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2017 WORLD WORKSHOP

Mean annual attachment, bone level, and tooth loss: A systematic review

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The proceedings of the workshop were jointly and simultaneously published in the *Journal of Periodontology* and *Journal of Clinical Periodontology*.

Abstract

Background: Rate of progression of periodontitis has been used to inform the design of classifications of periodontal diseases. However, the evidence underpinning this topic is unclear and no systematic review has yet been conducted.

Objectives: The focused question for this systematic review was: in adults, what is the progression of periodontitis in terms of clinical attachment loss, radiographic bone loss, and tooth loss?

Data sources: Highly sensitive electronic search was conducted for published data in MEDLINE, EMBASE, LILACS, and unpublished grey literature in OpenGrey up to February 2016. Reference lists of retrieved studies for full-text screening and reviews were hand-searched for potentially eligible studies.

Study eligibility criteria and participants: Prospective, longitudinal observational studies with follow-up of at least 12 months and presenting data on the primary outcome, change in clinical attachment level, in adults (age ≥18 years). Secondary outcomes, tooth loss and bone level change, were only assessed in studies reporting the primary outcome. Studies investigating specific disease populations or only on treated periodontitis patients were excluded.

Study appraisal and synthesis methods: Risk of bias and methodology were assessed using the Newcastle-Ottawa Scale with two additional questions on security of outcome assessment. Studies were pooled by abstracting or estimating mean annual attachment or bone level change and annual tooth loss. Random effects meta-analysis was conducted with investigation of effect of potential modifiers where possible.

Results: A total 11,482 records were screened for eligibility; 33 publications of 16 original studies reporting on more than 8,600 participants were finally included as eligible for the review. The studies represented populations from both developing and developed economies. Mean annual attachment loss was 0.1 mm per year (95% CI 0.068, 0.132; $I^2 = 99\%$) and mean annual tooth loss was 0.2 teeth per year (95% CI 0.10, 0.33; $I^2 = 94\%$). Observational analysis of highest and lowest mean attachment change quintiles suggested substantial differences between groups with minimal

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annual change in the lowest quintile and an average deterioration of 0.45 mm mean attachment loss per year in the highest group. This value increased to 0.6 mm per year with periodontitis alone. There was surprisingly little effect of age or gender on attachment level change. Geographic location, however, was associated with more than three times higher mean annual attachment loss in Sri Lanka and China (0.20 mm, 95% CI 0.15, 0.27; $I^2 = 83\%$) vs North America and Europe (0.056 mm, 95% CI 0.025, 0.087; $I^2 = 99\%$) $P < 0.001$.

Limitations: There were a limited number of studies (N = 16), high variability of design in key study components (sampling frames, included ages, data analyses), and high statistical heterogeneity that could not be explained.

Conclusions: Within the limitations of the research, the data show that mean annual attachment level change varies considerably both within and between populations. Overall, the evidence does not support or refute the differentiation between forms of periodontal diseases based upon progression of attachment level change.

KEYWORDS

chronic periodontitis, disease progression, epidemiology, periodontal attachment loss, periodontal diseases, systematic review

Periodontitis is characterized by non-reversible tissue destruction resulting in progressive attachment loss, eventually leading to tooth loss.[1] Severe periodontitis is the sixth most prevalent disease of mankind[2] and is a public health problem since it is so widely prevalent and causes disability, impaired quality of life, and social inequality.[3,4] The prevalence of periodontitis remains high globally, although periodontal health has shown signs of improvement in representative national and regional epidemiologic surveys in recent decades in countries with high incomes.[5,6] However, the most severe forms of periodontitis have remained constantly high, affecting approximately 10% of surveyed populations.[6–8]

Understanding the nature of the disease is crucial to research and development of more effective health promotion, disease prevention, and treatment. For instance, if there are different forms of periodontitis, should management strategies be tailored to the variants? It is unclear whether periodontitis comprises a group of distinct diseases (chronic periodontitis, aggressive periodontitis)[9,10] or a syndrome with a range of presentations.[11,12] In attempting to address these issues, the two most common criteria used to evaluate similarities and differences during the last half century or more of periodontal disease classification have included age of onset of disease and rate of progression. The word "rate" is used here, not in the usual epidemiologic sense of proportion of people affected by a condition, but instead in the sense of how quickly the disease deteriorates. Age of onset is not the topic of this review and will not be addressed further, although is investigated by another review.[13]

Rate of progression could be important as a distinguishing criterion of forms of periodontitis, and there is general consensus in most disease definitions that the primary measure of the condition is attachment level change.[14] Rapid disease progression was a criterion for periodontosis nearly half a century ago.[15] Rate of progression became embedded in the identity of certain classifications with labels such as rapidly progressive periodontitis and aggressive periodontitis.[9] However, even with promotion of this criterion to a defining characteristic, there was widespread unease about whether it was truly distinctive.[9,10,12,16,17]

Clearly, much uncertainty remains about the progression of attachment loss. Systematic reviews are designed to assemble, appraise, and make sense of the totality of the evidence[18] as far as possible. No previous systematic review has investigated rate of progression of attachment loss; therefore, the aim of this study was to critically and comprehensively evaluate the evidence for progression of periodontitis and associated determinants of progression.

METHODS

Focused question

In adults, what is the progression of periodontitis in terms of clinical attachment loss, radiographic bone loss, and tooth loss? The reason for limiting the investigation to adults, i.e., persons aged ≥18 years was a request to constrain the

investigation in this manner to avoid overlap with a separate investigation into periodontal diseases in younger individuals for the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions.[13]

Objectives:

- To investigate the evidence for progression of periodontitis, defined as change in attachment level during a period of 12 months or more – What is the evidence for different mean values of progression?
- Which risk factors are associated with different mean values of progression of periodontitis?
- Which etiologic factors are associated with different mean values of progression of periodontitis?

The protocol was registered prior to commencing the study on the PROSPERO database: CRD42016035581 (www.crd.york.ac.uk/PROSPERO). The manuscript has been prepared following the PRISMA statement for reporting of systematic reviews.[19]

Population

Included were studies on periodontally untreated adults aged ≥18 years. Studies including both adults and younger individuals without distinction were eligible, and it was planned to stratify for this criterion. The plan was to stratify data into studies based on baseline status of periodontitis populations, non-periodontitis populations, and mixed/unclear populations if available. Studies with participants in continuous periodontal maintenance after periodontal therapy were excluded.

Exposure

The primary outcome measure was clinical attachment level (CAL) change (or variants including relative attachment level change). All probing methods (manual, controlled force, etc.) were included. Change of probing depth (PD) was not considered. Secondary outcome measures were only included for studies which first presented attachment level change. For radiographic bone loss, all methods (film, digital, subtraction, customized film holders) were eligible. Tooth loss data were included irrespective of whether the cause of tooth loss was reported. Clearly, tooth loss might have been related to factors other than periodontitis.

Disease determinants, risk factors, and etiologic agents

The association of attachment level progression with disease determinants was recorded where available, including gender, age, socioeconomic position, genetics, lifestyle, health behaviors, nutritional, and microbiologic factors. Wherever possible, the quality of measurement of the determinant/exposure was assessed (see below).

Study follow-up duration

Any study duration or follow-up interval of at least 12 months was included. Data were recorded for all follow-ups, and the longest follow-up available was selected.

Types of studies

The aim was to be inclusive of research, and there are many possible approaches to designing eligibility criteria for this research question. Considered as eligible was any longitudinal, prospective, observational study with a follow-up of ≥12 months that assessed changes in CAL (or variants including relative attachment level) in adult individuals (≥18 years of age). Secondary outcomes were assessed only for those studies first reporting data for CALs and comprised radiographic bone loss, tooth loss, and risk factors associated with clinical attachment loss. Intervention studies, cross-sectional studies, and reviews were excluded. Included was any prospective longitudinal study whether population- or institution-based. Studies on specific disease populations, such as diabetes, were excluded because the aim of the review was to establish evidence as far as possible for periodontitis in general populations. Clearly, within population studies, accurate general health status might not be known. In addition, studies exclusively reporting data for treated periodontitis patients would not represent overall population values.

