This review aimed to determine the association between periodontal disease and stroke incidence by a meta-analysis of cohort studies. Cohort studies that evaluated the incidence of stroke (fatal or non-fatal, ischaemic or haemorrhagic) and baseline periodontal status and calculated relative risk values were included. The quality of the included studies was assessed using an evaluation grid. The analyses were conducted separately for three outcomes: periodontitis, gingivitis and loss of teeth. Adjusted values of relative risk or of hazard ratio were used to assess risk values in each study. Random effects meta-analyses were conducted when data could be pooled. From the 743 references retrieved, only nine cohort studies were suitable for inclusion in this review. Quality scores of the studies varied greatly. Three prospective studies, which used reliable indicators of periodontal disease, obtained the highest scores. Conversely, three studies that used a subjective evaluation of stroke incidence or diagnosed stroke without imaging obtained the lowest score. The results of the meta-analyses varied depending on the outcome considered and the type of stroke. The risk of stroke was significantly increased by the presence of periodontitis [relative risk 1.63 (1.25, 2.00)]. Tooth loss was also a risk factor for stroke [relative risk 1.39 (1.13, 1.65)]. The risk of stroke did not vary significantly with the presence of gingivitis. This review shows that periodontitis and tooth loss are associated with the occurrence of stroke.

Introduction
Periodontal disease, an infectious disease associated with an inadequate localized immunological response, is highly prevalent and affects up to 90% of the world’s population. Periodontal disease is characterized by a progressive loss of dental connective tissue and alveolar bone support and is a major cause of tooth loss in adults. The symptoms are spontaneous or induced bleeding gums (gingivitis), the formation of gingival pockets and bone loss (periodontitis) and finally tooth mobility. The various types of periodontal disease are mainly appreciated clinically (bleeding, pocket depth) and radiographically (bone loss) [1].

Periodontitis is related to an increase in systemic inflammation markers through exposure to Gram-negative bacteria [2,3], which are implicated in the aetiology of atherosclerosis and stroke [4].

The epidemiological link between periodontal disease and cerebral infarction was revealed in 1989 [5]. Since then, the association between periodontal disease and the occurrence of stroke has been explored using various types of epidemiological studies including cross-sectional [6], case-control [7–10] or cohort studies [11–18]. Three meta-analyses have been conducted and led to conflicting results. The first one found no association [19] whilst the other two [20,21] reported a moderately increased risk of stroke in persons with periodontitis. These reviews included case-control studies and did not consider ischaemic and haemorrhagic, fatal and non-fatal strokes separately. Therefore, the purpose of this review was to evaluate the association between periodontal disease and the incidence of ischaemic and haemorrhagic strokes through a meta-analysis of cohort studies.

Material and methods

Literature search
A literature search in PubMed, Embase, ISI Web of Science and the Cochrane database (January 1966 to
April 2012) was carried out using a combination of keywords (Table 1). Further information was retrieved through a manual search of recent reviews and relevant original studies. No language restriction was applied.

Inclusion criteria

Two authors independently read and analysed the titles and abstracts of the identified articles using the inclusion and exclusion criteria. When there was any doubt, the full text of the article was obtained and verified. A third author was consulted in the case of disagreement. The following inclusion criteria were applied: cohort studies, evaluation of the incidence of strokes (fatal or non-fatal, ischaemic or haemorrhagic), evaluation of periodontal status (periodontitis, gingivitis, tooth loss), calculation of relative risk values with periodontal status as a risk factor of stroke. Epidemiological cross-sectional and case-control studies were excluded. No restriction was applied concerning the way periodontal status was evaluated: at baseline or during follow-up, with a clinical examination or a questionnaire.

Quality of the included studies

To define the quality of the included studies, an evaluation grid [22] was used following the criteria presented in Table 2. Scores were attributed for each criterion: 2 points when the quality criterion was present, 1 point when the situation was unclear or intermediate and 0 points when the situation was unfavourable. Scores thus varied from a maximum of 16 (high quality) to a minimum of 0 (low quality).

