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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
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
Keywords:	Public health < INFECTIOUS DISEASES, Maternal medicine < OBSTETRICS, PRIMARY CARE





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R. O.

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.

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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

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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.

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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

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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 I² 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,

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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 casecontrol, 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

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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	Sample	Female	Female	Quality
			Design	Size	infertility	fertile	assessment
							%
1	Aggarwal et	India	cross-	500	267	233	87.5
	al., 2013 36		sectional				
2	Albayrak et	Kayseri,	cross-	300	150	150	87.5
	al.,2007 ²³	Turkey	sectional				
3	Biringer et al.	North	cross-	12584	1696	10888	100
	2015 ³³	Trondelag,	sectional				
		Sweden					
4	Klemetti et	Finlad	cross-	2291	239	959	100
	al., 2010 ⁹		sectional				
5	Bakhtiyar et	Lorestan,	case	720	180	540	70
	al., 2019 ¹⁸	Iran	control				
6	Alhassan et	Ghana	cross-	100	100		87.5
	al., 2014 ⁴⁰		sectional				
7	Alosaimi et	Riyadh,	cross-	406	206		100
	al., 2015 ⁴¹	Saudi Arabia	sectional				
8	Matsubaya et	Tokai, Japan	cross-	182	101	81	87.5
	al., 2001 ⁴²		sectional				

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9	Acma	z et	al.,	Kayseri,	cross-	133	86	47	87.5
	2013	24		Turkey	sectional				
10	Bai	et	al.,	Ningxia	cross-	740	380		100
	20194	3		province,	sectional				
				China					
11	Bazar	ganip	our	Kashan, Iran	cross-	300	238	62	100
	et al.,	2013	19		sectional				
12	Begur	n et	al.,	Karachi,	cross-	120	60	60	87.5
	20144	4		Pakistan	sectional				
13	Volgs	ten	et	Sweden	prevelence	825	122	291	88.9
	al., 20	0835							
14	Bring	henti	et	Italy	cross-	179	122	57	87.5
	al., 19	97 ²⁷			sectional				
15	Lansa	kara	et	Colombo,	cross-	354	177	177	87.5
	al., 20	11 ³⁷		Sri lanka	sectional				
16	Noorb	oala	et	Tehran, Iran	cross-	300	150	150	87.5
	al., 20	0920			sectional				
17	Salih	Joels	son	Sweden	cross-	3583	468	2972	100
	et al.,	2017	34		sectional				
18	Aydin	et	al.,	Istanbul,	cross-	88	88		87.5
	20152	5		turkey	sectional				
19	Tarlat	zis	et	greek	cohort	87	69		81.8
	al., 19	93 ⁴⁵							

BMJ Open

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

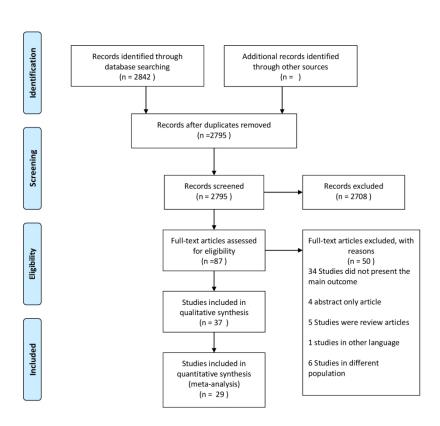
Figure 1: Flow diagram showing the included studies for systemic review and meta-analysis on the prevalence, risk factors, and psychological impact of infertility among women

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

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5		BMJ Open: first published
6		stp
7	Study or Subgroup Prevalence % Frevalence % Acmsz 2013 64.7 4.14 4.3% 64.70 [05.59, 72.81]	duc
8	Aggarwal 2013 53.4 2.23 4.4% 53.40 1490.3,57.77	list
9	Bai 2019 51.4 1.84 4.4% 51.40 [k7.79,55.01] - Baithpur 2019 25 1.61 4.4% 52.00 [k1.48,28.16] -	led
10	Baddur 2013 455 (1b 4.4% 450.9(4519,458) Batarganipour 2013 79.3 2.34 4.4% 79.30[74.71,63.86] Begurn 2014 50 4.56 4.2% 50.00[41.06,58.94]	as
11	Birningez 2015 13.5 0.2 4.4% 13.50 (12.2%) (1.406) * Birningheriti 1997 66.2 3.46 4.3% 66.20 (61.36,75.02) * Downey 1992 58.7 3.47 4.3% 58.70 (55.10) **	10
12	Guz 2003 50 5 4 2% 500 (H020, 05 80)	
13	Matsubaya 2001 55.5 28.8 4.3% 55.9 (42.9, 62.71) → Noomala 2009 50 28.9 4.3% 50.01 [4.3, 45.566] → Omani 2017 47.2 8.8 4.3% 57.91 (42.5, 53.5] →	36,
14	Saih 2017 13.1 0.56 4.4% 13.101(2.00,14.20) * Saloma 2018 50 2.99 4.3% 50.001414.14.55.88 9	br
15	Bbaragi 2008 272 258 4.4% 27.20216, 32.22 + Taritacis 1939 793 4.34 4.29.197.87.81 + Volgsten 2008 14.79 1.24 4.4% 14.79[12.36, 17.22] +	Jjop
16	Total (95% CU) 100.0% 45.85 (37.12,54.57) Hotorogeneity: Tau® 447.63, Chi® = 1371/7.17, cf = 22.0° < 0.00001); № = 100% Terstfor wearlietter: Z = 10.30.0° < 0.00001	ěn.
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18	Prevalence % Prevalence % Study or Subgroup Prevalence % M, Random, 99-C1 Ansusu 2014 30 45 109: % 200 (28.44, 75.1)	21- 1-
19	Aydro 2015 73 9 488 109% 72 90 (B473 80 07) Bakhflyar 2019 91.1 21.2 11.2% 91.10 (B6.94, 95.26) Bakhflyar 2013 72.20 21 112% 72.00 (F3.96, 72.71)	-05
20	Biringer 2015 206 0.98 11.2% 2060 [15.68,22.52] Birinder 1987 18 3.48 11.1% 10.001 [15.24.27]	713
21	Hernetti 2010 21.3 2.65 11.1% 21.30 (16.11, 26.46) Satomio 2018 74.3 3.69 11.1% 74.30 (67.07, 61.53)	32 (
22	Totat (6% C) Totat (6% C) Totat (5% C) 2124, 70.26 Heterogenet Tau" = 015.13, CA* = 3518.86, df = 8 (* 4.0.001), (* = 100% Testor overall effect 2 = 5.31 (* < 0.0001) (* = 100% Favours primary interfile Favours study sample	on 30 March 2022.
23	Forrest plot for the prevalence of primary infertility	30 I
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25	Forest plot depicting the prevalence of infertility and primary infertility	, ch
26		20)
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Odds Rati

