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REVIEW

The global prevalence of apical periodontitis: a systematic review and meta-analysis

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Abstract

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Background Apical periodontitis (AP) frequently presents as a chronic asymptomatic disease. To arrive at a true diagnosis, in addition to the clinical examination, it is mandatory to undertake radiographic examinations such as periapical or panoramic radiographs, or cone-beam computed tomography (CBCT). Thus, the worldwide burden of AP is probably underestimated or unknown. Previous systematic reviews attempted to estimate the prevalence of AP, but none have investigated which factors may influence its prevalence worldwide.

Objectives To assess: (i) the prevalence of AP in the population worldwide, as well as the frequency of AP in all teeth, nontreated teeth and root filled teeth; (ii) which factors can modify the prevalence of AP.

Methods A search was conducted in the PubMed-MEDLINE, EMBASE, Cochrane-CENTRAL, LILACS, Google scholar and OpenGrey databases, followed by hand searches, until September 2019. Cross-sectional, case–control and cohort studies reporting the prevalence of AP in humans, using panoramic or periapical radiograph or CBCT as image methods were included. No language restriction was applied. An adaptation of the Newcastle-Ottawa Scale was used to evaluate the quality of the studies. A meta-analysis was performed to determine the pooled prevalence of AP at the individual level. Secondary outcomes were the frequency of AP in all teeth, nontreated teeth and root filled teeth. Subgroup analyses using random-effect models were carried out to analyse the influence of explanatory covariables on the outcome.

Results The search strategy identified 6670 articles, and 114 studies were included in the meta-analysis, providing data from 34 668 individuals and 639 357 teeth. The prevalence of AP was 52% at the individual level (95% CI 42%–56%, I^2 = 97.8%) and 5% at the tooth level (95% CI 4%–6%; I^2 = 99.5%). The frequency of AP in root-filled teeth and nontreated teeth was 39% (95% CI 36%–43%; I^2 = 98.5%) and 3% (95% CI 2%–3%; I^2 = 99.3%), respectively. The prevalence of AP was greater in samples from dental care services (DCS; 57%; 95% CI 52%–62%; I^2 = 97.8%) and hospitals (51%; 95% CI 40%–63%; I^2 = 95.9%) than in those from the general population (GP; 40%; 95% CI 33%–46%; I^2 = 96.5%); it was also greater in people with a systemic condition (63%; 95% CI 56%–69%, I^2 = 89.7%) compared to healthy individuals (48%; 95% CI 43%–53%; I^2 = 98.3%).

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Registration The protocol registration in the Prospero is under the number CRD42019137771

Discussion The subgroup analyses identified explanatory factors related to the variability in the prevalence of AP. However, the high clinical heterogeneity and high risk of bias across the primary studies indicate that the findings must be interpreted with caution.

Conclusions Half of the adult population worldwide have at least one tooth with apical periodontitis. The prevalence of AP is greater in samples from the dental care services, but it is also high amongst community representative samples from the general population. The present findings should bring the attention of health policymakers, medical and dental communities to the hidden burden of endodontic disease in the population worldwide.

Keywords: epidemiology, periapical lesion, prevalence, survey.

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Introduction

Apical periodontitis (AP) is an inflammatory response related to pathogens and their toxins occupying the root canal system (Kakehashi *et al.* 1965, Sundqvist 1976). As AP is usually asymptomatic, its diagnosis is based on radiographic examinations (Abbott 2004), and the burden of endodontic disease is probably underestimated or even unknown. In contrast, clinically visible oral conditions such as caries and periodontal disease have been demonstrated to contribute substantially to the global burden of diseases (Marcenes *et al.* 2013, Vos *et al.* 2017). Acknowledging the periapical health status of populations is essential for policymakers, as it will result in better management of resources for the prevention and treatment of endodontic diseases.

The worldwide prevalence of people with at least one tooth with AP has been reported to range from 16% (Skudutyte-Rysstad & Eriksen 2006) to 86% (Georgopoulou *et al.* 2005, Al-Zahrani *et al.* 2017). The differences in the reported prevalence rates vary according to age (Kirkevang *et al.* 2007), level of education, access to dental care (Aleksejuniene *et al.* 2000) and the radiographic techniques applied during diagnosis (Kruse *et al.* 2019). Attempts to pool the available data by using systematic review approaches have been made in previous studies. However, some focused only on root filled teeth (Hamedy *et al.* 2016, Segura-Egea *et al.* 2016) and others on specific population groups, such as smokers (Walter *et al.* 2012), elderly people (Hamedy *et al.* 2016) and individuals with systemic conditions (Khalighinejad *et al.* 2016, Segura-Egea *et al.* 2016, Berlin-Broner *et al.* 2017). Pak *et al.* (2012) considered a more general population, but the authors included only studies where the tooth was the unit of analyses, and did not provide information on the prevalence of AP at the individual level. More recently, Miri *et al.* (2018) compiled data from different communities and reported that 52% of individuals had endodontic disease, without, however, identifying which factors may modify the prevalence of AP worldwide.

In the reviews conducted by Pak *et al.* (2012) and Miri *et al.* (2018), only cross-sectional studies published in English were selected. The cross-sectional design is the most appropriate study design to provide data on the prevalence of a disease (Fletcher & Fletcher 2005). However, baseline data from cohort studies can also give the necessary information (Hulley *et al.* 2001) and modify the global prevalence of AP. Language restrictions may also increase the publication bias, and essential pieces of evidence can be missed (Grégoire *et al.* 1995). Therefore, the existing systematic reviews on this topic lack methodological techniques to capture the global prevalence of AP and its risk indicators.

The aim of this study was to conduct a systematic review and meta-analysis with a broader search strategy to verify: (i) the worldwide pooled prevalence of AP (main outcome: person as the unit of analysis), as well as the frequency of AP in all teeth, nontreated teeth and root filled teeth (secondary outcomes: tooth as the unit of analysis); (ii) the factors affecting the prevalence of AP, by undertaking subgroup analyses related to the socioeconomic status of the country, the location of recruitment, the presence of systemic conditions, the risk of bias of the primary studies, the image method used to assess the AP, as well as the method of assessing the AP.

Material and methods

This study was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist (Moher *et al.* 2009), and the protocol was registered in the International Prospective Register of Systematic Reviews (CRD42019137771).

Search strategy

The study aimed to answer the following research question: 'What is the prevalence of apical periodontitis in the population worldwide?' (main outcome: person as the unit of analysis). Secondary outcomes were also considered (tooth as the unit of analysis): frequency of AP in all teeth, frequency of AP in root filled teeth and frequency of AP in nontreated teeth.

An electronic search was undertaken with no date or language restrictions for studies published up to 13th September 2019 in the US National Library of Medicine (PubMed-MEDLINE; 1946-present), Excerpta Medica (EMBASE; 1947-present), Cochrane-CENTRAL (1945-present) and Latin American and Caribbean Center on Health Sciences (LILACS; 1982-present) databases. The search strategies were carried out using free-text terms and keywords, and are presented in the Supplemental Material 1. Grey literature was also searched through Google scholar (first 400 links; Haddaway *et al.* 2015) and OpenGrey repository. Reference lists of the selected studies for full-text reading were screened manually.

Eligibility criteria

Cross-sectional, case–control and cohort studies were included if they reported the occurrence of AP using periapical radiographs, panoramic radiographs or cone-beam computed tomography (CBCT) images. In cohort studies, only the baseline prevalence data was collected. In repeated cross-sectional studies, the first and the last study of the series were selected. In case of the first or the last study of a repeated cross-sectional series did not fill the eligibility criteria, then the intermediate studies of the series were included. The following exclusion criteria were applied: (i) studies that did not provide information to calculate the prevalence or frequency of AP (person or tooth level), (ii) studies that did not provide full mouth data; (iii) studies in which the sample included mixed dentition, (iv) studies in which the method of assessing the periapical status was not clearly defined (e.g. it did not state if they used PAI score, Strindberg criteria, amongst others), (v) reviews, letters, posters, conference abstracts, case reports or case series and dissertation/thesis with data available in a journal article.

