J Clin Periodontol 2011; 38: 17–24 doi: 10.1111/j.1600-051X.2010.01642.x

Journal of Clinical Periodontology

# Insulin sensitivity and periodontal infection in a non-diabetic, non-smoking adult population

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*Timonen P, Suominen-Taipale L, Jula A, Niskanen M, Knuuttila M, Ylöstalo P: Insulin sensitivity and periodontal infection in a non-diabetic, non-smoking adult population. J Clin Periodontol 2011; 38: 17–24. doi: 10.1111/j.1600-051X.2010.01642.x*

***Abstract***

**Aim:** The aim of this study was to examine whether there is an association of *insulin sensitivity* with periodontal infection in a non-diabetic, non-smoking adult population.

**Materials and Methods:** A subpopulation of the Health 2000 Survey (effective $n = 2050$) consisted of dentate subjects without any indication of diabetes, aged between 30 and 64, and who had never smoked. The outcome variable was periodontal infection measured by means of the number of teeth with deepened periodontal pockets. Insulin sensitivity was measured using the homeostasis model assessment index for insulin resistance. Poisson regression models were used to estimate the relative risks and 95% confidence intervals.

**Results:** We found that insulin sensitivity was associated with periodontal infection in the age group 30–49, but not in persons aged 50–64. Controlling for body weight made the association between insulin sensitivity and periodontal infection disappear.

**Conclusion:** The lack of knowledge of the underlying causal model prevents making definite conclusions about the role of reduced insulin sensitivity in the pathogenesis of periodontal infection.

Key words: HOMA-IR; insulin resistance; non-diabetic adults; periodontal infection; periodontitis

Accepted for publication 9 October 2010

Reduced insulin sensitivity, also known as insulin resistance, can be the result of several different factors, such as genetics (Hong et al. 1997), obesity (Rasouli & Kern 2008) or other conditions such as chronic inflammation and infection (Pickup 2004). It is the main characteristic feature of metabolic syndrome (Reaven 1988), often precedes type 2 diabetes mellitus (Martin et al. 1992, Lillioja et al. 1993) and is also considered a risk factor for cardiovascular disease (Yip et al. 1998). Besides these systemic effects, insulin resistance is suggested to play a role in the pathogenesis of periodontal infection (Genco et al. 2005).

Insulin sensitivity can be measured using different methods. In this study, we used the homeostasis model assessment (HOMA) method to yield an estimate of insulin sensitivity, because it has been shown to be a feasible method in large epidemiological studies for subjects of various ethnicities and varying degrees of glucose tolerance (Wallace et al. 2004). The HOMA method derives an estimate of insulin sensitivity from a mathematical model of fasting plasma glucose and insulin concentrations (Matthews et al. 1985).

At present, there are a few studies on the relation of insulin-resistant condition or impaired glucose tolerance to periodontal infection. In these studies, insulin resistance has been found to be associated with different parameters of periodontal infection, such as the mean clinical attachment loss (Genco et al. 2005), clinical attachment loss and probing pocket depth (Benguigui et al. 2010), as well as the extent of periodontitis (D'Aiuto et al. 2008). Impaired glucose tolerance has, in turn, been found to associate with deepened periodontal pockets (Saito et al. 2004) and alveolar bone loss (Saito et al. 2006), and non-fasting serum glucose level has been found to associate with deepened periodontal pockets (Nibali et al. 2007).

**Conflict of interest and source of funding statement**

The authors declare that there are no conflicts of interest in this study.
The present study is part of the Health 2000 Survey, organized by the National Institute for Health and Welfare (THL) [former National Public Health Institute (KTL) of Finland], and partly supported by Finnish Dental Society Apollonia and the Finnish Dental Association. The personal grant received from the Finnish Dental Society Apollonia and the Finnish Dental Association is acknowledged by Petra Timonen.

Despite adjustment for confounding factors, it is possible that residual confounding exists, as earlier studies have used a heterogeneous study population in relation to age, smoking habits and diabetic status.

A nationally representative Health 2000 Survey was carried out between 2000 and 2001 in order to obtain information about the health and welfare of the Finnish adult population. The aim of our study was to examine whether insulin sensitivity, using the HOMA-IR index, associates with periodontal infection in a non-diabetic, non-smoking adult population.

## Materials and Methods

### Study population

A Health 2000 Survey was conducted between 2000 and 2001 by the National Institute for Health and Welfare (THL) (former National Institute of Public Health, KTL). The nationally representative sample included 8028 persons aged 30 years or older and was recruited from 80 health centre districts using a two-stage cluster sampling method. Of the sample, 88% participated in an interview and 79% attended a comprehensive health examination including a clinical oral examination. The subjects of this study included dentate subjects without diagnosed diabetes or any indication of diabetes, determined by laboratory tests or in the clinical health examination, were between 30 and 64 years old and had never smoked, i.e. had not smoked regularly over a period of at least 1 year during their life (effective $n = 2050$), (Aromaa & Koskinen 2004).