Odds Ratio

1.11 [0.91, 1.35]

100.0% 1.85 [1.08, 3.14]

0.2

0.2

Forest plot showing the risk factors associated with infertility

338x190mm (96 x 96 DPI)

. 95% CI

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Odds Ra

0.5 Favours Infertile

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IV, Random, 95% CI

Odds Rati

IV, Random, 95% CI

Favours Fertile

Favours Fertile

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 SE
 Weight IV, Random, 95% CI

 -0.0938
 0.1821
 30.8%
 0.91 [0.64, 1.30]

 0.3392
 0.1599
 34.8%
 1.40 [1.03, 1.92]

 0.1947
 0.2028
 24.9%
 1.21 [0.79, 1.87]

 -0.4447
 0.427
 9.4%
 0.64 [0.28, 1.48]

Study or Subgroup

Klemetti 2019 Lansakara 2011 Salomao 2018

log[Odds Ratio]

Forrest plot for the association between age and female infertility

100.0% 1.11 Heterogeneity: TauP = 0.02; ChP = 8.90, df = 3 (P = 0.03); P = 66% Test for overall effect: Z = 1.06 (P = 0.29) Forrest plot for the associative benefit

 Study of Subgroup
 log[Odds Ratio
 E
 Veidate N.
 N.

 Bringer 2015
 0.259
 0.0524
 37.2%
 1.29[1:16,1.42]

 Kiemet 2010
 0.0097
 0.1464
 21.9%
 1.01[0.76,1.5]

 Salih 2017
 -0.0676
 0.1039
 8.6%
 0.93 [0.76,1.15]

 Salih 2017
 -0.02676
 0.1039
 8.6%
 0.93 [0.76,1.15]

 Salomae 2018
 0.2441
 0.2399
 1.28 [0.80, 2.04]

 Forrest pick for the association between BMI and female infertility
 Odds Ratio

 Study or Subgroup
 log(Odds Ratio)
 SE
 Weight
 IV, Random, 95% CI

 Bringer 2015
 0.3355
 0.053
 35.5%
 1.40 (12.6, 15.6)

 Kiemetti 2010
 0.2574
 0.148
 32.7%
 1.29 (0.97, 17.2)

 Salin 2017
 1.289
 0.1652
 31.8%
 3.63 (2.63, 5.02)

est plot for the association between smoking and female infertility

2	
3	
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Study or Subgroup	log[Odds Ratio]	er.	Woight	Odds Ratio IV. Random, 95% Cl	Odds Ratio IV. Random, 95% Cl
					IV, Random, 95% CI
Baldur 2013	0.3418	0.0302	46.0%	1.41 [1.33, 1.49]	
Klemetti 2010	0.3006	0.1924	24.4%	1.35 [0.93, 1.97]	
Matsubaya 2001	1.1437	0.3642	10.9%	3.14 [1.54, 6.41]	
Noorbala 2009	0.7033	0.2452	18.8%	2.02 [1.25, 3.27]	
Total (95% CI)			100.0%	1.63 [1.24, 2.13]	•
Heterogeneity: Tau ² =	= 0.04; Chi ² = 6.96,	df = 3 (P	= 0.07); P	= 57%	
Test for overall effect	Z = 3.55 (P = 0.000	04)			0.2 0.5 1 2 5 Favours infertile Favours fertile

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

338x190mm (96 x 96 DPI)

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	Odds Ratio Odds Ratio Study or Subgroup log[Odds Ratio] SE Weight IV, Random, 95% CI IV, Random, 95% CI
	Bazarganpour 2013 -0.313 0.396 8.4% 0.73 [0.38, 1.42] Bringer 2015 0.1931 0.0997 24.8% 1.21 [1.0.147]
	Normer 1992 1.5686 0.8414 2.9% 4.80[1:37,1687] Klernetti 2010 0.6641 0.2446 12.9% 1.94 [1:20,3.14]
	Salin 2017 0.4925 0.1403 21.0% 1.64 [1.24, 2.15]
	Sbaragii 2008 0.4085 0.544 3.9% 1.50 [0.52, 4.37] Volgsten 2008 0.3879 0.1675 18.6% 1.47 [1.06, 2.05]
	Total (95% CI) 100.0% 1.40 (1.11, 1.75)
	Heterogeneity: Tau"= 0.04; Chi"= 14.10, df= 7 (P = 0.05); P= 50% Test for overall effect Z = 2.90 (P = 0.004) Favours infentile Favours infentile
	Forrest plot for the association between depression and female infertility
	Odds Ratio Odds Ratio Study or Subgroup log[Odds Ratio] SE Weight IV, Random, 95% CI IV, Random, 95% CI
	Bazarganipour 2013 0.1754 0.2871 16.6% 1.19 [0.68, 2.09]
	Biringer 2015 -0.0400 0.0652 17.8% 0.9610.84,109] Klemetti 2010 0.6034 0.2723 16.8% 1.831107,312] Salih 2017 1.7726 0.1047 11.7% 5.8914.79,723
	Salmana 2017 0.1712 0.100 1.175 5.000 1.50 Salomaa 2018 0.452 1.2045 1.150 1.2452 1.205 1.150 1.251 1.201 Salomaa 2018 0.4065 0.544 14.0% 1.50 0.52,4.37
	Total (95% CI) 100.0% 1.68 (0.71, 3.98]
	Heterogeneity, Tau" = 1 07; Chi" = 217, 26, df = 5 (P < 0.00001); P = 98% Test for overall effect, Z = 1.19 (P = 0.24) Favours interfile Favours interfile
	Forrest plot for the association between anxiety and female infertility
Fores	t plot showing the association of depression, anxiety, and infertility
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To enable PROSPERO to focus on COVID-19 submissions, this registration record has undergone basic automated checks for eligibility and is published exactly as submitted. PROSPERO has never provided peer review, and usual checking by the PROSPERO team does not endorse content. Therefore, automatically published records should be treated as any other PROSPERO registration. Further detail is provided here.