Study selection

Included studies were selected following a two-phase process. In phase one (screening phase), two reviewers (C.T-M. and C.M.) independently screened titles and abstracts of all identified electronic databases for studies that fulfilled the inclusion criteria. Articles without abstracts but with titles suggesting some relation to the objectives of this review were also preselected and submitted to the full-text analysis of eligibility. Both reviewers independently applied the same selection criteria in phase two (eligibility phase) to confirm or refute their eligibility. In advance of phase one and two, the reviewers undertook a pilot step, in which 30 studies were randomly chosen from the retrieved search (inter-agreement kappa = 0.93 for eligibility decision). Disagreements between the reviewers were discussed until a consensus was reached. If a disagreement persisted, the judgment of a third reviewer (F.B.Z.) was considered decisive.

Data collection and risk of bias (quality assessment)

Both reviewers (C.T-M. and C.M.) extracted the following data from the selected studies independently: (i) article identification: authors, country and year of publication; (ii) participants: gender, age, sample size, systemic conditions and location of recruitment; (iii) methods: method of image acquisition and method of assessing AP; (iv) results: number of people with at least one AP, total number of teeth, number of root filled teeth, number of nontreated teeth, number of teeth with AP, number of nontreated teeth with AP and number of root filled teeth with AP. In case of disagreement, the main reviewer (C.T-M.) double-checked the information in the primary study. The same was carried out for the quality assessment.

The methodology used for the quality assessment was based on the Newcastle-Ottawa Scale adapted for cross-sectional studies proposed by Herzog *et al.* (2013). The proposed scale was further adapted to the outcome of interest of this systematic review, and the items were divided into three domains [selection (representativeness of the sample, sample size and nonresponders), comparability (confounding factors) and outcome (blinding and calibration of the examiners) - Details in Supplemental Material 2)]. The scale was also used to analyse cohort and case–control studies, as the other specific items from the original Newcastle-Ottawa Scale were not crucial in light of the outcome of interest of this review. The second domain was only applied to studies with a group of comparison (e.g. comparing the prevalence of AP in diabetic and nondiabetic individuals). Studies with some group of comparison could achieve a maximum score of nine stars. On the other hand, those without any group of comparison could only achieve a maximum score of five stars since the second domain was not applied. Studies with a group of comparison were arbitrarily defined as high risk of bias if they scored between zero and three stars, moderate risk between four and six and low risk between seven and nine. Studies without a group of comparison were rated as high risk of bias if they scored between zero and two stars, moderate risk if they scored three and low risk if they scored four or five.

Data analysis

A meta-analysis was performed to determine the prevalence of individuals having at least one tooth with AP, as well as the frequency of all teeth, nontreated teeth and root filled teeth with AP using the statistical software R (Foundation for Statistical Computing, Vienna, Austria) version 1.2.5019, packages meta and metafor. Subgroup analyses were carried out to analyse whether the socioeconomic status of the country (UN/DESA 2014), the location of recruitment, the presence of systemic conditions, the risk of bias, the image method and the method of assessing AP influenced the prevalence of the disease at the individual level and tooth level. A random-effects model was employed in all analyses because the heterogeneity was considered high ($I^2 > 50\%$).

In the subgroup analyses, smoking was included in the group of systemic condition since it seems to modify the inflammatory response (Palmer *et al.* 2005). Also, in order to facilitate the data clustering, other methods of assessing AP were converted into PAI scores (Ørstavik *et al.* 1986). Alterations such as ‘widening of the periodontal ligament not exceeding two times the width of the lateral periodontal ligament space’ and ‘condensing osteitis’ were considered compatible with PAI ≥ 2. ‘Apical periodontal ligament exceeding at least two times the width of its lateral part’, ‘broken lamina dura’ and ‘discernible apical radiolucency’ were considered compatible with PAI ≥ 3.

Results

Study selection and study characteristics

A flowchart with a detailed description of the screening process is presented in Figure 1. Two articles could not be found (Hakala 1967, Ayad 1977); the journals where the articles were published were contacted, but no reply was received. Data from 34 668 individuals and 639 357 teeth were available. Five articles were published in languages other than English: three in Portuguese (Vidigal *et al.* 2010, Diogo *et al.* 2014, Maniglia Ferreira *et al.* 2014), one in Norwegian (Kerekes & Bervell 1976) and one in Polish (Bołtacz-Rzepkowska & Laszkiewicz 2005). Seventy-four studies had information to answer the main research question (Table 1), whilst 66, 61 and 84 articles provided data regarding the frequency of AP in all teeth, in nontreated teeth and in root filled teeth, respectively (Supplemental Material 3).

Six studies were cohort studies (Frisk & Hakeberg 2005, Kim 2010, Zhong *et al.* 2010, Hommez *et al.* 2012, Gomes *et al.* 2016, Timmerman *et al.* 2017). From the prospective ones (Frisk & Hakeberg 2005, Zhong *et al.* 2010, Timmerman *et al.* 2017), only data from baseline were collected. Seven studies were mistakenly classified by their authors as retrospective studies, when in fact they were cross-sectional (Bołtacz-Rzepkowska & Laszkiewicz 2005, Gumru *et al.* 2011, Ureyen Kaya *et al.* 2013, Willershausen *et al.* 2014, Hussein *et al.* 2016, Jalali *et al.* 2017, Piras *et al.* 2017). Four studies were classified as case–control, but based on their design, they were also cross-sectional studies (Hommez *et al.* 2008, Pasqualini *et al.* 2012, Leal *et al.* 2015, Poyato-Borrego *et al.* 2019). Only one study was a real case–control (Khalighinejad *et al.* 2017a).

Three serial cross-sectional studies were included: one from the Netherlands (Peters *et al.* 2011), which is the series study from De Cleen *et al.* (1993), and two (Eriksen *et al.* 1995, Skudutyte-Rysstad & Eriksen 2006) from Norway, which are the third and fourth series cross-sectional studies of Oslo citizens. The first and the second study were excluded as they did not provide any information on how AP was defined.

Risk of bias

Six studies were classified as low risk of bias, 25 as moderate and 83 as high. A detailed description of the quality assessment is shown in Supplemental Material 4.

Meta-analysis

Main outcome (prevalence of individuals with at least one tooth with AP)

According to the results of the pooled data, the global prevalence of individuals with at least one AP was 52%

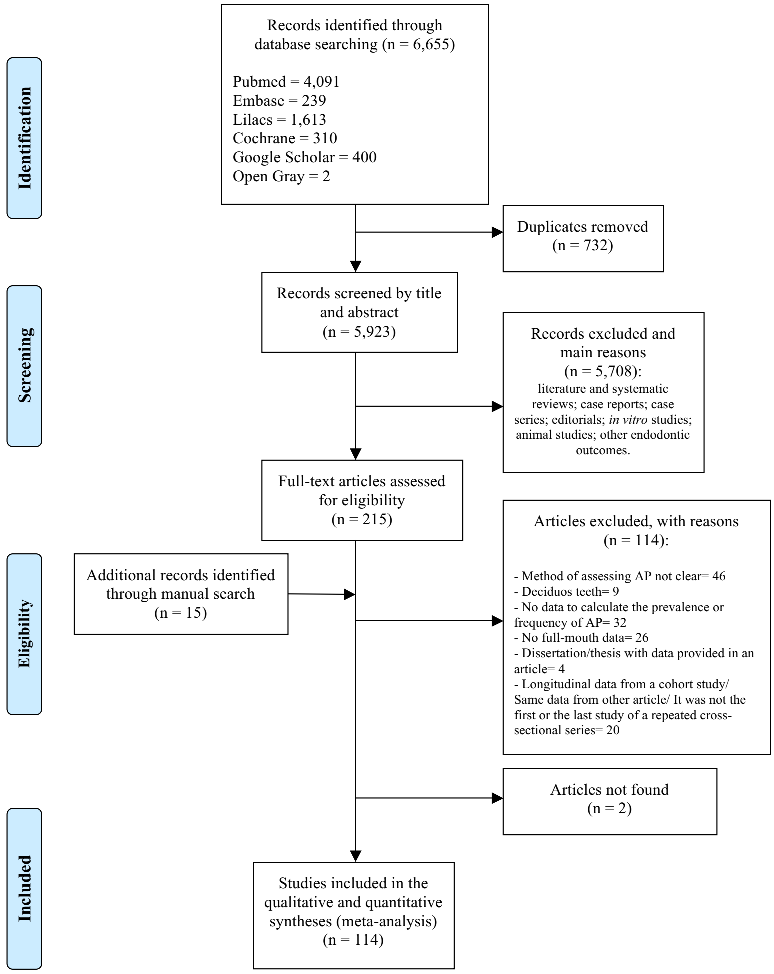

Figure 1 Flowchart of the selection process.