Informed consent was obtained from the participants. The ethical committee of Helsinki University Hospital approved the study protocol. Detailed information about the Health 2000 Survey is available in reports by Aromaa & Koskinen (2004) and Suominen-Taipale et al. (2008). Information about the Survey is also available at http://www.terveys2000.fi/indexe.html

### Clinical oral examination

The health examination was carried out in five field units comprising nurses, dentists and physicians. Five calibrated dentists of the Health 2000 research project carried out oral examinations in a dental chair using a headlamp, mouth mirror, fibre optic light and a WHO periodontal probe. The primary outcome variable was periodontal infection, which was measured in two ways: by means of the number of teeth with periodontal pockets 4 mm deep or deeper and by the number of teeth with periodontal pockets 6 mm deep or deeper. Periodontal pockets were probed on four surfaces of each tooth (apart from the third molars) in the following order: distal angle and midpoint on the buccal side, midpoint on the lingual side and mesial angle, but only the pocket depth of the deepest site on each tooth was recorded. The percentual agreement for deepened periodontal pockets in the parallel measurements, where field examiners were individually compared with the reference examiner under field circumstances, was 77% ($\kappa$ value of 0.41) (Vehkalahti et al. 2008, p. 19). The intra-examiner reliability assessment for pathologically deepened periodontal pockets showed a $\kappa$ value of 0.83 (Vehkalahti et al. 2004, p. 29).

### Explanatory variables

Fasting glucose levels were measured from a blood sample during a clinical health examination by nurses before the clinical oral examination and fasting insulin levels were measured later from frozen serum samples. Blood samples were analysed partly at the National Institute for Health and Welfare (THL) and partly in the laboratory of the Social Insurance Institution. The HOMA-IR was used to measure insulin sensitivity (Matthews et al. 1985). The HOMA-IR index values were calculated using the following formula: (fasting insulin $\times$ fasting glucose)/22.5. The HOMA-IR index was categorized into quintiles. As the distribution was skewed, the highest quintile was halved (quintiles 5a and 5b).

### Potential confounders

Covariates included factors that are known to associate with periodontitis, such as age, gender, educational level, dental plaque, toothbrushing frequency, dental attendance pattern and alcohol consumption. Age was included in the analyses as a continuous variable and the number of teeth was used as an offset variable. Education was classified into three categories: basic, intermediate and higher education. The basic category included subjects whose education was below high school level and who did not have formal vocational qualifications. The intermediate category included those who had graduated from high school or vocational school, and the highest category consisted of those with a university degree or who had graduated from polytechnics. The presence of dental plaque was assessed from three teeth, each as follows: from the buccal surface of the most posterior tooth of teeth in the upper right quadrant, from the lingual surface of the most posterior tooth of teeth in the lower left quadrant and from the buccal surface of the lower left canine (in the absence of the lower left canine, lower right canine). It was classified into three categories: no visible plaque (0), visible plaque in gingival margins only (1) and visible plaque also elsewhere (2), and the highest value of any of the indicator teeth was used in the analyses. Lipid-lowering medication was categorized according to those who had some form of lipid medication, those who had no lipid medication and those with missing information.

Toothbrushing frequency was categorized as twice a day or more, once a day and less frequently. The dental attendance pattern was categorized into those who regularly have dental check-ups versus those who never use dental health services or use them in a symptom-based manner. Body mass index (BMI), which is a measure of weight in relation to height ($kg/m^2$), was used as a continuous variable in the analysis. Alcohol use frequency (one dose being 12 grams of alcohol per week) was categorized into three categories: no use, moderate use (1–4 doses for women and 1–7 doses for men) or abundant use (more than four doses for women and more than seven doses for men). The total alcohol consumption was measured as g/week. The basic characteristics of the study population are shown in Table 1.

### Statistical analysis

As the distribution of the outcome variable was skewed, we used Poisson regression models to estimate the relative risks (RR) and 95% confidence intervals (95% CI). We used SUDAAN, version 9.0 statistical package, to take into account two-stage cluster sampling. The weighting of the sample was based on post-stratification according to gender, age and region.

*Table 1.* Subject characteristics of the study population according to HOMA-IR quintiles

