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Premature Ovarian Insufficiency Is Associated with Increased Risk of Depression, Anxiety, and Poor Life Quality: A Systematic Review and Meta-analysis

ABSTRACT

Background: Premature ovarian insufficiency (POI) seriously affects the reproductive health of women. Several studies have been conducted to show that POI appears to be associated with psychological and psychosocial problems, but whether POI increases the risk of mental health problems has not been identified. Therefore, this meta-analysis provides a preliminary systematic assessment of the studies published to date on the impact of POI on women's mental health.

Methods: We implemented a systematic search for studies on this topic up to October 2022. Pooled odds ratios (ORs) and 95% confident intervals (CIs) of prevalence were used to assess the impacts of POI on various psychological factors, and the publication bias was assessed by Egger's test.

Results: A total of 15 articles comprising 5820 participants were included in this meta-analysis. POI was found to be related to higher risk of 13 psychological and psychosocial problems identified and classified into 3 domains: depression (OR = 1.61; 95% CI: 1.11-2.33), anxiety (OR = 3.74; 95% CI: 1.78-7.87), and poor life quality (OR = 2.55, 95% CI: 1.63-3.97).

Conclusion: This meta-analysis reveals that women with POI have an increased risk of depression, anxiety, and poor life quality. The marital status of POI may be a possible influencing factor for depression, meaning that the unmarried status in POI is at high risk of psychological and psychosocial problems. We should pay attention to the mental health of women with POI who were unmarried.

Keywords: Premature ovarian insufficiency, depression, anxiety, poor life quality, meta-analysis

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Introduction

Premature ovarian insufficiency (POI) and other well-known disease premature ovarian failure (POF) are defined as the loss of normal ovarian functions prior to 40 years of age.[1] According to the results of a meta-analysis, the global pooled prevalence of POI was calculated as 3.7% with a 95% confident interval (CI) of 3.1%-4.3%.[2] These 2 diseases would deteriorate the fertility of women at their reproductive age and lead to higher risks of osteoporosis, cardiovascular diseases, and autoimmune diseases.[3-6] Further, POI and POF may increase the risk of psychiatric disorders and significantly impact life quality.[7-11]

Women with POI/POF often suffer from estrogen deficiency, which in turn is strongly correlated with cognitive impairment, and cognitive impairment is inextricably linked to mental health issues such as depression and anxiety.[12,13] The depression has caused a significant impact on individuals worldwide and the greatest burden of disease among mental disorders.[14] Therefore, an increasing number of scholars have paid attention to mental health issues such as depression in patients with POI/POF in recent years. A study of structured clinical interview[10] revealed that the lifetime prevalence of major depressive disorder in women with POI was 54.5%, considerably higher than that in either community- or clinic-based samples.[15]

Gibson-Helm et al[16] reported that the incidences of depression was 24% and 41% in women with idiopathic and iatrogenic POI, respectively. Previous studies have also demonstrated that women with POI would suffer more frequent and severe symptoms of depression than age-matched women without POI.[7,17] Unlike women who do not suffer from POI, the symptoms of depression were not limited to the period of their transition through perimenopause in patients with POI.[18] Another key factor associated with the prevalence of depression is marital status, and some previous studies have repeatedly shown that people who are divorced, separated, single, and widowed have poorer mental health than married women.[19,20] As estrogen plays a significant role in modulating neurotransmitter signaling in the emotional circuits, its deficiency may result in higher risk of depression in women with POI.[21,22] However, POI/POF are relatively rare conditions and most longitudinal cohort and case–control studies enrolled a relatively small number of POI/POF women. The impact of POI/POF on depression remains poorly characterized.

Considering the high comorbidity rates between depression and anxiety,[23] POI/POF might also be associated with anxiety symptoms. Loss of fertility is highly distressing and increases the risk of psychological problem, including anxiety, in women with POI/POF.[17,24] Women with both idiopathic and iatrogenic POI exhibited more severe anxiety than women without POI.[16,25] However, a recent study showed that the severity of anxiety among women with POI was not significantly different from age-matched women without POI.[7] A meta-analysis is therefore necessary to clarify the association between POI/POF and anxiety risk.

As an ongoing stressor, the infertility as a result of POI/POF has been associated with poor life quality (QoL) including fatigue, guilt, grief, loneliness, insomnia and other negative psychological experiences. Poor QoL could be considered as a broad and multidimensional subjective evaluation of one's negative aspects of life.[26] A qualitative study showed that disease and distorted self-concept could affect the biopsychosocial health of women with POI.[27] Patients with POI showed worse QoL and sexual function than age-matched women without POI,[28] and nearly half of the women with POF requested psychological support about their life quality.[29] A meta-analysis associated POI and poor QoL with low-to-medium effect size;[30] the odds ratio (OR), however, has not yet been reported. Therefore, it's necessary to systematically evaluate the strength of association of risk of poor QoL and POI/POF. Identifying whether women with POI/POF have a higher risk for poor QoL could benefit for patients on timely psychological and psychosocial interventions.

The psychological and psychosocial problems of women with POI/POF are complex and involve multiple manifestations of depression, anxiety, loss of self-esteem, poor QoL, and so on. A meta-analysis to clarify the risks of depression, anxiety and poor QoL would facilitate coordinated medical interventions for women with POI/POF. In this study, we aimed to systematically review the association of POI/POF with depression, anxiety and poor life quality, and to provide a quantitative estimate of these risks.

MAIN POINTS

- *Patients with premature ovarian insufficiency (POI) have an increased risk of depression, anxiety, and poor life quality.*
- *Women with POI who were unmarried have a high risk of depression.*
- *When treating POI, it is important to focus not only on the disease itself, but also on the impact this illness might have on a patient's mental health.*

Material and Methods

Literature Search Strategy

This meta-analysis followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.[29] A systematic review and literature search were performed up to October 31, 2022. PubMed, Web of Science, Embase, China National Knowledge Infrastructure (CNKI), and Wanfang Database were used to carried out the search. All potentially relevant articles were identified by 2 authors (Y.T. and H.D.). We only considered studies published in either English or Chinese. The protocol of this study was registered on INPLASY, and the number is INPLASY202310020. This is a systematic review and ethical approval is not necessary.

We searched with following key words: "psychology" or "psychological" or "mental" or "psychosocial" or "psychologically" or "mood" or "depression" or "anxiety" or "pressure" or "stress" or "insomnia" or "sleeplessness" or "poor sleep" or "positive mindset" or "fatigue" or "well-being" or "self-esteem" or "quality of life" and "premature ovarian insufficiency" or "premature ovarian failure" or "diminished ovarian reserve" or "premature menopause", a more detailed search strategy see Supplementary Materials. In addition, references cited in the related articles were also screened to identify relevant studies.

Inclusion and Exclusion Criteria

Two researchers independently conducted literature screening and data extraction using a standardized form to include studies that met the inclusion criteria. All discrepancies were discussed and resolved with the other authors. The inclusion criteria were as follows: (1) the study was randomized controlled trials, cohort, case–control, or observational studies; (2) clear diagnosis of biochemical POI/POF, which is defined as the cessation of normal ovarian function in women before age 40 years; (3) studies reported the clinical psychological and psychosocial symptoms, including depression, anxiety, self-esteem, fatigue, pressure, sleep quality, and quality of life; (4) the article included the biochemical POI/POF patients with organic disease of nervous system; (5) intervention studies are eligible only if pre-intervention data were available; (6) ORs/relative risks (RRs) and CIs were recorded or raw data available from which ORs and 95% CI could be calculated.