(95% CI 42%–56%; I^2 = 97.8%; Figure 2). The prevalence of AP was higher amongst individuals from developing and in transition countries than amongst those from developed countries (developing = 53%; 95% CI 44%–62%; I^2 = 98.1%; in transition = 80%; 95% CI 78%–82%; developed = 51%; 95% CI 47%–56%; I^2 = 97%; Supplemental Material 5).

AP was more prevalent when individuals were recruited from dental care services (DCS) than from the general population (GP); studies using samples from hospitals yielded results almost as high as those using samples from DCS (DCS = 57%; 95% CI 52%–62%; I^2 = 97.8%; GP = 40%; 95% CI 33%–46%; I^2 = 96.5%; hospitals = 51%; 95% CI 40%–63%; I^2 = 95.9%; Supplemental Material 6).

The prevalence of healthy individuals with at least one tooth with AP was 48% (95% CI 43%–53%; I^2 = 98.3%), lower than that of individuals with a systemic condition (63%; 95% CI 56%–69%; I^2 = 89.7%; Supplemental Material 7). The most frequent systemic conditions were diabetes (n = 6), cardiovascular disease (CVD; n = 5) and smoking (n = 4). The subgroup analysis of these conditions revealed that the pooled prevalence of individuals with at least one tooth with AP in type-2 diabetic patients was 75% ([66%; 83%]; I^2 = 63.8%; Segura-Egea *et al.* 2005, López-López *et al.* 2011, Marotta *et al.* 2012, Maniglia Ferreira *et al.* 2014, Sánchez-Domínguez *et al.* 2015, Al-Zahrani *et al.* 2017). Non-diabetic individuals had a prevalence of 62% (95% CI 40%–79%; I^2 = 86.5%; Segura-Egea *et al.* 2005, López-López *et al.* 2011, Marotta *et al.* 2012, Maniglia Ferreira *et al.* 2014). The prevalence of AP in individuals with CVD was 57% (95% CI 35%–76%;

Table 1 Characteristics of the selected studies (main outcome: prevalence of AP – person level)

Study	Country	*N*	Patients with ≥ 1AP *N* (%)	Gender	Age mean (SD/range)	Systemic condition	Method of assessing AP	Image method	Location of recruitment
Europe									
Kerekes & Bervell (1976)	Norway	200	69 (35)	n/m	19–81		Discernible apical radiolucency + condensing osteitis (in nontreated teeth)	Periapical rx	Dental care service
Allard & Palmqvist (1986)	Sweden	183	132 (72)	♂ = 95 ♀ = 88	>65		De Moor (2000)[a]	Periapical rx	General population
Bergström *et al.* (1987)	Sweden	250	117 (47)	n/m	21–60		De Moor (2000)[a]	Periapical rx	Musicians
Eckerbom *et al.* (1987)	Sweden	200	126 (63)	♂ = 93 ♀ = 107	≥20		Discernible apical radiolucency	Periapical rx	Dental care service
Falk *et al.* (1989)	Sweden	82	50 (61)	♂ = 40 ♀ = 42	20–70	Long-duration type-1 diabetes	De Moor (2000)[a]	Periapical rx	General population
		72	30 (42)	♂ = 38 ♀ = 34		Short-duration type-1 diabetes			
		77	39 (51)	♂ = 34 ♀ = 43		Nondiabetes			
Petersson *et al.* (1989)	Sweden	567	434 (77)	♀♂	>20		Discernible apical radiolucency	Periapical rx	Dental care service
Ödesjö *et al.* (1990)	Sweden	743	321 (43)	♂ = 392 ♀ = 351	>20		Radiolucent area in connection with the root	Periapical rx	General population
De Cleen *et al.* (1993)	Netherlands	184	82 (45)	♂ = 94 ♀ = 90	>20		PL exceeding at least two times the width of the lateral part or apical radiolucency	Panoramic rx	Dental care service
Eriksen *et al.* (1995)	Norway	118	17 (14)	♀♂	35 years old		PAI ≥ 3	Panoramic + periapical rx	General population
Soikkonen (1995)	Finland	169	70 (41)	♂ = 54 ♀ = 115	76–86		De Moor (2000)[a]	Panoramic + periapical rx	General population
Marques *et al.* (1998)	Portugal	179	47 (26)	n/m	30–39		PAI ≥ 3	Panoramic rx	General population
Sidaravicius *et al.* (1999)	Lithuania	147	103 (70)	n/m	35–44		PAI ≥ 3	Panoramic + periapical rx[b]	General population
De Moor *et al.* (2000)	Belgium	206	130 (63)	♀♂	>18		De Moor (2000)[a]	Panoramic rx	Dental care service

Table 1 Continued

Study	Country	*N*	Patients with ≥ 1AP *N* (%)	Gender	Age mean (SD/range)	Systemic condition	Method of assessing AP	Image method	Location of recruitment
Kirkevang *et al.* (2001)	Denmark	614	260 (42)	♂ = 311 ♀ = 303	≥20		PAI ≥ 3	Periapical rx	General population
Bołtacz-Rzepkowska & Laszkiewicz (2005)	Poland	439	168 (38)	♂ = 174 ♀ = 265	18–86		PL exceeding at least two times the width of the lateral part or apical radiolucency	Panoramic rx	Dental care service
Frisk & Hakeberg (2005)	Sweden	1220	511 (42)	♀	38–60		De Moor (2000)[a]	Panoramic rx	General population
Georgopoulou *et al.* (2005)	Greece	320	275 (86)	♂ = 111 ♀ = 209	16–77		PL exceeding at least two times the width of the lateral part or apical radiolucency	Periapical rx	Dental care service
Kabak & Abbott (2005)	Republic of Belarus	1423	1141 (80)	n/m	≥15		PL exceeding at least two times the width of the lateral part or apical radiolucency	Panoramic rx	Dental care service
Loftus *et al.* (2005)	Ireland	302	100 (33)	♂ = 127 ♀ = 175	16–98		PAI ≥ 4	Panoramic rx	Dental care service
Segura-Egea *et al.* (2005)	Spain	32	26 (81)	♂ = 12 ♀ = 20	43–74	type-2 diabetes	PAI ≥ 3	Periapical rx	Dental care service
		38	22 (58)	♂ = 16 ♀ = 22	43–74	Nondiabetes			
Skudutyte-Rysstad & Eriksen (2006)	Norway	146	23 (16)	♀♂	35–year–old		PAI ≥ 3	Panoramic + periapical rx	General population
Sunay *et al.* (2007)	Turkey	375	141 (38)	♂ = 147 ♀ = 228	16–82		PL exceeding at least two times the width of the lateral part	Panoramic rx	Dental care service
Gulsahi *et al.* (2008)	Turkey	1000	238 (24)	♂ = 393 ♀ = 607	16–80		PL exceeding at least two times the width of the lateral part or apical radiolucency	Panoramic rx	Dental care service
Hommez *et al.* (2008)	Belgium	43	20 (47)	♂ = 36 ♀ = 7	53 ± 9.9	Head and neck irradiated patients	De Moor (2000)[a]	Panoramic rx	Dental care service
		43	32 (74)	♂ = 36 ♀ = 7	53 ± 10.2	Nonirradiated			
Segura-Egea *et al.* (2008)	Spain	109 71	81 (74) 29 (41)	♂ = 66 ♀ = 114	35 ± 2.6 40 ± 3.1	Smokers Nonsmokers	PAI ≥ 3	Periapical rx	Dental care service