| | *n* | Total | HOMA-IR*,† | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | 1 | 2 | 3 | 4 | 5a | 5b |
| Quintiles (rounded values) | | | (0.2–0.9) | (0.9–1.3) | (1.3–1.7) | (1.7–2.4) | (2.5–3.3) | (3.4–24.1) |
| Age (mean) | 2050 | 46.0 (0.2) | 44.4 (0.4) | 46.1 (0.4) | 45.2 (0.5) | 46.9 (0.5) | 47.4 (0.7) | 46.9 (0.7) |
| Gender, proportion of males (%) | 762 | 39.2 (1.1) | 30.3 (2.2) | 39.3 (2.4) | 37.9 (2.4) | 40.0 (2.3) | 46.8 (3.5) | 50.4 (3.7) |
| Educational level (%) | 2050 | | | | | | | |
| Low | 451 | 22.3 (1.0) | 17.2 (1.9) | 22.0 (2.0) | 19.8 (1.8) | 24.2 (2.1) | 28.6 (3.1) | 27.7 (2.9) |
| Intermediate | 684 | 33.6 (1.0) | 28.6 (2.4) | 31.1 (2.6) | 36.3 (2.6) | 36.9 (2.3) | 29.4 (3.2) | 40.2 (3.8) |
| High | 915 | 44.2 (1.1) | 54.1 (2.4) | 46.9 (2.8) | 44.0 (2.8) | 38.9 (2.2) | 42.1 (3.8) | 32.1 (3.2) |
| Number of teeth (offset variable; mean) | 2050 | 25.1 (0.1) | 26.3 (0.2) | 25.5 (0.3) | 25.6 (0.2) | 24.7 (0.3) | 23.3 (0.6) | 23.8 (0.5) |
| Number of teeth with periodontal pockets $\geqslant$4 mm (mean) | 2050 | 3.0 (0.2) | 2.7 (0.2) | 2.6 (0.2) | 3.1 (0.3) | 3.4 (0.3) | 3.0 (0.3) | 3.7 (0.4) |
| Number of teeth with periodontal pockets $\geqslant$6 mm (mean) | 2050 | 0.3 (0.0) | 0.3 (0.1) | 0.2 (0.1) | 0.3 (0.1) | 0.4 (0.1) | 0.4 (0.1) | 0.7 (0.2) |
| Number of decayed teeth (mean) | 2050 | 0.5 (0.0) | 0.3 (0.1) | 0.4 (0.0) | 0.4 (0.1) | 0.6 (0.1) | 0.6 (0.1) | 0.8 (0.1) |
| Presence of plaque (%) | 2041 | | | | | | | |
| No plaque | 842 | 41.0 (1.3) | 47.3 (2.7) | 45.0 (2.7) | 42.0 (2.7) | 35.6 (2.4) | 39.7 (3.4) | 31.0 (3.0) |
| Plaque in gingival margins only | 1007 | 49.4 (1.3) | 45.1 (2.5) | 47.8 (2.7) | 49.3 (2.8) | 53.0 (2.4) | 48.8 (3.4) | 55.2 (3.6) |
| Plaque also elsewhere | 192 | 9.5 (0.8) | 7.6 (1.3) | 7.3 (1.3) | 8.7 (1.4) | 11.5 (1.6) | 11.5 (2.3) | 13.8 (2.7) |
| Toothbrushing frequency (%) | 1987 | | | | | | | |
| At least twice a day | 1358 | 67.7 (1.3) | 74.1 (2.2) | 72.0 (2.2) | 72.4 (2.5) | 63.8 (2.3) | 57.7 (3.6) | 54.8 (3.6) |
| Once a day | 550 | 28.1 (1.2) | 23.7 (2.1) | 23.3 (2.0) | 24.2 (2.3) | 31.8 (2.4) | 38.1 (3.8) | 37.2 (3.5) |
| Less frequently | 79 | 4.2 (0.5) | 2.1 (0.8) | 4.8 (1.1) | 3.4 (0.9) | 4.4 (1.0) | 4.1 (1.3) | 7.9 (1.9) |
| Dental attendance pattern (%) | 1988 | | | | | | | |
| Regularly | 1363 | 68.5 (1.2) | 75.7 (2.2) | 71.7 (2.3) | 67.7 (2.3) | 69.1 (2.5) | 59.6 (3.9) | 56.8 (3.9) |
| Never use or symptom-based use | 625 | 31.5 (1.2) | 24.3 (2.2) | 28.3 (2.3) | 32.3 (2.3) | 30.9 (2.5) | 40.4 (3.9) | 43.2 (3.9) |
| Body mass index (kg/m$^2$) | 2049 | 26.3 (0.1) | 23.3 (0.1) | 24.9 (0.2) | 25.9 (0.2) | 27.2 (0.2) | 28.9 (0.3) | 31.5 (0.3) |
| Lipid medication (%) | 1896 | | | | | | | |
| Yes | 70 | 3.5 (0.4) | 2.5 (0.8) | 3.2 (0.8) | 2.8 (0.8) | 4.3 (1.1) | 3.5 (1.3) | 5.5 (1.7) |
| No | 1826 | 88.8 (0.8) | 87.6 (1.6) | 89.9 (1.4) | 88.9 (1.6) | 89.2 (1.6) | 88.5 (2.1) | 88.3 (2.7) |
| Alcohol use frequency (%) | 2032 | | | | | | | |
| No use | 251 | 12.4 (0.8) | 10.8 (1.4) | 11.7 (1.6) | 11.0 (1.6) | 14.1 (1.6) | 16.5 (3.1) | 12.2 (2.4) |
| Moderate use | 1021 | 49.8 (1.2) | 51.8 (2.4) | 44.2 (2.6) | 50.6 (2.4) | 50.6 (2.2) | 52.3 (3.7) | 50.7 (3.6) |
| Abundant use | 760 | 37.9 (1.1) | 37.3 (2.5) | 44.2 (2.6) | 38.4 (2.4) | 35.3 (2.4) | 31.2 (3.2) | 37.1 (3.5) |
| Total alcohol consumption (g/week) | 2031 | 54.2 (2.5) | 47.1 (4.5) | 53.2 (3.9) | 54.3 (4.4) | 54.4 (5.2) | 56.4 (7.3) | 67.2 (8.7) |

*Homeostasis model assessment, insulin resistance.

