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META-ANALYSIS

Smoking increases risk of tooth loss: A meta-analysis of the literature

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Abstract

AIM: To quantitatively evaluate the impact of smoking on tooth loss.

METHODS: We performed a PubMed search to identify published articles that investigated the risk of tooth loss by smoking, from which RRs and their variance with characteristics of each study were extracted. The random-effects models were used to derive a pooled effect across studies. Potential sources of heterogeneity on the characteristics of the study and their influence on the pooled effect size were investigated using meta-regression models.

RESULTS: We identified 24 studies containing a total of 95973 participants for analysis. The pooled RR of ever-smokers compared with never- smokers was 1.73 (95%CI: 1.60-1.86, P < 0.001). In meta-regression analysis, only the mean age of participants alone was identified as a statistically significant source of heterogeneity. The effect of smoking on tooth loss was stronger when the mean age of study participants was higher, indicating possible enhancement of tooth loss due to aging by smoking. RR was significantly lower in former smokers (1.49, 95%CI: 1.32-1.69, P < 0.001) than in current smokers (2.10, 95%CI: 1.87-2.35, P < 0.001), indicating the substantial benefit of smoking cessation for reducing the risk of tooth loss.

CONCLUSION: Smoking is an independent risk factor for tooth loss regardless of many other confounders. Smoking cessation may attenuate this effect.

Key words: Meta-analysis; Oral health; Relative risk; Smoking; Tooth loss

Core tip: Smoking is known to be a major cause of tooth loss. However, it has never been known how it quantitatively attributes to tooth loss or whether smoking cessation counteracts or not. This study clarified that ever smoking increases risk of tooth loss by 73%. In addition, smoking cessation substantially attenuates this effect.

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INTRODUCTION

The World Health Organization Global Oral Health Program works to increase awareness of oral health worldwide as an important component of general health and quality of life[1]. A number of studies have investigated the association between tooth loss and cardiovascular diseases, including stroke, atherosclerosis and hypertension[2-8]. Several reviews outlined a possible role for tooth loss in carcinogenesis, independent of other known risk factors[9,10]. Tooth loss is one of the main impediments to oral health; and by affecting the patient's ability to chew and thus altering food choices and the digestive process, may lead to malnutrition[11,12]. The impact of tooth loss can be even more severe, impairing taste, phonetics, and aesthetics, often resulting in limited social and personal interaction[13,14]. A systematic review provided fairly strong evidence that tooth loss is associated with the impairment of oral health-related quality of life[15].

The etiology of tooth loss is complex, and includes factors such as age; sex; body mass index; physical activity; systemic disease, such as osteoporosis and diabetes; socioeconomic status (SES); and oral hygiene behavior[16-21]. Smoking is considered an important risk factor for tooth loss[16,18,19,22-26]. Although numerous studies have consistently reported a positive association, attempts to quantify the association have been hampered by their variation in background factors, such as country of the study, study design, age of participants, sex, and oral hygiene behavior.

The present study aims to: (1) confirm the association between smoking and tooth loss, and to quantify the impact systematically; (2) to confirm the difference in the impact of smoking on tooth loss between former and current smokers; and (3) to investigate the difference in the impact of smoking on tooth loss by the factors above. To our knowledge, this study is the first meta-analysis to quantify the impact of smoking on tooth loss.

MATERIALS AND METHODS

Search strategy

The initial literature search was conducted through PubMed using the free text search term: (tooth loss OR missing tooth OR oral health OR oral hygiene) AND (smoking OR smoke OR cigarette), with publication period updated to July 2010.

We selected candidate studies based on the following inclusion criteria: original article published in English; and the availability of RRs estimates of smoking for tooth loss in the article, namely hazard ratio, risk ratio, or odds ratio, with the reference group consisting of never smokers, and with adjustment for age at least, and their 95%CIs. Two investigators (FS and MS) independently reviewed all potentially relevant articles, and disagreements were resolved by discussion. The reference lists of the studies identified through this process were also checked.

Data extraction

Characteristics extracted from the articles included name of the first author, year of publication, country of study, study design (cohort or cross-sectional study), base population, sex distribution, number of participants, mean age of study population, measure of association (hazard ratio, risk ratio, or odds ratio), point estimate and its 95%CI of RR, adjustment for SES (yes or no), adjustment for behavior associated with oral health (yes or no), and definition of the number of teeth lost.

Data synthesis

For inclusion in quantitative analysis, studies had to provide sufficient data to allow calculation of an effect-size measure and its corresponding measure of variability. Because we extracted multiple estimates from several studies (*e.g.*, using pack-year units or stratified analysis), we pre-pooled RRs to derive one overall RR for each study using fixed-effects estimates weighted by the inverse of their variance as the RR for ever-smokers relative to never-smokers. All analyses were performed on the natural log scale. Because of the widely different methodological approaches used to examine the relationship in the individual studies, we used the random-effects models of DerSimonian-Laird[27] to derive a pooled effect across studies, in which the between-study variance was estimated in addition to the specified within-variance component. We investigated potential sources of heterogeneity on the characteristics of the study and their influence on the pooled effect size using meta-regression models. We examined heterogeneity using Cochrane's Q-test and the I^2 statistic[28]. I^2 can be interpreted as the proportion of the total variation in the estimated slopes for each study due to heterogeneity between studies. Variables considered as potential sources of heterogeneity were the country in which the study was conducted [United States (reference), Japan, Nordic, and others as dummy variables], study design (cohort or cross-sectional), base population (general population or other), sex included in the study (male, female, or both, as dummy variables), mean age of the study population (continuous), adjustment by SES, adjustment by behavior associated with oral health, and definition of the number of teeth lost (continuous).

Publication bias was assessed by a funnel plot with the fitted line corresponding to the regression test for funnel-plot asymmetry proposed by Egger *et al*[29].

