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# Epidemiology of perinatal depression in Italy: systematic review and meta-analysis

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**Abstract**

***Introduction.*** This review aims to synthesise the studies that have estimated the prevalence of perinatal depression in Italy, summarising the results of the existing literature based on their quality.

***Materials and methods.*** Systematic searches were conducted in four major databases, and a random effect meta-analysis was performed to achieve the pooled variance of perinatal depression.

***Results.*** The pooled prepartum risk of depression prevalence was 20.2% (CI 95% 15.3-24.5) while the postpartum risk of depression prevalence was 27.5% (CI 95% 17.8-37.3) for an Edinburgh Postnatal Depression Scale (EPDS) cut-off score ≥9 and 11.1% (CI 95% 6.0-16.2) for an EPDS cut-off score ≥12. Significant publication bias was found and was determined by the presence of a small study with a low prevalence and a large study with a high prevalence.

***Conclusion.*** The prevalence of perinatal risk of depression is similar to that reported in other countries. The high prevalence of prepartum risk suggests the need to activate specific prevention actions during this period.

**Key words**

- prepartum depression
- postpartum depression
- prevalence

## INTRODUCTION

Depression is one of the most frequent complications for women in the perinatal period, defined as the period from pregnancy to the first year after childbirth [1]. It is a moment characterised by greater vulnerability, often associated with anxiety, and an impoverishment of the quality of personal and family life, which can lead to compromise in the child's emotional, intellectual, and cognitive development. Several reasons may explain women's increased vulnerability to depression during and after pregnancy, including the physical, emotional, and hormonal changes associated with pregnancy and childbirth, as well as the life-changing and family redefinition that having a child brings [2]. Based on current research, the strongest predictors of depression during the perinatal period are maternity blues, previous depression, family psychiatric history, unplanned pregnancy, partner relationship difficulties, stressful life events, and poor social support [3-6].

Recent systematic reviews highlight a prevalence of depressive disorder of 15-20% in the prenatal period and 16-18% in the postpartum period, with higher proportions in low- and middle-income countries [7, 8].

In Italy, several studies have investigated the diffusion of depression in the perinatal period, reporting highly variable prevalence estimates. Most of the studies were conducted locally on small samples, making results difficult to compare because of the period in which the screening was performed (in pregnancy, at delivery, and 1, 3, 6, and 12 months after delivery), the various instruments used, and the chosen cut-off values. The most commonly used screening tools are the Whooley questions [9], the Edinburgh Postnatal Depression Scale (EPDS) [10], the Beck Depression Inventory (BDI) [11, 12], the Center for Epidemiological Studies-Depression Scale (CES-D) [13], the Patient Health Questionnaire-9 (PHQ-9) [14, 15]. Among the tools mentioned, the most communly used for assessing the risk of depression in women during pregnancy and after childbirth [16, 3] is the EPDS. As indicated in the validation study of the Italian version [17], the choice of the cut-off value to use depends on the objectives of the evaluation: a cut-off of 9/10 seems to be the most suitable in screening programmes or population surveys, while a cut-off of 12/13 is usually recommended in clinical assessment and research, particularly in ef-

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fectiveness studies in practise (effectiveness), in which it is intended to treat only people with a higher probability of developing depression in the perinatal period. Different cut-offs result in different values of sensitivity, specificity, and positive and negative predictive values. A recent Italian study showed high internal consistency with a Cronbach's alpha of 0.80 during pregnancy and 0.87 following delivery [18].

The present systematic review aims to revise the studies that have estimated the prevalence of perinatal depression in Italy, summarizing the results of the existing literature based on their quality.

## METHOD

This systematic review adheres to the PRISMA guidelines [19-21].

The Web of Science, Pubmed, PsycoInfo and Scopus electronic databases were systematically queried, considering papers published from January 1, 2000, to May 20, 2022. The following MESH terms and free words were combined to construct the search string: "depression" "maternal depression" "postpartum", "perinatal", "prenatal", "postnatal", "pregnancy", "prevalence", "incidence", "mother", "maternal", "Italian study", "Italian women". Finally, the bibliographies of the included studies were evaluated to identify additional relevant studies, including grey literature.

