy, and other skin diseases (37).

Finally, reducing nickel exposure through skin contact seems to be one of the most effective means of reducing the prevalence of nickel hypersensitivity. Therefore, despite the safety of intraoral appliances, extraoral appliances in patients with known nickel hypersensitivity should be used with caution. These appliances are in direct contact with the facial skin, which might favour allergic reactions resulting from different immunological mechanisms (33).

Strengths and limitations

The strengths of the present systematic review include the predefined protocol, the extensive literature search,

and the strict methodology implemented during every stage of it in accordance with existing guidelines (16, 17). Furthermore, the 30 included studies provided data for the performance of many adequately powered meta-analyses. Because a random-effects model was used for data synthesis, the results describe the average effect of orthodontic treatment among the included studies, as well as the effects of other significant factors, on nickel hypersensitivity. Unexplained excessive heterogeneity was not present, and publication bias diagnostics and sensitivity analyses indicated that the results were fairly robust. Even though the majority of studies were conducted in universities, the results could probably be generalized to the average patient, owing to the generic patient inclusion criteria and the inclusion of vast school populations from various countries.

Nevertheless, serious methodological limitations were found in 11 included original studies (Appendix S6), which might affect the credibility of the meta-analyses (38). For example, only six trials clearly described the used orthodontic appliance, including type and nickel content. Moreover, the timing of nickel hypersensitivity assessment and the reading of patch test results varied between studies (Appendix S5). In addition, there is an ongoing debate concerning patch testing, with researchers claiming that it might sensitize the patient to nickel, and that the reading of the test results might be influenced by factors such as medications and ultraviolet radiation (39). This is one reason why the reproducibility of patch test results ranges between 60% and 90%, according to the allergen (39). Finally, allergic reactions are characterized by their heterogeneous appearance, complicating the assessment of positive patch test results. Hence, irritant reactions and positive test results are difficult to distinguish, and require outcome assessment by dermatologists, which was not performed in all included trials.

Conclusions

According to the existing evidence, we could not show that orthodontic treatment influences the prevalence of nickel hypersensitivity. However, there was evidence of confounding by various influencing factors, such as patient sex, piercings, or allergic history, which could not be removed, owing to incomplete data. On the other hand, the existing evidence indicated that there was a significantly lower risk of nickel hypersensitivity when orthodontic treatment preceded piercing than when orthodontic treatment occurred after piercing. This protective role of orthodontic treatment against nickel allergy was robust to possible confounding. This might, in part, be explained by orally induced tolerance via nickel ions released during orthodontic treatment.

Regarding the clinical recommendations with the GRADE approach for our confidence in the meta-analysis results regarding nickel hypersensitivity, the following effects can be adequately substantiated with a high GRADE score:

- It is expected that 5 female patients with nickel hypersensitivity would need to be found in order to find 1 male patient with nickel hypersensitivity (NNT = 5).
- Accordingly, it is expected that 5 patients with piercings and nickel hypersensitivity would need to be found in order to find 1 patient without piercings, but with nickel hypersensitivity (NNT = 5).
- One would need to treat orthodontically 6 patients before they have their ears pierced, rather than treat them after piercing, in order to avoid an additional case of nickel hypersensitivity (NNT = 6).

Recommendations about the absolute effect of orthodontic treatment on nickel hypersensitivity are weaker, owing to the existence of confounding. We recommend that future studies on the subject include large patient samples and assess, among other factors, both orthodontic treatment and other confounding factors such as sex, piercings (and the number thereof), history of allergy, and frequent contact with metallic objects. Finally, authors are encouraged to either provide the raw patient data or conduct multivariable analyses to determine the adjusted effect of each factor, when confounders are taken into account (controlled for).

Acknowledgements

We thank the following authors for providing missing articles, additional data and/or clarifications for the systematic review: Ronny Fors (Umeå University, Umeå,

Schweden); Guilherme R. Janson (University of São Paulo, Bauru, Brazil); Christian Stab Jensen (Statens Serum Institute, Copenhagen, Denmark); and Heidi M. Kerosuo (University of Tromsø, Tromsø, Norway).

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Searches conducted in the electronic databases together with the search strategies and their results.

Appendix S2. Predetermined inclusion/exclusion criteria used for study selection according to the PICOS approach.

Appendix S3. Studies excluded from the systematic review, with reasons.

Appendix S4. References for the 30 studies included in the systematic review.

Appendix S5. Additional information for the included studies (supplement to Table 1)

Appendix S6. Assessment of methodological limitations for the included studies.

Appendix S7. Forest plot for the sensitivity analysis of the overall nickel prevalence according to the studies' precision.

Appendix S8. Details for the GRADE assessment of the primary outcomes (regarding risk of bias, all outcomes start from 'low', due to the inclusion of non-randomized studies; no reason to further downgrade).

Appendix S9. Sensitivity analysis including meta-regression with mean reported patient age.

References

- 1 Rietschel R L, Fowler J F, Warshaw E M et al. Detection of nickel sensitivity has increased in North American patch-test patients. *Dermatitis* 2008; **19**: 16–19.
- 2 Simonsen A B, Deleuran M, Johansen J D, Sommerlund M. Contact allergy and allergic contact dermatitis in children – a review of current data. *Contact Dermatitis* 2011; **65**: 254–265.
- 3 Moritz C G, Andersen K E. Allergy contact dermatitis in children and adolescents. *Contact Dermatitis* 1999; **41**: 121–130.
- 4 Danish Ministry of Environment. Statutory order of the Danish ministry of environment regarding prohibition of sale and labeling of certain nickel containing products. Copenhagen, Denmark: Statutory Order No. 854, 16th December 1991.
- 5 Johansen J D, Menné T, Christophersen J, Kaaber K, Veien N. Changes in the pattern of sensitization to common contact allergens in Denmark between 1985–86 and 1997–98, with a special view to the effect of preventive strategies. *Br J Dermatol* 2000; **142**: 490–495.
- 6 EC. Commission Directive 2004/96/EC of 27 September 2004 amending Council Directive 76/769/EEC as regards restrictions on the marketing and use of nickel for piercing post assemblies for the purpose of adapting its Annex I to technical progress. *Official Journal of the European Union*, 28th September 2004, L301/51.
- 7 Schnuch A, Uter W. Decrease in nickel allergy in Germany and regulatory interventions. *Contact Dermatitis* 2003; **49**: 107–108.
- 8 Gözl L, Knickenberg A C, Keilig L et al. Nickel ion concentration in saliva of patients treated with orthodontic fixed appliances: a prospective cohort study. *J Orof Orthop* (in press).
- 9 Mikulewicz M, Chojnacka K. Trace metal release from orthodontic appliances by in vivo studies: a systematic literature

- review. *Biol Trace Elem Res* 2010; **137**: 127–138.
- 10 Eliades T, Athanasiou A E. In vivo aging of orthodontic alloys: implications for corrosion potential, nickel release, and biocompatibility. *Angle Orthod* 2002; **72**: 222–237.
 - 11 Gözl L, Bayer S, Keilig L et al. Possible implications of Ni(II) on oral IL-1 β -induced inflammatory processes. *Dent Mater* 2014; **30**: 1325–1335.
 - 12 Noble J, Ahing S I, Karaïskos N E, Wiltshire W A. Nickel allergy and orthodontics, a review and report of two cases. *Br Dent J* 2008; **204**: 297–300.
 - 13 Fors R, Stenberg B, Stenlund H, Persson M. Nickel allergy in relation to piercing and orthodontic appliances – a population study. *Contact Dermatitis* 2012; **67**: 342–350.
 - 14 Kolokitha O E, Kaklamano E G, Papadopoulos M A. Prevalence of nickel hypersensitivity in orthodontic patients: a meta-analysis. *Am J Orthod Dentofacial Orthop* 2008; **134**: 722.e1–722.e12.
 - 15 Van Hoogstraten I M, Andersen K E, Von Blomberg B M et al. Reduced frequency of nickel allergy upon oral nickel contact at an early age. *Clin Exp Immunol* 1991; **85**: 441–445.
 - 16 Higgins J P T, Green S (eds). *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available at: <http://handbook.cochrane.org/> (accessed 18 January 2014).
 - 17 Liberati A, Altman D G, Tetzlaff J et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol* 2009; **62**: e1–e34.
 - 18 Beller E M, Glasziou P P, Altman D G et al. PRISMA for abstracts: reporting systematic reviews in journal and conference abstracts. *PLoS Med* 2013; **10**: e1001419.
 - 19 Stroup D F, Berlin J A, Morton S C et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000; **283**: 2008–2012.
 - 20 Papageorgiou S N, Antonoglou G N, Tsiranidou E, Jepsen S, Jäger A. Bias and small-study effects influence treatment effect estimates: a meta-epidemiological study in oral medicine. *J Clin Epidemiol* 2014; **67**: 984–992.
 - 21 International Contact Dermatitis Research Group. European Standard Series (ICDRG 1984). *Contact Dermatitis* 1984; **11**: 63–64.
 - 22 Downs S H, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health* 1998; **52**: 377–384.
 - 23 Guyatt G H, Oxman A D, Schünemann H J, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. *J Clin Epidemiol* 2011; **64**: 380–382.
 - 24 Papageorgiou S N, Tsiranidou E, Antonoglou G N, Deschner J, Jäger A. Choice of effect measure for meta-analyses of dichotomous outcomes influenced the identified heterogeneity and direction of small-study effects. *J Clin Epidemiol* 2015 (Epub ahead of print), doi: 10.1016/j.jclinepi.2015.01.004.
 - 25 Papageorgiou S N. Meta-analysis for orthodontists: Part I – how to choose effect measure and statistical model. *J Orthod* 2014; **41**: 317–326.
 - 26 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; **7**: 177–188.
 - 27 Graham P L, Moran J L. Robust meta-analytic conclusions mandate the provision of prediction intervals in meta-analysis summaries. *J Clin Epidemiol* 2014; **65**: 503–510.
 - 28 Schuster G, Reichle R, Bauer R R, Schopf P M. Allergies induced by orthodontic alloys: incidence and impact on treatment. Results of a survey in private orthodontic offices in the Federal State of Hesse, Germany. *J Orofac Orthop* 2004; **65**: 48–59.
 - 29 Volkman K K, Inda M J, Reichl P G, Zacharisen M C. Adverse reactions to orthodontic appliances in nickel-allergic patients. *Allergy Asthma Proc* 2007; **28**: 480–484.
 - 30 Veien N K, Hattel T, Justesen O, Norholm A. Why do young girls become nickel sensitive? *Contact Dermatitis* 1986; **15**: 306–307.
 - 31 Brandão M H, Gontijo B, Girundi M A, de Castro M C. Ear piercing as a risk factor for contact allergy to nickel. *J Pediatr (Rio J)* 2010; **86**: 149–154.
 - 32 Warshaw E M, Kingsley-Loxo J L, DeKoven J G et al. Body piercing and metal allergic contact sensitivity: North American Contact Dermatitis Group data from 2007 to 2010. *Dermatitis* 2014; **25**: 255–264.
 - 33 Novak N, Gros E, Bieber T, Allam J P. Human skin and oral mucosal dendritic cells as 'good guys' and 'bad guys' in allergic immune responses. *Clin Exp Immunol* 2010; **161**: 28–33.
 - 34 Di Gioacchino M, Ricciardi L, De Pità O et al. Nickel oral hyposensitization in patients with systemic nickel allergy syndrome. *Ann Med* 2014; **46**: 31–37.
 - 35 Tammaro A, De Marco G, Persechino S, Narcisi A, Camplone G. Allergy to nickel: first results on patients administered with an oral hyposensitization therapy. *Int J Immunopathol Pharmacol* 2009; **22**: 837–840.
 - 36 Thyssen J P, McFadden J P, Kimber I. The multiple factors affecting the association between atopic dermatitis and contact sensitization. *Allergy* 2014; **69**: 28–36.
 - 37 Ross-Hansen K, Menné T, Johansen J D et al. Nickel reactivity and filaggrin null mutations – evaluation of the filaggrin bypass theory in a general population. *Contact Dermatitis* 2011; **64**: 24–31.
 - 38 Papageorgiou S N. Meta-analysis for orthodontists: Part II – is all that glitters gold? *J Orthod* 2014; **41**: 327–336.
 - 39 Brasch J, Henseler T, Aberer W et al. Reproducibility of patch tests. A multicenter study of synchronous left-versus right-sided patch tests by the German Contact Dermatitis Research Group. *J Am Acad Dermatol* 1994; **31**: 584–591.