Table 1 Continued

Study	Country	N	Patients with ≥ 1AP N (%)	Gender	Age mean (SD/range)	Systemic condition	Method of assessing AP	Image method	Location of recruitment
López-López *et al.* (2011)	Spain	50	37 (74)	♂ = 20 ♀ = 30	61 ± 10.3	Type-2 diabetes	PAI ≥ 3	Panoramic rx	Dental care service
		50	21 (42)	♂ = 22 ♀ = 28	62 ± 10.4	Nondiabetes			
Peters *et al.* (2011)	Netherlands	178	65 (37)	♂ = 84 ♀ = 94	>18		PL exceeding at least two times the width of the lateral part	Panoramic rx	Dental care service
Segura-Egea *et al.* (2011)	Spain	50	46 (92)	♂ = 53 ♀ = 47	60 ± 9.6	Smokers	PAI ≥ 3	Periapical rx	Dental care service
		50	22 (44)		58 ± 9.6	Nonsmokers			
López-López *et al.* (2012)	Spain	397	135 (34)	♂ = 194 ♀ = 203	52 ± 15.7		PAI ≥ 3	Panoramic rx	Dental care service
Pasqualini *et al.* (2012)	Italy	51	43 (84)	♂ = 40 ♀ = 11	48 ± 5.7	Cardiovascular disease	Broken lamina dura + PL >2 mm of diameter	Periapical rx	Hospital
		49	26 (53)	♂ = 39 ♀ = 10	47 ± 7.1	Noncardiovascular disease			
Castellanos-Cosano *et al.* (2013a)	Spain	58	39 (67)	♂ = 41 ♀ = 17	36 ± 11	Bleeding disorders	PAI ≥ 3	Panoramic rx	Dental care service
		58	28 (48)	♂ = 41 ♀ = 17	34 ± 10.2	Nonbleeding disorders			
Castellanos-Cosano *et al.* (2013b)	Spain	42	33 (79)	♂ = 30 ♀ = 12	59 ± 8.6	Liver disease	PAI ≥ 3	Panoramic rx	Hospital
		42	21 (50)	♂ = 30 ♀ = 12	59 ± 8.7	Nonliver disease			Dental care service
Jersa & Kundzina (2013)	Latvia	312	224 (72)	n/m	35–44		PAI ≥ 3	Panoramic rx	Dental care service
Kalender *et al.* (2013)	Turkey	1006	684 (68)	♂ = 423 ♀ = 583	18–50		PAI ≥ 2	Panoramic + periapical rx	Dental care service
Di Filippo *et al.* (2014)	England	136	67 (49)	♂ = 63 ♀ = 73	>16		PL exceeding at least two times the width of the lateral part	Panoramic rx	Dental care service
Diogo *et al.* (2014)	Portugal	157	46 (29)	♂ = 68 ♀ = 89	18–84		PAI ≥ 3	Panoramic rx	Dental care service
Willershausen *et al.* (2014)	Germany	248	95 (38)	♂ = 201 ♀ = 47	62 ± 10.1	Acute myocardial infaction	PL exceeding at least two times the width of the lateral part	panoramic rx or periapical rx or CBCT	Hospital
		249	59 (24)	♂ = 179 ♀ = 70	63 ± 10.5	Nonacute myocardial infaction			Dental care service

Table 1 Continued

Study	Country	*N*	Patients with ≥ 1AP *N* (%)	Gender	Age mean (SD/range)	Systemic condition	Method of assessing AP	Image method	Location of recruitment
Lemagner *et al.* (2015)	France	100	78 (78)	♂ = 47 ♀ = 53	47 ± 15.8		Discernible apical radiolucency > 0.5 mm	CBCT	Dental care service
López-López *et al.* (2015)	Spain	12	3 (25)	♀	62 ± 1.7	Osteoporosis	Discernible apical radiolucency	Panoramic rx	Dental care service
		36	9 (25)			Osteopenia			
		27	2 (7)			Nonbone problem			
Sánchez-Domínguez *et al.* (2015)	Spain	59	40 (68)	♂ = 41 ♀ = 42	66 ± 10.6	Poor-controlled type-2 diabetes	PAI ≥ 3	Panoramic rx	Dental care service
		24	12 (50)		66 ± 10.6	Good-controlled type-2 diabetes			
Grønkjær *et al.* (2016)	Denmark	110	51 (46)	♂ = 84 ♀ = 26	39–82	Cirrhosis	PL exceeding at least two times the width of the lateral part or apical radiolucency	Panoramic rx	Hospital
Liljestrand *et al.* (2016)	Finland	353	266 (75)	♂ = 261 ♀ = 92	33–82	Stable CAD or ACS	PAI ≥ 3	Panoramic rx	Hospital
		123	76 (62)	♂ = 63 ♀ = 60		No significant CAD			
Peršić Bukmir *et al.* (2016)	Croatia	108	93 (86)	♂ = 82	38.8 ± 13.6	Smokers	PAI ≥ 3	Panoramic + periapical rx	Dental care service
		151	118 (78)	♀ = 177	41.9 ± 16.2	Nonsmokers			
Huumonen *et al.* (2017)	Finland	5335	1440 (27)	♂ = 2828♀ = 2507	30–95		PL exceeding at least two times the width of the lateral part or broken lamina or apical radiolucency	Panoramic rx	General population
Kielbassa *et al.* (2017)	Austria	1000	605 (61)	♂ = 430 ♀ = 570	19–91		PAI ≥ 2	Panoramic rx	Dental care service
Piras *et al.* (2017)	Italy	110	70 (64)	♂ = 49 ♀ = 61	46 ± 13.8	Inflammatory Bowel Disease	PAI (threshold not mentioned)	Panoramic + periapical rx	Hospital
		110	65 (59)	♂ = 53 ♀ = 57	41 ± 13.1	Noninflammatory Bowel Disease			Dental care service
Vengerfeldt *et al.* (2017)	Estonia	486	1914 (39)	♂ = 256[e] ♀ = 3989[e]	≥20		PAI ≥ 3	Panoramic rx	Dental care service
Virtanen *et al.* (2017)	Sweden	42	25 (60)	♂ = 57	51 ± 2.9 (patients w/o AP)	Smokers	PAI ≥ 2	Periapical rx	General population
		78	24 (31)	♀ = 63	53 ± 2.7 (patients w/AP)	Nonsmokers			

Table 1 Continued

Study	Country	*N*	Patients with ≥ 1AP *N* (%)	Gender	Age mean (SD/range)	Systemic condition	Method of assessing AP	Image method	Location of recruitment
Bürklein *et al.* (2020)	Germany	500	305 (61)	♂ = 203 ♀ = 297	50.2 ± 12.4		PDL exceeding at least twice the width of the lateral part or radiolucency in connection with the apical part of the root or a lateral root canal	CBCT	Dental care service
Peršić Bukmir *et al.* (2019)	Croatia	599	455 (76)	♂ = 190 ♀ = 409	19–70		PAI ≥ 3	Panoramic + periapical rx[d]	Dental care service
Poyato-Borrego *et al.* (2019)	Spain	54	19 (35)	♂ = 31 ♀ = 23	43.1 ± 14.0	Inflammatory Bowel Disease	PAI ≥ 3	Panoramic rx	Hospital
		54	9 (17)	♂ = 31 ♀ = 23	43.1 ± 13.8	noninflammatory Bowel Disease			Dental care service
North America									
Chen *et al.* (2007)	USA	206	94 (46)	♂ = 103[c] ♀ = 121[c]	55–94		PL exceeding at least two times the width of the lateral part or broken lamina dura	Panoramic rx	General population
Gomes *et al.* (2016)	USA	62	18 (29)	♂ = 143 ♀ = 135	22–89	Cardiovascular disease	De Moor (2000)[a]	Panoramic rx	General population
		216	43 (20)			Noncardiovascular disease			
Jalali *et al.* (2017)	USA	131	65 (50)	♂ = 19 ♀ = 112	22–83	Rheumatoid arthritis	PAI ≥ 3	Panoramic + periapical rx	Dental care service
		131	71 (54)	♂ = 19 ♀ = 112	24–83	Nonrheumatoid arthritis			
Khalighinejad *et al.* (2017a)	USA	50	27 (54)	♀	26 ± 3.2	Pre-eclampsia	PAI ≥ 3	Panoramic rx	Hospital
		50	16 (32)	♀	24 ± 2.8	Non-pre-eclampsia			
Khalighinejad *et al.* (2017b)	USA	40	29 (73)	♂ = 28 ♀ = 12	59 ± 4.5	End-stage renal disease	PAI ≥ 3	Panoramic + pulp test	Hospital
		40	16 (40)	♂ = 26 ♀ = 14	52 ± 3.1	nonEnd-stage renal disease			Dental care service
Latin America									
Terças *et al.* (2006)	Brazil	200	135 (68)	♂ = 88 ♀ = 112	≥20		PAI ≥ 3	Periapical rx	Dental care service
Marotta *et al.* (2012)	Brazil	30	24 (80)	♂ = 12 ♀ = 18	40–69	Type-2 diabetes	Discernible apical radiolucency	Panoramic + periapical rx	Dental care service
		60	52 (87)	♂ = 24 ♀ = 36	41–70	Nondiabetes			

