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Prevalence of Apical Periodontitis and Conventional Nonsurgical Root Canal Treatment in General Adult Population: An Updated Systematic Review and Meta-analysis of Cross-sectional Studies Published between 2012 – 2020.

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TITLE PAGE

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ABSTRACT

Introduction: This study aimed to summarize data on apical periodontitis (AP) and nonsurgical root canal treatment (NSRCT) prevalence and risk factors related to age, gender, and quality of restorative and endodontic treatment in the general population from cross-sectional studies published between 2012 and 2020.

Methods: An electronic search was performed in the following databases: Web of Science, Scopus, and PubMed. The conducted literature search covered studies published between 2012 and 2020, without restrictions on language. The STROBE and NOS tools were used for quality assessment of the included studies.

Results: Sixteen articles were included in the review. In total, 200.041 teeth were examined. On average, 6.3% of teeth had AP, and 7.4% had NSRCT. Forty-one percent of RCT teeth had AP, while 3.5% of untreated teeth had AP. Females are less prone to AP in endodontically treated teeth only, compared to males ($P < .001$). Variable stratification of age subgroups among included studies prevented us from conducting a meta-analysis. An increase in AP frequency was found in teeth with inadequate restorative and endodontic treatment ($P < .001$, and $P < .001$, respectively). Due to high heterogeneity, these results should be taken with caution.

Conclusions: There is an increased AP prevalence in the adult general population compared to data from 2012 (6.3% versus 5.4 %), both in endodontically treated (41.3% versus 35.9%) and untreated teeth (3.5% versus 2.1 %). Additionally, AP developed more frequently in females

with endodontically treated teeth and in teeth with inadequate compared to adequate restorative and endodontic treatment.

KEY WORDS

Periapical periodontitis, Conventional nonsurgical root canal treatment, Epidemiology, Prevalence, Population, Systematic review, Meta-analysis

INTRODUCTION

Oral diseases (ODs) represent a range of clinical conditions that affect hard and soft oral tissues and are usually chronic and progressive in nature (e.g. dental caries, periodontal disease, and oral cancers) (1). Although largely preventable, ODs are among the most prevalent diseases globally, with a significant impact on general health and socioeconomic status of affected individuals (2).

As an inflammatory OD, apical periodontitis (AP) develops typically from the exposure of the vital pulp to different oral microbiota as a result of dental caries, accidental trauma or iatrogenic causes (3, 4). The colonization of microorganisms leads to necrosis of the dental pulp and development of infection in the periapical region of affected teeth. Consequent activation of the host's immune response results in local acute and/or chronic inflammation, resorption and destruction of periapical tissues, and formation of periapical lesions (i.e. granuloma and/or cyst) (3-5).

Epidemiological studies bring useful knowledge about trends in incidence and prevalence of diseases and their risk factors. These data are valuable for planning appropriate health care strategies to prevent or decrease the occurrence of considered disorders (6). In 2012, Pak *et al.* (7) systematically reviewed data of 33 cross-sectional studies published between 1987 and 2011, addressing the prevalence of AP and conventional nonsurgical root canal treatment (NSRCT) in the adult worldwide population. Based on epidemiological data on over 300,000 analyzed teeth, the authors reported a prevalence of approximately 5% of AP (broadly equivalent to one periapical lesion per patient) and 10% of NSRCT (broadly equivalent to two treatments per patient) in the adult population; the prevalence of AP in treated and untreated teeth was 36% and 2%, respectively (7). In recent years, several systematic reviews investigating the epidemiology

of AP were also published, but they were restricted only to elderly (8, 9), smokers (10), and patients with compromised general health (e.g. diabetes mellitus, cardiovascular diseases, etc.) (11, 12, 13), not to the general population.

Eight years after the review of Pak *et al.* (7), the epidemiology of AP, including the evaluation of risk factors for disease development, is still an important topic, especially because of AP impact on general health (11). Moreover, the influence of person- (i.e. age and gender) and tooth-specific risk factors (i.e. quality of restorative and endodontic treatment) on the prevalence of AP and NSRCT is still under debate, and the obtained results from primary studies are inconclusive and inconsistent. Besides, a previous systematic review (7) did not evaluate the potential influence of specific risk factors on the prevalence of AP and NSRCT in the general adult population. Notwithstanding, in the meantime, a significant number of original scientific reports from different countries have been published, potentially modifying the conclusions drawn in the 2012 systematic review. Thus, to explore more valuable epidemiological data regarding the prevalence of AP and NSRCT, this updated systematic review and meta-analysis intended to summarize currently existing evidence on AP and NSRCT prevalence and risk factors related to age, gender, and quality of restorative and endodontic treatment in the general worldwide population from cross-sectional studies published between 2012 and 2020.

MATERIALS AND METHODS

A detailed protocol of this systematic review and meta-analysis was defined and agreed by all authors, following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols statement (PRISMA-P) (14, 15) as well as the Cochrane handbook

(16). The study was registered in the International prospective register of systematic reviews: PROSPERO database (CRD42020166285). The PRISMA checklist was added as a Supplementary Table 1.

Focus Questions

Specific focused questions were:

1. What is the prevalence of AP and NSRCT in the general adult population?

2. What is the prevalence of AP in endodontically treated and untreated teeth in the general adult population?

3. Is there a difference in the prevalence of AP, NSRCT, AP in treated and untreated teeth between gender and age-specific subgroups in the general adult population?

4. Is there a difference in the prevalence of AP regarding the quality of root canal filling and coronal restoration procedures in endodontically treated teeth?

Eligibility criteria

The following inclusion criteria were applied:

- Cross-sectional studies with participants with a radiographic and/or tomographic evaluation of the prevalence of both AP and NSRCT,

- Articles published from January 2012 to January 2020 with no limits applied for the language of publication,

- Studies conducted only on adult individuals (older than 16 years) with permanent teeth,

- Third molars not included in the evaluation of investigated parameters, and

- Studies with 20 or more subjects.

The exclusion criteria were:

- Studies that failed to meet the abovementioned inclusion criteria,

- Literature and systematic reviews, meta-analyses, case reports and case series,

- Studies that dealt with smokers and individuals with reported systemic disease,

- Studies in which analyses were presented only per patient and not per tooth, and

- Studies that reported duplicated data.

Literature Search Strategy

A comprehensive electronic search was performed in the following national and international databases: Clarivate Analytics Web of Science (including Web of Science Core Collection - WoS, Korean Journal Database - KJD, Russian Science Citation Index - RSCI, SciELO Citation Index - SCIELO), Scopus and PubMed. Key terms and strategy differed according to the database being searched, using the most common free keywords and relevant controlled vocabulary (Medical Subject Headings – MeSH, https://www.ncbi.nlm.nih.gov/mesh). The search algorithms are presented in detail in Table 1.

Furthermore, cross-validation was made with grey literature through Google Scholar and available repositories (e.g. Networked Digital Library of Theses and Dissertations, Open Access Theses and Dissertations). In addition, all this search was supplemented by checking bibliographies of the most relevant books and review articles. Finally, references of all primary studies were manually screened to ensure the reliability of data collected. For duplicates removal and further analysis, all records obtained were imported into EndNote Online (Clarivate Analytics 2020, https://www.myendnoteweb.com).

Study Selection

The relevance of each article was assessed based on its title and abstract, followed by a full-text evaluation. Study selection was performed independently by 3 reviewers (A.J., N.N., and J.J) using the pre-specified eligibility criteria. Any disagreement was discussed and decided

on with a fourth side (J.M). The articles that fulfilled all criteria after reading the full-text were selected for detailed data processing.

Data extraction

General information about each article that met eligibility criteria and an acceptable quality rating (i.e. authors' names, publication year, the country where the study was conducted) was collected to create a table of evidence. To answer all focus questions, the following data were extracted: number of participants (males/females), average age, the total number of analyzed teeth, number of those with AP, number of teeth with NSRCT, number of treated versus untreated teeth with AP, type of radiographic (RTG) analysis, number of observers, inter and/or intra calibration rates, parameters for AP and RCT evaluation and the tooth most frequently affected with AP and the most frequently affected tooth with RCT.

Quality Assessment of Individual Studies

Critical appraisal of potential studies was performed independently by two reviewers (J.J., O.P.) using the Newcastle-Ottawa Scale (NOS) adapted for cross-sectional studies (17, 18) and The STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement (19). The methodological quality of a study was evaluated using the NOS star rating system, in which a study is judged on three broad aspects, including the sample selection, the comparability of the groups, and the outcome assessment. Studies awarded with 7–9 and 5–6 stars are considered high-quality and moderate-quality, respectively, while studies with fewer than five stars are regarded to be at a high risk of bias (low-quality studies) (20). Quality of study reporting was evaluated using the STROBE statement checklist for cross-sectional studies. The STROBE checklist items were appraised with 32 questions, which could be answered as yes, no, or not applicable. The STROBE score was calculated for each study as the number of questions

adequately reported in the study divided by the number of applicable questions. Based on the STROBE score expressed as a percentage, studies were categorized into high (>80% of the STROBE criteria achieved), moderate (50-80% of the STROBE criteria fulfilled), or low (<50% of the STROBE criteria met) reporting quality level (21). All disagreements between the two reviewers were resolved by consensus and discussion including a third reviewer (B.M.).

Statistical analysis

The relevant data from the studies included in the qualitative analysis were extracted and presented in tables. Descriptive analysis was used to identify similarities and variations between the studies. Only the studies that provided all necessary information were considered for meta-analysis that was done using Review Manager (RevMan) software package, Version 5.3. Statistical heterogeneity was calculated using heterogeneity test, I^2, and a value of >50% was considered substantial according to the Cochrane Handbook for Systematic Reviews of Interventions (16). A random-effects model was used when heterogeneity was present, and if heterogeneity was not present, a fixed-effect model was used. The level of significance was set at .05. Due to the small number of studies included in each meta-analysis (< 10), the assessment of the publication bias via funnel plot was not suggested (16). Geo-mapping of the AP prevalence data was done using R version 3.6.1 (R Core Team, Vienna, Austria) and the R package rworldmap version 1.3-6 (22).

