Global prevalence of infertility: a systematic review and meta-analysis of Community-based studies

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Abstract

Background: The prevalence of infertility has rarely been synthesized at the global level. **Objective:** To conduct a systematic review and meta-analysis to assess the community-based global prevalence of infertility. **Search Strategy**: PubMed, MEDLINE, Web of Science, and Science Direct were searched from inception until October 2022. **Selection Criteria:** Studies were included if they were published in English, had quantitative data, and reported the community-based prevalence of infertility. **Data Collection and Analysis:** Two authors independently extracted data. Random-effects meta-analysis was used to derive the pooled prevalence of infertility. Variations in the prevalence estimates in different subgroups. Univariate meta-regression was used to explore possible sources of heterogeneity. **Main Results:** The findings indicated the pooled prevalence of infertility was 12.87% (95% CI,12.41%-13.33%). The prevalences of primary infertility and secondary infertility were 7.34% and 6.01%, respectively. The overall prevalence of infertility among people was the highest in Africa (16.73%) and lowest in the North America (8.84%). Lower prevalence in cohort or prospective follow-up studies (9.75%) than in cross-sectional studies (12.93%). Women aged 35 and above had a higher prevalence of infertility (11.68%) compared to women below 35 years old (5.92%). The prevalence of infertility increased with the number of years, and increased with the degree of literature bias from low to high. **Conclusions**: This community-based study estimated the global prevalence of infertility to be 12.87% and suggested that an upward trend of the prevalence of infertility may persist in the future.

Introduction

Infertility is a disease of the reproductive system defined by the failure to achieve a pregnancy after a period of regular unprotected sexual intercourse[1]. It is estimated that 48 million couples and 186 million people worldwide suffer from infertility[2-4]. These infertility patients always suffer from various psychological stress and are more prone to anxiety and depression, which in turn affects the quality of life, leading to disharmonious relationships among family members, and even domestic violence[5, 6]. Moreover, infertility places a huge financial burden on patients , with the cost of assisted reproductive treatment for infertile couples to obtain a live birth ranging from approximately $17,100 to $24,200 [7]. In many parts of the world, especially in low- and middle-income countries, having children is highly valued and expected[8]. For couples, involuntary infertility can lead to public stigmatization, economic deprivation, social isolation and even loss of status[9, 10]. In addition, on a societal level, it increases the burden on society's health care system, economy and disease[11]. The existence of a large number of infertile people will not only lead to a lower birth rate, but will even affect the demographic structure of a country and national security[12]. With the steady increase in infertility rates in recent years and the harm it causes to individuals, societies and nations, it has become a global public health problem.

Estimating the prevalence of infertility is crucial for gaining insights into its current status and to aid governments and societies in determining appropriate resource allocation for addressing this issue. However,

there are still difficulties in assessing infertility rates. One important reason for this is that the definition of infertility varies around the world due to differences in countries and populations. For example, sociology defines it by the childless[13], while not elsewhere as a duration of two years, etc[14-16]. WHO believes that it should be defined in terms of 12 months (one year)[17], and that such a definition may be timely to help doctors and patients better understand when to seek professional help and begin treatment[18]. Another reason is the difference between the hospital population and the community population. The hospital population is limited to a specific hospital or medical institution, without considering other individuals who haven't sought treatment at that medical facility. This can lead to selection bias, making the research results non-representative of the entire community or population. Currently, most reviews do not screen the population but directly combine infertility prevalence, which can lead to an overestimation of infertility rates[19].

Globally, the prevalence of infertility varies widely due to different definitions of infertility and population differences[1, 4, 20]. Though several previous studies tried to estimate the prevalence of infertility, the definition of infertility and the population were not clearly definite, which may remarkedly influence the estimating of infertility prevalence. Therefore, a system review and meta-analysis was conduct to estimate global infertility rates, based on community-based populations. The definition of infertility has been critically defined to ensure accurate understanding in order to provide a comprehensive assessment of the global prevalence of infertility.

Methods

Search strategy

This systematic review was registered with PROSPERO (CRD42022380418) and followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Table S1). A systematic search was performed in online academic databases: PubMed, MEDLINE, Web of Science, and ScienceDirect. Search terms were a combination of free text and controlled vocabulary (ie, MeSH terms) for each database, including: "infertility", "childlessness", "sterility", "infecundity", "infertile", "prevalence", "point prevalence", and "period prevalence" All studies published between database inception and Oct 30, 2022. To find additional potentially eligible studies, a secondary search of the gray literature was performed on Google Scholar and checked the reference lists of relevant studies.

