Systematic Review:

Prevalence of Rheumatic Heart Disease in Iran: A Systematic Review and Meta-analysis

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ABSTRACT

Context: Rheumatic Heart Disease (RHD) remains the prominent cause of morbidity and mortality among young individuals in developing countries. The present research aimed to estimate the prevalence of RHD in Iran.

Data Sources: In this review, all population-based studies with a sample size of ≥500 participants related to the prevalence of RHD were included. The search was conducted in national and international databases. The combination of medical subject headings and free-term text items concerning the incidence, prevalence, rheumatic fever, RHD, and Iran were used in this study.

Data Extraction: In this systematic review, 490 papers were identified. A total of 296 articles were screened; of which, 9 qualified articles were selected for the final data analysis. All studies were of cross-sectional, and descriptive natures. Two authors used the data extraction form to independently extract relevant data from the included studies. Disagreements between the authors were reconciled through discussion and consensus.

Results: The overall prevalence of RHD was calculated as 0.02% (20/100000 population). This prevalence rate is estimated based on studies conducted in the northern, southern, eastern, western, and central regions of the country; therefore it could be an estimation of the relevant prevalence rate in Iran. However, there were no updated and high-quality data in this regard. Thus, the reported rate might be underestimated.

Conclusions: There is a need for a nationwide survey to investigate the precise prevalence of RHD in Iran. This can be achieved by creating a national database of RHD.

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1. Context

Acute Rheumatic Fever (ARF) is an autoimmune disease caused by infection with the Streptococcus pyogenes, or Group A β hemolytic Streptococcus (GABHS) (1, 2). It is a disease of childhood (5-15 years) (3). As the disease progresses in recurrences or untreated cases, permanent heart valve damage (Rheumatic Heart Disease; RHD) develops in approximately 60%-65% of patients (2, 4). The common complications of RHD are heart failure, atrial fibrillation, and stroke (5). With the progress of the disease, cardiac surgery often becomes necessary, and patients who failed to undergo such treatment often die prematurely. The mean age of death due to RHD is <25 years (2).

Despite the declined prevalence of RHD in developed countries since the early 1900s, it remains the major cause of morbidity and mortality among adolescents in developing countries (1, 6, 7). It has been estimated that >34.2 million individuals suffer from RHD globally (8). Moreover, up to 1.4 million individuals die from RHD annually (9, 10); accordingly, 99% of the cases occur in endemic areas, mainly in Low- and Middle-Income Countries (LMICs) (11, 12). The lack of sufficient and reliable data from most regions is among the reasons that the regional burdens of RHD may be underestimated (13, 14).

The highest incidence rates belong to Africa, Australia, and New Zealand's indigenous populations, as well as Asia (7). A recent analysis of the Global Burden of Disease (2015) revealed that the number of RHD cases in the Eastern Mediterranean Region (EMR) has increased from 18350 to 27047 (a 47% increase) from 1990 to 2015. Based on this report, 80% of total RHD-induced deaths were reported from Egypt, Pakistan, Iran, Afghanistan, and Yemen (12). The number of prevalent cases of RHD in Iran was equal to <500000 cases in 2013, which increased to <5% in age-standardized RHD prevalence from 1990 (15).

It is expected to increase global focus on RHD as a result of the Executive Board of the World Health Organization recommendation in June 2017 for the prioritization of ARF/RHD Prevention and Control Strategy (5). The main target of the World Heart Federation (WHF) is to reduce premature RHD-related deaths in individuals aged under 25 years by 25% until 2025. This aim could be achieved by f health promotion, enhanced monitoring, and employing efficient prevention strategies (8, 16). A crucial prerequisite for achieving this goal is access to high-quality data on the prevalence of RHD (11). Case ascertainment might be improved following the existence of registries (17).

Few studies have estimated the prevalence of RHD in some provinces of Iran; however, there is no national data on the prevalence of RHD in Iran. Iran could not be categorized as low- or moderate- to high-risk populations due to the lack of reported literature on RHD. The effective management of RHD and developing policies for the control of it depend on determining whether or not the disease is endemic in the country. Thus, we aimed to review the reported cases of RHD to determine the prevalence of RHD in Iran.

