

Prevalence of Methicillin-Resistant Staphylococcus Aureus (MRSA) infection in patients with Cystic Fibrosis: a meta-analysis

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Abstract

Background Methicillin-resistant staphylococcus aureus (MRSA) infection is increasingly being reported among patients with cystic fibrosis (CF) and contributes to pulmonary morbidity in CF, with poorer prognosis. The aim of this study was to assess the prevalence of MRSA infection in patients with CF. Methods We conducted this study according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Databases of MEDLINE/PubMed, WHO-Virtual Health Library (VHL), ScienceDirect, Google Scholar and OpenGrey were searched to recruit the relevant articles. Pooled prevalence with the corresponding 95% confidence interval (CI) was calculated using OpenMeta Analyst software, and heterogeneity among studies was estimated using the I² statistics. Results According to our inclusion criteria, 27 studies included a total of 47,413 patients were analyzed. The pooled prevalence of MRSA in patients with CF was 15.2% (95% CI 9.70%– 20.7%). Subgroup analyses and meta-regression showed that the prevalence of MRSA in patients with CF was significantly associated with different geographical areas (P<0.001), data collection method (P<0.001), sample obtaining source (P<0.001), and study year (P = 0.006). Conclusions prevalence of MRSA infection is increasing in patients with CF. the results of this study could provide a reference for further controlling transmission and the management of patients with CF. Healthcare providers need to be aware of the clinically important association between MRSA infection and CF to ensure effective management.

Introduction

Cystic fibrosis (CF) is an autosomal recessive multisystem genetic disease, and one of the commonest life-threatening disorders caused by mutations in the CF transmembrane conductance regulator (CFTR) gene on chromosome 7, leading to production of thick secretions that predispose to chronic pulmonary infections, digestive tract disorders, as well as other systems impairment [1-2]. Most of patients with CF develop respiratory failure brought on by recurrent and chronic bacterial infection leading to persistent lung infections & obstructive lung disease, which is the most common cause of death in this population [3]. Respiratory tract colonization by these pathogenic microorganisms in patients with CF represents a serious health problem and it is considered a major cause of morbidity and mortality [4-5].

Patients with cystic fibrosis are susceptible to respiratory tract colonization and infections by different microorganisms due to their thick viscid secretions and impaired mucociliary clearance mechanism [6]. Classic organisms isolated from patients with cystic fibrosis include methicillin-sensitive *staphylococcus aureus* (MSSA), methicillin-resistant *staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa*, and *Burkholderia cepacia* [3]. MRSA is considered among pathogens of the highest prevalence, and a significant cause of increased morbidity and mortality among patients with CF [7]. Methicillin resistance seriously compromises the choice of antibiotic treatment in these patients [8]. Recent epidemiologic studies have evaluated the role of MRSA as contributor to clinical outcomes in patients with CF, and a risk factor for failure to recover lung function after an acute pulmonary exacerbation [9-10].

Studies have demonstrated that patients with MRSA detected in their sputum cultures and bronchial secretions had more hospital admissions per year as well as increased length of hospitalization and impaired pulmonary function tests than in patients without MRSA even after hazard ratios adjustment. Thus, it greatly impairs the quality of life of the affected patients. Furthermore, it has been linked with poor survival [11-13].

Several studies assessed the prevalence of MRSA in patients with CF and reported a progressive increase in the prevalence. However, these studies remain inconsistent with wide variation in the data obtained from these studies, and to the best of our knowledge, there is no meta-analysis of existing contemporary evidence on the prevalence of MRSA in patients with CF. The systematic measurements of the prevalence of MRSA will show the magnitude of this problem and the results of this study can provide a comprehensive view of MRSA prevalence in this susceptible population and may contribute to its control and management.

Methods

Search strategy and inclusion criteria:

The methodology was developed from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [14]. Medline/PubMed, WHO-Virtual Health Library (VHL), Google Scholar, ScienceDirect and OpenGrey were searched for all studies on association between MRSA infection and CF. We performed a systematic literature search of the database up to February 2019 using the search terms “methicillin-resistant staphylococcus aureus”, “MRSA”, “cystic fibrosis”, and “CF” to ensure maximal coverage of possible literature.