Definition of infertility

We used the World Health Organization (WHO) definition of infertility as our definition: inability to conceive after 12 months (or more) of unprotected intercourse[17]. It is classified as primary or secondary. Primary infertility is denoted for those women who have not conceived previously. In secondary infertility, there is at least one conception, but it fails to repeat[21].

Study selection

Inclusion criteria were original studies that reported the community-based prevalence of infertility. The following exclusion criteria were applied: (i) irrelevant to prevalence of infertility; (ii) unable to access full text; (iii) editorials, animal studies, conference papers, short newsletters, reviews, conference papers, or brief communications; (iv) conducted in special groups or not population based; (v) unclear or inconsistently applied definitions of infertility; (vi) did not distinguishing infertility from childlessness; (vii) studies that were unclear or no available and numerator denominator. If several publications used the same dataset, the publication that provided the most data was selected.

Duplicated studies were removed from the list of literature retrieved in the first step using Endnote 20.0 software (Clarivate, PA, USA). Second, two reviewers (Zhou and Li) screened the literature independently in two stages: title and abstract screening, full-text retrieval followed by screening according to the inclusion and exclusion criteria. Disagreements were resolved through discussions between the two reviewers, or with the help of a third reviewer (Hao).

Data extraction and risk of bias assessment

The items of each eligible study were extracted by two reviewers (Zhou and Li), including the first author, year of publication, year of investigation, study settings, research type, study population, sample size, definition of infertility, and prevalence of infertility and subtypes (primary and secondary). In parallel, the two reviewers assessed the relevant studies using the 10-item Hoy risk of bias tool (Table S2), designed for prevalence studies. Each item was rated on a dichotomous scale, with 1 indicating low risk of bias and 0 indicating high risk of bias. An overall score was calculated for each study as the mean score of the two reviewers, ranging from 0 to 10, with a score of at least 9 indicating a low risk of bias, 7–8 indicating a moderate risk, and less than 7 indicating a high risk. We calculated inter-rater reliability using the kappa coefficient for each item (Table S3).

Data analysis

A meta-analysis was performed to synthesize community-based global prevalence of infertility. To account for differences in study participants and diagnosed infertility among the included studies, we used random-effects models to calculate pooled estimates and 95% CI. For studies reporting prevalence of primary and secondary infertility, we also performed random-effects models to calculate pooled prevalence and 95%CI between the two groups. Higgins' I^2 statistic and Q-test were used to detect heterogeneity across studies. An I^2 value greater than 50% or a p-value less than 0.05 indicated significant heterogeneity. We used funnel plot to assess potential publication bias, for which p <0.1 was regarded as significant.

Subgroup analyses were conducted to estimate the infertility prevalence for participants or studies with different characteristics. Subgroup analyses were performed by study region (Africa, Asia, North Americas, Oceania, and Europe), year of investigation (1940-1990, 1991-2000, 2001-2010, and 2011-2022), female age (before 35 years versus above 35 years), research type (cross-sectional study and cohort or prospective study), and risk of bias (high, medium and low). Unordered multi-categorical information was compared two by two using the Bonferroni method, and grade information was analyzed for correlation using chi-square trend test.

Univariate meta-regression analysis is used in the text to explore possible sources of heterogeneity (Table S4). The dependent variable was infertility prevalence and the independent variables were year of investigation (dummy variable: 1940-1990), female age (dummy variable: before 35 years), study region (dummy variable: Africa), research type (dummy variable: cohort/prospective study), risk of bias (dummy variable: high), or sample size (defined as a continuous variable). We used a random effects meta-regression model with a restricted maximum likelihood approach. The proportion of prevalence estimates explained by any meta-regression model was estimated by the R^2 statistic.

To assess the stability of the results, we performed sensitivity analysis using leave-one-out method to assess the dependence of the findings on any individual study.