The exclusion criteria were as follows: (1) the biochemical POI/POF diagnosis was unclear or with no clear explanation as to how disease were diagnosed; (2) clinical data were lacking; (3) the experimental group were not biochemical POI/POF patients; (4) the article included the biochemical POI/POF patients with organic disease of nervous system; (5) duplicated records; and (6) the article was not empirical study (news reports, case reports, expert comments, reviews).

Data Extraction and Quality Assessment

Data extraction was performed independently by 2 researchers. First author's name, year of publication, nation, research type, sample size, ratio of unmarried status in POI/POF, mean age, source of subjects, clinical characteristics, as well as ORs and 95% CI of psychological

and psychosocial symptoms were recorded. The ratio of unmarried status in POI/POF was defined as the percentage of people who were divorced, separated, single and widowed among patients with POI/POF. If a study did not present the OR values, We calculated the OR value = odds of case exposure/odds of control exposure with the raw data. The quality of eligible studies was evaluated by the Newcastle-Ottawa Scale (NOS) score,[31] with a range of 0 to 9. Studies with a score of more than 4 were eligible for inclusion. An included study score of 7-9 points was considered a high-quality study, 5-6 points was considered a moderate-quality study, and 0-4 points was considered a low-quality study. If there is a potential dispute between 2 researchers regarding the inclusion and evaluation of an article, the rest of the authors could be the arbitrators.

Statistical Analysis

All statistical analyses in the present study were conducted with Comprehensive Meta-Analysis software (CMA) version 3.0 (Biostat, Inc., Englewood, NJ, USA).[32] Pooled ORs value and 95% CI as the main indices were used to assess potential impact of POI on various psychological factors, and a *P*-value less than 0.05 was considered to be statistically significant. Between-study heterogeneity was evaluated by Q test and I^2 statistic. If I^2 was greater than 50%, between study heterogeneity was considered to be significant and the random-effects model was applied. We then conducted subgroup analysis and meta-regression analyses to explore heterogeneity in effect sizes. The publication bias was assessed by Egger's test and funnel plot.[33] If publication bias was shown, we used the trim and fill method to evaluate the influence of bias on the obtained results. A sensitivity analysis using the leave-one-out method was carried out to assess the stability of meta-analysis.

Results

Description of the Included Studies

We identified 424 studies concerning the psychological and psychosocial problems associated with POI/POF. After removing duplications and applying the inclusion/exclusion criteria, a total of 15 studies were identified, including 5820 participants with 1761 POI patients and 4059 controls. The detailed screening process of included articles was presented in Figure 1. Of the 15 studies, 9 were case–control studies, and the remaining 6 were cross-sectional studies.[7,8,10,16,24,34-43] Of the 15 studies, 6 studies were conducted in America, 3 in China, 2 in Brazil, and 1 each in Australia, Turkey, Kuwait, and Sweden. The characteristics of all the studies are presented in Table 1. The subgroup analysis of research type, survey method and country-type were conducted. Also, meta regression analysis of

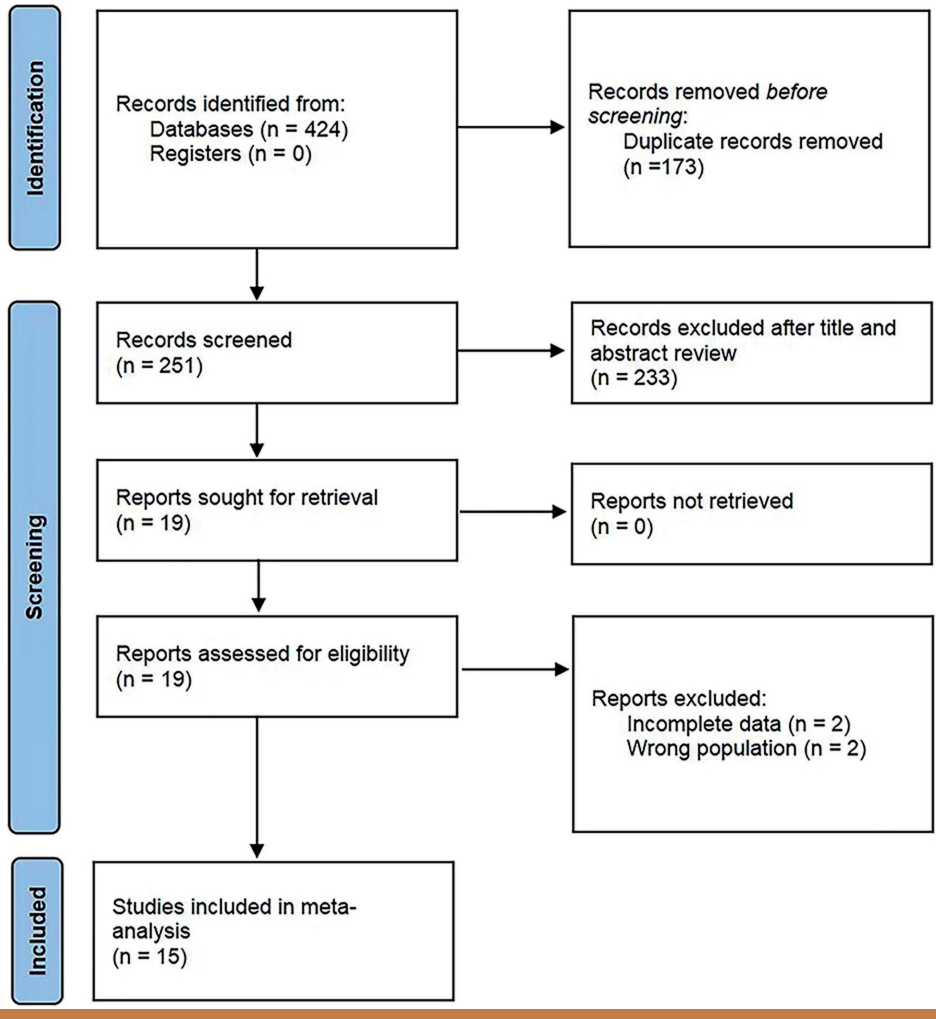

Figure 1. The study selection process.