2. Evidence Acquisition

In this study, we performed a comprehensive search on the Web of Science, Scopus, PubMed, and Google Scholar as well as Persian databases, such as Scientific Information Database (SID), IranMedex, IranDoc, and New Information System of Iranian Medical Research (NOPA); these databases were searched to extract all related studies reporting the incidence or prevalence of ARF/RHD published from 1970 onward. We applied a search strategy that supported both Medical Subject Headings (MeSH) and free term text items related to "incidence, prevalence, rheumatic heart disease, rheumatic fever, and Iran" using Boolean operators, published in Persian or English. To complete the search, we scrutinized all references of all extracted articles to find further data sources. We also searched the dissertation database of all universities of medical sciences in Iran to identify the dissertations on the subject related to the present study. The latest search was conducted on the 24th of March 2020.

All descriptive, cross-sectional, and population-based (school-based or community-based) studies with a sample size of ≥500 participants that reported the incidence or prevalence of ARF/RHD figured out or confirmed by echocardiography, regardless of the age and gender of participants were included in this study. Only full-text studies published in English and Persian were considered for the review. We excluded all studies that used only auscultation for RHD screening without echocardiography confirmation.

The first author (Zainab Qazizadeh) performed a systematic search for articles using the search strategy. Two other authors (Leila Shahbaznejad & Mohammad Sadegh Rezai) separately screened the titles and abstracts of the searched articles by applying the predefined inclu-

sion and exclusion criteria. Any disagreement was discussed and wherein consensus could not be attained, was solved by the third author (Leila Shahmoradi). Finally, irrelevant or repeated papers were excluded. The full text of eligible articles was assessed for final inclusion. For duplicates, studies that were published in more than one report, the most comprehensive one was considered. Articles finalized for inclusion were managed using EndNote. Finally, for reporting systematic reviews, the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist was used.

The quality of the articles was independently evaluated by two experts. A modified version of the Newcastle-Ottawa Quality Assessment (NOS) has been exploited for quality assessment. The inquired articles were divided into two categories. The poor-quality articles with a score of 1 or 2, and high-quality ones with a score of 3 to 5. Disagreements were resolved by consensus, mutual discussion, and consulting with the third expert.

Two reviewer authors used the data extraction form to extract the relevant data from the included studies independently. To enhance the validity and reliability of the obtained data, the data extraction process was repeated (not divided between the two authors). Discrepancies amongst authors were solved through debate and consensus. The extracted data from each study included the following: the surname of the first author, the year of publication, location, source population size, study duration, study design, target age, and reported prevalence, i.e. captured by the data extraction form.

All analyses were performed using STATA. In the present study, we estimated the incidence or prevalence of ARF/RHD for Iran by incorporating the incidence or prevalence rates reported in all studies conducted in different provinces. We used the forest plot for presenting the meta-analysis results (18). We appraised heterogeneity and inconsistency between studies using the I2 statistic. I2 ranges from 0 to 100% and values of ≥50% were considered as high heterogeneity and inconsistency (18, 19). The values of I2 in this study were significant; thus,
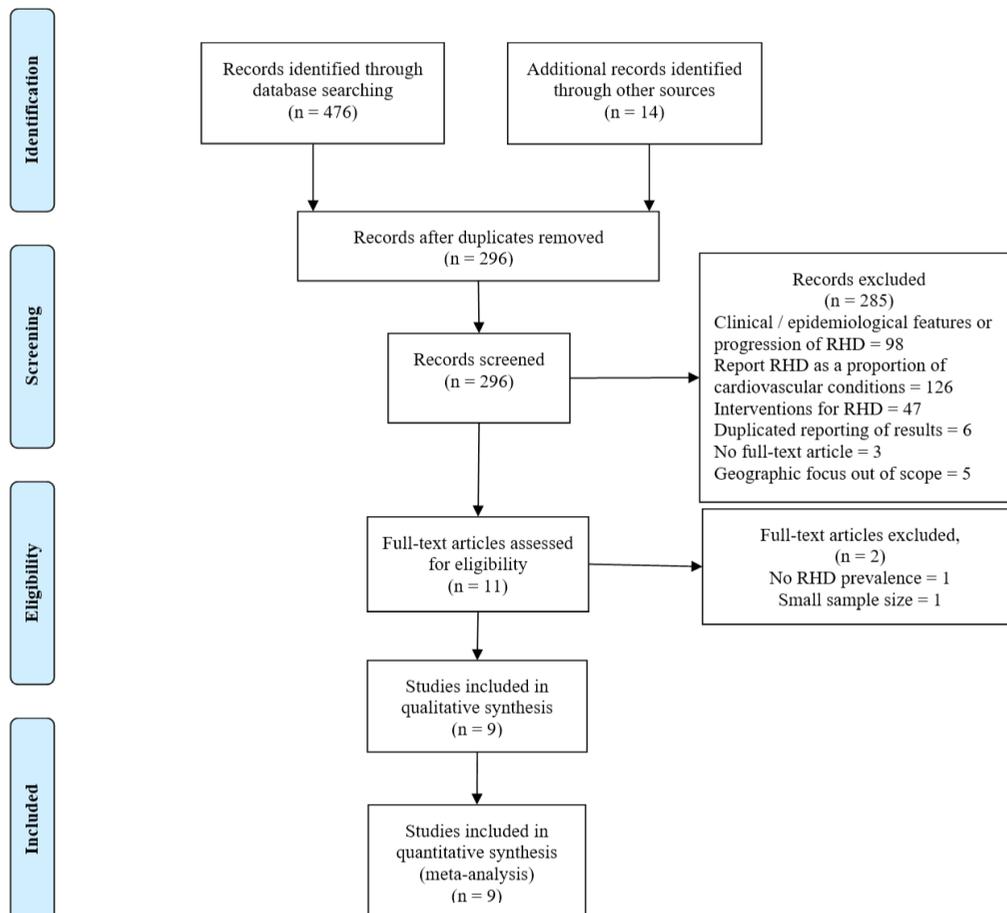