†The HOMA indices are categorized into quintiles and the highest quintile is halved (quintiles 5a and 5b).

HOMA-IR, homeostasis model assessment index for insulin resistance.

The interaction between the explanatory variable and potential confounders for periodontal infection was studied by adding the product terms for insulin resistance and other covariates one by one in the regression model. Because it is not clear whether BMI is an aetiological factor of periodontitis and thus should be controlled in the analyses, we also constructed multivariate models where BMI was also included as a covariate. In addition, we performed stratified analyses according to BMI categories.

## Results

The mean values of the HOMA-IR index in relation to the number of teeth with deepened periodontal pockets 4 mm or deeper and 6 mm or deeper are presented in Table 2. The mean index values were higher for those with many teeth with deep (6 mm or more) periodontal pockets. No essential differences were found in the HOMA-IR index values in relation to the number of teeth with periodontal pockets 4 mm deep or deeper. Regression analyses showed that among the total population, aged 30–64 years, after adjustment for confounding factors, a weak association of the HOMA-IR index with the number of teeth with deep periodontal pockets (6 mm deep or deeper) was found, but not in the case of teeth with pocket depth 4 mm or more (Table 3).

There was a statistically significant interaction between the HOMA-IR index and age ($p = 0.01$), and based on these findings, stratified analyses were performed. We found a stronger adjusted association in the 30–49 age group than in the total study population (30–64 years) both in the case of the number of teeth with deepened (4 mm deep or deeper) and deep periodontal pockets (6 mm deep or deeper) (Tables 3 and 4). In the 50–64 age group, there was practically no association between the HOMA-IR index and the number of teeth with deepened periodontal pockets (Table 4).

The results of the analyses where BMI was also included in the regression models are shown in Table 5. Among the total population, as well as in the 30–49 and 50–64 age groups, there was no consistent association between the HOMA-IR index and deepened periodontal pockets (Table 5).

When we performed analyses in different BMI categories, we found that there was no consistent association between the HOMA-IR index and the number of teeth with deepened periodontal pockets in normoweight or

*Table 2*. Mean values with standard errors of the HOMA-IR* index in relation to the number of teeth with deepened periodontal pockets

| Number of teeth with deepened periodontal pockets | *n* | Mean (SE) |
|---|---|---|
| Teeth with periodontal pockets ⩾4 mm | | |
| Total | 2050 | 1.83 (0.04) |
| 0 | 869 | 1.76 (0.05) |
| 1–3 | 580 | 1.83 (0.06) |
| 4–6 | 183 | 1.82 (0.09) |
| 7+ | 418 | 1.99 (0.09) |
| Teeth with periodontal pockets ⩾6 mm | | |
| Total | 2050 | 1.83 (0.04) |
| 0 | 1789 | 1.81 (0.04) |
| 1–3 | 206 | 1.93 (0.10) |
| 4–6 | 29 | 2.04 (0.26) |
| 7+ | 26 | 2.46 (0.34) |

The values are means with standard errors in parentheses.
*Homeostasis model assessment, insulin resistance.
HOMA-IR, homeostasis model assessment index for insulin resistance.

*Table 3*. Association of HOMA-IR* index in relation to the number of teeth with deepened periodontal pockets

| HOMA-IR* index | RR 95% CI | | | |
|---|---|---|---|---|
| | teeth with periodontal pockets ⩾4 mm | | teeth with periodontal pockets ⩾6 mm | |
| | unadjusted | adjusted† | unadjusted | adjusted† |
| Quintiles‡ | | | | |
| 1. (0.2–0.9) | 1.0 | 1.0 | 1.0 | 1.0 |
| 2. (0.9–1.3) | 1.0 (0.8–1.2) | 0.9 (0.7–1.1) | 0.9 (0.5–1.6) | 0.7 (0.4–1.2) |
| 3. (1.3–1.7) | 1.2 (1.0–1.4) | 1.0 (0.9–1.3) | 0.9 (0.5–1.5) | 0.7 (0.4–1.1) |
| 4. (1.7–2.4) | 1.4 (1.1–1.6) | 1.1 (0.9–1.3) | 1.3 (0.8–2.2) | 0.9 (0.5–1.5) |
| 5a. (2.5–3.3) | 1.3 (1.0–1.6) | 1.0 (0.8–1.3) | 1.7 (0.9–3.2) | 1.1 (0.5–2.1) |
| 5b. (3.4–24.1) | 1.6 (1.2–2.0) | 1.1 (0.9–1.4) | 2.5 (1.3–4.9) | 1.5 (0.8–2.8) |

*Homeostasis model assessment, insulin resistance.
†Adjusted for gender, age, education, presence of plaque, toothbrushing frequency, dental attendance pattern and alcohol consumption (g/week).
‡The highest quintile is halved (quintiles 5a and 5b).
RR, relative risks; 95% CI, 95% confidence intervals; HOMA-IR, homeostasis model assessment index for insulin resistance.

overweight subjects, whereas among obese subjects, there was an association, although not consistent, in the 30–49 age group (Table 6).

The Pearson correlation between BMI and the log-transformed HOMA-IR index was 0.52.