Table 1. Characteristics of 15 Studies Included in the Meta-analysis

Author	Year	Nation	Research Type	n (POI/POF)	n (Control)	Age (POI/POF)	Age (Control)	Ratio of Unmarried Status in POI/POF	Source of Subject	Psychological and Psychosocial Factors	Survey Method	NOS
Ventura et al[38]	2007	USA	Case–control	100	60	18-42	N/A	N/A	Hospital	Depression, anxiety	Self-report	6
Ventura et al[37]	2006	USA	Case–control	332	50	18-42	18-42	N/A	Hospital	Depression, poor concentration and loneliness	Self-report	6
Benetti-Pinto et al[8]	2011	Brazil	Case–control	58	58	39.4 ± 6.5	39.0 ± 6.8	0.224	Hospital	Negative feelings	Self-report	8
Davis et al[24]	2010	USA	Case–control	98	60	32.4 ± 5.2	31.0 ± 6.9	0.384	Community	Depression, anxiety	Self-report	9
Ates et al[7]	2022	Turkey	Case–control	62	62	37.4 ± 4.1	36.2 ± 3.4	0.177	Hospital	Depression, anxiety, fatigue	Self-report	8
Schmidt et al[10]	2011	USA	Cross-sectional	174	100	31.6 ± 5.3	34.7 ± 11.6	0.3	Hospital	Depression	Interview	8
Sun et al[35]	2022	China	Case–control	50	52	30.32 ± 6.9	29.9 ± 4.98	N/A	Hospital	Depression, anxiety, fatigue	Self-report	7
Liu et al[41]	2019	China	Case–control	63	60	37.1 ± 3.1	36.3 ± 4.2	0.238	Hospital	Depression, anxiety	Interview	8
Nicoloro-SantaBarbara et al [43]	2017	USA	Cross-sectional	51	51	34.27 ± 3.7	31.74 ± 4.88	0.098	Hospital	Depression	Self-report	8
Omu et al [34]	2016	Kuwait	Case–control	42	42	28 ± 4.2 (20 to 39)	18 to 39	0.548	Hospital	Depression, childlessness fear, divorce worry, loneliness, grief, poor concentration, guilt, regret, mood swings and aggression	Interview	7
Huang et al[39]	2021	China	Cross-sectional	293	471	33.76 ± 5.47	54.98 ± 3.65	N/A	Community	Depression, fatigue, mood swings	Self-report	9
Ida et al[40]	2021	Sweden	Cross-sectional	22	162	38.9 (22 to 56)	35 (19 to 58)	0.43	Community	Lower well being	Self-rReport	8
Gibson-Helm et al[16]	2014	Australia	Cross-sectional	25	23	29	36	0.12	Community	Depression, anxiety	Self-report	7
Vanderhoof et al[36]	2007	USA	Cross-sectional	330	2747	18-42	N/A	N/A	Hospital	Depression, panic disorder	Self-report	6
Menezes et al[42]	2020	Brazil	Case–control	61	61	35.03 ± 7.68	34.49 ± 7.55	0.213	Hospital	Depression, anxiety	Self-report	8

POI/POF, premature ovarian insufficiency/premature ovarian failure; NOS, Newcastle Ottawa Scale; N/A, not applicable.

publication year and mean age were performed. The quality of all included studies was evaluated by the quality assessment following the NOS. For more details, please see the Supplementary Table 1 in the Supplementary Materials.

Profiles of Depression in Patients with POI/POF

A total of 13 studies showed data on depression. According to the results of meta-analysis, significant heterogeneity among the results of depression was observed (I^2 = 81.13%, P < .001). Thus, a sensitivity analysis was performed to explore the studies that contributed to the heterogeneity case-by-case. The result of sensitivity analysis exhibited no alteration in the overall trend (Supplementary Figure 1A). Therefore, a random-effects model was applied to evaluate the association between POI/POF and the risk of depression. As shown in Figure 2, The pooled analysis showed women with POI/POF were more likely to have depression symptom than women without POI (OR = 2.73; 95% CI: 1.87-3.97). The Egger's test detected a significant publication bias (P = .003; Supplementary Figure 1B). By supplementing the virtual literature using the method of the trim and fill, it the association between POI/POF and risk of depression remained stable (OR = 1.61; 95% CI: 1.11-2.33).

We conducted subgroup analysis to explore the source of heterogeneity. The results revealed that the factor of survey method (interview vs. self-reported) was significant (P = .031). There was no significant effect of research type (case–control vs. cross-sectional) on depression (P = .110). The pooled OR value of developing country was higher than developed country, although not statistically significant (P = .621). For more details, please refer to Table 2. The impact of mean age and publication year on depression were evaluated by meta-regression analysis. As predictors, the ratio of unmarried status in POI/POF (b = 4.007, P = .007) was found to be an important source of heterogeneity (70%). And mean age was found to be a moderator (b = −0.042) although not significant (P = .326), which also accounted for 10% of the heterogeneity of depression (Table 3). Publication year had no significant effect.

Profiles of Anxiety in Patients with POI/POF

Eight studies were included in the analysis of anxiety. Q test and I^2 statistic showed significant heterogeneity among the results of anxiety (I^2 = 78.82%, P < .001). As with depression, the sensitivity analysis exhibited in the overall trend (Supplementary Figure 2A). Based on the random-effects model, as shown in Figure 3, the pooled OR value was 3.74 (95% CI: 1.78-7.87) for anxiety. In the Egger's test (Supplementary Figure 2B) no significant publication bias was detected (P = .074). For the subgroup analysis, the number of studies in survey method and research type couldn't meet the criterion, which the number of included studies in "Cross-sectional" or "Interview" subgroup could not reach 3. There was no significant effect of socioeconomic status (developed vs. developing country) on anxiety (P = .568). Publication year was found to be a moderator (b = −0.071, P = .299), which accounted for 10% of the heterogeneity of anxiety through the meta-regression analysis (Table 3).

Profiles of Poor Life Quality in Patients with POI/POF

QoL was defined as subjective evaluation of negative aspects of life. Eight studies referring to QoL among women with POI/POF were