Table 1 Continued

Study	Country	*N*	Patients with ≥ 1AP *N* (%)	Gender	Age mean (SD/range)	Systemic condition	Method of assessing AP	Image method	Location of recruitment
Costa *et al.* (2014)	Brazil	67	34 (51)	♂ = 38 ♀ = 29	64 ± 10.1	Cardiovascular disease	PAI ≥ 3	Periapical rx	Hospital
		36	9 (25)	♂ = 14 ♀ = 22	57 ± 10.6	Noncardiovascular disease			
Hebling *et al.* (2014)	Brazil	98	42 (43)	♂ = 41 ♀ = 57	60–94		PAI ≥ 3	Periapical rx	Institutionalized people
Maniglia Ferreira *et al.* (2014)	Brazil	40	32 (80)	♂ = 13 ♀ = 27	37–68	Type-2 diabetes	PAI ≥ 3	Panoramic + periapical rx	Dental care service
		40	21 (53)	♂ = 16 ♀ = 24	35–70	Nondiabetes			
Leal *et al.* (2015)	Brazil	33	18 (55)	♀	15–40	Low-birth weight preterm births	PAI (threshold not mentioned)	Periapical rx	Hospital
		30	6 (20)	♀	15–41	Normal-birth weight and term births			
Hoppe *et al.* (2017)	Brazil	112	27 (24)	♂	20–53		De Moor (2000)[a]	Periapical rx	Military police officers
Africa and Middle East									
Marmary & Kutiner (1986)	Israel	889	394 (44)	n/m	n/m		Discernible apical radiolucency	Periapical rx	Dental care service
Touré *et al.* (2008)	Senegal	208	124 (60)	♂ = 114 ♀ = 94	32 ± 11.2		PAI ≥ 3	Periapical rx	Dental care service
Al-Omari *et al.* (2011)	Jordan	294	246 (84)	♂ = 158 ♀ = 136	16–59		De Moor (2000)[a]	Panoramic rx	Dental care service
Harjunmaa *et al.* (2015)	Malawi	1024	241 (24)	♀	25 ± 6.2		Discernible apical radiolucency > 1 mm	Panoramic rx	Hospital
Oginni *et al.* (2015)	Nigeria	756	508 (67)	♂ = 414 ♀ = 342	♂ = 48 ± 10.7 ♀ = 45 ± 12.6		PAI ≥ 3	Periapical rx	Dental care service
Ahmed *et al.* (2017)	Sudan	200	95 (47)	♂ = 47 ♀ = 153	34 ± 12.9		PL exceeding at least two times the width of the lateral part or apical radiolucency	Panoramic + periapical rx	Dental care service
Al-Zahrani *et al.* (2017)	Saudi Arabia	100	86 (86)	♂ = 60 ♀ = 40	49 ± 8.5	Type-2 diabetes	PAI ≥ 3	Panoramic + periapical rx	Dental care service
Asia and the Pacific									
Tsuneishi *et al.* (2005)	Japan	672	469 (70)	♂ = 244 ♀ = 428	♂ = 53 ± 14.9 ♀ = 51 ± 14.9		PAI ≥ 3	Periapical rx	Dental care service

Table 1 Continued

Study	Country	*N*	Patients with ≥ 1AP *N* (%)	Gender	Age mean (SD/range)	Systemic condition	Method of assessing AP	Image method	Location of recruitment
Archana *et al.* (2015)	India	1340	865 (65)	n/m	>18		PAI ≥ 3	Panoramic rx	Dental care service
Hussein *et al.* (2016)	Malaysia	233	59 (25)	♂ = 86 ♀ = 147	16–70		PAI ≥ 3	Panoramic + periapical rx	Dental care service
Timmerman *et al.* (2017)	Australia	695	179 (26)	♂ = 290 ♀ = 405	10–88		PAI ≥ 3	Panoramic rx	Dental care service

ACS, Acute Coronary Syndrome; AP, apical periodontitis; CAD, Coronary Artery Disease; n/m, not mentioned; PAI, periapical index (Ørstavik *et al.* 1986); PL, periodontal ligament; Rx, radiography.
[a]Method according to De Moor *et al.* (2000) or similar.
[b]Periapical Rx only in root filled teeth.
[c]Including edentulous.
[d]Periapical Rx only in root filled teeth or in teeth with AP on the panoramic.
[e]Including patients from the categories <20 years of age.

I^2 = 96.4%; Pasqualini *et al.* 2012, Costa *et al.* 2014, Willershausen *et al.* 2014, Gomes *et al.* 2016, Liljestrand *et al.* 2016). Control individuals from the same studies revealed a prevalence of individuals with at least one tooth with AP of 35% (95% CI 20%–55%; I^2 = 94.7%). Smokers were also taken into account in the analysis, and the pooled proportion was 80% (95% CI 65%–89%; I^2 = 83.1%); nonsmokers had a prevalence of AP of 49% (95% CI 26%–72%; I^2 = 94.5%; Segura-Egea *et al.* 2008, 2011, Peršić Bukmir *et al.* 2016, Virtanen *et al.* 2017).

Studies presenting a moderate or high risk of bias were associated with a higher prevalence of individuals with at least one AP than those with low risk of bias (high risk 52%; 95% CI 47%–57%; I^2 = 98.4%; moderate risk 57%; 95% CI 50%–64%; I^2 = 92.5%; low risk 29%; 95% CI 20%–41%; I^2 = 94%).

Regarding the image method used to evaluate the periapical area, studies that used periapical radiograph had a higher prevalence of people with at least one tooth with AP (56%; 95% CI 50%–62%; I^2 = 95.3%) than studies that used panoramic radiograph (46%; 95% CI 40%–52%; I^2 = 98.3%). Results from the combination of both image methods yielded a proportion similar to the periapical radiograph alone (60%; 95% CI 49%–70%; I^2 = 95.3%; Supplemental Material 8), and the use of CBCT images was associated with a prevalence of AP of 70% (95% CI 51%–84%; I^2 = 90%).

Using methods of assessing AP compatible with PAI ≥ 2 resulted in almost the same prevalence of AP as using methods compatible with PAI ≥ 3 (53%; 95% CI 45%–60%; I^2 = 96.3% vs. 52%; 95% CI 48%–57%; I^2 = 98%). However, assessing AP with PAI ≥ 4 decreased the prevalence of individuals with at least one tooth with AP substantially (33%; 95% CI 28%–39%).

Secondary outcomes (frequency of all teeth, nontreated and root filled teeth with AP)

In general, the frequency of teeth with AP was 5% (95% CI 4%–6%; I^2 = 99.5%). Nontreated teeth had a frequency of 3% of periapical lesions, whereas 39% of the root filled teeth had AP (nontreated = 3%; 95% CI 2%–3%; I^2 = 99.3%; root filled = 39%; 95% CI 36%–43%; I^2 = 98.5%; Supplemental material 9, Supplemental material 10 and Supplemental material 11).