RESULTS

Study Selection

Database screening with removal of duplicates, identified 1208 studies (Fig. 1). After screening the titles, 379 studies were left. The number of studies was further reduced to 95 following

abstracts examination. Full texts of these 95 studies were then assessed for eligibility and 79 were excluded due to reasons listed in Supplementary Table 2. Finally, 16 articles were included in the present analysis (23-38).

Characteristics of Included Studies and Description of Study Populations

All included studies were cross sectional, written in English and published between 2012 and 2020. The most important characteristics are listed in Tables 2, 3 and 4.

General information regarding study populations are given in Table 2. The total number of subjects was 8872, while per study it ranged from 100 to 1160. Female to male ratio varied from 0.83 to 3.26; this information was not provided in 4 studies (25, 26, 29, 34). Where specified, the mean age of the participants varied between 26 and 52 years. The common unit of reporting in the included literature was the tooth. In total, 200,041 teeth were examined, from 2,368 to 30,098 per study (Table 2). On average, 6.3% of teeth had AP, 7.4% had RCT; also, 41.3% of RCT teeth had AP, while only 3.5% of untreated teeth had AP (Table 2).

The locations of the survey sites with observed AP prevalence, are shown in Figure 2. The map in Figure 2A is based on the data published between 1987 and 2011 in the adult worldwide population (39-71), while Figure 2B offers insight into the results of the studies that are included in this review (23-38). The map depicted in Figure 2A shows that most surveys conducted until 2012 have occurred in North America and Europe. By contrast, little information on AP prevalence was available from the Asian region, while no survey has covered South America, Africa, and Australia/Oceania. The first data on the prevalence of AP in Africa and Australia were obtained after 2015 (Fig. 2B). No study from the South American region satisfied eligibility criteria to be included in this systematic review.

Age related AP and NSRCT frequencies

Regarding the age of the subjects, the studies included in the qualitative analysis have provided very variable subgroups, therefore preventing us from performing a meta-analysis. Six studies (25, 26, 29, 30, 34, 38) did not find a significant difference in prevalence of AP and/or RCT between different age subgroups. Out of those with a significant difference in age related prevalence, subjects older than 50 years were most affected in the majority of included studies (23, 25, 27, 28, 31, 32, 36). Only Alrahabi *et al.* (32) have found AP more frequently than RCT in the younger (36-45 years) versus older group (46-55 years), while other studies have reported the same age groups for both AP and RCT frequencies.

Meta-analyses of AP and NSRCT frequencies: Female Versus Male Subjects

Of the 12 studies presenting female to male ratio, the number of analyzed teeth in each subgroup was available in 8, while in 7 studies only (23, 27, 31, 32, 35-37) the number of teeth with AP was available for meta-analysis for the female versus male subgroup (Table 3). There was no significant difference in AP prevalence between female and male subjects (P = .32), with obvious great heterogeneity between the studies (I^2 = 93%, Fig.3A). Of the 7 studies presenting the number of teeth with RCT, data from 6 (23, 31, 32, 35-37) were available for meta-analysis (Table 3) and there was no difference between female and male subjects (P = .21), with a high heterogeneity between the studies (I^2 = 85%, Fig. 3B). Significant decrease in AP frequency in treated teeth was found for female subjects, based on the available data from 5 studies (23, 32, 35-37) with 4822 analyzed teeth [Odds Ratio (OR) = .81; 95% Confidence Interval (CI) .72 - .91; P = .0006; I^2 = 0%, Fig. 3C]. In contrast, no difference was found between female and male subjects for the occurrence of AP in untreated teeth (P = .64; I^2 = 93%, Fig. 3D).

Meta-analyses of AP frequency: Adequate Versus Inadequate Tooth Treatment

The data from 8 studies regarding the quality of RCT and the occurrence of AP were available for meta-analysis (24-27, 29, 30, 36, 38). An evident predominance of AP frequency was observed in inadequately treated teeth [OR = 4.65; 95% CI (2.75 – 7.84); $P < .00001$]. However, there was a great heterogeneity between the studies ($I^2 = 97\%$, Fig.4A).

Meta-analyses of AP frequency: Acceptable Versus Unacceptable Coronal Restoration

A slight increase in AP frequency was found in teeth with unacceptable coronal restoration [OR = 1.54; 95% CI (1.16 – 2.05); $P = .003$], also with a high heterogeneity between the studies ($I^2 = 85\%$, Fig.4B).

Description of Radiographic Characteristics

Radiographic (RTG) evaluation was performed using cone beam computed tomography (CBCT) in four studies (28, 31, 37, 38), two used combination of digital panoramic radiography (DPR) and periapical radiography (PR) (33, 35), while the others only used DPR (23-27, 29, 30, 32) (Table 4). On average, two observers per study have performed the RTG evaluation (range from 1-5, standard deviation 1), all calibrated, with an inter- and/or intra-observer agreement >0.8. AP evaluation was mostly performed using the criteria described by Ørstavik *et al.* (72) and De Moor *et al*. (40), while RCT was mostly evaluated according to De Moor *et al*. (40) and European Society of Endodontology guidelines (73). AP was most frequently reported in mandible, and molars were the most affected teeth. RCT teeth were almost equally distributed through mandible and maxilla, molars being treated most frequently.

Quality Assessment

The detailed results of the evaluation of the methodological and reporting quality of the 16 cross-sectional studies included in this review are presented in Supplementary Tables 3 and 4, respectively.

Based on the NOS scale, the overall methodological quality was high, with only one study being classified as moderate (25) (Supplementary Table 3). Four of them reached the maximum score (33, 36, 37, 38), while the remaining studies scored 8 or 7 stars. Deficiencies identified in the studies were mainly related to unjustified sample size, or to the used statistical test that was not completely or appropriately described.

Regarding the critical appraisal of the reporting quality, more than 80% of items in the STROBE cross-sectional checklist were reported in four studies included in this review (33, 34, 36, 37), classified as high level (Supplementary Table 4). According to the STROBE criteria, the reporting quality of other studies was assessed as moderate. Recorded reporting deficiencies were primarily related to providing the name and role of the funder (item 22), explaining how missing data were managed (item 12c), describing analytical methods in sampling strategy (item 12d), reporting missing data (item 14b), or explaining how the study size was reached (item 10).

DISCUSSION

Recent meta-analyses have shown strong evidence of a link between AP, systemic low-grade inflammation (80), and impairment of systemic health (11-13). However, the gravity of the problem does not seem to have attracted the attention needed by such a common disease. In most of the cases, AP is a direct consequence of dental caries which leads to pulp necrosis and continuous spreading of infection in the periapical region. Given the epidemic burden of dental

caries worldwide (i.e. 2, 4 billion people affected, or 35% of the global population) (81), it is reasonable to investigate the epidemiology of AP, including the predisposing risk factors.

This systematic review and meta-analysis updated the previous work of Pak *et al.* (7) published in 2012. In the final qualitative and quantitative review, based on very rigorous eligibility criteria, we included 16 cross-sectional studies published between 2012 and 2020. Our results indicate a slight increase in the worldwide prevalence of AP in the general adult population compared to previous research. Namely, 6.3 % (12,602) of 200,041 analyzed teeth were affected. In contrast to the previous review, we reported a decrease in the percentage of teeth with NSRCT (9.6 % vs. 7.4%). Notwithstanding, these results should be taken with caution because the authors of the primary studies did not report whether the NSRCT was completed or directly related to the infection or the restoration. Moreover, we observed a significant increase in AP among endodontically treated (41.3% vs. 35.9%) and untreated teeth (3.5% vs. 2.1%) compared to the previous review. A slight increase of AP prevalence in the general adult population (from 5.4% to 6.3%) between two analyzed periods was expected based on the continuous increase of age-standardized incidence of dental caries in the last 30 years (81). However, the worrying results are related to AP prevalence increase among endodontically treated teeth (from 35.9% to 41.3%). These findings suggest that the quality of restorative and endodontic treatment has to be significantly improved to minimize, or even reverse, future increase in this investigated category. To address this issue, endodontic treatment should be limited to specialists in this field or much more effort has to be invested in the improvement of the general dentists' training skills. Otherwise, a continuous increase in AP prevalence among endodontically treated teeth could also be expected in the future.

Although participants' age and gender are not usually identified as independent variables in studies of endodontic outcomes, this study aimed to investigate whether significant differences exist between males and females, and between different age groups regarding the prevalence of AP in the general adult worldwide population. Our results indicate that females are less prone to AP development only in endodontically treated teeth compared to males [OR= .81; 95% CI (.72 - .91), $P < .001$]. Conversely, no significant differences were observed between males and females in other investigated categories. Although the results of primary studies regarding the gender of participants as a predisposing factor for AP development are conflicting, it has to be stressed that several studies reported significant differences in oral hygiene habits between males and females (82, 83) and greater interest of women in receiving dental care and attendance for check-ups (84).

Regarding the relationship between age and prevalence of AP and CNRCT in the adult general population, variable stratification of age subgroups among included studies prevented us from conducting a meta-analysis. Similarly, Rutz da Silva *et al.* (9) concluded that meta-analysis of AP prevalence among elders was not possible due to the inability to select only data related to elderly subjects. Nevertheless, we have shown that 7 studies (23, 25, 27, 28, 31, 32, 36) reported a significantly higher prevalence of AP and CNRCT among subjects older than 50 years. These findings are expected due to the physiological aging of dental pulp in elders (85), making a positive outcome of NSRCT in this population even more challenging.

In previous epidemiological studies, attempts have been made to identify potential tooth-specific risk factors for the development of AP (85-92). Namely, Kirkevang *et al.* (85-92) have reported that in order to detect AP the most decisive risk indicator is a root-filled tooth that should be always exposed to radiographic examination if the patient is new to the dentist. They

also concluded that patients with radiographically estimated inadequate root canal treatment and coronal restoration are more prone to develop AP (85-92). In this regard, we investigated whether these situations could be linked to the more frequent occurrence of AP in endodontically treated teeth. A meta-analysis of 8 studies (24-27, 29, 30, 36, 38) has shown a significantly higher prevalence of AP in treated teeth among those with inadequate root canal treatment [OR = 4.65; 95% CI (2.75 – 7.84); $P < .00001$]. The same trend was observed for inadequate coronal restoration. Endodontically treated teeth with poor coronal restoration are more prone to develop AP compared to those with adequate restoration [OR = 1.54; 95% CI (1.16 – 2.05); $P = .003$]. These findings are in accordance with the results of a systematic review conducted by Gillen et al. (93), who concluded that the odds for the healing of AP increased with both adequate endodontic and restorative treatment. However, all these findings have to be interpreted with caution due to high heterogeneity. The sources of this heterogeneity are lined in the inadequacies of primary studies included in this systematic review (i.e. inconsistent results, small sample size, and the number of included studies).