Inclusion Criteria:

- Prospective, longitudinal studies.
- Duration of follow-up at least 12 months.
- Adults ≥18 years of age. Studies that also included younger participants within a combined data set were included although data was stratified separately.
- Study reporting progression of periodontitis using attachment level assessments.
- Periodontally healthy, untreated periodontitis or participants not part of periodontitis treatment investigations. This was set broadly as it was anticipated that population studies would not report detailed periodontal treatment status of participants.
- Tobacco use was not an eligibility criterion. Population studies would include both tobacco and non-tobacco users; it was planned to analyze the effect on periodontal health if data were available.

Exclusion Criteria:

- Studies investigating solely specific systemic disease populations, e.g., diabetes.

- Experimental studies testing the effect of interventions on periodontitis.
- Cross-sectional or retrospective studies.
- Studies only recruiting participants for periodontitis treatment or previously treated for periodontitis.

Search strategy

A highly sensitive search was conducted. Electronic databases (MEDLINE via OVID, EMBASE via OVID, LILACS) were searched using a string of medical subject headings and free-text terms (see Appendix 1 in online *Journal of Periodontology*). OpenGrey was searched for unpublished, grey literature. The search strategy was developed with author ADI, a medical librarian with extensive experience in designing searches for systematic reviews. The search strategy was first designed for the MEDLINE database and was then modified appropriately for the other databases searched. There were no language or publication date restrictions. Reference lists of all studies included for full-text screening and previous reviews were searched for missing records. The search results were downloaded to a bibliographic database and duplicate records were removed.

Study selection

Titles and abstracts (if available) of the studies identified in the searches were screened by two of the review authors (NG and FM), in duplicate and independently. Subsequently, the full text of all publications appearing to meet the inclusion criteria or for which there was not sufficient information in the title and abstract to make a decision, were obtained. At this first stage, any study considered as potentially relevant by at least one of the reviewers was included for the next screening phase. Subsequently, the full-text publications were also evaluated in duplicate and independently by the same review examiners. The examiners were calibrated with the first 10 full-text, consecutive publications. Any disagreement on the eligibility of studies was resolved through discussion between both reviewers until consensus was reached or through arbitration by a third reviewer (IN). All potentially relevant studies that did not meet the eligibility criteria were excluded and the reasons for exclusion noted. Publications in languages other than English, Greek, Portuguese, or Spanish were sent to an interpreter with clear instructions on inclusion and exclusion criteria. Interexaminer agreement following full-text assessment was calculated via kappa statistics. In addition, the final list of eligible studies was circulated to all members of the review group and the workshop chairmen for evaluation of possibly missing studies.

There were several studies which accounted for more than one publication since it was common to find publications investigating the same population at different follow-up intervals and/or secondary analysis of the same data. For this reason, a decision was made to pool together all relevant publications for any given principal study. FM and NG assessed the pooled studies independently and included only those reporting data on the primary and/or secondary outcomes assessed in this review for the original study sample. Disagreement on the selection of the studies was resolved in the same manner as in previous stages.

Unclear or missing data

Regarding studies for which a clear decision on eligibility could not be made following full-text assessment or when there were missing data, the corresponding authors were contacted up to twice, one month apart, to seek the information needed to aid the final decision. In the absence of response, and/or if the data could not be used, these studies were excluded from the final review.

Data extraction and management

Study details were collected using a form specifically designed for data extraction for this review and which was first piloted in a small number of studies. Two of the review authors (NG and FM) independently extracted all relevant data from all included studies except publications written in any language other than English, Greek, Portuguese or Spanish. In this case, data extraction (and quality assessment) was completed by interpreters who received clear instructions on how to collect the data using the data collection form. Any disagreements were resolved through debate and consensus or through assessment of a third reviewer (IN).

The following study details were extracted:

- Type of study
- Number of centers
- Sample frame (e.g., community, university)
- Age of participants
- Periodontal status
- Definition of periodontitis cases
- Duration of follow-up
- Type of attachment level measurement (e.g., probing attachment level (PAL), CAL, Relative attachment level (RAL), etc.)
- Method of attachment level measure (e.g., manual probe, pressure sensitive probe, etc.)
- Frequency of CAL measurement
- Method for radiographic assessment of bone loss
- Cause of tooth loss reported in study (yes/no)
- Risk factors reported in study
- Number of participants (baseline/last follow-up)

- Outcomes
  - Mean attachment level change
  - Mean attachment level change stratified by subgroups
  - Mean radiographic bone loss
  - Mean radiographic bone loss stratified by subgroups
  - Mean tooth loss
  - Mean tooth loss stratified by subgroups

Quality assessment

Risk of bias was assessed using the Newcastle-Ottawa Scale, appropriately modified (see Appendix 2 in online *Journal of Periodontology*), because it is the mostly widely used tool for epidemiologic studies.

Other domains of methodologic quality comprised:

- Security of measurement of attachment level. Studies were assessed as secure if the method involved appropriate training and calibration of examiners, insecure if training was absent or inadequate or unclear if unreported.
- Security of assessment of bone level change. Studies were assessed as secure if the method involved standardized positioning of the radiographs, e.g., cephalostat or customized film holders, insecure if standardization was absent or inadequate or unclear if unreported.

Data synthesis

Data were first entered into evidence tables stratified by study design. Decisions on which studies to include in a meta-analysis were made depending on the similarity of chief study characteristics related to each research question, i.e., mean progression of periodontitis and association of progression with disease determinants.

When a study provided the mean progression at a known time point, it was assumed that the progression was constant with time in order to estimate the mean progression rate, i.e., the mean progression per year. When a study only provided the relevant progression information for subgroups (e.g., gender or age groups), the mean annual progression for the study was estimated as a weighted mean, with the weights being inversely proportional to the variance if the latter could be calculated or directly proportional to the frequency otherwise. The same approach was used when estimating the mean annual progression for each of the three age subgroups, namely age <30, 30–50, and >50 years. Assuming that the data were normally distributed in each study, the lowest and highest quintiles (i.e., the 20th and 80th percentiles) of annual progression were calculated for each study from its mean and standard deviation.

Statistical heterogeneity of mean annual progression between relevant studies was assessed using both the chi-square test and the I^2 measures. The I^2 was interpreted according to the guidance of the Cochrane Handbook:

- 0% to 40%: might not be important
- 30% to 60%: may represent moderate heterogeneity
- 50% to 90%: may represent substantial heterogeneity
- 75% to 100%: considerable heterogeneity

If meta-analysis appeared appropriate, it was used to provide an overall estimate of the mean annual progression, with its 95% confidence interval (CI), using a random-effects approach if there was evidence of statistical heterogeneity and a fixed-effects approach otherwise. Statistical heterogeneity was anticipated, and it was planned to investigate the contribution of risk of bias, security of disease progression method, and type of population, i.e., initially healthy or periodontitis. Similar methods were planned to assess the association between mean progression and potential modifiers. However, the available data were limited for meta-analysis, allowing only few exploratory analyses. For these analyses of association, a chi-square test of heterogeneity between the overall mean annual progression for each subgroup of the potential modifier (e.g., males and females) was performed to determine the effect of the factor (i.e., gender, geographic location, or age group) on the mean annual progression. Statistical analyses were conducted by AP, a biostatistician experienced in systematic reviews and meta-analysis. A significance level of 0.05 was used for all statistical hypothesis tests. Data were analysed using appropriate software.*

RESULTS

Search

A total of 11,482 potentially eligible records were found through the sensitive searches. A total 11,286 publications were excluded following review of the titles and abstracts and finally the full publications of 196 records were retrieved (Figure 1).

Interexaminer agreement at full-text screening was excellent (kappa score = 0.756).[20] Following careful assessment of the full papers, 116 records were excluded. Of the remaining 80 records, 4 original studies accounting for only one publication were included in the final review, while 76 publications were nested into 12 different original studies which had more than one publication (e.g., different follow-up intervals). Finally, 29 of the nested publications were also included which resulted in a total of 33 publications of 16 studies which were included for data extraction and quality assessment. The reasons for exclusion of all studies that were not included at

* Stata Statistical Software, Release 14, College Station, TX.