People from developing countries had 2% more AP in all teeth than people from developed countries (developing = 6%; 95% CI 5%–8%; I^2 = 99.7%; in

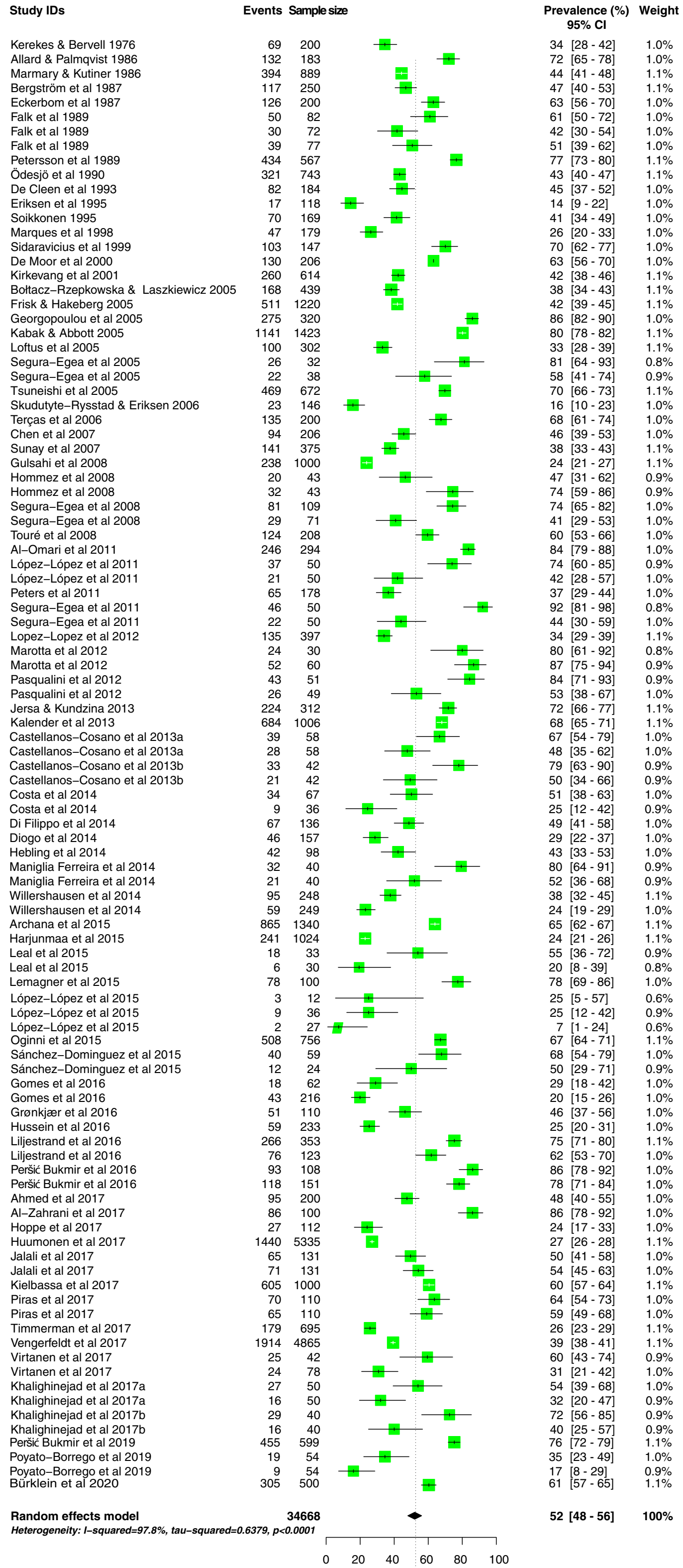

Figure 2 Prevalence of AP (main outcome) in the population worldwide.

transition = 12%; 95% CI 12%–12%; developed = 4%; 95% CI 4%–5%; I^2 = 99.1%). This pattern remained consistent when the analysis was made separately for nontreated teeth (2% of difference; developing = 4%; 95% CI 3%–5%; I^2 = 99.6%; in transition = 3%; 95% CI 3%–3%; developed = 2%; 95% CI 2%–3%; I^2 = 98.7%), and it was more pronounced when considering root filled teeth (11% of difference; developing = 46%; 95% CI 40%–51%; I^2 = 98.3%; in transition = 48%; 95% CI 42%–55%; developed = 35%; 95% CI 31%–39%; I^2 = 98.3%).

People recruited from DCS had 2% more teeth with AP than those from the GP (DCS = 5%; 95% CI 4%–6%; I^2 = 99.5%; GP = 3%; 95% CI 2%–4%; I^2 = 99.1%). Individuals recruited from hospitals had a frequency of AP in all teeth of 7% (95% CI 2%–19%; I^2 = 99.7%). The difference between the frequency of AP in individuals from DCS and GP was higher when considering only root filled teeth compared to nontreated teeth (9% vs. 2%; root filled teeth DCS = 40%; 95% CI 37%–43%; I^2 = 97.8%; GP = 31%; 95% CI 22%–41%; I^2 = 98.6% vs. nontreated DCS = 3%; 95% CI 2%–3%; I^2 = 99.3%; GP = 1%; 95% CI 1%–2%; I^2 = 98.4%).

Healthy individuals had a lower frequency of teeth with AP than individuals with a systemic condition (healthy = 4%; 95% CI 4%–5%; I^2 = 99.5%; systemic condition = 8%; 95% CI 6%–11%; I^2 = 96.7%). This difference was similar in nontreated and in root filled teeth (nontreated healthy individuals = 2%; 95% CI 2%–3%; I^2 = 99.3%; systemic condition = 6%; 95% CI 3%–9%; I^2 = 97.7%; root filled teeth healthy individuals = 39%; 95% CI 36%–43%; I^2 = 98.6%; systemic condition = 44%; 95% CI 33%–56%; I^2 = 90.4%).

As demonstrated in the person-level analysis, high- and moderate-risk studies had a greater frequency of AP in all teeth and nontreated teeth than low-risk studies (all teeth high risk = 5%; 95% CI 4%–6%; I^2 = 99.5%; moderate risk = 6%; 95% CI 4%–8%; I^2 = 99.1%; low risk = 3%; 95% CI 1%–5%; I^2 = 98.7%; nontreated high risk = 3%; 95% CI 2%–3%; I^2 = 99.3%; moderate risk = 3%; 95% CI 1%–5%; I^2 = 99.4%; low risk = 2%; 95% CI 1%–3%; I^2 = 98%). However, in root filled teeth the opposite pattern was noticed (high risk = 39%; 95% CI 36%–43%; I^2 = 98.6%; moderate risk = 37%; 95% CI 30%–45%; I^2 = 97.6%; low risk = 48%; 95% CI 41%–55%; I^2 = 80.1%).

Periapical radiograph or panoramic radiograph did not influence the frequency of AP in all teeth or in nontreated teeth (all teeth periapical radiograph = 5%; 95% CI 4%–6%; I^2 = 99.5%; panoramic radiograph = 5%; 95% CI 4%–6%; I^2 = 99.6%; panoramic + periapical radiograph = 4%; 95% CI 3%–6%; I^2 = 98.8%; nontreated teeth periapical radiograph = 3%; 95% CI 2%–4%; I^2 = 99.4%; panoramic radiograph = 3%; 95% CI 2%–4%; I^2 = 99.3%; panoramic + periapical radiograph = 2%; 95% CI 2%–3%; I^2 = 97.4%). On the other hand, in root filled teeth, the frequency of AP using periapical radiograph was 8% higher than using only panoramic radiograph and 3% higher than using panoramic radiograph complemented with periapical radiograph (root filled teeth periapical radiograph = 43%; 95% CI 38%–48%; I^2 = 97.6%; panoramic radiograph = 35%; 95% CI 31%–40%; I^2 = 98.8%; panoramic + periapical radiograph = 40%; 95% CI 32%–49%; I^2 = 97.7%). Using CBCT to evaluate root filled teeth yielded a much higher frequency of AP than the other methods (65%; 95% CI 44%–81%; I^2 = 97.2%); the same as not apparent when analysing nontreated and all teeth (nontreated 1%; 95% CI 0%–3%; I^2 = 96.9%; all teeth 6%; 95% CI 2%–13%; I^2 = 98.9%).

Using PAI ≥ 4 (or similar approaches) to determine AP decreased the frequency of endodontic lesions in all teeth compared to studies that considered PAI ≥ 2 or ≥ 3 (PAI ≥ 2 = 6%; 95% CI 5%–8%; I^2 = 99.5%; PAI ≥ 3 = 5%; 95% CI 4%–6%; I^2 = 99.5%; PAI ≥ 4 = 2%; 95% CI 1%–2%; I^2 = 66.5%). In nontreated teeth and in root filled teeth the same pattern was observed (nontreated teeth PAI ≥ 2 = 4%; 95% CI 3%–6%; I^2 = 99.1%; PAI ≥ 3 = 2%; 95% CI 2%–3%; I^2 = 99.4%; PAI ≥ 4 = 1%; 95% CI 1%–2%; I^2 = 90.5%; root-filled teeth PAI ≥ 2 = 48%; 95% CI 41%–55%; I^2 = 98.2%; PAI ≥ 3 = 38%; 95% CI 35%–42%; I^2 = 98.3%; PAI ≥ 4 = 14%; 95% CI, 4%–39%; I^2 = 97.4%).