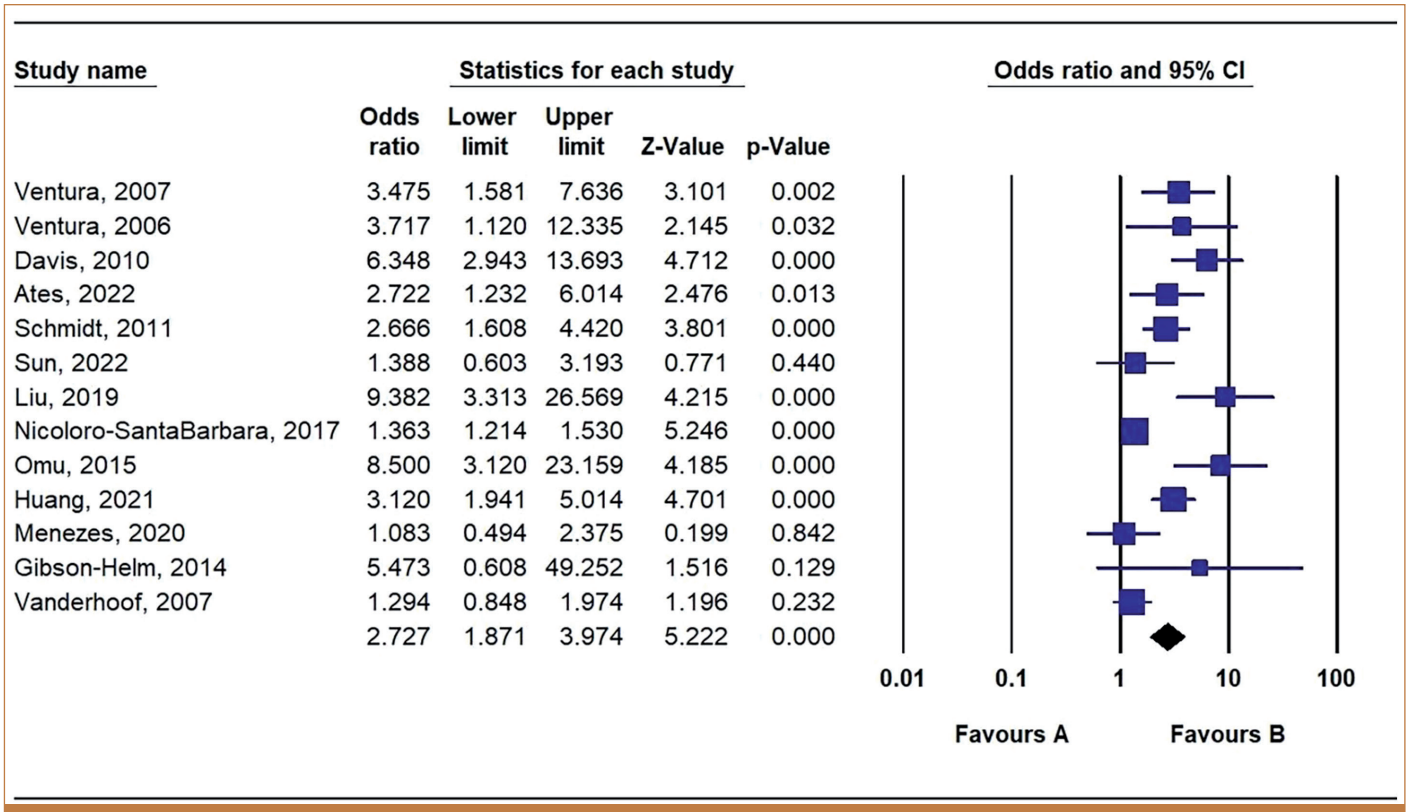

Figure 2. Forest plots for the association between POI/POF and risk of depression (random-effects model). The squares and diamonds represent individual studies and pooled effect sizes, respectively. And the lines represent 95% CIs for each main study. POI/POF, premature ovarian insufficiency/premature ovarian failure; CIs, confident intervals.

Table 2. Subgroup Analysis of the Depression for Women with POI/POF

Category	Subgroup	Number of Studies	Effect Size (95% CI)	I^2	*P*	
Survey method	Interview	3	5.63 (2.53-12.56)	64.85	*P*<.001	.031
	Self-report	10	2.15 (1.50-3.07)	72.18	*P*<.001	
Research-type	Case-control	8	3.45 (1.98-6.02)	68.52	*P*<.001	.110
	Cross-sectional	5	1.95 (1.28-2.96)	78.20	*P*<.01	
Country-type	Developed country	7	2.48 (1.56-3.94)	79.64	*P*<.001	.621
	Developing country	6	3.01 (1.63-5.57)	72.90	*P*<.001	

POI/POF, premature ovarian insufficiency/premature ovarian failure; CIs, confident intervals.

Table 3. Results of Meta-regression Analysis of the Depression Anxiety and Poor Life Quality for Women with POI/POF

Predictors	Number of Studies	Tau^2	I^2	*Q*	R^2	*b*	Test of Predictors (*P*)
Ratio of unmarried status to depression	8	0.54	85.60%	48.60	70%	4.007	.007**
Age to poor life quality	11	0.43	85.33%	68.18	26%	−0.030	.282
Age to depression	13	0.32	81.13%	63.59	10%	−0.042	.326
Publication year to anxiety	8	0.87	78.82%	33.04	10%	−0.071	.299

**Indicates that this *P*-value is <.01.
POI/POF, premature ovarian insufficiency/premature ovarian failure.

identified for the meta-analysis. A total of 13 factors associated with poor QoL were clarified, which included fatigue, lower well-being, panic disorder, negative feeling, childlessness fear, divorce worry, loneliness, grief, poor concentration, guilt, regret, mood swings, and aggression. As the study of Omu et al (2016) considered serval aspects of poor QoL as influenced by POI/POF, we computed a pooled OR value (OR=7.59; 95% CI: 4.99-11.54) of this article (Supplementary Figure 3). Similarly, significant heterogeneity was observed in the QoL data (I^2=85.33%, *P* < .001). After omitting one study at a time, the sensitivity analysis revealed the stability of this result (Supplementary Figure 4A). Then, the association between POI/POF and QoL was assessed by the random-effects model. As shown in Figure 4, the pooled OR of the 8 studies (OR=2.55; 95% CI: 1.63-3.97) showed that the diagnose of POI/POF was a risk factor for the poor QoL. No publication bias (Supplementary Figure 4B) was observed for QoL (*P*=.516).

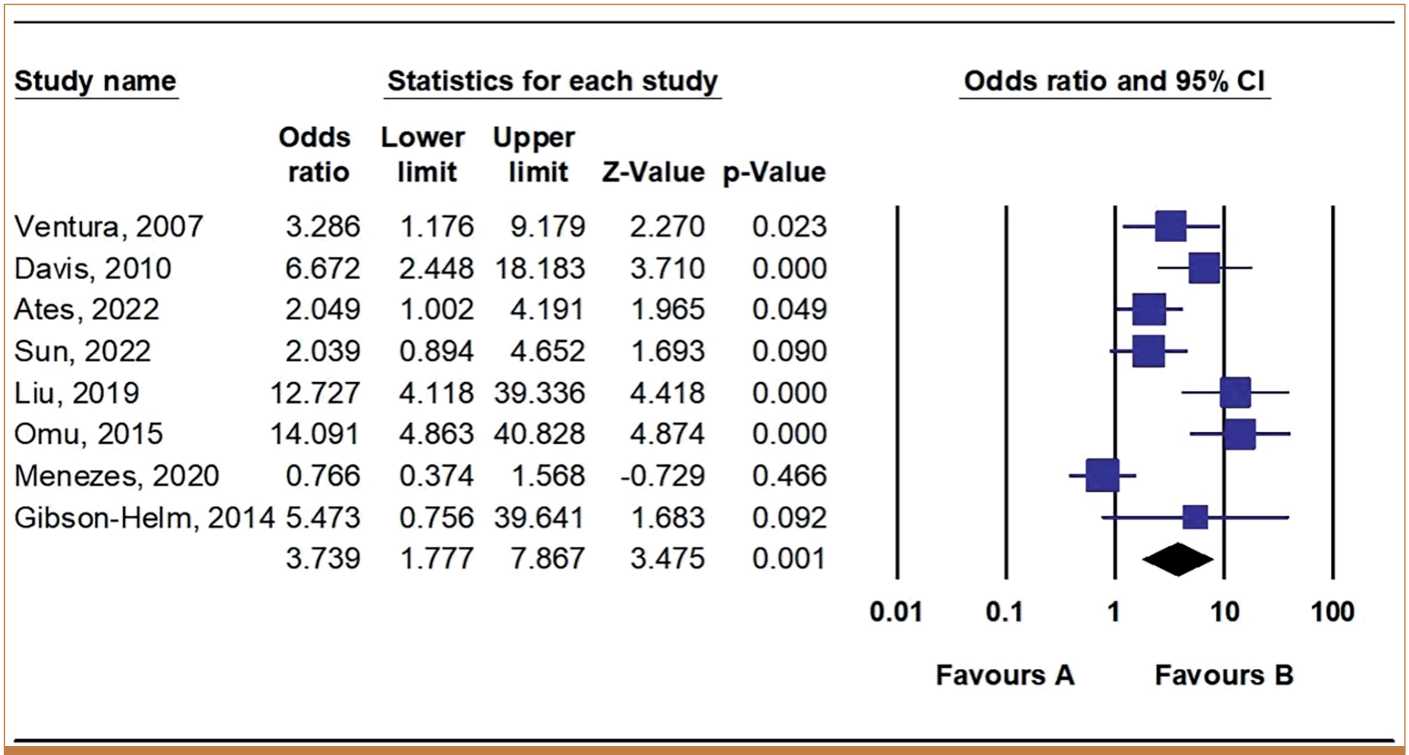

Figure 3. Forest plots for the association between POI/POF and risk of anxiety (random-effects model). The squares and diamonds represent individual studies and pooled effect sizes, respectively. And the lines represent 95% CIs for each main study. POI/POF, premature ovarian insufficiency/premature ovarian failure; CIs, confident intervals.