Figure 1. Flow chart illustrating search results

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Table 1. Characteristics of the included studies

Study (ref.)	Province	Study Duration (y)	Source (Population Size)	Target Age (y)	Type of Study	Prevalence (%)
Padmavati, 1978 (21)	Abadan	1 year: 1971	70000	All	Cross-sectional	0.1
Jahanshahinasab, 1992 (22)	Kermanshah	2 years: 1991-1992	7688	<18	Cross-sectional	0.12
Niyabati, 1994 (23)	Tehran	2 years: 1993-1994	1845963	<18	Cross-sectional	0.02
Molavi, 2003 (24)	Kermanshah	2 years: 1994-1995	23961	7-12	Cross-sectional	0.01
Haqiqi, 1995 (25)	Tehran	2 years: 1993-1994	94567	<18	Cross-sectional	0.02
Barzigar, 1995 (26)	Gilan	3 years: 1990-1992	422000	7-18	Cross-sectional	0.02
Dadgar, 2000 (27)	Khorasan	4 years: 1990-1993	1054385	6-19	Cross-sectional	0.02
Zeinaloo, 2001 (28)	Zanjan	3 years: 1991-1993	320000	6-20	Cross-sectional, Descriptive	0.04
Mahmoudi, 2003 (29)	Hamedan	1 year: 1993	167786	7-18	Cross-sectional	0.01

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we used a random-effects model (at a 95% Confidence Interval; CI), to present a more conservative estimation of the ARF/RHD incidence or prevalence. All estimates were reported per 1000 population at 95% CI. Furthermore, publication bias was evaluated employing Egger's test and funnel plots (18, 20). The significance level to detect publication bias was considered AT $P<0.10$.

3. Results

We presented the first systematic review and meta-analysis estimating the prevalence of RHD in Iran. In this review, 490 relevant articles were identified through an electronic database search. A total of 11 articles were assessed for eligibility; of which, 9 qualified articles met the inclusion criteria of this systematic review and meta-analysis (Figure 1).

These studies were conducted in different provinces; Tehran, Khorasan, Kermanshah, Hamedan, Gilan, Zanjan, Khoozestan, and were published between 1976 and 2003. The study duration ranged from 1 to 20 years.