Data extraction and analyses

The analyses were conducted separately for three types of outcome: periodontitis, gingivitis and tooth loss. For periodontitis, several indicators were combined: periodontitis versus none, pocket depth \(>3\) vs. \(0–3\) mm and bone loss \(>1.5\) vs. \(<0.5\) mm. Tooth loss included baseline indicators (edentulousness, number of missing teeth) and incidence of tooth loss.

All types of incident strokes were considered, but haemorrhagic or ischaemic and fatal or non-fatal strokes were distinguished when possible.

Adjusted values of relative risks (RRs) or hazard ratios (HRs) were used to assess risk values in each study. When several adjusted values were available in one study, the value obtained in the model that included all the confounding factors was chosen. For any given outcome, when various risk values were available in a study, risk was expressed as the most severe value compared with the reference value. The 95% confidence intervals of the RRs or HRs were directly extracted from the studies’ data.

Meta-regression analyses were conducted to explore the influence of study characteristics on risk values for the three outcomes. The following characteristics were considered: type of study (retrospective versus prospective); sex of the participants (male versus both sexes); quality of the study (score \(<10\) or \(\geq10\)); type of periodontal evaluation (questionnaire versus clinical examination); stroke outcome (fatal versus not fatal); type of stroke (ischaemic versus ischaemic and haemorrhagic); type of risk (RR versus HR); confounding factors accounted for (complete versus incomplete); use of imaging for stroke diagnosis (yes versus no).

### Table 1 PubMed search strategy

<table>
<thead>
<tr>
<th>ID</th>
<th>Search terms</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>((((((((“Intracranial Embolism and Thrombosis “[MeSH]) OR (“Intracranial Embolism and Thrombosis “[MeSH]) OR (“Intracranial Arteriosclerosis “[MeSH]) OR (transient ischemic attack) OR (brain infarction) OR (cerebral infarction)) OR (cerebrovascular diseases)) OR (cerebrovascular disease)) OR (cerebrovascular disorder)) OR (stroke)) OR (“Cerebrovascular Disorders”[Mesh]) OR (“Ischemic Attack, Transient”[Mesh]) OR (“Stroke”[Mesh])) OR (tia)</td>
<td>323 232</td>
</tr>
<tr>
<td>#2</td>
<td>Search periodontal diseases OR periodontitis OR bone loss OR tooth loss OR attachment loss OR periodontal pocket OR periodontal index OR teeth OR dental OR tooth OR CAL</td>
<td>548 402</td>
</tr>
<tr>
<td>#3</td>
<td>Search (“Comparative Study”[Mesh]) OR (“Disease-Free Survival”[MeSH]) OR (“Comparative Study”[Mesh]) OR (incidence) OR (cohort*) OR (“Prognosis”[MeSH]) OR (case NEAR control*) OR (cases NEAR control*) OR (case control*) OR (case-controlled) OR (case-control) OR (cases) OR (“Morbidity”[MeSH]) OR (“Epidemiologic Studies”[MeSH]) OR (survival) OR (mortality) OR (“local control”) OR (“loco regional control”) NOT (((“Follow-Up Studies”[Mesh]) OR (“Longitudinal Studies”[Mesh]) OR (“Disease-Free Survival”[MeSH]) OR (“Comparative Study”[Mesh]) OR (incidence) OR (cohort*) OR (“Prognosis”[MeSH]) OR (case NEAR control*) OR (cases NEAR control*) OR (case control*) OR (case-controlled) OR (case-control) OR (cases) OR (“Morbidity”[MeSH]) OR (“Epidemiologic Studies”[Mesh]) OR (survival) OR (mortality) OR (“local control”) OR (“loco regional control”)) AND (((“randomized controlled trial”[Publication Type]) OR (“controlled clinical trial”[Publication Type]) OR (random*) OR (“clinical trial”) OR (“clinical trials”)))</td>
<td>2 910 335</td>
</tr>
<tr>
<td>#4</td>
<td>Search #1 AND #2 AND #3</td>
<td>743</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>--------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>Population (representative of the general population or not)</td>
<td>Retrospective</td>
<td>Prospective</td>
</tr>
<tr>
<td>Military men</td>
<td>General population</td>
<td>Male doctors</td>
</tr>
<tr>
<td>Percentage of drop-outs (reported or not)</td>
<td>0.67</td>
<td>5</td>
</tr>
<tr>
<td>Type of stroke (ischaemic, haemorrhagic strokes distinguished or not)</td>
<td>Ischaemic and haemorrhagic</td>
<td>Ischaemic or haemorrhagic</td>
</tr>
<tr>
<td>Definition of stroke [International Classification of Disease (ICD-8/9) or not]</td>
<td>ICD8</td>
<td>ICD9</td>
</tr>
<tr>
<td>Assessment of periodontal disease (complete, simple clinical examination, tooth count or questionnaire)</td>
<td>Simple clinical examination</td>
<td>Simple clinical examination</td>
</tr>
<tr>
<td>Confounding factors (main confounders considered or not)</td>
<td>BMI is lacking</td>
<td>+</td>
</tr>
<tr>
<td>Exclusion criteria (exclusion of patients with history of CVD or not)</td>
<td>Excluded</td>
<td>–</td>
</tr>
<tr>
<td>Quality score</td>
<td>9</td>
<td>13</td>
</tr>
</tbody>
</table>

