BMJ Open

A Review on the Prevalence, Risk Factors, and Psychological Impact of Infertility among Women

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-057132
Article Type:	Original research
Date Submitted by the Author:	06-Sep-2021
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Keywords:	Public health < INFECTIOUS DISEASES, Maternal medicine < OBSTETRICS, PRIMARY CARE

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A Review on the Prevalence, Risk Factors, and Psychological Impact of Infertility among Women

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ABSTRACT

Objectives: Infertility is a multidimensional stressor associated with dysfunction in sexual relationships, anxiety, and depression and affects life. These effects may be long-lasting. Determining the psychological impact of infertility among females provides a better assessment that helps formulate the preventive strategy. This study aimed to assess the prevalence, risk factors, and psychological impact of infertility among females.

Study design: Systematic review and meta-analysis

Methods: A systematic search was performed in MEDLINE, CINAHL, and ScienceDirect. All studies published from the inception of databases until 2020 were retrieved. A critical appraisal was undertaken to assess the quality of data using the Joanna Briggs Institute Meta-Analysis. The analysis was performed using Review Manager software.

Results: Twenty-nine studies were incorporated into a random-effects model. The findings indicated the overall pooled prevalence to be 48.85% and 51.5% for infertility and primary infertility, respectively. Smoking was significantly related to infertility, with the odds being 1.85 (95% CI: 1.08, 3.14) times higher than females who do not smoke. There was a statistical significance between infertility and psychological distress among females, with the odds being 1.63 (95% CI: 1.24, 2.13). A statistical significance was noted between depression and infertility among females, with the odds being 1.40 (95% CI: 1.11, 1.75) compared to those fertile.

Conclusions: The study results highlight an essential and increasing mental disorder among females associated with infertility and may be overlooked. Acknowledging the problem and providing positive, supportive measures to females with infertility ensure more positive outcomes during the therapeutic process.

Keywords: infertility, prevalence, risk factors, psychological impact

PROSPERO registration number: CRD42021226414

Words count: 2450

ARTICLE SUMMARY

Strengths and limitations of this study

- Meta-analysis of studies according to preferred reporting items for systematic reviews and meta-analyses guidelines
- Included studies published from the inception of databases until 2020
- Only studies with low risk of bias were included in the analyses
- Heterogeneity and subgroup analyses were performed
- The search was restricted to English-language articles only

INTRODUCTION

Infertility is defined by the World Health Organization (WHO) as the inability to conceive after one year (or longer) of unprotected intercourse [1]. It is classified as primary or secondary. Primary infertility is denoted for those women who have not conceived previously [2]. In secondary infertility, there is at least one conception, but it fails to repeat [2]. In 2002, the WHO estimated that infertility affects approximately 80 million people in all parts of the world [3]. It affects 10%–15% of couples in their lifetime [4 5]. The prevalence of infertility is concerned, it is high (up to 21.9%): primary infertility at 3.5% and secondary infertility at 18.4% [6]. It is generally accepted that infertility rates are not estimated correctly. The reasons could hinder the measurement of the

prevalence, imperfect measurement methods, and unknown kinds of infertility resulting from cultural biases [7].

Infertility is a multidimensional stressor requiring several kinds of emotional adjustments [4]. It is associated with dysfunction in sexual relationships, anxiety, depression, difficulties in marital life, and identity problems [8]. The impact of infertility may be long-lasting, even beyond the initial period of childlessness has passed [9 10]. In the general population, major depression is two to three times as common among women as among men [11]. In the United States, the 12-month prevalence of any mood disorder is 14.1% in females and 8.5% in males, whereas any anxiety disorder is 22.6% in females and 11.8% in males [12]. Thus, depression is one of the most common negative emotions associated with infertility [13 14], which the local social and cultural context may influence.

Determining the psychological impact of infertility among women worldwide provides a better assessment than discrete primary studies. Identifying this impact helps gain a clear understanding of the issue and serves as a basis for an appropriate preventive strategy. In addition, it applies to primary prevention that could potentially prevent conditions affecting adverse psychological wellbeing. This systematic review and meta-analysis aimed to assess the prevalence, risk factors, and psychological impact of infertility among females.

MATERIALS AND METHODS

Study design and search strategy

A systematic review and meta-analysis of studies were conducted to assess the psychological impact of infertility among women. The study followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [15].

A systematic search was performed in MEDLINE (PubMed), CINAHL (EBSCOhost), and ScienceDirect. The search was done using text words such as "psycholog*," "mental," "quality of life," "anxiety, "depression," "stress," and "infertil*." The search terms were flexible and tailored to various electronic databases. All studies published from the inception of these databases until 2020 were retrieved to assess their eligibility for inclusion in this study. The search was restricted to full-text and English-language articles. To find additional potentially eligible studies, reference lists of included citations were cross-checked.

Eligibility criteria

The inclusion criteria involved studies that reported the psychological impact of infertility among women. Studies with cross-sectional, case-control, and cohort designs, published in the English language, conducted in the community, and performed at health institution levels were included. Case series/reports, conference papers, proceedings, articles available only in an abstract form, editorial reviews, letters of communication, commentaries, systematic reviews, and qualitative studies were excluded.

Study selection and screening

All records identified by our search strategy were exported to the EndNote software. Duplicate articles were removed. Two independent reviewers screened the titles and abstracts of the identified articles. The full text of eligible studies was obtained and read thoroughly to assess their suitability. A consensus discussion was held in the event of a conflict between the two reviewers, and a third reviewer was consulted. The search method is presented in the PRISMA

flowchart showing the studies that were included and excluded with reasons for exclusion (Figure 1).

Quality assessment and bias

A critical appraisal was undertaken to assess data quality using the Joanna Briggs Institute Meta-Analysis for cross-sectional, case-control, and cohort studies [16]. Two reviewers performed bias assessments independently. The risk of bias was considered low when more than 70% of the answers were "yes," moderate when 50%–69% of the answers were "yes," and high when up to 49% of the answers were "yes." Studies that showed a high and moderate risk of bias were excluded from the review.

Data extraction process

Two reviewers independently extracted data using the NVivo software (v.12). The process included the first author, publication year, study location, study design and setting, study population, sample size, psychological impact, infertility definition, and data in calculating effect estimates for psychological impact.

Result synthesis and statistical analysis

The outcomes were reported as the odds ratio (OR) and 95% confidence interval (CI). The analysis was performed using the Review Manager software (v.5.4; Nordic Cochrane Centre, Copenhagen, Denmark). A random-effects model was employed to pool data. The I^2 statistic was used to assess heterogeneity, with a guide as outlined: 0%–40% might not be important; 30%–60% may represent moderate heterogeneity; 50%–90% may represent substantial heterogeneity,

and 75%–100% may represent considerable heterogeneity [17]. A subgroup analysis was performed based on countries (developed and developing) and comorbidity (presence and absence of comorbidity) if an adequate number of studies were available. Funnel plots were used to assess publication bias if indicated.

RESULTS

Characteristics of included studies

A total of 2,842 articles were retrieved through an electronic search using different search terms, of which 2,795 articles were found to be eligible. Forty-seven duplicate records were removed. Of the 2,795 articles screened for eligibility, 2,708 were excluded by their title and abstract evaluation. The full text of 87 articles was searched. Subsequently, 50 articles were excluded: 34 did not present the main outcomes, six were performed in different populations, 5 were review articles, 4 had only abstracts, and one was published in a non-English language. A total of 37 studies underwent quality assessment, of which eight were excluded because of a moderate and high risk of bias (Figure 1).

Finally, 29 studies were included in the review: 20 were cross-sectional, six were case-control, two were cohort, and one was prevalence study. Different countries were involved. Five studies were conducted in Iran [18-22], four in Turkey [23-26], three in Italy [27-29], three in America [30-32], three in Sweden [33-35], two in India [36 37], two in the Netherlands [38 39], one in Finland [9], one in Africa [40], one in Saudi Arabia [41], one in Japan [42], one in China [43], one in Pakistan [44], and one in Greece [45]. The smallest sample size was 87 [45], and the largest was 98,320 [39]. Overall, this study included 123,520 women (Table 1).

Prevalence

Of the included studies, approximately 17 were conducted in a hospital-based setting, four [9 23 33 37] in a community-based setting, and two [18 44] in both hospital- and community-based settings. A slight difference in the prevalence of infertility was observed in the review. A lower prevalence (10.4%) of infertility [9] was observed in a community-based setting, and a higher prevalence (79.3%) [43 45] was noted in a hospital-based setting. The overall pooled prevalence of infertility was 45.85% (95% CI: 37.12, 54.57). Twenty-three articles were included for the estimation of pooled prevalence of infertility among females (Figure 2). Out of this, nine were used for the estimation of pooled prevalence of primary infertility.

The overall pooled prevalence of primary infertility was 51.5% (95% CI: 32.74, 70.26) (Figure 1). The lowest prevalence (18%) of primary infertility was reported in a hospital-based study [27], and the highest prevalence (91.1%) was observed in both community- and hospital-based studies conducted in Iran [18] (Figure 2).

Risk factors of infertility

In this study, risk factors such as age, body mass index (BMI), smoking, and family income were evaluated for their association with infertility. Five studies were included to assess age older than 35 years as a risk factor for infertility regarding the association between age and infertility among females [9 18 32 37]. The pooled meta-regression analysis showed no significant difference in the occurrence of infertility in females aged 35 years or older compared to those younger than 35 years, with the odds being 1.10 (95% CI: 0.83, 1.45). Similarly, there was no association between BMI and infertility in four studies [9 32-34], with odds of 1.11 (95% CI: 0.91, 1.36). However, smoking was found to be significantly related to infertility in three studies [9 33 34], with

the odds being 1.85 (95% CI: 1.08, 3.14) times higher compared to those who do not smoke (Figure 3). There was no difference observed (OR: 0.85; 95% CI: 0.59, 1.23) regarding the association between low income and infertility in five studies [9 20 24 37 44].

The psychological impact of infertility

In this study, psychological impact—including distress, depression, and anxiety—was evaluated. Four studies were included to assess the psychological distress caused by infertility [9 20 39 42]. The pooled meta-regression analysis showed a statistical significance between infertility and psychological distress among females, with the odds being 1.63 (95% CI: 1.24, 2.13) (Figure 4).

Eight studies were included to assess the association between depression and infertility among females [9 19 29 30 32-35]. Four studies showed significant [9 30 34 35] associations, and four showed no significant [19 29 32 33] associations. The pooled meta-regression analysis showed a statistical significance between depression and infertility among females, with the odds being 1.40 (95% CI: 1.11, 1.75) compared to those fertile. However, there was no association between anxiety and infertility in the six studies [9 19 29 32-34], with a pooled meta-regression analysis of OR of 1.68 (95% CI: 0.71, 3.98) (Figure 5).

DISCUSSION

Infertility is a worldwide public health agenda affecting an individual's personal, social, and economic life and the family as a whole. This study was conducted to determine the pooled prevalence and risk factors of infertility among females. In this meta-analysis, the pooled prevalence of infertility and primary infertility among females was 45.85% (95% CI: 37.12, 54.57) and 51.5% (95% CI: 32.74, 70.26), respectively. The prevalence of infertility among

females in this study is higher than in a review conducted in 2007 (between 3.5% and 16.7%) [46]. It is because most of the sample size for the research articles in this meta-analysis is from an infertility clinic. Regarding primary infertility, it is similar to a review in Africa at 49.9% (95% CI: 41.34, 58.48) [46].

Various risk factors were assessed in terms of their association with infertility among females. Age was not found to be associated with infertility; however, a study on a sample comprising 7,172 couples showed that the odds of being diagnosed with unexplained and tubal factor infertility are almost twice as high in women older than 35 years as those younger than 30 years [47]. There was no association noted between BMI and infertility among females. Vahrati et al. [48] found that a large proportion of females seeking medical help to become pregnant are obese, and the risk of infertility is three times higher in those obese than nonobese [49]. Smoking is a crucial risk factor for females, and it shows that females who smoke have a 1.8 times higher risk of developing infertility than those who do not. One study pointed toward a significant association with a 60% increase in the risk of infertility among females who smoke cigarettes [50]. A meta-analysis identified the pertinent literature available from 1966 through late 1997 and reported an OR of 1.60 for infertility among females who smoke compared to those who do not across all study designs [50].