For a long time, conventional imaging techniques (i.e. digital panoramic and periapical radiography) have been used to diagnose periapical radiolucencies and to distinguish them from a healthy periapex. In this systematic review, nine studies used DPR, one study used PR, while two studies combined both techniques (Table 4). Although it has been suggested that PR is more accurate in the assessment of periapical radiolucencies (94), several advantages of the DPR method were listed (e.g. the relatively low exposure to ionizing radiation, visibility of all teeth, the convenience and speed of imaging, etc.) (95). Nevertheless, the conventional imaging techniques show some limits, including anatomic three-dimensional compression of structures, geometric alteration, and/or superimposition of anatomic structures (96). Therefore, the accurate

estimation of periapical radiolucencies might be limited using the conventional imaging techniques, and results regarding the most affected teeth with AP and NSRCT given in the primary studies should be taken with caution. On the other hand, only four studies included in this systematic review employed CBCT analysis (28, 31, 37, 38). As a novel clinical tool, CBCT provides three-dimensional information of investigated pathology and has a higher sensitivity and specificity compared to conventional radiography without superimpositions of adjacent structures (97). Its superiority over conventional techniques in detecting periapical radiolucencies has been reported in several studies (98, 99). Recent guidelines have however advised the use of CBCT for strictly specific indications, and not for routine diagnostic imaging (100). Also, it is important to emphasize that beam hardening artefacts (e.g. radiopaque materials such as metal posts, metal restorations and root filling materials) may reduce imaging quality and represent a limitation of CBCT assessment (97).

The following facets can be considered as a strength of this systematic review: (i) an *a priori* protocol was developed and registered in the PROSPERO database, (ii) a comprehensive literature search with no language restriction was performed in three electronic databases, including the grey literature, in an attempt to avoid relevant studies being missed, (iii) the literature search and data extraction were carried out by two independent reviewers, and any doubts were resolved by a third reviewer, (iv) the use of strict eligibility criteria resulted in the inclusion of 16 studies with approximately 10 000 individuals and 200 000 analyzed teeth from different countries and continents as appropriate representativeness of the general world population, (v) the meta-analysis was performed to determine the association between gender, quality of restorative and endodontic treatment, and the development of AP and RCT, and (vi)

the process followed standard recommendations to critically appraise the quality of cross-sectional studies using the STROBE and NOS tools.

Several inadequacies in the methodology of the included cross-sectional studies may lead to some limitations of this systematic review. Although the majority of studies reported a satisfying calibration agreement between observers, the appropriate selection of radiography technique (conventional radiography versus CBCT) used for AP assessment could influence the final results. Also, a standardized method for the AP assessment should be proposed, in order to obtain results that are comparable between different populations. The sample size calculation based on previous publications or pilot studies has been scarcely reported in primary studies. Moreover, variable stratification of age-related subgroups disabled a meta-analysis of pooled data from the primary studies. Therefore, a unique predefined stratification into specific subgroups is essential to evaluate and compare the available data between studies. All the included studies did not report the STROBE statement of quality reporting of cross-sectional studies. All these inadequacies may lead to high heterogeneity in quantitative analyses of the included studies. Thus, the leading endodontic societies in the world should proceed with the development of guidelines for conducting observational studies in Endodontics (101).

The obtained epidemiological data indicate an evident increase of AP incidence in endodontically treated and untreated teeth compared to the last report. These findings are worrying, mainly because the estimated worldwide incidence of caries will continue to grow in the future (1, 2, 81). From the clinician's perspective, an increased incidence of AP can be expected more in males than females with root-filled teeth, and in the older age subgroups compared to younger. Furthermore, inadequate restorative and endodontic procedures on affected teeth are significant predictors of possible AP development. Bearing in mind the

association of AP with impaired systemic health (e.g. diabetes mellitus, cardiovascular disease, etc.) (11-13), it is relevant to persistently work in resolving this undeniable health condition in the general population.

Finally, we have to emphasize that this systematic review was performed strictly according to guidelines made by Kattan *et al.* (102) and Nagendrababu *et al.* (103) on conducting these types of studies in Endodontics. In contrast, it should be stressed that no specific guidelines exist for conducting epidemiological cross-sectional studies. As a consequence, different sources of heterogeneity may occur (i.e. clinical, methodological, and statistical) (104). Thus, a comparison between conducted studies is difficult owing to the wide variability of evaluated parameters (e.g. specific radiographic parameters used for the evaluation of AP prevalence). Therefore, in the future experts in this field should provide reliable guidelines with clear directions and specific parameters for evaluation based on the current best available evidence.

In conclusion, this updated systematic review and meta-analysis, based on available data from cross-sectional studies published between 2012 and 2020, demonstrate an increased prevalence of AP in the adult general population compared to data published in 2012 (7). This increase was observed both in endodontically treated and untreated teeth. Moreover, females are less prone to the development of AP in endodontically treated teeth compared to males, and AP developed more frequently in treated teeth with inadequate compared to adequate restorative and endodontic treatment. However, these results should be interpreted with caution due to high heterogeneity.

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Figure Legends

Figure 1 – A flow diagram of the study search and identification. n, number of hits, WoS - Web of Science Core Collection, KJD - Korean Journal Database, RSCI - Russian Science Citation Index, SCIELO - SciELO Citation Index

* The list of studies and reasons for exclusions are presented in Supplementary Table 2.

† Analysis of apical periodontitis (AP) prevalence in gender subgroups (23, 27, 31, 32, 35-37)

‡ Analysis of conventional nonsurgical root canal treatment (NSRCT) prevalence in gender subgroups (23, 31, 32, 35-37)

§ Analysis of AP prevalence of treated teeth in gender subgroups (23, 32, 35-37)

ǀ Analysis of AP prevalence of untreated teeth in gender subgroups (23, 32, 35-37)

¶ Impact of the NSRCT quality on the prevalence of AP in treated teeth (24-27, 29, 30, 36, 38)

Impact of the coronary restoration on the prevalence of AP in treated teeth (26, 29, 36, 38)

Figure 2 – The global prevalence of AP among the general adult population: (A) AP prevalence rates between 1987 and 2011 (39-71), (B) AP prevalence rates between 2012 and 2020 (23-38).

* Countries in grey color have no relevant AP prevalence data available.

Figure 3 – A forest plot of comparison: male versus female. (A) frequency of apical periodontitis (AP), (B) conventional nonsurgical frequency of root canal treatment (NSRCT), (C) frequency of AP in NSRCT treated teeth, (D) frequency of AP in untreated teeth.

Figure 4 – A forest plot of comparison: (A) adequate versus inadequate treatment in root canal treated (RCT) teeth with apical periodontitis (AP),

Table 1. Electronic Databases and Search Strategy.

Database (n)		Search strategy #1 and #2
WoS, KJD, RSCI, SCIELO* (n=870)	#1	TOPIC:((Periapical AND (lesion$ OR tissue$ OR disease$ OR radiolucency OR abscess$ OR pathos?s)) OR (apical AND (periodontitis OR radiolucency)))
	#2	TOPIC: (epidemiology OR prevalence OR occurrence OR frequency OR population)
Scopus (n=717)	#1	TITLE-ABS-KEY ((periapical AND (lesion* OR tissue* OR disease* OR radiolucency OR abscess* OR pathosis OR pathoses)) OR (apical AND (periodontitis OR radiolucency)))
	#2	TITLE-ABS-KEY (epidemiology OR prevalence OR occurrence OR frequency OR population)
PubMed (n=606)	#1	(periapical[All Fields] AND lesion[All Fields]) OR ("periapical tissue"[MeSH** Terms] OR ("periapical"[All Fields] AND "tissue"[All Fields]) OR "periapical tissue"[All Fields]) OR ("periapical diseases"[MeSH Terms] OR ("periapical"[All Fields] AND "diseases"[All Fields]) OR "periapical diseases"[All Fields] OR ("periapical"[All Fields] AND "disease"[All Fields]) OR "periapical disease"[All Fields]) OR (periapical[All Fields] AND radiolucency[All Fields]) OR ("periapical abscess"[MeSH Terms] OR ("periapical"[All Fields] AND "abscess"[All Fields]) OR "periapical abscess"[All Fields]) OR (periapical[All Fields] AND pathosis[All Fields]) OR (periapical[All Fields] AND pathoses[All Fields]) OR ("periapical periodontitis"[MeSH Terms] OR ("periapical"[All Fields] AND "periodontitis"[All Fields]) OR "periapical periodontitis"[All Fields] OR ("apical"[All Fields] AND "periodontitis"[All Fields]) OR "apical periodontitis"[All Fields]) OR (apical[All Fields] AND radiolucency[All Fields])
	#2	("epidemiology"[Subheading] OR "epidemiology"[All Fields] OR "epidemiology"[MeSH Terms]) OR ("epidemiology"[Subheading] OR "epidemiology"[All Fields] OR "prevalence"[All Fields] OR "prevalence"[MeSH Terms]) OR ("epidemiology"[Subheading] OR "epidemiology"[All Fields] OR "occurrence"[All Fields] OR "epidemiology"[MeSH Terms] OR "occurrence"[All Fields]) OR ("epidemiology"[Subheading] OR "epidemiology"[All Fields] OR "frequency"[All Fields] OR "epidemiology"[MeSH Terms] OR "frequency"[All Fields]) OR ("population"[MeSH Terms] OR "population"[All Fields] OR "population groups"[MeSH Terms] OR ("population"[All Fields] AND "groups"[All Fields]) OR "population groups"[All Fields])

* WoS - Web of Science Core Collection, KJD - Korean Journal Database, RSCI - Russian Science Citation Index, SCIELO - SciELO Citation Index

** MESH - Medical Subject Headings

Table 2. Summarized data of the Prevalence of Apical Periodontitis (AP), Conventional Nonsurgical Root Canal Treatment (NSRCT), and Treated and Untreated Teeth with AP of Cross- Sectional Studies Included in Final Review.