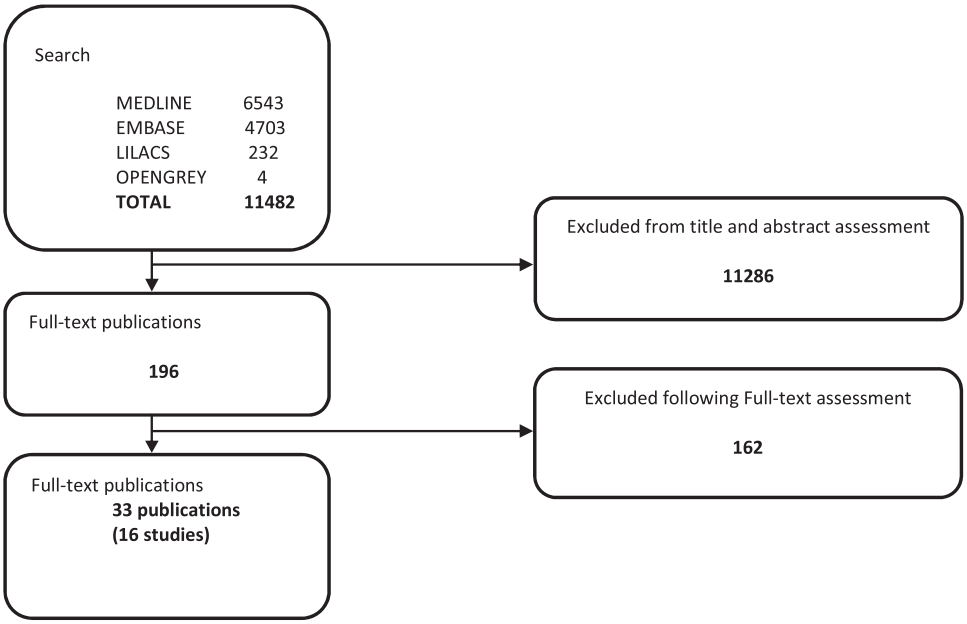

FIGURE 1 Flow chart of inclusion of studies

the stage of full-text review were recorded (see Appendix 3 in online *Journal of Periodontology*).

Study characteristics

Location

The following study geographic locations (supplementary Table 1 in online *Journal of Periodontology*) were found; two studies from Brazil,[21,22] two from China,[23–28] one from Germany,[29,30] one from Indonesia,[31,32] one from Japan,[33,34] one from New Zealand,[35] one from Norway and Sri Lanka,[36–41] and seven from the United States.[42–54]

Sample characteristics

Eight studies were epidemiologic samples,[21,23–29,33,34,45,46,49,51,55] one was a birth cohort,[35] one was a community cohort,[31,32] two were specialist periodontal clinic or practice patients,[43,44] and the status of four was unclear.[22,36,42,53,54]

The age groups of included participants varied. Five studies reported data on only participants <50 years,[23,24,31,32,35–41,43] three studies reported only ≥50 years of age,[33,34,42] seven studies included a wide age range,[21,22,25–30,44–52,55] and one study was unclear.[53,54]

Both male and female participants were included in 11 studies,[21,23–35,43–52,55] women only in two studies,[22,42] men only in one study, [36–41] and unclear in one study.[53,54]

Study duration/follow-up was ≤5 years in nine studies,[21–24,33,34,42–45,47–52] 6 to 10 years in four studies,[25–30,35–41,55] and >10 years in three studies.[31,32,46,53,54]

The completeness of follow-up of the initial sample was at least 80% in two studies,[23,24,35] 50% to 79% in five studies,[25–34,42,55] below 50% in four studies,[21,36–41,47–54] and unclear in five studies.[22,43–46]

Generally, participants of the population studies included both those with and without periodontitis as would be a normal population finding. The proportion of each within the study was not stated in most publications. Periodontitis was an inclusion criterion for two studies,[43,44] and one excluded "severe" periodontitis.[45]

CAL was measured by manual probing in most studies. Controlled force probes were employed fully or for the PD component alone in four studies.[31–34,42,45] Bone level was assessed on dental radiographs using linear measurement in both included studies.[42,45]

Risk of bias and methodologic quality

Based on the Newcastle-Ottawa Scale (Table 1), seven publications were rated 6 or 7 stars, eight were rated 4 or 5 stars, and one was at 3 stars of a maximum of 7. Security of measurement of the primary outcome, attachment level change, was graded as secure for 14 of 16 studies and insecure for the remaining two. In relation to bone level measurement of the two studies, one was assessed as secure and the other insecure.

Mean annual attachment level change

Random-effects meta-analysis of nine studies with 13 data sets showed a mean annual attachment loss (Table 2) of 0.10 mm (95% CI 0.068, 0.132) with considerable heterogeneity (I^2 = 99%) (Figure 2). When considering interproximal sites only, mean annual attachment loss was very

TABLE 1 Risk of bias (Newcastle-Ottawa Scale [NOS]) and methodologic quality of included studies

	Selection			Comparability	Outcome				
Study (ID)	**Representativeness of exposed cohort**	**Ascertainment of exposure**	**Demonstration that outcome of interest was not present at start of study**	**Comparability of cohorts on basis of design or analysis**	**Assessment of outcome**	**Adequacy of follow-up of cohorts**	**NOS total stars, maximum = 7**	**Security of measurement of attachment level**	**Security of measurement of bone level change**
Cheng-de China Suda et al. 2000 (23) Pei et al. 2015 (24)	1*	1*	1*	1*	1*	4	5	Secure	n/a
Dunedin, New Zealand Thomson et al. 2013 (35)	1*	1*	1*	1*2*	1*	2*	7	Secure	n/a
Gusheng village, China Baelum et al. 1997 (25) Dahlen et al. 1995 (26)	1*	1*	1*	3	1*	2*	5	Secure	n/a
Java, Indonesia Timmerman et al. 2000 (31) Van der Velden et al. 2006 (32)	2*	1*	1*	2*	1*	2*	7	Secure	n/a
Niigata, Japan Hirotomi et al. 2002, 2010 (33, 34)	1*	1*	1*	1*2*	1*	2	6	Secure	n/a
Buffalo, NY OsteoPerio, LaMonte 2013 (42)	3	1*	1*	1*2*	1*	2	5	Secure	Secure
Piedmont, USA Brown et al. 1994 (51) Beck et al. 1997 (49) (unpublished data)	1*	1*	1*	1*2*	1*	2*	7	Secure	n/a

(Continues)

TABLE 1 (Continued)

Study (ID)	Selection			Comparability	Outcome				
	Representativeness of exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on basis of design or analysis	Assessment of outcome	Adequacy of follow-up of cohorts	NOS total stars, maximum = 7	Security of measurement of attachment level	Security of measurement of bone level change
Porto Alegre, Brazil Haas et al. 2012 (21)	1*	1*2*	1*	n/a	1*	2*	6	Secure	n/a
Norway Loe et al. 1978 (38)	2*	1*	1*	n/a	1*	3	4	Secure	n/a
West Pomerania, NE Germany SHIP Gatke et al. 2012 (29) Kocher et al. 2016 (30) (unpublished)	1*	1*	1*	1*2*	1*	2*	7	Secure	n/a
Tecumseh, MI Ismail et al. 1990 (54)	1*	1*	1*	3	1*	3	4	Secure	n/a
Virginia Commonwealth University, VA Gunsolley et al. 1995 (43)	3	1*	1*	3	1*	4	3	Secure	n/a
Single publication studies									
Reno, NV Harris 2003 (44)	3	1*	1*	2*	1*	1*	5	Insecure	n/a
Erie County, USA Machtei et al. 1999 (45)	2*	1*	1*	1*2*	1*	3	6	Secure	Insecure
Sao Luis, Brazil Pereira et al. 2015 (22)	3	1*	1*	2*	1*	3	4	Secure	n/a
Baltimore, MD Ship et al. 1996 (46)	3	4	4	1*2*	1*	1*	4	Insecure	n/a

*represents star(s) awarded in rating systems.