All analyses were conducted using the *metan* and *metareg* commands in STATA ver 10.1 (Stata Corporation, College Station, Texas, USA) and were two-sided. Tests were considered statistically significant when the P value were less than 0.05, except in meta-regression analysis, for which we defined a threshold P value of less than 0.1.

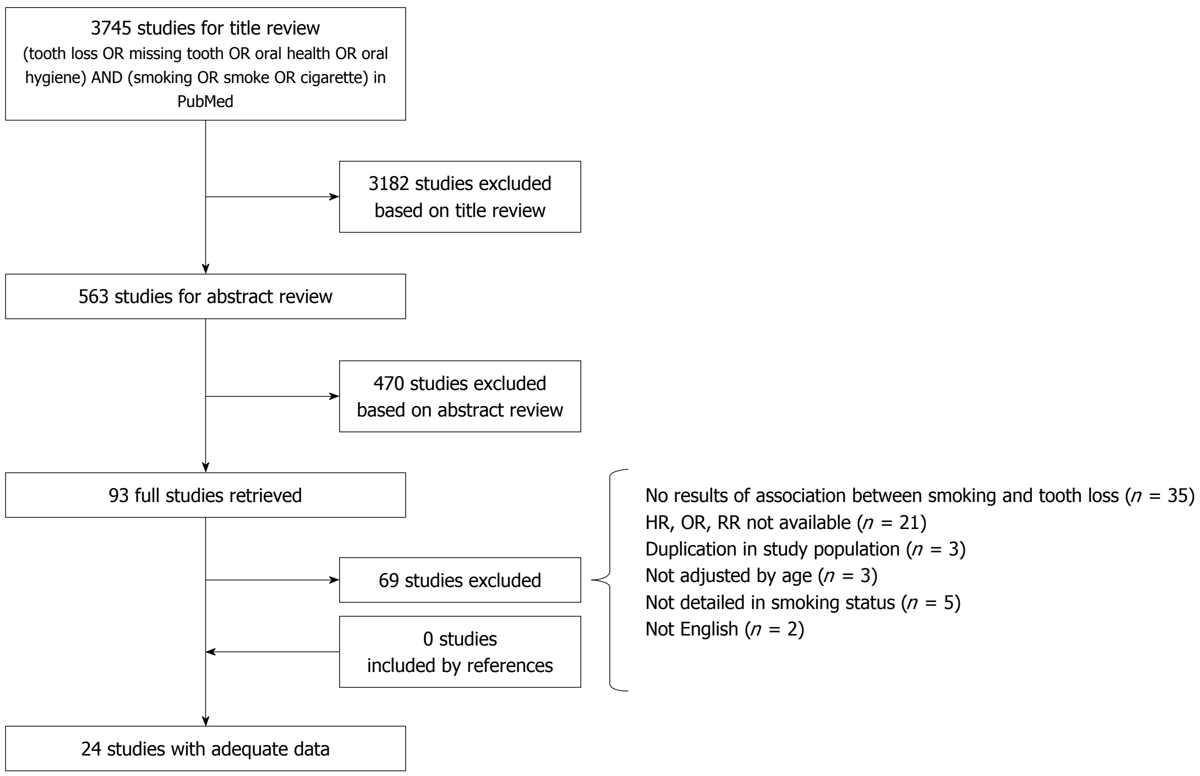


Figure 1 Selection of literature.

RESULTS

Search results

A total of 3745 potentially relevant reports were identified. Of these, 93 full papers were obtained based on title and abstract review (Figure 1), of which 24 with a total of 95973 participants were identified as having sufficient data for inclusion[16-26,30-42].

Table 1 shows the baseline characteristics of participants from each study. By country, seven papers were from the USA, six from Japan, three each from Brazil and Finland, and one each from Sweden, Norway, Germany, Italy, and Australia. Of these, five were cohort studies, with a mean follow-up of 9.4 years; 16 were conducted in general populations; 16 were conducted in both sexes; 15 investigated the risk of tooth loss in current and former *vs* never- smokers; nine investigated the risk of tooth loss in ever- *vs* never-smokers; 15 were adjusted by SES; and 15 were adjusted by behavior associated with oral health. The studies varied in study size (range, 166-8409 for cross-sectional studies, 693-43112 for cohort studies), mean age of the study population (21.5-81.0 years), and definition of the number of teeth lost as a dependent variable. All studies used multivariate analysis to calculate the RR of tooth loss by smoking.

Association between smoking history and risk of tooth loss

Results for the meta-analysis of RRs of tooth loss in ever- *vs* never-smokers are shown in Figure 2. A forest plot of the random-effects model analysis showed that four of the five earliest studies[16-18,30,31] tended to show a higher RR of tooth loss in ever-smokers than those published later. Pooled RR as estimated by the random-effects model was 1.73 (95%CI: 1.60-1.86). Significant heterogeneity was seen between studies, with a P value of < 0.001 and I^2 of 67.4%.

Modifiable factors in smoking history and risk of tooth loss

We used meta-regression analysis to investigate sources of heterogeneity for the relationship between smoking and tooth loss (Table 2). In univariate meta-regression analysis, mean age of the study population (P = 0.009) and definition of the number of teeth lost (P = 0.040) were identified as potential sources of heterogeneity. Figure 3A and B show the results of meta-analyses sorted by mean age of study population and definition of the number of teeth lost. In multivariate meta-regression with significant modifiers detected by these two variables, mean age of the study population remained as the potentially strongest source of heterogeneity (P = 0.030).