– 0 low quality; ±, 1 unclear or intermediate; +, 2 high quality; ICD, International Classification of Disease; CVD, cardiovascular disease. Usual confounders: social status (SES), hypertension, diabetes, smoking, body mass index (BMI), age, sex, heredity, cholesterol.
Subgroups and sensitivity analyses were defined depending on the study characteristics that were significant in the meta-regressions.

STATA 12 (Statacorp, College Station, TX, USA) software was used to conduct random effects meta-analyses when data could be pooled. Forest plot graphs were drawn. Data were pooled whatever the length of follow-up. Heterogeneity in the study results was evaluated by examining forest plots and confidence intervals of risk values and by using formal tests for homogeneity based on the $I^2$ statistics. In some studies, several risk values were available for fatal and non-fatal strokes or for different types of outcome from the same category. A sensitivity analysis was thus conducted to assess the influence on the global risk of the inclusion and exclusion of these data.

Results

Literature search and inclusion of the studies

From the 743 references retrieved, only nine cohort studies (eight prospective and one retrospective) were included in the review (Fig. 1).

Characteristics and quality of the included studies

The characteristics of the nine studies are presented in Table 2. Five studies were conducted in North America and started in the 1970–1980 period. The number of participants ranged from 1137 to 51 529. The length of follow-up ranged from 12 years to a maximum of 57 years.

Quality scores varied from 7 to 13, and only four studies had a score of 12 or more (Table 2). Three prospective studies, which used reliable indicators of periodontal diseases whilst taking into consideration the major confounding factors, obtained the highest scores [11,14,16]. The study with the lowest score had a large number of patients lost at the start, included a subjective evaluation of incident strokes and took no account of major confounding factors [13].

It should be noted that only five studies included all of the confounding risk factors in the calculation of the adjusted risk values. In some studies, the patients’ previous history of stroke was not taken into account. Smoking was the only factor considered in all of the studies. Participants were classified as being regular smokers, former smokers or non-smokers, and the number of cigarettes smoked per day was specified except for two studies [12,14]. The number of pack-years was indicated in four studies [12,15,18,23] and smoking exposure was evaluated using a comprehensive smoking index [24,25] in one study [16].

Incident ischaemic strokes were defined using the International Classification of Disease (ICD) in six studies. Two studies did not use imaging to establish the diagnosis of stroke [12,13]. One study used imaging but it did not apply the ICD classification [23]. The ICD classification only distinguishes between ischaemic and haemorrhagic stroke. The TOAST [26] classification was not used and thus stroke subtypes could not be explored.