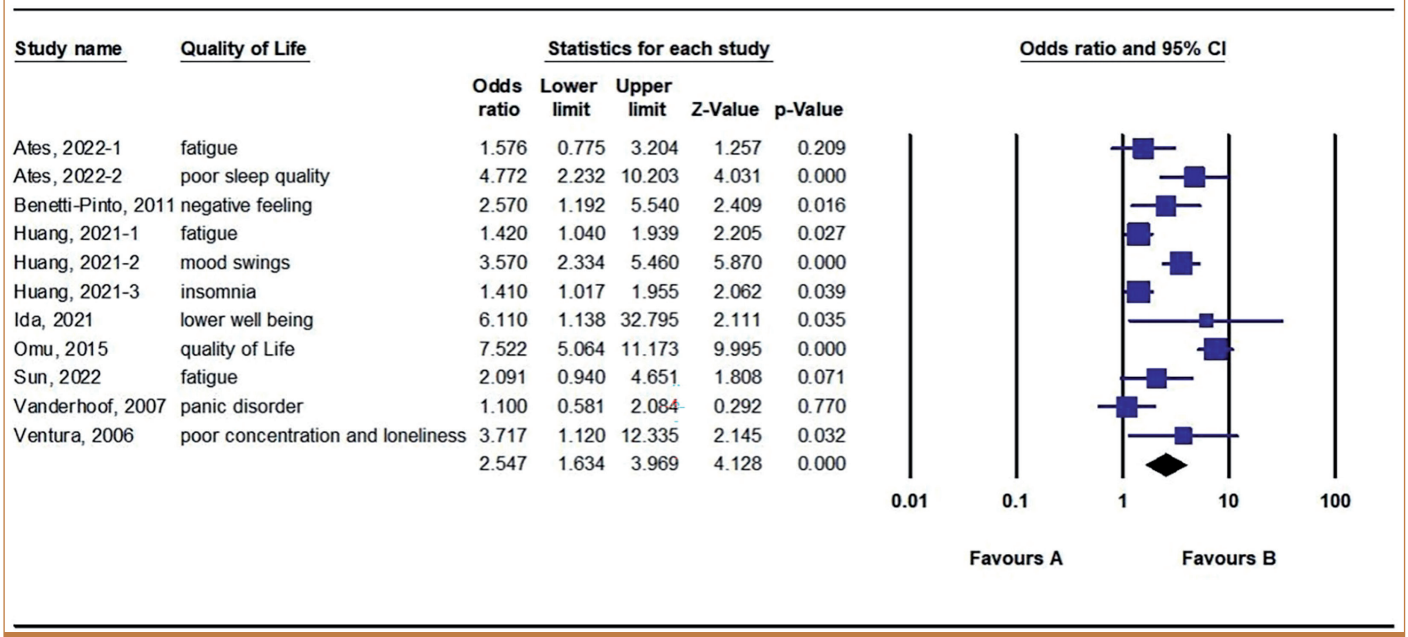

Figure 4. Forest plots for the association between POI/POF and risk of poor life quality (random-effects model). The squares and diamonds represent individual studies and pooled effect sizes, respectively. And the lines represent 95% CIs for each main study. POI/POF, premature ovarian insufficiency/premature ovarian failure; CIs, confident intervals.

Results of subgroup analysis showed the effect of survey method (interview vs. self-reported) and socioeconomic status (developed vs. developing country) was not significant (all *P*'s > .05). And subgroup analysis of research type (case–control vs. cross-sectional) could not meet the criterion as number of included studies is insufficient. According to results of meta-regression analysis, mean age was found to be a moderator ($b = -0.030$) although not significant ($P = .282$), which accounted for 26% of the heterogeneity of poor QoL. For more details, please refer to Table 3.

Discussion

POI/POF negatively affects women's psychological and psychosocial health in a nonnegligible way. In this study, we performed the meta-analysis to examine the potential influence of POI/POF on these psychological and psychosocial problems. The results of this meta-analysis were based on 9 case–control studies and 6 cross-sectional studies, with a sample size of 1761 patients with POI/POF. Our results showed the women with the diagnosis of POI/POF could have significantly higher risk of depression, anxiety, and poor life quality, as compared with the age-matched women without POI, with all pool ORs value greater than 1 statistically significant. As far as we know, this is the first meta-analysis to evaluate the risk of depression and anxiety and poor QoL together among women with POI/POF. We also noted high between-study heterogeneities and certain publication bias with the included studies.

Many previous studies have reported greater levels of depression and lower levels of self-esteem in women with POI.[11,17,24,44,45] In line with these findings, our results confirmed supported that POI/POF could increase the risk of depression. The association between the POI/POF and depression is likely related to the loss of fertility potential and ovarian steroid deficiency. A meta-analysis by Georgakis et al[46] indicated that women with earlier age at menopause had a higher risk of depression and vice versa. These findings may be due to premature ovarian steroid deficiency in patients with POI/POF, and endogenous estrogens may have neuroprotective and antidepressant effects, which is consistent with previous reports of an increased risk of depression in patients experiencing an advanced age of menopause due to oophorectomy.[47,48] The adverse association between age of POI/POF patients and risk of depression also supported this speculation. Furthermore, several neuroimaging studies have indicated that the activity of regions involved in emotion regulation may be modulated by ovarian steroids, confirming to some extent that sex hormone deficiency in patients with POI/POF is a potential factor contributing to the increased risk of depression.[49,50]

Apart from the role of age and endogenous estrogens in patients with POI/POF, our results revealed the significant association between ratio of unmarried status in POI/POF patients and risk of depression. Consistent with prior studies,[20,51,52] women in unmarried status were more likely to report higher lifetime and 12-month prevalence rate of depression than married women. Combined with the stress of infertility due to POI/POF, women with POI/POF may be at high risk of depression. The marital status may be a possible moderator accounting for the heterogeneity of depression. Therefore, it is critical to pay attention to depression in women with POI/POF, particularly women with POI who were unmarried.

In addition, our subgroup analysis found that socioeconomic status was not a source of heterogeneity. The growing trend of using cognitive behavioral therapy in developing countries,[53,54] which is a remarkably effective therapy for reducing depression in women with POI,[55] may account for the fact that the OR for depression in women with POI/POF in developing countries is not significantly different from the value in developed countries.

Anxiety and depression are commonly comorbid and share psychopathological bases.[56] We also found a significant association between POI/POF and the risk of anxiety, consistent with earlier studies. For instance, Ventura et al[38] reported higher prevalence of anxiety in women with POI as compared to women without POI. Menezes et al[42] showed moderate to severe levels of undiagnosed anxiety or depression in one-third of POI patients.