The inclusion criteria were: 1) studies reporting prevalence estimates of depression in the perinatal period; 2) studies using the EPDS as a screening tool for assessing the risk of depression; and 3) studies conducted in Italy.

Studies reporting prevalence estimates of depression in association with anxiety and studies using screening tools other than the EPDS were excluded.

After the exclusion of the duplicates through the titles, the abstracts were analysed to select the studies pertinent to the topic based on the exclusion/inclusion criteria.

The complete text of the studies considered eligible for this review was acquired.

Two reviewers independently assessed the methodological quality of the extracted studies. For the quality assessment, the "checklist for prevalence studies" developed by the working group of the Joanna Briggs Institute, Australia [22] was used (*Figure 1*).

The checklist questionnaire contains 9 items with a four-level response method: "yes/no/unclear/not applicable". The items investigate the representativeness and size of the sample, recruitment methods, setting, validity of the tools used, appropriateness of the statistical methods, reproducibility of the study, and adherence to the study by the people recruited.

Disagreements regarding the qualitative evaluation of the studies were resolved with the help of a third

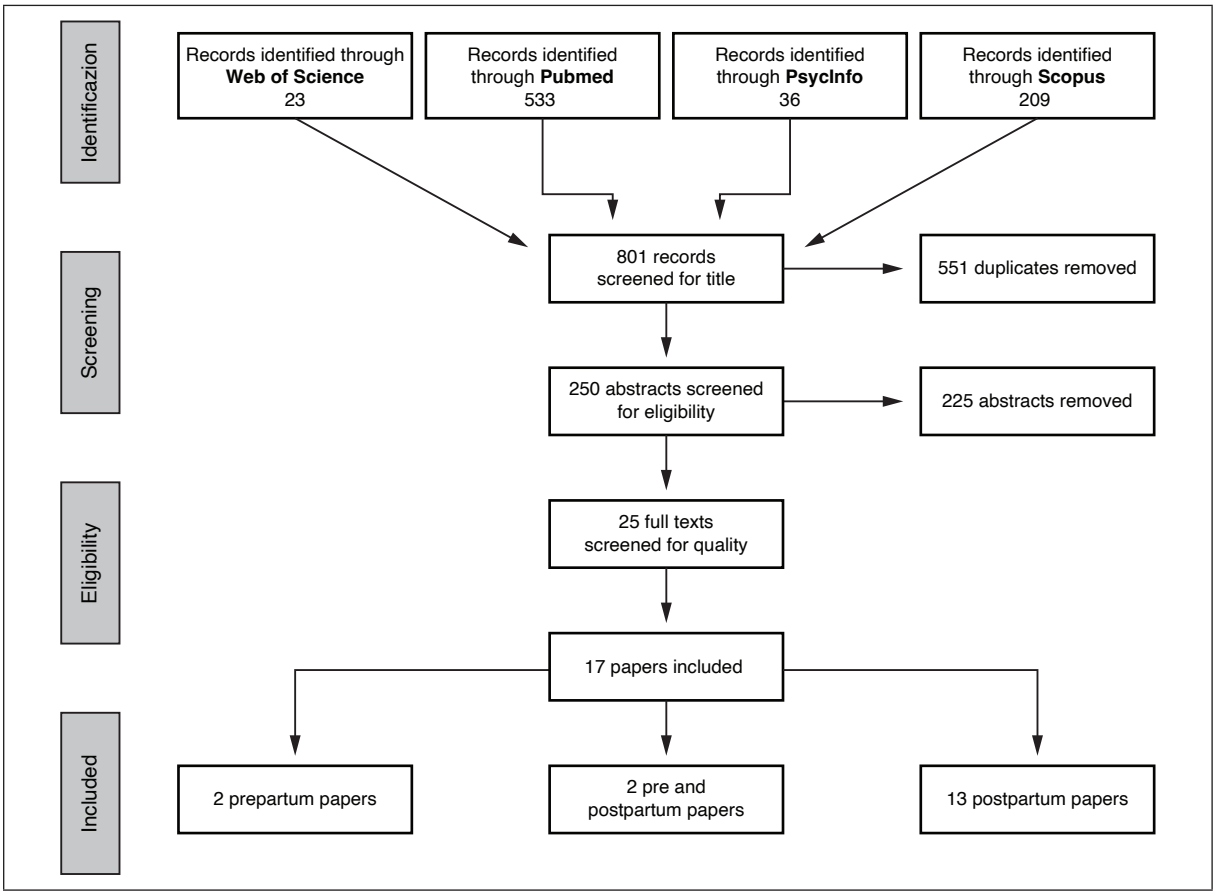


**Figure 1**
Flowchart of the systematic review literature search illustrating the identification of included studies.

reviewer. Studies reporting a score ≥5 out of a maximum possible score of 9 were considered to be of good quality.

Prevalence estimates of pre- and postpartum depression were extracted from studies rated as having good methodological quality, and 95% confidence intervals were calculated where they were not available.