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

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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 I² 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 I² 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

Nik Muhammad Arif Nik Ahmad nik_arif25@yahoo.com

Organisational affiliation of the review

Universiti Sains Malaysia

Review team members and their organisational affiliations

Dr Nik Muhammad Arif Nik Ahmad. Universiti Sains Malaysia 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

NIHR	National Institute for Health Research
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15 December 2020

Anticipated completion date 15 June 2021

Funding sources/sponsors

Grant number(s)

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

Nil

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

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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.

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PRISMA 2020 Checklist

		BMJ Open	I 136/b	Page 32 of 33
	ΜΛΟ	020 Checklist	A systematic review. A systematic review in the context of existing knowledge. A systematic review in the context of existing knowledge. A systematic review in the context of existing knowledge. A systematic review in the context of existing knowledge. A systematic review and how studies were grouped for the syntheses. A systematic review and how studies were grouped for the syntheses. A systematic review and how studies were grouped for the syntheses. A systematic review and how studies were grouped for the syntheses. A strategies for all databases, registers and websites, including how many reviewers screened each record 6 systemetry worked independently, and if applicable, details of automation tools used in the process. B strategies for all databases, registers and websites, including how many reviewers screened each record 6 second take mere sought. Specify whether all results that were compatible with each stude more sources. A systemation conterning data from sudy investigators, and if applicable, details of automation tools used in the applicable details or a	
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TITLE			0 0	
Title	1	Identify the report as a systematic review.	n 30	1
ABSTRACT			S	
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	arch	2
INTRODUCTION			20	
Rationale	3	Describe the rationale for the review in the context of existing knowledge.		
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.		5
METHODS			<u>n</u>	
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	ade	
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to date when each source was last searched or consulted.	ថ្មីdentify studies. Specify the ភ្និ	5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	5 5	5
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many re and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in		6
2 Data collection 3 process	9			6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which resu		7
8	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, fund assumptions made about any missing or unclear information.	sources). Describe any ⊳	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 m study and whether they worked independently, and if applicable, details of automation tools used in the process.	के ang reviewers assessed each रहे	6
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentat		7
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study inte comparing against the planned groups for each synthesis (item #5)).	rvention characteristics and	6
	13b		Geregery statistics, or data	7
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Pro	7
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was pe 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 analys	ुत sis, meta-regression).	7
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	ор р	-
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting bias	yrigint.	6
Certainty	15	Describe any methods use to cassess certainty (or confidence) in the body of evidence for an butcomem		_

PRISMA 2020 Checklist

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Section and Topic	ltem #	Checklist item	4 - 057713	Location where iten is reported
assessment			0 2	
RESULTS			2 2	
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the review, ideally using a flow diagram.	amber of studies included in	Fig 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were explain why they w	ર્ટ્યૂuded.	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 (e.g. confidence/credible interval), ideally using structured tables or plots.	estimate and its precision	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 estimation of the summary estimation of the summary estimates of statistical heterogeneity. If comparing groups, describe the direction of the summary estimates of statistical heterogeneity.		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 assesse	ष्ट्री.	-
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	2.	-
DISCUSSION				
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	A D	8-10
	23b	Discuss any limitations of the evidence included in the review.	<u>r.</u>	12
	23c	Discuss any limitations of the review processes used.	0 V	12
	23d	Discuss implications of the results for practice, policy, and future research.	024	12
OTHER INFORMAT	ΓΙΟΝ		2	
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review	ew was not registered.	2
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	<u></u>	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 re	view.	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 studies; data used for all analyses; analytic code; any other materials used in the review.	extracted from included	15



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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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R. O.

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

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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 randomeffects 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.

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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 BMJ Open: first published as 10.1136/bmjopen-2021-057132 on 30 March 2022. Downloaded from http://bmjopen.bmj.com/ on April 19, 2024 by guest. Protected by copyright

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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.

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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 elie (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

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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 I² 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

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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 crosssectional, 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).

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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 metaregression 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

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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

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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	Sample	Female	Quality
			Design	Size	infertility	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	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

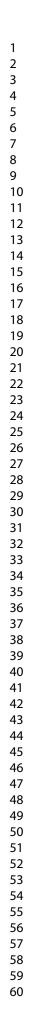
Figure 1: Flow diagram showing the included studies for systemic review and meta-analysis on the prevalence, risk factors, and psychological impact of infertility among women

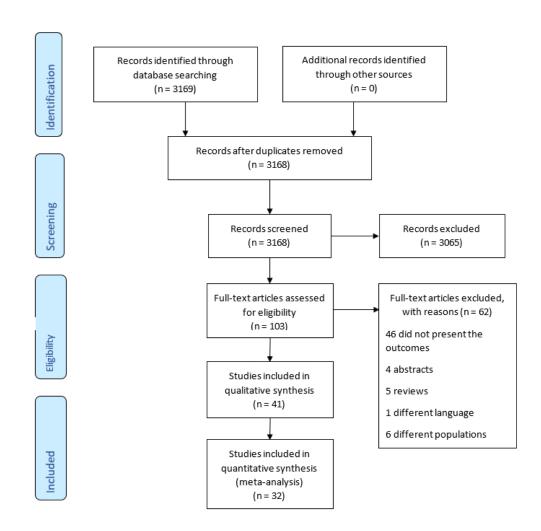
Figure 2: Forest plot depicting the prevalence of infertility

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

Figure 4: Forest plot depicting the psychological impact of infertility

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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)