TABLE 2 Summary table of meta-analyses: mean annual attachment level change

Analysis	Mean annual attachment level change (mm)	95% CI	Number of data sets	I^2%
General population, including both full-mouth and partial-mouth recording	0.100	0.068, 0.13	13	99
Only interproximal sites	0.093	0.022, 0.16	6	99
Only periodontitis	0.57	−0.38, 1.51	5	99
Postmenopausal women	0.052	−0.084, 0.19	2	89
Subgroup analyses				
Effect of geographic location				
North America and Europe	0.056	0.025, 0.087	8	99
Sri Lanka and China only	0.20	0.15, 0.26	5	82
Difference between North America/Europe and Sri Lanka/China, P <0.001				
Effect of gender				
Males only	0.067	0.023, 0.11	2	50
Females only	0.070	0.064, 0.076	2	0
Difference between males and females, $P = 0.893$				
Effect of age				
Age <30 years	0.12	0.068, 0.16	8	99
Age 30–50 years	0.074	0.052, 0.096	5	95
Age >50 years	0.13	0.072, 0.19	4	98
Difference between age groups, $P = 0.093$				

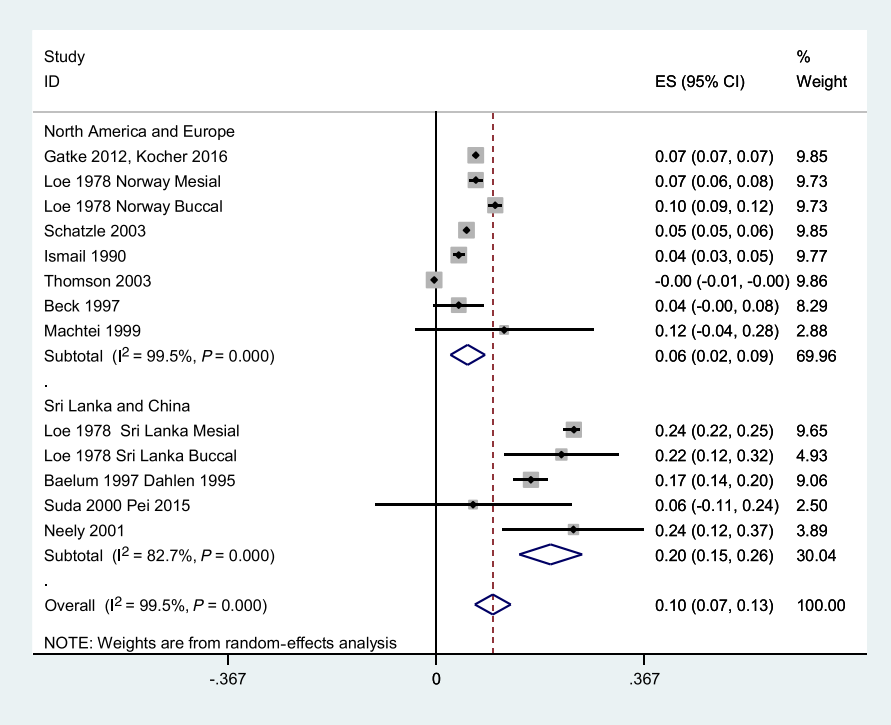

FIGURE 2 Random effects of meta-analysis: Mean annual attachment level change

similar to the estimate for all sites, 0.093 mm (95% CI 0.022, 0.16; $I^2 = 99\%$) (Figure 3). The estimate for the four studies reporting data only for periodontitis was considerably higher at 0.57 mm, although with very wide uncertainty (95% CI -0.38, 1.51) and high heterogeneity ($I^2 = 99\%$) (Figure 4). The combined estimate for the two studies reporting data for postmenopausal women was 0.052 mm (95% CI -0.084, 0.19; $I^2 = 90\%$) (Figure 5). The small values of <1 mm change are of course not measurable but represent the effect of calculating mean change.

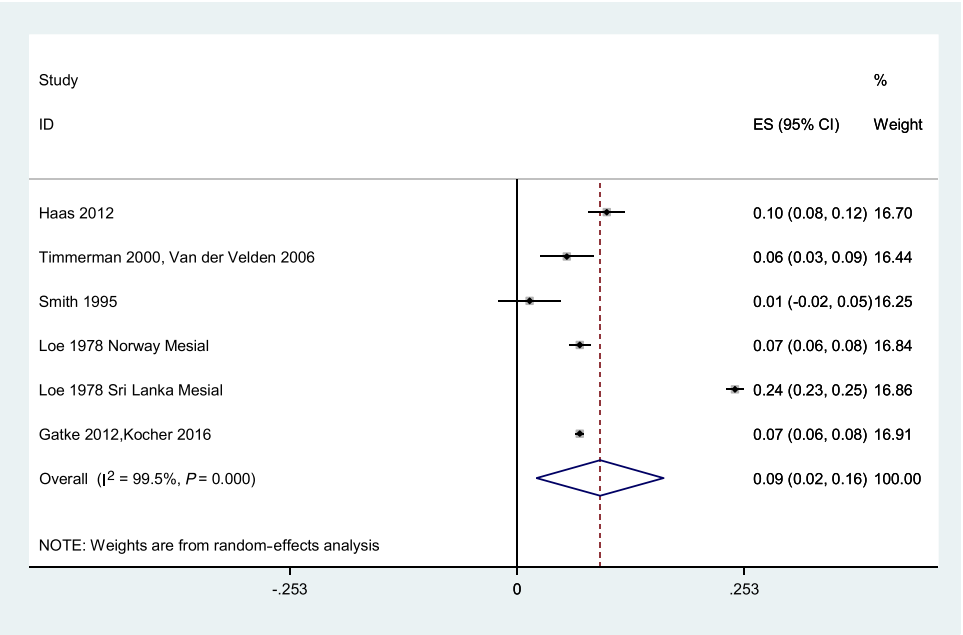

FIGURE 3 Random effects of meta-analysis: Mean annual attachment level change, interproximal sites only

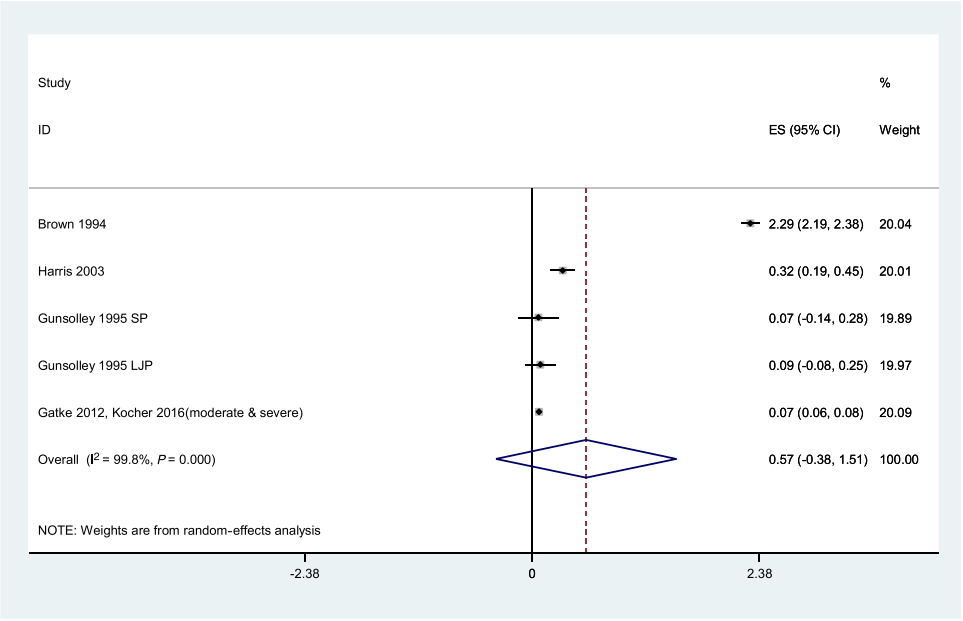

FIGURE 4 Random effects of meta-analysis: Mean annual attachment level change, periodontitis only

Exploration of subgroups

Geographic location was associated with statistically significantly greater mean annual attachment loss for Sri Lanka and China (0.20 mm, 95% CI 0.15, 0.27; $I^2 = 83\%$) vs North America and Europe (0.056 mm, 95% CI 0.025, 0.087; $I^2 = 99\%$) P<0.001 (Table 2, Figure 2). There was no evidence of a difference for gender; males had 0.067 mm (95% CI 0.023, 0.11; $I^2 = 51\%$), females averaged 0.070 mm (95% CI 0.064, 0.076; $I^2 = 0.0\%$) $P = 0.89$ (Figure 6). Similarly, differences between age groups were not statistically significant; age <30 years had 0.16 mm (95% CI 0.068,0.16; $I^2 = 99\%$), age 30 to 50 years 0.074 mm (95% CI 0.052,0.096; $I^2 = 96\%$), and age >50 years 0.13 mm (95% CI, 0.072, 0.19; $I^2 = 99\%$) $P = 0.093$ (Figure 7).