One of the major biases was the heterogeneity in the indicators used to evaluate periodontal diseases. A clinical oral examination was conducted in seven studies, whilst in two studies participants evaluated their own oral status through a questionnaire [12,23]. An in-depth clinical and radiological examination allowing the measurement of loss of attachment and bone support for each tooth was conducted in only one study [16]. In the other six studies, periodontal diseases were evaluated using global indicators of oral status [11,13–15,17,18].

Data and analyses

Two meta-regressions were conducted for periodontitis and loss of teeth. Due to the small number of values, it was not possible to conduct a meta-regression for gingivitis. The type of periodontal evaluation and the use of imaging for stroke diagnosis were related to risk values for periodontitis and tooth loss ($P = 0.03$). The three studies that used questionnaires for periodontal evaluation and no imaging for stroke diagnosis were excluded from the random effects meta-analyses. The data were combined for the retrospective and prospective studies, male and female participants, studies with various quality scores, fatal and non-fatal strokes, RRs and HRs, and for risk values calculated with different numbers of confounding factors. Two subgroups, ischaemic and ischaemic + haemorrhagic stroke, were nonetheless created to explore their risk values separately.
Periodontitis and stroke

The pooled risk estimate was 1.63 (1.25, 2.00) for ischaemic and ischaemic + haemorrhagic strokes together (Fig. 2). There was no heterogeneity between studies. When duplicate data from the same study (values for fatal or non-fatal stroke) were deleted, almost identical risk estimates were found with no heterogeneity.

No heterogeneity was observed and a slightly higher risk was calculated [1.72 (1.20, 2.25)] for the subgroup that included ischaemic + haemorrhagic strokes. The risk estimate was also almost identical when duplicate values were excluded.

For the subgroup ‘ischaemic stroke’, no heterogeneity was observed but a lower pooled risk was found: 1.53 (1.00, 2.07). The exclusion of duplicate data, probably due to a lack of power, resulted in a non-significant pooled risk value of 1.44 (0.88, 1.94).

Gingivitis and stroke

The pooled risk estimate was 1.10 (0.77, 1.43) when ischaemic and ischaemic + haemorrhagic strokes were considered together. No heterogeneity was observed. Risk estimates in the two subgroups remained low and non-significant, even after excluding duplicates.

Tooth loss and stroke

The pooled risk estimate was 1.39 (1.13, 1.65) when ischaemic and ischaemic + haemorrhagic strokes were considered together (Fig. 3). There was no heterogeneity observed between studies. When duplicate data from the same study were deleted, approximately identical risk estimates were found with no heterogeneity.

No heterogeneity was observed and a pooled risk estimate of 1.50 (1.00, 2.02) was calculated for the subgroup that included only ischaemic stroke. The risk estimate became non-significant [1.41 (0.96, 2.06)] when duplicate values were excluded.

For ischaemic and haemorrhagic strokes, no heterogeneity was observed and a significant pooled risk estimate was found: 1.35 (1.05, 1.66). The exclusion of duplicate data did not modify the results.

Discussion

The results suggested a link between stroke and periodontal diseases. The association was significant for periodontitis and tooth loss. The risk of ischaemic or haemorrhagic stroke was higher in persons with periodontitis [estimated adjusted risk 1.63 (1.25, 2.00)].

Tooth loss was also found to be a significant risk factor for stroke [estimated adjusted risk 1.39 (1.13, 1.65)].