Results

Study Characteristics

A total of 6904 articles were retrieved through an electronic search. After qualifying screening, 27 community-based studies were ultimately included in this meta-analysis, including 17 countries and 118,619,426 participants (Figure 1). The detailed characteristics of included studies are provided in Table 1. Among these 27 studies, 24 (88.8%) were cross-sectional studies and 3 (11.2%) were cohort or prospective studies. The sample size of these studies range from 315 to 29,700,000. The geographical locations of the included studies are shown in Figure 2A, the studies were from [22-24]Africa (n = 3),[25-32]Asia (n = 8), [33-39]European (n = 7), [40-43]North America (n = 4), and[44-48]Oceania (n = 5) regions, respectively. An Australian-based study reported the lowest prevalence of infertility (3.55%), and the highest prevalence of infertility (39.68%) was observed in Palau (Figure 2B).

Quality assessment and bias

The average score of 27 included studies were 7.8 (SD:0.56, range: 6.5-9). According to 3 studies were ranked low risk, 23 were ranked moderate risk, and 1 was ranked high risk (Table S2). The detailed scores of these

studies were shown in Figure S1 and S2.

Pooled Prevalence of infertility

The pooled prevalence of infertility from a random-effects meta-analysis of 27 studies was 12.87% (95% CI,12.41%-13.33%; I^2=99.98%) (Figure 3A). The pooled prevalences of primary infertility and secondary infertility were 7.34% (95% CI,3.65%-11.02%; I^2=99.76%) and 6.01% (95%CI,4.16%-7.85%; I^2=99.64%), respectively (Figure 3B).

Subgroup analysis

Figure 4 presents the prevalence of infertility for participants or studies with different characteristics. In terms of geographical region, the prevalence of infertility for participants from Africa, Asia, Europe, North America, and Oceania were 16.73%, 14.91%, 13.83%, 8.84%, and 16.45% respectively (P <0.001). There are differences between each other. The prevalence rates in survey years groups were 9.06, 10.81, 14.32, and 17.2 respectively (P<0.001). The prevalence of infertility increases with the number of years, Showing a significant linear trend (P_{trend} <0.001). Combined rates of infertility Compared to cross-sectional studies, the prevalence is significantly lower in cohort or prospective follow-up studies (9.75% vs 12.93%, P <0.001). Globally, the prevalence of infertility for women [?]35 years old is significantly higher than that for women ¡35 years old (11.68% vs 5.92%,P_{trend} <0.001). From low to high levels of literature bias, the prevalence increased from 9.72% to 11.75 to 16.7% (P_{trend} <0.001). Detailed subgroup analysis forest maps were shown in Figure S3 to S6. The funnel plot results are shown in Figure S7.

Sensitivity analysis

We conducted the sensitivity analysis by removing each included study, (Figure S8) and we found no single study had an excessive influence on the pooled prevalence (the pooled prevalence of infertility among children varied from 12.12% to 13.24%). Results were robust.

Discussion

This systematic review and meta-analysis of 27 community-based studies indicated the pooled prevalence of infertility was 12.87%, with primary and secondary infertility prevalence rates were 7.34% and 6.01%, respectively. The pooled infertility prevalence was significantly diffed across regions, survey years, population characteristics, and bias levels.

The pooled infertility prevalence in our study was similar to a global meta-analysis at 12.6% (95% CI 10.7% to 14.6%)[49]. However, our rates are comparatively lower than an April 2023 report by the World Health Organization (WHO), which indicates that about 17.5% of adults worldwide suffer from infertility. This may be due to the fact that WHO covers almost all countries worldwide and only 17 countries were included in this study, resulting in our rates being inconsistent with them. In contrast, a meta-analysis on global female infertility with a prevalence of 46.25%, reported significantly higher rates as they included 20 hospital-based studies and only 4 community-based studies[19]. On the other hand, our combined prevalence is higher than in some studies. Boivin et al. estimated the prevalence of infertility at 24 months in 25 surveys, with a median prevalence of 9%[50]. Possibly because some women with low fertility may become pregnant within 12-24 months. Additionally, the prevalence of infertility decreases significantly as the duration of judgment increases, as reported in a study estimating the prevalence and trends of infertility from 1990 to 2010, which found a primary infertility prevalence of 1.9% but using a five-year exposure time[51]. In summary, our combined prevalence rates fall between the high and low rates observed in other studies, which may reflect the impact of various factors, including research type, screening criteria, geographic region, and cultural background. Further studies should explore these factors in greater depth to obtain a more accurate assessment of the global prevalence of infertility.