A total of 4006350 individuals was evaluated concerning RHD prevalence in various geographical locations in Iran. The final sample included 7 provinces, Khoozestan (n=1 article), Kermanshah (n=2), Tehran (n=2), Gilan (n=1), Khorasan (n=1), Zanjan (n=1), Hamedan (n=1),
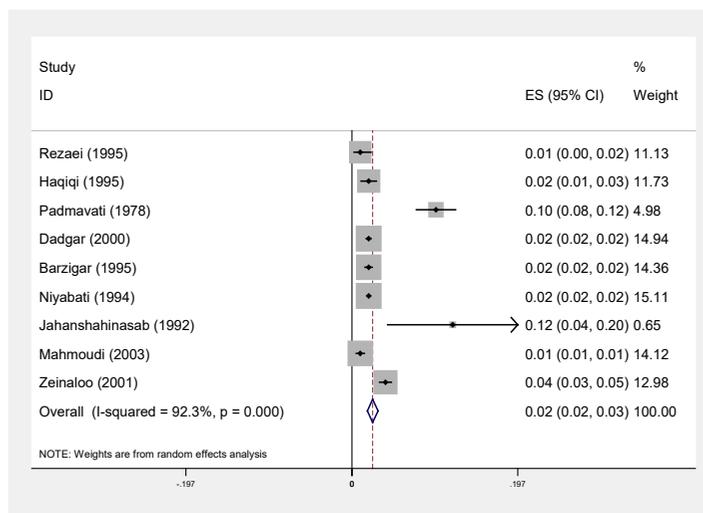

Figure 2. Forest plot for RHD prevalence in the reviewed articles
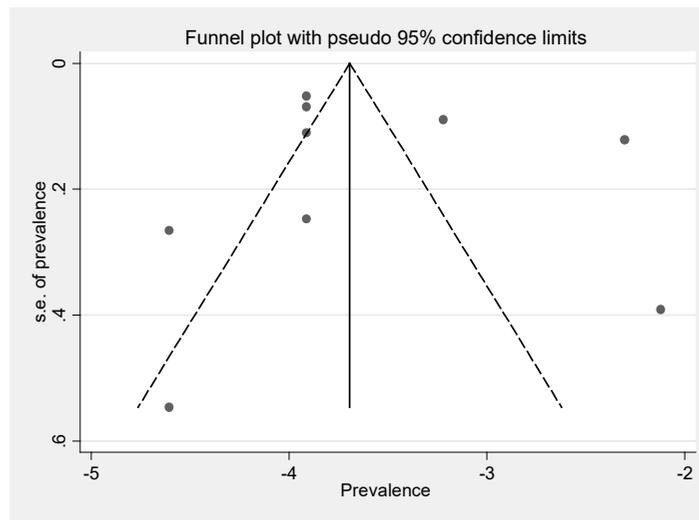
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Figure 3. Funnel plot with pseudo 95% confidence limit

i.e. published between 1978 and 2003. The duration of the study ranged from 1 to 4 years, with a Mean±SD of 2.2±1.0 years.

Only one study investigated RHD prevalence in all age groups and the remaining 8 studies investigated prevalence in children and adolescents. The result of our literature review and the characteristics of each study are presented in Table 1.

Table 1 presents the relevant prevalence rates reported per study. The overall prevalence of RHD was calculated and expressed with 95% CIs. The estimates of prevalence of RHD in Iran was 0.02% (95% CI: 0.02%-0.03%) and heterogeneity was substantial, I2=92.3%, P<0.001) (Figure 2).

Egger's regression test and Funnel plot (Figure 3) showed that publication bias presented no significant influence on the overall prevalence of RHD (β=1.92, P=0.575). As per Figure 4, the result of sensitivity analysis to evaluate the effect of each study on the overall estimate suggested that the effect of each study on the overall estimate was not different.

4. Discussion

In this systematic review, we studied all reported studies concerning the prevalence of RHD in Iran. All reviewed studies were published between 1976 and 2003. These studies were performed in 7 of the 31 provinces in Iran, i.e. located in the northern, southern, eastern, western, and central regions of the country; thus, it
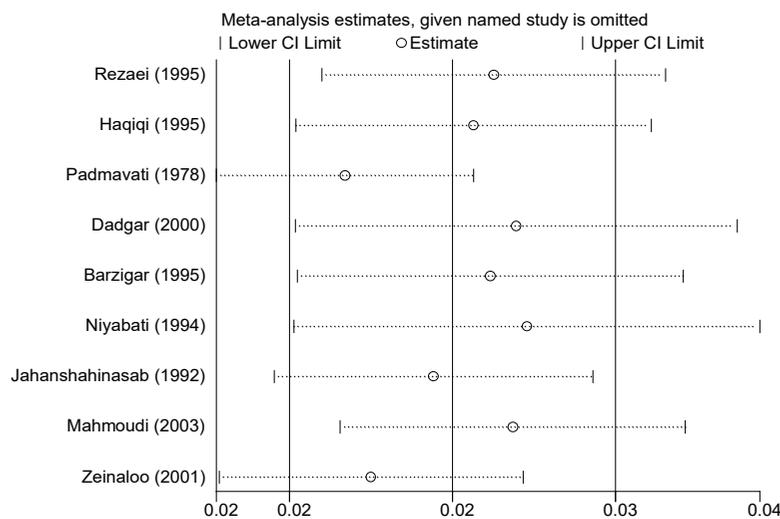