Appendix S1. Searches conducted in the electronic databases together with the search strategies and their results

Electronic database	Search strategy used	Limits	Hits
General sources			
CDSR searched via Cochrane Library on 29.07.2013 www.thecochranelibrary.com	(orthodon* OR malocclusion OR "fixed appliance" OR "removable appliance" OR braces OR brackets) AND (Nickel OR Ni) NOT ("NiTi" OR "Nickel-Titanium" OR "Ni-Ti")	All text	9
CENTRAL searched via Cochrane Library on 29.07.2013 www.thecochranelibrary.com	(orthodon* OR malocclusion OR "fixed appliance" OR "removable appliance" OR braces OR brackets) AND (Nickel OR Ni) NOT ("NiTi" OR "Nickel-Titanium" OR "Ni-Ti")	All text	34
DARE searched via Cochrane Library on 29.07.2013 www.thecochranelibrary.com	(orthodon* OR malocclusion OR "fixed appliance" OR "removable appliance" OR braces OR brackets) AND (Nickel OR Ni) NOT ("NiTi" OR "Nickel-Titanium" OR "Ni-Ti")	All text	1
EMBASE searched via ScienceDirect on 29.07.2013 www.embase.com	(orthodon* OR malocclusion OR "fixed appliance" OR "removable appliance" OR braces OR brackets) AND (Nickel OR Ni OR Ni2+) AND (atop* OR allerg* OR hypersensi* OR hyposensi* OR "oral tolerance" OR "contact dermatitis" OR "Ni level" OR "Nickel level" OR saliva OR serum OR urine OR blood OR "body fluid" OR "bodily fluid" OR periodon* OR "gingival inflammation" OR "gingival index" OR "bleeding index" OR "bleeding on probing" OR "attachment loss" OR "attachment level" OR "probing depth" OR "adverse effect" OR carcinog* OR cytotox* OR mutag* OR genotox* OR oestrog* OR estrog*) NOT ("NiTi" OR "Nickel-Titanium" OR "Ni-Ti")	Limit to humans	65
MEDLINE searched via PubMed (1950 – 29.07.2013) www.ncbi.nlm.nih.gov/sites/entrez/	(orthodon* OR malocclusion OR "fixed appliance" OR "removable appliance" OR braces OR brackets(Text Word)) AND (Nickel OR Ni OR Ni2+(Text Word)) AND ((atop* OR allerg* OR hypersensi* OR hyposensi* OR "oral tolerance" OR "contact dermatitis"(Text Word)) OR ("Ni level" OR "Nickel level" OR saliva OR serum OR urine OR blood OR "body fluid" OR "bodily fluid"(Text Word)) OR (periodon* OR "gingival inflammation" OR "gingival index" OR "bleeding index" OR "bleeding on probing" OR "attachment loss" OR "attachment level" OR "probing depth"(Text Word)) OR ("adverse effect" OR carcinog* OR cytotox* OR mutag* OR genotox* OR oestrog* OR estrog*(Text Word))) NOT ("NiTi" OR "Nickel-Titanium" OR "Ni-Ti"(Text Word))	Limit to humans	144
MEDLINE searched via PubMed (1950 – 29.07.2013) www.ncbi.nlm.nih.gov/sites/entrez/	((("orthodontic appliance design"(MeSH Major Topic)) OR ("orthodontic appliances"(MeSH Major Topic)) OR ("orthodontic brackets/adverse effects"(MeSH Major Topic)) OR ("orthodontic retainers"(MeSH Major Topic)) OR ("orthodontic wires"(MeSH Major Topic)) OR ("orthodontics/adverse effects"(MeSH Major Topic)) OR ("orthodontics, corrective/adverse effects"(MeSH Major Topic))) AND ("nickel"(MeSH Major Topic)) NOT ("NiTi" OR "Nickel-Titanium" OR "Ni-Ti"(Text Word))	Limit to humans	79
Scopus (1966 - 29.07.2013) www.scopus.com	orthodon* AND (Nickel OR Ni OR Ni2+) AND ("nickel level" OR "Ni level" OR "Ni2+ level" OR hypersens* OR hyposensi* OR "oral tolerance" OR "contact dermatitis" OR allerg* OR atop* OR periodon* OR "bleeding on probing" OR "attachment loss" OR "attachment level" OR "probing depth" OR "gingival index" OR "adverse effect" OR carcinog* OR cytotox* OR mutag* OR genotox* OR oestrog* OR estrog*)	Title/abstract/keywords Limit to humans	361
Open access sources			
DOAJ searched on 29.07.2013 http://www.doaj.org/	(orthodon* OR malocclusion OR "fixed appliance" OR "removable appliance" OR braces OR brackets) AND (Nickel OR Ni) NOT ("NiTi" OR "Nickel-Titanium" OR "Ni-Ti")	All fields	10
Regional sources			
BBO (including LILACS) searched on 29.07.2013 http://regional.bvsalud.org/php/index.php?la	(orthodon* OR malocclusion OR "fixed appliance" OR "removable appliance" OR braces OR brackets) AND (Nickel OR Ni OR Ni2+) AND ("nickel level" OR "Ni level" OR "Ni2 level" OR hypersens* OR allerg* OR atop* OR allerg* OR hypersensi* OR hyposensi* OR "oral tolerance" OR "contact dermatitis" OR periodon*	Exclude Animal Studies	83

ng=en	OR "bleeding on probing" OR "attachment loss" OR "attachment level" OR "probing depth" OR "gingival index" OR "adverse effect" OR carcinog* OR cytotox* OR mutag* OR oestrog* OR estrogen* NOT ("NiTi" OR "Nickel-Titanium" OR "Ni-Ti")		
IndMed (1985 - 29.07.2013) http://indmed.nic.in/	orthodontic AND (Nickel OR Ni)	-	3
Scielo searched on 29.07.2013 http://www.scielo.org/php/index.php?lang=en	(orthodon* OR malocclusion OR "fixed appliance" OR "removable appliance" OR braces OR brackets) AND (Nickel OR Ni OR Ni2) AND ("nickel level" OR "Ni level" OR "Ni2 level" OR atop* OR allerg* OR hypersensi* OR hyposensi* OR "oral tolerance" OR "contact dermatitis" OR periodon* OR "bleeding on probing" OR "attachment loss" OR "attachment level" OR "probing depth" OR "gingival index" OR adverse OR biologic OR carcinog* OR cytotox* OR mutag* OR oestrog* OR estrogen*)	-	17
Grey literature sources			
Conference Paper Index searched via Cambridge Scientific Abstracts (1982 – 29.07.2013) http://journals.cambridge.org/action/search	(orthodon* OR malocclusion OR "fixed appliance" OR "removable appliance" OR braces OR brackets) AND (Nickel OR Ni OR Ni2+) NOT ("NiTi" OR "Nickel-Titanium" OR "Ni-Ti") AND ("nickel level" OR "Ni level" OR "Ni2+ level" OR atop* OR allerg* OR hypersensi* OR hyposensi* OR "oral tolerance" OR "contact dermatitis" OR periodon* OR "bleeding on probing" OR "attachment loss" OR "attachment level" OR "probing depth" OR "gingival index" OR adverse OR biologic OR carcinog* OR cytotox* OR mutag* OR oestrog* OR estrogen*)	Limit to Abstracts/dissertation /miscellaneous/research articles Exclude book reviews/front matter/back matter Limit to Biomedical Sciences	53
Digital Dissertations searched via UMI/ProQuest on 29.07.2013 http://proquest.umi.com/login	(orthodon* OR malocclusion OR "fixed appliance" OR "removable appliance" OR braces OR brackets) AND (Nickel OR Ni OR Ni2+) NOT ("NiTi" OR "Nickel-Titanium" OR "Ni-Ti") AND ("nickel level" OR "Ni level" OR "Ni2+ level" OR atop* OR allerg* OR hypersensi* OR hyposensi* OR "oral tolerance" OR "contact dermatitis" OR periodon* OR "bleeding on probing" OR "attachment loss" OR "attachment level" OR "probing depth" OR "gingival index" OR adverse OR biologic OR carcinog* OR cytotox* OR mutag* OR oestrog* OR estrogen*)	Limit to Dentistry Limit to Dental Care	335
German National Library of Medicine (ZB MED) searched on 29.07.2013 http://www.medpilot.de	(orthodon* OR malocclusion OR "fixed appliance" OR "removable appliance" OR braces OR brackets) AND (Nickel OR Ni OR Ni2+) NOT ("NiTi" OR "Nickel-Titanium" OR "Ni-Ti") AND ("nickel level" OR "Ni level" OR "Ni2+ level" OR atop* OR allerg* OR hypersensi* OR hyposensi* OR "oral tolerance" OR "contact dermatitis" OR periodon* OR "bleeding on probing" OR "attachment loss" OR "attachment level" OR "probing depth" OR "gingival index" OR adverse OR biologic OR carcinog* OR cytotox* OR mutag* OR oestrog* OR estrogen*)	Limit to Medizin/Gesundheit Exclude Books	34
ISI Web of Knowledge (1945 - 29.07.2013) http://apps.webofknowledge.com/	Topic=((orthodon* OR malocclusion OR "fixed appliance" OR "removable appliance" OR braces OR brackets) AND (Nickel OR Ni OR Ni2+) NOT ("NiTi" OR "Nickel-Titanium" OR "Ni-Ti") AND ("nickel level" OR "Ni level" OR "Ni2+ level" OR atop* OR allerg* OR hypersensi* OR hyposensi* OR "oral tolerance" OR "contact dermatitis" OR periodon* OR "bleeding on probing" OR "attachment loss" OR "attachment level" OR "probing depth" OR "gingival index" OR "adverse effect" OR carcinog* OR cytotox* OR mutag* OR genotox* OR oestrog* OR estrogen*))	Limit to Dentistry Oral Surgery Medicine	68
metaRegister of Controlled Trials (all registers active and archived) searched on 29.07.2013 http://www.controlled-trials.com/mrct/	orthodon% AND Nickel	-	5
OpenSIGLE (1980 - 29.07.2013) http://www.opengrey.eu/	(orthodon* OR malocclusion OR "fixed appliance" OR "removable appliance" OR braces OR brackets) AND (Nickel OR Ni)	-	1

Scirus searched on 29.07.2013 http://www.scirus.com/	(keyword:orthodon* OR keyword:malocclusion OR keyword:"fixed appliance" OR keyword:"removable appliance" OR keyword:braces OR keyword:brackets) AND (keyword:Nickel OR keyword:Ni)	In Keywords Limit to Medicine; Abstracts/articles/arti cles in press/conferences/pre prints/theses and dissertations.	273
Overall articles from electronic search			1575
\$ Highly-sensitive search strategy tested, in all databases, but included too few results and was omitted in many databases. BBO, Bibliografia Brasileira de Odontologia; CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials; DARE, Database of Abstracts of Reviews of Effects; DOAJ, Database of Open Access Journals; ISI, Institute for Scientific Information; LILACS, Literatura Latino-Americana e do Caribe em Ciências da Saúde; MeSH, Medical Subject Headings; Scielo, Scientific Eletronic Library on line; UMI, University Microfilms International.			

Appendix S2. Pre-determined inclusion/exclusion criteria used for study selection according to the PICOS approach

Category	Inclusion criteria	Exclusion criteria
Study population	Patients of any age or gender	Animal studies Patients with systemic diseases affecting biological reactions Patients receiving any treatment that could affect the immune response
Intervention / exposure	Human patients with/without previous exposure to Nickel through: a) body piercings, b) use of metallic objects, or c) orthodontic treatment with Nickel-containing appliances	-
Outcomes	Patients of any age or gender Measurements of nickel sensitization prevalence in form of positive patch-test scores with the ICDRG scale Information about the association of gender, ear piercing, or previous nickel contact and nickel hypersensitivity of orthodontic patients	Other methods of investigating nickel sensitization excluded
Study design	Randomized controlled trials Longitudinal observational studies Cross-sectional observational studies	Surveys Non-clinical study designs Narrative or systematic reviews*
*Reference lists were checked for additional eligible studies. ICDRG, International Contact Dermatitis Research Group.		

ndix S3. Studies excluded from the systematic review with reasons.