Publication bias

We also assessed potential publication bias in selected studies. A funnel plot (Figure 4) shows the distribution of log-transformed RR and standard error in each study, with the fitted line corresponding to the regression test for funnel-plot asymmetry (solid line). Studies with large standard errors with weaker associations seemed less reported; however, the association remained significant even after exclusion of studies with large standard errors greater

Table 1 Baseline characteristics of patients of the 24 included studies

Author (yr)	Country	Study design	Base population	Sex	*n*	Mean age (yr) of subjects	Measure of association	Pattern of comparison (*vs* never smokers)	Relative risk	Adjustment for socioeconomic status	Adjustment for behavior associated with oral health[3]	Definition, No. of tooth loss
Eklund *et al*[16] (1994)	United States	Cohort	General population	M/F	2207	42.0	RR	Ever	1.88 (1.04-3.38)[1]	Yes	Yes	Incidence of tooth loss
Norlén *et al*[18] (1996)	Sweden	Cross-sectional	General population	M	483	68.0	OR	Former	2.60 (1.34-5.03)	Yes	Yes	> 16 loss
								Current	3.02 (1.50-6.07)			
								Ever	2.79 (1.73-4.52)[2]			
Slade *et al*[30] (1997)	Australia	Cohort	General population	M/F	693	73.0	RR	Former	2.55 (1.48-4.40)	No	Yes	Incidence of tooth loss
								Current	2.06 (0.92-4.62)			
								Ever	2.39 (1.52-3.74)[2]			
Suominen-Taipale *et al*[31] (1999)	Finland	Cross-sectional	General population	M/F	213	40.0	OR	Ever	1.4 (1.0-2.0)	Yes	No	28 loss
Xie *et al*[17] (1999)	Finland	Cross-sectional	General population	M/F	293	81.0	OR	Ever	3.12 (1.56-6.23)	No	No	28 loss
Yoshida *et al*[33] (2001)	Japan	Cross-sectional	Petroleum chemical plant employees	M	2015	39.5	OR	Former	1.27 (0.89-1.81)	No	Yes	> 1 loss
								Current	1.54 (1.20-1.96)			
								Ever	1.45 (1.18-1.77)[2]			
Randolph *et al*[32] (2001)	United States	Cross-sectional	General population	M/F	3050	74.1	OR	Former	1.26 (1.04-1.54)	Yes	No	> 14 loss
								Current	1.69 (1.31-2.20)			
								Ever	1.40 (1.20-1.63)[2]			
Ylöstalo *et al*[19] (2004)	Finland	Cross-sectional	General population	M/F	8409	31.0	OR	Ever	1.73 (1.39-2.15)[2]	Yes	Yes	> 6 loss
Cunha-Cruz *et al*[22] (2004)	Brazil	Cross-sectional	University employees	M/F	3840	40.0	OR	Ever	1.62 (1.35-1.96)	Yes	Yes	> 26 loss
Klein *et al*[34] (2004)	United States	Cross-sectional	General population	M/F	2794	65.0	OR	Former	1.57 (1.25-1.98)	Yes	No	> 1 loss
								Current	4.04 (2.52-6.49)			
								Ever	1.88 (1.53-2.31)[2]			
Tanaka *et al*[35] (2005)	Japan	Cross-sectional	Hospital	F	1002	29.8	OR	Former	1.42 (0.91-2.20)	Yes	No	> 1 loss
								Current	1.56 (1.18-2.06)[2]			
								Ever	1.52 (1.20-1.93)[2]			
Susin *et al*[20] (2005)	Brazil	Cross-sectional	General population	M/F	974	48.7	OR	Ever	1.50 (1.18-1.90)[2]	No	No	> 7 loss
Susin *et al*[37] (2006)	Brazil	Cross-sectional	General population	M/F	612	21.5	OR	Ever	1.30 (1.02-1.66)[2]	Yes	No	> 1 loss
Okamoto *et al*[36] (2006)	Japan	Cross-sectional	Hospital	M	1332	43.5	OR	Former	1.11 (0.68-1.85)	No	No	> 1 loss
								Current	1.59 (1.21-2.08)[2]			
								Ever	1.46 (1.15-1.85)[2]			
Krall *et al*[23] (2006)	United States	Cohort	People who received dental care	M	789	49.0	HR	Former	1.3 (0.9-1.7)	Yes	Yes	Incidence of tooth loss
								Current	2.1 (1.5-3.1)			
								Ever	1.7 (1.3-2.2)[2]			
Ojima *et al*[40] (2007)	Japan	Cross-sectional	General population	M/F	1314	30.0	OR					
				Total				Former	0.80 (0.45-1.43)[2]	No	Yes	> 1 loss
								Current	1.91 (1.41-2.59)[2]			
								Ever	1.58 (1.21-2.07)[2]			
				M				Former	1.25 (0.55-2.86)			
								Current	2.21 (1.40-3.50)			
								Ever	1.93 (1.30-2.88)[2]			
				F				Former	0.52 (0.23-1.18)			
								Current	1.70 (1.13-2.55)			
								Ever	1.34 (0.93-1.93)[2]			

Mundt *et al*[24] (2007)	Germany	Cross-sectional	General population	M/F	2501	49.5	OR	Former	1.71 (1.27-2.30)	Yes	Yes	> 26 loss
								Current	2.58 (2.03-3.27)			
								Ever	2.19 (1.82-2.64)[2]			
Dietrich *et al*[25] (2007)	United States	Cohort	Health professional	M	43112	56.0	HR	Former	1.57 (1.53-1.62)[2]	Yes	Yes	Incidence of tooth loss
								Current	2.25 (2.14-2.37)[2]			
								Ever	1.75 (1.69-1.80)[2]			
Hanioka *et al*[38] (2007)	Japan	Cross-sectional	General population	M/F	3999	60.0	OR					
				Total				Former	1.18 (0.87-1.59)	No	Yes	> 20 loss
								Current	2.19 (1.71-2.80)			
								Ever	1.70 (1.40-2.05)[2]			
				M				Former	1.29 (0.92-1.80)			
								Current	2.22 (1.61-3.06)			
								Ever	1.72 (1.36-2.17)[2]			
				F				Former	0.86 (0.46-1.60)			
								Current	2.14 (1.45-3.15)			
								Ever	1.66 (1.19-2.31)[2]			
Musacchio *et al*[39] (2007)	Italy	Cross-sectional	General population	M	1226	76.8	OR	Former	3.42 (2.42-4.82)	Yes	No	28 loss
								Current	4.01 (2.59-6.20)			
								Ever	3.64 (2.77-4.77)[2]			
Haugejorden *et al*[26] (2008)	Norway	Cross-sectional	General population	M/F	1092	47.9	OR	Ever	2.2 (1.3-3.7)	Yes	Yes	> 20 loss
Cunha-Cruz *et al*[41] (2008)	United States	Cohort	People who received dental care	M/F	12631	51.0	RR	Former	1.3 (1.1-1.4)	No	Yes	Incidence of tooth loss
								Current	2.3 (2.0,2.6)			
								Ever	1.8 (1.6-2.0)[2]			
Moedano *et al*[21] (2009)	United States	Cross-sectional	Hospital	M/F	166	69.1	OR	Ever	1.19 (0.49-2.87)	Yes	No	> 10 loss
Yanagisawa *et al*[42] (2010)	Japan	Cross-sectional	General population	M	1088	59.6	OR	Former	1.35 (0.94-1.94)	No	Yes	> 8 loss
								Current	1.67 (1.12-2.50)			
								Ever	1.49 (1.14-1.94)[2]			