Figure 4. Sensitivity analysis

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can be a representative sample of the total population of the country. The reported prevalence ranged from 0.01% to 0.12% in different provinces. The overall prevalence of RHD was calculated to be 0.02% (20/100000 population). Based on Seckeler's and Hoke's study, there were no available data on the prevalence of RHD in Iran from 1970 to 2010 for computing the worldwide survey of ARF/RHD. Additionally, the incidence of ARF, as the trigger of the incidence of RHD, has been reported as 40-100 cases per 100000 population from 1970 to 1990 in Iran, i.e. almost a high incidence. However, this rate was unavailable since 1991 (1). In GBD's study, the RHD prevalence was estimated as 2.1 and 2.5 per 100000 individuals in men and women in Iran, respectively. This prevalence is calculated only based on fatal data (30). According to RHD Atlas, the crude prevalence of RHD has increased by 82% from 1990 to 2013; i.e. significant (31). The prevalence of estimated RHD seems to be underestimated due to the lack of morbidity data. The present study data, i.e. calculated according to population-based studies also revealed that the actual prevalence of RHD in Iran is higher than the available reported rates.

There is a problem with the lack of adequate and high-quality studies on the prevalence of RHD in developing countries (32, 33). The high-quality population-based studies respecting the incidence of ARF or prevalence of RHD globally are also scarce (11, 12). For instance, until 2008, the population-based studies on the incidence of ARF were only restricted to 10 countries (11).

The availability of data on the prevalence of RHD and its associated deaths varies widely across different countries and regions. The available data on RHD from Iran was limited to fatal cases (30). Iran is ranked third concerning RHD-induced deaths in the EMR region, in 2015 (12). The RHD-induced death rate in this region increased from 18350 in 1990 to 27047 cases in 2015 (a 47% increase); thus, it suggests a higher mortality rate from RHD than the reported rate in the global burden of disease study (34).

According to the global map of low- and moderate-to high-risk countries concerning RHD, Iran could not be categorized as a low- or moderate- to a high-risk population, i.e. due to the lack of reported literature on RHD (35). Accordingly, the lack of complete and accurate information at the national level prevents the adequate analysis of the RHD situation and determining distribution patterns. The present study aimed to address this data gap. However, there were no data since 2003. Therefore, the reported rates of RHD are likely to be underestimated. More accurate judgment of the regional prevalence of disease requires a nationwide epidemiological study of the disease; this is because of the ethnic, socio-economic, and cultural diversities. As a result, it seems necessary to launch a national registry for ARF/RHD.

The strength of this study included large sample size, meticulous methodology, and quality assessment. However, this review was associated with some limitations. There was a paucity of new studies on RHD prevalence in the country. Most studies were performed on school-age children and the prevalence in all age groups has rarely been studied. Moreover, some studies used school-based screening, which could likely present bias in favor of lower RHD prevalence. The registry-based and population-based studies were conducted in India and reported the prevalence of RHD peaks to be around 30-40 years or so (36). In conclusion, prevalence reported based on investigations in school-age groups may cause an underestimation of disease burden.

No studies were available from deprived provinces, i.e. considered to have a high prevalence of the disease. This is because of their socio-economic situation, poverty, and low access to the healthcare system. This restriction can affect the calculation of the actual prevalence of RHD. Therefore, it seems necessary to conduct a national study with sampling from all provinces of the country to calculate the prevalence of disease and recognize its pattern.

5. Conclusion

This systematic review and meta-analysis study highlighted the lack of studies on the RHD prevalence in Iran. There is a necessity for updated information on the prevalence of RHD to prepare a basis for health policymaking, resource allocation, and health management in Iran. We need to conduct a new investigation to address the gaps in understanding of RHD prevalence. It should be emphasized that the existence of a national RHD registry for collecting comprehensive epidemiological data is the main step for planning, designing, and implementing national programs to prevent and control the disease.

Ethical Considerations

Compliance with ethical guidelines

There are no ethical considerations to be noted.

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