The criteria for paper inclusion were any study published in English that presented the prevalence estimates of MRSA in patients with CF or sufficient data for estimation. If two or more studies shared the same patient population, the study with more complete data or a larger sample size was included to avoid duplication. Infection was defined as the presence of this microorganism as detected by isolation from the specimens obtained from patients with CF, whether it was described as intermittent or persistent colonization in the included studies. Study exclusion criteria included the following: case reports, case series, editorial letters, reviews, abstracts, and studies lacking the data of interest.

The titles and abstracts of all papers retrieved from this search were screened for potential inclusion in this review. Then, potentially relevant studies were reviewed for inclusion according to the defined eligibility criteria. Any disparity was resolved by discussion and consensus. Quality of the studies was assessed using a quality assessment tool for prevalence studies suggested by Hoy et al, which is a tool that addresses internal and external validity issues of prevalence studies based on combined criteria [15]. Data extraction form was developed to extract the relevant information, and the following data were extracted: authors, study region, data collection method, samples' sources, year of publication, gender, patients' age group, number of patients with CF and number of patients with MRSA.

Statistical analysis:

Pooled prevalence from the random effects model with the corresponding 95% confidence interval (CI) was calculated using OpenMeta Analyst software version 10.10 for analysis [16]. Heterogeneity among studies was estimated using the I^2 statistics and publication bias was estimated by visual examination of the funnel plot. We detected a substantial level of heterogeneity ($I^2 = 99.7\%$) in estimated effect size between the included studies. Therefore, factors associated with the studies themselves (study area, data collection methods, sampling source, publication year and sample size) may have a moderating effect on the overall results. We therefore conducted subgroup analyses and meta-regression to determine the extent to which these variables moderated the overall results. Chi-square (X^2) test was used to assess the differences between the categorical subgroups and the significance level was set at 0.05.

Results

The schematic flow of study identification and selection process is presented in (Figure 1). The initial search retrieved records for 750 published articles. Full texts of 50 studies were screened and 23 studies of which were subsequently omitted because of low quality and insufficient data to estimate the outcomes of interest. Lastly, a total of 27 eligible studies published from 1988 to 2019 which met the eligibility for data extraction and analyses were used for qualitative and quantitative syntheses; 15 studies from Europe [4, 8, 17-29], 9 studies from the Americas [5, 30-37], 2 studies from Asia [38-39] and 1 study from Africa [40]. Overall, this analysis included a total of 47,413 patients. Most of the reviewed studies included all of the age groups (children and adult patients), whereas 7 studies were conducted exclusively among children. CF patients in these studies were diagnosed by positive sweat tests and/or presence of the CFTR mutations. The main characteristics of these included studies are shown in (Table 1 in the Supplementary Files).

Meta-analysis for the included studies showed that the prevalence of MRSA in this population from the random effects model was 15.2% (95% CI 9.70 %– 20.7%) (Figure2). A slight publication bias was detected based on visual examination of the funnel plot (figure 3). In subgroup analysis, the pooled prevalence of MRSA infection among patients with CF was 8.70% (95% CI 6.40 % – 10.9%) in Europe, 19.0% (95% CI 6.20 % – 13.8%) in the Americas, and 27.5% (95% CI -0.026% – 0.576%) in Asia (Figure 1). There was a statistical difference in prevalence between different geographical areas ($X^2 = 140.4$, $P < 0.001$), Specimen obtaining sources ($X^2 = 84.42$, $P < 0.001$), and data collection methods ($X^2 = 6373.6$, $P < 0.001$) (Table 2 in the Supplementary Files). Furthermore, meta-regression analyses were done to analyze whether the continuous variables (sample size and publication year) affected the heterogeneity among studies in this meta-analysis. The results showed that publication year was correlated with the outcome ($P = 0.006$), and sample size had no moderating effects on the outcome of this analysis ($P = 0.936$) (Figure 4 A-B).

Discussion

During the disease course, patients with CF are susceptible to infection with several microorganisms including MRSA, leading to frequent episodes of debilitating inflammatory exacerbations and progressive lung damage, influencing the quality of life and life expectancy [41]. Most of the included studies in this meta-analysis assessed the prevalence of MRSA infection in the European CF population, which is consistent with the distribution areas of patients with CF, which is found predominantly in Caucasian populations of European ancestry [3]. In this meta-analysis, we have an updated estimate of the global prevalence of MRSA colonization in CF population. Existing evidence from the reviewed studies showed that 15.2% of CF patients were infected to the MRSA.