Authors	Year	Country (*)	Number of participants (F/M)	Age	Number of analyzed teeth	Average number of teeth per patient	Total number of all teeth with AP (%)	Total number of teeth with RCT (%)	Number of treated teeth with AP (%)	Number of untreated teeth with AP (%)
Lopez-Lopez J et al. (23)	2012	Spain	397 (203/194)	52	9390	23.6	259 (2.8)	604 (6.4)	144 (23.8)	115 (1.3)
Mukhaimer et al. (24)	2012	Palestine	258 (142/116)	39	6482	25.2	978 (15.1)	855 (13.2)	509 (59.5)	469 (8.3)
Jersa & Kundzina (25)	2013	Latvia	312 (-/-)	-	7065	24	502 (7.1)	1255 (17.8)	384 (30.6)	90 (1.6)
Ureyen Kaya et al. (26)	2013	Turkey	1000 (-/-)	-	23268	23.3	287 (1.2)	601 (2.6)	95 (15.8)	192 (0.89)
Di Filippo et al. (27)	2014	UK (London)	136 (73/63)	-	3396	25	138 (4.1)	115 (3.4)	44 (38.3)	94 (2.86)
Dutta et al. (28)	2014	UK (Dundee)	245 (117/128)	-	3595	14.7	209 (5.8)	171 (4.8)	81 (47.4)	128 (3.7)
Archana et al. (29)	2015	India	1340 (-/-)	-	30098	22.5	1759 (5.8)	1234 (4.1)	462 (37.4)	1297 (4.5)
Oginni et al. (30)	2015	Nigeria	756 (342/414)	46.5	21468	27.4	3083 (9.4)	2625 (12.2)	1068 (40.7)	2015 (10.7)
Lemagner et al. (31)	2015	France	100 (53/47)	47.1	2368	23.7	204 (8.6)	431 (18.2)	176 (40.8)	28 (1.5)
Alrahabi et al. (32)	2016	Saudi Arabia (Al Madinah Al Munawwarah)	630 (314/316)	-	15686	24.9	667 (4.3)	997 (6.4)	346 (34.7)	321 (2.2)
Hussein et al. (33)	2016	Malaysia	233 (147/86)	26	6409	27.5	112 (1.8)	43 (0.7)	16 (37.2)	96 (1.5)
Timmerman et al. (34)	2017	Australia	605 (-/-)	-	14174	23.9	300 (2.1)	267 (1.8)	106 (39)	194 (1.4)
Ahmed et al. (35)	2017	Sudan	200 (153/47)	34	4976	24.9	163 (3.3)	80 (1.6)	26 (32.5)	137 (2.8)
Kielbassa et al. (36)	2017	Austria	1000 (570/430)	49.9	22586	11.4	1454 (6.4)	2504 (11.1)	1066 (42.6)	388 (1.9)
Bürklein et al. (37)	2019	Germany (Bochum)	500 (297/203)	50	8244	16.5	310 (3.8)	677 (8.2)	288 (42.5)	22 (0.3)
Meirinhos et al. (38)	2019	Portugal	1160 (663/497)	48.4	20836	18	2177 (10.5)	2305 (11.1)	1280 (55.5)	897 (4.8)
Total			**8872**		**200041**	**22.3**‡	**12602 (6.3)** †	**14764 (7.4)** †	**6091 (41.3)** §	**6483 (3.5)** ‖

-, not presented in the original study; M, male; F, female; AP, apical periodontitis; RCT, root canal treatment; UK, United Kingdom;
* Specific location of sampling was added for studies from the same country
† Percentage calculated on total number of analyzed teeth
§ Percentage calculated on total number of teeth with RCT
‖ Percentage calculated on total number of untreated teeth
‡ An average number of teeth per patient for all analyzed sample

Table 3. Summarized data of the Prevalence of Apical Periodontitis (AP), Conventional Nonsurgical Root Canal Treatment (NSRCT), and Treated and Untreated Teeth with AP Related to Gender Subgroups of Cross-Sectional Studies Included in Final Review.

Authors	Year	Number of participants		Number of analyzed teeth		Total number of all teeth with AP (%)		Total number of teeth with RCT (%)		Number of treated teeth with AP (%)		Number of untreated teeth with AP (%)	
		F	M	F	M	F	M	F	M	F	M	F	M
Lopez-Lopez J et al. (23)	2012	203	194	4970	4420	106 (2.1)	153 (3.5)	287 (5.8)	317 (7.2)	62 (21.6)	82 (25.9)	44 (0.9)	71 (1.7)
Mukhaimer et al. (24)	2012	142	116	-	-	-	-	-	-	-	-	-	-
Jersa & Kundzina (25)	2013	-	-	-	-	-	-	-	-	-	-	-	-
Ureyen Kaya et al. (26)	2013	-	-	-	-	-	-	-	-	-	-	-	-
Di Filippo et al. (27)	2014	76	63	1875	1521	57 (3)	81 (5.3)	-	-	-	-	-	-
Dutta et al. (28)	2014	117	128	-	-	79	130	88	83	41	40		
Archana et al. (29)	2015	-	-	-	-	-	-	-	-	-	-	-	-
Oginni et al. (30)	2015	756	414	9712	11756	-	-	-	-	-	-	-	-
Lemagner et al. (31)	2015	53	47	1244	1124	108 (8.7)	96 (8.5)	235 (18.9)	196 (17.4)	-	-	-	-
Alrahabi et al. (32)	2016	314	316	7841	7845	413 (5.3)	254 (3.2)	588 (7.5)	409 (5.2)	202 (34.4)	144 (35.2)	211 (2.9)	110 (1.5)
Hussein et al. (33)	2016	147	86	-	-	-	-	-	-	-	-	-	-
Timmerman et al. (34)	2017	-	-	-	-	-	-	-	-	-	-	-	-
Ahmed et al. (35)	2017	153	47	3874	1102	105 (2.7)	58 (5.3)	62 (1.6)	18 (1.6)	18 (29)	8 (44.4)	87 (2.3)	50 (4.6)
Kielbassa et al. (36)	2017	570	430	12707	9879	12707 (6.3)	9879 (6.6)	804 (11.7)	650 (10.3)	1484 (39.9)	1020 (46.5)	592 (1.9)	474 (2)
Bürklein et al. (37)	2019	297	203	4812	3432	188 (3.9)	122 (3.6)	440 (9.1)	237 (6.9)	175 (39.8)	113 (47.7)	265 (6.1)	124 (3.9)
Meirinhos et al. (38)	2019	663	497	11828	9008	-	-	-	-	-	-	-	-

-, not presented in the original study; M, male; F, female; AP, apical periodontitis; RCT, root canal treatment;

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Table 4. Radiographic Characteristics of Cross-sectional Studies Included in Final Review.

Authors	Year	Type of RTG analysis	Number of observers	Calibration Y/N, inter and or intra, <0.8 or >0.8	Parameters for AP evaluation	Parameters for RCT evaluation	The most affected tooth with AP	The most affected tooth with RCT
Lopez-Lopez J et al. (23)	2012	DPR	3	Y, inter and intraobserver agreement, >0.8	(72)	-	-	-
Mukhaimer et al. (24)	2012	DPR	2	Y, interobserver agreement, >0.8	(40)	(40)	Mandibular 1st molars	Maxillary 1st premolars
Jersa & Kundzina (25)	2013	DPR	1	Y, intraobserver agreement, >0.8	(72)	(77)	-	-
Ureyen Kaya et al. (26)	2013	DPR	3	Y, intraobserver agreement, >0.8	(72)	(79)	Mandibular 1st molars	Mandibular 1st molars
Di Filippo et al. (27)	2014	DPR	2	Y, interobserver agreement, >0.8	(40)	(73)	Mandibular molars	-
Dutta et al. (28)	2014	CBCT	2	Y, inter and intraobserver agreement, >0.8	(40)	(40)	Maxillary anterior teeth	Mandibular molars
Archana et al. (29)	2015	DPR	3	Y, interobserver agreement, >0.8	(72)	(76)	Mandibular and maxillary 1st molars	Mandibular and maxillary 1st molars
Oginni et al. (30)	2015	PR	1	Y, intraobserver agreement, >0.8	(72)	(40)	Maxillary central incisors, mandibular 1st molars	Maxillar central incisors, mandibular 1st molars
Lemagner et al. (31)	2015	CBCT	2	Y, inter and intraobserver agreement, >0.8	(75)	-	Maxillary molars	Mandibular 2nd molars
Alrahabi et al. (32)	2016	DPR	2	N	(40)	(40)	Mandibular and maxillar 1st molars	Mandibular and maxillary 1st molars
Hussein et al. (33)	2016	DPR, PR	2	Y, interobserver agreement, >0.8	(72)	-	Mandibular molars	Mandibular molars
Timmerman et al. (34)	2017	DPR	2	Y, inter and intraobserver agreement, >0.8	(72)	(78)	-	-
Ahmed et al. (35)	2017	DPR, PR	1	Y, intraobserver agreement, >0.8	(72)	(40)	Mandibular 2nd molars	Maxillary molars
Kielbassa et al. (36)	2017	DPR	2	Y, interobserver agreement, >0.8	(74)	(73)	Premolars	Premolars
Bürklein et al. (37)	2019	CBCT	2	Y, interobserver agreement, >0.8	(40)	(40)	Mandibular molars teeth	Mandibular molars
Meirinhos et al. (38)	2020	CBCT	5	Y, inter and intraobserver agreement, >0.8	(75)	(75)	Maxillary molars	Maxillary molars

-, not presented in the original study; AP, apical periodontitis; RCT, root canal treatment, RTG, radiographic; DPR, digital panoramic radiography; PR, periapical radiography; CBCT, cone beam computed tomography; Y, yes; N, no;

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5, 6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6, 7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7, 8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7, 8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7, 8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	-
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9-12
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9-12
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9-12
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9-12
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	-
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12-15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17, 18
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Acknowledgement

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Supplementary Table 2. Excluded studies.