				Prevalence		Preva	lence
Study or Subgroup	Prevalence	SE	Weight	IV, Random, 95% CI		IV, Rando	m, 95% Cl
Acmaz 2013	64.7	4.1	4.1%	64.70 [56.66, 72.74]			
Aggarwal 2013	53.4	2.2	4.2%	53.40 [49.09, 57.71]			+
Akalewold 2022	27.6	2.2	4.2%	27.60 [23.29, 31.91]			+
Albayrak 2007	50	2.9	4.2%	50.00 [44.32, 55.68]			+
Nosaimi 2015	50.7	2.5	4.2%	50.70 [45.80, 55.60]			+
3ai 2019	79.3	2.3	4.2%	79.30 [74.79, 83.81]			+
3akhtiyar 2019	25	1.6	4.2%	25.00 [21.86, 28.14]			+
Saldur 2013	45.5	0.2	4.2%	45.50 [45.11, 45.89]			•
Bazarganipour 2013	79.3	2.3	4.2%	79.30 [74.79, 83.81]			+
Begum 2014	50	4.6	4.1%	50.00 [40.98, 59.02]			-
Biringer 2015	13.5	0.3	4.2%	13.50 [12.91, 14.09]			- A
Bringhenti 1997	68.2	3.5	4.1%	68.20 [61.34, 75.06]			-
Downey 1992	58.7	3.5	4.1%	58.70 [51.84, 65.56]			-
3uz 2003	50	5	4.0%	50.00 [40.20, 59.80]			
⊲emetti 2010	10.4	0.6	4.2%	10.40 [9.22, 11.58]			•
ansakara 2011	50	2.7	4.2%	50.00 [44.71, 55.29]			+
Matsubaya 2001	55.5	3.7	4.1%	55.50 [48.25, 62.75]			
Noorbala 2009	50	2.9	4.2%	50.00 [44.32, 55.68]			+
Omani 2017	47.8	2.8	4.2%	47.80 [42.31, 53.29]			+
Salih 2017	13.1	0.6	4.2%	13.10 [11.92, 14.28]			•
Salomao 2018	50	3	4.2%	50.00 [44.12, 55.88]			+
Sbaragli 2008	27.2	2.6	4.2%	27.20 [22.10, 32.30]			+
Farlatzis 1993	79.3	4.3	4.1%	79.30 [70.87, 87.73]			
/olgsten 2008	14.8	1.2	4.2%	14.80 [12.45, 17.15]			•
fotal (95% CI)			100.0%	46.25 [37.73, 54.77]			•
Heterogeneity: Tau ² =	444.95: Chi ² =	1242	2.90. df=	23 (P < 0.00001); I ² = 100%		1.	
Test for overall effect: 2					-100	-50 0) 50 1 Infertility

2A. Forest plot for the prevalence of infertility

				Prevelance		P	revelance
Study or Subgroup	Prevelance	SE	Weight	IV, Random, 95% CI		IV, Ra	andom, 95% Cl
Alhassan 2014	38	4.85	10.9%	38.00 [28.49, 47.51]			
Aydin 2015	73.9	4.68	10.9%	73.90 [64.73, 83.07]			
Bakhtiyar 2019	91.1	2.12	11.2%	91.10 [86.94, 95.26]			-
Baldur 2013	72.3	0.21	11.2%	72.30 [71.89, 72.71]			
Biringer 2015	20.6	0.98	11.2%	20.60 [18.68, 22.52]			-
Bringhenti 1997	18	3.48	11.1%	18.00 [11.18, 24.82]			-
Diamond 2017	54	1.25	11.2%	54.00 [51.55, 56.45]			•
Klemetti 2010	21.3	2.65	11.1%	21.30 [16.11, 26.49]			-
Salomao 2018	74.3	3.69	11.1%	74.30 [67.07, 81.53]			-
Total (95% CI)			100.0%	51.50 [32.74, 70.26]			-
Heterogeneity: Tau ² =	= 815.13; Chi ² =	= 3518	.96, df = 8	8 (P < 0.00001); I ² = 100%	100		
Test for overall effect					-100	-50	0 50 10 Primary infertility

2B. Forest plot for the prevalence of primary infertility

Forest plot depicting the prevalence of infertility

435x480mm (38 x 38 DPI)

				Odds Ratio	Odds Ratio
Study or Subgroup	log[Odds Ratio]	SE	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Bakhtiyar 2019	-0.0938	0.1821	30.8%	0.91 [0.64, 1.30]	
Klemetti 2010	0.3392	0.1599	34.8%	1.40 [1.03, 1.92]	⊢ ∎
Lansakara 2011	0.1947	0.2208	24.9%	1.21 [0.79, 1.87]	
Salomao 2018	-0.4447	0.427	9.4%	0.64 [0.28, 1.48]	
Total (95% CI)			100.0%	1.10 [0.83, 1.45]	-
Heterogeneity: Tau ² =	: 0.03; Chi² = 5.12,	df = 3 (P	= 0.16); P	'= 41%	0.2 0.5 1 2
Test for overall effect:	Z = 0.67 (P = 0.50)				Favours infertility Favours fertility
3A. Forest plot for	the association	betwe	en age a	and female infertili	ity
				Odds Ratio	Odds Ratio
Study or Subgroup	log[Odds Ratio]	SE	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Biringer 2015	0.2509	0.0524	37.2%	1.29 [1.16, 1.42]	
Klemetti 2010	0.0097	0.1464	21.9%	1.01 [0.76, 1.35]	+
Salih 2017	-0.0676	0.1039	28.6%	0.93 [0.76, 1.15]	 -
Salomao 2018	0.2441	0.2399	12.2%	1.28 [0.80, 2.04]	
Total (95% CI)			100.0%	1.11 [0.91, 1.35]	•
Heterogeneity: Tau ² =	: 0.02; Chi ² = 8.90,	df = 3 (P	= 0.03); P	'= 66%	0.2 0.5 1 2
Test for overall effect:	Z = 1.06 (P = 0.29)				Favours infertility Favours fertility
3B. Forest plot for	the association	betwe	en body	mass index and fe	emale infertility
				Odds Ratio	Odds Ratio
Study or Subgroup	log[Odds Ratio]	SE	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Biringer 2015	0.3355	0.0536	35.5%	1.40 [1.26, 1.55]	
Klemetti 2010	0.2574	0.1448	32.7%	1.29 [0.97, 1.72]	
Salih 2017	1.2891	0.1652	31.8%	3.63 [2.63, 5.02]	_ _
Total (95% CI)			100.0%	1.85 [1.08, 3.14]	
Heterogeneity: Tau ² =	: 0.20; Chi ² = 31.36 Z = 2.26 (P = 0.02)		P < 0.000	01); I² = 94%	0.2 0.5 1 2
	$z = z.z_0 (P = 0.02)$				Favours infertility Favours fertility

Forest plot depicting the risk factors associated with infertility

489x411mm (38 x 38 DPI)