The increased risk of anxiety in patients with POI is likely to be due to genetic mutations. Since POI has a highly heterogeneous etiology, genetic mutations are one of them. For instance, females carry the expansion of fragile X messenger ribonucleoprotein 1 (FMR1), which is defined as having 55-220 CGG repeats in the 5′ untranslated region of the FMR1 gene, explains the occurrence of POI in about 10% of cases.[57] It is noteworthy that FMR1 premutation is also strongly associated with a high prevalence of psychiatric disorders, including anxiety.[58,59] Therefore, we hypothesize that FMR1 premutation plays a role in the increased risk of POI and anxiety. However, the study of Ates et al[7] revealed that total anxiety score, the severity of anxiety did not differ significantly between the POI and groups without POI. Despite these controversial results, the above findings and our study suggest that genetic mutations may be associated with a higher risk of depression and anxiety in POI/POF, and that strategies to address emotional symptoms such as depression and anxiety should be investigated in order to help patients cope with the disease not only physically but also psychologically.

Previous studies revealed that women with POI/POF had negative feelings,[8] fatigue,[39] and impaired self-esteem.[17,44,60] Li et al[30] also found lower overall life quality in POI/POF patients. In agreement with these findings, our results demonstrated that women with POI/POF were more likely to having poor life quality (OR = 2.55). As expected, the increased likelihood of having poor life quality could be due to the negative consequences—future infertility of POI and their role within the family. Cross-cultural evidence has indicated that the infertility is stigmatized.[61,62] And there is a complex relationship among perceived social support, social relations, and self-esteem.[63] This stigmatization is an important factor that may contribute to the poor life quality of women with POI.[24]

The poor life quality among women with POI are always ignored in the clinical diagnosis. The diagnosis of POI and consequent infertility could represent a devastating life experience, inducing grief and altering life perspective,[11] amidst other mental and physical consequences. Our meta-regression analysis showed that the unmarried status had a significant effect on depression, accounting for 70% of the heterogeneity. Therefore, more attention should be given to depression among women with POI/POF who were unmarried.

In conclusion, this meta-analysis included 1761 POI/POF patients from 15 studies and confirmed the associations between the POI/POF and depression, anxiety, poor life quality. Further, the marital status may represent a possible moderating factor for the risk of depression and poor life quality in women with POI/POF. Identifying the potential influence caused by POI/POF is important for the coordinated medical interventions with special attendance of gynecologist, psychotherapist, and psychiatrist.

Limitations

The limitations of this study are as follows: First, divergent measurements to assess depression, anxiety and life quality were included in this meta-analysis. This may be source of heterogeneity in the pooled ORs, especially for depression, needs to be further investigated. Second, some studies with lower methodological quality were included to ensure an adequate sample size. Thus, the heterogeneity of anxiety could not be elucidated clearly, although we aimed to rectify this issue by conducting a sensitivity analysis. Third, not all potentially confounding factors were considered in our study. For example, smoking and life style were not presented and evaluated in most of the studies. Moreover, the sample size of some of the included studies was relatively small. And the long-term effect of POI/POF on depression and anxiety should be warranted.

Availability of Data and Materials: *The data are extracted from published studies and are available in the article, and the datasets are not subject to restrictions.*

Peer-review: *Externally peer-reviewed.*

Author Contributions: *Concept – C.L., F.Z., H.D., X.Y.; Design – Y.T., H.D.; Supervision – X.Y., H.D.; Resources – Y.T., H.D.; Materials – Y.T., Z.X.; Data Collection and/or Processing – Y.T., Z.X.; Analysis and/or Interpretation – X.Z., Y.T.; Literature Search – Y.T., H.D., X.Z.; Writing – Y.T., H.D.; Critical Review – Z.X., C.L., H.D., X.Z., X.Y., F.Z.*

Declaration of Interests: *The authors have no conflicts of interest to declare.*

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Supplementary Table 1. Quality assessment of included studies.

	Selection				Comparability	Exposure			
Study	Adequate definition of cases	Representativeness of the cases	Selection of Controls	Definition of Controls	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-Response rate	Score
Ventura 2007	★	★	☆	★	★☆	☆	★	★	6
Ventura 2006	★	★	☆	★	★☆	☆	★	★	6
Benetti-Pinto 2011	★	★	☆	★	★★	☆	★	★	7
Davis 2010	★	★	★	★	★★	☆	★	★	7
Ates 2022	★	★	☆	★	★★	☆	★	★	7
Schmidt 2011	★	★	☆	★	★★	☆	★	★	7
Sun 2022	★	★	☆	★	☆☆	☆	★	★	5
Liu 2019	★	★	☆	★	★★	★	★	★	8
Nicoloro-SantaBarbara 2017	★	★	☆	★	★☆	☆	★	★	6
Omu2016	★	★	☆	★	★☆	☆	★	★	6
Huang 2021	★	★	★	★	★★	☆	★	★	7
Ida 2021	★	★	★	★	★★	☆	★	★	7
Gibson-Helm 2014	★	★	★	★	★★	☆	★	★	7
Vanderhoof 2007	★	★	☆	★	★★	☆	★	★	7
Menezes 2020	★	★	☆	★	★☆	☆	★	★	6

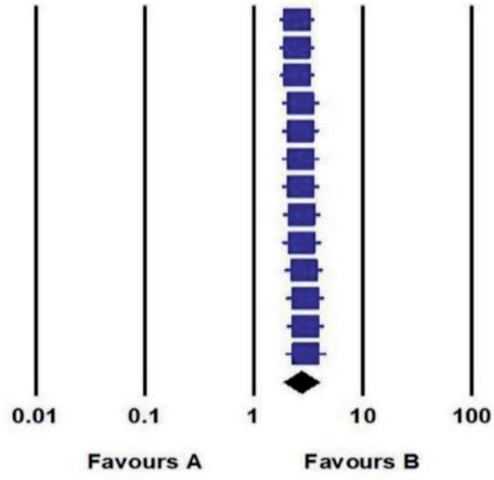
★ means that this element could score 1; ☆ means that this element could score 0.

A

Study name	Point	Lower limit	Upper limit	Z-Value	p-Value
Liu, 2019	2.487	1.729	3.578	4.912	0.000
Omu, 2015	2.497	1.732	3.600	4.905	0.000
Davis, 2010	2.503	1.735	3.611	4.904	0.000
Ventura, 2007	2.673	1.805	3.959	4.908	0.000
Ventura, 2006	2.681	1.819	3.953	4.980	0.000
Gibson-Helm, 2014	2.682	1.832	3.929	5.069	0.000
Huang, 2021	2.693	1.804	4.021	4.846	0.000
Ates, 2022	2.737	1.837	4.076	4.953	0.000
Schmidt, 2011	2.752	1.828	4.144	4.848	0.000
Sun, 2022	2.895	1.937	4.327	5.186	0.000
Menezes, 2020	2.961	1.983	4.423	5.305	0.000
Nicoloro-SantaBarbara, 2017	2.978	2.010	4.414	5.438	0.000
Vanderhoof, 2007	3.008	1.954	4.629	5.004	0.000
	2.727	1.871	3.974	5.222	0.000