## Discussion

In these data, there was an association between the HOMA-IR index and the number of teeth with deepened periodontal pockets in the 30–49 age group, but only when BMI was not used as a covariate in the models. When BMI was used as a covariate, the association between the HOMA-IR index and the number of teeth with deepened periodontal pockets was practically non-existent. In line with these findings, there was no consistent association between the HOMA-IR index and the number of teeth with deepened periodontal pockets in normoweight or overweight subjects.

The results of this study can be interpreted in two ways and the interpretation depends on the underlying causal model (Fig. 1). The first interpretation is that body weight is mostly the determinant of insulin sensitivity without any link to periodontal infection other than through insulin sensitivity (Fig. 1a). On the condition that this assumption holds, our findings are in agreement with earlier findings, for example findings obtained by Genco et al. (2005), who reported that subjects with the highest insulin resistance index values had an increased risk for periodontal attachment loss, and with the findings obtained by Saito et al. (2004), who found that subjects who developed impaired glucose tolerance were significantly more likely to have deep periodontal pockets than subjects with normal glucose tolerance, and also with the findings of the recent study by Benguigui et al. (2010), who reported an association between insulin resistance and periodontitis in the total population.

In the present study, we did not address the possible mechanism, but biological mechanisms exist that could explain how reduced insulin sensitivity affects periodontium. Firstly, insulin resistance most likely activates a systemic low-grade inflammatory response similar to the one observed in type 2 diabetic persons by activating innate immunity and a network of inflammatory signalling pathways. As a result of this activation, there is an enhancement in the production of pro-inflammatory cytokines, acute-phase reactants and other inflammatory mediators (Pickup 2004). Secondly, post-prandial hyperglycaemia, a short-term rise in the blood glucose level after a meal, has been shown to increase oxidative stress and lower antioxidant concentrations in serum (Ceriello et al. 1998) and in inflammatory cells (Mohanty et al. 2000), and also enhance the production of pro-inflammatory molecules (Devaraj et al. 2005, Iwata et al. 2007). It is possible that systemic low-grade inflammation and activated inflammatory cells, combined with the effect of periodontal pathogens, may predispose to periodontal destruction.

Needless to say, despite the above-mentioned possible biological explanation, an alternative explanation is that the association of the HOMA-IR index with deepened periodontal pockets is partly or totally explained by behavioural factors in common or by other factors not included in this study, such as increased body weight or dyslipidaemia, for example. It must also be noted that the existence of residual confounding is supported by the fact that the adjustment for confounding factors attenuated the association considerably. These observations concur with the findings of Benguigui et al. (2010), where the adjustment for smoking by excluding smokers considerably attenuated the association of the HOMA-IR index with the parameters of periodontal infection, and a study by Han et al.

*Table 4*. Association of the HOMA-IR* index in relation to the number of teeth with deepened periodontal pockets in the age groups 30–49 and 50–64 years

| HOMA-IR* index | RR 95% CI | | | |
|---|---|---|---|---|
| | teeth with periodontal pockets ⩾4mm | | teeth with periodontal pockets ⩾6mm | |
| | unadjusted | adjusted† | unadjusted | adjusted† |
| *30–49 years* | | | | |
| Quintiles | | | | |
| 1. (0.2–0.9) | 1.0 | 1.0 | 1.0 | 1.0 |
| 2. (0.9–1.3) | 1.0 (0.8–1.3) | 0.9 (0.7–1.2) | 0.3 (0.1–0.7) | 0.2 (0.1–0.6) |
| 3. (1.3–1.7) | 1.3 (1.0–1.6) | 1.2 (0.9–1.5) | 0.8 (0.4–1.5) | 0.6 (0.3–1.3) |
| 4. (1.7–2.4) | 1.4 (1.1–1.9) | 1.2 (0.9–1.5) | 1.6 (0.7–3.6) | 0.9 (0.4–2.2) |
| 5a. (2.5–3.3) | 1.3 (1.0–2.0) | 1.2 (0.8–1.8) | 2.1 (0.8–6.1) | 1.4 (0.5–3.9) |
| 5b. (3.4–24.1) | 1.8 (1.4–2.5) | 1.4 (1.0–1.8) | 4.9 (1.8–13.0) | 2.3 (0.9–5.7) |
| *50–64 years* | | | | |
| Quintiles | | | | |
| 1. (0.2–0.9) | 1.0 | 1.0 | 1.0 | 1.0 |
| 2. (0.9–1.3) | 1.0 (0.7–1.3) | 0.9 (0.7–1.2) | 1.1 (0.5–2.4) | 1.0 (0.5–2.2) |
| 3. (1.3–1.7) | 1.0 (0.8–1.4) | 0.9 (0.7–1.2) | 0.9 (0.4–2.0) | 0.7 (0.3–1.5) |
| 4. (1.7–2.4) | 1.1 (0.8–1.4) | 1.0 (0.7–1.3) | 1.0 (0.5–1.8) | 0.8 (0.5–1.6) |
| 5a. (2.5–3.3) | 1.0 (0.7–1.4) | 0.9 (0.6–1.2) | 1.2 (0.5–2.6) | 0.9 (0.4–2.1) |
| 5b. (3.4–24.1) | 1.1 (0.8–1.6) | 1.0 (0.7–1.4) | 1.1 (0.5–2.5) | 0.9 (0.4–2.1) |

*Homeostasis model assessment, insulin resistance. The highest quintile is halved (quintiles 5a and 5b).
†Adjusted for gender, education, presence of plaque, toothbrushing frequency, dental attendance pattern, alcohol consumption (g/week).
RR, relative risks; 95% CI, 95% confidence intervals; HOMA-IR, homeostasis model assessment index for insulin resistance.