Nr	Paper	Reason
1	(No authors) Poster Presentations. Journal of Developmental Origins of Health and Disease. 2009;1(SupplementS1):S61-S337.	Not relevant to review
2	(No authors) XXist CINP Congress: Glasgow, Scotland, 12-16 July 1998. The International Journal of Neuropsychopharmacology. 1998;1(SupplementS1):S1-S268.	Not relevant to review
3	Ahlawat AANJY. Utilization of oral health services in the state of Connecticut (1420042 m3 - m.p.h.): Southern Connecticut State University; 2004.	Not relevant to review
4	Attard NJAZGAY. On treatment outcomes of implant-supported mandibular prostheses in edentulous patients (NQ94305 M3 - Ph.D.): University of Toronto (Canada); 2004.	Not relevant to review
5	Baricevic M, Ratkaj I, Mladinic M, Zeljezic D, Kraljevic SP, Loncar B, et al. In vivo assessment of DNA damage induced in oral mucosa cells by fixed and removable metal prosthodontic appliances. Clinical Oral Investigations. 2012;16(1):325-31.	Not relevant to review
6	Cristaudo A, Bordignon V, Petrucci F, Caimi S, De Rocco M, Picardo M, et al. Release of palladium from biomechanical prostheses in body fluids can induce or support PD-specific IFN γ T cell responses and the clinical setting of a palladium hypersensitivity. International journal of immunopathology and pharmacology. 2009;22(3):605-14.	Not relevant to review
7	Fors R, Persson M, Bergström E, Stenlund H, Stymne B, Stenberg B. Nickel allergy - Prevalence in a population of Swedish youths from patch test and questionnaire data. Contact dermatitis. 2008;58(2):80-7.	Not relevant to review
8	Guzzi G, Pigatto PD, Severi G. Oral cancer: An association with dental metal restorations and allergy to metals? (1). International Journal of Dermatology. 2007;46(8):885.	Not relevant to review
9	Hasan MAACSGCPRY. An evaluation of the effect of stainless steel crowns, placed in pediatric patients in the operating room, on the gingival health (1449944 m3 - m.s.): State University of New York at Buffalo; 2007.	Not relevant to review
10	Mihailov T, Stanev Y. Study on the possible contact sensibilisation caused by steel alloys. Bulgarian Medicine. 2003;11(5):31-2.	Not relevant to review
11	Bachmann J. (New therapeutic possibilities in orthodontics in patients with nickel allergy). Fortschritte der Kieferorthopädie. 1987;48(6):492-503. Epub 1987/12/01. Neue therapeutische Möglichkeiten in der Kieferorthopädie bei Patienten mit Nickelallergie.	Descriptive review
12	Eliades T. Orthodontic materials research and applications: part 2. Current status and projected future developments in materials and biocompatibility. Am J Orthod Dentofacial Orthop. 2007;131(2):253-62. Epub 2007/02/06.	Descriptive review
13	Leite LP, Bell RA. Adverse hypersensitivity reactions in orthodontics. Seminars in orthodontics. 2004;10(4):240-3.	Descriptive review
14	Noble J, Ahing SI, Karaikos NE, Wiltshire WA. Should I be concerned if a patient requiring orthodontic treatment has an allergy to nickel? Journal (Canadian Dental Association). 2008;74(10):897-8. Epub 2009/01/10.	Descriptive review
15	Pigatto P, Martelli A, Marsili C, Fiocchi A. Contact dermatitis in children. Italian Journal of Pediatrics. 2010;36(2).	Descriptive review
16	Pigatto PD, Guzzi G. Nickel and medico-surgical devices. Nickel e dispositivi medico-chirurgici. 2005;59(2):72-6.	Descriptive review
17	Synodinos PN, Voulgari E, Papagrigorakis MI. Hypersensitivity reactions to orthodontic materials. Hellenic Orthodontic Review ISSN/EISSN: 11081279 Year: 2005 Volume: 8 Issue: 2	Descriptive review
18	Cressey BD, Scheinman PL. Periorcular dermatitis from systemic exposure to nickel in a palatal expander and dental braces. Dermatitis : contact, atopic, occupational, drug : official journal of the American Contact Dermatitis Society, North American Contact Dermatitis Group. 2012;23(4):179. Epub 2012/07/26.	Case report
19	de Silva BD, Doherty VR. Nickel allergy from orthodontic appliances. Contact dermatitis. 2000;42(2):102-3. Epub 2000/03/07.	Case report
20	Dickson G. Contact dermatitis and cervical headgear. British dental journal. 1983;155(4):112. Epub 1983/08/20.	Case report
21	Pazzini CA, Pereira LJ, Marques LS, Generoso R, de Oliveira G, Jr. Allergy to nickel in orthodontic patients: clinical and histopathologic evaluation. General dentistry. 2010;58(1):58-61. Epub 2010/02/05.	Case report
22	(No authors) What's new in contact dermatitis? Metal allergies. Journal of Drugs in Dermatology. 2009;8(3):307-8.	Non-clinical study
23	Bachmann J. (New therapeutic possibilities in orthodontics in patients with nickel allergy). ; Neue therapeutische Möglichkeiten in der Kieferorthopädie bei Patienten mit Nickelallergie. Fortschritte der Kieferorthopädie. 1987;48(6):492-503.	Non-clinical study
24	Chvartzaid DY. A Survey Regarding the Nature and Type of Dental Implant Complications in Private Practices in the Province of Ontario (MR76191 M3 - M.Sc.): University of Toronto (Canada); 2011.	Non-clinical study
25	de Souza RM, de Menezes LM. Re: Nickel, chromium, and iron levels in the saliva of patients with simulated fixed orthodontic appliances - Response. Angle Orthodontist. 2008;78(3):IV-V.	Non-clinical study

26	Deblock L. Orthodontic wires at the beginning of the 3rd millennium: innovation or improvement? Les fils orthodontiques au début du troisième millénaire: innovation ou amélioration? 2002;73(1):59, 61-3; discussion 9-6370.	Non-clinical study
27	Grimsdottir MR, Hensten-Pettersen A, Kullmann A. Proliferation of nickel-sensitive human lymphocytes by corrosion products of orthodontic appliances. <i>Biomaterials</i> . 1994;15(14):1157-60. Epub 1994/11/01.	Non-clinical study
28	Guzi G. Re: Nickel, chromium and iron levels in the saliva of patients with simulated fixed orthodontic appliances. <i>Angle Orthodontist</i> : Vol. 78, 345-350. <i>Angle Orthod</i> . 2008;78(3):iii; author reply iv-v. Epub 2008/05/17.	Non-clinical study
29	Jia W, Beatty MW, Reinhardt RA, Petro TM, Cohen DM, Maze CR, et al. Nickel release from orthodontic arch wires and cellular immune response to various nickel concentrations. <i>Journal of biomedical materials research</i> . 1999;48(4):488-95.	Non-clinical study
30	Kerosuo HM, Dahl JE. Adverse patient reactions during orthodontic treatment with fixed appliances. <i>Am J Orthod Dentofacial Orthop</i> . 2007;132(6):789-95. Epub 2007/12/11.	Non-clinical study
31	Ozeki K, Yuhta T, Aoki H, Asaoka T, Daisaku T, Fukui Y. Deterioration in the superelasticity of Ti sputter coated on NiTi orthodontic wire. <i>Bio-Medical Materials and Engineering</i> . 2003;13(4):355-62.	Non-clinical study
32	Rubright E. Nitinol wires: Serendipity and research. <i>Iowa Dental Bulletin</i> . 1976;9(1):13-5.	Non-clinical study
33	Sonis AL. Introduction. <i>Seminars in orthodontics</i> . 2004;10(4):239.	Non-clinical study
34	Volkman KK, Inda MJ, Reichl PG, Zacharisen MC. Adverse reactions to orthodontic appliances in nickel-allergic patients. <i>Allergy and Asthma Proceedings</i> . 2007;28(4):480-4.	Non-clinical study
35	Yang Z, Luo W, Hou J, Zhao Z, Jian F, Wamalwa P, et al. Development of a behavior model of pain induced by experimental tooth movement in rats. <i>European journal of oral sciences</i> . 2009;117(4):380-4.	Animal study
36	Almeida FRdY. Compliance, titration and side effects of oral appliances in snoring and obstructive sleep apnea patients (NR10376 M3 - Ph.D.): The University of British Columbia (Canada); 2005.	No exposure to nickel
37	Cristaudo A, Bordignon V, Petrucci F, Caimi S, De Rocco M, Picardo M, et al. Release of palladium from biomechanical prostheses in body fluids can induce or support PD-specific IFN γ T cell responses and the clinical setting of a palladium hypersensitivity. <i>International journal of immunopathology and pharmacology</i> . 2009;22(3):605-14. Epub 2009/10/14.	No exposure to nickel
38	Fors R, Persson M, Bergstrom E, Stenlund H, Stymne B, Stenberg B. Nickel allergy--prevalence in a population of Swedish youths from patch test and questionnaire data. <i>Contact dermatitis</i> . 2008;58(2):80-7. Epub 2008/01/12.	No exposure to nickel
39	Kushlinskii NE, Solovykh EA, Karaoglanova TB, Boyar U, Gershtein ES, Troshin AA, et al. Matrix metalloproteinases and inflammatory cytokines in oral fluid of patients with chronic generalized periodontitis and various construction materials. <i>Bulletin of experimental biology and medicine</i> . 2012;153(1):72-6. Epub 2012/07/19.	No exposure to nickel
40	Agaoglu G, Arun T, Izgi B, Yarat A. Nickel and chromium levels in the saliva and serum of patients with fixed orthodontic appliances. <i>Angle Orthod</i> . 2001;71(5):375-9. Epub 2001/10/19.	No Nickel hypersensitivity
41	Amini F, Borzabadi Farahani A, Jafari A, Rabbani M. In vivo study of metal content of oral mucosa cells in patients with and without fixed orthodontic appliances. <i>Orthod Craniofac Res</i> . 2008;11(1):51-6. Epub 2008/01/18.	No Nickel hypersensitivity
42	Amini F, Jafari A, Amini P, Sepasi S. Metal ion release from fixed orthodontic appliances--an in vivo study. <i>Eur J Orthod</i> . 2012;34(1):126-30. Epub 2011/02/10.	No Nickel hypersensitivity
43	Amini F, Jafari A, Amini P, Sepasi S. Metal ion release from fixed orthodontic appliances-an in vivo study. <i>European Journal of Orthodontics</i> . 2012;34(1):126-30.	No Nickel hypersensitivity
44	Amini F, Rakhshan V, Mesgarzadeh N. Effects of long-term fixed orthodontic treatment on salivary nickel and chromium levels: a 1-year prospective cohort study. <i>Biological trace element research</i> . 2012;150(1-3):15-20. Epub 2012/05/31.	No Nickel hypersensitivity
45	Amini F, Rakhshan V, Sadeghi P. Effect of fixed orthodontic therapy on urinary nickel levels: a long-term retrospective cohort study. <i>Biological trace element research</i> . 2012;150(1-3):31-6. Epub 2012/07/24.	No Nickel hypersensitivity
46	Angelieri F, Carlin V, Martins RA, Ribeiro DA. Biomonitoring of mutagenicity and cytotoxicity in patients undergoing fixed orthodontic therapy. <i>Am J Orthod Dentofacial Orthop</i> . 2011;139(4 Suppl):e399-404. Epub 2011/04/01.	No Nickel hypersensitivity
47	Babacan H, Sokucu O, Marakoglu I, Ozdemir H, Nalcaci R. Effect of fixed appliances on oral malodor. <i>American journal of orthodontics and dentofacial orthopedics : official publication of the American Association of Orthodontists, its constituent societies, and the American Board of Orthodontics (Internet)</i> . 2011; (3):351-5 pp.). Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/987/CN-00785987/frame.html .	No Nickel hypersensitivity
48	Başaran G, Özer T, Kaya FA, Kaplan A, Hamamci O. Interleukine-1 β and tumor necrosis factor- α levels in the human gingival sulcus during orthodontic treatment. <i>Angle Orthodontist</i> . 2006;76(5):830-6.	No Nickel hypersensitivity