In this review, gingivitis did not significantly influence the occurrence of stroke. Unlike periodontitis, gingivitis is a superficial inflammation of the periodontal tissues without loss of attachment or bone

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of stroke</th>
<th>Indicator</th>
<th>ES</th>
<th>95% CI</th>
<th>% weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morrison</td>
<td>Fatal</td>
<td>Periodontitis versus no</td>
<td>1.63</td>
<td>0.720</td>
<td>3.670</td>
</tr>
<tr>
<td>Wu</td>
<td>Fatal</td>
<td>Periodontitis versus no</td>
<td>2.140</td>
<td>1.160</td>
<td>3.930</td>
</tr>
<tr>
<td>Holmlund</td>
<td>Fatal</td>
<td>Severe periodontitis versus no</td>
<td>1.390</td>
<td>0.180</td>
<td>10.450</td>
</tr>
<tr>
<td>Wu</td>
<td>Non-fatal</td>
<td>Periodontitis versus no</td>
<td>1.660</td>
<td>1.150</td>
<td>2.390</td>
</tr>
<tr>
<td>Subgroup</td>
<td>Ischaemic and haemorrhagic</td>
<td></td>
<td>1.72</td>
<td>1.20</td>
<td>2.25</td>
</tr>
<tr>
<td>Jimenez</td>
<td>Fatal/non-fatal</td>
<td>Pocket depth &gt;3 vs. 0-4</td>
<td>1.070</td>
<td>0.590</td>
<td>1.930</td>
</tr>
<tr>
<td>Jimenez</td>
<td>Fatal/non-fatal</td>
<td>Bone loss &gt;1.5 vs. &lt;0.5</td>
<td>3.520</td>
<td>1.590</td>
<td>7.810</td>
</tr>
<tr>
<td>Wu</td>
<td>Fatal</td>
<td>Periodontitis versus no</td>
<td>2.900</td>
<td>1.450</td>
<td>5.620</td>
</tr>
<tr>
<td>Wu</td>
<td>Non-fatal</td>
<td>Periodontitis versus no</td>
<td>2.110</td>
<td>1.300</td>
<td>3.420</td>
</tr>
<tr>
<td>Subgroup</td>
<td>Ischaemic</td>
<td></td>
<td>1.53</td>
<td>1.00</td>
<td>2.07</td>
</tr>
<tr>
<td>Pooled ES</td>
<td></td>
<td></td>
<td>1.63</td>
<td>1.25</td>
<td>2.00</td>
</tr>
</tbody>
</table>

Figure 2 Forest plot for periodontitis outcomes. ES, estimated adjusted risk [relative risk (RR) or hazard ratio (HR)].

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of stroke</th>
<th>Indicator</th>
<th>ES</th>
<th>95% CI</th>
<th>% weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morrison</td>
<td>Fatal</td>
<td>Edentulous versus no</td>
<td>1.63</td>
<td>0.770</td>
<td>3.420</td>
</tr>
<tr>
<td>Wu</td>
<td>Fatal</td>
<td>Edentulous versus no</td>
<td>1.340</td>
<td>0.760</td>
<td>2.370</td>
</tr>
<tr>
<td>Tu</td>
<td>Fatal</td>
<td>Lost teeth &gt;9 vs. &lt;4</td>
<td>1.640</td>
<td>0.960</td>
<td>2.800</td>
</tr>
<tr>
<td>Holmlund</td>
<td>Fatal</td>
<td>Teeth present &lt;10 vs. &gt;25</td>
<td>2.010</td>
<td>0.780</td>
<td>5.160</td>
</tr>
<tr>
<td>Heitmann (women)</td>
<td>Fatal/non-fatal</td>
<td>Edentulous versus no</td>
<td>5.320</td>
<td>1.980</td>
<td>14.300</td>
</tr>
<tr>
<td>Heitmann (men)</td>
<td>Fatal/non-fatal</td>
<td>Edentulous versus no</td>
<td>2.430</td>
<td>0.950</td>
<td>6.280</td>
</tr>
<tr>
<td>Wu (non-fatal)</td>
<td>Non-fatal</td>
<td>Edentulous versus no</td>
<td>1.230</td>
<td>0.910</td>
<td>1.660</td>
</tr>
<tr>
<td>Subgroup</td>
<td>Ischaemic and haemorrhagic</td>
<td></td>
<td>1.35</td>
<td>1.05</td>
<td>1.66</td>
</tr>
<tr>
<td>Wu</td>
<td>Fatal</td>
<td>Edentulous versus no</td>
<td>2.120</td>
<td>1.140</td>
<td>3.950</td>
</tr>
<tr>
<td>Wu</td>
<td>Non-fatal</td>
<td>Edentulous versus no</td>
<td>1.410</td>
<td>0.960</td>
<td>2.060</td>
</tr>
<tr>
<td>Subgroup</td>
<td>Ischaemic</td>
<td></td>
<td>1.50</td>
<td>1.00</td>
<td>2.02</td>
</tr>
<tr>
<td>Pooled ES</td>
<td></td>
<td></td>
<td>1.39</td>
<td>1.13</td>
<td>1.65</td>
</tr>
</tbody>
</table>