Three meta-analyses were conducted, one referring to prepartum and two to postpartum, one of which including studies with an EPDS cut-off score ≥9 and the other included studies with an EPDS cut-off score ≥12. Studies that were screened after the first three months of delivery were considered. This last distinction was necessary due to the great heterogeneity of the sample in terms of the cut-off and sample size. Where studies reported prevalence estimates relating to different cut-off scores, the number of events to consider was obtained by summing the relevant data.

The Statistical Package for Social Science (SPSS) version 28 was used for the analyses. Heterogeneity between included studies and overall estimates was calculated with the random effects model, and the test for heterogeneity was applied using the $Chi^2$ and the $I^2$ statistics. The $I^2$ represents the percentage of the total study variation due to heterogeneity rather than chance. An $I^2$ value below 25% indicates a low degree of heterogeneity, 25-75% indicates moderate heterogeneity, and a value above 75% indicates high heterogeneity [23].

## RESULTS

A total of 801 studies were extracted. Of these, 551 were eliminated because they were duplicates, and of the remaining 250, after careful examination of the abstracts, 225 studies were excluded because they did not meet the inclusion criteria. The remaining 25 studies were evaluated for methodological quality, and 17 were found to be of good quality and therefore included in the final evaluation. Of these, 2 studies reported data relating to the antepartum period, 13 to the postpartum period, and 2 studies to both the antepartum and postpartum periods (*Figure 1*).

Most of the included studies were carried out in the Departments of Gynaecology and Obstetrics of various Italian Hospitals and Paediatric Clinics. Two studies were conducted at local Maternal-Child Health Centres and one at vaccination centres (*Table 1*) [24-48].

Most of the studies included in this review were conducted in northern and central Italy. In particular, eight studies recruited participants in northern regions, six in central Italy and only one in southern Italy. Finally,