The discrepancy between prevalence rates reported from the reviewed studies might be attributable to several factors. In this meta-analysis, we have found that the prevalence of MRSA showed regional epidemiological differences. This finding was also reported by previous review done Christopher H. Goss et al [9]. While rates of MRSA have been reported to be considerably lower in most European CF centres, the prevalence tends to be a little higher in other countries where there is overcrowded living condition and inadequate implementation of infection control measures.

MRSA poses a concern because of its rising prevalence and its rapidly growing antibiotic resistance attributed to its resilience and different molecular properties that facilitate the acquisition of different antibiotic resistance genes [42]. In this meta-analysis, we found that the prevalence of MRSA infection has climbed up over years. This increase is in line with previous reviews done by LiPuma, Kahl and Jennings et al [3, 10, 43]. They reported that MRSA infection among CF population has demonstrated a notable increase in prevalence over the last decades. Analysis of data from the Cystic Fibrosis Foundation Patient Registry in the United States indicates that the prevalence of MRSA infection in CF patients increased steadily during the last years [3]. Also, this observation has been noted in a reference centre for the treatment of CF patients in Buenos Aires, Argentina, where the prevalence of MRSA has climbed from 23% in 1995 up to 32% in 2011 [34].

Sputum specimen is a common and readily available method for clinical evaluation of the lung microorganisms in patients with CF. It is less sensitive than other more invasive procedures such as bronchoalveolar lavage, but it remains an accurate indicator of lower airway microbiology [44]. Most of the included studies data came from the results of sputum samples. This meta-analysis showed that the colonization prevalence of MRSA from sputum culture alone was lower than that from specimens obtained from sputum with other more invasive sampling.

Other possible risk factors of MRSA infection in patients with CF have been assessed by a few of the included studies. Some of these studies had demonstrated that older age [22], MRSA detection in family members [17], occupational exposure [38], frequent hospitalization [21, 34, 37], CF-related diabetes [34], pancreatic insufficiency [21], pre-existing bronchiectasis [21], and *Pseudomonas aeruginosa* co-infection [17, 31] could be implicated in the increasing burden of MRSA infection in patients with CF.

Limitations: The findings of this study need to be considered in the context of some limitations. The inclusion of studies published only in English may compromise representativeness. As well, because of the lack of uniformity across studies, we did not assess the factors that possibly increase the risk of MRSA infection among patients with CF.

Conclusion

We have summarized data of several studies exploring the prevalence of MRSA among patients with CF in this study. MRSA infection occurs with increased frequency in patients with CF. The results of this study could have an important implication for further controlling transmission, and could provide a reference for the management of patients with CF. Healthcare providers need to be aware of the clinically important association between MRSA infection and CF to ensure effective management.

Abbreviations

MRSA: methicillin-resistant staphylococcus aureus; CF: cystic fibrosis

Declarations

- **Ethical approval and consent to participate:** not applicable
- **Consent for publication:** not applicable.
- **Availability of data and material:** The dataset generated during this study are available from the corresponding author on reasonable request.
- **Competing interests:** The authors declare that they have no competing interests.
- **Funding:** No fund.
- **Authors' contribution:** (SM) conceptualized the research idea and designed the study; (SM, AA and AI) undertook articles searching; (SM, ME, AE and MS) undertook data extraction and analysis; All authors interpreted the results and drafted the manuscript. All authors revised and approved the final manuscript.
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Figure Legends

- **Figure 1: flow chart for study selection process.**
- **Figure 2: pooled prevalence of prevalence of MRSA colonization in CF patients.**
- **Figure 3: Funnel plot for publication bias assessment.**
- **Figure 4 A-B: Meta regression scatters plots for correlation between prevalence and sample size or publication year.**

Tables

Due to technical limitations, tables are only available as a download in the supplemental files section.