*Table 5*. Association of HOMA-IR* index in relation to number of teeth with deepened periodontal pockets in the whole study population and in age groups 30–49 and 50–64 years after adjustment for BMI and other covariates†

| HOMA-IR* index | RR 95% CI | | |
|---|---|---|---|
| | adjusted† 30–64 years | adjusted† 30–49 years | adjusted† 50–64 years |
| *Teeth with periodontal pockets ⩾4 mm* | | | |
| Quintiles | | | |
| 1. (0.2–0.9) | 1.0 | 1.0 | 1.0 |
| 2. (0.9–1.3) | 0.9 (0.7–1.0) | 0.9 (0.7–1.2) | 0.9 (0.7–1.2) |
| 3. (1.3–1.7) | 1.0 (0.8–1.2) | 1.1 (0.9–1.4) | 0.9 (0.6–1.2) |
| 4. (1.7–2.4) | 1.0 (0.8–1.2) | 1.0 (0.8–1.4) | 0.9 (0.7–1.2) |
| 5a. (2.5–3.3) | 0.9 (0.7–1.2) | 1.0 (0.7–1.5) | 0.8 (0.5–1.2) |
| 5b. (3.4–24.1) | 1.0 (0.8–1.3) | 1.0 (0.7–1.5) | 0.9 (0.6–1.4) |
| *Teeth with periodontal pockets ⩾6 mm* | | | |
| Quintiles | | | |
| 1. (0.2–0.9) | 1.0 | 1.0 | 1.0 |
| 2. (0.9–1.3) | 0.6 (0.3–1.2) | 0.2 (0.1–0.5) | 1.0 (0.5–2.2) |
| 3. (1.3–1.7) | 0.6 (0.4–1.1) | 0.5 (0.3–1.2) | 0.7 (0.3–1.6) |
| 4. (1.7–2.4) | 0.8 (0.5–1.4) | 0.7 (0.3–1.9) | 0.8 (0.4–1.6) |
| 5a. (2.5–3.3) | 0.9 (0.4–1.9) | 1.1 (0.4–3.1) | 0.9 (0.3–2.2) |
| 5b. (3.4–24.1) | 1.2 (0.6–2.4) | 1.5 (0.5–4.5) | 0.9 (0.4–2.1) |

*Homeostasis model assessment, insulin resistance. The highest quintile is halved (quintiles 5a and 5b).
†Adjusted for gender, education, presence of plaque, toothbrushing frequency, dental attendance pattern, alcohol consumption (g/week) and BMI (continuous variable).
RR, relative risks; 95% CI, 95% confidence intervals; HOMA-IR, homeostasis model assessment index for insulin resistance; BMI, body mass index.

(2010), where the association between high glucose and periodontitis was found to be confounded by age, gender and smoking.

In order to study in more detail the role of body weight in the association of insulin sensitivity with periodontal infection, BMI was included in the regression models, which resulted in considerable attenuation of the association. Whether this adjustment is necessary is not clear; if the adverse effect of high body weight was mediated through reduced insulin sensitivity, body weight would not be a confounder and adjustment would not be needed, but, on the other hand, if body weight had an effect on periodontium through other mechanisms, body weight would then be a true confounder and adjustment would be needed in order to obtain unbiased estimates (Fig. 1). Previously, when studying the role of insulin resistance or impaired glucose tolerance in periodontal infection, body weight has not been adjusted in multivariate regression models (Genco et al. 2005, D'Aiuto et al. 2008, Benguigui et al. 2010, for example). Not to adjust for obesity when studying the relation of insulin sensitivity to periodontal condition can be justified based on the following facts: obesity is one of the main causes for reduced insulin sensitivity and there is currently no conclusive evidence that obesity has an effect on the periodontium through other mechanisms.

It must be emphasized that the results of the stratified analyses showed practically no association between insulin sensitivity and periodontal infection among normoweight or overweight subjects. Despite the association that was found among obese subjects in the 30–49 age group, we are tempted to interpret this in a manner that insulin sensitivity is not an important determinant of periodontal infection, because it is not difficult to imagine that the association among the obese can attributed to residual confounding related to the variation of body weight within this stratum.