Infertility among females has a vast impact on psychological distress. In the current study, females with infertility have a 1.6 times higher risk of being psychologically distressed than those fertile. This is similar to a study in Taiwan [51], which found that 40.2% of the females with infertility suffer from mental disorders. A review of studies conducted in many countries suggested that women endure the major burdens caused by infertility and experience intense anxiety from being blamed for their failure to give birth [52]. Infertility also contributes to the risk

of having depression, with females suffering from infertility having a 1.4 times higher chance of being depressed, where other studies showed 67.0% [53] and 35.3% [54] of women with infertility were depressed. Recent research has shown that prevalence can range from 11% [35] to 27% [51] and 73% [53]. Another study in Sweden [35] reported that major depression was the most common disorder among couples suffering from infertility, with a prevalence of 10.9% in females and 5.1% in males. It shows that infertility increases the risk of depression. Therefore, it should be considered a serious warning and given a particular focus.

The risk of anxiety in females with infertility is also high. A meta-analysis by Kiani et al. [56] showed a pooled prevalence of 36.17% (CI: 22.47, 49.87) among females having anxiety because of infertility. In another systematic review, Sawyer et al. [55] reported a 14.8% prevalence of anxiety in females with infertility and a prevalence of 14.0% among women in their pre- and postnatal periods. In most societies, having a child is closely related to a woman's identity. Being a mother is equated with being female [56], which results in high levels of stress and a sense of worthlessness in those childless [57]. In addition, a female who cannot conceive is at risk of social insecurity and becomes anxious because she foresees a future with no child to take care of them in old age or case of illness [58].

Strengths and limitations

This study showed the prevalence of infertility worldwide and the risk of psychological problems among such females, including studies from different countries. It also focused on the quantitative aspect of the problem to get a better view of the intervention.

However, this study is not without limitations. The differences in definitions, diagnostic cut points, study designs, and source populations make performing a meta-analysis on infertility

difficult. On the contrary, there are diverse instruments to determine psychological distress, depression, and anxiety that make comparing results difficult. Another limitation was the use of various instruments to assess psychological problems in the general population. None of the tools was developed specifically to investigate the incidence of factors concerning females.

CONCLUSIONS

This study identified that the risk of psychological distress among females with infertility is 60% higher than that among the general population. Furthermore, the risks of anxiety and depression are 60% and 40% times higher, respectively. These results highlight an important and increasing mental disorder among females that may be overlooked. Psychological distress should concern attending physicians and should be assessed to avoid any unwanted events from happening. Acknowledging the problem and taking positive, supportive measures to help females with infertility ensure more positive outcomes during the therapeutic process.

Acknowledgement: The authors would like to thank Madam Nurul Azurah Mohd Roni, a librarian from Hamdan Tahir Library, for her assistance with the database searches.

Author contributions: Conceptualization, NHNH, MNN and ISB; methodology, NHNH, MNN and ISB; validation MNN and NHNH; formal analysis, MNN and NANMA; investigation, NANMA; resources, MNN and NHNH; data curation, NHNH and NANMA; writing of original draft preparation and NANMA; writing of review and editing, NHNH, MNN, ISB and NANMA; visualization, NHNH, MNN and ISB; project administration, NHNH; All authors have read and agreed to the published version of the manuscript.

Funding: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors

Competing interests: None declared

Patient consent for publication: Not required.

Provenance and peer review: Not commissioned; externally peer reviewed.

Data availability statement: All data relevant to the study are included in the article.

Supplemental material: Protocol (PROSPERO registration number: CRD42021226414)

Patient and public involvement: It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

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TABLES

Table 1. Summary of research articles included in this systemic review and meta-analysis of infertility (n = 29).

No	Authors	Study Area	Study Design	Sample Size	Female infertility	Female fertile	Quality assessment %
1	Aggarwal et al., 2013 [36]	India	cross-sectional	500	267	233	87.5
2	Albayrak et al.,2007[23]	Kayseri, Turkey	cross-sectional	300	150	150	87.5
3	Biringer et al., 2015[33]	North Trondelag, Sweden	cross-sectional	12584	1696	10888	100
4	Klemetti et al., 2010[9]	Finlad	cross-sectional	2291	239	959	100
5	Bakhtiyar et al., 2019[18]	Lorestan, Iran	case control	720	180	540	70
6	Alhassan et al., 2014[40]	Ghana	cross-sectional	100	100		87.5
7	Alosaimi et al., 2015[41]	Riyadh, Saudi Arabia	cross-sectional	406	206		100
8	Matsubaya et al., 2001[42]	Tokai, Japan	cross-sectional	182	101	81	87.5

9	Acmaz et al., 2013 [24]	Kayseri, Turkey	cross-sectional	133	86	47	87.5
10	Bai et al., 2019[43]	Ningxia province, China	cross-sectional	740	380		100
11	Bazarganipour et al., 2013[19]	Kashan, Iran	cross-sectional	300	238	62	100
12	Begum et al., 2014[44]	Karachi, Pakistan	cross-sectional	120	60	60	87.5
13	Volgsten et al., 2008[35]	Sweden	prevelence	825	122	291	88.9
14	Bringhenti et al., 1997[27]	Italy	cross-sectional	179	122	57	87.5
15	Lansakara et al., 2011[37]	Colombo, Sri lanka	cross-sectional	354	177	177	87.5
16	Noorbala et al., 2009[20]	Tehran, Iran	cross-sectional	300	150	150	87.5
17	Salih Joelsson et al., 2017[34]	Sweden	cross-sectional	3583	468	2972	100
18	Aydin et al., 2015[25]	Istanbul, turkey	cross-sectional	88	88		87.5
19	Tarlatzis et al., 1993[45]	greek	cohort	87	69		81.8

20	Ramezan et al., 2004[21]	Tehran, Iran	cross-sectional	370	370		87.5
21	Aarts et al., 2011[38]	Netherlands	cross-sectional	472	472		87.5
22	Baldur et al., 2013[39]	Denmark	cohort	98320	44773	53547	100
23	Diamond et al., 2017[31]	United states	cross-sectional	1594	1594		87.5
24	Downey et al., 1992[30]	New York City	case control	201	118	83	80
25	Fassino et al., 2002[28]	italy	case control	172	172		90
26	Guz et al., 2003[26]	Turkey	case control	100	50	50	80
27	Omani et al., 2017[22]	Tehran, Iran	cross-sectional	312	149		100
28	Salomao et al., 2018[32]	brazil	case control	280	140	140	80
29	Sbaragli et al., 2008[29]	Siena, Italy	case control	302	82	71	100

FIGURES

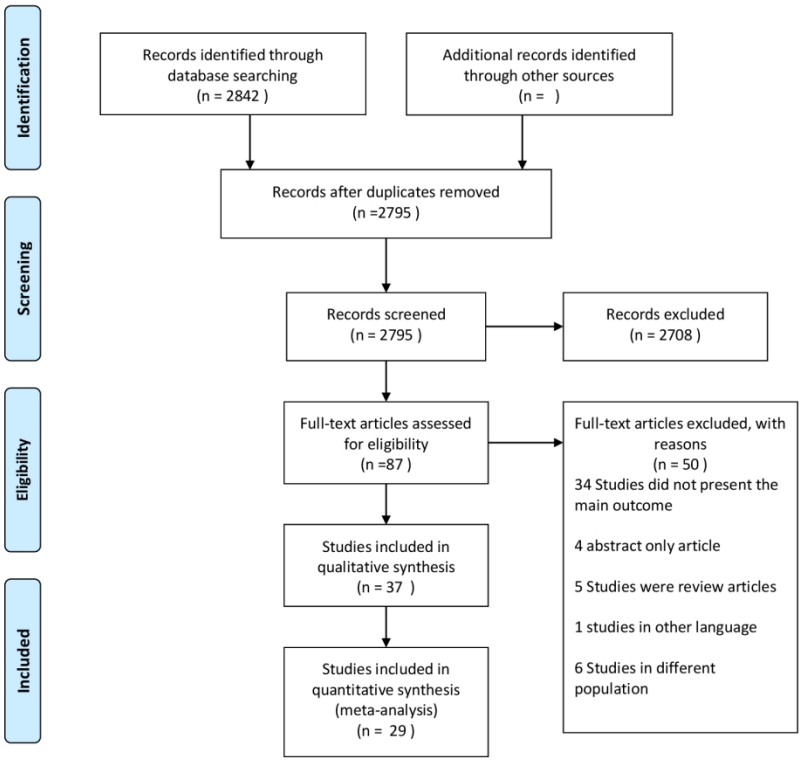
Figure 1: Flow diagram showing the included studies for systemic review and meta-analysis on the prevalence, risk factors, and psychological impact of infertility among women

Figure 2: Forest plot depicting the prevalence of infertility and primary infertility

Figure 3: Forest plot showing the risk factors associated with infertility

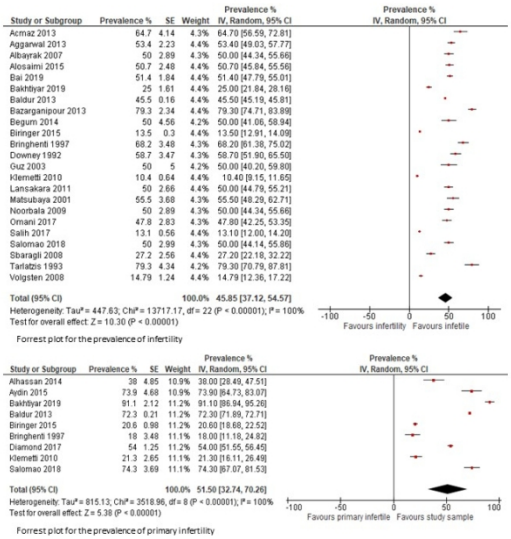
Figure 4: Forest plot depicting the association between psychological distress and infertility among females

Figure 5: Forest plot showing the association of depression, anxiety, and infertility



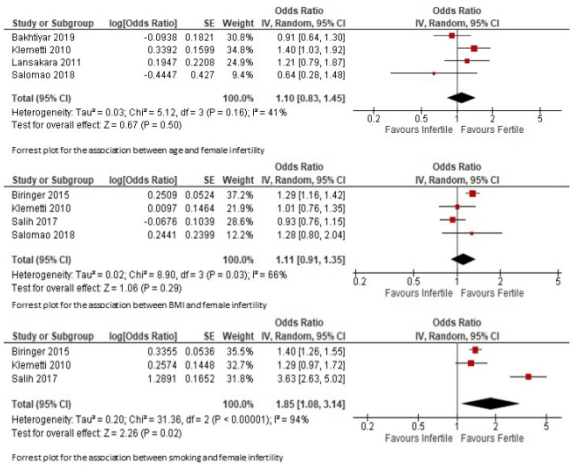
Flow diagram showing the included studies for systemic review and meta-analysis on the prevalence, risk factors, and psychological impact of infertility among women

215x279mm (200 x 200 DPI)



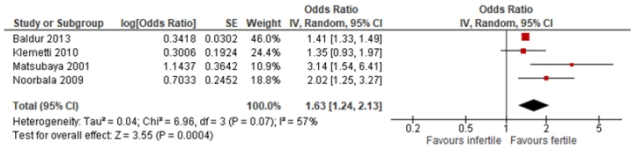
Forest plot depicting the prevalence of infertility and primary infertility

338x190mm (96 x 96 DPI)



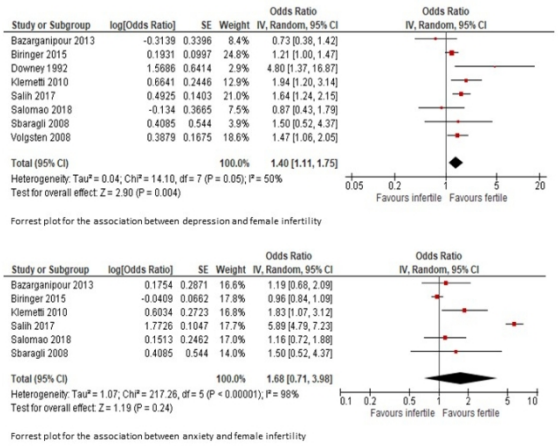
Forest plot showing the risk factors associated with infertility

338x190mm (96 x 96 DPI)



Forest plot depicting the association between psychological distress and infertility among females

338x190mm (96 x 96 DPI)



Forest plot showing the association of depression, anxiety, and infertility

338x190mm (96 x 96 DPI)

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PROSPERO
International prospective register of systematic reviews

Citation

Nik Muhammad Arif Nik Ahmad, Nik Hazlina Nik Hussain, Norhayati Mohd Noor, Shaiful Bahari Ismail. Psychological impact of infertility among women: a systematic review and meta-analysis. PROSPERO 2021 CRD42021226414 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021226414

Review question

What are the psychological impact of infertility among woman?

Searches

A systematic search will be performed in the MEDLINE (PubMed), CINAHL (EBSCOhost) and ScienceDirect. The search will be done using the text words: “psycholog*”, “mental”, “quality of life”, “anxiety”, “depression”, “stress” and “infertil*” will be used.