[1]Relative risk was calculated from coefficient and standard error; [2]Within-study summary estimate by meta-analysis with fixed effect model; [3]Behaviors associated with oral health include tooth brushing frequencies, existence of periodontal disease at the baseline survey, use of floss, frequency of dental clinic visit and reason for visit and occupation (dentist or not), use of interdental brush, self-check of teeth and gum a using mirror, and experience of tooth brushing instruction. M: Male; F: Female.

than 0.2 (Figure 5). Egger's test also excluded the possibility of publication bias in estimating summary statistics ($P = 0.968$).

Difference in risk of tooth loss between former and current smokers

The potential difference in tooth loss events between former and current smokers was examined by stratified analysis (Figure 6). Nine studies were excluded from analysis because they did not assess the risk in former and current smokers separately. The meta-analysis revealed summary estimates of 1.49 (95%CI: 1.32-1.69) and 2.10 (95%CI: 1.87-2.35) for former and current smokers, respectively, indicating that former smokers have a significantly lower probability of tooth loss than current smokers.

DISCUSSION

This study is the first meta-analysis of the impact of smoking on tooth loss, and includes the difference in impact between former and current smokers. We found an approximately 70% greater risk of tooth loss in ever- than never-smokers. Moreover, we found that former smokers had a statistically significantly lower risk of tooth loss than current smokers, with current smokers showing a 110% increase in risk compared with 49% in former smokers. We also evaluated potential sources of heterogeneity by factors thought

Table 2 Source of heterogeneity by meta-regression analysis

Factors	Univariate			Multivariate		
	Coefficient	SE	*P* value	Coefficient	SE	*P* value
Published year	-0.0063553	0.01429	0.661	-	-	-
Country (*vs* United States)						
Japan	-0.0922341	0.11903	0.447	-	-	-
Finland, Norway, Sweden	0.1485642	0.14826	0.328	-	-	-
Other countries	0.1828302	0.12939	0.173	-	-	-
Study design (cohort *vs* cross-sectional)	0.0667818	0.12342	0.594	-	-	-
Base Population of Study (general population *vs* others)	-0.0761659	0.10297	0.467			
Sex (male *vs* female)						
Male	0.0739773	0.11212	0.517	-	-	-
Female	-0.1176073	0.24732	0.639	-	-	-
Mean age of study population	0.0080805	0.00284	0.009	0.0067276	0.00288	0.030
Adjustment for socioeconomic status (Yes *vs* No)	-0.0723939	0.10375	0.493	-	-	-
Adjustment for behavior associated with oral health (Yes *vs* No)	-0.0054823	0.10733	0.960	-	-	-
Definition number of tooth loss in the study (range: 1-28)	0.0093892	0.00430	0.040	0.0065434	0.00414	0.129

Author	Year of publication	*n*	Mean age (yr) of study population	ES (95%CI)	% Weight
Eklund *et al*[16]	1994	2207	42	1.88 (1.04-3.38)	1.34
Norlén *et al*[18]	1996	500	68	2.79 (1.73-4.52)	1.86
Slade *et al*[30]	1997	693	73	2.38 (1.52-3.74)	2.05
Suominen-Taipale *et al*[31]	1999	213	40	1.40 (1.00-1.96)	3.10
Xie *et al*[17]	1999	293	81	3.12 (1.56-6.24)	1.01
Yoshida *et al*[33]	2001	2015	39.5	1.45 (1.18-1.77)	5.18
Randolph *et al*[32]	2001	3050	74.1	1.40 (1.20-1.63)	6.26
Ylöstalo *et al*[19]	2004	8409	31	1.73 (1.39-2.15)	4.90
Cunha-Cruz *et al*[22]	2004	3840	40	1.62 (1.35-1.94)	5.64
Klein *et al*[34]	2004	2915	65	1.88 (1.53-2.30)	5.17
Tanaka *et al*[35]	2005	1002	29.8	1.52 (1.20-1.93)	4.58
Susin *et al*[20]	2005	974	48.7	1.50 (1.18-1.90)	4.52
Susin *et al*[37]	2006	612	21.5	1.30 (1.02-1.66)	4.45
Okamoto *et al*[36]	2006	1332	43.5	1.46 (1.15-1.85)	4.56
Krall *et al*[23]	2006	789	49	1.69 (1.32-2.16)	4.37
Ojima *et al*[40]	2007	1314	30	1.58 (1.21-2.07)	4.02
Mundt *et al*[24]	2007	2501	49.5	2.19 (1.82-2.64)	5.55
Dietrich *et al*[25]	2007	43112	56	1.75 (1.69-1.80)	8.43
Hanioka *et al*[38]	2007	3999	60	1.70 (1.40-2.05)	5.47
Musacchio *et al*[39]	2007	1226	76.8	3.64 (2.77-4.77)	3.99
Haugejorden *et al*[26]	2008	1092	47.9	2.20 (1.30-3.72)	1.61
Cunha-Cruz *et al*[41]	2008	12631	51	1.82 (1.63-2.02)	7.27
Moedano *et al*[21]	2009	166	69.1	1.19 (0.49-2.89)	0.65
Yanagisawa *et al*[42]	2010	1088	59.6	1.49 (1.14-1.94)	4.03
Overall (I^2 = 67.4%, *P* = 0.000)				1.73 (1.60-1.86)	100.00