When the regression models included both HOMA-IR and BMI, BMI associated with periodontal infection in the 30–49 age group with a continuous risk estimate of 1.03 (data not shown). This can be interpreted in such a way that the effect of body weight is for the most part mediated through mechanisms other than insulin sensitivity and that adjustment for body weight in this study is justified. Speculation on the mediating mechanisms between body weight and periodontal infection/periodontitis is beyond the scope of this study and these mediating mechanisms are to a large extent unknown or not confirmed, although insulin resistance (Genco et al. 2005) and lipid metabolism and other

*Table 6.* Association of HOMA-IR* index with number of teeth with deepened periodontal pockets in BMI categories in the whole study population and in age groups 30–49 and 50–64 years after adjustment for covariates†

| HOMA-IR* index | RR 95% CI† | | |
|---|---|---|---|
| | teeth with periodontal pockets ⩾4 mm | | |
| | BMI < 25 | BMI 25.0–29.9 | BMI ⩾ 30 |
| *30–64 years* | | | |
| Quintiles | | | |
| 1. (0.2–0.9) | 1.0 | 1.0 | 1.0 |
| 2. (0.9–1.3) | 0.9 (0.7–1.1) | 0.8 (0.6–1.1) | 0.9 (0.4–1.9) |
| 3. (1.3–1.7) | 1.1 (0.9–1.5) | 0.8 (0.6–1.2) | 1.4 (0.8–2.5) |
| 4. (1.7–2.4) | 1.1 (0.8–1.4) | 0.8 (0.6–1.1) | 1.6 (0.9–2.7) |
| 5a. (2.5–3.3) | 1.3 (0.9–2.0) | 0.8 (0.5–1.3) | 1.2 (0.7–2.2) |
| 5b. (3.4–24.1) | 0.5 (1.2–1.2) | 1.0 (0.7–1.5) | 1.3 (0.8–2.1) |
| *30–49 years* | | | |
| Quintiles | | | |
| 1. (0.2–0.9) | 1.0 | 1.0 | 1.0 |
| 2. (0.9–1.3) | 0.9 (0.7–1.3) | 0.8 (0.5–1.3) | 0.3 (0.1–1.3) |
| 3. (1.3–1.7) | 1.2 (0.9–1.7) | 0.9 (0.6–1.4) | 1.7 (0.5–5.2) |
| 4. (1.7–2.4) | 1.1 (0.7–1.7) | 0.8 (0.5–1.2) | 2.3 (0.8–7.2) |
| 5a. (2.5–3.3) | 1.1 (0.6–2.0) | 0.9 (0.5–1.6) | 1.9 (0.6–5.7) |
| 5b. (3.4–24.1) | 0.9 (0.4–2.1) | 1.0 (0.6–1.6) | 1.8 (0.6–5.5) |
| *50–64 years* | | | |
| Quintiles | | | |
| 1. (0.2–0.9) | 1.0 | 1.0 | 1.0 |
| 2. (0.9–1.3) | 1.0 (0.7–1.4) | 0.9 (0.6–1.3) | 1.0 (0.4–2.4) |
| 3. (1.3–1.7) | 1.1 (0.7–1.6) | 0.7 (0.5–1.2) | 1.3 (0.6–2.7) |
| 4. (1.7–2.4) | 1.0 (0.6–1.5) | 0.9 (0.6–1.3) | 1.1 (0.5–2.1) |
| 5a. (2.5–3.3) | 1.4 (0.8–2.5) | 0.8 (0.4–1.4) | 1.0 (0.4–2.1) |
| 5b. (3.4–24.1) | 0.1 (0.0–0.5) | 1.0 (0.6–1.8) | 1.0 (0.6–2.0) |

*Homeostasis model assessment, insulin resistance. The highest quintile is halved (quintiles 5a and 5b).
†Adjusted for gender, education, presence of plaque, toothbrushing frequency, dental attendance pattern, alcohol consumption (g/week).
RR, relative risks; 95% CI, 95% confidence intervals; HOMA-IR, homeostasis model assessment index for insulin resistance; BMI, body mass index.

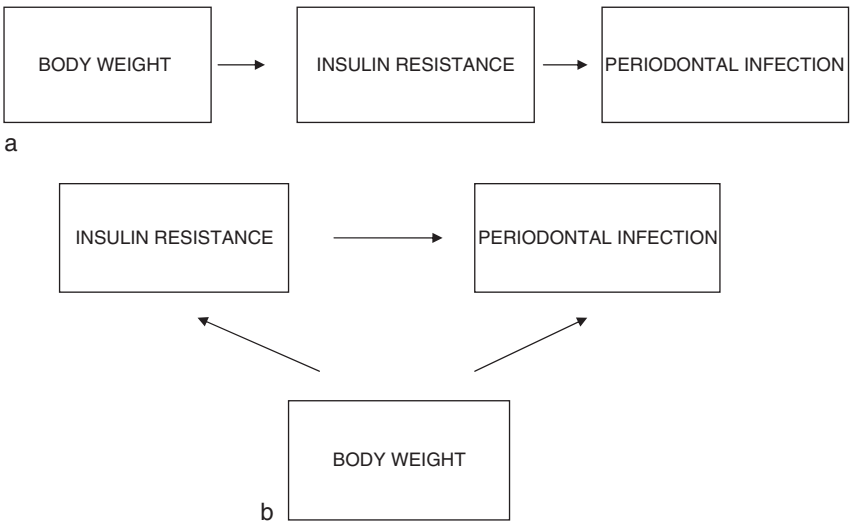


*Fig. 1* Two possible mechanisms for the causal relations between body weight, insulin resistance and periodontal infection.

molecules secreted by adipose tissue (Saito & Shimazaki 2007) have been proposed.

