Prevalence of nickel hypersensitivity in orthodontic patients: a meta-analysis
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CRD summary
This review concluded that orthodontic treatment was not associated with an increase in prevalence of nickel hypersensitivity unless subjects had a history of nickel exposure from cutaneous piercing. The review had a strong protocol, but the execution and reporting of the review were not ideal and the authors’ conclusions should be viewed with caution.

Authors' objectives
To investigate the effect of orthodontic therapy on the prevalence of nickel hypersensitivity and compare it with prevalence in the general population.

Searching
EMBASE and MEDLINE were searched from inception to November 2007 for articles in any language. Twelve other data sources, which included Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL) and MetaRegister of Controlled Trials were searched to November 2007 without language restrictions. Search terms were reported. Reference lists of relevant articles were searched. Unpublished and ongoing studies were searched for in databases of research registers.

Study selection
Two separate criteria were used to identify studies on orthodontic patients and studies on the general population.

Orthodontic patients: Studies that investigated prevalence of nickel hypersensitivity before orthodontic therapy and/or after placement or removal of orthodontic appliances were eligible for inclusion. Eligible studies included male and female patients of any age and assessed nickel sensitisation using positive patch-test scores (International Contact Dermatitis Research Group scale). The orthodontic intervention could be any fixed or removal appliance. Studies were excluded if they had fewer than 10 participants or were case series, case reports or review articles. Included studies assessed nickel hypersensitivity in participants in the age range of nine to 48 years who were treated with fixed and/or removable orthodontic appliances in orthodontic departments, student health services or schools.

General population: Studies that investigated prevalence of nickel hypersensitivity in the general unselected population were eligible for inclusion. Studies had to report nickel sensitisation in the form of positive patch-test scores and had to include patients of comparable age to those who usually had orthodontic therapy. Studies were excluded if they had fewer than 10 participants or were case series, case reports or review articles. Participant ages ranged from five to 18 years.

Two authors independently undertook the selection process. Disagreements were resolved through discussion.

Assessment of study quality
Study validity was assessed on selection bias, attrition bias, performance bias and detection bias.

The authors did not state how many reviewers performed the quality assessment.

Data extraction
Data were extracted in duplicate on the level of positive nickel patch-test scores and used to calculate odds ratios (ORs) of positive patch-test scores before and after orthodontic therapy, together with 95% confidence intervals (CI). Event rates were calculated for studies that reported nickel hypersensitivity only after placement.

Methods of synthesis
Pooled odds ratios and their 95% CIs were calculated with a random-effects meta-analysis. Statistical heterogeneity was
assessed using the Cochran test and the $I^2$ statistic. Subgroups were explored based on the presence/absence of cutaneous piercing and the sequence of piercing relative to orthodontic treatment. Publication bias was assessed with funnel plots and Egger’s linear regression method.

**Results of the review**

Eight studies (n=1,459 participants) were included in the review of nickel hypersensitivity with orthodontics: two trials of sensitivity before and after orthodontics and six studies after orthodontic therapy. Sample size ranged from 28 to 477 participants. Quality assessment indicated that all of the studies suffered from both selection and performance bias. Publication bias was not found with the Egger test, but funnel plot assessment showed asymmetry.

Four studies of nickel sensitivity in the general population (n=2,832 participants) were included in the review for comparison with orthodontic patients. Few individual results were presented from these studies as the authors stated that they were published elsewhere and were only for comparison in this review.

**Before and after orthodontic therapy** (two trials, n=66 participants): There was no significant difference between nickel hypersensitivity before and after orthodontic therapy. There was no evidence of statistical heterogeneity ($I^2=0\%$).

**Orthodontic therapy compared with the general population**:
Prevalence of nickel hypersensitivity was statistically higher in the eight orthodontic studies than in the four general population studies (prevalence 21\% versus 12\%, $p=0.037$). When results were broken down into subgroups based on piercing exposure, there was no significant difference between orthodontic treatment without cutaneous piercing (n=250 participants) and the general population. However, there was a statistically significant higher prevalence of nickel hypersensitivity in orthodontic treatment with piercings (n=751 participants) compared with the general population (prevalence 30\% versus 12\%, $p=0.002$) and a statistically significant higher prevalence of nickel hypersensitivity in the cutaneous piercing before orthodontic treatment (n=466 participants) compared with the general population (prevalence 36\% versus 12\%, $p=0.000$). The level of statistical heterogeneity in these analyses was significant ($I^2=81\%$ to 94\%).

**Authors’ conclusions**
Orthodontic treatment was not associated with an increase in prevalence of nickel hypersensitivity unless subjects had a history of nickel exposure from cutaneous piercing.

**CRD commentary**
Inclusion criteria for the review were clearly defined and several relevant databases were searched. The risk of language bias was minimal. Publication bias was assessed and could not be ruled out entirely. Study selection and data extraction were performed in duplicate to minimise error and bias in the review; it was unclear how many authors undertook quality assessment. Quality assessment was not based on a validated tool, but appeared to evaluate relevant aspects of study quality; all studies were reported as suffering from both selection and performance bias. A random-effects meta-analysis was undertaken, which was appropriate, and heterogeneity and subgroups were explored. The authors’ conclusions on nickel sensitivity before and after orthodontic therapy were based on only two small studies, and hence may have been prone to bias. The authors’ conclusions on nickel sensitivity with orthodontic therapy compared with the general population were based on meta-analyses with larger sample sizes, but suffered from significant statistical heterogeneity and a lack of detail about individual analyses and so were difficult to verify. Overall, the review had a strong protocol but the execution and reporting of the review were not ideal and the authors’ conclusions should be viewed with caution.

**Implications of the review for practice and research**
**Practice**: The authors stated that many orthodontic patients had nickel sensitivity and the clinician should be prepared to manage possible reactions.

**Research**: The authors stated that high validity studies were needed to produce strong evidence to further support these results.

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