Figure 3 Forest plot for tooth loss outcomes. ES, estimated adjusted risk [relative risk (RR) or hazard ratio (HR)].
loss. Patients with chronic gingivitis may even have an ability to resist inflammation and periodontal destruction.

In contrast, tooth loss was found to be a significant risk factor for stroke. Tooth loss is the ultimate stage of periodontal disease and may be associated with an increase in C-reactive protein (CRP), which itself is implicated in atherosclerosis and thus in the occurrence of stroke [4]. The total number of teeth lost may then reflect the past inflammatory state of a patient [27]. People with few or no teeth would thus have an increased risk of systemic diseases such as stroke. However, this association can be interpreted differently. Tooth loss may be due to other dental diseases such as dental caries, although periodontitis is a major cause. There is also a slight decrease in the risk of death from cardiovascular diseases in people who lost their teeth during their youth [14]. Because of this early loss, patients have not been exposed to periodontal infection for the rest of their lives. Finally, tooth loss may cause masticatory deficiencies, nutritional difficulties and may significantly modify eating habits, thus indirectly increasing the risk of cerebrovascular diseases [28].

Our results indicated that the incidence of stroke was slightly higher in persons with periodontitis. Comparisons with the results of previous meta-analyses need to be made with caution because the objectives and methods of such reviews varied greatly [19,21].

In two reviews [19,29], case-control and cross-sectional observational studies were included along with cohort studies. The pooled risk values were probably over-estimated by the use of odds ratios and exposure to the risk factor (periodontitis) might not have preceded the occurrence of stroke.

In two other reviews, inclusion was limited to cohort studies but no distinction was made between ischaemic and haemorrhagic strokes [21]. One review that did not focus specifically on cerebrovascular diseases considered only four cohort studies [11,12,18,30] and found high pooled risk values: 2.85 (1.78, 4.56) [21]. A recent review [20] focused on stroke and considered six prospective studies [11–13,16,23,30]. A pooled adjusted RR of 1.47 (1.13, 1.92) was found, and Sfyroeras et al. [20] therefore concluded that periodontitis was an independent risk factor for the occurrence of stroke.