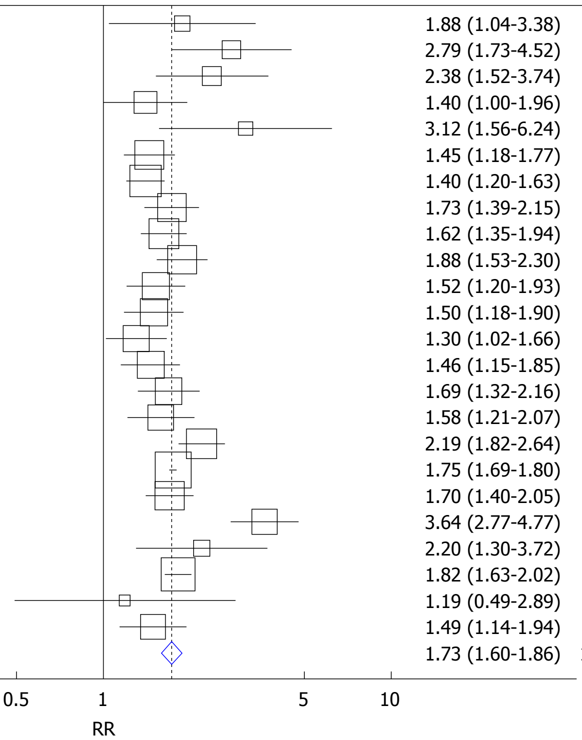


Figure 2 Forest plots of relative risk. The size of the squares corresponds to the weight of the study in the meta-analysis. Combined relative risk was calculated using the random-effects model. Weights are from random effects analysis.

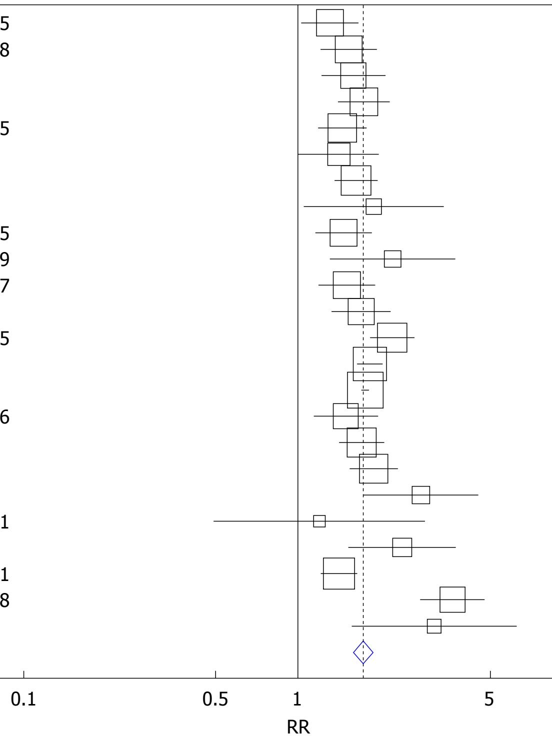
to influence the effect of smoking on tooth loss. Results showed no statistically significant heterogeneity by country (included in the present study), study design, sex, oral health behavior, or SES except age. Although the risk of tooth loss by smoking showed heterogeneity by participant age, RRs of all studies were significantly higher in ever-smokers than in never-smokers, except for one study, which had the smallest number of participants of all studies analyzed[21].

Several mechanisms have been hypothesized to explain the association between smoking and tooth loss. Systemic effects of smoking include dysfunction of gingival fibroblasts, a decrease in microcirculatory function and immune system deficiency *via* effects of chemicals included in tobacco smoke[10,43]. Bacterial organisms in periodontal region are reported to contribute to tissue destruction among smokers[44-46]. These lines of evidences are consistent with findings in this study and are suggestive of importance of implementation of smoking cessation in the dental field[47].

We speculate that several factors might explain why the effect of smoking on tooth loss was modified by age.

A

Author	*n*	Mean age (yr) of study population	ES (95%CI)	% Weight
Susin *et al*[37]	612	21.5	1.30 (1.02-1.66)	4.45
Tanaka *et al*[35]	1002	29.8	1.52 (1.20-1.93)	4.58
Ojima *et al*[40]	1314	30	1.58 (1.21-2.07)	4.02
Ylöstalo *et al*[19]	8409	31	1.73 (1.39-2.15)	4.90
Yoshida *et al*[33]	2015	39.5	1.45 (1.18-1.77)	5.18
Suominen-Taipale *et al*[31]	213	40	1.40 (1.00-1.96)	3.10
Cunha-Cruz *et al*[22]	3840	40	1.62 (1.35-1.94)	5.64
Eklund *et al*[16]	2207	42	1.88 (1.04-3.38)	1.34
Okamoto *et al*[36]	1332	43.5	1.46 (1.15-1.85)	4.56
Haugejorden *et al*[26]	1092	47.9	2.20 (1.30-3.72)	1.61
Susin *et al*[20]	974	48.7	1.50 (1.18-1.90)	4.52
Krall *et al*[23]	789	49	1.69 (1.32-2.16)	4.37
Mundt *et al*[24]	2501	49.5	2.19 (1.82-2.64)	5.55
Cunha-Cruz *et al*[42]	12631	51	1.82 (1.63-2.02)	7.27
Dietrich *et al*[25]	43112	56	1.75 (1.69-1.80)	8.43
Yanagisawa *et al*[42]	1088	59.6	1.49 (1.14-1.94)	4.03
Hanioka *et al*[38]	3999	60	1.70 (1.40-2.05)	5.47
Klein *et al*[34]	2915	65	1.88 (1.53-2.30)	5.17
Norlén *et al*[18]	500	68	2.79 (1.73-4.52)	1.86
Moedano *et al*[21]	166	69.1	1.19 (0.49-2.89)	0.65
Slade *et al*[30]	693	73	2.38 (1.52-3.74)	2.05
Randolph *et al*[32]	3050	74.1	1.40 (1.20-1.63)	6.26
Musacchio *et al*[39]	1226	76.8	3.64 (2.77-4.77)	3.99
Xie *et al*[17]	293	81	3.12 (1.56-6.24)	1.01
Overall (I^2 = 67.4%, P = 0.000)			1.73 (1.60-1.86)	100.00