49	Bildt MM, Bloemen M, Kuijpers-Jagtman AM, Von Den Hoff JW. Matrix metalloproteinases and tissue inhibitors of metalloproteinases in gingival crevicular fluid during orthodontic tooth movement. <i>European Journal of Orthodontics</i> . 2009;31(5):529-35.	No Nickel hypersensitivity
50	Bishara SE, Barrett RD, Selim MI. Biodegradation of orthodontic appliances. Part II. Changes in the blood level of nickel. <i>American Journal of Orthodontics and Dentofacial Orthopedics</i> . 1993;103(2):115-9.	No Nickel hypersensitivity
51	Eliades T, Trapalis C, Eliades G, Katsavrias E. Salivary metal levels of orthodontic patients: a novel methodological and analytical approach. <i>Eur J Orthod</i> . 2003;25(1):103-6. Epub 2003/03/01.	No Nickel hypersensitivity
52	Faccioni F, Franceschetti P, Cerpelloni M, Fracasso ME. In vivo study on metal release from fixed orthodontic appliances and DNA damage in oral mucosa cells. <i>American Journal of Orthodontics and Dentofacial Orthopedics</i> . 2003;124(6):687-93.	No Nickel hypersensitivity
53	Flageul F. (Orthodontic use of alloys called "shape memory"). ; L'utilisation orthodontique des alliages dits "à mémoire de forme". <i>Revue d'orthopédie dento-faciale</i> . 1988;22(1):31-8.	No Nickel hypersensitivity
54	Fors R, Persson M. Nickel in dental plaque and saliva in patients with and without orthodontic appliances. <i>Eur J Orthod</i> . 2006;28(3):292-7. Epub 2006/01/18.	No Nickel hypersensitivity
55	Gjerdet NR, Erichsen ES, Remlo HE, Evjen G. Nickel and iron in saliva of patients with fixed orthodontic appliances. <i>Acta odontologica Scandinavica</i> . 1991;49(2):73-8. Epub 1991/04/01.	No Nickel hypersensitivity
56	Gursoy UK, Sokucu O, Uitto VJ, Aydin A, Demirel S, Tokar H, et al. The role of nickel accumulation and epithelial cell proliferation in orthodontic treatment-induced gingival overgrowth. <i>Eur J Orthod</i> . 2007;29(6):555-8. Epub 2007/11/09.	No Nickel hypersensitivity
57	Hafez HS, Selim EM, Kamel Eid FH, Tawfik WA, Al-Ashkar EA, Mostafa YA. Cytotoxicity, genotoxicity, and metal release in patients with fixed orthodontic appliances: a longitudinal in-vivo study. <i>American journal of orthodontics and dentofacial orthopedics : official publication of the American Association of Orthodontists, its constituent societies, and the American Board of Orthodontics (Internet)</i> . 2011; (3):(298-308 pp.). Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/236/CN-00798236/frame.html .	No Nickel hypersensitivity
58	Kerosuo H, Moe G, Hensten-Pettersen A. Salivary nickel and chromium in subjects with different types of fixed orthodontic appliances. <i>Am J Orthod Dentofacial Orthop</i> . 1997;111(6):595-8. Epub 1997/06/01.	No Nickel hypersensitivity
59	Knickenberg AC. Metallionen-Konzentrationen im Speichel Kieferorthopädisch behandelter Patienten. Uni-Bonn Dissertation Bourauel	No Nickel hypersensitivity
60	Kocadereli L, Atac PA, Kale PS, Ozer D. Salivary nickel and chromium in patients with fixed orthodontic appliances. <i>Angle Orthod</i> . 2000;70(6):431-4. Epub 2001/01/04.	No Nickel hypersensitivity
61	Marigo M, Nouer DF, Genelhu MC, Malaquias LC, Pizzolo VR, Costa AS, et al. Evaluation of immunologic profile in patients with nickel sensitivity due to use of fixed orthodontic appliances. <i>Am J Orthod Dentofacial Orthop</i> . 2003;124(1):46-52. Epub 2003/07/18.	No Nickel hypersensitivity
62	Matos de Souza R, Macedo de Menezes L. Nickel, chromium and iron levels in the saliva of patients with simulated fixed orthodontic appliances. <i>The Angle orthodontist (Internet)</i> . 2008; (2):(345-50 pp.). Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/864/CN-00629864/frame.html .	No Nickel hypersensitivity
63	Menezes LM, Quintao CA, Bolognese AM. Urinary excretion levels of nickel in orthodontic patients. <i>Am J Orthod Dentofacial Orthop</i> . 2007;131(5):635-8. Epub 2007/05/08.	No Nickel hypersensitivity
64	Natarajan M, Padmanabhan S, Chitharanjan A, Narasimhan M. Evaluation of the genotoxic effects of fixed appliances on oral mucosal cells and the relationship to nickel and chromium concentrations: an in-vivo study. <i>Am J Orthod Dentofacial Orthop</i> . 2011;140(3):383-8. Epub 2011/09/06.	No Nickel hypersensitivity
65	Natarajan M, Padmanabhan S, Chitharanjan A, Narasimhan M. Evaluation of the genotoxic effects of fixed appliances on oral mucosal cells and the relationship to nickel and chromium concentrations: an in-vivo study. <i>American journal of orthodontics and dentofacial orthopedics : official publication of the American Association of Orthodontists, its constituent societies, and the American Board of Orthodontics (Internet)</i> . 2011; (3):(383-8 pp.). Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/233/CN-00798233/frame.html .	No Nickel hypersensitivity
66	Petoumeno E, Kislyuk M, Hoederath H, Keilig L, Bourauel C, Jäger A. Corrosion susceptibility and nickel release of nickel titanium wires during clinical application. <i>Korrosionsverhalten und Nickelabgabe von Nickel-Titan-Drähten im Verlauf der klinischen Anwendung</i> . 2008;69(6):411-23.	No Nickel hypersensitivity
67	Petoumenou E, Arndt M, Keilig L, Reimann S, Hoederath H, Eliades T, et al. Nickel concentration in the saliva of patients with nickel-titanium orthodontic appliances. <i>American Journal of Orthodontics and Dentofacial Orthopedics</i> . 2009;135(1):59-65.	No Nickel hypersensitivity
68	Sahoo N, Kailasam V, Padmanabhan S, Chitharanjan AB. In-vivo evaluation of salivary nickel and chromium levels in conventional and self-ligating brackets. <i>Am J Orthod Dentofacial Orthop</i> . 2011;140(3):340-5. Epub 2011/09/06.	No Nickel hypersensitivity
69	Sahoo N, Kailasam V, Padmanabhan S, Chitharanjan AB. In-vivo evaluation of salivary nickel and chromium levels in conventional and self-ligating brackets. <i>American journal of orthodontics and dentofacial orthopedics : official publication of the American Association of Orthodontists, its constituent societies, and the American</i>	No Nickel hypersensitivity

	Board of Orthodontics (Internet). 2011; (3):(340-5 pp.). Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/235/CN-00798235/frame.html .	
70	Singh DP, Sehgal V, Pradhan KL, Chandna A, Gupta R. Estimation of nickel and chromium in saliva of patients with fixed orthodontic appliances. <i>World journal of orthodontics</i> . 2008;9(3):196-202. Epub 2008/10/07.	No Nickel hypersensitivity
71	Speer C, Pelz K, Hopfenmüller W, Holtgrave EA. Investigations on the influencing of the subgingival microflora in chronic periodontitis. A study in adult patients during fixed appliance therapy. <i>Untersuchungen zur Beeinflussung der subgingivalen Mikroflora bei chronischer parodontitis Eine Studie bei Erwachsenen während Multibandbehandlung</i> . 2004;65(1):34-47.	No Nickel hypersensitivity
72	Szarmach IJ, Kasacka I, Buczek P, Tankiewicz A, Pawlak D. Oral cavity status and IgE level in orthodontic patients. <i>Advances in medical sciences</i> . 2006;51 Suppl 1:210-2. Epub 2007/04/27.	No Nickel hypersensitivity
73	Venza M, Visalli M, Cicciù D, Valenti A, Passi P, Teti D. Polyamines in nickel-titanium archwire-induced gingivitis in adolescents. <i>Journal of Periodontology</i> . 2004;75(6):877-85.	No Nickel hypersensitivity
74	Venza M, Visalli M, Ruggeri P, Cicciù D, Teti D. Age-related salivary polyamine increase in adolescents wearing orthodontic Ni-Ti archwires. <i>Amino Acids</i> . 2002;22(2):119-30.	No Nickel hypersensitivity
75	Westphalen GH, Menezes LM, Pra D, Garcia GG, Schmitt VM, Henriques JA, et al. In vivo determination of genotoxicity induced by metals from orthodontic appliances using micronucleus and comet assays. <i>Genetics and molecular research : GMR</i> . 2008;7(4):1259-66. Epub 2008/12/11.	No Nickel hypersensitivity
76	Pazzini CA, Marques LS, Ramos-Jorge ML, Júnior GO, Pereira LJ, Paiva SM. Longitudinal assessment of periodontal status in patients with nickel allergy treated with conventional and nickel-free braces. <i>The Angle orthodontist (Internet)</i> . 2012; (4):(653-7 pp.). Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/787/CN-00844787/frame.html .	No Nickel hypersensitivity
77	Ramadan AA. Effect of nickel and chromium on gingival tissues during orthodontic treatment: a longitudinal study. <i>World journal of orthodontics</i> . 2004;5(3):230-4; discussion 5. Epub 2004/12/23.	No Nickel hypersensitivity
78	Athanasiou AE, Pafliotelis J. (Allergic reactions to orthodontic materials and a protocol for the management of patients). ; <i>Allergikes antidraesis sta orthodontika ylika kai protokollo antimetopises ton asthenon. Orthodontike Epitheorisi: epistimoniko periodiko tis Orthodontikis Etaireias tis Ellados / OEE</i> . 1989;1(2):37-42.	Not retrievable
79	Athanasiou AE, Pafliotelis J. (Allergic reactions to orthodontic materials and a protocol for the management of patients). <i>Orthodontike epitheorese : epistemoniko periodiko tes Orthodontikes Etaireias tes Ellados / OEE</i> . 1989;1(2):37-42. Epub 1989/04/01. <i>Allergikes antidraesis sta orthodontika ylika kai protokollo antimetopises ton asthenon</i> .	Not retrievable
80	Fernández-Miñano E, Ortiz C, Vicente A, Calvo JL, Ortiz AJ. Metallic ion content and damage to the DNA in oral mucosa cells of children with fixed orthodontic appliances. <i>Biometals : an international journal on the role of metal ions in biology, biochemistry, and medicine (Internet)</i> . 2011; (5):(935-41 pp.). Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/140/CN-00812140/frame.html .	Not retrievable
81	Greppi L, Smith DC, Woodside DG, Varrela T. Nickel hypersensitivity reactions in orthodontic patients (abstract). <i>Journal of Dental Research (Internet)</i> . 1991; (Spec Iss):(361, Abstract no: 768 pp.). Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/594/CN-00775594/frame.html .	Not retrievable
82	Greppi L, Smith DC, Woodside DG. Nickel hypersensitivity reactions in orthodontic patients (abstract). <i>European Journal of Orthodontics (Internet)</i> . 1993; (4):(336 p.). Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/593/CN-00775593/frame.html .	Not retrievable
83	Hamula DW, Hamula W, Sernetz F. Pure titanium orthodontic brackets. <i>Journal of clinical orthodontics : JCO</i> . 1996;30(3):140-4. Epub 1996/03/01.	Not retrievable
84	Ize-Iyamu IN, Ogbogu P. Nickel chromium brackets and its effect on the oral microflora. <i>African journal of medicine and medical sciences</i> . 2011;40(4):367-71. Epub 2012/07/13.	Not retrievable
85	Levrini L, Lusvardi G, Gentile D. Nickel ions release in patients with fixed orthodontic appliances. <i>Minerva stomatologica</i> . 2006;55(3):115-21. Epub 2006/04/01.	Not retrievable
86	Ousehal L, Lazrak L. Change in nickel levels in the saliva of patients with fixed orthodontic appliances. <i>La modification du taux de nickel dans la salive chez des patients porteurs d'appareillages orthodontiques fixes</i> . 2012;10(2):190-7.	Not retrievable
87	Roesel N. Quantitative systemische Bestimmung von Legierungsbestandteilen im Zusammenhang mit der Eingliederung festsitzender kieferorthopädischer Multibracketapparaturen- eine prospektive klinische Studie - .2007	Not retrievable
88	(No authors) Nickel allergy and fixed orthodontic appliances. <i>Dental Abstracts</i> . 2008;53(5):279-80.	Not retrievable
89	Lenza MA, Moore RN, Cohen DM, Hoffman M. Nickel sensitivity to orthodontic archwires (abstract). <i>Journal of Dental Research (Internet)</i> . 1993; (Spec Iss (IADR Abstracts)):(368, Abstract no: 2115 pp.). Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/700/CN-00794700/frame.html .	Not retrievable