We also found a statistically significant interaction between the HOMA-IR index and age. In the stratified analyses according to age group, the association of the HOMA-IR index with teeth with deepened periodontal pockets was found in younger persons (30–49 years), but not in older persons (50–64 years). There are two possible explanations for this; either age-related biological factors modify the association of the HOMA-IR with periodontal infection or there are age-related, non-biological factors such as a cohort effect, related to previous use and availability of dental health care services, for example, and the effect of competing risks that prevent the detection of the possible effect of insulin resistance. We are tempted to believe that the reasons for this modifying effect of age are non-biological, because we are not aware of any possible biological mechanism that could explain why the effect of insulin resistance can be seen in younger persons but not in older persons, and because it is generally known that in situations where confounding is strong and the relation between exposure and outcome is weak, misclassification of confounders can lead to biased estimates.

#### Methodological considerations

The HOMA method is derived from a mathematical assessment of the balance between hepatic glucose output and insulin secretion from fasting levels of glucose and insulin (Matthews et al. 1985). It is a technique generally used in clinical practice instead of other, more labour-intensive and invasive techniques, and can be used to estimate insulin sensitivity in epidemiological studies too (Wallace et al. 2004). Moreover, in this context, it is important to emphasize that the HOMA-IR measures only one component of glucose metabolism, namely insulin sensitivity, and in this paper, we did not study the interaction between insulin sensitivity and other components of glucose metabolism, such as insulin secretion, for example. According to the previous literature, there is a good correlation between estimates of insulin sensitivity derived by the HOMA-IR index and other measurements, such as the euglycaemic clamp (Matthews et al. 1985, Bonora et al. 2000) and the minimal model (Garcia-Estevez et al. 2003).

In this population of non-diabetic subjects, the distribution of the HOMA-IR index was highly skewed. As the distribution was skewed, we categorized it into quintiles, which are

normally considered to be a sufficient number of exposure categories unless the exposure–response relation is complicated (Rothman & Greenland 1998, pp. 205–206). We purposely did not dichotomize our outcome variable, because we are unable to make a distinction between periodontally healthy and diseased. The distribution of our outcome variable made it possible to use the Poisson regression model, which has certain advantages; it takes into account the extent of periodontal infection, and secondly, it yields a risk estimate (RR), which has a meaningful interpretation.

The strengths of this study were the large sample size, which made it possible to confine to subjects aged 30–64 who had never smoked, and the availability of information on many of the potential confounders. In order to eliminate the confounding effect of smoking and age, the study population was confined to non-smoking persons who were under 65 years old. In addition, we adjusted for age, gender, educational level, number of teeth, presence of plaque, toothbrushing frequency, dental attendance pattern, alcohol consumption and lipid-lowering medication. Moreover, we performed stratified analyses according to age and BMI categories.

One of the limitations of this study was the cross-sectional study design, which means we cannot determine a possible cause–effect relation of insulin resistance to periodontal infection. Nor can we rule out the possibility that the direction of a possible association between periodontal infection and reduced insulin sensitivity could be the opposite or bidirectional. Such interpretations are supported by the findings that deep pockets are reported to be a risk factor for glucose intolerance (Saito et al. 2004), that periodontal disease has been shown to predict diabetes (Demmer et al. 2008) and that periodontal infection has been reported to cause a low-grade inflammation (Nibali et al. 2007, D'Aiuto et al. 2008), for example.

The participants in this study were sampled from a general adult population where periodontal infection is fairly common, but, owing to several restrictions, the number of subjects with severe periodontal infection was low, meaning that the amount of subjects with teeth with periodontal pockets 6 mm deep or deeper was small. This increases the role of random occurrence and may lead to inconsistencies in risk estimates.

### Concluding remarks

Body weight has been shown to explain about 25% of the variability in insulin sensitivity (Abbasi et al. 2002), which is in accordance with what was found in these data, where the correlation between BMI and insulin sensitivity was 0.52. How the findings of this study are interpreted depends on the underlying causal model. When BMI was excluded from the model, we found in this non-diabetic, non-smoking adult population that reduced insulin sensitivity was associated with periodontal infection, which supports the hypothesis that reduced insulin sensitivity plays a role in the pathogenesis of periodontitis. On the other hand, if body weight is a true confounder in the association between insulin sensitivity and periodontal infection, the interpretation is totally different; there exists practically no association between insulin sensitivity and periodontal infection.

The lack of knowledge of the underlying model prevents us from drawing definitive conclusions, and the causal relations between insulin resistance and periodontal infection still remain unclear. Further research is called for on the role of insulin sensitivity in the pathogenesis of periodontal infection.

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**Clinical Relevance**

*Scientific rationale for the study*: To date, the role of reduced insulin sensitivity in the pathogenesis of periodontal infection has been poorly documented.

*Principal findings*: An association of insulin sensitivity with the number of teeth with deepened periodontal pockets was found in persons aged 30–49 years. Adjustment for socio-demographic, behavioural factors and especially body weight attenuated the association considerably.

*Practical implications*: Further studies on the role of glucose metabolism in a non-diabetic population are needed.