No	Study	Reason
1	Abella F, Patel S, Duran-Sindreu F, Mercadé M, Bueno R, Roig M. Evaluating the periapical status of teeth with irreversible pulpitis by using cone-beam computed tomography scanning and periapical radiographs. J Endod. 2012;38(12):1588–1591. doi:10.1016/j.joen.2012.09.003	A
2	Alafif H. Impact of the quality of coronal restoration and root canal filling on the periapical health in adult syrian subpopulation. Indian J Dent. 2014;5(2):75–80. doi:10.4103/0975-962X.135265	A
3	Alfouzan K, Baskaradoss JK, Geevarghese A, Alzahrani M, Alhezaimi K. Radiographic Diagnosis of Periapical Status and Quality of Root Canal Fillings in a Saudi Arabian Subpopulation. Oral Health Prev Dent. 2016;14(3):241–248. doi:10.3290/j.ohpd.a35299	A
4	Alharmoodi R, Al-Salehi S. Assessment of the quality of endodontic re-treatment and changes in periapical status on a postgraduate endodontic clinic. J Dent. 2020;92:103261. doi:10.1016/j.jdent.2019.103261	A
5	Alkis HT, Kustarci A. Radiographic assessment of the relationship between root canal treatment quality, coronal restoration quality, and periapical status. Niger J Clin Pract. 2019;22(8):1126–1131. doi:10.4103/njcp.njcp_129_1	A
6	Bonfanti E, Maddalone M, Pellegatta A, Citterio CL, Baldoni M. Digital Orthopantomography vs Cone Beam Computed Tomography-Part 2: A CBCT Analysis of Factors Influencing the Prevalence of Periapical Lesions. J Contemp Dent Pract. 2019;20(6):664–669.	A
7	Cakici EB, Yildirim E, Cakici F, Erdogan AS. Assessment of periapical health, quality of root canal filling, and coronal restoration by using cone-beam computed tomography. Niger J Clin Pract. 2016;19(5):673–677. doi:10.4103/1119-3077.188697	A
8	Costa FFNP, Pacheco-Yanes J, Siqueira JF Jr, et al. Association between missed canals and apical periodontitis. Int Endod J. 2019;52(4):400–406. doi:10.1111/iej.13022	A
9	Costa GM, Santos Soares SM, Pelli Paiva PC, et al. Factors Affecting the Periapical Status of Root-Filled Canals: A Cross-Sectional Study at the Undergraduate Level. Int J Dent. 2017;2017:7413204. doi:10.1155/2017/7413204	A
10	Craveiro MA, Fontana CE, de Martin AS, Bueno CE. Influence of coronal restoration and root canal filling quality on periapical status: clinical and radiographic evaluation. J Endod. 2015;41(6):836–840. doi:10.1016/j.joen.2015.02.017	A
11	Davies A, Mannocci F, Mitchell P, Andiappan M, Patel S. The detection of periapical pathoses in root filled teeth using single and parallax periapical radiographs versus cone beam computed tomography - a clinical study. Int Endod J. 2015;48(6):582–592. doi:10.1111/iej.12352	A
12	de Sousa Gomide Guimarães MRF, Samuel RO, Guimarães G, et al. Evaluation of the relationship between obturation length and presence of apical periodontitis by CBCT: an observational cross-sectional study. Clin Oral Investig. 2019;23(5):2055–2060. doi:10.1007/s00784-018-2623-7	A
13	Farah RI, Aldakhili AS, Alnasser AS. A Radiographic Study of the Association between Apical Periodontitis and Technical Quality of Intraradicular Posts and Root Canal Fillings: A Cross-sectional Study in Qassim Region, Saudi Arabia. Contemp Clin Dent. 2017;8(4):579–586. doi:10.4103/ccd.ccd_605_17	A
14	Frisk F, Hugosson A, Kvist T. Is apical periodontitis in root filled teeth associated with the type of restoration?. Acta Odontol Scand. 2015;73(3):169–175. doi:10.3109/00016357.2014.950182	A
15	Goldstein GR, Iyer S, Doan PD, Scibetta S. Detection of radiolucencies around endodontically treated teeth on routine CT scans. J Prosthodont. 2015;24(3):179–181. doi:10.1111/jopr.12219	A
16	Gomes AC, Nejaim Y, Silva AI, et al. Influence of Endodontic Treatment and Coronal Restoration on Status of Periapical Tissues: A Cone-beam Computed Tomographic Study. J Endod. 2015;41(10):1614–1618. doi:10.1016/j.joen.2015.07.008	A
17	Guedes LMF, Guedes OA, Costa MVC, Carvalhosa AA, Estrela CRA, Estrela C. Prevalence of granulomas, abscesses and periapical cysts in	A

	inflammations of endodontic origin. Dental Press Endod. 2018;8(3):41-6. DOI: //doi.org/10.14436/2358-2545.8.3.041-046.oar	
18	Gumru B, Tarcin B, Iriboz E, Turkaydin DE, Unver T, Ovecoglu HS. Assessment of the periapical health of abutment teeth: A retrospective radiological study. Niger J Clin Pract. 2015;18(4):472–476. doi:10.4103/1119-3077.151763	A
19	Huumonen S, Vehkalahti MM, Nordblad A. Radiographic assessments on prevalence and technical quality of endodontically-treated teeth in the Finnish population, aged 30 years and older. Acta Odontol Scand. 2012;70(3):234–240. doi:10.3109/00016357.2011.637510	A
20	Ilić J, Vujašković M, Tihaček-Šojić L, Milić-Lemić A. Frequency and quality of root canal fillings in an adult Serbian population. Srp Arh Celok Lek. 2014;142(11-12):663–668. doi:10.2298/sarh1412663i	A
21	Kalender A, Orhan K, Aksoy U, Basmaci F, Er F, Alankus A. Influence of the quality of endodontic treatment and coronal restorations on the prevalence of apical periodontitis in a Turkish Cypriot population. Med Princ Pract. 2013;22(2):173–177. doi:10.1159/000341753	A
22	Karabucak B, Bunes A, Chehoud C, Kohli MR, Setzer F. Prevalence of Apical Periodontitis in Endodontically Treated Premolars and Molars with Untreated Canal: A Cone-beam Computed Tomography Study. J Endod. 2016;42(4):538–541. doi:10.1016/j.joen.2015.12.026	A
23	Keser G, Pekiner F N. Comparative Evaluation of Periapical Lesions Using Periapical Index Adapted for Panoramic Radiography and Cone Beam Computed Tomography. CLINICAL AND EXPERIMENTAL HEALTH SCIENCES.2018;8(1):50-55.	A
24	Khullar P, Raisingani D, Gupta S, Khatri RK. A survey report on effect of root canal fillings and coronal restorations on the periapical status of endodontically treated teeth in a selected group of population. Int J Clin Pediatr Dent. 2013;6(2):89–94. doi:10.5005/jp-journals-10005-1196	A
25	Moreno JO, Alves FR, Gonçalves LS, Martinez AM, Rôças IN, Siqueira JF Jr. Periradicular status and quality of root canal fillings and coronal restorations in an urban Colombian population. J Endod. 2013;39(5):600–604. doi:10.1016/j.joen.2012.12.020	A
26	Nascimento EHL, Gaêta-Araujo H, Andrade MFS, Freitas DQ. Prevalence of technical errors and periapical lesions in a sample of endodontically treated teeth: a CBCT analysis. Clin Oral Investig. 2018;22(7):2495–2503. doi:10.1007/s00784-018-2344-y	A
27	Nur BG, Ok E, Altunsoy M, Ağlarci OS, Çolak M, Güngör E. Evaluation of technical quality and periapical health of root-filled teeth by using cone-beam CT. J Appl Oral Sci. 2014;22(6):502–508. doi:10.1590/1678-775720140110	A
28	Pedro FM, Marques A, Pereira TM, et al. Status of Endodontic Treatment and the Correlations to the Quality of Root Canal Filling and Coronal Restoration. J Contemp Dent Pract. 2016;17(10):830–836. Published 2016 Oct 1. doi:10.5005/jp-journals-10024-1939	A
29	Ruiz XF, Duran-Sindreu F, Shemesh H, et al. Development of Periapical Lesions in Endodontically Treated Teeth with and without Periodontal Involvement: A Retrospective Cohort Study. J Endod. 2017;43(8):1246–1249. doi:10.1016/j.joen.2017.03.037	A
30	Saidi A, Naaman A, Zogheib C. Accuracy of Cone-beam Computed Tomography and Periapical Radiography in Endodontically Treated Teeth Evaluation: A Five-Year Retrospective Study. J Int Oral Health. 2015;7(3):15–19.	A
31	Shimasadat M, Mahsasadat M, Aboufazel A. Prevalence of Chronic Apical Periodontitis Among Patients Referred to the Department of Endodontics at the Kermanshah School of Dentistry (2014-2015). DENTAL AND MEDICAL PROBLEMS. 2016;53(4):496-500	A
32	Song M, Park M, Lee CY, Kim E. Periapical status related to the quality of coronal restorations and root fillings in a Korean population. J Endod. 2014;40(2):182–186. doi:10.1016/j.joen.2013.10.017	A
33	Souza-Nunes LA, Verner FS, Rosado LPL, Aquino SN, Carvalho ACP, Junqueira RB. Periapical and Endodontic Status Scale for Endodontically Treated Teeth and Their Association with Maxillary Sinus Abnormalities: A Cone-beam Computed Tomographic Study. J Endod. 2019;45(12):1479–1488. doi:10.1016/j.joen.2019.09.005	A
34	Tarim Ertas E, Ertas H, Sisman Y, Sagsen B, Er O. Radiographic assessment of the technical quality and periapical health of root-filled teeth performed by general practitioners in a Turkish subpopulation. ScientificWorldJournal. 2013;2013:514841. doi:10.1155/2013/514841	A
35	Tassoker M, Akugnlu F. Radiographic evaluation of periapical status and frequency of endodontic treatment in a Turkish population: a retrospective study. JOURNAL OF ISTANBUL UNIVERSITY FACULTY OF DENTISTRY. 2016;50(2):10-16.	A