For single studies where meta-analysis was not possible, additional observations were found. Overall mean annual attachment level change was greater for those with at least one site showing CAL loss of at least 3 mm compared with all participants combined (those initially 26 years old, 0.05 mm loss vs 0.02 mm gain; initially 32 years old, 0.12 mm vs

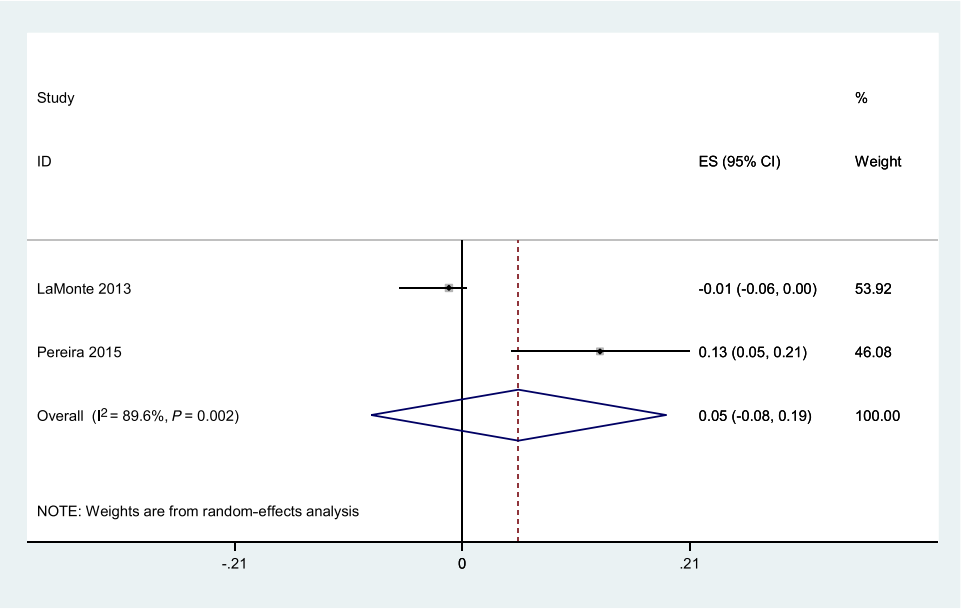

FIGURE 5 Random effects of meta-analysis: Mean annual attachment level change, postmenopausal women only

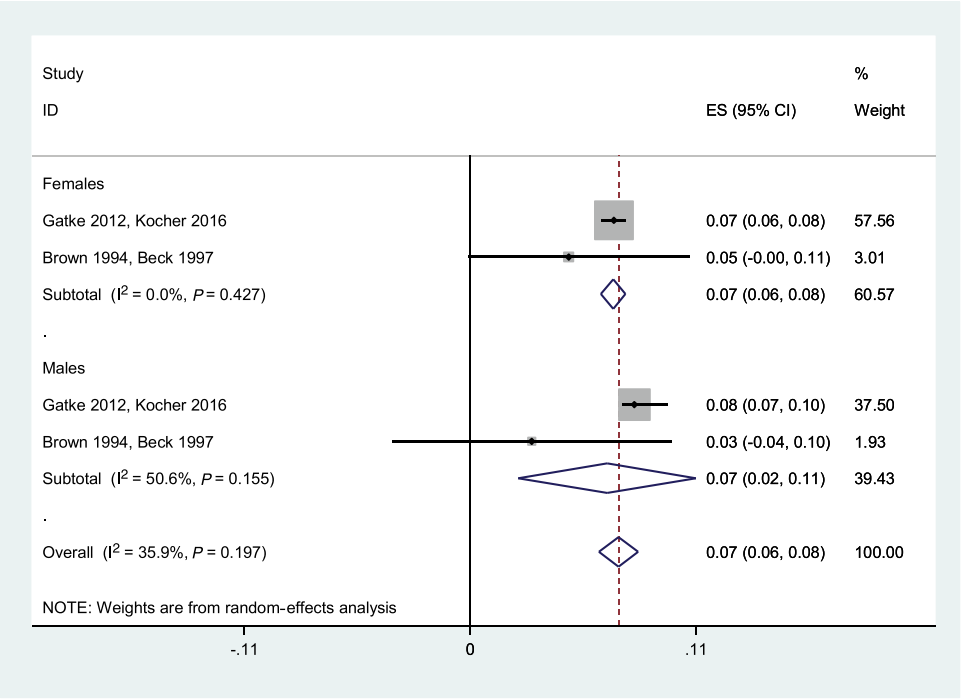

FIGURE 6 Random effects of meta-analysis: Mean annual attachment level change, subgroup analysis, effect of gender

0.03 mm).[35] Selecting the 30 participants with greatest change vs the 30 people with the least change in a rural Chinese population found change of 0.14 mm compared with 0.12mm.[55]

Overall, ethnicity was associated with higher mean annual attachment loss in black (0.074 mm) than white participants (0.006 mm) in one study.[50,51] For presumed periodontitis-only data (sites which lost at least 3 mm attachment), there was little effect of gender, ethnicity, age, or education.[51] In another study, older age, being male, non-white, or from a low socio-economic background was statistically significantly associated with greater attachment loss.[21] Age, calculus, gingival index but not smoking or plaque levels were statistically significantly associated with greater mean annual attachment loss in a secondary analysis of data from Sri Lanka.[40] Elsewhere, younger age (20 to 29 years), being male, current smokers vs never smokers, <10 years school education, and existing diabetes were all statistically significantly associated with greater attachment level change.[29,30]

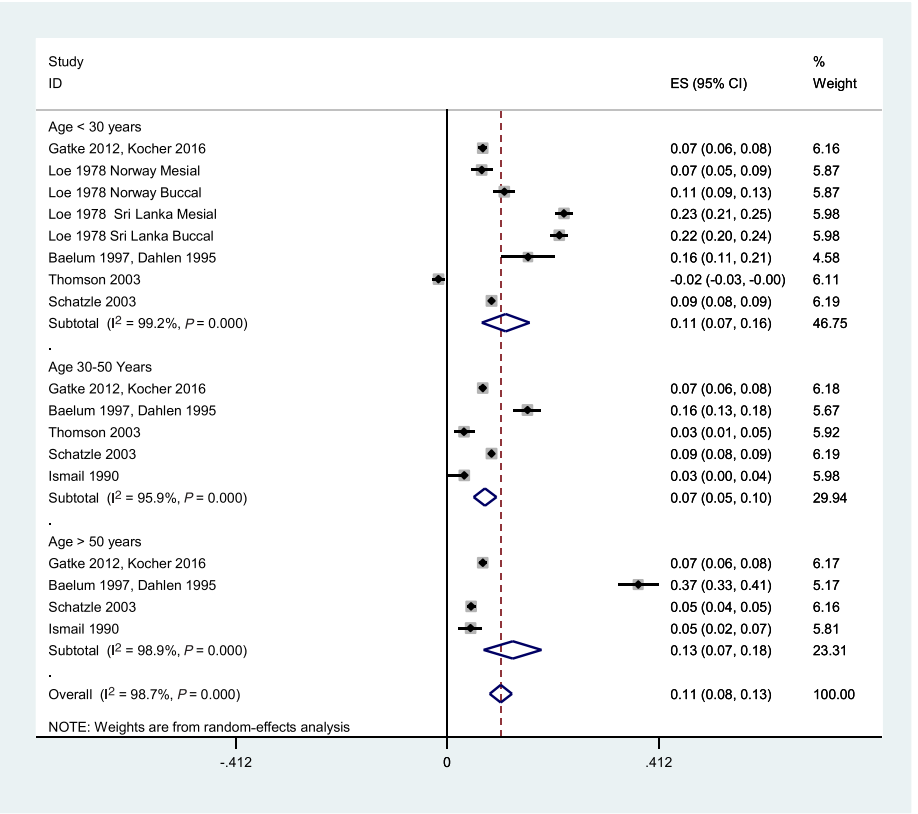

FIGURE 7 Random effects of meta-analysis: Mean annual attachment level change, subgroup analysis, effect of age