Appendix S4. References for the 30 studies included in the systematic review

- 1 Bass J K, Fine H, Cisneros G J. Nickel hypersensitivity in the orthodontic patient. *Am J Orthod Dentofacial Orthop* 1993; **103**: 280–285.
- 2 Costa M T, Ribeiro-Dias F, Lenza M A. Nickel hypersensitivity in individual undergoing orthodontic therapy. *Rev Bras Alerg Immunopatol* 2003; **26**: 02–11.
- 3 De Paiva V C X. Hipersensibilidade ao níquel presente no aparelho ortodôntico fixo metálico. Avaliação clínica, periodontal, histopatológica e imunoistoquímica. Master dissertation, Pontifical Catholic University of Minas Gerais, Belo Horizonte, Brazil, 2005
- 4 Fors R, Persson M, Bergstrom E, Stenlund H, Stymne B, Stenberg B. Lifestyle and nickel allergy in a Swedish adolescent population: effects of piercing, tattooing and orthodontic appliances. *Acta Derm Venereol* 2012; **92**: 664–668.
- 5 Fors R, Persson M, Bergström E, Stenlund H, Stymne B, Stenberg B. Nickel allergy--prevalence in a population of Swedish youths from patch test and questionnaire data. *Contact Dermatitis* 2008; **58**: 80–87.
- 6 Fors R, Stenberg B, Stenlund H, Persson M. Nickel allergy in relation to piercing and orthodontic appliances--a population study. *Contact Dermatitis* 2012; **67**: 342–350.
- 7 Fors R. Nickel allergy in a Swedish adolescent population and its relation to orthodontic treatment and lifestyle factors. Doktorat dissertation, Department of Odontology, Umeå University, Umeå, Sweden, 2008.
- 8 Genelhu M C, Marigo M, Alves-Oliveira L F, Malaquias L C, Gomez R S. Characterization of nickel-induced allergic contact stomatitis associated with fixed orthodontic appliances. *Am J Orthod Dentofacial Orthop* 2005; **128**: 378–381.
- 9 Janson G R, Dainesi E A, Consolaro A, Woodside D G, de Freitas M R. Nickel hypersensitivity reaction before, during, and after orthodontic therapy. *Am J Orthod Dentofacial Orthop* 1998; **113**: 655–660.
- 10 Jensen C S, Lisby S, Baadsgaard O, Volund A, Menne T. Decrease in nickel sensitization in a Danish schoolgirl population with ears pierced after implementation of a nickel-exposure regulation. *Brit J Dermatol* 2002; **146**: 636–642.

- 11 Johansson K, Kerosuo H, Lammintausta K. Nickel sensitization in orthodontically treated and non-treated female adolescents. *Contact Dermatitis* 2011; **64**: 132–137.
- 12 Kalimo K, Mattila L, Kautiainen H. Nickel allergy and orthodontic treatment. *J Eur Acad Dermatol Venereol* 2004; **18**: 543–545.
- 13 Kerosuo H, Kullaa A, Kerosuo E, Kanerva L, Hensten-Pettersen A. Nickel allergy in adolescents in relation to orthodontic treatment and piercing of ears. *Am J Orthod Dentofacial Orthop* 1996; **109**: 148–154.
- 14 Koppenburg P, Bacher M, Geis-Gerstorfer J, Sauer K H, Kratzenstein B, Weber H. [Orthodontic appliance--a step toward sensitization to metals? An interdisciplinary study]. *Fortschr Kieferorthop* 1988; **49**: 62–69.
- 15 Marigo M, Nouer D F, Genelhu M C et al. Evaluation of immunologic profile in patients with nickel sensitivity due to use of fixed orthodontic appliances. *Am J Orthod Dentofacial Orthop* 2003; **124**: 46–52.
- 16 Menezes L M, Campos L C, Quintão C C, Bolognese A M. Hypersensitivity to metals in orthodontics. *Am J Orthod Dentofacial Orthop* 2004; **1**: 58–64.
- 17 Mortz C G, Lauritsen J M, Bindslev-Jensen C, Andersen K E. Nickel sensitization in adolescents and association with ear piercing, use of dental braces and hand eczema. The Odense Adolescence Cohort Study on Atopic Diseases and Dermatitis (TOACS). *Acta Derm Venereol* 2002; **82**: 359–364.
- 18 Pacor M L, Di Lorenzo G, Martinelli N et al. Results of double-blind placebo-controlled challenge with nickel salts in patients affected by recurrent aphthous stomatitis. *Int Arch Allergy Immunol* 2003; **131**: 296–300.
- 19 Pantuzo M C, Zenobio E G, de Andrade Marigo H, Zenobio M A. Hypersensitivity to conventional and to nickel-free orthodontic brackets. *Braz Oral Res* 2007; **21**: 298–302.
- 20 Pazzini C A, Junior G O, Marques L S, Pereira C V, Pereira L J. Prevalence of nickel allergy and longitudinal evaluation of periodontal abnormalities in orthodontic allergic patients. *Angle Orthod* 2009; **79**: 922–927.
- 21 Pazzini C A, Pereira L J, Carlos R G, de Melo G E, Zampini M A, Marques L S. Nickel: periodontal status and blood parameters in allergic orthodontic patients. *Am J Orthod Dentofacial Orthop* 2011; **139**: 55–59.
- 22 Röhrl K, Stenberg B. Lifestyle factors and hand eczema in a Swedish adolescent population. *Contact Dermatitis* 2010; **62**: 170–176.
- 23 Saglam A M Ş, Baysal V, Ceylan A M. Nickel and cobalt hypersensitive reaction before and after orthodontic therapy in children. *J Contemp Dent Pract* 2004; **5**: 79–90.

- 24 Schuster G, Reichle R, Bauer R R, Schopf P M. Allergies induced by orthodontic alloys: incidence and impact on treatment. Results of a survey in private orthodontic offices in the Federal State of Hesse, Germany. *J Orofac Orthop* 2004; **65**: 48–59.
- 25 Staerkjaer L, Menne T. Nickel allergy and orthodontic treatment. *Eur J Orthod* 1990; **12**: 284–289.
- 26 Todd D J, Burrows D. Nickel allergy in relationship to previous oral and cutaneous nickel contact. *Ulster Med J* 1989; **58**: 168–171.
- 27 van der Burg C K, Bruynzeel D P, Vreeburg K J, von Blomberg B M, Scheper R J. Hand eczema in hairdressers and nurses: a prospective study. I. Evaluation of atopy and nickel hypersensitivity at the start of apprenticeship. *Contact Dermatitis* 1986; **14**: 275–279.
- 28 Van Hoogstraten IM, Andersen KE, Von Blomberg BM et al. Reduced frequency of nickel allergy upon oral nickel contact at an early age. *Clin Exp Immunol* 1991; **85**: 441–445.
- 29 Westphalen G H, Menezes L M, Prá D, Garcia G G, Schmitt V M, Henriques J A, Medina-Silva R. In vivo determination of genotoxicity induced by metals from orthodontic appliances using micronucleus and comet assays. *Genet Mol Res* 2008; **7**: 1259–1266.
- 30 Westphalen G H. Evaluation of hypersensitivity to metals and genetic toxicity associated with the use of fixed orthodontic appliances. Doctoral dissertation, Catholic University of Rio Grande do Sul, Porto Alegre, Brazil, 2006.

Appendix S5. Additional information for the included studies (supplement to Table 1)

Nr.	Study	Study info (design; country; setting)	Participants (sample size; sex; mean age or range; source; medical history; ortho history)	Exposure (intervention; product; nickel content; duration)	Assessment of nickel hypersensitivity (method; area (if relevant); application duration; assessor; criteria)+Abbreviation for assessor	Controlled variables (type; timing)	Timing of assessment	Reported results/prevalence/factors
1	Bass et al., 1993	Cross-sectional; University dept.; U.S.A.	29 pts (11/18); 1 dropout; mean 20.3 yrs; no previous ortho Tx	Fixed SS ortho- appliances (Bd/Br) with SS or Ni-Ti wires	Ni patch test (5% nickel sulfate in petroleum; upper arm; left for 48 hrs; reading at 48-72 hrs; photographs assessed by 1 Ortho and 2 Derma)	GI and PI (4mos)	-Before ortho- Tx -Pat. with pos. results tested at 1, 2, 3 and 4 mos -Pat. with neg. results tested at 3mos	Overall prevalence Bef: 5/29 pts (17.2%) -Prevalence for gender: F 5/18 pts (27.8%) or M 0/11 pts (0.0%) -From the initially patch-negative pts, after ortho- Tx 2/23 (8.7%) tested positive
2	Costa et al., 2003	Cross-sectional; university; Brazil	65 pts (30/35); mean 21 yrs; indication for orthodontic appliances	Fixed ortho- appliances and nickel- containing wires (55% nickel)	Ni patch test (5% nickel sulfate in petroleum from LenzaFarm, Belo Horizonte, MG and control test with vaseline; inside of the arm; left for 48 hrs; reading at 48 hrs; assessed by two observers according to ICDRG)		-Bef ortho-Tx -Pat with neg. results retested at 1 yr	Overall prevalence: 6/65 pts (9.2%) -Gender: M 0/30 pts (0.0%) or F 6/35 pts (17.1%) -History of allergy to metals: yes 6/15 pts (40.0%) or 0/50 pts (0.0%) -From the initially patch-negative pts, after ortho- Tx 1/60 (16.7%) tested positive
3	de Paiva 2005	Cross-sectional; university; Brazil	22 pts (6/16); mean 15.9 yrs; fixed ortho-appliances for maximal 3 yrs; gingival overgrowth of 1/3 of crown; no possibility of angular cheilitis; no medications that can induce gingival overgrowth; no lip incompetence; no pregnant women	Fixed ortho- appliances (Morelli® brackets, Dental Morelli Ltda., Sorocaba, SP, Brazil; 14% nickel)	Ni patch test (5% nickel sulfate; left for 48 hrs; reading at 48 hrs; assessed according to ICDRG)	PI; GI; gingival enlargement; PD	Clinical/perio dental assessment -Before ortho- Tx -At 30 days follow-up	Overall prevalence: 9/22 pts (40.1%) -Gender: M 0/6 pts (0.0%) or F 9/16 pts (56.3%)
4	Fors et al., 2012a; Fors et al. 2008; Fors 2008; Röhl and Stenberg 2010; Fors et	Cross-sectional; secondary schools; Sweden	6364 pts received briefings; from them 6095 pts (96%) completed questionnaire; from them 4439 pts (70%) consented to patch test; 63 dropouts (patch fell off); in the end 4376 pts (1400/2976); mean 17.4 yrs	Orthodontic appliances	Ni patch test (patch containing 24 allergens; product TRUE Test® from Mekos Laboratories A/S, Hillerød, Denmark; no testing in summer; left for 48 hrs; reading at 96 hrs; assessed by a school nurse or one Derma according to ICDRG; unclear cases were photographed and assessed by Derma) Self-reported questionnaire about nickel-sensitivity (results not	Questionnaire (gender; Piercings; Piercing timing; smoking, tattoo; atopy; educational programmes; life style; ortho-Tx)	Single patch test	Overall prevalence: 486/4447 pts (10.9%) -Gender: M 40/1474 pts (2.7%) or F 446/2973 pts (15.0%) -Originating city: Umeå 323/3371 pts (9.9%) or Örebro 109/1005 pts (10.8%) -Educational program: natural sciences 38/573 pts (6.6%), social sciences 135/1402 pts (9.6%), arts 27/292 pts (9.2%) or vocational 287/2180 pts (13.2%) -Piercing: yes 445/2863 pts (15.5%) or no 41/1578 pts (2.6%) -Piercing age: 1-8 yrs 184/984 pts (18.7%), 9-11