Discussion

The pooled data from the primary studies revealed that 52% of the adult population worldwide have at least one tooth with AP. The present findings arise from a comprehensive search of the literature on the topic, confirming that AP is a highly prevalent disease. In addition, this review is novel in detecting socioeconomic, medical and methodological factors affecting the prevalence of AP. Importantly, the high prevalence of AP should prompt health policymakers, medical and dental communities to take action with regard to the hidden burden of the endodontic disease in the global population.

A nondiagnosed AP may lead to future tooth loss (Frisk & Hakeberg 2005). This is especially relevant in developing countries where tooth loss in the adult population remains high (Seerig *et al.* 2015), compromising their quality of life (Haag *et al.* 2017). Furthermore, a nontreated AP may be a source of systemic inflammation (Gomes *et al.* 2013), and studies have hypothesized that its presence may be associated with systemic illness such as cardiovascular disease and diabetes (Khalighinejad *et al.* 2016). Preventive measures, for example caries control, should be taken at the population level. At the individual level, teeth that could be more prone to AP (restored and root filled teeth, teeth with carious lesion; Kirkevang *et al.* 2004) are condidates for a periapical radiographic examination, in conjunction with clinical tests, for AP screening.

The prevalence of AP was slightly higher in the developing countries than in the developed ones. The same was observed in the secondary analyses using the tooth as the unit of observation. It is well known that people from developed countries have lower rates of tooth loss than those living in poorer countries (Seerig *et al.* 2015). The remaining teeth are subjected to dental problems such as caries, and treatments such as root canal treatment, characteristics closely associated with the presence of AP (Kirkevang *et al.* 2004). It is reasonable to assume that the small difference in the frequency of teeth with AP between the subgroups may be related to these factors.

Another possible reason for this small difference may be related to the recruitment of samples from DCS in the majority of the studies included in the meta-analysis. Irrespective of the country, samples from DCS are more likely to present oral problems than the GP (Kirkevang 2018). In fact, the subgroup analysis revealed that people from DCS had a higher prevalence of AP compared to those from the GP; the same was noticed at the tooth level. However, even in the GP, the prevalence of AP was very high, around 40%. Studies exploring data from individuals that seek dental treatment may be useful for planning the amount of human and financial resources needed to treat this specific group of individuals but not for planning preventive and treatment health policies at a broader level (Hulley *et al.* 2001). All studies pertaining to the GP subgroup included in this meta-analysis were from developed countries. Generalizing these results to countries with more inequalities does not seem appropriate, but it is possible to infer that the prevalence of AP would be higher in the GP from developing countries.

The frequency of AP was higher in root filled teeth than in nontreated teeth regardless of where the individuals were recruited. The nature of the cross-sectional studies, from which the majority of the data was collected, does not allow to identify whether the lesions were developing and progressing or in the process of healing; thus, some of the AP associated with root filled teeth may not represent active diseases. Furthermore, some detected AP might be scar tissues without any sign of inflammation (Kruse *et al.* 2017).

Individuals recruited from hospitals had a prevalence of AP similar to those from DCS. It can be speculated that people recruited from hospitals already have other illness and treatments as a priority in their lives, and oral health issues thus tend to be neglected. On the other hand, it can also be argued that this result might be a consequence of the so-called association between the endodontic disease and systemic conditions, which has been the focus of several investigations in the past decades. Out of the 114 included articles, twenty-seven explored some systemic condition (at the individual level). The pooled data of this meta-analysis showed that 63% of the participants with some systemic condition had at least one AP, whilst 48% of healthy individuals had endodontic lesions. At the tooth level, the general health status also affected the frequency of AP in both nontreated and root filled teeth. Most studies included in this category were related to diabetes, CVD and smoking habits. However, the present analysis does not allow to infer whether the association of systemic diseases with AP exists since no attempt at controlling confounders was made. Also, the studies included in the healthy category cannot exclude the possibility of having participants with some systemic condition since this information was not available in the majority of them.

Previous systematic reviews tried to answer the question of whether the mentioned assumption can be valid. Berlin-Broner *et al.* (2017) performed a systematic review of the association between CVD and AP. The authors concluded that the majority of the primary studies found a positive relationship between the dental and the systemic conditions, but the evidence was not strong enough to guarantee the association. In another systematic review of the literature which included CVD, diabetes, liver disease, blood disorders and osteoporosis, Khalighinejad *et al.* (2016)

stated that there might be an association between some of these systemic conditions and the endodontic disease, but the majority of the studies had a moderate or a high risk of bias. The same was concluded by Tibúrcio-Machado *et al.* (2017) in a literature review after evaluating the quality of the studies about diabetes. In the quality assessment analysis carried out in the included articles, only two studies had a low risk of bias; fourteen had moderate risk, whilst 11 had a high risk of bias.

AP usually presents without symptoms, and its diagnosis is mainly made through radiographic images. Based on the data included here, fifty-six studies used exclusively panoramic radiograph, 33 only periapical radiograph, 20 panoramic with periapical radiograph, one periapical radiograph with pulp test, three studies CBCT and one study used one of the three image methods on a case-by-case basis. Studies that made the diagnosis using periapical radiograph had 10% more people with at least one AP than the ones using panoramic radiograph. Panoramic with periapical radiograph was associated with a slightly higher prevalence of AP than the periapical radiograph alone. In the tooth-based analyses, the difference was only noticed in root filled teeth, to which the majority of the lesions are related. As already expected, the studies that used CBCT reported higher proportions of individuals and root filled teeth with AP compared to those that used panoramic and periapical radiograph.

Self-reported validated tools for predicting the presence of root canal treatments have been demonstrated to be accurate, but the same has not been observed for the presence of AP (Gomes *et al.* 2012, Franciscatto *et al.* 2019). Magnetic resonance imaging (MRI) has been shown to be a promising nonionizing method to detect AP, but coils to apply in tooth-based protocols have not been developed (Di Nardo *et al.* 2018). Thus, periapical radiograph, panoramic radiograph and CBCT are still the conventional methods used in AP diagnosis. Panoramic images are less effective for the evaluation of the periapical area of all teeth, except for the maxillary second molars and both maxillary and mandibular third molars (Ridao-Sacie *et al.* 2007), from which it could be inferred that the use of panoramic images alone is not adequate for the purpose of AP screening. Pooled data from *in vitro* studies using artificial periapical lesions has revealed that CBCT has better diagnostic accuracy than periapical radiograph (Leonardi Dutra *et al.* 2016). In an *ex vivo* study using human mandibles with real AP, Kruse *et al.* (2019) found that CBCT was associated with a higher risk of false-positive and false-negative diagnosis than periapical radiograph, especially in root-filled teeth. Combining the evidence collected so far with the ALARA and ALADA principles, CBTC should not be the method of choice for AP diagnosis in epidemiologic studies.

Seventy-one out of 114 included articles carried out the periapical assessment using the Periapical Index (PAI). The index, developed by Ørstavik *et al.* (1986), was based on the study of Brynolf (1967), which compared the histological progression of an AP with the appearance of the lesion in the radiographic image. The 5-point ordinal scale is usually dichotomized into 'healthy' and 'diseased' using the cut-off between PAI 2 and PAI 3, but some studies prefer to use the threshold between PAI 1 and PAI 2. In order to facilitate the subgroup analysis, studies that considered an AP if the tooth presented a condensing osteitis or a periodontal ligament not exceeding two times the width of its lateral part were clustered with studies that considered a diseased tooth if the tooth presented small changes in the bone structure (PAI 2). Teeth with a periodontal ligament exceeding two times the width of its lateral part, a broken lamina dura or a discernible AP were grouped with studies that considered an AP if the tooth showed a PAI ≥ 3.

The prevalence of individuals having at least one AP was similar when considering the AP being either PAI ≥ 2 or PAI ≥ 3. However, the prevalence of the disease was lower if only PAI ≥ 4 were considered. PAI 4 is characterized by a well-defined radiolucent area, whereas PAI 5 is apical periodontitis with exacerbating features; thus, the results were already expected since a smaller portion of radiographically identifiable periapical lesions has these characteristics (Brynolf 1967). In the secondary analyses, the frequency of all teeth and nontreated teeth was only 1% and 2% higher, respectively, in the subgroup PAI ≥ 2 compared to PAI ≥ 3. This difference increased in the root filled teeth (8%), which can be explained by the fact that a treated tooth has more chances of being classified as PAI 2 than a nontreated one (Brynolf 1967).