The search terms will be flexible and tailored to various electronic databases. All studies published from the inception of databases till 2020 will be retrieved in order to assess their eligibility for inclusion in this study. The search will be restricted to full-text and English language articles. To find additional potentially eligible studies, reference lists of included citations will be cross-checked.

Types of study to be included

Cross-sectional, case-control and cohort designs will be included

Condition or domain being studied

The primary outcome of this study is the psychological impact among women with infertility. Psychological impact refers to stress, depression, sleep disorders, eating disorders, and addictions (Szkodziak, 2020). The relationship between mental disorders and human physiology was first described in detail and highlighted by Hans Hugo Selye in 1955, who stated that the stressor acts on the target (the body or some part of it) directly and indirectly through the pituitary and the adrenal glands.

Participants/population

Women with primary and secondary infertility

Intervention(s), exposure(s)

Infertility is defined as a disease of reproductive system in which pregnancy does not occur after one year of continues intercourse (Masearenhas M et al.; 1990). Worldwide, infertility affects 10-15% of couples where the woman is trying to conceive (Evers, 2002; Bonde and Olsen, 2008)

Infertility may work as a painful emotional experience (Dural et al.; 2016, Cousineau, 2007). Psychosocial issues affect the female gender more than her spouse (Inhorn et al.; 2015). It can cause stress, anxiety, depression, diminished self-esteem, declined sexual satisfaction, and reduced quality of life (Kamel, 2010; Van Balen et al.; 2009).

Psychological impact in primary and secondary infertile women

Comparator(s)/control

Not applicable

Main outcome(s)

Determining the psychological impact among infertile woman at a worldwide level gives a better figure than

discrete primary studies. The identification of psychological impact among infertile woman allows a clearer understanding of the issue and serves as a basis for an appropriate preventive strategy to be established. This applies to primary prevention that could potentially prevent conditions affecting adverse psychological wellbeing.

Measures of effect

The outcomes will be reported in odds ratio and 95% confidence interval. The analysis will be performed with Review Manager software version 5.4 (Nordic Cochrane Centre). We will use a random-effects model to pool data. The I^2 statistic will be used to assess heterogeneity and use the guide as outlined: 0% to 40% might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; and 75% to 100% would be considerable heterogeneity (Higgins et al., 2020). Subgroup analysis will be performed based on countries (developed and developing countries) and comorbidity (presence and absence of comorbidity). Funnel plots will be used to assess the publication bias.

Additional outcome(s)

None

Measures of effect

None

Data extraction (selection and coding)

Two reviewers will independently extract data into NVIVO software version 12. This will include first author, year of publication, study location, study design, setting, study population, sample size, psychological impact, infertility definition and data for calculation of effect estimates for psychological impact.

Risk of bias (quality) assessment

A critical appraisal will be done to assess the data quality, by using the Joanna Briggs Institute Meta-Analysis for cross-sectional, case-control and cohort studies (Aromataris and Munn, 2020). Two authors will perform bias assessments independently

Strategy for data synthesis

The outcomes will be reported in odds ratio and 95% confidence interval. The analysis will be performed with Review Manager software version 5.4 (Nordic Cochrane Centre). We will use a random-effects model to pool data. The I^2 statistic will be used to assess heterogeneity and use the guide as outlined: 0% to 40% might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; and 75% to 100% would be considerable heterogeneity (Higgins et al., 2020). Subgroup analysis will be performed based on countries (developed and developing countries) and comorbidity (presence and absence of comorbidity). Funnel plots will be used to assess the publication bias.

Analysis of subgroups or subsets

Subgroups will be performed based on the type of psychological impact

Contact details for further information

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Organisational affiliation of the review

Universiti Sains Malaysia

Review team members and their organisational affiliations

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Professor Nik Hazlina Nik Hussain. Universiti Sains Malaysia
Professor Norhayati Mohd Noor. Universiti Sains Malaysia
Professor Shaiful Bahari Ismail. Universiti Sains Malaysia

Type and method of review

Meta-analysis, Systematic review

Anticipated or actual start date

15 December 2020

Anticipated completion date
15 June 2021

Funding sources/sponsors
Nil

Grant number(s)

State the funder, grant or award number and the date of award

Nil

Conflicts of interest

Language
English

Country
Malaysia

Stage of review
Review Ongoing

Subject index terms status
Subject indexing assigned by CRD

Subject index terms
MeSH headings have not been applied to this record

Date of registration in PROSPERO
15 January 2021

Date of first submission
16 December 2020

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.
The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

15 January 2021
15 January 2021

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	5
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	7
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	7
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	6
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	7
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	6
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	7
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	7
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	7
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	7
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	-
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	6
Certainty	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	-

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
assessment			
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Fig 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	8
Study characteristics	17	Cite each included study and present its characteristics.	Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	8
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Fig 2-5
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Fig 1
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	8-10
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	8-10
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	-
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	-
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	-
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	8-10
	23b	Discuss any limitations of the evidence included in the review.	12
	23c	Discuss any limitations of the review processes used.	12
	23d	Discuss implications of the results for practice, policy, and future research.	12
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	2
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	2
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	-
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	13
Competing interests	26	Declare any competing interests of review authors.	13
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	15

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi:

PRISMA 2020 Checklist

10.1136/bmj.n71

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BMJ Open

Worldwide Prevalence, Risk Factors, and Psychological Impact of Infertility among Women: A Systematic Review and Meta-Analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-057132.R1
Article Type:	Original research
Date Submitted by the Author:	25-Jan-2022
Complete List of Authors:	Nik Hazlina, Nik Hussain; Universiti Sains Malaysia - Kampus Kesihatan, Women's Health Development Unit Norhayati, Mohd Noor; Universiti Sains Malaysia - Kampus Kesihatan, Department of Family Medicine Shaiful Bahari, Ismail ; Universiti Sains Malaysia - Kampus Kesihatan, Department of Family Medicine Nik Ahmad, Nik Muhammad Arif; Universiti Sains Malaysia - Kampus Kesihatan, Women's Health Development Unit
Primary Subject Heading:	Reproductive medicine
Secondary Subject Heading:	General practice / Family practice, Epidemiology, Obstetrics and gynaecology, Public health
Keywords:	Public health < INFECTIOUS DISEASES, Maternal medicine < OBSTETRICS, PRIMARY CARE, Reproductive medicine < GYNAECOLOGY, MENTAL HEALTH

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Worldwide Prevalence, Risk Factors, and Psychological Impact of Infertility among Women: A Systematic Review and Meta-Analysis

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ABSTRACT

Objectives: To assess the prevalence, risk factors, and psychological impact of infertility among females. This review summarizes the available evidence, effect estimates, and strength of statistical associations between infertility and its risk factors.

Study design: Systematic review and meta-analysis

Data sources: MEDLINE, CINAHL, and ScienceDirect were searched through 23 January 2022.

Eligibility Criteria: The inclusion criteria involved studies that reported the psychological impact of infertility among women. We included cross-sectional, case-control, and cohort designs, published in the English language, conducted in the community, and performed at health institution levels on prevalence, risk factors, and psychological impact of infertility in women.

Data extraction and synthesis Two reviewers independently extracted and assess the quality of data using the Joanna Briggs Institute Meta-Analysis. The outcomes were assessed with random-effects model and reported as the odds ratio (OR) with 95% confidence interval (CI) using the Review Manager software. **Results:** Thirty-two studies with low risk of bias involving 124,556 women were included. The findings indicated the overall pooled prevalence to be 46.25% and 51.5% for infertility and primary infertility, respectively. Smoking was significantly related to infertility, with the OR of 1.85 (95% CI: 1.08, 3.14) times higher than females who do not smoke. There was a statistical significance between infertility and psychological distress among females, with the OR of 1.63 (95% CI: 1.24, 2.13). A statistical significance was noted between depression and infertility among females, with the OR of 1.40 (95% CI: 1.11, 1.75) compared to those fertile.

Conclusions: The study results highlight an essential and increasing mental disorder among females associated with infertility and may be overlooked. Acknowledging the problem and providing positive, supportive measures to females with infertility ensure more positive outcomes during the therapeutic process. This review is limited by the differences in definitions, diagnostic cut points, study designs, and source populations.

PROSPERO registration number: CRD42021226414

Keywords: infertility, prevalence, risk factors, psychological impact

Words count: 2479

ARTICLE SUMMARY

Strengths and limitations of this study

- Meta-analysis of studies according to preferred reporting items for systematic reviews and meta-analyses guidelines
- Joanna Briggs Institute Meta-Analysis for assessing the quality of included studies
- Only studies with a low risk of bias were included in the analyses
- Heterogeneity and subgroup analyses were performed
- The search was restricted to English-language articles only

INTRODUCTION

Infertility is defined by the World Health Organization (WHO) as the inability to conceive after one year (or longer) of unprotected intercourse [1]. It is classified as primary or secondary. Primary infertility is denoted for those women who have not conceived previously [2]. In secondary infertility, there is at least one conception, but it fails to repeat [2]. In 2002, the WHO estimated that infertility affects approximately 80 million people in all parts of the world [3]. It affects 10%–15% of couples in their lifetime [4 5]. The prevalence of infertility is concerned, it is high (up to 21.9%): primary infertility at 3.5% and secondary infertility at 18.4% [6]. It is generally accepted that infertility rates are not estimated correctly. The reasons could hinder the measurement of the prevalence, imperfect measurement methods, and unknown kinds of infertility resulting from cultural biases [7].

Infertility is a multidimensional stressor requiring several kinds of emotional adjustments [4]. It is associated with dysfunction in sexual relationships, anxiety, depression, difficulties in marital life, and identity problems [8]. The impact of infertility may be long-lasting, even beyond the initial period of childlessness has passed [9 10]. In the general population, major depression is two to three times as common among women as among men [11]. In the United States, the 12-month prevalence of any mood disorder is 14.1% in females and 8.5% in males, whereas any anxiety disorder is 22.6% in females and 11.8% in males [12]. Thus, depression is one of the most common negative emotions associated with infertility [13 14], which the local social and cultural context may influence.

Determining the psychological impact of infertility among women worldwide provides a better assessment than discrete primary studies. Identifying this impact helps gain a clear understanding of the issue and serves as a basis for an appropriate preventive strategy. In addition, it applies to primary prevention that could potentially prevent conditions affecting adverse psychological

wellbeing. We aimed to perform a systematic review and meta-analysis on infertility among females with regards to its pooled prevalence, risk factors, and psychological impact in observational studies conducted worldwide. This review will summarize the available evidence, effect estimates, and strength of statistical associations between infertility and its risk factors.

MATERIALS AND METHODS

Study design and search strategy

A systematic review and meta-analysis of studies were conducted to assess the psychological impact of infertility among women. The study followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [15].

A systematic search was performed in MEDLINE (PubMed), CINAHL (EBSCOhost), and ScienceDirect. The search was done using text words such as "infertility," "prevalence," "risk factor," "psychology," "mental," "quality of life," "anxiety, "depression," and "stress." The search terms were flexible and tailored to various electronic databases (Supplementary file). All studies published from the inception of these databases until 23 January2022 were retrieved to assess their eligibility for inclusion in this study. The search was restricted to full-text and English-language articles. To find additional potentially eligible studies, reference lists of included citations were cross-checked.

Eligibility criteria

The inclusion criteria involved studies that reported the psychological impact of infertility among women. Studies with cross-sectional, case-control and cohort designs, published in the English language, conducted in the community, and performed at health institution levels were included.

Case series/reports, conference papers, proceedings, articles available only in an abstract form, editorial reviews, letters of communication, commentaries, systematic reviews, and qualitative studies were excluded.

Study selection and screening

All records identified by our search strategy were exported to the EndNote software. Duplicate articles were removed. Two independent reviewers screened the titles and abstracts of the identified articles. The full text of eligible studies was obtained and read thoroughly to assess their suitability. A consensus discussion was held in the event of a conflict between the two reviewers, and a third reviewer was consulted. The search method is presented in the PRISMA flowchart showing the studies that were included and excluded with reasons for exclusion (Figure 1).

Quality assessment and bias

A critical appraisal was undertaken to assess data quality using the Joanna Briggs Institute Meta-Analysis for cross-sectional, case-control, and cohort studies [16]. Two reviewers performed bias assessments independently. The risk of bias was considered low when more than 70% of the answers were "yes," moderate when 50%–69% of the answers were "yes," and high when up to 49% of the answers were "yes." Studies that showed a high and moderate risk of bias were excluded from the review.

Data extraction process

Two reviewers independently extracted data using the NVivo software (v.12). The process included the first author, publication year, study location, study design and setting, study population, sample size, psychological impact, infertility definition, and data in calculating effect estimates for psychological impact.