Figures

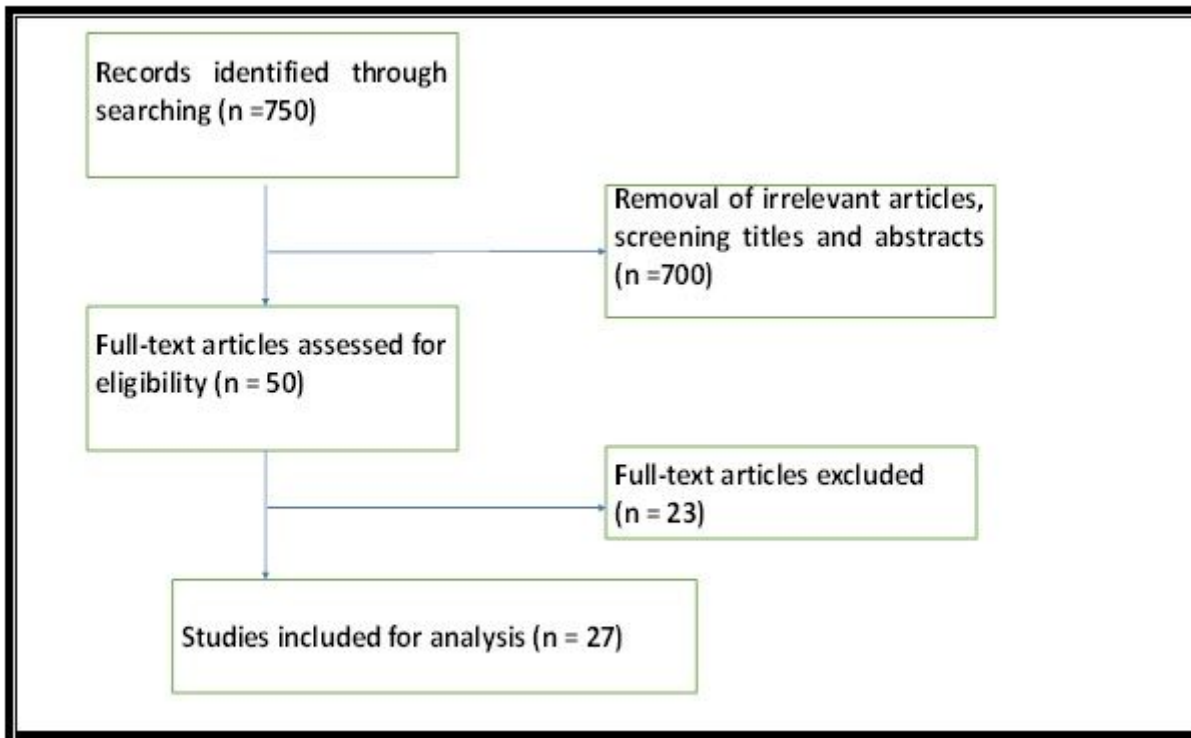


Figure 1

Figure 1: flow chart for study selection process.