al. 2012b		reported)					yrs 174/1008 pts (17.3%) or 12-19 yrs 85/844 pts (10.1%) -Multiple piercings: yes 168/746 pts (22.5%) or no (i.e. only one) 278/2119 pts (13.1%) -Tattoo: yes 55/255 pts (21.6%) or no 418/4156 pts (10.1%) -Vegetarian diet: yes 86/660 pts (13.0%) or no 386/3726 pts (10.4%) -Smoking frequency: daily 77/375 pts (20.5%), occasionally 90/671 pts (13.4%), earlier-not now 49/442 pts (11.1%) or no 262/2915 pts (9.0%) -Atopy: yes 239/2126 pts (11.2%) or no 220/2224 pts (9.9%) -Ortho-Tx: yes 246/2037 pts (12.1) or no 238/2403 pts (9.9%) -Ortho-Tx before piercing: yes 28/353 pts (7.9%) or no (i.e. after piercing) 156/875 pts (17.8%) Overall prevalence: 26/48 pts (31.0%) -Gender: M 8/17 pts (47.1%) or F 18/31 pts (58.1%) -Age significantly lower in patients with hypersensitivity symptoms -Exposure duration to ortho-appliances not significantly associated with nickel hypersensitivity	
5	Genelhu et al., 2005	Cross-sectional; university; Brazil	48 pts (17/31); 10-44 yrs; previous allergic history; divided into 2 groups: pts with clinical manifestation of nickel hypersensitivity or without	Fixed ortho-appliances	Clinical evaluation (gingival hyperplasia, labial desquamation)	Age; gender; exposure duration to ortho-appliances; allergic history	During ortho-Tx	
6	Janson et al., 1998	Cross-sectional; university; Brazil	170 pts divided in 3 groups: -Bef ortho-Tx: 60 pts (27/33); 8-24 yrs -During ortho-Tx: 66 pts (21/45); 12-31 yrs -After ortho-Tx: 44 pts (17/27); 12-28 yrs	Fixed ortho-appliances (Sandvik do Brasil S.A. Indústria e Comércio; AISI 302 alloy 8% Ni)	Ni patch: (one 5% nickel sulfate patch in white petrolatum and one placebo; inner side of the upper arm; left in place 48 hrs; readings at 48 and 96 hrs; assessed by 2 Orthos, 2 Dernas and 1 Patho	History of nickel hypersensitivity; use of metal objects such as earrings, glasses and clothing accessories; amalgam fillings; dental prostheses	Bef ortho-Tx or during ortho-Tx or 2-6 mos after completion of ortho-Tx	-Overall prevalence: 48/170 pts (28.2%) -Gender: M 9/65 pts (13.8%) or F 39/105 pts (37.1%) -History of allergic reaction: yes 28/45 (62.2%) or no 20/125 pts (16.0%) -Use of metallic objects: yes 41/111 pts (36.9%) or no 7/59 pts (11.9%) -Ortho-Tx: Before 18/60 pts (30.0%), during 17/66 pts (25.8%) or after 13/44 pts (29.5%)
7	Jensen et al., 2002	Cross-sectional; public schools and high-schools; Denmark	Only female pts with caucasian skin type; no pregnant pts - 580 pts Public schools (before regulation): 427 pts, mean 12,4 yrs; from those 305 pts patch tested High schools (after regulation): 534 pts, mean 18,8 yrs; from those 275	History of orthodontic appliances or ear piercings	Ni patch test (TRUE test from Mekos Laboratories AS, Hillerod, Denmark; 3 concentrations of nickel sulfate and one placebo; left for 48 hrs; readings at 48 and 96 hrs; assessed according to ICDRG; photographs for second opinion	Type of school; timing of ear piercing; history of ortho-Tx; timing of ortho-Tx (before or after ear piercing)	Mixed	Overall prevalence: 59/580 pts (10.2%) -Type of school: public school 12/305 pts (3.9%) or high school 47/275 pts (17.1%) -Ears pierced: yes 57/447 pts (12.8%) or no 2/133 pts (1.5%) -Ortho-Tx: yes 21/170 (12.4%) or no 38/410 (9.3%) -Ortho-Tx before ear-piercing: yes 4/80 (5.0%) or no (i.e. after ear-piercing) 17/90 pts (18.9%) Only timing of ear piercing and type of school

			patch tested					statistically significant
8	Johannson et al., 2011	Cross-sectional; schools/university/municipal health center; Finland	170 pts -30 pts about to start (16 pts) or already in ortho-Tx (14 pts); mean 14.7 yrs -140 pts without ortho-Tx; mean 13.7 yrs; 11 dropouts (did not attend follow-up)	Fixed ortho-appliances (Bd/Br/TP/HG) with high- or low nickel content (8-12% for the fixed-appliances-up to 50% or more for the wires)	Ni patch test (5% nickel sulfate in petrolatum from Chemotechnique Diagnostics, Vellinge, Sweden; upper arm; left for 48 hrs; reading at 72-120 hrs; assessed according to ICDRG by 1 Ortho trained by 1 Derma; unclear readings were assessed blindly by the Derma	Piercings	-Timing of first test mixed -Second test at 1 yr follow-up	Overall prevalence: 29/159 pts (18.2%) for T1 and 33/159 (20.8%) for T2 -Ortho-Tx: yes 21/129 pts (13.2%) for T1, 27/129 pts (17.0%) for T2 or no 7/30 pts (23.3%) for T1, 6/30 pts (20.0%) for T2 -Piercings: pts with three or more piercings increased odds for reaction (OR=4.7, 95% CI=1.7-13.0, P=0.003) -Pts with previous skin symptoms after contact had increased odds for reaction (OR=9.4, 95% CI=3.7-23.9, P<0.001)
9	Kalimo et al., 2004	Cross-sectional; university; Finland	153 pts (32/121); mean 22.0 yrs -70 pts with history of ortho-Tx (55 pts with fixed- and 15 pts with removable appliances) -83 pts without history of ortho-Tx	Fixed or removable ortho-appliances	Ni patch test (5% nickel sulfate in petrolatum from Chemotechnique Diagnostics, Vellinge, Sweden; left for 48hrs; reading at 71- 96 hrs according to ICDRG	Piercings	Single patch test	Overall prevalence: 65/153 pts (42.5%) -Gender: M 3/32 pts (xx) or F 62/121 pts (51.2%) -Piercing: yes 61/113 (54.0%) or no 4/40 pts (10.0%) -Ortho-Tx: yes 30/70 pts (42.9%) or no 35/83 (42.2%) -Type of ortho-appliances: fixed 25/55 pts (45.5%) or 5/15 pts (33.3%) -Ortho-Tx before piercing: yes 10/20 pts (50%) or no (i.e. after piercing) 16/32 pts (50%) Overall prevalence: 132/700 pts (18.9%) -Ears pierced: yes 126/411 (30.7%) or no 6/289 (2.1%) -More than 1 piercing per earlobe: not clearly reported -Skin symptoms after metal contact: not clearly reported
10	Kerosuo et al., 1996	Cross-sectional; university; Finland	700 pts (283/417); 17-18 yrs	Metallic fixed orthodontic appliances, HG, QH or combination (Tx duration 3-40 mos; 4 pts had received QH for less than 3 mos)	Ni patch test (5% nickel sulfate in petrolatum from Chemotechnique Diagnostics Ab, Malmo, Sweden; upper back; left for 48 hrs; reading at 72-120 hrs; assessed by one Ortho trained from one Derma	Ear piercing; skin symptoms; gender	Single patch test	-Ortho-Tx: yes 84/477 (17.6%) or no 48/223 (21.5%) -Ortho-Tx before ear-piercing: yes 9/54 (16.7%) or no (i.e. after piercing) 75/215 (57.6%) -Type of ortho-appliance: fixed appliance 50/172 (29.1%), QH 10/35 (28.6%) or HG 24/62 (38.7%) Ear piercing and skin symptoms the only significant factors
11	Koppenburg et al., 1988	Cross-sectional; university; Germany	472 pts undergoing ortho-Tx	Fixed ortho-appliances	Questionnaire		Single assessment	Overall incidence (for history of Ni/Cr allergy): 53/472 pts (11.2%)

12	Marigo et al., 2003	Cross-sectional; university; Brazil	35 pts; mean 14.3 yrs; two groups were formed: -26 pts (8/18); 10-21 yrs; with clinical manifestation of contact dermatitis; patch-positive -9 pts (3/6); 11-21 yrs; no clinical clinical manifestation of contact dermatitis; patch-negative	Fixed ortho-appliances	Ni patch test (5% nickel sulfate in petroleum jelly; product from Alergofar, Rio de Janeiro, Brazil; forearm; left for 48-72 hrs) Lymphocyte proliferation test under nickel antigens (nickel corrosion extracts from ortho-appliances and hexahydrated nickel sulfate in doses of 1.25, 2.50 and 5.00 µg/mL; dosage measured with atomic absorption spectrophotometer; proliferation assays according to Gazzineli et al.)	Clinical manifestations; duration of ortho-Tx	Single test	-Positive clinical manifestations and positive nickel patch test were associated with higher lymphocyte proliferation counts. -Pts with > 24 mos of exposure to ortho-Tx showed lower lymphocyte proliferation counts compared to pts with < 24 mos of exposure to ortho-Tx.
13	Menezes et al., 2004	Longitudinal; university; Brazil	55pts seeking ortho-Tx; from those 38 pts (17/21) included; 9-25 yrs	Fixed ortho-appliances	Ni patch test (5% nickel sulfate and 7 other antigens 3 cm apart; left for 48 hrs; readings at 48 hrs, 48.5 hrs and 72 hrs; assessed by 1 Derma according to ICDRG	Gender; ortho-Tx	-Before ortho-Tx -2 mos follow-up	-Positive clinical manifestations and positive nickel patch test were associated with higher lymphocyte proliferation counts. -Pts with > 24 mos of exposure to ortho-Tx showed lower lymphocyte proliferation counts compared to pts with < 24 mos of exposure to ortho-Tx.
14	Mortz et al., 2002	Cross-sectional; 40 schools; Denmark	1501 pts; attending the 8th grade in 40 schools in Denmark; from them 1146 were patch-tested	Fixed ortho-appliances	Ni patch test (patch test with nickel sulfate in 3 different concentration and one placebo; TRUE Test® from Mekos Laboratories A/S, Hillerød, Denmark; upper back; left for 48 hrs; reading at 72 hrs; assessed by one Derma) -Ni patch test (5% nickel sulfate from Lo Pharma, Milan, Italy; left for 48 hrs; readings at 48 hrs and 96 hrs; assessed according to ICDRG	Gender; ear piercings; ortho-Tx; timing of piercings with regard to ortho-Tx; hand eczema;	Single patch test	Overall prevalence: 8/38 pts (21.1%) for T1 and 8/38 pts (21.1%) for T2 -Before or after ortho-Tx: before 8/38 pts (21.1%) or after 8/38 pts (21.1%) -Gender (before ortho-Tx): M 2/17 pts (11.8%) or F 6/21 pts (28.6%) -Gender (after ortho-Tx): M 2/17 pts (11.8%) or F 7/21 pts (33.3%)
15	Pacor et al., 2003	Cross-sectional (for the nickel patch test) and RCT (for the oral nickel challenge); university; Italy	380 pts (176/204) with recurrent aphthous stomatitis and ortho-appliances were patch tested; mean 46.0 yrs; no atopic diseases; no smokers or ex-smokers -28/380 pts reported initial symptoms after insertion of the appliances -352/380 pts reported worsening of symptoms after insertion of the appliances From the initial patients, those who reacted to the	Fixed ortho-appliances	-VAS scale for subjective symptoms -Oral nickel challenge (nickel sulfate administered in doses of 1.25 mg, 2.50 mg and 5 mg in gelatine capsules or placebo capsules at 1 hr intervals; sham was administered beforehand and only non-responsive patients receive the nickel or placebo		-Single patch test -Clinical examination at baseline and after 6 mos follow-up	Overall prevalence: 98/1146 pts (8.6%) -Gender: M 13/526 pts (2.5%) or F 85/620 pts (13.7%) -Ear piercing: yes 83/614 pts (27.0%) or no 15/532 pts (2.8%) -Ortho-Tx: yes 40/380 pts (10.5%) or no 58/766 (7.6%) -Ortho-Tx timing: before piercing 1/60 pts (1.7%), after piercing 31/152 pts (20.4%) or same year as piercing 4/18 pts (22.2%)