Odds Ratio	-
IV, Random, 95% Cl	
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				Odds Ratio	Odds Ratio
Study or Subgroup	log[Odds Ratio]	SE	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Baldur 2013	0.3418	0.0302	46.0%	1.41 [1.33, 1.49]	
Klemetti 2010	0.3006	0.1924	24.4%	1.35 [0.93, 1.97]	+
Matsubaya 2001	1.1437	0.3642	10.9%	3.14 [1.54, 6.41]	
Noorbala 2009	0.7033	0.2452	18.8%	2.02 [1.25, 3.27]	
Total (95% CI)			100.0%	1.63 [1.24, 2.13]	•
Heterogeneity: Tau ² =	0.04; Chi ² = 6.96, ¹	df = 3 (P :	= 0.07); l ²	= 57%	0.2 0.5 1 2
Test for overall effect:	Z = 3.55 (P = 0.000	04)			0.2 0.5 1 2 Favours infertility Favours fertility
4A. Forest plot for	the association	betwee	en distre	ss and female infe	rtility
				Odds Ratio	Odds Ratio
Study or Subgroup	log[Odds Ratio]	SE	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Bazarganipour 2013	-0.3139	0.3396	8.4%	0.73 [0.38, 1.42]	
Biringer 2015	0.1931	0.0997	24.8%	1.21 [1.00, 1.47]	+ - -
Downey 1992	1.5686	0.6414	2.9%	4.80 [1.37, 16.87]	· · · · · · · · · · · · · · · · · · ·
Klemetti 2010		0.2446	12.9%	1.94 [1.20, 3.14]	— • —
Salih 2017	0.4925	0.1403	21.0%	1.64 [1.24, 2.15]	
Salomao 2018		0.3665	7.5%	0.87 [0.43, 1.79]	
Sbaraqli 2008	0.4085		3.9%	1.50 [0.52, 4.37]	
Volgsten 2008		0.1675		1.47 [1.06, 2.05]	
Total (95% CI)			100.0%	1.40 [1.11, 1.75]	◆
Heterogeneity: Tau ² = 1	0.04: Chi ² = 14.10.	df = 7 (P	= 0.05); [²= 50%	
Test for overall effect: 2			,,		0.05 0.2 1 5 Favours infertility Favours fertility
	the association	betwee	n depre	ssion and female i	nfertility
4B. Forest plot for					
				Odds Ratio	Odds Ratio
Study or Subgroup	log[Odds Ratio]	SE		IV, Random, 95% CI	
Study or Subgroup Bazarganipour 2013	log[Odds Ratio] 0.1754	SE 0.2871	16.6%	IV, Random, 95% Cl 1.19 [0.68, 2.09]	Odds Ratio
Study or Subgroup Bazarganipour 2013 Biringer 2015	log[Odds Ratio] 0.1754 -0.0409	SE 0.2871 0.0662	16.6% 17.8%	IV, Random, 95% Cl 1.19 [0.68, 2.09] 0.96 [0.84, 1.09]	Odds Ratio
Study or Subgroup Bazarganipour 2013 Biringer 2015 Klemetti 2010	log[Odds Ratio] 0.1754 -0.0409 0.6034	SE 0.2871 0.0662 0.2723	16.6% 17.8% 16.8%	IV, Random, 95% CI 1.19 [0.68, 2.09] 0.96 [0.84, 1.09] 1.83 [1.07, 3.12]	Odds Ratio
Study or Subgroup Bazarganipour 2013 Biringer 2015 Klemetti 2010 Salih 2017	log[Odds Ratio] 0.1754 -0.0409 0.6034	SE 0.2871 0.0662	16.6% 17.8% 16.8% 17.7%	IV, Random, 95% Cl 1.19 [0.68, 2.09] 0.96 [0.84, 1.09]	Odds Ratio
Study or Subgroup Bazarganipour 2013 Biringer 2015 Klemetti 2010	log[Odds Ratio] 0.1754 -0.0409 0.6034 1.7726	SE 0.2871 0.0662 0.2723	16.6% 17.8% 16.8% 17.7%	IV, Random, 95% CI 1.19 [0.68, 2.09] 0.96 [0.84, 1.09] 1.83 [1.07, 3.12]	Odds Ratio
Study or Subgroup Bazarganipour 2013 Biringer 2015 Klemetti 2010 Salih 2017	log[Odds Ratio] 0.1754 -0.0409 0.6034 1.7726	SE 0.2871 0.0662 0.2723 0.1047 0.2462	16.6% 17.8% 16.8% 17.7% 17.0%	IV, Random, 95% CI 1.19 [0.68, 2.09] 0.96 [0.84, 1.09] 1.83 [1.07, 3.12] 5.89 [4.79, 7.23]	Odds Ratio
Study or Subgroup Bazarganipour 2013 Biringer 2015 Klemetti 2010 Salih 2017 Salomao 2018	log[Odds Ratio] 0.1754 -0.0409 0.6034 1.7726 0.1513 0.4085	SE 0.2871 0.0662 0.2723 0.1047 0.2462 0.544	16.6% 17.8% 16.8% 17.7% 17.0% 14.0%	IV, Random, 95% CI 1.19 [0.68, 2.09] 0.96 [0.84, 1.09] 1.83 [1.07, 3.12] 5.89 [4.79, 7.23] 1.16 [0.72, 1.88] 1.50 [0.52, 4.37] 1.68 [0.71, 3.98]	Odds Ratio

Forest plot depicting the psychological impact of int

495x481mm (38 x 38 DPI)

Search strategy

PubMed

- 1. infertil*[Title/Abstract]
- 2. prevalence[Title/Abstract]
- (#1) AND (#2) 3.
- 4. risk factor
- (#1) AND (#4) 5.
- 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) eliez
- 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