Result synthesis and statistical analysis

The outcomes were reported as the odds ratio (OR) and 95% confidence interval (CI). The analysis was performed using the Review Manager software (v.5.4; Nordic Cochrane Centre, Copenhagen, Denmark). A random-effects model was employed to pool data. The I^2 statistic was used to assess heterogeneity, with a guide as outlined: 0%–40% might not be important; 30%–60% may represent moderate heterogeneity; 50%–90% may represent substantial heterogeneity, and 75%–100% may represent considerable heterogeneity [17]. A subgroup analysis was performed based on countries (developed and developing) and comorbidity (presence and absence of comorbidity) if an adequate number of studies were available. Funnel plots were used to assess publication bias if indicated.

RESULTS

Characteristics of included studies

A total of 3,169 articles were retrieved through an electronic search using different search terms. Forty-eight duplicate records were removed. Of the 3,168 articles screened for eligibility, 3,065 were excluded by their title and abstract evaluation. The full text of 103 articles was searched. Subsequently, 62 articles were excluded: 46 did not present the main outcomes, six were performed in different populations, 5 were review articles, 4 had only abstracts, and one was

published in a non-English language (Figure 1). A total of 41 studies underwent quality assessment, of which nine had moderate and high risk of bias.

Finally, 32 studies with low risk of bias were explored in the review: 22 were cross-sectional, eight were case-control, and two were cohort studies. Different countries were involved. Five studies were conducted in Iran [18-22], four in Turkey [23-26], three in Italy [27-29], three in America [30-32], three in Sweden [33-35], two in India [36 37], two in the Netherlands [38 39], one in Finland [9], two in Africa [40 41], one in Saudi Arabia [42], one in Japan [43], two in China [44 45], one in Pakistan [46], and two in Greece [47 48]. The smallest sample size was 87 [47], and the largest was 98,320 [39]. Overall, this study included 124,556 women (Table 1).

Prevalence

Of the included studies, 20 were conducted in a hospital-based setting, four [9 23 33 37] in a community-based setting, and two [18 46] in both hospital- and community-based settings. A slight difference in the prevalence of infertility was observed in the review. A lower prevalence (10.4%) of infertility [9] was observed in a community-based setting, and a higher prevalence (79.3%) [44 47] was noted in a hospital-based setting. The overall pooled prevalence of infertility was 46.25% (95% CI: 37.73, 54.77). Twenty-four articles were included for the estimation of pooled prevalence of infertility among females (Figure 2). The funnel plot was asymmetry. Out of this, nine were used for the estimation of pooled prevalence of primary infertility.

The overall pooled prevalence of primary infertility was 51.5% (95% CI: 32.74, 70.26) (Figure 1). The lowest prevalence (18%) of primary infertility was reported in a hospital-based study [27], and the highest prevalence (91.1%) was observed in both community- and hospital-based studies conducted in Iran [18] (Figure 2).

Risk factors of infertility

In this study, risk factors such as age, body mass index (BMI), smoking, and family income were evaluated for their association with infertility. Five studies were included to assess age older than 35 years as a risk factor for infertility regarding the association between age and infertility among females [9 18 32 37]. The pooled meta-regression analysis showed no significant difference in the occurrence of infertility in females aged 35 years or older compared to those younger than 35 years, with the odds being 1.10 (95% CI: 0.83, 1.45). Similarly, there was no association between BMI and infertility in four studies [9 32-34], with odds of 1.11 (95% CI: 0.91, 1.36). However, smoking was found to be significantly related to infertility in three studies [9 33 34], with the odds being 1.85 (95% CI: 1.08, 3.14) times higher compared to those who do not smoke (Figure 3). There was no difference observed (OR: 0.85; 95% CI: 0.59, 1.23) regarding the association between low income and infertility in five studies [9 20 24 37 46].

The psychological impact of infertility

In this study, psychological impact—including distress, depression, and anxiety—was evaluated. Four studies were included to assess the distress caused by infertility [9 20 39 43]. The pooled meta-regression analysis showed a statistical significance between infertility and psychological distress among females, with the odds being 1.63 (95% CI: 1.24, 2.13) (Figure 4).

Eight studies were included to assess the association between depression and infertility among females [9 19 29 30 32-35]. Four studies showed significant [9 30 34 35] associations, and four showed no significant [19 29 32 33] associations. The pooled meta-regression analysis showed a statistical significance between depression and infertility among females, with the odds being

1.40 (95% CI: 1.11, 1.75) compared to those fertile. However, there was no association between anxiety and infertility in the six studies [9 19 29 32-34], with a pooled meta-regression analysis of OR of 1.68 (95% CI: 0.71, 3.98) (Figure 4).

DISCUSSION

Infertility is a worldwide public health agenda affecting an individual's personal, social, and economic life and the family as a whole. This study was conducted to determine the pooled prevalence and risk factors of infertility among females. In this meta-analysis, the pooled prevalence of infertility and primary infertility among females was 45.85% (95% CI: 37.12, 54.57) and 51.5% (95% CI: 32.74, 70.26), respectively. The prevalence of infertility among females in this study is higher than in a review conducted in 2007 (between 3.5% and 16.7%) [49]. It is because most of the sample size for the research articles in this meta-analysis is from an infertility clinic. Regarding primary infertility, it is similar to a review in Africa at 49.9% (95% CI: 41.34, 58.48) [50].

Various risk factors were assessed in terms of their association with infertility among females. Age was not found to be associated with infertility; however, a study on a sample comprising 7,172 couples showed that the odds of being diagnosed with unexplained and tubal factor infertility are almost twice as high in women older than 35 years as those younger than 30 years [51]. There was no association noted between BMI and infertility among females. Vahrati et al. [52] found that a large proportion of females seeking medical help to become pregnant are obese, and the risk of infertility is three times higher in those obese than nonobese [53]. Smoking is a crucial risk factor for females, and it shows that females who smoke have a 1.8 times higher risk of developing infertility than those who do not. One study pointed toward a significant

association with a 60% increase in the risk of infertility among females who smoke cigarettes [54]. A meta-analysis identified the pertinent literature available from 1966 through late 1997 and reported an OR of 1.60 for infertility among females who smoke compared to those who do not across all study designs [54].

Infertility among females has a vast impact on psychological distress. In the current study, females with infertility have a 1.6 times higher risk of being psychologically distressed than those fertile. This is similar to a study in Taiwan [55], which found that 40.2% of the females with infertility suffer from mental disorders. A review of studies conducted in many countries suggested that women endure the major burdens caused by infertility and experience intense anxiety from being blamed for their failure to give birth [56]. Infertility also contributes to the risk of having depression, with females suffering from infertility having a 1.4 times higher chance of being depressed, whereas other studies showed 67.0% [57] and 35.3% [58] of women with infertility were depressed. Recent research has shown that prevalence can range from 11% [35] to 27% [55] and 73% [57]. Another study in Sweden [35] reported that major depression was the most common disorder among couples suffering from infertility, with a prevalence of 10.9% in females and 5.1% in males. It shows that infertility increases the risk of depression. Therefore, it should be considered a serious warning and given a particular focus.

The risk of anxiety in females with infertility is also high. A meta-analysis by Kiani et al. [59] showed a pooled prevalence of 36.17% (CI: 22.47, 49.87) among females having anxiety because of infertility. In another systematic review, Sawyer et al. [60] reported a 14.8% prevalence of anxiety in females with infertility and a prevalence of 14.0% among women in their pre- and postnatal periods. In most societies, having a child is closely related to a woman's identity. Being a mother is equated with being female [59], which results in high levels of stress and a sense of

worthlessness in those childless [61]. In addition, a female who cannot conceive is at risk of social insecurity and becomes anxious because she foresees a future with no child to take care of them in old age or case of illness [62].

Strengths and limitations

This study showed the prevalence of infertility worldwide and the risk of psychological problems among such females, including studies from different countries. It also focused on the quantitative aspect of the problem to get a better view of the intervention.

However, this study is not without limitations. The differences in definitions, diagnostic cut points, study designs, and source populations make performing a meta-analysis on infertility difficult. On the contrary, there are diverse instruments to determine psychological distress, depression, and anxiety that make comparing results difficult. Another limitation was the use of various instruments to assess psychological problems in the general population. None of the tools was developed specifically to investigate the incidence of factors concerning females.

CONCLUSIONS

This study identified that the risk of psychological distress among females with infertility is 60% higher than that among the general population. Furthermore, the risks of anxiety and depression are 60% and 40% times higher, respectively. These results highlight an important and increasing mental disorder among females that may be overlooked. Psychological distress should concern attending physicians and should be assessed to avoid any unwanted events from happening. Acknowledging the problem and taking positive, supportive measures to help females with infertility ensure more positive outcomes during the therapeutic process.

Acknowledgment: The authors would like to thank Madam Nurul Azurah Mohd Roni, a librarian from Hamdan Tahir Library, for her assistance with the database searches.

Author contributions: Conceptualization, NHNH, MNN and ISB; methodology, NHNH, MNN and ISB; validation MNN and NHNH; formal analysis, MNN and NANMA; investigation, NANMA; resources, MNN and NHNH; data curation, NHNH and NANMA; writing of original draft preparation and NANMA; writing of review and editing, NHNH, MNN, ISB and NANMA; visualization, NHNH, MNN and ISB; project administration, NHNH; All authors have read and agreed to the published version of the manuscript.

Funding: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors

Competing interests: None declared

Patient consent for publication: Not required.

Provenance and peer review: Not commissioned; externally peer reviewed.

Data availability statement: All data relevant to the study are included in the article.

Supplementary file: Search strategy

Patient and public involvement: It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

Ethical Approval Statement: Not applicable

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TABLES

Table 1. Summary of research articles included in this systemic review and meta-analysis of infertility (n = 32).

No	Authors	Study Area	Study Design	Sample Size	Female infertility	Quality assessment (%)
1	Aggarwal et al., 2013 [36]	India	cross-sectional	500	267	87.5
2	Albayrak et al.,2007[23]	Kayseri, Turkey	cross-sectional	300	150	87.5
3	Biringer et al., 2015[33]	North Trondelag, Sweden	cross-sectional	12584	1696	100
4	Klemetti et al., 2010[9]	Finlad	cross-sectional	2291	239	100
5	Bakhtiyar et al., 2019[18]	Lorestan, Iran	case control	720	180	70
6	Alhassan et al., 2014[40]	Ghana	cross-sectional	100	100	87.5
7	Alosaimi et al., 2015[42]	Riyadh, Saudi Arabia	cross-sectional	406	206	100
8	Matsubaya et al., 2001[43]	Tokai, Japan	cross-sectional	182	101	87.5
9	Acmaz et al., 2013 [24]	Kayseri, Turkey	cross-sectional	133	86	87.5
10	Bai et al., 2019[44]	Ningxia province, China	cross-sectional	740	380	100
11	Bazarganipour et al., 2013[19]	Kashan, Iran	cross-sectional	300	238	100
12	Begum et al., 2014[46]	Karachi, Pakistan	cross-sectional	120	60	87.5
13	Volgsten et al., 2008[35]	Sweden	cross-sectional	825	122	88.9
14	Bringhenti et al., 1997[27]	Italy	cross-sectional	179	122	87.5
15	Lansakara et al., 2011[37]	Colombo, Sri Lanka	cross-sectional	354	177	87.5
16	Noorbala et al., 2009[20]	Tehran, Iran	cross-sectional	300	150	87.5
17	Salih Joelsson et al., 2017[34]	Sweden	cross-sectional	3583	468	100
18	Aydin et al., 2015[25]	Istanbul, Turkey	cross-sectional	88	88	87.5

19	Tarlatzis et al., 1993[47]	Greece	cohort	87	69	81.8
20	Ramezan et al., 2004[21]	Tehran, Iran	cross-sectional	370	370	87.5
21	Aarts et al., 2011[38]	Netherlands	cross-sectional	472	472	87.5
22	Baldur et al., 2013[39]	Denmark	cohort	98320	44773	100
23	Diamond et al., 2017[31]	United states	cross-sectional	1594	1594	87.5
24	Downey et al., 1992[30]	New York City	case control	201	118	80
25	Fassino et al., 2002[28]	Italy	case control	172	172	90
26	Guz et al., 2003[26]	Turkey	case control	100	50	80
27	Omani et al., 2017[22]	Tehran, Iran	cross-sectional	312	149	100
28	Salomao et al., 2018[32]	Brazil	case control	280	140	80
29	Sbaragli et al., 2008[29]	Siena, Italy	case control	302	82	100
30	Akalewold et al., 2022	Ethiopia	cross-sectional	409	66	100
31	Kleanthi et al., 2021	Greece	case control	177		90
32	Peng et al., 2021	China	case control	450		100