Distribution of highest and lowest mean annual attachment level change

Lowest and highest quintiles (i.e., the 20th and 80th percentiles) were calculated for each study from the mean and standard deviation assuming that the data were normally distributed in each case (Table 3, Figure 8). Caution should be exercised when interpreting these results due to the assumption of normality and also in consideration of their high between-study variability when the quintiles were combined to provide an overall estimate. However, the data overall show much different mean annual attachment level change for the lowest quintile (-0.23 mm, i.e., gain) versus highest (0.45 mm loss) (Table 3). Values were similar for interproximal sites alone; lowest quintile -0.048 mm, highest quintile 0.23 mm. The respective values were higher for the studies reporting on periodontitis alone; lowest quintile 0.22 mm, highest quintile 0.91 mm).

Mean annual tooth loss

Meta-analysis of included studies showed overall mean annual tooth loss was 0.20 (95% CI 0.13, 0.26, $I^2 = 91\%$) (Table 4, Figure 9). There was no evidence of a difference comparing the geographic groupings of North America, Europe, Japan, and Oceania; mean annual tooth loss 0.21 (95% CI 0.10, 0.33; $I^2 = 94\%$) vs South America and Asia mean annual tooth loss 0.19 (95% CI 0.11, 0.28; $I^2 = 83\%$) $P = 0.80$

The data from single studies where meta-analysis was not possible showed little difference in mean annual tooth loss between males (0.17) and females (0.13) in one study.[29,30] Small differences in mean annual tooth loss with age were also reported in a Brazilian population: age <30 years (0.02) vs age ≥50 years, 0.03.[21] Elsewhere, annual tooth loss increased with advancing age: age <30 years: 0.04 (95% CI 0.027, 0.053), 30 to 50 years: 0.13 (95% CI 0.16, 0.15), and >50 years: 0.23 (95% CI 0.21, 0.25). Similarly, annual tooth loss was more than twice the magnitude comparing severe periodontitis 0.38 (95% CI 0.34, 0.42) vs moderate periodontitis 0.17 (95% CI 0.15, 0.19).[30] In a rural Chinese population, comparing the 30 participants with the worst attachment loss at 10 years vs 30 people with the least attachment loss, annual tooth loss was 0.53 vs 0.18.[5] In another study, comparison of those with progressing disease (>one site with attachment loss of >2 mm) with non-progressing disease (all others) showed the same annual tooth loss of 0.07.[31]

Mean annual bone level change

Only two included studies also reported on bone level (Table 5). These were not comparable (general population

TABLE 3 Quintiles of mean annual attachment level change

Study	SD (mm)	N	Mean annual attachment level change (mm)	1st quintile (mm)	2nd quintile (mm)	3rd quintile (mm)	4th quintile (mm)
Kocher et al. 2016	0.09	1,892	0.07	−0.0058	0.047	0.093	0.15
Loe et al. 1978 Norway Mesial	0.077	167	0.07	0.0048	0.050	0.089	0.14
Loe et al. 1978 Norway Buccal	0.092	167	0.10	0.027	0.081	0.13	0.18
Loe et al. 1978 Sri Lanka Mesial	0.071	196	0.24	0.18	0.22	0.26	0.30
Loe et al. 1978 Sri Lanka Buccal	0.071	196	0.22	0.16	0.20	0.24	0.28
Schatzle et al. 2003	0.068	1,557	0.054	−0.0036	0.037	0.071	0.11
Neely et al. 2001	0.67	114	0.24	−0.32	0.072	0.41	0.81
Ismail et al. 1990	0.066	165	0.04	−0.016	0.023	0.057	0.096
Baelum et al. 1997, Dahlen et al. 1995	0.28	323	0.17	−0.067	0.097	0.24	0.40
Thomson et al. 2003	0.033	831	−0.0034	−0.031	−0.012	0.0049	0.024
Beck et al. 1997	0.39	292	0.04	−0.28	−0.058	0.14	0.36
Suda et al. 2000, Pei et al. 2015	1.79	413	0.065	−1.44	−0.39	0.52	1.57
Machtei et al. 1991	1.63	415	0.12	−1.25	−0.29	0.53	1.49
Overall mean				−0.23			0.45
Postmenopausal women							
LaMonte 2013, Osteoperio Buffalo	0.26	995	−0.012	−0.23	−0.078	0.054	0.21
Pereira 2015	0.15	15	0.13	0.0018	0.089	0.17	0.25
Overall mean				−0.11			0.23
Interproximal sites only							
Haas et al. 2012	0.26	697	0.1	−0.12	0.033	0.17	0.32
Timmerman et al. 2000, Van der Velden et al. 2006	0.19	155	0.056	−0.10	0.0086	0.10	0.21
Smith et al. 1995	0.29	264	0.014	−0.23	−0.059	0.088	0.26
Loe et al. 1978 Norway Mesial	0.077	167	0.07	0.0048	0.050	0.089	0.14
Loe et al. 1978 Sri Lanka Mesial	0.071	196	0.24	0.18	0.22	0.26	0.30
Kocher et al. 2016 (SHIP)	0.11	1,872	0.07	−0.023	0.042	0.099	0.16
Overall mean				−0.048			0.23
Periodontitis only							
Brown et al. 1994	0.79	260	2.3	1.62	2.09	2.48	2.95
Harris 2003	0.34	30	0.32	0.034	0.23	0.41	0.61
Gunsolley et al. 1995 SP	0.45	20	0.066	−0.31	−0.048	0.18	0.44
Gunsolley et al. 1995 LJP	0.36	21	0.086	−0.21	−0.0044	0.18	0.39
Kocher et al. 2016 (moderate and severe disease)	0.1	932	0.07	−0.014	0.044	0.095	0.15
Overall mean				0.22			0.91

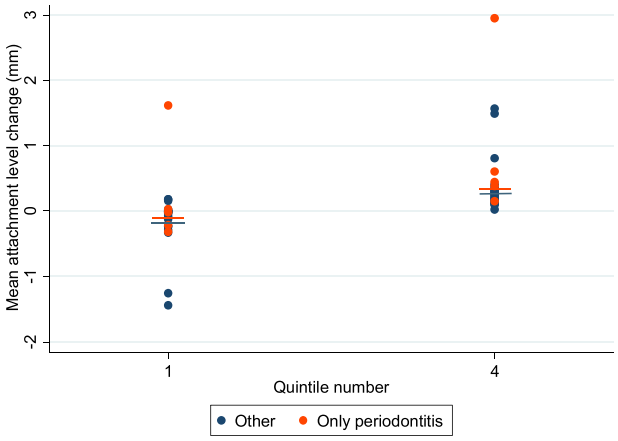

FIGURE 8 Distribution (with means) of highest and lowest quintiles, mean annual attachment level change (mm)

study[45] vs post-menopausal women[42]) and therefore meta-analysis was not performed. Annual bone level loss was low with similar values in both studies 0.04 mm[5] and 0.038 mm.[42]

DISCUSSION

Key findings

Overall, in a general population including both people with and without periodontitis, mean annual attachment loss was 0.1 mm per year, and mean annual tooth loss was 0.2 teeth per year. Observational analysis of highest and lowest mean attachment change quintiles suggests substantial differences between groups with minimal annual change in the lowest quintile and a substantial average deterioration of 0.45 mm mean attachment loss per year in the highest group. This value increased to 0.6 mm per year with periodontitis alone. There was surprisingly little effect of age or gender on attachment level change. Geographic location, however, was associated with more than three times higher mean annual attachment loss in countries with developing economies (0.2 mm) compared with developed economies (0.06 mm, P <0.001).