In our study, we compared the prevalence of primary and secondary infertility and found that the former was slightly higher than the latter, which is consistent with the results of some studies[25, 52] but contrary to others[22, 28]. These differences may be related to the wide variation in the prevalence of infertility

among different regions and populations, and should be taken into consideration when developing prevention and treatment strategies. Notably, some studies do not report the prevalence of primary and secondary infertility[45, 46, 53], whereas our combined values include both types of infertility. Future studies should focus on reporting the prevalence of primary and secondary infertility separately. It is important for understanding and managing these distinct types of infertility.

Our study also found that prevalence varied among people in different regions, with Africa having the highest prevalence and North America having the lowest prevalence. This is consistent with other studies, with Mascarenhas et al. reporting the highest infertility rates in South Asia, Sub-Saharan Africa, North Africa/Middle East, Central/Eastern Europe and Central Asia[51]. It may be related to the high prevalence of infectious diseases[54] and relatively poor human resources for health and medical conditions[55], among other factors. Gonorrhea, syphilis, vaginitis, etc., which may affect reproductive organ health and lead to infertility[56, 57]. The prevalence of infertility is on the rise with the increase of time. In modern society, women are getting married later and having children later, and the postponement of the childbearing age is an important factor in the increase of infertility[58]. Because one of the consequences of delaying childbirth can lead to impaired fertility, age is the most important factor in determining fertility in both men and women[59]. In addition, changes in lifestyle[60] and an increase in disease[61, 62]may adversely affect the reproductive system, leading to an increase in the prevalence of infertility. Our study found a difference in prevalence between women older and younger than 35 years old. This may be because, at an even earlier age, the number and quality of oocytes decrease but manifest clinically at around 35 years of age[63, 64]. Further evidence comes from a study of 2112 pregnant women in the UK, which reported that increasing age for both men and women affected the time taken to conceive[65]. The study adjusted for confounding factors such as coital frequency, body mass index (BMI), smoking and other lifestyle factors and still found women aged >35 were 2.2 times more likely than women aged [?]25 to take more than 2 years to become pregnant.

Our study compared the prevalence of infertility between cohort or prospective follow-up studies and cross-sectional studies, and found that the former was significantly lower than the latter. According to a cohort study of 2,300 women, the proportion of those with infertility was approximately 12%[66], while a cross-sectional study found that the prevalence of infertility was approximately 15.7%[41]. The reason for this difference is that cross-sectional studies are conducted at a single time point and often only capture transient or known symptoms of infertility. In contrast, cohort studies allow researchers to track individual changes over time, which can better control for time factors and fully consider potential risk factors for infertility. Overall, infertility is a complex issue that requires consideration of multiple factors. Targeted measures are needed for populations in different geographical regions and age groups, such as increased investment in medical resources, improved lifestyle, and reduced environmental pollution, to effectively control the incidence of infertility. Furthermore, more research is needed to further explore the causes and solutions of infertility.

Strengths and limitations

This study has several advantages: (i) The strengths of this study include the comprehensive search strategies, a double review process, and stringent selection criteria. The study also used a standardized tool to evaluate the quality of the literature. (ii) In our systematic review, we included only studies that were conducted in the community-based population so that our results could be more accurate and representative. (iii) We strictly limited the definition of infertility in our study to ensure the comparability of the combined prevalence. The standardized definitions of infertility subtypes and an adequate subgroup analysis reduced heterogeneity.

Several limitations of this study should also be recognized. First, although we unified the definitions of the prevalence of infertility and its subtypes before pooling the prevalence estimates, substantial heterogeneity was detected. Besides, even for the prevalence of infertility, for which the contributing data points successfully covered all the 6 WHO regions, the prevalence estimation at the regional level was not optimal given that more than half of the included studies were concentrated in only 2 regions (Asian Region and European Region), and the small number of studies in some countries which may not represent the true estimate in

that countries.

Conclusion

The findings from this study may provide crucial data for use in future research and clinical practice. Our study shows that the community-based global prevalence of infertility was 12.87% and that infertility was generally more common in persons who were from Africa or Oceania and in women aged 35 and above. An upward trend of the prevalence of infertility during the past 7 decades was observed and may persist in the future. More high-quality epidemiologic investigations on community-based infertility appear to be needed, especially for different subgroups of infertility and within the Region of the Americas, and the Region of Asia.