36	Thampibul P, Jantarat J, Arayasantiparb R. Post-treatment apical periodontitis related to the technical quality of root fillings and restorations in Thai population. Aust Endod J. 2019;45(2):163–170. doi:10.1111/aej.12302	A
37	Tolias D, Koletsi K, Mamai-Homata E, Margaritis V, Kontakiotis E. Apical periodontitis in association with the quality of root fillings and coronal restorations: a 14-year investigation in young Greek adults. Oral Health Prev Dent. 2012;10(3):297–303.	A
38	Winward BJ, Yaccino JM, Kirkpatrick TC. A panoramic survey of air force basic trainees: how research translates into clinical practice. J Endod. 2014;40(9):1332–1337. doi:10.1016/j.joen.2014.05.016	A
39	Abella F, Patel S, Durán-Sindreu F, Mercadé M, Bueno R, Roig M. An evaluation of the periapical status of teeth with necrotic pulps using periapical radiography and cone-beam computed tomography. Int Endod J. 2014;47(4):387–396. doi:10.1111/iej.12159	B
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41	Torabinejad M, Rice DD, Maktabi O, Oyoyo U, Abramovitch K. Prevalence and Size of Periapical Radiolucencies Using Cone-beam Computed Tomography in Teeth without Apparent Intraoral Radiographic Lesions: A New Periapical Index with a Clinical Recommendation. J Endod. 2018;44(3):389–394. doi:10.1016/j.joen.2017.11.015	B
42	Baruwa AO, Martins JNR, Meirinhos J, et al. The Influence of Missed Canals on the Prevalence of Periapical Lesions in Endodontically Treated Teeth: A Cross-sectional Study. J Endod. 2020;46(1):34–39.e1. doi:10.1016/j.joen.2019.10.007	C
43	Oginni AO, Adeleke AA, Mejabi MO, Sotunde OA. Risk Factors for Apical Periodontitis Sub-Urban Adult Population. Niger Postgrad Med J. 2015;22(2):105–109.	C
44	Huumonen S, Ørstavik D. Radiographic follow-up of periapical status after endodontic treatment of teeth with and without apical periodontitis. Clin Oral Investig. 2013;17(9):2099–2104. doi:10.1007/s00784-013-0926-2	D
45	Kirkevang LL, Vaeth M, Wenzel A. Ten-year follow-up observations of periapical and endodontic status in a Danish population. Int Endod J. 2012;45(9):829–839. doi:10.1111/j.1365-2591.2012.02040.x	D
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47	Najim U, Norderyd O. Prevalence of intrabony defects in a Swedish adult population. A radiographic epidemiological study. Acta Odontol Scand. 2017;75(2):123–129. doi:10.1080/00016357.2016.1265665	D
48	Al-Nazhan SA, Alsaeed SA, Al-Attas HA, Dohaithem AJ, Al-Serhan MS, Al-Maflehi NS. Prevalence of apical periodontitis and quality of root canal treatment in an adult Saudi population. Saudi Med J. 2017;38(4):413–421. doi:10.15537/smj.2017.4.16409	E
49	Aminoshariae A, Kulild J, Gutmann J. The association between smoking and periapical periodontitis: a systematic review [published online ahead of print, 2019 Nov 26]. Clin Oral Investig. 2019;10.1007/s00784-019-03094-6. doi:10.1007/s00784-019-03094-6	E
50	An GK, Morse DE, Kunin M, Goldberger RS, Psoter WJ. Association of Radiographically Diagnosed Apical Periodontitis and Cardiovascular Disease: A Hospital Records-based Study. J Endod. 2016;42(6):916–920. doi:10.1016/j.joen.2016.03.011	E
51	Andersen MG, Beck-Nielsen SS, Haubek D, Hintze H, Gjørup H, Poulsen S. Periapical and endodontic status of permanent teeth in patients with hypophosphatemic rickets. J Oral Rehabil. 2012;39(2):144–150. doi:10.1111/j.1365-2842.2011.02250.x	E
52	Balto HA, Alabdulaaly L, Bahammam S, Al-Ekrish AA. Comparative analysis of prevalence of apical periodontitis in smokers and non-smokers using cone-beam computed tomography. Saudi Dent J. 2019;31(1):52–57. doi:10.1016/j.sdentj.2018.09.006	E
53	Castellanos-Cosano L, Machuca-Portillo G, Sánchez-Domínguez B, Torrés-Lagares D, López-López J, Segura-Egea JJ. High prevalence of radiolucent periapical lesions amongst patients with inherited coagulation disorders. Haemophilia. 2013;19(3):e110–e115. doi:10.1111/hae.12089	E

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A - Only previously treated teeth

B - Only non-treated teeth

C - Repeated sample/study results

D - Inappropriate study design

E - Not general population

F - Mixed dentition analysis

G - Not only adult population / unable to extract data related to adult population

H - Analysis presented only per patient not per tooth

Supplementary Table 3 Methodological Quality Assessment of Cross-sectional Studies included in Final Review According to NOS Criteria (N = 16)

	NOS criteria								
	Selection				Comparability	Exposure			
Study	Representativeness of the sample	Sample size	Ascertainment of exposure	Non-respondents	The subjects in different outcome groups are comparable, based on the study design or analysis	Assessment of the outcome	Statistical test	**Total awarded stars (max of 9 stars)**	**Quality**
Lopez-Lopez et al., (23)	★	-	★★	NA	★★	★★	★	8	high
Mukhaimer et al., (24)	★	-	★★	NA	★★	★★	-	7	high
Jersa & Kundzina (25)	★	-	★★	NA	★	★★	-	6	moderate
Ureyen Kaya et al. (26)	★	-	★★	NA	★★	★★	-	7	high
Di Filippo et al. (27)	★	-	★★	NA	★★	★★	★	8	high
Dutta et al. (28)	★	-	★★	NA	★★	★★	★	8	high
Archana et al. (29)	★	-	★★	NA	★	★★	★	7	high
Oginni et al. (30)	★	-	★★	NA	★★	★★	★	8	high
Lemagner et al. (31)	★	-	★★	NA	★★	★★	★	8	high
Alrahabi et al. (32)	★	-	★★	NA	★★	★★	-	7	high
Hussein et al. (33)	★	★	★★	NA	★★	★★	★	9	high
Timmerman et al. (34)	★	★	★★	NA	★	★★	★	8	high
Ahmed et al. (35)	★	-	★★	NA	★★	★★	★	8	high
Kielbassa et al. (36)	★	★	★★	NA	★★	★★	★	9	high
Bürklein et al. (37)	★	★	★★	NA	★★	★★	★	9	high
Meirinhos et al. (38)	★	★	★★	NA	★★	★★	★	9	high

NOS: NewCastle-Ottawa scale; N: Total number of included studies; NA: Not Applicable

Supplementary Table 4 Reporting Quality Assessment of Cross-sectional Studies included in Final Review According to STROBE Statement (N = 16)

	STROBE Item No																																					
Study	**1a**	**1b**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12a**	**12b**	**12c**	**12d**	**12e**	**13a**	**13b**	**13c**	**14a**	**14b**	**15**	**16a**	**16b**	**16c**	**17**	**18**	**19**	**20**	**21**	**22**	**Score**	**Maximum**	**Percentage**	**Quality**
Lopez-Lopez et al., (23)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	NA	N	N	N	N	NA	Y	NA	Y	Y	Y	NA	N	N	Y	Y	Y	N	20	28	71.43%	moderate
Mukhaimer et al., (24)	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N	Y	NA	N	N	Y	Y	NA	Y	NA	Y	N	Y	NA	N	Y	Y	Y	Y	N	20	28	71.43%	moderate
Jersa & Kundzina (25)	N	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	N	Y	NA	Y	N	Y	Y	NA	N	NA	Y	N	NA	NA	N	Y	Y	Y	Y	N	18	27	66.67%	moderate
Ureyen Kaya et al. (26)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N	Y	NA	N	N	N	N	NA	N	NA	Y	N	NA	NA	N	Y	Y	Y	Y	N	17	27	62.96%	moderate
Di Filippo et al. (27)	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N	Y	NA	N	N	Y	Y	NA	Y	NA	Y	N	Y	NA	N	N	Y	Y	Y	N	19	28	67.86%	moderate
Dutta et al. (28)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	NA	N	N	N	N	NA	Y	NA	Y	Y	Y	NA	N	N	Y	Y	Y	N	20	28	71.43%	moderate
Archana et al. (29)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N	Y	NA	N	N	N	N	NA	N	NA	Y	Y	NA	NA	N	N	Y	Y	Y	N	17	27	62.96%	moderate
Oginni et al. (3N)	N	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	N	Y	NA	N	N	N	N	NA	Y	NA	Y	Y	Y	NA	N	Y	Y	Y	Y	N	18	28	64.29%	moderate
Lemagner et al. (3Y)	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	NA	N	Y	N	N	NA	Y	NA	Y	Y	Y	NA	Y	Y	Y	Y	Y	N	22	28	78.57%	moderate
Alrahabi et al. (32)	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	NA	NA	N	N	N	NA	N	NA	Y	N	Y	NA	Y	Y	N	Y	Y	N	18	27	66.67%	moderate
Hussein et al. (33)	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	N	Y	Y	Y	Y	28	30	93.33%	high
Timmerman et al. (34)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y	Y	NA	Y	NA	Y	N	Y	NA	N	Y	Y	Y	Y	Y	26	28	92.86%	high
Ahmed et al. (35)	N	Y	Y	Y	N	N	Y	Y	Y	N	N	Y	N	Y	NA	N	N	N	N	NA	Y	NA	Y	Y	Y	NA	Y	N	Y	Y	Y	N	16	28	57.14%	moderate
Kielbassa et al. (36)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	N	N	NA	Y	Y	Y	Y	Y	NA	Y	Y	Y	Y	Y	N	26	30	86.67%	high
Bürklein et al. (37)	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	NA	N	Y	N	NA	Y	NA	Y	Y	Y	NA	Y	N	Y	Y	Y	N	22	27	81.48%	high
Meirinhos et al. (38)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	N	N	N	NA	Y	Y	Y	Y	Y	NA	N	N	Y	Y	Y	N	23	29	79.31%	moderate