Pag	ge 27 of 29		BMJ Open	136/br	
1 2	PRISMA 2020) for A	bstracts Checklist		
3 4 5	Section and Topic	ltem #	Checklist item		Reported (Yes/No)
6	TITLE			3	
7	Title	1	Identify the report as a systematic review.	5 2	Yes
8 9	BACKGROUND			M	
10	Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addra	sses.	Yes
11	METHODS			¢0¢	
12 13	Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	י ר	Yes
14 15	Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies a was last searched.	and the date when each	Yes
16	Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.		Yes
17 18	Synthesis of results	6	Specify the methods used to present and synthesise results.	from	Yes
19	RESULTS			htt	
20 21	Included studies	7	Give the total number of included studies and participants and summarise relevant	haracteristics of studies.	Yes
22 23 24	Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included stug each. If meta-analysis was done, report the summary estimate and confidence/cred groups, indicate the direction of the effect (i.e. which group is favoured).		Yes
25	DISCUSSION				
26 27 28	Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.e. inconsistency and imprecision).	study risk of bias,	Yes
29	Interpretation	10	Provide a general interpretation of the results and important implications.		Yes
30 31	OTHER			0	
32	Funding	11	Specify the primary source of funding for the review.	200	N/R
33	Registration	12	Provide the register name and registration number.		Yes
34 35 36 37 38 39 40 41 42 43 44 45 46 47	<i>From:</i> Page MJ, McKenzie reviews. BMJ 2021;372:n71.	JE, Bos doi: 10.	suvt PM_Boutron I_Hoffmann TC_Mulrow CD_et al_The PRISMA 2020 statement: an und	÷	systematic



47

PRISMA 2020 Checklist

		BMJ Open 1366	Page 28 of
PRISM	/A 20)20 Checklist	
		020 Checklist	
Section and Topic	ltem #	Checklist item	Location where item is reported
TITLE		0 0	
Title	1	Identify the report as a systematic review.	1
ABSTRACT		<u> </u>	
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTION	1	Describe the rationale for the review in the context of existing knowledge	
Rationale	3		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:oertainty (or:oo/tfidgoca) in the body of evidence:forcanioutcome	+

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PRISMA 2020 Checklist

Section and Topic	ltem #	Checklist item		Location where iter is reporte
assessment				
RESULTS		ے پر		
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the and the review, ideally using a flow diagram.	umber of studies included in	Fig 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were	cluded.	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 (e.g. confidence/credible interval), ideally using structured tables or plots.	t estimate and its precision	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 estimation confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of		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 asses	d.	-
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.		-
DISCUSSION		n on		
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 INFORMA	ΓΙΟΝ	ьу		
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the read	ew 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 $lpha$	view.	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 studies; data used for all analyses; analytic code; any other materials used in the review.	a extracted from included	15

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For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml 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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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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R. O.

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 randomeffects 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 BMJ Open: first published as 10.1136/bmjopen-2021-057132 on 30 March 2022. Downloaded from http://bmjopen.bmj.com/ on April 19, 2024 by guest. Protected by copyright

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

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

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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 Englishlanguage 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

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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.

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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 I² 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 Page 9 of 29

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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 crosssectional, 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; I² = 100%) (Figure 1). The lowest prevalence (18%) of primary infertility was reported in a hospital-

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based study ²⁷, and the highest prevalence (91.1%) was observed in both community- and hospitalbased studies conducted in Iran¹⁸ (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; I² = 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 metaregression 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

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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

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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	Sample	Female	Quality
			Design	Size	infertility	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

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18	Aydin et al.,	Istanbul,	cross-	88	88	87.5
	2015 ²⁵	Turkey	sectional			
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

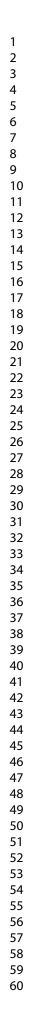
Figure 1: Flow diagram showing the included studies for systemic review and meta-analysis on the prevalence, risk factors, and psychological impact of infertility among women

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

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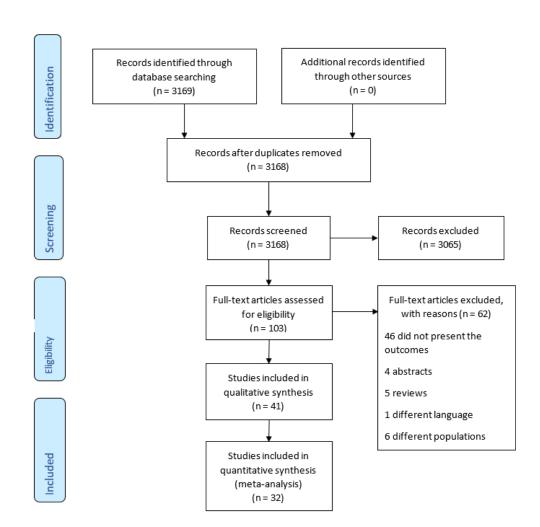


Figure 1: Flow diagram showing the included studies for systemic review and meta-analysis on the prevalence, risk factors, and psychological impact of infertility among women

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				Prevalence		Preva	lence
Study or Subgroup	Prevalence	SE	Weight	IV, Random, 95% CI		IV, Rando	m, 95% CI
Acmaz 2013	64.7	4.1	4.1%	64.70 [56.66, 72.74]			
Aggarwal 2013	53.4	2.2	4.2%	53.40 [49.09, 57.71]			+
Akalewold 2022	27.6	2.2	4.2%	27.60 [23.29, 31.91]			+
Albayrak 2007	50	2.9	4.2%	50.00 [44.32, 55.68]			-
Alosaimi 2015	50.7	2.5	4.2%	50.70 [45.80, 55.60]			-
Bai 2019	79.3	2.3	4.2%	79.30 [74.79, 83.81]			-
Bakhtiyar 2019	25	1.6	4.2%	25.00 [21.86, 28.14]			+
Baldur 2013	45.5	0.2	4.2%	45.50 [45.11, 45.89]			•
Bazarganipour 2013	79.3	2.3	4.2%	79.30 [74.79, 83.81]			-
Begum 2014	50	4.6	4.1%	50.00 [40.98, 59.02]			-
Biringer 2015	13.5	0.3	4.2%	13.50 [12.91, 14.09]			•
Bringhenti 1997	68.2	3.5	4.1%	68.20 [61.34, 75.06]			-
Downey 1992	58.7	3.5	4.1%	58.70 [51.84, 65.56]			-
Guz 2003	50	5	4.0%	50.00 [40.20, 59.80]			
Klemetti 2010	10.4	0.6	4.2%	10.40 [9.22, 11.58]			•
Lansakara 2011	50	2.7	4.2%	50.00 [44.71, 55.29]			+
Matsubaya 2001	55.5	3.7	4.1%	55.50 [48.25, 62.75]			-
Noorbala 2009	50	2.9	4.2%	50.00 [44.32, 55.68]			-
Omani 2017	47.8	2.8	4.2%	47.80 [42.31, 53.29]			-
Salih 2017	13.1	0.6	4.2%	13.10 [11.92, 14.28]			•
Salomao 2018	50	3	4.2%	50.00 [44.12, 55.88]			-
Sbaragli 2008	27.2	2.6	4.2%	27.20 [22.10, 32.30]			+
Tarlatzis 1993	79.3	4.3	4.1%	79.30 [70.87, 87.73]			-
Volgsten 2008	14.8	1.2	4.2%	14.80 [12.45, 17.15]			•
Total (95% CI)			100.0%	46.25 [37.73, 54.77]			•
Heterogeneity: Tau ² =	444.95; Chi ² =	1242	2.90, df=	23 (P < 0.00001); I ² = 100%	-100	1	
Test for overall effect: 2					-100	-50 (0 50 100
							mendity