Statistics with study removed

Odds ratio (95% CI) with study removed



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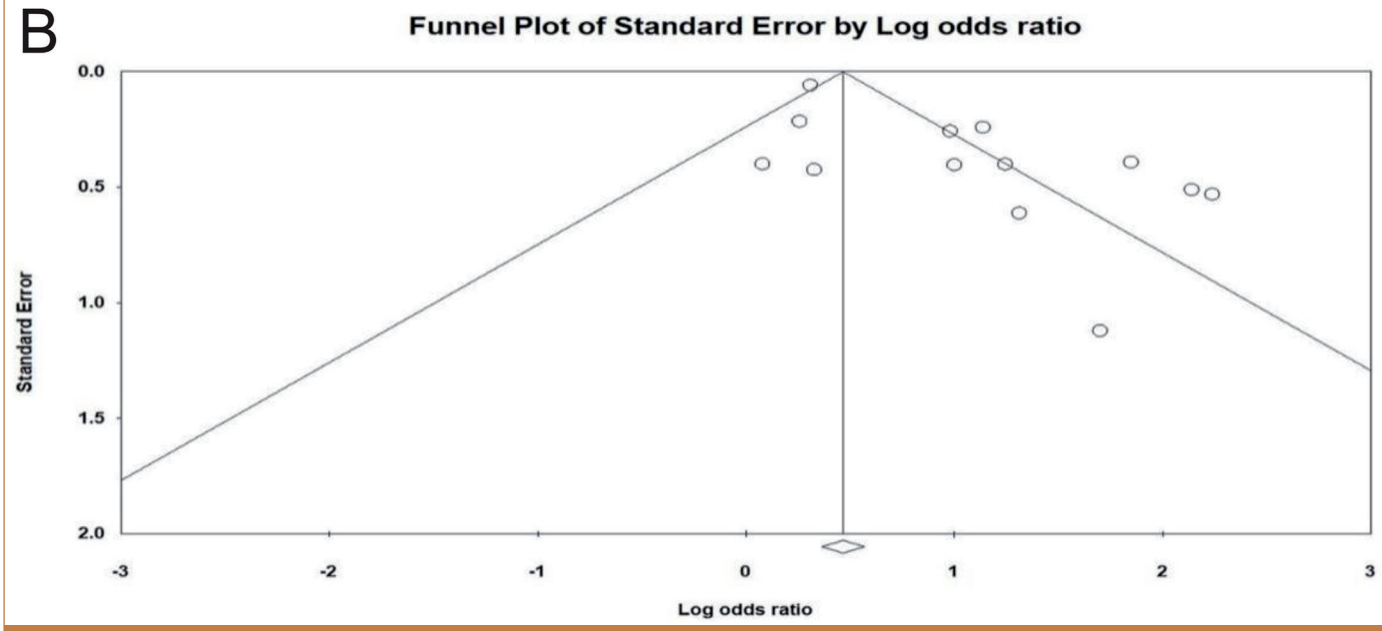
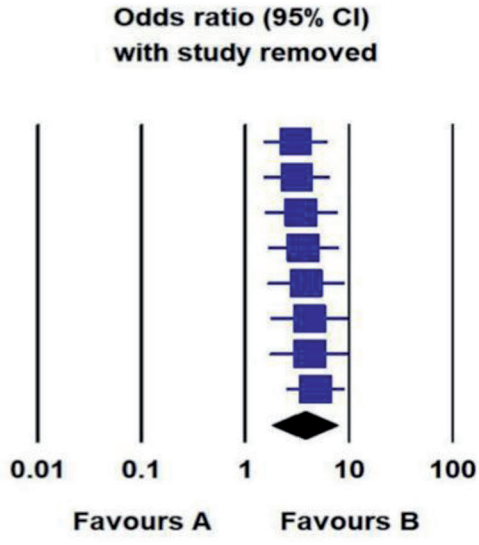


Supplementary Figure 1. Publication bias and sensitivity analysis for the association between POI/POF and risk of depression. A. Sensitivity analysis for the risk of depression. B. Egger's test and funnel plot for the risk of depression. POI/POF, premature ovarian insufficiency/premature ovarian failure; CI, confident interval.

A

Study name	Statistics with study removed				
	Point	Lower limit	Upper limit	Z-Value	p-Value
Omu, 2015	3.049	1.487	6.251	3.043	0.002
Liu, 2019	3.134	1.489	6.599	3.007	0.003
Davis, 2010	3.448	1.525	7.794	2.975	0.003
Gibson-Helm, 2014	3.633	1.645	8.028	3.190	0.001
Ventura, 2007	3.849	1.643	9.019	3.102	0.002
Sun, 2022	4.168	1.744	9.962	3.211	0.001
Ates, 2022	4.190	1.721	10.203	3.156	0.002
Menezes, 2020	4.752	2.498	9.040	4.751	0.000
	3.739	1.777	7.867	3.475	0.001



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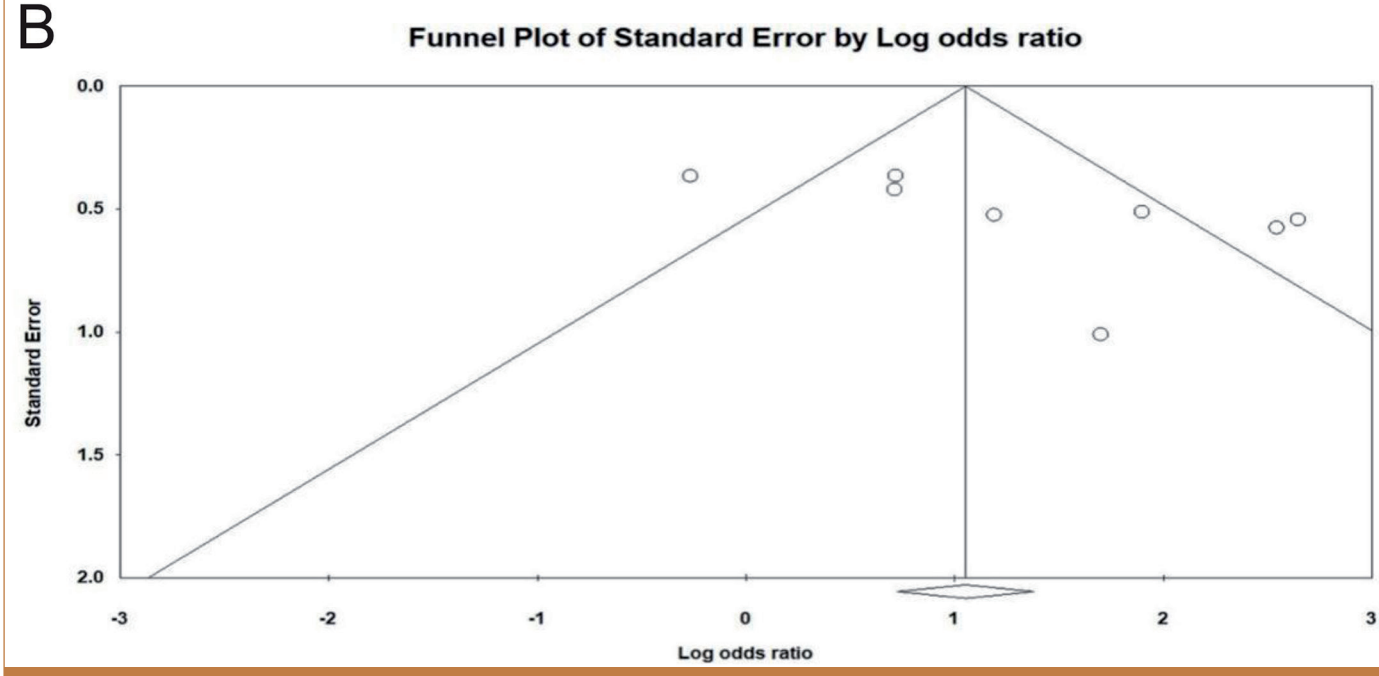
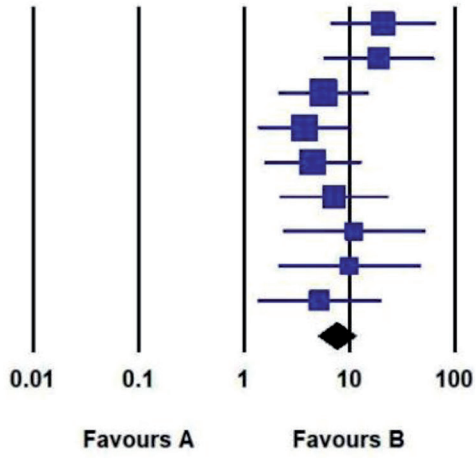


Supplementary Figure 2. Publication bias and sensitivity analysis for the association between POI/POF and risk of anxiety. A. Sensitivity analysis for the risk of anxiety. B. Egger's test and funnel plot for the risk of anxiety. POI/POF, premature ovarian insufficiency/premature ovarian failure; CI, confident interval.