N: Total number of included studies; Y: Reported on the article; N: Not reported; NA: Not Applicable

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

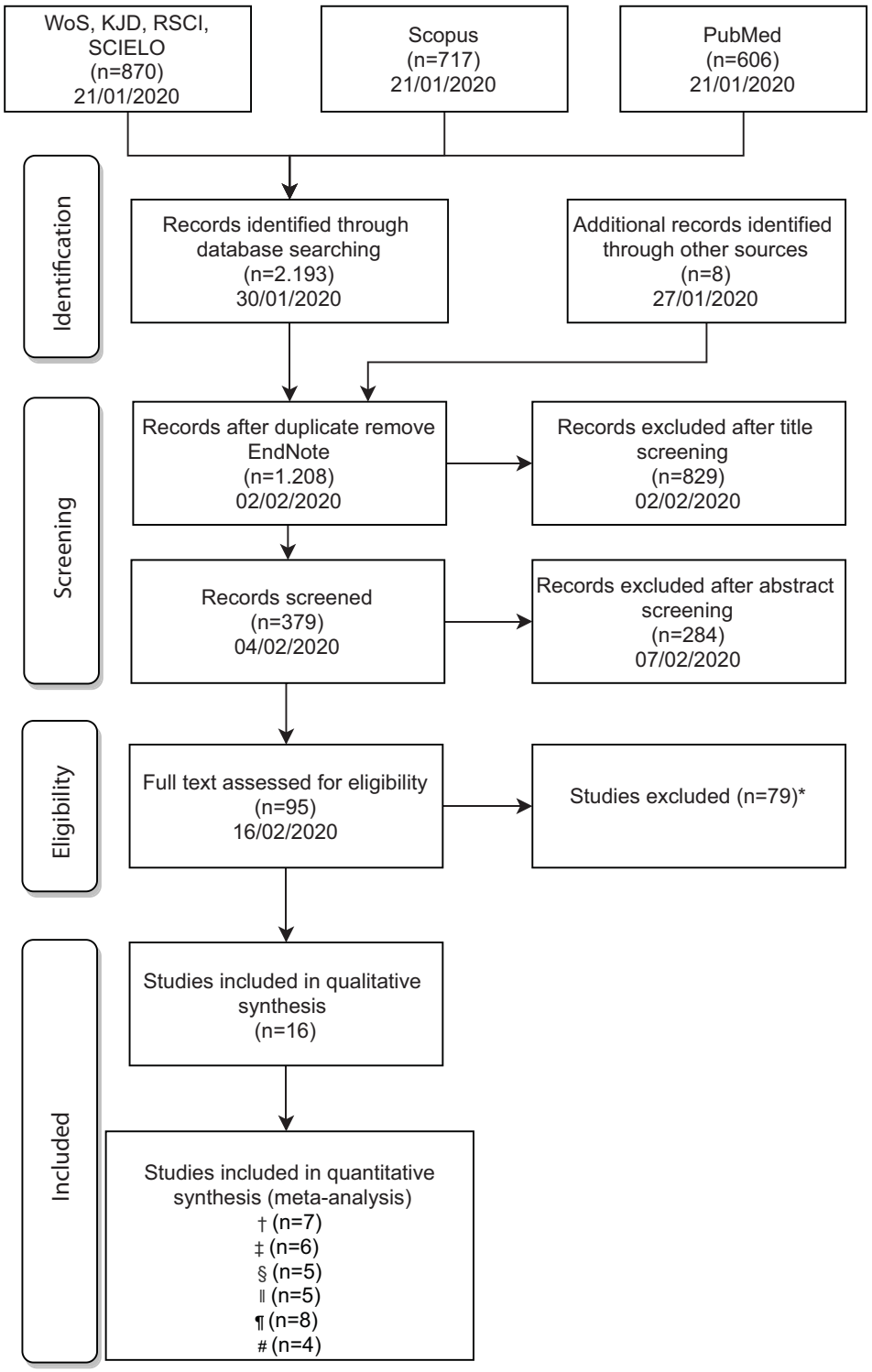
	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported

Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed

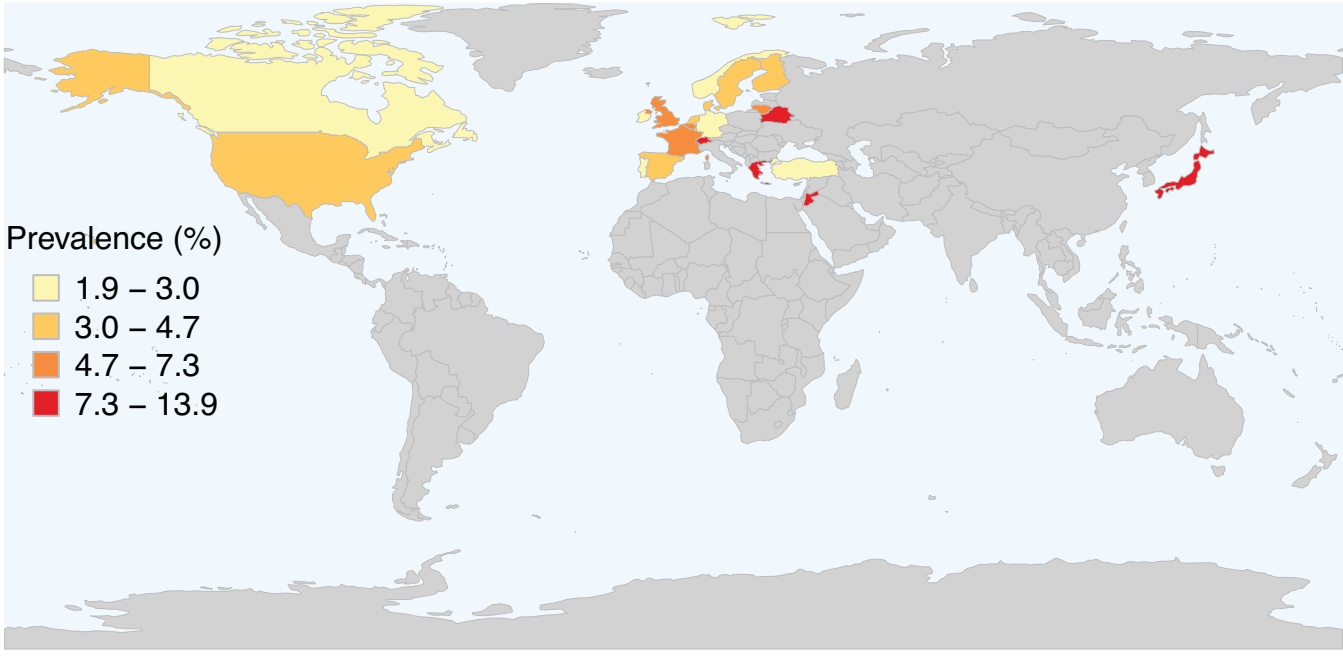
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
Outcome data	15*	Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

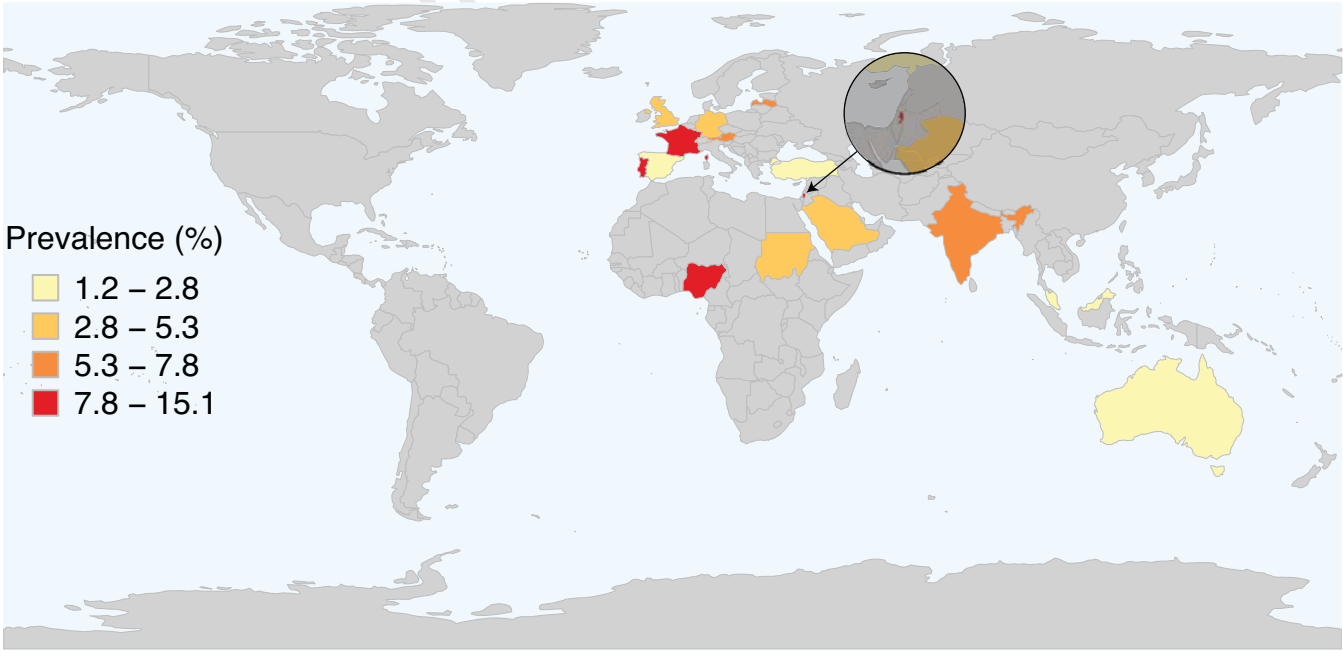
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.