Note: The quality assessment was performed based on the Joanna Briggs Institute Meta-Analysis for cross-sectional, case-control, and cohort studies

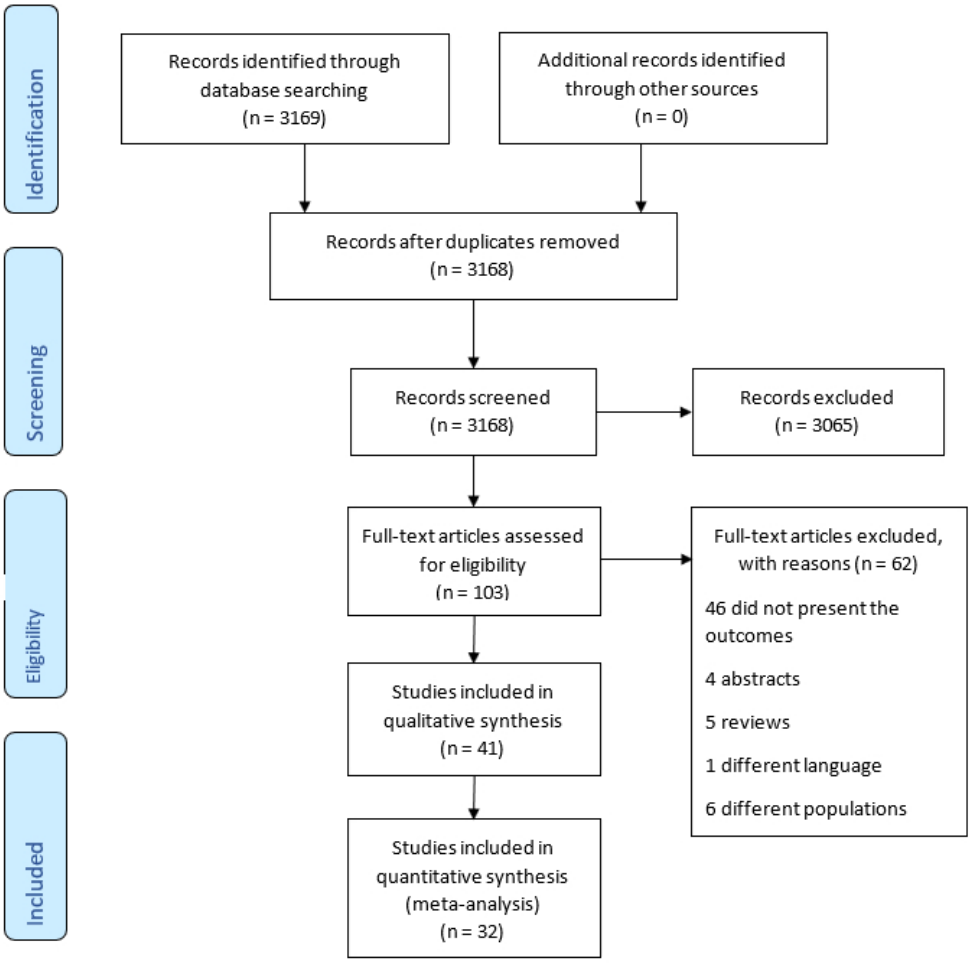
FIGURES

Figure 1: Flow diagram showing the included studies for systemic review and meta-analysis on the prevalence, risk factors, and psychological impact of infertility among women

Figure 2: Forest plot depicting the prevalence of infertility

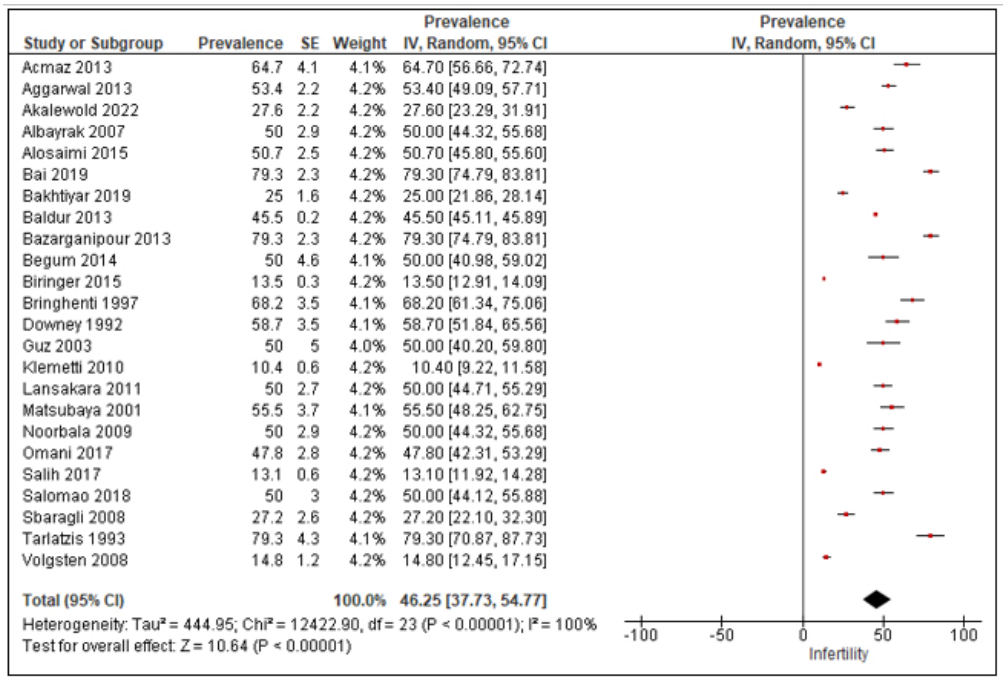
Figure 3: Forest plot depicting the risk factors associated with infertility

Figure 4: Forest plot depicting the psychological impact of infertility

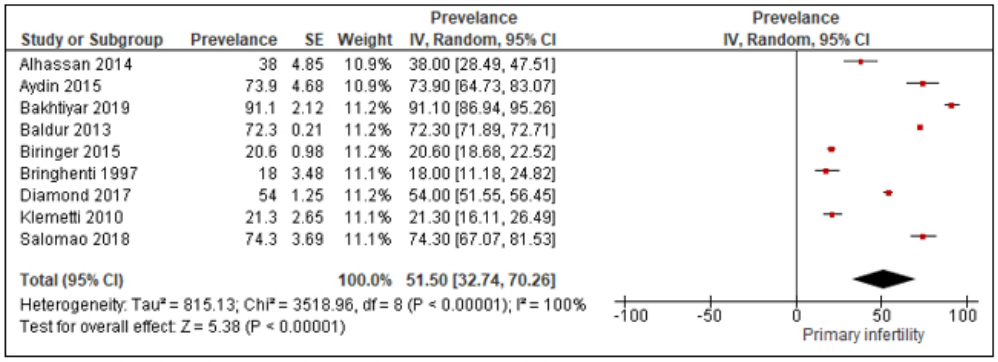


Flow diagram showing the included studies for systemic review and meta-analysis on the prevalence, risk factors, and psychological impact of infertility among women

463x454mm (38 x 38 DPI)



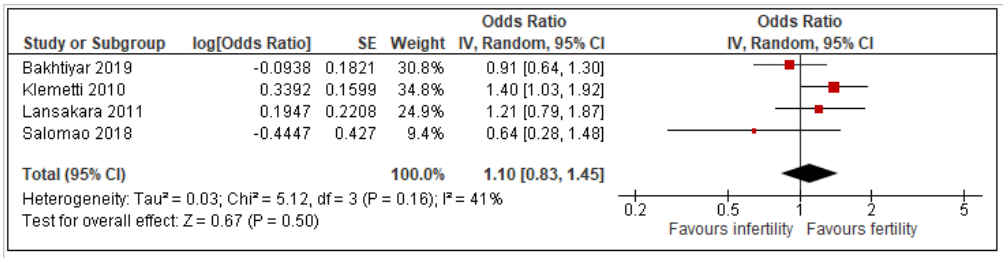
2A. Forest plot for the prevalence of infertility



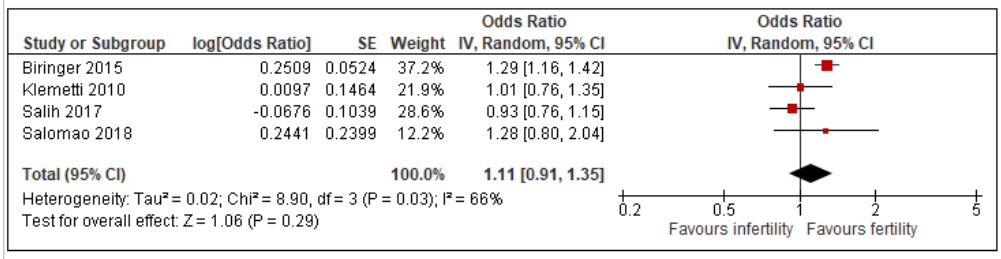
2B. Forest plot for the prevalence of primary infertility

Forest plot depicting the prevalence of infertility

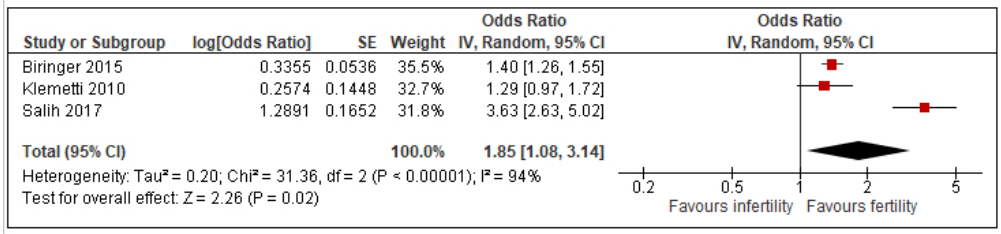
435x480mm (38 x 38 DPI)



3A. Forest plot for the association between age and female infertility



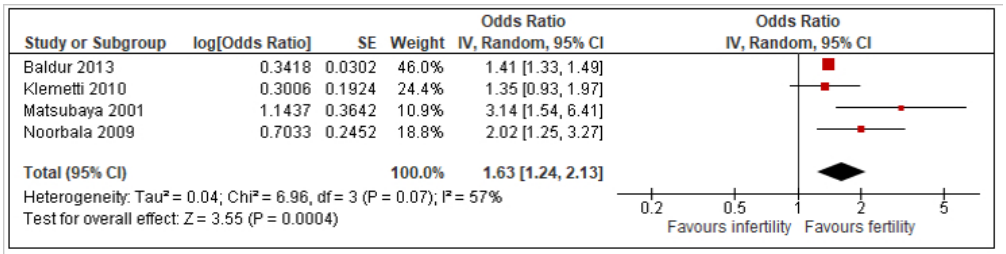
3B. Forest plot for the association between body mass index and female infertility



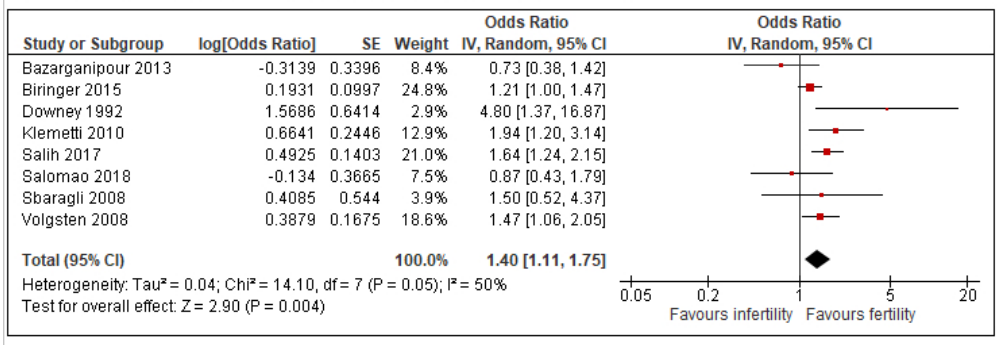
3C. Forest plot for the association between smoking and female infertility

Forest plot depicting the risk factors associated with infertility

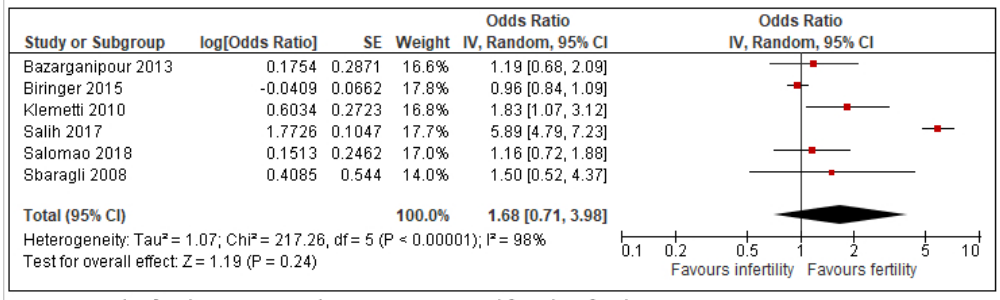
489x411mm (38 x 38 DPI)