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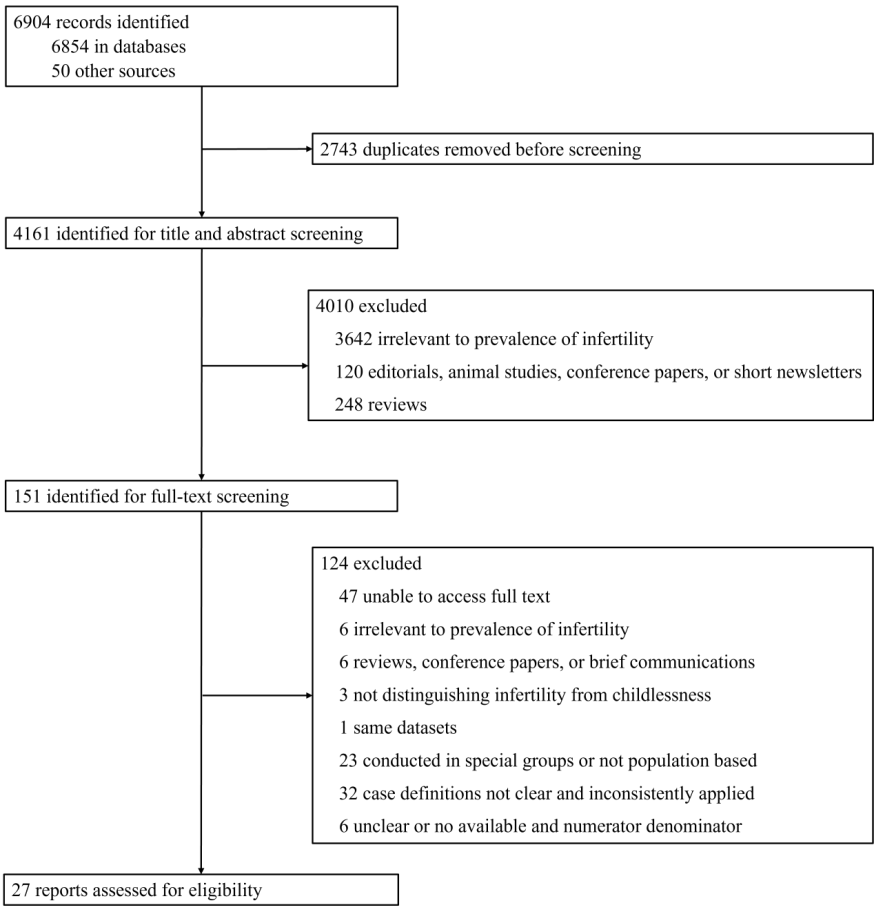