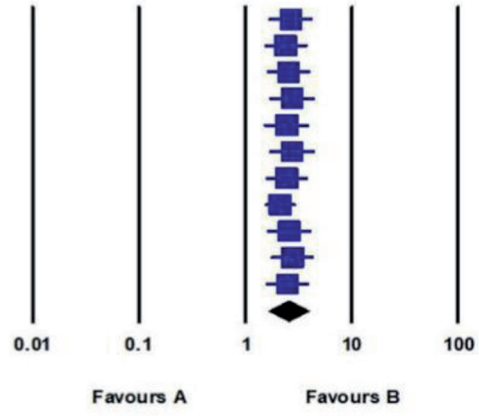
Study name	Quality of Life.	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Omu, 2015-1	childlessness fear	20.855	6.539	66.514	5.133	0.000
Omu, 2015-2	divorce worry	19.000	5.645	63.951	4.755	0.000
Omu, 2015-3	loneliness	5.667	2.120	15.148	3.458	0.001
Omu, 2015-4	grief	3.750	1.358	10.356	2.550	0.011
Omu, 2015-5	poor concentration	4.500	1.561	12.971	2.785	0.005
Omu, 2015-6	guilt	7.125	2.151	23.603	3.213	0.001
Omu, 2015-7	regret	11.111	2.349	52.560	3.037	0.002
Omu, 2015-8	mood swings	10.000	2.105	47.507	2.896	0.004
Omu, 2015-9	aggression	5.200	1.346	20.091	2.391	0.017
		7.589	4.990	11.542	9.473	0.000



Supplementary Figure 3. The pooled effect size for the study of *Omu et al* considered serval aspects of poor life quality influenced by POI/POF, which included childlessness fear, divorce worry, loneliness, grief, poor concentration, guilt, regret, mood swings and aggression. POI/POF, premature ovarian insufficiency/premature ovarian failure; CI, confident interval.

A

Study name	Quality of Life	Statistics with study removed				
		Point	Lower limit	Upper limit	Z-Value	p-Value
Ates, 2022-1	fatigue	2.678	1.661	4.317	4.043	0.000
Ates, 2022-2	poor sleep quality	2.397	1.503	3.821	3.672	0.000
Benetti-Pinto, 2011	negative feeling	2.550	1.580	4.113	3.835	0.000
Huang, 2021-1	fatigue	2.747	1.686	4.476	4.058	0.000
Huang, 2021-2	mood swings	2.454	1.502	4.008	3.586	0.000
Huang, 2021-3	insomnia	2.749	1.687	4.480	4.058	0.000
Ida, 2021	lower well being	2.446	1.552	3.856	3.853	0.000
Omu, 2015	quality of Life	2.131	1.526	2.976	4.439	0.000
Sun, 2022	fatigue	2.600	1.613	4.189	3.925	0.000
Vanderhoof, 2007	panic disorder	2.784	1.745	4.441	4.297	0.000
Ventura, 2006	poor concentration and loneliness	2.483	1.561	3.950	3.841	0.000
		2.547	1.634	3.969	4.128	0.000



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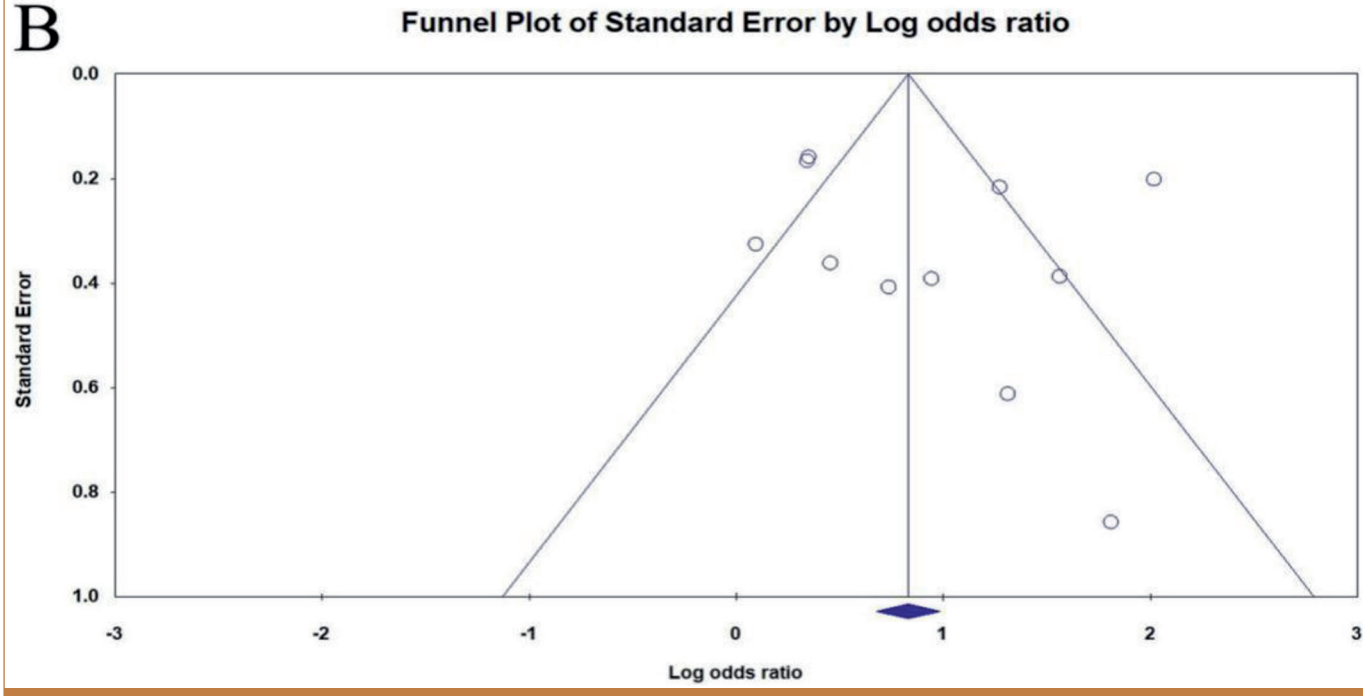

Supplementary Figure 4. Publication bias and sensitivity analysis for the association between POI/POF and risk of poor life quality. A. Sensitivity analysis for the risk of poor life quality. B. Egger's test and funnel plot for the risk of poor life quality. POI/POF, premature ovarian insufficiency/premature ovarian failure; CI, confident interval.