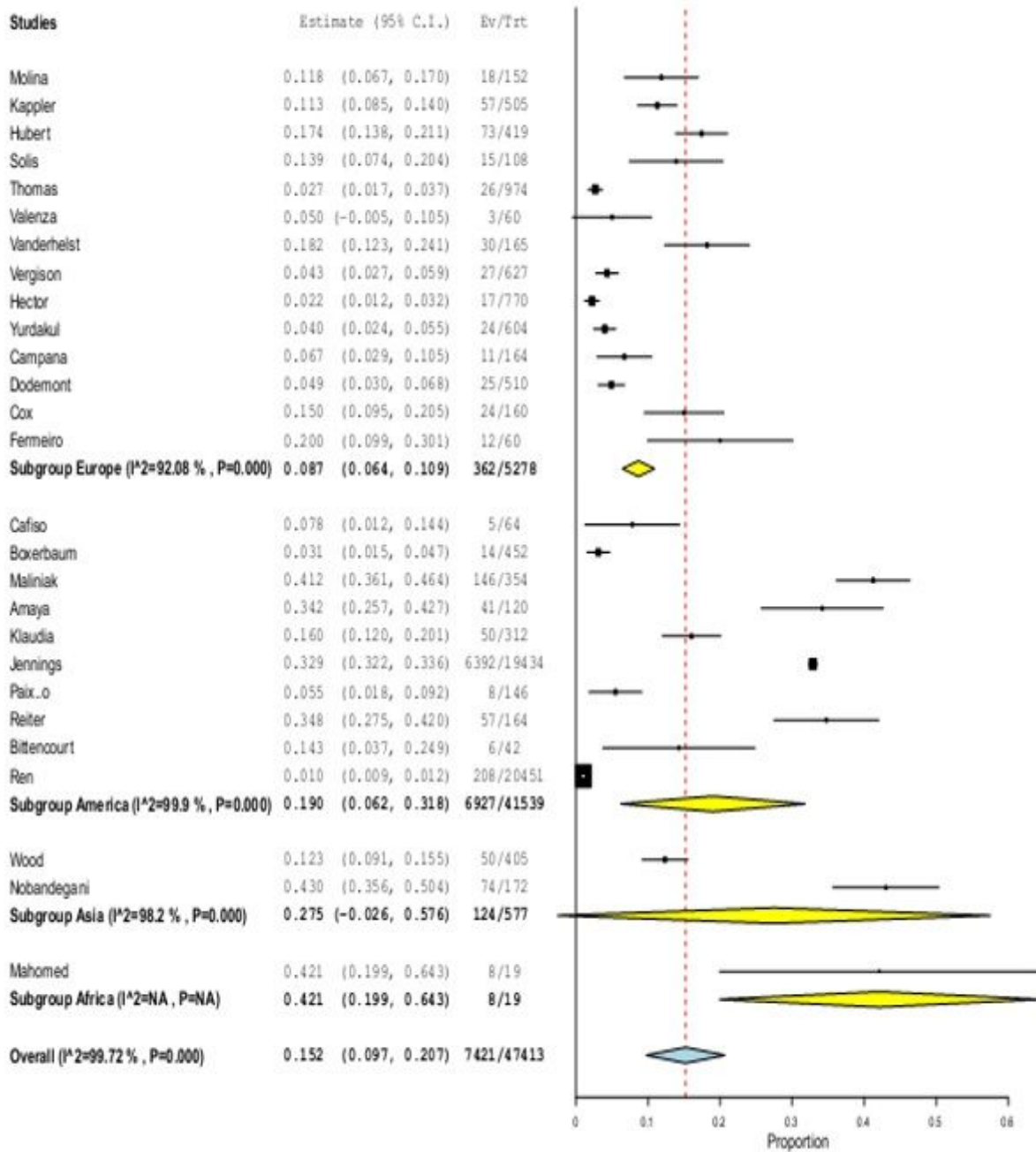


Figure 2

Figure 2: pooled prevalence of prevalence of MRSA colonization in CF patients.