2A. Forest plot for the prevalence of infertility

				Prevelance		Pr	revelance
Study or Subgroup	Prevelance	SE	Weight	IV, Random, 95% CI		IV, Ra	ndom, 95% Cl
Alhassan 2014	38	4.85	10.9%	38.00 [28.49, 47.51]			
Aydin 2015	73.9	4.68	10.9%	73.90 [64.73, 83.07]			
Bakhtiyar 2019	91.1	2.12	11.2%	91.10 [86.94, 95.26]			-
Baldur 2013	72.3	0.21	11.2%	72.30 [71.89, 72.71]			-
Biringer 2015	20.6	0.98	11.2%	20.60 [18.68, 22.52]			-
Bringhenti 1997	18	3.48	11.1%	18.00 [11.18, 24.82]			
Diamond 2017	54	1.25	11.2%	54.00 [51.55, 56.45]			•
Klemetti 2010	21.3	2.65	11.1%	21.30 [16.11, 26.49]			-
Salomao 2018	74.3	3.69	11.1%	74.30 [67.07, 81.53]			-
Total (95% CI)			100.0%	51.50 [32.74, 70.26]			•
Heterogeneity: Tau ² =	815,13; Chi ² =	3518	.96, df = 8	3 (P < 0.00001); I ² = 100%	-100	-50	0 50 10
	,	Heterogeneity: Tau ² = 815.13; Chi ² = 3518.96, df = 8 (P < 0.00001); l ² = 100% Test for overall effect: Z = 5.38 (P < 0.00001)					

2B. Forest plot for the prevalence of primary infertility

Figure 2: Forest plot depicting the prevalence of infertility

435x480mm (38 x 38 DPI)

				Odds Ratio		Odds Ratio	
Study or Subgroup	log[Odds Ratio]			IV, Random, 95% CI		IV, Random, 95% Cl	
Bakhtiyar 2019	-0.0938	0.1821	30.8%	0.91 [0.64, 1.30]			
Klemetti 2010		0.1599	34.8%	1.40 [1.03, 1.92]			
Lansakara 2011		0.2208	24.9%	1.21 [0.79, 1.87]			
Salomao 2018	-0.4447	0.427	9.4%	0.64 [0.28, 1.48]			
Total (95% CI)			100.0%	1.10 [0.83, 1.45]		+	
Heterogeneity: Tau ² =	: 0.03; Chi² = 5.12, I	df = 3 (P	= 0.16); P	²= 41%	0.2		÷
Test for overall effect:	Z = 0.67 (P = 0.50)				0.2	Favours infertility Favours fertility	5
3A. Forest plot for	the association	betwe	en age a	and female infertil	ity		
				Odds Ratio		Odds Ratio	
Study or Subgroup	log[Odds Ratio]	SE	Weight	IV, Random, 95% CI		IV, Random, 95% Cl	
Biringer 2015	0.2509	0.0524	37.2%	1.29 [1.16, 1.42]		-	
Klemetti 2010	0.0097	0.1464	21.9%	1.01 [0.76, 1.35]		+	
Salih 2017	-0.0676	0.1039	28.6%	0.93 [0.76, 1.15]			
Salomao 2018	0.2441	0.2399	12.2%	1.28 [0.80, 2.04]			
Total (95% CI)			100.0%	1.11 [0.91, 1.35]		•	
Heterogeneity: Tau ² =	: 0.02; Chi ² = 8.90,	df = 3 (P	= 0.03); P	²= 66%	0.2	0.5 1 2	
Test for overall effect:	Z = 1.06 (P = 0.29)				0.2	Favours infertility Favours fertility	5
3B. Forest plot for	the association	betwe	en body	mass index and f	emale	e infertility	
				Odds Ratio		Odds Ratio	
Study or Subgroup	log[Odds Ratio]	SE	Weight	IV, Random, 95% CI		IV, Random, 95% Cl	
Biringer 2015	0.3355	0.0536	35.5%	1.40 [1.26, 1.55]			
Klemetti 2010	0.2574	0.1448	32.7%	1.29 [0.97, 1.72]		+-■	
Salih 2017	1.2891	0.1652	31.8%	3.63 [2.63, 5.02]			_
Total (95% CI)			100.0%	1.85 [1.08, 3.14]			
Heterogeneity: Tau ² =	: 0.20; Chi ² = 31.36	, df = 2 (F	o < 0.000	01); I² = 94%	0.2	0.5 1 2	<u> </u>

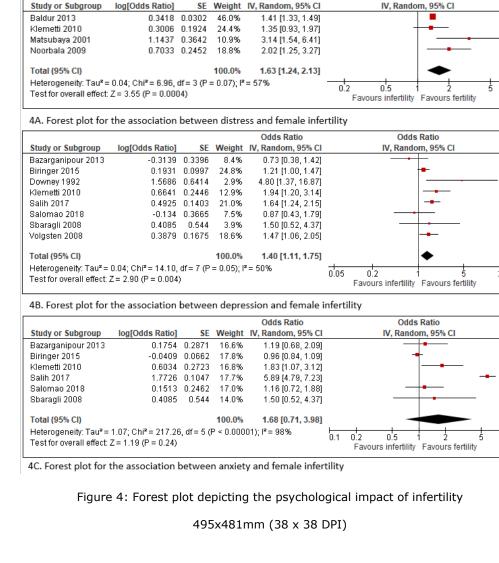
3C. Forest plot for the association between smoking and female infertility