There are some limitations related to the present meta-analysis which deserve to be discussed. The high clinical heterogeneity identified in the primary studies hampered the attempt to cluster only studies with similar characteristics since their variability had multiple sources. Another limitation is related to the comparison of the AP prevalence between healthy individuals and individuals with systemic diseases. Some data were extracted from between-study comparisons, and others combined estimates from within-study comparisons. This approach may be prone to bias; however, it allowed the estimation of the effect of systemic conditions on the prevalence of AP, emphasizing the need of the medical history investigation of the patients in the endodontic setting. In addition, most of the primary studies were carried out in Europe using nonrepresentative samples, and the gathered information was obtained from studies published in a period of more than 40 years. Thus, it is acknowledged that the pooled data in the present meta-analysis may not truly represent the worldwide current scenario on the prevalence of AP. However, the present review followed a careful and comprehensive literature search strategy, which resulted in a robust identification of the best available evidence about this topic. Finally, the high risk of bias across the primary studies also indicates that the findings must be interpreted with caution, meaning that they may be overestimated, especially due to the scarcity of community representative samples.

A methodological strength of this systematic review is the high sensitivity of the search. Considering articles in other languages than English allowed the inclusion of five studies that would have been missed if a language restriction had been applied. Moreover, the inclusion of cohort and case–control studies allowed the inclusion of more articles since the baseline of a cohort gives information about the prevalence, and the two groups of a case–control also provide this data. Nonetheless, even with a more restricted search strategy, Miri *et al.* (2018) also found the same prevalence of AP in the population worldwide. Probably, the inclusion of articles in English and with cross-sectional design provided sufficient information, as these articles constitute the most significant part of the body of evidence regarding the prevalence of AP. Another important strength of this meta-analysis is the subgroup analyses. They brought essential characteristics that can be involved in the prevalence of the endodontic disease.

Interestingly, it seems that 12 included studies were classified incorrectly regarding the study design in the original publications. Six articles described as retrospectives or cohort had, in fact, a cross-sectional design (Bołtacz-Rzepkowska & Laszkiewicz 2005, Gumru *et al.* 2011, Willershausen *et al.* 2014, Grønkjær *et al.* 2016, Hussein *et al.* 2016, Piras *et al.* 2017). A study is classified as retrospective when data from the predictor is obtained from information collected in the past, and the aim is to verify the influence of this predictor on the outcome of interest. When data from the predictors and the outcome are from the same time-point, the study is classified as cross-sectional (Hulley *et al.* 2001). Four out of five studies described as case–control were, in fact, cross-sectional paired with control groups (Hommez *et al.* 2008, Pasqualini *et al.* 2012, Leal *et al.* 2015, Poyato-Borrego *et al.* 2019); only one study was a real case–control, in which the AP was the predictor (Khalighinejad *et al.* 2017a). The case–control design is usually given to a study in which the outcome is rare, and the predictor is collected based on information from the past; in this situation, a group without the outcome of interest is controlled by important characteristics to be compared to the case group (Hulley *et al.* 2001).

The quality assessment of the primary studies was carried out using a tool based on a modified Newcastle-Ottawa Scale for cross-sectional studies because a valid scale for this study design has not been developed yet. The cohort and case–control studies as well were evaluated using this scale, since only the prevalence data was necessary for this meta-analysis. The main detected flaws were regarding the sample selection process. Amongst the studies that collected data in DCS, some of them stated that the aim was to evaluate the prevalence of AP in their city/country, which is not a suitable way to achieve representativeness of an entire population. Sample calculation or data collection from an entire subpopulation was provided by 33 studies, and only one reported the nonresponse rates.

Regardless of the outcome being measured either by an objective or subjective method, training and calibration of the observers are mandatory to avoid introducing bias in the study (Hulley *et al.* 2001). The diagnosis of an AP is subjective, and a consistent training programme is time-consuming but strictly necessary. One of the advantages of applying the PAI system is the existing training material provided by Dr. Ørstavik (upon request), with which the observer has the opportunity to learn the fundamentals of the scale, to practice and to calibrate the results with the standard reference established through a consensus between five endodontists, one dental radiologist, four general practitioners and one dental assistant (Ørstavik *et al.* 1986). Only 36 studies undertook the training process adequately, and 52 went through this phase partially. Another precaution to avoid bias for studies using control groups is the observer being blind to the predictors. Only six out of 25 studies were careful in taking this precaution. Also, when using a control group, the comparability between the participants is relevant. This meta-analysis selected two essential characteristics that, once not respected, could become the control group noncomparable to the study group: location of recruitment and age. As already mentioned, the prevalence of the endodontic disease depends on where people are recruited and their age (Kirkevang 2018). Comparing the AP prevalence between people from hospitals and DCS may introduce selection bias, and many primary studies undertook this comparison. Even though it was not possible to analyse the effect of ageing in the prevalence and frequency of AP since the majority of the studies did not provide the data stratified by age, it seems that the prevalence is higher as the age increases, especially in populations with low rates of tooth extractions and accumulation of dental treatments, for example root canal treatments (Kirkevang 2018).

Some additional considerations are necessary. First, adjustments made in the statistical analyses of the studies were not considered, because only the descriptive data were required for this meta-analysis. Moreover, until recently, there was no checklist to describe observational studies (i.e. Strobe checklist). Thus, studies previously published could have followed the required steps but failed to report the information. The authors acknowledge the effort of all researchers in carrying out the studies on the prevalence of the endodontic disease and stress that more studies are needed, especially those where representative samples are recruited, which could provide deeper knowledge on the endodontic status at a broader population level. In addition, it is recommended that future research on this topic should provide information on the prevalence of AP at both tooth and individual levels, preferably stratified by age, as well as information on sociodemographic, oral and medical covariables as possible risk indicators. A careful sample selection process will provide unbiased data, which would be more relevant for researchers, dental practitioners and policymakers. Finally, the present systematic review should be updated regularly to analyse the trends of modification in the pooled estimates of the prevalence of AP worldwide. Ultimately, this information will be essential to evaluate whether all the scientific and technological progress experienced by Endodontology, associated with the public health strategies, will be, in fact, translated into a reduction in the prevalence of the endodontic disease in the world.

Conclusion

The results from this meta-analysis confirmed a high global prevalence of AP, with 52% of pooled samples worldwide reporting at least one tooth with AP. Subgroup analysis revealed the following factors have an influence on the prevalence of AP: socioeconomic status of the country (greater prevalence of AP in samples from developing countries); location of recruitment (greater prevalence of AP in samples from DCS); the systemic conditions (greater prevalence of AP amongst individuals with one or more systemic conditions); the risk of bias of the primary studies (greater prevalence of AP in studies with higher risk of bias); the image method used (higher prevalence of AP in studies using CBCT); the method used to assess the AP (methods compatible with PAI ≥ 4 decreased the prevalence of AP). The present findings should bring the attention of health policymakers, medical and dental communities to the hidden burden of the endodontic disease in the population worldwide.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Supplementary Material 1. Search strategies.

Supplementary Material 2. Quality assessment tool used to analyse the risk of bias of the included studies.

Supplementary Material 3. Characteristics of the selected studies (secondary outcomes: prevalence of AP in all teeth, nontreated teeth and root-filled teeth).

Supplementary Material 4. Quality assessment of the primary studies.

Supplementary Material 5. Subgroup analysis of prevalence of AP (main outcome) according to the socioeconomic status of the country.

Supplementary Material 6. Subgroup analysis of prevalence of AP (main outcome) in the different locations of recruitment.

Supplementary Material 7. Subgroup analysis of prevalence of AP (main outcome) in healthy individuals and with systemic conditions.

Supplementary Material 8. Subgroup analysis of prevalence of AP (main outcome) according to the method of image.

Supplementary Material 9. Prevalence of AP in all teeth (secondary outcome) in the population worldwide.

Supplementary Material 10. Prevalence of AP in nontreated teeth (secondary outcome) in the population worldwide.

Supplementary Material 11. Prevalence of AP in root-filled teeth (secondary outcome) in the population worldwide.