B

Author	*n*	Mean age (yr) of study population	Definition of No. of tooth loss	ES (95%CI)	% Weight
Susin *et al*[37]	612	21.5	1	1.30 (1.02-1.66)	4.45
Tanaka *et al*[35]	1002	29.8	1	1.52 (1.20-1.93)	4.58
Ojima *et al*[40]	1314	30	1	1.58 (1.21-2.07)	4.02
Yoshida *et al*[33]	2015	39.5	1	1.45 (1.18-1.77)	5.18
Okamoto *et al*[36]	1332	43.5	1	1.46 (1.15-1.85)	4.56
Krall *et al*[23]	789	49	1	1.69 (1.32-2.16)	4.37
Cunha-Cruz *et al*[41]	12631	51	1	1.82 (1.63-2.02)	7.27
Dietrich *et al*[25]	43112	56	1	1.75 (1.69-1.80)	8.43
Klein *et al*[34]	2915	65	1	1.88 (1.53-2.30)	5.17
Slade *et al*[30]	693	73	1	2.38 (1.52-3.74)	2.05
Ylöstalo *et al*[19]	8409	31	6	1.73 (1.39-2.15)	4.90
Susin *et al*[20]	974	48.7	7	1.50 (1.18-1.90)	4.52
Yanagisawa *et al*[42]	1088	59.6	8	1.49 (1.14-1.94)	4.03
Moedano *et al*[21]	166	69.1	10	1.19 (0.49-2.89)	0.65
Randolph *et al*[32]	3050	74.1	14	1.40 (1.20-1.63)	6.26
Norlén *et al*[18]	500	68	16	2.79 (1.73-4.52)	1.86
Haugejorden *et al*[26]	1092	47.9	20	2.20 (1.30-3.72)	1.61
Hanioka *et al*[38]	3999	60	20	1.70 (1.40-2.05)	5.47
Cunha-Cruz *et al*[22]	3840	40	26	1.62 (1.35-1.94)	5.64
Mundt *et al*[24]	2501	49.5	26	2.19 (1.82-2.64)	5.55
Suominen-Taipale *et al*[31]	213	40	28	1.40 (1.00-1.96)	3.10
Eklund *et al*[16]	2207	42	28	1.88 (1.04-3.38)	1.34
Musacchio *et al*[39]	1226	76.8	28	3.64 (2.77-4.77)	3.99
Xie *et al*[17]	293	81	28	3.12 (1.56-6.24)	1.01
Overall (I^2 = 67.4%, P = 0.000)				1.73 (1.60-1.86)	100.00

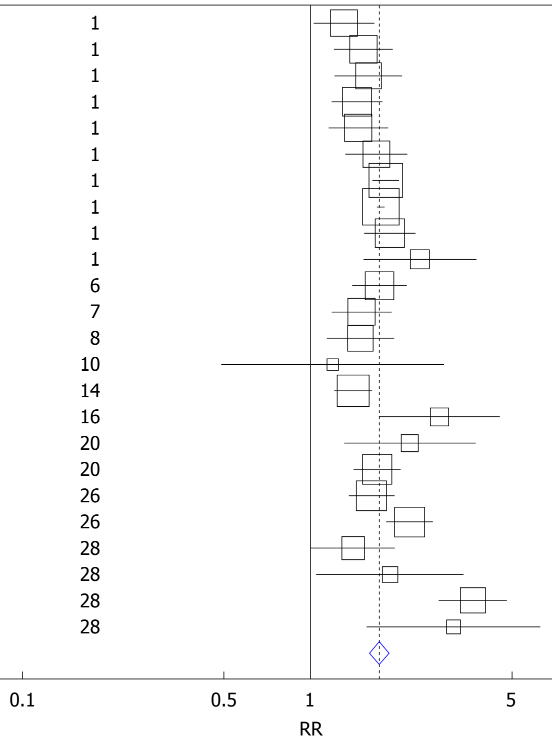


Figure 3 Forest plots of relative risk sorted by mean age of the study population (A) and by the number of teeth lost defined as representing a case (B). A: The size of the squares corresponds to the weight of the study in the meta-analysis. Combined relative risk was calculated using the random-effects model; B: The studies with definition of 1 means those losing one or more teeth were defined as cases. The size of the squares corresponds to the weight of the study in the meta-analysis. Combined relative risk was calculated using the random-effects model. Weights are from random effects analysis.

First, because we did not include data on smoking dose and duration, we could not exclude confounding by these factors. Some studies have indicated that the effect of smoking is dose- and duration-dependent[19,24,25,36]. Par-

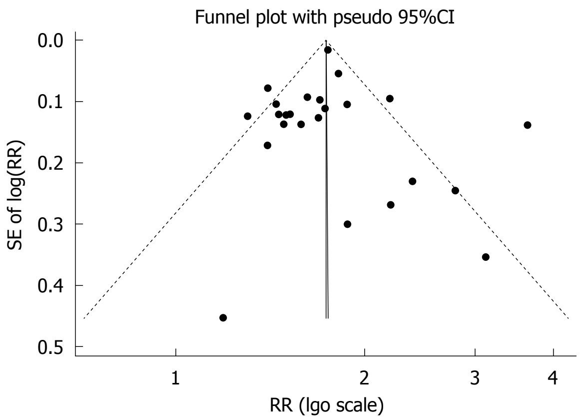


Figure 4 Funnel plot of included studies for the evaluation of publication bias.