			patch test (70/380 pts), received oral nickel challenge		capsules)			
16	Pantuzo et al., 2007	Cross- sectional; university; Brazil	58 pts (28/30); 11-30 yrs; no systematic diseases; no medications	Fixed ortho- appliances (Morelli® brackets, Dental Morelli Ltda., Sorocaba, SP, Brazil; 14% nickel)	-Ni patch test (5% nickel sulfate in petroleum; product name Substance 27, FDA Allergenic Ltda., Rio de Janeiro, RJ, Brazil; upper arm following previous technique (Marks and Deleo, 1992); left for 48 hrs; reading at 48 hrs; assessed according to ICDRG) -Cutaneous sensitivity test 30 days later (20 discs of 2.0 mm diameter with high-nickel and 20 discs with low-nickel content; internal part of forearm; left for 48 hrs)			Overall prevalence: 70/380 pts (18.4%) The same patients were re-evaluated after 6 mos: complete remission of RAS in 28/70 pts (40.0%), partial remission of RAS in 31/70 pts (44.3%) and unchanged condition of RAS in 11/70 pts (15.7%) The 70 pts that were patch-positive received oral nickel challenge: positive 32/70 pts (45.7%) or negative 38/70 pts (45.3%) In the 32 pts with positive response to the oral nickel challenge appliances were replaced by Ni- free ones: 21/32 pts (65.6%) partially improved and 11/32 pts (34.4%) remained unchanged
17	Pazzini et al., 2009; Pazzini et al. 2011	Prospective longitudinal; university; Brazil	96 pts (38/58); 10-43 yrs; white; after nickel patch tests two groups were formed: -16 pts allergic to Ni -16 pts not allergic to nickel (matched for age and sex with the first group)	Fixed ortho- appliances (Morelllli, Sorocaba, SP, Brazil; 10- 14% nickel)	Ni patch test (5% nickel sulfate in petroleum; product FDA allergenic, Epitest Ltd Oy, Tuusula, Finland; 2 patches at the dorsal region of the pt placed 10cm apart; left for 48 hrs; reading at 48 hrs; assessed according to ICDRG)	-GI (Loe-Index) 4 times/yr -Blood tests for IgE and nickel content	Single patch test 9 mos after start of ortho-Tx	Overall prevalence: 16/96 pts (17.2%) -Allergic to nickel pts had significantly higher GI at 9 mos and 12 mos and significantly higher band cell counts (single test) compared to non-allergic pts
18	Saglam et al., 2004	Longitudinal; university; Turkey	82pts (27/55); mean 14.3 yrs; no previous ortho-Tx	Edgewise SS fixed ortho- appliances (Bd/Br) including Ni- Ti wires	Ni patch test (5% nickel sulfate and 1% cobalt in petrolatum and one placebo; upper back; left for 48 hrs; reading at 48.5 hrs or at 72 hrs when unclear; assessed by two Dermas)	GI (Loe Index)	Single patch test	Overall prevalence: 8/82 pts (9.8%) -Gender: M 0/27 pts (0.0%) or 8/55 pts (14.5%) -Previous personal history of allergy: yes 3/25 pts (12.0%) or no 5/57 pts (8.8%) -Previous family history of allergy: yes 3/23 pts (13.0%) or no 5/59 pts (8.5%) -Use of metallic objects: yes 2/8 pts (25.0%) or 7/74 pts (9.5%) -Ortho-Tx: yes (during or after ortho-Tx) 5/74 pts (6.8%) or no (before ortho-Tx started) 3/8 pts (37.5%) Overall prevalence (reported by orthodontist): 139 allergic reactions; number of patients estimated at 60000 (not directly given); approximate incidence of 0.23% -45% extraoral allergic symptoms compared to 17% intraoral and 38% combination thereof -treatment discontinued in 19%, shortly interrupted in 33% and modified to nickel-free
19	Schuster et al., 2004	Cross-sectional survey (questionnaire) ; ortho- practices; Germany	questionnaire sent at 89 ortho-offices; 68/89 (76%) response rate; estimated number of 60000 pts in the last 5 yrs (not directly given)	Fixed ortho- appliances	Questionnaire			

								materials in 53% of the cases
20	Staerkjaer and Mezze, 1990	Cross-sectional; private clinics and university clinic; Denmark	1085 pts (0/1085); mean 13.6 yrs; girls in active ortho-Tx; from these only 9 pts were patch-tested	Orthodontic appliances	Questionnaire Ni patch test (5% nickel sulfate in petrolatum)		Single patch test	Overall prevalence: 1/9 pts (11.1%) (the patient was also the only one from the 9 that had aphthous ulcers)
21	Todd and Burow 1989	questionnaire study; Department of Dermatology, Northern Ireland	294 pts (26/268) attending a patch test clinic; , 268F, 26M; patients included in a West European multicentre study	Orthodontic appliances	Ni patch test (5% nickel sulfate in petrolatum; patient`s back; left for 48 hrs; reading at 72 hrs	Gender; ear piercings; ortho-Tx	Single patch test	Overall prevalence: 80/294 pts (27.2%) -Gender: M 4/26 (15.5%) or F 76/268 (28.4%) -Ear piercing: yes 77/247 (31.2%) or no 3/47 (6.4%) -Ortho-Tx: yes 23/68 pts (33.8%) or 58/226 pts (25.7%) -Ortho-Tx before ear-piercing: yes 9/36 (25.0%) or no (i.e. after ear-piercing) 13/26 pts (50%) Overall prevalence: 47/303 pts (15.5%) -Pt subgroups: hairdressers 22/86 pts (25.6%) or 25/217 pts (11.5); hairdressers had their ears pierced earlier (9.5 yrs) than the nurses (12.3 yrs) -Gender: M 2/41 pts (4.9%) or F 45/262 pts (17.2%) -Ortho-Tx: yes 10/94 pts (10.6%) or no 35/168 pts (20.8%) Overall prevalence: 436/2150 pts (20.3%) Age: ≤35 yrs 312/1121 pts (27.8%) or >35 yrs 124/1029 pts (12.1%) Gender: M 36/630 pts (5.7%) or F 400/1520 pts (26.3%) Piercing: yes 384/1222 pts (31.4%) or no 52/928 pts (5.6%)
22	van der Burg et al. 1986	prospective cross-sectional; university; Netherlands	303 junior hairdressers and junior nurses -86 ; junior hairdressers (12/74); mean 18 yrs -217 junior nurses (29/188); mean 19 yrs	Orthodontic appliances	Ni patch test (8 allergens including 5% nickel sulfate; left for 48 hrs; reading at 48.25 hrs; assessed according to ICDRG	Pt subgroups; ear piercings; ortho-Tx; dental prostheses; history of metal allergy	Single patch test	
23	van Hoogstraten et al. 1991	questionnaire study; West European dermatology clinics; Belgium, Denmark, England, Finland, Netherlands, Northern Ireland, Spain	2176 pts (641/1535); mean 38.4 yrs	Orthodontic appliances	Ni patch test (European standard skin test battery; upper back; left for 48 hrs; readings at 24, 48 and 72 hrs; assessed according to ICDRG)	Ear piercings; ortho-Tx; timing of piercings with regard to ortho-Tx	Single patch test	Only for a subgroup of young patients (M and F up to 30 yrs) with piercings, overall prevalence: 187/551 pts (33.9%) Piercing age: 10-14 yrs 106/281 pts (37.7%), 15-20 yrs 64/202 pts (31.7), 21-25 yrs 10/46 pts (21.7%), 26-30 yrs 7/22 pts (31.8%) Ortho-Tx: yes 51/163 pts (31.3%) or no 136/388 pts (35.1%) Ortho-Tx before piercing: yes 28/121 pts (23.1%) or no (i.e. after piercing) 23/42 pts (54.8%) Reported statistically significant reduced nickel allergy frequency for orthodontically treated

						patients in some of the clinics (Netherlands and Denmark)
24	Westphalen 2006; Westphalen et al. 2008	Prospective longitudinal; university; Brazil	20 pts (6/14) about to receive ortho-Tx; mean 16.0 yrs; no smoking or drinking; no illness with genetic damage	Fixed ortho-appliances (Bd/Br from 3M Unitek®, Monrovia, CA, USA; 3-5% nickel)	Ni patch test (left for 48 hrs; readings at 48 and 72 hrs; assessed by a Derma according to ICDRG) Also measure nickel genotoxicity (not reported here)	-Before ortho-Tx -After 2 mos follow-up Overall prevalence: 4/20 pts (20.0%) -Ortho-Tx: before 4/20 pts (20.0%) or after 5/20 pts (25%) -Gender (after ortho-Tx): M 0/7 pts (0.0%) or F 5/16 pts (31.3%)

pts, patients; yrs, years; Tx, treatment; SS, stainless steel; Bd, band; Br, bracket; Ni-Ti, nickel-titanium; Ni, nickel; Ortho, orthodontist; Derma, dermatologist; mos, pathologist; GI, ginigival index; PI, plaque index; Bef, before; F, female; M, male; PD, probing depth; hrs, hours; ICDRG, International Contact Dermatitis Research Group; TP, transpalatal arch; HG, headgear; QH, quadhelix; Cr, cromium; RCT, randomized controlled trial; VAS, visual analogue scale; IgE, interferon E; RAS, recurrent aphthous stomatitis.

Appendix S6. Assessment of methodological limitations for the included studies

		1	2	3	4	5	6	7	8	9	10	11	12
Author/year		Bass et al., 1993	Costa et al., 2003	de Paiva 2005	Fors et al. 2008; Fors 2008(?); Röhrl and Stenberg 2010;	Genelhu et al., 2005	Janson et al., 1998	Jensen et al., 2002	Johannson et al., 2011	Kalimo et al., 2004	Kerosuo et al., 1996	Koppenburg et al., 1988	Marigo et al., 2003
Reporting	Is the hypothesis/aim/objective of the study clearly described?	1	1	1	1	1	1	1	1	0	1	0	1
	Are the main outcomes to be measured clearly described in the Introduction or Methods section?	1	1	1	1	1	1	1	1	0	1	0	1
	Were inclusion and exclusion criteria clearly stated? Automatically yes, if random selection or large survey without patient selection.	0	0	1	1	0	0	1	0	0	1	0	0
	Are the characteristics of the patients included clearly described?	1	0	1	1	1	1	1	0	1	1	0	1
	Are the orthodontic appliances used clearly described? Including type of appliances and nickel content	0	0	0	0	0	1	0	1	0	1	0	1
	Are the distributors of principal confounders (age, gender, piercing) in each group of subjects to be compared clearly described?	1	0	0	1	1	1	0	0	0	1	0	0
	Are the main findings of the study clearly described?	1	1	1	1	1	1	1	1	1	0	1	0
	Does the study provide estimates of the random variability in the data for the main outcomes? Providing either SD,SE, 95%CIs were applicable or complete raw data from 2x2 contingency tables.	1	1	1	1	0	1	0	1	1	1	0	0
	Have all important adverse events that may be a consequence of nickel-containing appliances been reported?	1	1	1	1	0	1	1	1	1	1	0	0
	Have the characteristics of patients lost to follow-up been described?	1	0	0	1	1	1	1	1	1	1	0	0
	Have actual probability values been reported for the main outcomes except where the probability value is less than 0.001? Automatically no if no analysis was conducted.	0	0	1	1	0	0	1	1	1	0	0	0
External validity	Were the patients asked to participate in the study representative of the entire population from which they were recruited? Automatically yes if random or no particular selection according to a characteristic.	1	0	0	0	0	0	1	0	1	1	0	1
	Were those subjects who were prepared to participate representative of the entire population from which they were recruited? Automatically yes if random or no particular selection according to a characteristic.	1	0	0	1	0	0	1	0	1	1	0	1
	Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	1	1	1	1	1	1	1	1	1	1	1	1
Internal validity - bias	Was an attempt made to blind those assessing the nickel sensitivity?	0	0	0	0	0	0	0	1	0	0	0	0
	If any of the results of the study were based on “data dredging”, was that made clear?	1	1	1	0	1	1	0	1	1	0	1	1
	Do the analyses adjust for different lengths of follow-up of patients?	1	1	1	1	1	0	1	0	0	0	0	1
	Were the statistical tests used to assess the main outcomes appropriate?	0	1	1	1	1	1	1	1	1	1	0	1