Figure 1 Flow chart of study selection

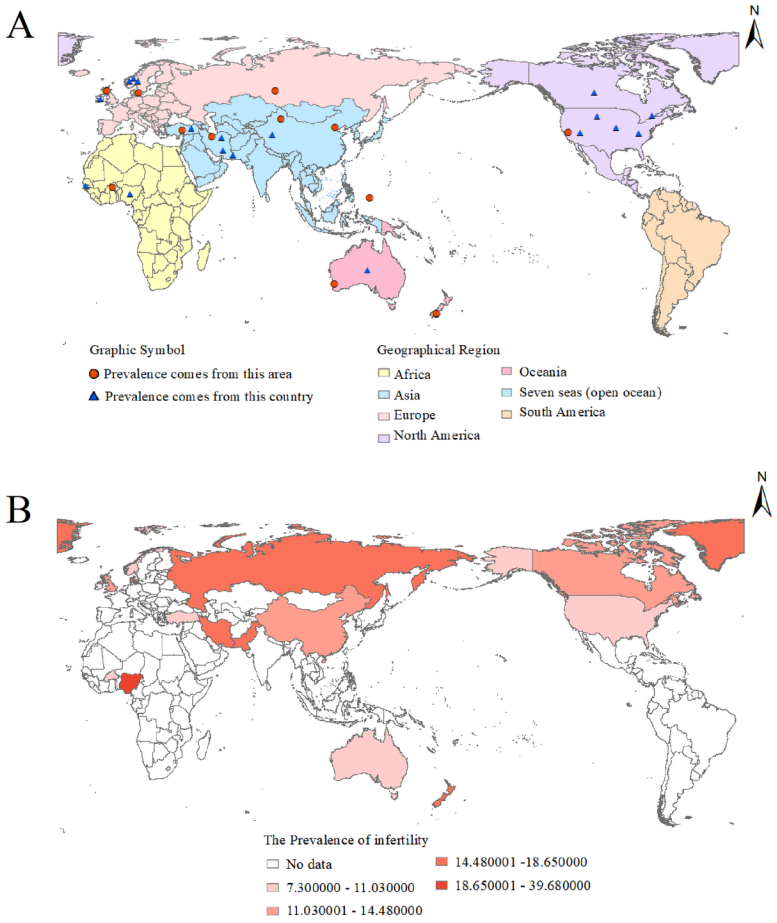

Figure 2 World Map. (A) Map of literature distribution; (B) National combined prevalence density map.

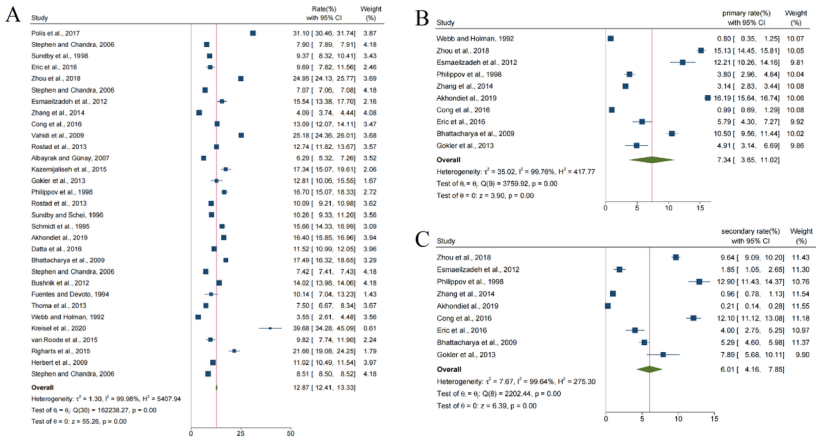

Figure 3 Forest plot. (A) Total prevalence of infertility; (B) Combined rate of primary infertility; (C) Combined rate of secondary infertility.

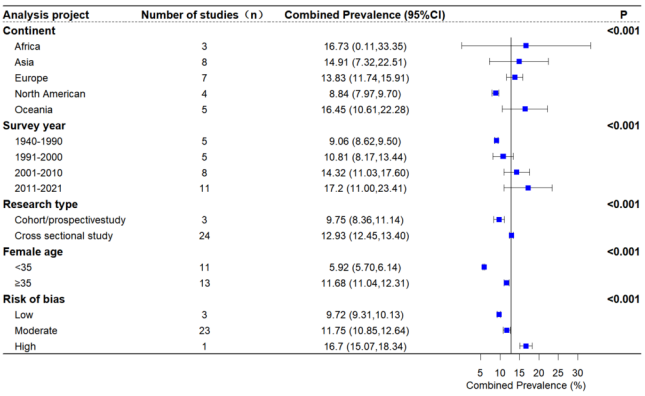

Figure 4 Sub-group analysis chart of infertility combined rate

Table 1 Summary of research articles included in this systemic review and meta-analysis of infertility

Study characteri	Year of survey
Webb and Holman, 1992	1988
Kreisel et al., 2020	2016
van Roode et al., 2015	2015
Stephen and Chandra, 2006	1982
	1988
	1995
	2002
Zhou et al., 2018	2011
Esmaeilzadeh et al., 2012	2010
Polis et al., 2017	2013
Bushnik et al., 2012	2010
Philippov et al., 1998	1998
Rostad et al., 2013	1940
	1950
Zhang et al., 2014	2012
Fuentes and Devoto, 1994	1990
Righarts et al., 2015	2010
Sundby and Schei, 1996	1993
Schmidt et al., 1995	1989
Herbert et al., 2009	1996
Sundby et al., 1998	1993
Akhondiet al., 2019	2011
Cong et al., 2016	2014

Datta et al., 2016	2012
Thoma et al., 2013	2002
Vahidi et al., 2009	2005
Eric et al., 2016	2014
Albayrak and Günay, 2007	2004
Bhattacharya et al., 2009	2007
Kazemijaliseh et al., 2015	2015
Gokler et al., 2013	2012