4A. Forest plot for the association between distress and female infertility



4B. Forest plot for the association between depression and female infertility



4C. Forest plot for the association between anxiety and female infertility

Forest plot depicting the psychological impact of infertility

495x481mm (38 x 38 DPI)

Search strategy

PubMed

1. infertil*[Title/Abstract]
2. prevalence[Title/Abstract]
3. (#1) AND (#2)
4. risk factor
5. (#1) AND (#4)
6. psycholog*
7. mental
8. quality of life
9. anxiety
10. depression
11. stress
12. (((((#6) OR (#7)) OR (#8)) OR (#9)) OR (#10)) OR (#11)
13. (#1) AND (#12)

ScienceDirect

infertility

infertility AND prevalence

infertility AND risk factor

infertility AND (psycholog/ OR mental OR quality of life OR anxiety OR depression OR stress)

PRISMA 2020 for Abstracts Checklist

Section and Topic	Item #	Checklist item	Reported (Yes/No)
TITLE			
Title	1	Identify the report as a systematic review.	Yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	Yes
Synthesis of results	6	Specify the methods used to present and synthesise results.	Yes
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	Yes
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
OTHER			
Funding	11	Specify the primary source of funding for the review.	N/R
Registration	12	Provide the register name and registration number.	Yes

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

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

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	5
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	7
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	7
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	6
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	7
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	6
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	7
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	7
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	7
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	7
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	-
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	6
Certainty	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	-

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
assessment			
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Fig 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	8
Study characteristics	17	Cite each included study and present its characteristics.	Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	8
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Fig 2-5
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Fig 1
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	8-10
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	8-10
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	-
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	-
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	-
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	8-10
	23b	Discuss any limitations of the evidence included in the review.	12
	23c	Discuss any limitations of the review processes used.	12
	23d	Discuss implications of the results for practice, policy, and future research.	12
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	2
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	2
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	-
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	13
Competing interests	26	Declare any competing interests of review authors.	13
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	15

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

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BMJ Open

Worldwide Prevalence, Risk Factors, and Psychological Impact of Infertility among Women: A Systematic Review and Meta-Analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-057132.R2
Article Type:	Original research
Date Submitted by the Author:	07-Mar-2022
Complete List of Authors:	Nik Hazlina, Nik Hussain; Universiti Sains Malaysia - Kampus Kesihatan, Women's Health Development Unit Norhayati, Mohd Noor; Universiti Sains Malaysia - Kampus Kesihatan, Department of Family Medicine Shaiful Bahari, Ismail ; Universiti Sains Malaysia - Kampus Kesihatan, Department of Family Medicine Nik Ahmad, Nik Muhammad Arif; Universiti Sains Malaysia - Kampus Kesihatan, Women's Health Development Unit
Primary Subject Heading:	Reproductive medicine
Secondary Subject Heading:	General practice / Family practice, Epidemiology, Obstetrics and gynaecology, Public health
Keywords:	Public health < INFECTIOUS DISEASES, Maternal medicine < OBSTETRICS, PRIMARY CARE, Reproductive medicine < GYNAECOLOGY, MENTAL HEALTH

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Worldwide Prevalence, Risk Factors, and Psychological Impact of Infertility among Women: A Systematic Review and Meta-Analysis

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ABSTRACT

Objectives: To assess the prevalence, risk factors, and psychological impact of infertility among females. This review summarizes the available evidence, effect estimates, and strength of statistical associations between infertility and its risk factors.

Study design: Systematic review and meta-analysis

Data sources: MEDLINE, CINAHL, and ScienceDirect were searched through 23 January 2022.

Eligibility Criteria: The inclusion criteria involved studies that reported the psychological impact of infertility among women. We included cross-sectional, case-control, and cohort designs, published in the English language, conducted in the community, and performed at health institution levels on prevalence, risk factors, and psychological impact of infertility in women.

Data extraction and synthesis Two reviewers independently extracted and assess the quality of data using the Joanna Briggs Institute Meta-Analysis. The outcomes were assessed with random-effects model and reported as the odds ratio (OR) with 95% confidence interval (CI) using the Review Manager software. **Results:** Thirty-two studies with low risk of bias involving 124,556 women were included. The findings indicated the overall pooled prevalence to be 46.25% and 51.5% for infertility and primary infertility, respectively. Smoking was significantly related to infertility, with the OR of 1.85 (95% CI: 1.08, 3.14) times higher than females who do not smoke. There was a statistical significance between infertility and psychological distress among females, with the OR of 1.63 (95% CI: 1.24, 2.13). A statistical significance was noted between depression and infertility among females, with the OR of 1.40 (95% CI: 1.11, 1.75) compared to those fertile.

Conclusions: The study results highlight an essential and increasing mental disorder among females associated with infertility and may be overlooked. Acknowledging the problem and providing positive, supportive measures to females with infertility ensure more positive outcomes

during the therapeutic process. This review is limited by the differences in definitions, diagnostic cut points, study designs, and source populations.

PROSPERO registration number: CRD42021226414

Keywords: infertility, prevalence, risk factors, psychological impact

Words count: 2479

ARTICLE SUMMARY

Strengths and limitations of this study

- Meta-analysis of studies according to preferred reporting items for systematic reviews and meta-analyses guidelines
- Joanna Briggs Institute Meta-Analysis for assessing the quality of included studies
- Only studies with a low risk of bias were included in the analyses
- Heterogeneity and subgroup analyses were performed
- The search was restricted to English-language articles only

INTRODUCTION

Infertility is defined by the World Health Organization (WHO) as the inability to conceive after one year (or longer) of unprotected intercourse [1]. It is classified as primary or secondary. Primary infertility is denoted for those women who have not conceived previously [2]. In secondary infertility, there is at least one conception, but it fails to repeat [2]. In 2002, the WHO estimated that infertility affects approximately 80 million people in all parts of the world [3]. It affects 10%–15% of couples in their lifetime [4 5]. The prevalence of infertility is concerned, it is high (up to 21.9%): primary infertility at 3.5% and secondary infertility at 18.4% [6]. It is generally accepted that infertility rates are not estimated correctly. The reasons could hinder the measurement of the prevalence, imperfect measurement methods, and unknown kinds of infertility resulting from cultural biases [7].

Infertility is a multidimensional stressor requiring several kinds of emotional adjustments [4]. It is associated with dysfunction in sexual relationships, anxiety, depression, difficulties in marital life, and identity problems [8]. The impact of infertility may be long-lasting, even beyond the initial period of childlessness has passed [9 10]. In the general population, major depression is two to three times as common among women as among men [11]. In the United States, the 12-month prevalence of any mood disorder is 14.1% in females and 8.5% in males, whereas any anxiety disorder is 22.6% in females and 11.8% in males [12]. Thus, depression is one of the most common negative emotions associated with infertility [13 14], which the local social and cultural context may influence.

Determining the psychological impact of infertility among women worldwide provides a better assessment than discrete primary studies. Identifying this impact helps gain a clear understanding of the issue and serves as a basis for an appropriate preventive strategy. In addition, it applies to

primary prevention that could potentially prevent conditions affecting adverse psychological wellbeing. We aimed to perform a systematic review and meta-analysis on infertility among females with regards to its pooled prevalence, risk factors, and psychological impact in observational studies conducted worldwide. This review will summarize the available evidence, effect estimates, and strength of statistical associations between infertility and its risk factors.

MATERIALS AND METHODS

Study design and search strategy

A systematic review and meta-analysis of studies were conducted to assess the psychological impact of infertility among women. The study followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [15].

A systematic search was performed in MEDLINE (PubMed), CINAHL (EBSCOhost), and ScienceDirect. The search was done using text words such as "infertility," "prevalence," "risk factor," "psychology," "mental," "quality of life," "anxiety, "depression," and "stress." The search terms were flexible and tailored to various electronic databases (Supplementary file). All studies published from the inception of these databases until 23 January 2022 were retrieved to assess their eligibility for inclusion in this study. The search was restricted to full-text and English-language articles. To find additional potentially eligible studies, reference lists of included citations were cross-checked.

Eligibility criteria

The inclusion criteria involved studies that reported the psychological impact of infertility among women. Studies with cross-sectional, case-control and cohort designs, published in the English

language, conducted in the community, and performed at health institution levels were included. Case series/reports, conference papers, proceedings, articles available only in an abstract form, editorial reviews, letters of communication, commentaries, systematic reviews, and qualitative studies were excluded.

Study selection and screening

All records identified by our search strategy were exported to the EndNote software. Duplicate articles were removed. Two independent reviewers screened the titles and abstracts of the identified articles. The full text of eligible studies was obtained and read thoroughly to assess their suitability. A consensus discussion was held in the event of a conflict between the two reviewers, and a third reviewer was consulted. The search method is presented in the PRISMA flowchart showing the studies that were included and excluded with reasons for exclusion (Figure 1).

Quality assessment and bias

A critical appraisal was undertaken to assess data quality using the Joanna Briggs Institute Meta-Analysis for cross-sectional, case-control, and cohort studies [16]. Two reviewers performed bias assessments independently. The risk of bias was considered low when more than 70% of the answers were "yes," moderate when 50%–69% of the answers were "yes," and high when up to 49% of the answers were "yes." Studies that showed a high and moderate risk of bias were excluded from the review.

Data extraction process

Two reviewers independently extracted data using the NVivo software (v.12). The process included the first author, publication year, study location, study design and setting, study population, sample size, psychological impact, infertility definition, and data in calculating effect estimates for psychological impact.

Result synthesis and statistical analysis

The outcomes were reported as the odds ratio (OR) and 95% confidence interval (CI). The analysis was performed using the Review Manager software (v.5.4; Nordic Cochrane Centre, Copenhagen, Denmark). A random-effects model was employed to pool data. The I^2 statistic was used to assess heterogeneity, with a guide as outlined: 0%–40% might not be important; 30%–60% may represent moderate heterogeneity; 50%–90% may represent substantial heterogeneity, and 75%–100% may represent considerable heterogeneity [17]. A subgroup analysis was performed based on countries (developed and developing) and comorbidity (presence and absence of comorbidity) if an adequate number of studies were available. Funnel plots were used to assess publication bias if indicated.

RESULTS

Characteristics of included studies

A total of 3,169 articles were retrieved through an electronic search using different search terms. Forty-eight duplicate records were removed. Of the 3,168 articles screened for eligibility, 3,065 were excluded by their title and abstract evaluation. The full text of 103 articles was searched. Subsequently, 62 articles were excluded: 46 did not present the main outcomes, six were performed in different populations, 5 were review articles, 4 had only abstracts, and one was

published in a non-English language (Figure 1). A total of 41 studies underwent quality assessment, of which nine had moderate and high risk of bias.

Finally, 32 studies with low risk of bias were explored in the review: 22 were cross-sectional, eight were case-control, and two were cohort studies. Different countries were involved. Five studies were conducted in Iran [18-22], four in Turkey [23-26], three in Italy [27-29], three in America [30-32], three in Sweden [33-35], two in India [36 37], two in the Netherlands [38 39], one in Finland [9], two in Africa [40 41], one in Saudi Arabia [42], one in Japan [43], two in China [44 45], one in Pakistan [46], and two in Greece [47 48]. The smallest sample size was 87 [47], and the largest was 98,320 [39]. Overall, this study included 124,556 women (Table 1).

Prevalence

Of the included studies, 20 were conducted in a hospital-based setting, four [9 23 33 37] in a community-based setting, and two [18 46] in both hospital- and community-based settings. A slight difference in the prevalence of infertility was observed in the review. A lower prevalence (10.4%) of infertility [9] was observed in a community-based setting, and a higher prevalence (79.3%) [44 47] was noted in a hospital-based setting. The overall pooled prevalence of infertility was 46.25% (95% CI: 37.73, 54.77; $I^2 = 100\%$). Twenty-four articles were included for the estimation of pooled prevalence of infertility among females (Figure 2). The funnel plot was asymmetry with smaller studies and lower prevalence being missing on the left side. The results of the assessment of bias based on the funnel plot asymmetry were not shown but available on request. Out of this, nine were used for the estimation of pooled prevalence of primary infertility.

The overall pooled prevalence of primary infertility was 51.5% (95% CI: 32.74, 70.26; $I^2 = 100\%$) (Figure 1). The lowest prevalence (18%) of primary infertility was reported in a hospital-

based study [27], and the highest prevalence (91.1%) was observed in both community- and hospital-based studies conducted in Iran [18] (Figure 2).