At a first glance these low values may seem remarkable, but it has to be considered that very few sites in a subject progress beyond a 3 mm threshold of attachment level change. Thus, most sites have no or little progression with time, which may be within the range of periodontal measurement error. Furthermore, these mean values are further influenced by the observation that the periodontal attachment level change may also decrease.[29,35,50,51] To what extent remission measurements reflect biologic changes or measurement error is open to debate, but they have a big influence on these mean values.

Overall completeness and applicability of the evidence

The limited number of studies that were eligible to be included in this review might seem surprising considering the long and distinguished history of periodontal epidemiology. However, most prior studies have been either cross-sectional in design or have used relatively short follow-up periods of <1 year. The review focused on studies that could contribute to an investigation of attachment level change during a period of at least 12 months and this, in part, accounts for the limited number of eligible studies. Retrospective studies were excluded on the basis that the design of a prospective study was more likely to be robust since it was designed a priori to address the research question. The same could not be said of retrospective studies. Subject-based mean attachment level change was our primary outcome and is justified in terms of its fundamental importance to epidemiology and disease classification. Nevertheless, within the included studies, a total of 8,607 participants contributed to follow-up data. Other studies presented data in different formats such as numbers of sites (overall or per participant) with different thresholds of attachment level change. They were not included for two reasons; first, there was substantial heterogeneity in the definition of what constituted a progressing site, making statistical combination in meta-analysis not possible or highly selective. Second, the number of progressing sites would be less informative to the review aims because they depend on the number of teeth present and do not include remission. The completeness of data in this review on bone level change and tooth loss is even less as, a priori, it was planned only to include these data if presented in studies also reporting the primary outcome of attachment level change. The reason for this approach was that to include all studies on bone and tooth loss would have required additional searches resulting in a substantially increased workload for all stages of the review. It was not possible to embark on this within the available time scale. A further limitation was the difficulty in assessing the evidence for

TABLE 4 Summary of meta-analyses: mean annual tooth loss

Analysis	Mean annual tooth loss	95% CI	Number of data sets	I^2%
General population. studies	0.20	0.13, 0.26	10	91
Subgroup analyses				
North America, Europe, Japan, Oceania	0.21	0.10, 0.33	6	94
South America and Asia	0.19	0.11, 0.28	4	82
Difference between groups $P = 0.80$				

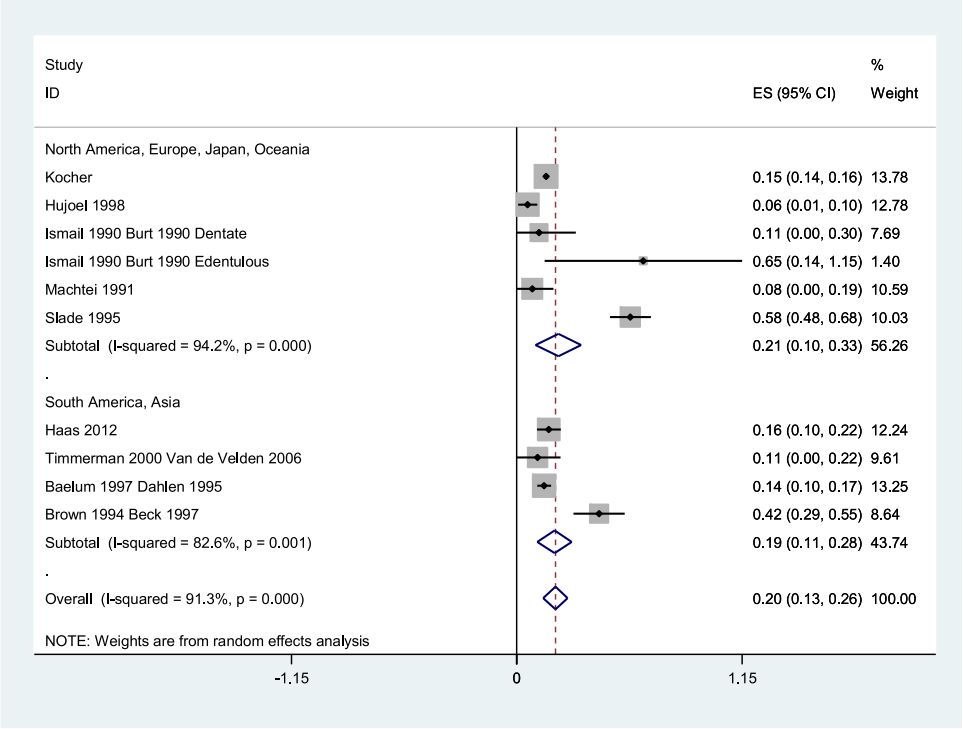

FIGURE 9 Random effects meta-analysis: Mean annual tooth loss

TABLE 5 Mean annual bone level change (mm): single studies (no meta-analysis)

Study	n	SD	Mean	95% CI LL	95% CI UL
General population excluding severe periodontitis					
Machtei et al. 1999	415	.002[a]	.04	.04	.04
Postmenopausal women					
LaMonte et al. 2013	1025	.219	.038	.025	.051

[a]SE given as 0.00, taken as 0.0001.
LL, lower limit; UL, upper limit.

the second and third objectives, i.e., risk factors and etiologic factors. The data were analyzed as far as they allowed, but were prevented from more investigation typically by a lack of reporting or of reporting in formats that could not be combined.

Aspects of the included studies that favor applicability of the evidence are the number of large population-based surveys in both developing and developed economies, with a spread of included ages. Challenges to applicability are mainly presented by the lack of consistency as discussed below.

Overall quality, strength, and consistency of the evidence

The Newcastle-Ottawa Scale demonstrated that 11 of 16 studies received at least 5 stars of a possible 7, indicating reasonably low levels of risk of bias. Furthermore, only two studies showed an insecure method of measurement of attachment level,[44,46] and one an insecure method of bone level.[45]

The consistency of evidence is much more problematic. While the total number of included participants, 8,607, might appear to be a substantial number, the high statistical heterogeneity and the major differences in study design are troubling to the development of an overview of the data. Key differences in methodology include sampling frames (random or convenience population-based samples, patient populations, birth cohorts, practice samples), included ages (some studies only <50 years and others only ≥50 years), men- or women-only studies, study duration (from 2 to 28 years), full-mouth and partial-mouth recording and inclusion of only teeth present at both baseline and follow-up vs all teeth at baseline whether lost at follow-up. Remaining teeth in a mouth may represent "healthy survivor" teeth because those extracted tend to be more periodontally affected.[56] Thus, the loss of teeth due to progression of periodontitis could result in underestimation of attachment level change.[16] While some studies have shown a clear effect of this phenomenon,[49] others have reported little or no differences when modelling the analysis in different ways.[42]

The included studies might also represent the effect of period/cohort effects such as the differences between the two Chinese samples, which were recruited approximately a decade apart. The Gusheng population had a mean annual attachment loss (0.17 mm/year) almost three times that of the Cheng-de cohort (0.065 mm/year). The first cohort resembles much more that of a low-income country such as the Sri Lanka cohort from 1978, and oral health may be influenced by malnutrition and low level of personal hygiene, whereas attachment progression of the Cheng-de cohort is comparable to the European and United States cohorts. The Cheng-de cohort might reflect the dynamic change of Chinese economy, where for example malnutrition, hygiene, access to medical care, etc. have progressed. To what extent period and cohort effects influence these values cannot be explained with the available data.

The statistical heterogeneity in particular suggests that there are important differences in outcomes between studies that could not be explained. Consequently, the overall estimates from the meta-analyses, despite representing best-available evidence, should be used with caution and likely represent a low strength of evidence.