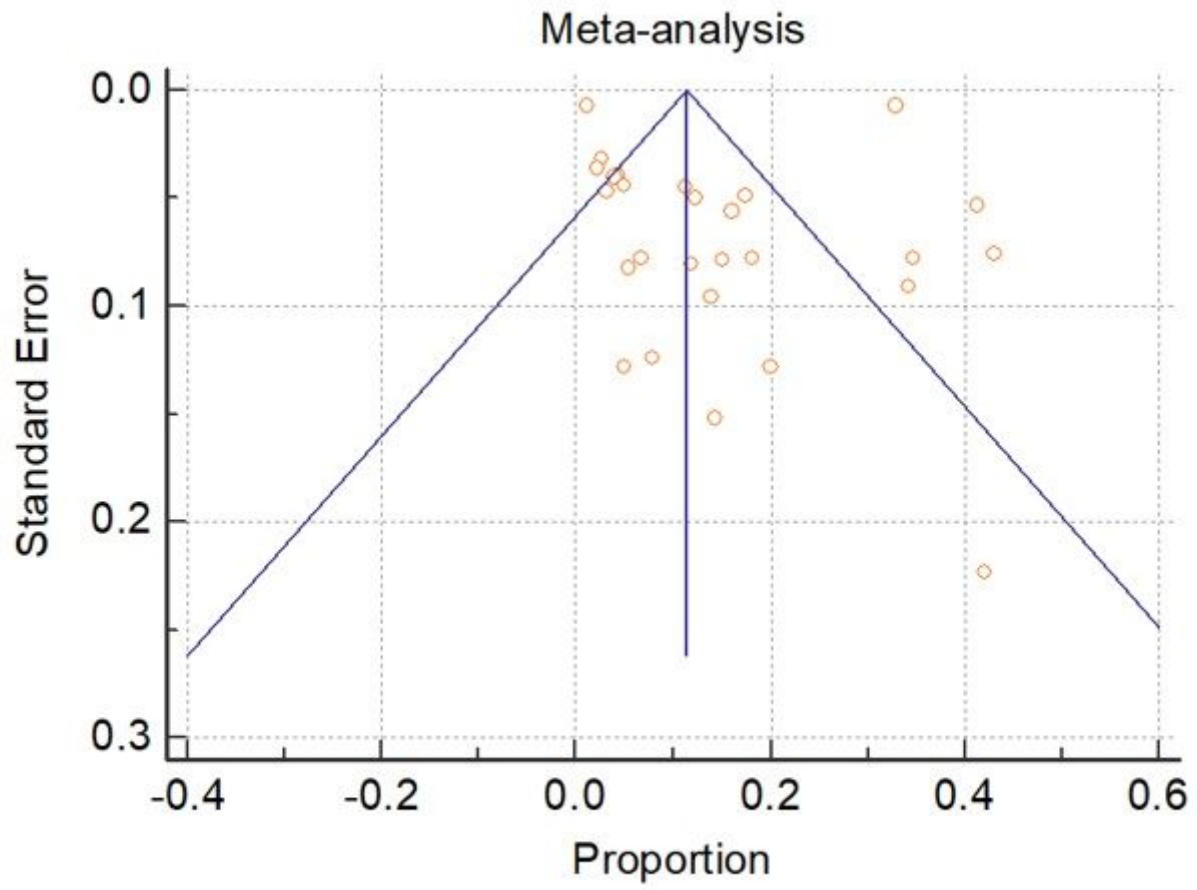


Figure 3

Figure 3: Funnel plot for publication bias assessment.

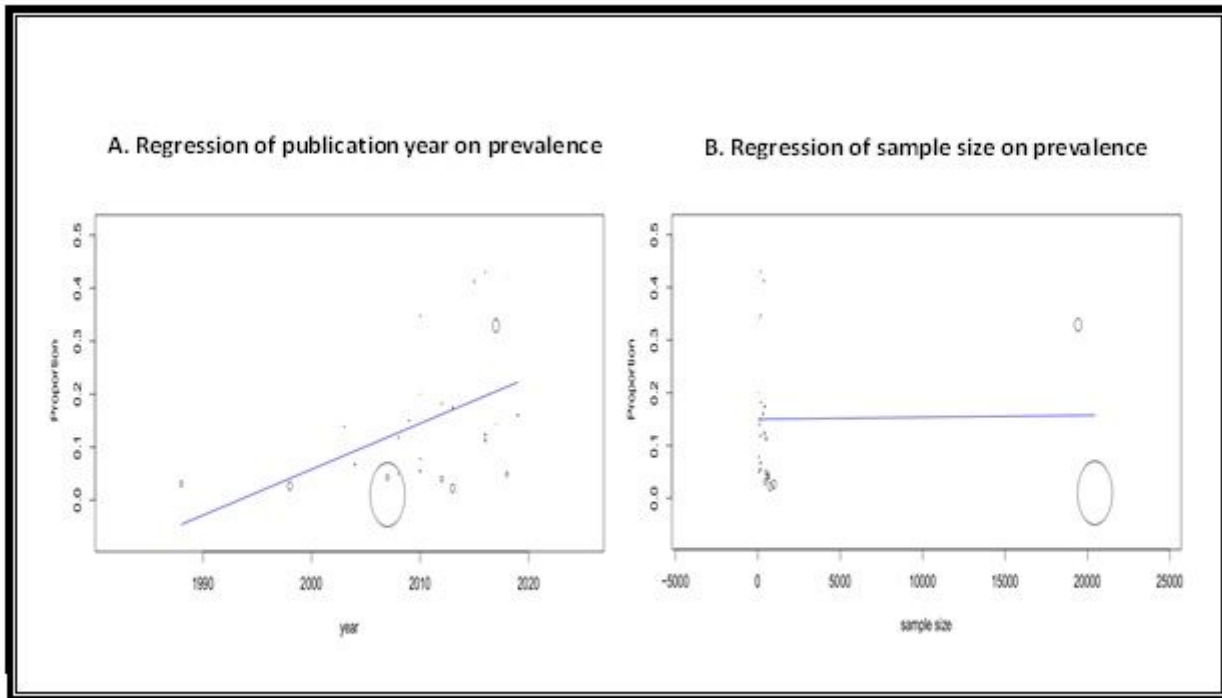


Figure 4

Figure 4 A-B: Meta regression scatters plots for correlation between prevalence and sample size or publication year.

Supplementary Files

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