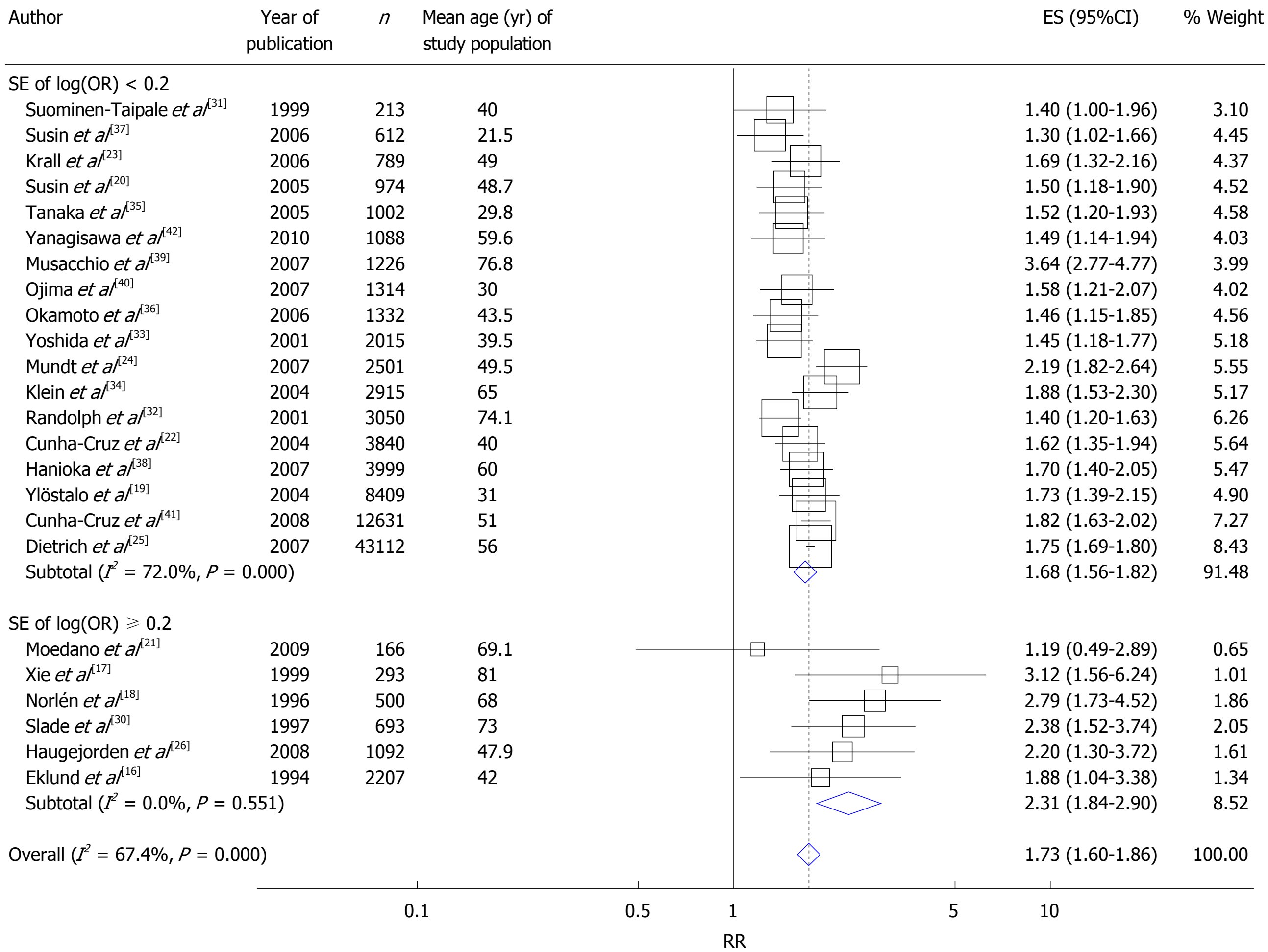


Figure 5 Subset-analysis according to the precision of studies. Weights are from random effects analysis.

ticularly among current smokers, older smokers may also have a lower daily consumption. Second, because tooth loss is a cumulative and irreversible event, older subjects may tend to have fewer teeth than younger smokers, and might therefore tend to be defined as case subjects. Third, chronic diseases such as diabetes and osteoporosis, which are considered as risk factors for tooth loss, may be more prevalent in older than younger people[17,21].

Several technical limitations of this meta-analysis warrant mention. One major limitation is the data source we used. Analyses were based on abstracted rather than individual patient data (IPD). In general, an IPD-based meta-analysis would allow a more robust estimation of the association. Second, the validity of meta-analyses is significantly threatened by potential publication bias. Although we detected no evidence of publication bias using