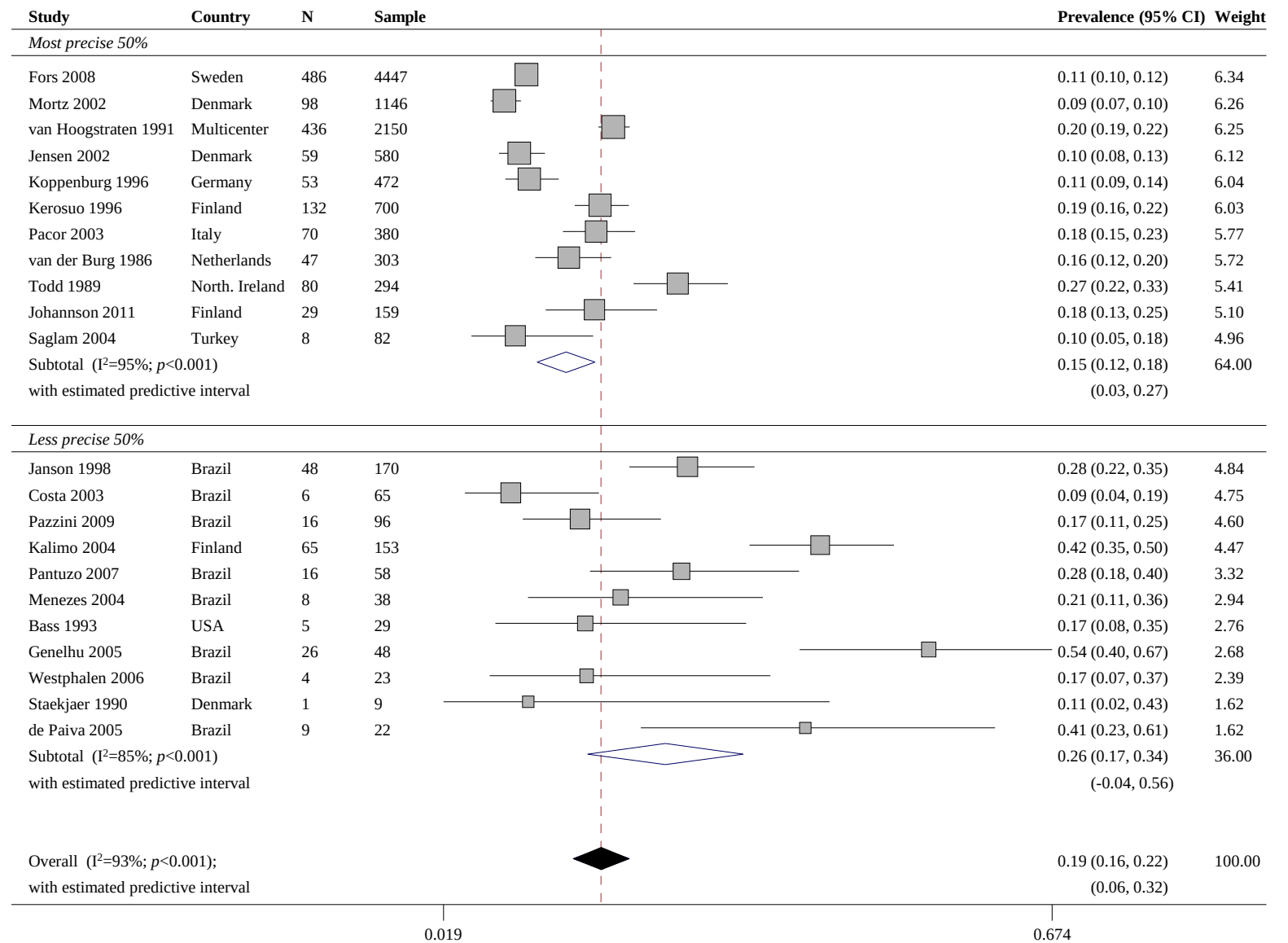
Internal validity - confounding	Was compliance with the orthodontic appliance used reliable? (not applicable for fixed appliances)	1	1	1	0	1	1	0	1	0	0	0	0
	Were the main outcome measures used accurate (valid and reliable)?	1	1	1	1	0	1	1	1	1	1	0	1
	Were the patients in different intervention groups recruited from the same population?	0	1	1	1	1	1	1	0	1	1	1	1
	Were the baseline characteristics comparable?	1	0	1	1	1	0	1	0	0	1	0	1
	Were study subjects in the exposed and non-exposed groups recruited over the same period of time?	1	1	1	1	1	1	1	0	1	1	1	1
	Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	0	0	0	1	0	0	0	0	0	0	0	0
	Were losses of patients to follow-up taken into account?	0	0	0	1	1	1	1	1	1	1	0	1
Power	Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?	0	0	0	5	0	0	2	0	0	2	1	0
Sum		17	13	17	26	15	17	20	15	15	20	6	15

Appendix 6. Assessment of methodological limitations for the included studies (continued)

		13	14	15	16	17	18	19	20	21	22	23	24
Author/year		Menezes et al., 2004	Moritz et al., 2002	Pacor et al., 2003	Pantuzo et al., 2007	Pazzini et al., 2009; Pazzini et al. 2011	Saglam et al., 2004	Schuster et al., 2004	Staerkjaer and Mezze, 1990	Todd and Burrow 1989	van der Burg et al. 1986	van Hoogstraten et al. 1991 van Hoogstraten 2000, van Hoogstraten 2003, Westphalen et al. 2006	
Reporting	Is the hypothesis/aim/objective of the study clearly described?	1	1	1	1	1	1	0	0	1	1	1	1
	Are the main outcomes to be measured clearly described in the Introduction or Methods section?	1	1	0	1	1	1	0	1	1	0	1	1
	Were inclusion and exclusion criteria clearly stated? Automatically yes, if random selection or large survey without patient selection.	0	1	1	1	1	1	1	1	0	1	1	1
	Are the characteristics of the patients included clearly described?	1	1	1	1	1	1	0	1	1	1	1	1
	Are the orthodontic appliances used clearly described? Including type of appliances and nickel content	0	0	0	0	1	0	0	0	0	0	0	1
	Are the distributors of principal confounders (age, gender, piercing) in each group of subjects to be compared clearly described?	1	1	1	1	1	0	0	0	0	1	1	0
	Are the main findings of the study clearly described?	1	0	1	1	1	1	1	1	1	1	1	1
	Does the study provide estimates of the random variability in the data for the main outcomes? Providing either SD, SE, 95%CI's were applicable or complete raw data from 2x2 contingency tables.	1	1	1	1	1	1	0	1	1	1	0	1
	Have all important adverse events that may be a consequence of nickel-containing appliances been reported?	1	1	1	1	1	1	0	0	1	1	1	1
	Have the characteristics of patients lost to follow-up been described?	1	1	1	1	1	1	0	0	1	1	1	1
	Have actual probability values been reported for the main outcomes except where the probability value is less than 0.001? Automatically no if no analysis was conducted.	1	0	0	1	1	1	0	0	1	0	0	1
External validity	Were the patients asked to participate in the study representative of the entire population from which they were recruited? Automatically yes if random or no particular selection according to a characteristic.	0	1	0	0	1	1	1	0	0	0	0	0
	Were those subjects who were prepared to participate representative of the entire population from which they were recruited? Automatically yes if random or no particular selection according to a characteristic.	0	1	0	0	1	1	0	0	0	0	0	0
	Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	1	1	1	1	1	1	1	1	0	1	1	1
Internal validity - bias	Was an attempt made to blind those assessing the nickel sensitivity?	0	0	0	0	0	0	0	0	0	0	0	0
	If any of the results of the study were based on “data dredging”, was that made clear?	0	1	1	1	1	1	1	1	0	0	0	1
	Do the analyses adjust for different lengths of follow-up of patients?	1	1	0	0	1	0	0	0	0	0	0	0
	Were the statistical tests used to assess the main outcomes appropriate?	1	1	0	1	1	1	0	1	1	1	1	1
	Was compliance with the orthodontic appliance used reliable? (not applicable for fixed appliances)	1	0	1	1	1	1	1	0	0	0	0	1

Internal validity - confounding	Were the main outcome measures used accurate (valid and reliable)?	1	1	1	1	1	1	0	0	1	1	1	1
	Were the patients in different intervention groups recruited from the same population?	1	1	1	1	1	1	1	1	1	1	1	1
	Were the baseline characteristics comparable?	1	1	0	1	1	1	1	1	0	1	1	0
	Were study subjects in the exposed and non-exposed groups recruited over the same period of time?	1	1	1	1	1	1	1	1	1	1	1	1
	Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	0	1	0	0	0	0	0	0	0	0	0	0
	Were losses of patients to follow-up taken into account?	1	1	1	1	1	1	0	0	1	1	1	1
Power	Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?	0	3	0	0	0	0	0	3	1	1	5	1
Sum		18	23	15	19	23	20	9	14	14	16	20	19

Appendix S7. Forest plot for the sensitivity analysis of the overall nickel prevalence according to the studies' precision



Appendix S8. Details for the GRADE assessment of the primary outcomes*

Outcome	Inconsistency	Indirectness	Imprecision	Publication bias	Large Effect	Dose Response	Residual Confounding
Gender	Moderate heterogeneity (61%) with studies agreeing on the effect direction (all on the left side of the forest plot); no reason to downgrade	Directly relevant; no reason to downgrade.	Adequate sample; 95% CI does not include the null-effect; no reason to downgrade.	No evidence of bias; no reason to downgrade.	Very large effect, which was included in the the 95% CI, and the consistent prediction interval; decided to rate up by two for very large effect.	No reason to rate up.	Adjusted analysis dealing for confounding factors yielded similar odds ratios compared to the crude analysis; decided to rate up one for absence of residual confounding.
Piercing	Low heterogeneity (24%) with studies agreeing on the effect direction (all on the left side of the forest plot); no reason to downgrade	Directly relevant; no reason to downgrade.	Adequate sample; 95% CI does not include the null-effect; no reason to downgrade.	No evidence of bias; no reason to downgrade.	Very large effect, which was included in the mean effect, the 95% CI, and the consistent prediction interval; decided to rate up by two for very large effect.	Patients with multiple piercings more prone to Nickel hypersensitivity compared to patients with single piercings; decided to upgrade by one.	Adjusted analysis dealing for confounding factors yielded similar odds ratio compared to the crude analysis, only diminished; decided to rate up one for absence of residual confounding.
Orthodontic treatment	Moderate heterogeneity (56%) with studies disagreeing on the effect direction (both on the left and the right side of the forest plot); decided to downgrade by one.	Directly relevant; no reason to downgrade.	Adequate sample; 95% CI does include the null-effect, but does not include a large effect; no reason to downgrade.	Slight indication of small-study effects, but no sign of funnel plot asymmetry and elimination of the most imprecise 50% does not change the results of the meta-analysis (OR=1.10; 95% CI=0.87,1.39; P=0.430); no reason to downgrade.	Trivial effects; no reason to rate up.	No reason to rate up.	Adjusted analysis dealing for confounding factors yielded opposite odds ratio compared to the crude analysis, indicating that outcome might be confounded; decided not to rate up one for absence of residual confounding.
Orthodontic Timing	Low heterogeneity (23%), with uncertainty about its estimate, and confidence regarding decision unaffected; no reason to downgrade.	Directly relevant; no reason to downgrade.	Adequate sample; 95% CI does not include the null-effect; no reason to downgrade.	No evidence of bias; no reason to downgrade.	Large effect, which was included in the mean effect and the 95% CI, while the prediction interval was consistent; decided to rate up by one for large effect.	No reason to rate up.	Adjusted analysis dealing for confounding factors yielded similar mean odds ratio compared to the crude analysis, only underpowered; decided to rate up one for absence of residual confounding.

*Regarding risk of bias, all outcomes start from "low", due to the inclusion of non-randomized studies; no reason to further downgrade.
OR, odds ratio; CI, confidence interval.

Appendix S9. Sensitivity analysis including meta-regression with mean reported patient age

Outcome or factor	<i>p</i>
Prevalence of nickel hypersensitivity	0.917
Gender	0.268
Piercing	0.765
Orthodontic treatment	0.867
Timing of orthodontic treatment	0.710