Risk factors of infertility

In this study, risk factors such as age, body mass index (BMI), smoking, and family income were evaluated for their association with infertility. Five studies were included to assess age older than 35 years as a risk factor for infertility regarding the association between age and infertility among females [9 18 32 37]. The pooled meta-regression analysis showed no significant difference in the occurrence of infertility in females aged 35 years or older compared to those younger than 35 years, with the odds being 1.10 (95% CI: 0.83, 1.45; $I^2 = 41\%$). Similarly, there was no association between BMI and infertility in four studies [9 32-34], with odds of 1.11 (95% CI: 0.91, 1.36; $I^2 = 66\%$). However, smoking was found to be significantly related to infertility in three studies [9 33 34], with the odds being 1.85 (95% CI: 1.08, 3.14; $I^2 = 94\%$) times higher compared to those who do not smoke (Figure 3). There was no difference observed (OR: 0.85; 95% CI: 0.59, 1.23; $I^2 = 34\%$) regarding the association between low income and infertility in five studies [9 20 24 37 46].

The psychological impact of infertility

In this study, psychological impact—including distress, depression, and anxiety—was evaluated. Four studies were included to assess the distress caused by infertility [9 20 39 43]. The pooled meta-regression analysis showed a statistical significance between infertility and psychological distress among females, with the odds being 1.63 (95% CI: 1.24, 2.13; $I^2 = 57\%$) (Figure 4).

Eight studies were included to assess the association between depression and infertility among females [9 19 29 30 32-35]. Four studies showed significant [9 30 34 35] associations, and four showed

no significant [19 29 32 33] associations. The pooled meta-regression analysis showed a statistical significance between depression and infertility among females, with the odds being 1.40 (95% CI: 1.11, 1.75; $I^2 = 50\%$) compared to those fertile. However, there was no association between anxiety and infertility in the six studies [9 19 29 32-34], with a pooled meta-regression analysis of OR of 1.68 (95% CI: 0.71, 3.98; $I^2 = 98\%$) (Figure 4).

DISCUSSION

Infertility is a worldwide public health agenda affecting an individual's personal, social, and economic life and the family as a whole. This study was conducted to determine the pooled prevalence and risk factors of infertility among females. In this meta-analysis, the pooled prevalence of infertility and primary infertility among females was 45.85% (95% CI: 37.12, 54.57) and 51.5% (95% CI: 32.74, 70.26), respectively. The prevalence of infertility among females in this study is higher than in a review conducted in 2007 (between 3.5% and 16.7%) [49]. It is because most of the sample size for the research articles in this meta-analysis is from an infertility clinic. Regarding primary infertility, it is similar to a review in Africa at 49.9% (95% CI: 41.34, 58.48) [50].

Various risk factors were assessed in terms of their association with infertility among females. Age was not found to be associated with infertility; however, a study on a sample comprising 7,172 couples showed that the odds of being diagnosed with unexplained and tubal factor infertility are almost twice as high in women older than 35 years as those younger than 30 years [51]. There was no association noted between BMI and infertility among females. Vahrati et al. [52] found that a large proportion of females seeking medical help to become pregnant are obese, and the risk of infertility is three times higher in those obese than nonobese [53]. Smoking is a crucial

risk factor for females, and it shows that females who smoke have a 1.8 times higher risk of developing infertility than those who do not. One study pointed toward a significant association with a 60% increase in the risk of infertility among females who smoke cigarettes [54]. A meta-analysis identified the pertinent literature available from 1966 through late 1997 and reported an OR of 1.60 for infertility among females who smoke compared to those who do not across all study designs [54].

Infertility among females has a vast impact on psychological distress. In the current study, females with infertility have a 1.6 times higher risk of being psychologically distressed than those fertile. This is similar to a study in Taiwan [55], which found that 40.2% of the females with infertility suffer from mental disorders. A review of studies conducted in many countries suggested that women endure the major burdens caused by infertility and experience intense anxiety from being blamed for their failure to give birth [56]. Infertility also contributes to the risk of having depression, with females suffering from infertility having a 1.4 times higher chance of being depressed, whereas other studies showed 67.0% [57] and 35.3% [58] of women with infertility were depressed. Recent research has shown that prevalence can range from 11% [35] to 27% [55] and 73% [57]. Another study in Sweden [35] reported that major depression was the most common disorder among couples suffering from infertility, with a prevalence of 10.9% in females and 5.1% in males. It shows that infertility increases the risk of depression. Therefore, it should be considered a serious warning and given a particular focus.

The risk of anxiety in females with infertility is also high. A meta-analysis by Kiani et al. [59] showed a pooled prevalence of 36.17% (CI: 22.47, 49.87) among females having anxiety because of infertility. In another systematic review, Sawyer et al. [60] reported a 14.8% prevalence of anxiety in females with infertility and a prevalence of 14.0% among women in their pre- and

postnatal periods. In most societies, having a child is closely related to a woman's identity. Being a mother is equated with being female [59], which results in high levels of stress and a sense of worthlessness in those childless [61]. In addition, a female who cannot conceive is at risk of social insecurity and becomes anxious because she foresees a future with no child to take care of them in old age or case of illness [62].

Strengths and limitations

This study showed the prevalence of infertility worldwide and the risk of psychological problems among such females, including studies from different countries. It also focused on the quantitative aspect of the problem to get a better view of the intervention.

However, this study is not without limitations. The differences in definitions, diagnostic cut points, study designs, and source populations make performing a meta-analysis on infertility difficult. On the contrary, there are diverse instruments to determine psychological distress, depression, and anxiety that make comparing results difficult. Another limitation was the use of various instruments to assess psychological problems in the general population. None of the tools was developed specifically to investigate the incidence of factors concerning females. Although the risk factors identified in this review are not new, calling attention to the psychological impact of infertility is worthwhile.

CONCLUSIONS

This study identified that the risk of psychological distress among females with infertility is 60% higher than that among the general population. Furthermore, the risks of anxiety and depression are 60% and 40% times higher, respectively. These results highlight an important and increasing

mental disorder among females that may be overlooked. Psychological distress should concern attending physicians and should be assessed to avoid any unwanted events from happening. Acknowledging the problem and taking positive, supportive measures to help females with infertility ensure more positive outcomes during the therapeutic process.

Acknowledgment: The authors would like to thank Madam Nurul Azurah Mohd Roni, a librarian from Hamdan Tahir Library, for her assistance with the database searches.

Author contributions: Conceptualization, NHNH, MNN and ISB; methodology, NHNH, MNN and ISB; validation MNN and NHNH; formal analysis, MNN and NANMA; investigation, NANMA; resources, MNN and NHNH; data curation, NHNH and NANMA; writing of original draft preparation and NANMA; writing of review and editing, NHNH, MNN, ISB and NANMA; visualization, NHNH, MNN and ISB; project administration, NHNH; All authors have read and agreed to the published version of the manuscript.

Funding: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors

Competing interests: None declared

Patient consent for publication: Not required.

Provenance and peer review: Not commissioned; externally peer-reviewed.

Data availability statement: All data relevant to the study are included in the article.

Supplementary file: Search strategy

Patient and public involvement: It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

Ethical Approval Statement: Not applicable

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TABLES

Table 1. Summary of research articles included in this systemic review and meta-analysis of infertility (n = 32).

No	Authors	Study Area	Study Design	Sample Size	Female infertility	Quality assessment (%)
1	Aggarwal et al., 2013 [36]	India	cross-sectional	500	267	87.5
2	Albayrak et al.,2007[23]	Kayseri, Turkey	cross-sectional	300	150	87.5
3	Biringer et al., 2015[33]	North Trondelag, Sweden	cross-sectional	12584	1696	100
4	Klemetti et al., 2010[9]	Finlad	cross-sectional	2291	239	100
5	Bakhtiyar et al., 2019[18]	Lorestan, Iran	case control	720	180	70
6	Alhassan et al., 2014[40]	Ghana	cross-sectional	100	100	87.5
7	Alosaimi et al., 2015[42]	Riyadh, Saudi Arabia	cross-sectional	406	206	100
8	Matsubaya et al., 2001[43]	Tokai, Japan	cross-sectional	182	101	87.5
9	Acmaz et al., 2013 [24]	Kayseri, Turkey	cross-sectional	133	86	87.5
10	Bai et al., 2019[44]	Ningxia province, China	cross-sectional	740	380	100
11	Bazarganipour et al., 2013[19]	Kashan, Iran	cross-sectional	300	238	100
12	Begum et al., 2014[46]	Karachi, Pakistan	cross-sectional	120	60	87.5
13	Volgsten et al., 2008[35]	Sweden	cross-sectional	825	122	88.9
14	Bringhenti et al., 1997[27]	Italy	cross-sectional	179	122	87.5
15	Lansakara et al., 2011[37]	Colombo, Sri Lanka	cross-sectional	354	177	87.5
16	Noorbala et al., 2009[20]	Tehran, Iran	cross-sectional	300	150	87.5
17	Salih Joelsson et al., 2017[34]	Sweden	cross-sectional	3583	468	100

18	Aydin et al., 2015[25]	Istanbul, Turkey	cross-sectional	88	88	87.5
19	Tarlatzis et al., 1993[47]	Greece	cohort	87	69	81.8
20	Ramezan et al., 2004[21]	Tehran, Iran	cross-sectional	370	370	87.5
21	Aarts et al., 2011[38]	Netherlands	cross-sectional	472	472	87.5
22	Baldur et al., 2013[39]	Denmark	cohort	98320	44773	100
23	Diamond et al., 2017[31]	United states	cross-sectional	1594	1594	87.5
24	Downey et al., 1992[30]	New York City	case control	201	118	80
25	Fassino et al., 2002[28]	Italy	case control	172	172	90
26	Guz et al., 2003[26]	Turkey	case control	100	50	80
27	Omani et al., 2017[22]	Tehran, Iran	cross-sectional	312	149	100
28	Salomao et al., 2018[32]	Brazil	case control	280	140	80
29	Sbaragli et al., 2008[29]	Siena, Italy	case control	302	82	100
30	Akalewold et al., 2022	Ethiopia	cross-sectional	409	66	100
31	Kleanthi et al., 2021	Greece	case control	177		90
32	Peng et al., 2021	China	case control	450		100

Note: The quality assessment was performed based on the Joanna Briggs Institute Meta-Analysis for cross-sectional, case-control, and cohort studies

FIGURES

Figure 1: Flow diagram showing the included studies for systemic review and meta-analysis on the prevalence, risk factors, and psychological impact of infertility among women