Tooth loss data are especially challenging to interpret. Tooth loss, if not exfoliation, could be due to many reasons, including but not limited to severe periodontitis. Tooth extraction will be influenced by availability of dental professionals, existing disease (including periodontitis, caries, and endodontic disease), patient preferences, financial considerations related to affordability of the treatment, professional practices, and cultural norms.[57,58] This might help to explain the lack of difference in annual tooth loss comparing studies conducted in North America, Europe, Japan, and Oceania (potentially higher economic development) with South America and Asia (lower economic development) although the heterogeneity within these two strata was very high. Only limited information was available in the reported studies to tease out if tooth loss was determined by periodontal status because tooth loss was not reported according to periodontal severity or progression. In the SHIP and Gusheng cohorts, tooth loss was much more pronounced in subjects with periodontitis in comparison with healthy subjects, whereas no such relation was found in the Java cohort. In the United States and Germany, chronic periodontitis is closely related to tooth loss in persons aged ≥40 years.[59,60]

Additional approaches to assessing progression of periodontal diseases, such as quantitative assessment of bone height and density, show promise[61] and would have been included if data had been presented in the included studies. These techniques have limited relevance to population epidemiology but could be valuable in small, more controlled institution-based studies. Interestingly, radiographic assessments did not form part of the common data set recently recommended for periodontal epidemiology.[62]

Potential biases in the review process

In order to minimize the risk of bias in the review process, the review protocol was registered a priori CRD42016035581 (www.crd.york.ac.uk/PROSPERO). Screening, eligibility decisions, and data abstraction were carried out in duplicate and independently. The search was also designed to minimize bias, including development of a highly sensitive electronic search strategy of multiple databases, no language restrictions, and searching for grey literature. Sources of potential biases were changes to the protocol during the review process. Two post hoc analyses were included based on the data collected. These were subgrouped by geographic location and estimation of quintiles of attachment level change. Since both were treated as purely exploratory, the level of bias introduced would seem to be low.

Agreements and disagreements with other reviews

To our knowledge, there has been no systematic review of this topic. Progression of periodontitis has been considered in previous comprehensive narrative reviews.[16,63,64] These reviews report values of mean annual attachment level change ranging from 0.04 to 1.04 mm. The findings from the current systematic review are consistent with the values, although the narrative reviews included fewer studies.

Implications for practice and policy

Within the limitations of the research, the data show that mean annual attachment level change varies considerably both within and between populations. This finding has important implications both for classifying periodontal diseases and for the management of periodontal health.

In relation to classification, mean annual attachment level change was a challenging concept in the 1999 Workshop on Disease Classification.[9] However, rapid attachment level loss was considered a key characteristic of aggressive periodontitis,[65] whereas chronic periodontitis showed slow to moderate progression but could demonstrate periods of rapid progression.[66] Therefore, while it was accepted that the use of progression thresholds was problematic to defining different types of disease, the final classification incorporated such elements. Previous workshops have also struggled with such issues and accepted the substantial variability of presentation of periodontitis, including progression of attachment level change.[11,67] Furthermore, severity of attachment loss at initial assessment (and by implication annual attachment loss at that point) can be a poor predictor of trajectory.[11,68] A recent review of aggressive periodontitis highlighted the variability in mean annual attachment level progression, although the values cited are

within those found in the present systematic review. Despite the variability, one of the distinctive criteria recommended for case definition was "relatively high progression rate of periodontal tissues loss".[69] The operationalization of such a characteristic is unclear. Also, the data in the incorporated studies represent "progression" of disease based on mean values of all sites and do not inform the behavior or biologic mechanisms of attachment level change at individual sites. This is a significant limitation of the current research base.

The 2015 Task Force Update to the 1999 classification enlarged on this issue.[10] In relation to chronic periodontitis, they acknowledged a spectrum of annual attachment level change, including a slow, continuous pattern of disease progression, bursts of periodontal destruction around certain teeth in relatively short periods (random burst pattern), and many bursts of destructive periodontal disease activity at a high frequency during certain periods (multiple burst pattern). Age of onset (detection) was recommended as the general guideline to distinguish aggressive from chronic periodontitis and not annual attachment level change, although this could provide supportive evidence. Overall, the results of this new systematic review do not support or refute the continuing differentiation between forms of periodontal diseases based upon progression of attachment level change.

Prevention of periodontitis includes both prevention of gingivitis or if already established, treatment of gingivitis.[1] This review has not sought to ask whether preventive outcomes are different across people who will go on to follow low or high trajectories of mean annual attachment loss. Since it is not currently possible to screen for such tendencies, a universal approach to prevention is indicated rather than attempting to identify individuals at high risk.[70] However, management of periodontal health should also be conceived broadly to include healthy lifestyle promotion and risk factor reduction through the combined engagement of policy makers, health professionals, and empowered individuals[1] and with an understanding of the impact of social inequalities.[71]

Implications for further research

The unexplained high levels of statistical heterogeneity point to a need for future studies to investigate attachment level change. Many population-based studies collect data from six sites per tooth and from all teeth other than third molars. This is recommended as part of developing a standardized data set as proposed for reporting periodontitis prevalence.[62] Standardized statistical analysis will be equally important. Important key limitations of the existing data are the presentation chiefly of the difference in full-mouth mean attachment level between baseline and final evaluations. Even though some studies report little impact on the method of analysis,[42] it is recommended instead data analysis based on the change in attachment level for each site at each time point still present.[29,49,72] This would reduce the tendency to underestimate change from the loss of teeth due to periodontitis. Employing repeated follow-up, perhaps annually, rather than one final assessment after several years might also help to prevent this effect, although this would be impractical for large epidemiologic studies.

However, since many sites will show no or minimal change, calculating a full-mouth mean value will both lose information and not adequately characterize periodontal health. A consensus on more meaningful data presentations is urgently required and could include separate estimation of change for regressing and progressing sites (above an arbitrary threshold of for instance 3 mm) as well as the proportion of sites affected or, if the data are normally distributed, mean values percentile. A percentile-based analysis (on tertiles, quartiles, quintiles, etc.) might help to dissect the within-population variation of periodontal disease as well to understand if there is a link between periodontal health and tooth loss.

Characterizing participants at baseline by diagnosis, i.e., periodontitis and non-periodontitis is challenging. First, gingivitis and periodontitis are increasingly viewed as part of a continuum,[1] and therefore an arbitrary threshold for diagnosis might lack validity. This is highlighted by the high prevalence values of at least mild forms of periodontitis which typically affect almost half of most populations.[6–8] Similar difficulties exist with case definitions for other chronic conditions such as hypertension, diabetes, etc. For these conditions, case definitions are based on natural history/treatment studies, where subjects beyond a certain threshold have different health/treatment outcomes. As an analogy for periodontitis, a starting point might be to look across cohorts to determine whether there are subjects with a certain baseline periodontal status, who go on to lose more attachment and teeth and then define them as periodontally "healthy" or "severe."

In addition to periodontal data, a consensus is required for a standardized data set of potential modifiers of attachment level change including certain oral microbiomes, genetic factors, lifestyle, general health, and socioeconomic measures.[62]

Finally, tooth loss, as a measure of periodontitis progression requires further research. Prevention of tooth loss is arguably the chief objective of prevention and treatment of periodontitis and is implicit in definitions of oral health.[73] Although this parameter would potentially seem to be ideal in terms of being an objective measure and a true endpoint for assessing the impact of periodontal diseases,[74] the many contributors to tooth loss/retention (e.g., patient preference, caries, dental professional treatment planning) complicate the interpretation of the data currently beyond very general observations. Further modelling in both existing data sets and in future research studies might help to unravel the associations between periodontal health and tooth loss.

CONCLUSIONS

Within the many limitations of the data, it is possible to conclude that mean annual attachment level change is highly variable both within and between populations. The differences in magnitude of mean annual change are clinically important, representing progression values potentially commensurate with tooth retention during a lifetime to tooth loss within three decades. Only geographic location or ethnic status, a likely proxy for socioeconomic position (and its associated risk determinants), showed evidence of a statistically significant effect on mean change. Most of the substantial statistical heterogeneity between studies could not be explained from available data. Overall, the evidence does not support or refute the differentiation between forms of periodontal diseases based upon progression of attachment level change in adults ≥18 years of age.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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