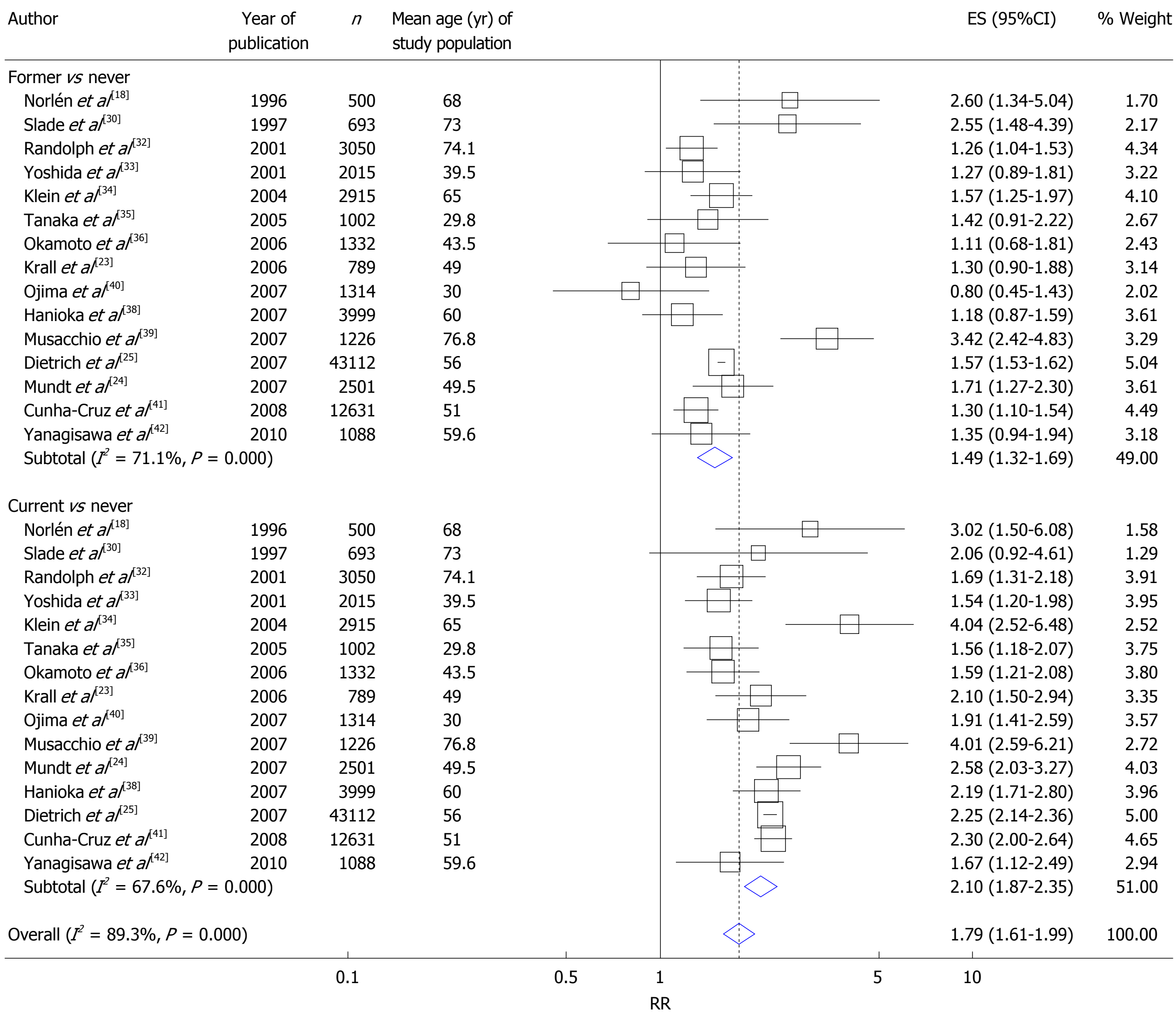


Figure 6 Subset meta-analysis according to smoking status. Weights are from random effects analysis.

graphical and statistical methods, it is difficult to completely rule out this possibility. A third limitation might be potential heterogeneity across studies, although we applied a random-effect model. Further, although we evaluated as many candidate characteristics as possible, unmeasured potential sources of heterogeneity might have remained. Although we tried to evaluate the different impact of smoking between former and current smokers, we did not directly compare two groups because RRs directly comparing two groups were not available in most of the studies. There have been discussions on how to precisely estimate the pooled estimates of RRs combining several levels of groups with strong correlations[48-50], we chose Greenland and Longnecker's methods[48] instead of Hamling's method[49] based on a recent study by Orsini *et al*[50] reporting negligible difference in estimation. Finally, we abstracted data only from English-language articles, and we only used PubMed search results because of lack of access. Therefore, bias might have occurred in our search strategy. However, given the nature of the studies we were looking for, namely clinical studies of adequate quality, we consider our search within MEDLIINE to be sufficient.

In conclusion, we demonstrated that smoking is a risk factor for tooth loss regardless of many other confounders, and that smoking cessation has a protective effect against tooth loss. Although our conclusions should be interpreted cautiously, our results nevertheless raise a critical point regarding the long-standing debate on whether smoking is a risk factor for tooth loss. Implementation of smoking cessation in the dental field is encouraged.

COMMENTS

Background

The World Health Organization Global Oral Health Program works to increase awareness of oral health worldwide as an important component of general health and quality of life. Number of tooth loss is one of the main impediments to oral health and smoking behavior could be the one of the modifiable causes of tooth loss, therefore, quantitative evaluation of the impact of smoking on tooth loss is needed.

Research frontiers

Smoking behavior is a risk factor for the risk of tooth loss, however, the effects of confounders such as sex, age, and other comorbidity on tooth loss have limited its interpretability among population. Therefore, more quantitative evaluation of the association between smoking and tooth loss is essential.

Innovations and breakthroughs

Previous studies have suggested that smoking behavior could be a risk of tooth loss, however, it has not been quantitatively evaluated. This meta-analysis of the literatures clarified that (1) ever-smoking increased the risk by 73% relative to non-smokers; and (2) risk increase among former smokers was different from that in current smokers (49% and 110%, compared to non-smokers). The latter suggests that it is important to consider smoking cessation to reduce the risk of tooth loss among smokers.

Applications

The study results suggest that the smoking increased the risk of tooth loss. Smoking cessation might be recommended to reduce the risk of tooth loss.

Peer review

This is a good quantitative study in which authors analyzed the impact of smoking on number of teeth loose with consideration of potential heterogeneity of studies. The results are interesting and suggest that smoking behavior should be considered in the oral health policy and practice.

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