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

489x411mm (38 x 38 DPI)

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or Subgroup	log[Odds Ratio]	\$F	Weight	Odds Ratio IV, Random, 95% CI	Odds Ratio IV, Random, 95% Cl
r 2013	0.3418		46.0%	1.41 [1.33, 1.49]	
etti 2010		0.1924	24.4%	1.35 [0.93, 1.97]	+
baya 2001 ala 2009		0.3642 0.2452	10.9% 18.8%	3.14 [1.54, 6.41] 2.02 [1.25, 3.27]	
			100.0%		
(95% CI) odeneity: Tau² =	0.04; Chi² = 6.96,	df = 3 (P =		1.63 [1.24, 2.13] = 57%	
	Z = 3.55 (P = 0.000				0.2 0.5 1 2 5 Favours infertility Favours fertility
orest plot for	the association	betwee	n distre	ss and female infe	rtility
				Odds Ratio	Odds Ratio
or Subgroup	log[Odds Ratio]			IV, Random, 95% CI	IV, Random, 95% Cl
ganipour 2013 er 2015		0.3396 0.0997	8.4% 24.8%	0.73 [0.38, 1.42] 1.21 [1.00, 1.47]	
ey 1992		0.6414	24.0%	4.80 [1.37, 16.87]	
tti 2010		0.2446	12.9%	1.94 [1.20, 3.14]	
2017		0.1403	21.0%	1.64 [1.24, 2.15]	
iao 2018 gli 2008	-0.134 0.4085	0.3665 0.544	7.5% 3.9%	0.87 [0.43, 1.79] 1.50 [0.52, 4.37]	
en 2008		0.1675	18.6%	1.47 [1.06, 2.05]	
95% CI)			100.0%	1.40 [1.11, 1.75]	▲
geneity: Tau² =	0.04; Chi² = 14.10, Z = 2.90 (P = 0.004				0.05 0.2 1 5 20
					Favours infertility Favours fertility
prest plot for	the association	betwee	n aepre	ssion and female i	Odds Ratio
or Subgroup	log[Odds Ratio]	SE	Weight	IV, Random, 95% CI	IV, Random, 95% CI
ganipour 2013		0.2871	16.6%	1.19 [0.68, 2.09]	•
er 2015 etti 2010		0.0662	17.8% 16.8%	0.96 [0.84, 1.09] 1.83 [1.07, 3.12]]
2017		0.1047	17.7%	5.89 [4.79, 7.23]	
nao 2018		0.2462	17.0%	1.16 [0.72, 1.88]	
gli 2008	0.4085	0.544	14.0%	1.50 [0.52, 4.37]	
(95% CI) ogeneity: Tau² =	1.07; Chi² = 217.2	6, df= 5 (l	100.0% P < 0.000	1.68 [0.71, 3.98] 01); I ² = 98%	
or overall effect:)	Z = 1.19 (P = 0.24)				Favours infertility Favours fertility
prest plot for t	the association	betwee	n anxiet	y and female infer	tility
Figure	e 4: Forest p	lot de	picting	g the psycholo	gical impact of infertility
		495	5v481	mm (38 x 38 [
		475	774011	IIII (30 × 30 I	J 1)
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Search strategy

PubMed

- 1. infertil*[Title/Abstract]
- 2. prevalence[Title/Abstract]
- (#1) AND (#2) 3.
- 4. risk factor
- (#1) AND (#4) 5.
- 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) eliez
- 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

Pag	ge 27 of 29		BMJ Open	136/br	
1 2	PRISMA 2020	0 for A	bstracts Checklist		
3 4 5	Section and Topic	ltem #	Checklist item		Reported (Yes/No)
6	TITLE			3	
7	Title	1	Identify the report as a systematic review.	5 2	Yes
8 9	BACKGROUND			M	
10	Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addra	sses.	Yes
11	METHODS			¢0¢	
12 13	Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	י ר	Yes
14 15	Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies a was last searched.	and the date when each	Yes
16	Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.		Yes
17 18	Synthesis of results	6	Specify the methods used to present and synthesise results.	from	Yes
19	RESULTS			htt	
20 21	Included studies	7	Give the total number of included studies and participants and summarise relevant	haracteristics of studies.	Yes
22 23 24	Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included stug each. If meta-analysis was done, report the summary estimate and confidence/cred groups, indicate the direction of the effect (i.e. which group is favoured).		Yes
25	DISCUSSION				
26 27 28	Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.e. inconsistency and imprecision).	study risk of bias,	Yes
29	Interpretation	10	Provide a general interpretation of the results and important implications.		Yes
30 31	OTHER			0	
32	Funding	11	Specify the primary source of funding for the review.	200	N/R
33	Registration	12	Provide the register name and registration number.		Yes
34 35 36 37 38 39 40 41 42 43 44 45 46 47	<i>From:</i> Page MJ, McKenzie reviews. BMJ 2021;372:n71.	JE, Bos doi: 10.	suvt PM_Boutron I_Hoffmann TC_Mulrow CD_et al_The PRISMA 2020 statement: an und	÷	systematic



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PRISMA 2020 Checklist

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PRISM	/A 20)20 Checklist	
)20 Checklist	
Section and Topic	ltem #	Checklist item	Location where item is reported
TITLE		0 0	
Title	1	Identify the report as a systematic review.	1
ABSTRACT		<u> </u>	
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTION		Describe the rationale for the review in the context of existing knowledge	
Rationale	3		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 bias escience)	6
Certainty	15	Describe any methods used toeassessecortainty (or or intide or a) in the doody of a vidence for lanious coment	+

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PRISMA 2020 Checklist

Section and Topic	ltem #	Checklist item		Location where iter is reporte
assessment		<u> </u>		
RESULTS		2 2		
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the and the review, ideally using a flow diagram.	umber of studies included in	Fig 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded	luded.	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 (e.g. confidence/credible interval), ideally using structured tables or plots.	estimate and its precision	Fig 2-5
Results of	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.		Fig 1
syntheses	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimation confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of		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 asses	d.	-
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.		-
DISCUSSION		9 9		
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 INFORMA	TION	ьу		
Registration and	24a	Provide registration information for the review, including register name and registration number, or state that the register	ew was not registered.	2
protocol	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 $lpha$	view.	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 studies; data used for all analyses; analytic code; any other materials used in the review.	a extracted from included	15

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