Figure 2: Forest plot depicting the prevalence of infertility

Figure 3: Forest plot depicting the risk factors associated with infertility

Figure 4: Forest plot depicting the psychological impact of infertility

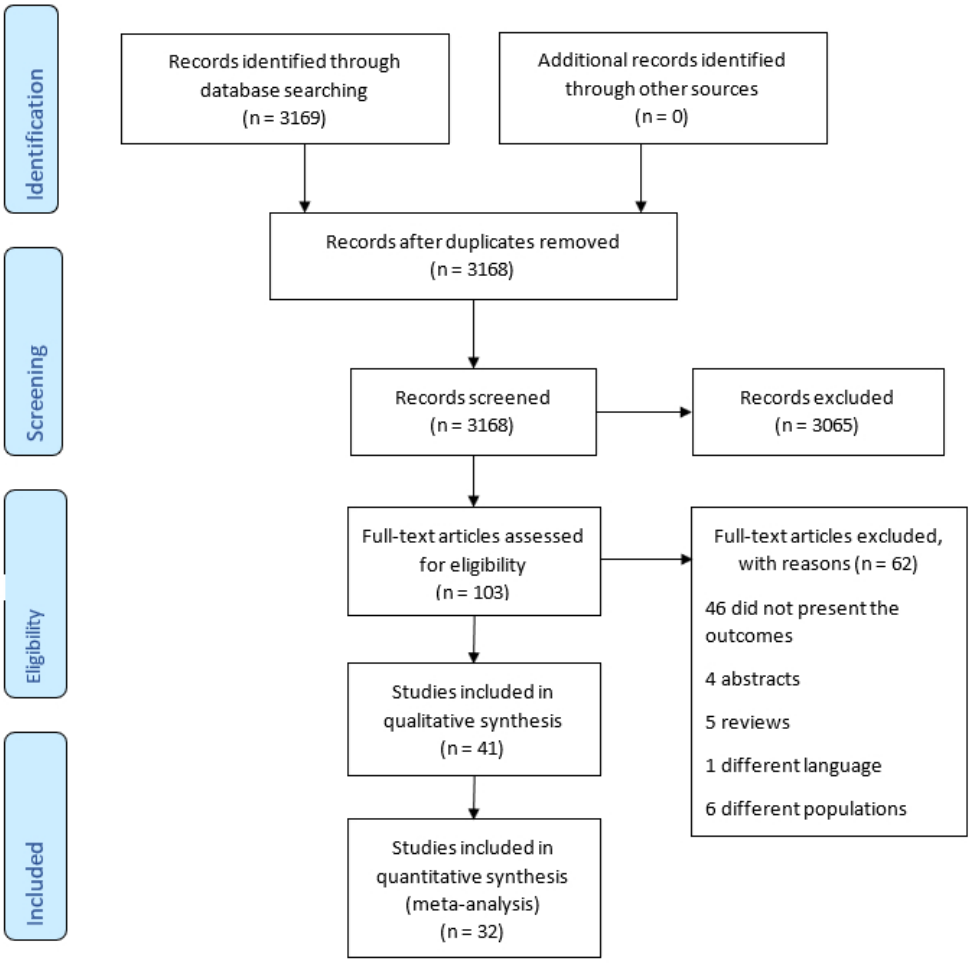
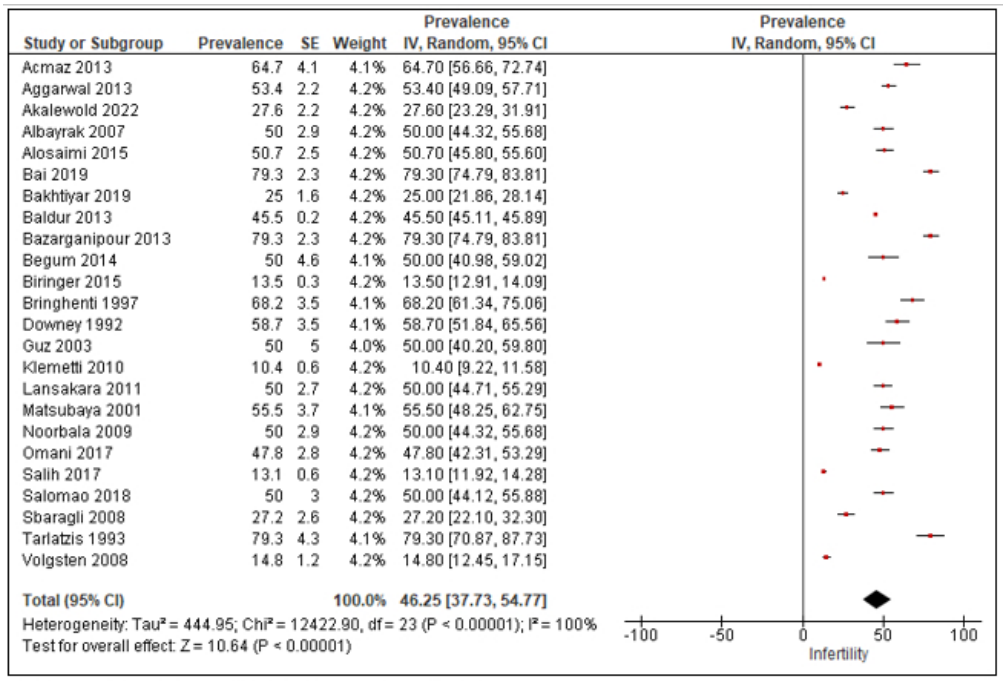
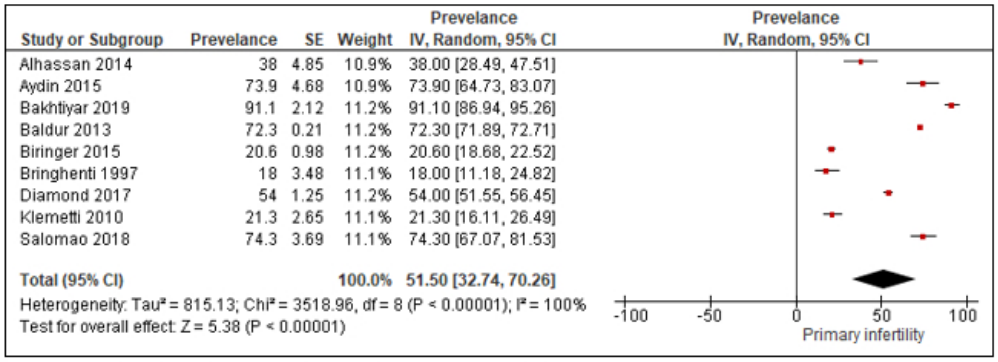


Figure 1: Flow diagram showing the included studies for systemic review and meta-analysis on the prevalence, risk factors, and psychological impact of infertility among women

463x454mm (38 x 38 DPI)



2A. Forest plot for the prevalence of infertility



2B. Forest plot for the prevalence of primary infertility

Figure 2: Forest plot depicting the prevalence of infertility

435x480mm (38 x 38 DPI)

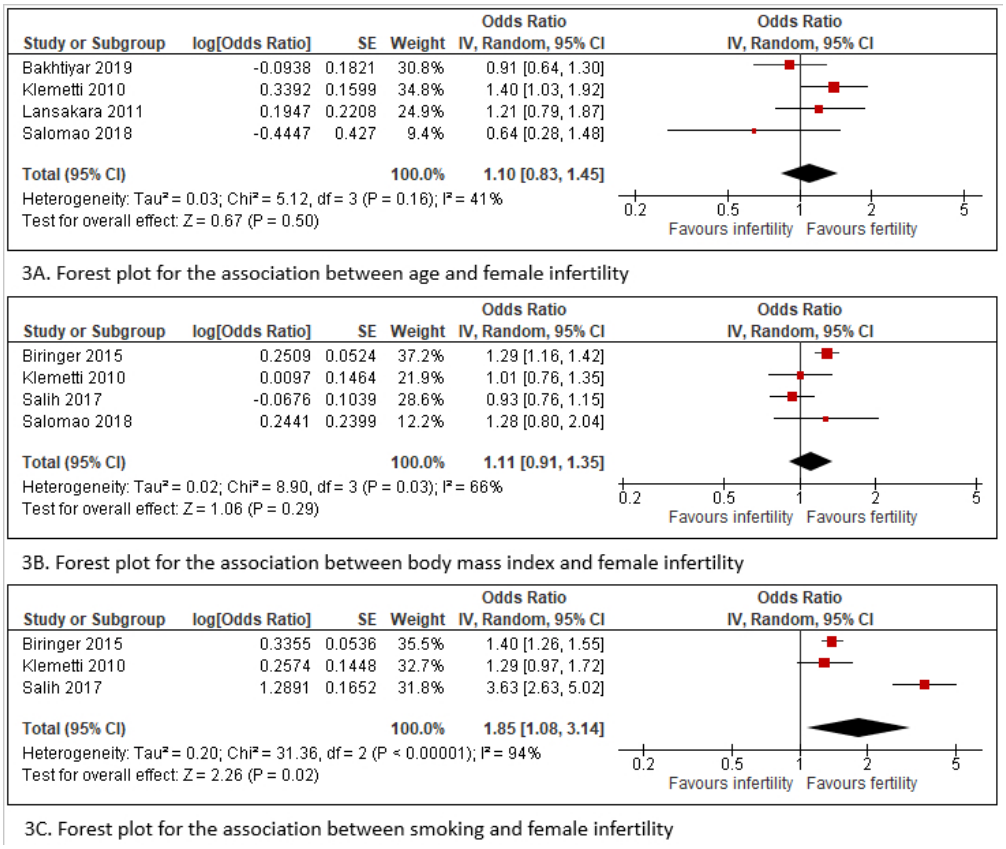
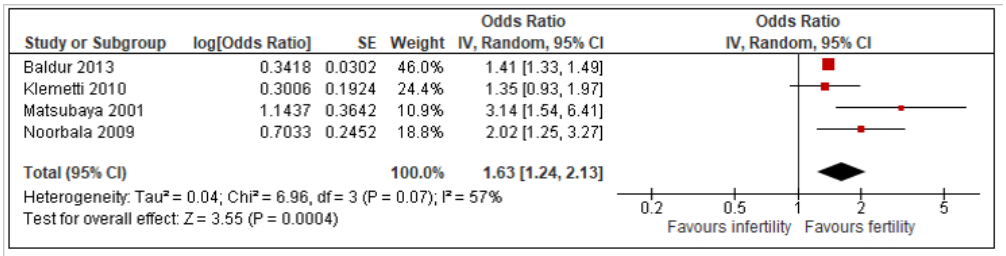
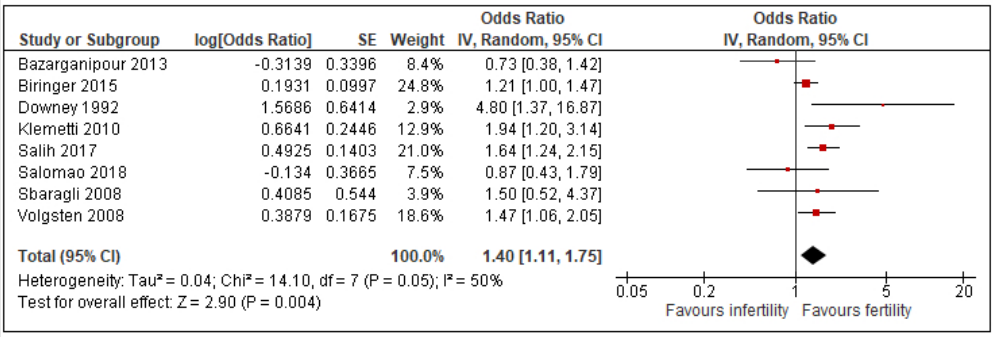


Figure 3: Forest plot depicting the risk factors associated with infertility

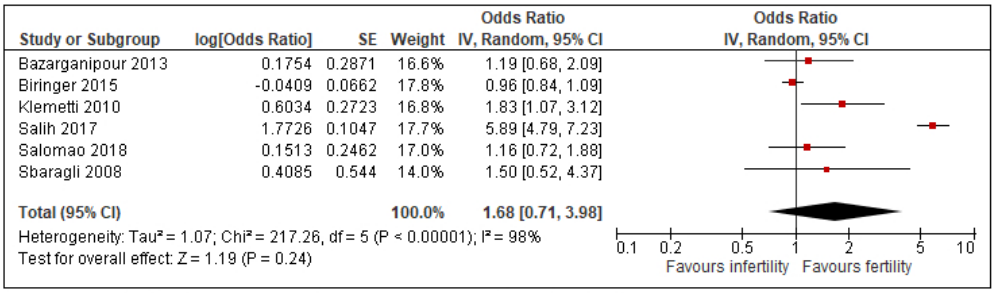
489x411mm (38 x 38 DPI)



4A. Forest plot for the association between distress and female infertility



4B. Forest plot for the association between depression and female infertility



4C. Forest plot for the association between anxiety and female infertility

Figure 4: Forest plot depicting the psychological impact of infertility

495x481mm (38 x 38 DPI)

Search strategy

PubMed

1. infertil*[Title/Abstract]
2. prevalence[Title/Abstract]
3. (#1) AND (#2)
4. risk factor
5. (#1) AND (#4)
6. psycholog*
7. mental
8. quality of life
9. anxiety
10. depression
11. stress
12. (((((#6) OR (#7)) OR (#8)) OR (#9)) OR (#10)) OR (#11)
13. (#1) AND (#12)

ScienceDirect

infertility

infertility AND prevalence

infertility AND risk factor

infertility AND (psycholog/ OR mental OR quality of life OR anxiety OR depression OR stress)

PRISMA 2020 for Abstracts Checklist

Section and Topic	Item #	Checklist item	Reported (Yes/No)
TITLE			
Title	1	Identify the report as a systematic review.	Yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	Yes
Synthesis of results	6	Specify the methods used to present and synthesise results.	Yes
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	Yes
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
OTHER			
Funding	11	Specify the primary source of funding for the review.	N/R
Registration	12	Provide the register name and registration number.	Yes

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

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PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	5
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	7
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	7
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	6
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	7
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	6
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	7
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	7
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	7
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	7
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	-
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	6
Certainty	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	-

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
assessment			
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Fig 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	8
Study characteristics	17	Cite each included study and present its characteristics.	Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	8
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Fig 2-5
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Fig 1
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	8-10
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	8-10
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	-
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	-
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	-
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	8-10
	23b	Discuss any limitations of the evidence included in the review.	12
	23c	Discuss any limitations of the review processes used.	12
	23d	Discuss implications of the results for practice, policy, and future research.	12
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	2
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	2
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	-
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	13
Competing interests	26	Declare any competing interests of review authors.	13
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	15

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

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