The present results are in accordance with the current understanding of the pathogenesis of periodontitis and stroke. Inflammation plays an essential role in the aetiology of ischaemic stroke whilst haemorrhagic stroke has a different aetiology (subarachnoid and intracerebral haemorrhage). A recent study has linked the presence of serum anti-periodontal pathogen antibodies (anti-Prevotella intermedia) and atherothrombotic risk associated with ischaemic stroke [31]. The periodontium is a gateway for infectious agents, especially Porphyromonas gingivalis which is able to invade epithelial cells of the blood vessels and thus to cause bacteraemia and to elevate inflammatory parameters [4]. In this field, it has been demonstrated that the treatment of periodontitis reduces the level of serum inflammatory markers, which are involved in the origin of ischaemic strokes [32–34]. Although the mechanisms of action remain unknown, periodontal diseases might influence the occurrence of atherosclerotic diseases. Lipopolysaccharides from the outer membrane of Gram-negative bacteria are one of the main triggers of the inflammatory response. They cause the production of pro-inflammatory cytokines [35,36] and the disruption of lipid metabolism, thus promoting atherosclerosis [35,37]. This background endotoxaemia, which worsens with the severity of periodontal disease, promotes atherosclerosis [38]. Indeed, cytokines induce adhesion molecules, ICAM-1, which facilitate the adhesion of monocytes to endothelial cells and their migration into tissues. Monocytes then differentiate into macrophages, which internalize the oxidized low-density lipoprotein in the endothelium and become foam cells, which form the fatty streaks seen in atherosclerotic lesions. This mechanism is favoured by smoking, which is a major thrombogenic factor in that it decreases high-density lipoprotein and increases low-density lipoprotein. In addition, lipopolysaccharides contribute to a higher level of CRP in patients with periodontal disease [36,39]. Several studies have also shown that CRP is a predictor of ischaemic stroke in patients with no vascular history [38,40,41]. The precise role of CRP in the onset of atherosclerosis is not known. Its involvement is suggested by its ability to activate complement and to trigger the formation of foam cells [35,36]. However, epidemiological and clinical studies are needed to clarify the pathogenesis of these inflammatory diseases and their relationships with each other.

In this review, the characteristics of the studies varied greatly. Studies based on unreliable evaluations were excluded in view of the results of the meta-regression. Despite this, risk ratios varied greatly from 1.39 (0.18, 10.45) [17] in a study that had mixed fatal ischaemic and haemorrhagic strokes and evaluated periodontitis through a basic clinical examination to 3.52 (1.59, 7.81) [16] in a study which explored the relationship between ischaemic stroke and periodontal bone loss. The low-quality studies may thus have lowered the pooled risk values. They did not lead to an overestimation of the relationship between periodontal disease and stroke.
Concerning the quantification of tooth loss, heterogeneity in the measurement of the outcomes was also very high. In some studies, patients were asked if they had lost at least one tooth during the study period, whilst in others edentulous patients were compared with dentate patients. Thus the measurement of the main independent risk factor was probably not very accurate, leading to uncertainty in the calculation of RR or HR values.

A number of risk factors, especially diabetes, social status and smoking, are common to the onset of ischaemic stroke and periodontitis [42,43]. These factors need to be considered as confounding factors in the calculation of adjusted RR or HR values. In Jimenez et al. [16], the HR values slightly decreased after adjustment (smoking index, cholesterol, hypertension, diabetes) but were still significant. The crude HR was 3.98 (1.83–8.63) and the adjusted HR was 3.52 (1.59–7.81). This indicates that periodontitis can be considered an independent risk factor for stroke. Previous studies have clearly shown that smoking increases the risk of both periodontitis and ischaemic stroke [44,45].

In this field, it can be noticed that in Joshipura et al. [23] the multivariate adjusted HR value was higher for patients who were regular smokers at baseline (HR 1.67, 95% CI 1.26–2.23) than for non-smokers (HR 0.61, 95% CI 0.34–1.12). Social status is also a common risk factor for many chronic diseases including periodontal diseases and stroke [46]. Deprived people tend to live in unfavourable environments, which influence their lifestyle (oral hygiene, tobacco use etc.) and thus increase the incidence of periodontal, cardiovascular or ischaemic diseases. Moreover, deprived populations have less access to medical and dental care leading to a greater number of missing teeth [14] and more after-effects after a stroke. In this review, participants from four studies [12,16,18,23] were selected according to their occupational status; their social status was favourable and homogeneous, but these samples were not representative of the general population.

**Conclusion**

Our results are in accordance with those of previous reviews suggesting a link between stroke and periodontal diseases [18,20,21,43]. Pooled data were calculated based on results from cohort studies with various quality scores. More epidemiological and clinical studies are thus needed to clarify the relationship between these inflammatory diseases. In the future, the development and use of more valid and reliable clinical indicators will be essential to evaluate more accurately the presence of periodontal diseases. This would allow the harmonization of the outcomes used and strengthen the validity of the results.

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The authors declare no financial or other conflicts of interest.
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