WoS, KJD, RSCI, SCIELO (n=870) 21/01/2020
Scopus (n=717) 21/01/2020
PubMed (n=606) 21/01/2020
Identification
Records identified through database searching (n=2.193) 30/01/2020
Additional records identified through other sources (n=8) 27/01/2020
Screening
Records after duplicate remove EndNote (n=1.208) 02/02/2020
Records excluded after title screening (n=829) 02/02/2020
Records screened (n=379) 04/02/2020
Records excluded after abstract screening (n=284) 07/02/2020
Eligibility
Full text assessed for eligibility (n=95) 16/02/2020
Studies excluded (n=79)*
Included
Studies included in qualitative synthesis (n=16)
Studies included in quantitative synthesis (meta-analysis)
† (n=7)
‡ (n=6)
§ (n=5)
ǁ (n=5)
¶ (n=8)
# (n=4)

A.


Prevalence (%)
1.9 – 3.0
3.0 – 4.7
4.7 – 7.3
7.3 – 13.9

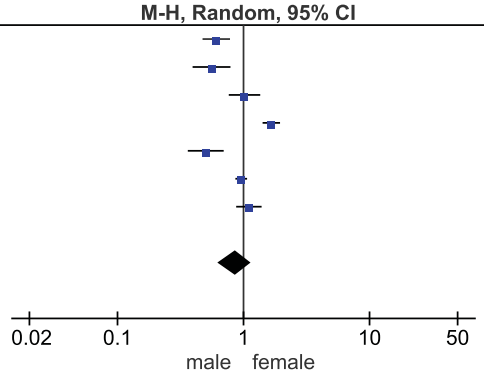
B.


Prevalence (%)
1.2 – 2.8
2.8 – 5.3
5.3 – 7.8
7.8 – 15.1

A.

Study or Subgroup	female Events	female Total	male Events	male Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Lopez-Lopez J et al. 2012	106	4970	153	4420	14.3%	0.61 [0.47, 0.78]	2012
Di Filippo et al. 2014	57	1875	81	1521	13.1%	0.56 [0.39, 0.79]	2014
Lemagner et al. 2015	108	1244	96	1124	13.9%	1.02 [0.76, 1.36]	2015
Alrahabi et al. 2016	413	7841	254	7845	15.2%	1.66 [1.42, 1.95]	2016
Ahmed et al. 2017	105	3874	58	1102	13.4%	0.50 [0.36, 0.70]	2017
Kielbassa et al. 2017	804	12707	650	9879	15.6%	0.96 [0.86, 1.07]	2017
Bürklein et al. 2019	188	4812	122	3432	14.5%	1.10 [0.87, 1.39]	2019
Total (95% CI)		**37323**		**29323**	**100.0%**	**0.86 [0.64, 1.16]**	
Total events	1781		1414				

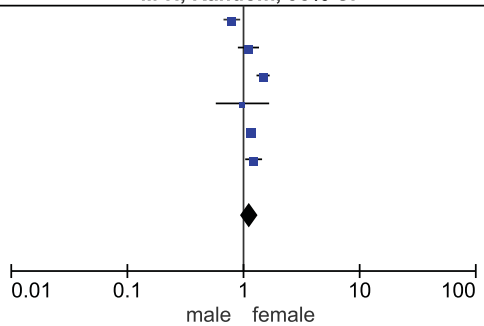
Heterogeneity: Tau² = 0.15; Chi² = 83.33, df = 6 (P < 0.00001); I² = 93%
Test for overall effect: Z = 1.00 (P = 0.32)



B.

Study or Subgroup	female Events	female Total	male Events	male Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Lopez-Lopez J et al. 2012	287	4970	317	4420	18.2%	0.79 [0.67, 0.94]	2012
Lemagner et al. 2015	235	1244	196	1124	16.5%	1.10 [0.89, 1.36]	2015
Alrahabi et al. 2016	588	7841	409	7845	19.4%	1.47 [1.29, 1.68]	2016
Ahmed et al. 2017	62	3874	18	1102	7.2%	0.98 [0.58, 1.66]	2017
Kielbassa et al. 2017	1484	12707	1020	9879	20.6%	1.15 [1.06, 1.25]	2017
Bürklein et al. 2019	400	4812	237	3432	18.1%	1.22 [1.03, 1.44]	2019
Total (95% CI)		**35448**		**27802**	**100.0%**	**1.12 [0.94, 1.33]**	
Total events	3056		2197				

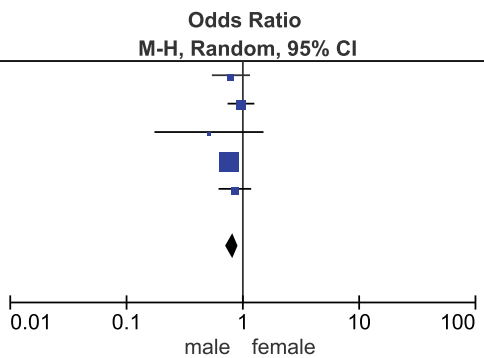
Heterogeneity: Tau² = 0.04; Chi² = 34.37, df = 5 (P < 0.00001); I² = 85%
Test for overall effect: Z = 1.27 (P = 0.21)



C.

Study or Subgroup	female Events	female Total	male Events	male Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Lopez-Lopez J et al. 2012	62	287	82	317	10.0%	0.79 [0.54, 1.15]	2012
Alrahabi et al. 2016	202	588	144	409	20.3%	0.96 [0.74, 1.26]	2016
Ahmed et al. 2017	18	62	8	18	1.2%	0.51 [0.17, 1.50]	2017
Kielbassa et al. 2017	592	1484	474	1020	54.8%	0.76 [0.65, 0.90]	2017
Bürklein et al. 2019	175	400	113	237	13.7%	0.85 [0.62, 1.18]	2019
Total (95% CI)		**2821**		**2001**	**100.0%**	**0.81 [0.72, 0.91]**	
Total events	1049		821				

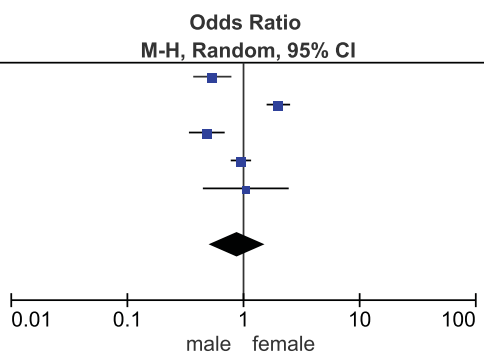
Heterogeneity: Tau² = 0.00; Chi² = 2.95, df = 4 (P = 0.57); I² = 0%
Test for overall effect: Z = 3.42 (P = 0.0006)



D.

Study or Subgroup	female Events	female Total	male Events	male Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Lopez-Lopez J et al. 2012	44	4683	71	4103	20.5%	0.54 [0.37, 0.79]	2012
Alrahabi et al. 2016	211	7253	110	7436	21.8%	2.00 [1.58, 2.52]	2016
Ahmed et al. 2017	87	3812	50	1084	20.8%	0.48 [0.34, 0.69]	2017
Kielbassa et al. 2017	212	11223	176	8859	22.0%	0.95 [0.78, 1.16]	2017
Bürklein et al. 2019	13	4412	9	3195	14.8%	1.05 [0.45, 2.45]	2019
Total (95% CI)		**31383**		**24677**	**100.0%**	**0.88 [0.50, 1.53]**	
Total events	567		416				

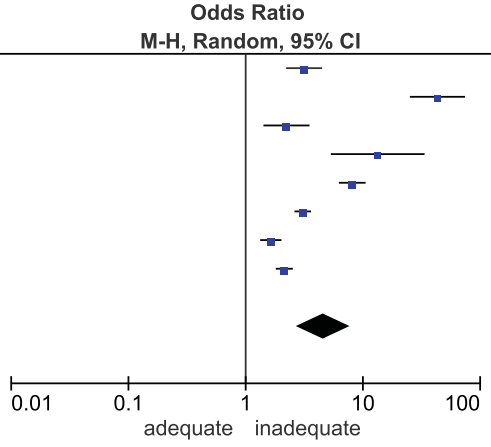
Heterogeneity: Tau² = 0.35; Chi² = 60.52, df = 4 (P < 0.00001); I² = 93%
Test for overall effect: Z = 0.47 (P = 0.64)



A.

Study or Subgroup	Inadequate Events	Inadequate Total	Adequate Events	Adequate Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Jersa & Kundzina 2012	342	970	42	285	12.8%	3.15 [2.21, 4.48]	2012
Mukhaimer et al. 2012	493	637	16	218	11.9%	43.22 [25.14, 74.31]	2012
Ureyen Kaya et al. 2013	60	280	35	321	12.4%	2.23 [1.42, 3.50]	2013
Di Filippo et al. 2014	35	51	9	64	9.6%	13.37 [5.33, 33.55]	2014
Archana et al. 2015	332	517	130	717	13.2%	8.10 [6.24, 10.53]	2015
Oginni et al. 2015	596	1050	472	1575	13.4%	3.07 [2.61, 3.61]	2015
Kielbassa et al. 2017	855	1821	169	482	13.3%	1.64 [1.33, 2.02]	2017
Meirinhos et al. 2020	768	1191	512	1114	13.4%	2.13 [1.81, 2.52]	2020
Total (95% CI)		**6517**		**4776**	**100.0%**	**4.65 [2.75, 7.84]**	
Total events	3481		1385				

Heterogeneity: Tau² = 0.52; Chi² = 209.98, df = 7 (P < 0.00001); I² = 97%
Test for overall effect: Z = 5.75 (P < 0.00001)



B.

Study or Subgroup	unacceptable Events	unacceptable Total	acceptable Events	acceptable Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Ureyen Kaya et al. 2013	106	353	70	400	20.8%	2.02 [1.43, 2.85]	2013
Archana et al. 2015	185	416	277	819	24.7%	1.57 [1.23, 2.00]	2015
Kielbassa et al. 2017	784	1317	515	1133	27.5%	1.77 [1.50, 2.07]	2017
Meirinhos et al. 2020	181	769	1635	7354	27.0%	1.08 [0.90, 1.28]	2020
Total (95% CI)		**2855**		**9706**	**100.0%**	**1.54 [1.16, 2.05]**	
Total events	1256		2497				

Heterogeneity: Tau² = 0.07; Chi² = 20.64, df = 3 (P = 0.0001); I² = 85%
Test for overall effect: Z = 3.01 (P = 0.003)