**Table 1**
Characteristics of the studies included in the systematic reviews (Italy)

| | | | | | Before childbirth | | After childbirth | | |
|---|---|---|---|---|---|---|---|---|---|
| Author (year) | Healthcare centre | Region/city | N. of women participants | N. of women at risk of depression | % prevalence (CI 95%) | Screening time | % prevalence (CI 95%) | Screening time | Cut-off EPDS |
| § Monti *et al.* (2008) [24] | 6 Obstetrics and Gynaecology Unit | Emilia-Romagna | 234 | 31 | | | 13.2±4.7 | 3 months | ≥13 |
| | | | 217 | 12 | | | 5.5±3.2 | 9 months | |
| | | | 167 | 8 | | | 4.8±3.3 | 18 months | |
| § Currò *et al.* (2009) [25] | Pediatric Unit. A. Gemelli Hospital | Rome | 1,122 | 298 | | | 26.6±2.5 | 15-20 days | ≥10 |
| § Piacentini *et al.* (2009) [26] | 3 Hospitals | Bergamo | 509 | 38 | | | 7.5±2.3 | 8-12 weeks | ≥12 |
| De Magistris *et al.* (2010) [27] | Neonatal Intensive Care Unit | Cagliari | 113 | 26 | | | 23.0±8.9 | >4 weeks | ≥10 |
| | | | 100 | 8 | | | 8.0±5.5 | 4-8 weeks | |
| Aceti *et al.* (2011) [28] | Obstetrics and Gynaecology Unit Umberto I Hospital | Rome | 453 | 92 | 20.3±4.2 | 3° trimester | | | ≥12 |
| § Gremigni *et al.* (2011) [29] | Obstetrics and Gynaecology Unit | Ancona | 70 | 39 | | | 55.7±17.5 | 3 months | >9 |
| § Aceti *et al.* (2012) [30] | Obstetrics and Gynaecology Unit Umberto I Hospital | Rome | 253 | 49 | 19.3±5.1 | 3° trimester | | | ≥12 |
| § Balestrieri *et al.* (2012) [31] | 4 Obstetrics and Gynaecology Unit | Ascoli, Bari, Verona, Udine | 1,608 | 175 | 10.9±1.6 | 12-15 weeks | | | 10-12 |
| | | | | 133 | 8.3±1.4 | | | | ≥13 |
| | | | | 75 | 4.7±1.1 | | | | ≥15 |

*Continues*

**Table 1**
*Continued*

| Author (year) | Healthcare centre | Region/city | N. of women participants | N. of women at risk of depression | Before childbirth | | After childbirth | | Cut-off EPDS |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | % prevalence (CI 95%) | Screening time | % prevalence (CI 95%) | Screening time | |
| § Giardinelli *et al.* (2012) [32] | Obstetrics and Gynaecology Unit, Careggi Hospitals | Florence | 590 | 129 | 21.9±3.2 | 28-32 weeks | | | ≥10 |
| | | | | 70 | 11.9±2.7 | | | | 10-12 |
| | | | | 60 | 10.2±2.6 | | | | ≥13 |
| | | | | 78 | | | 13.2±2.48 | 12 weeks | ≥10 |
| | | | | 45 | | | 7.6%±2.2 | | 10-12 |
| | | | | 33 | | | 5.6±1.9 | | ≥13 |
| § Elisei *et al.* (2013) [33] | Prenatal Clinic, Hospital Santa Maria della Misericordia | Perugia | 85 | 5 | | | 5.5±5.1 | 72 hours | ≥12 |
| | | | | 5 | | | 5.5±5.1 | | 13-14 |
| | | | | 26 | | | 30±11.7 | | 9-12 |
| | | | | 6 | | | 7.4±5.6 | 3 months | ≥15 |
| | | | | 8 | | | 9.3±6.5 | | 13-14 |
| | | | | 20 | | | 24.1±10.3 | | 9-12 |
| § Mirabella *et al.* (2014) [34] | Local maternal-child health centres | Bergamo, Treviso | 567 | 42 | | | 7.4±1.87 | 6-12 weeks | ≥12 |
| Cattaneo *et al.* (2015) [35] | Maggiore Hospital | Milan | 122 | 29 | | | 23.8±8.6 | 2-5 days | ≥10 |
| | | | | 19 | | | 15.6±7.0 | 2 months | |
| | | | | 11 | | | 9.0±5.3 | 6 months | |
| Vismara *et al.* (2016) [36] | Hospitals and local maternal-child health centres | Cagliari. Turin. Cesena, Rome | 181 | 36 | | | 19.9±6.5 | 3 months | 9-12 |
| | | | | 31 | | | 17.1±6.1 | | >13 |
| | | | | 21 | | | 11.6±5.0 | 6 months | 9-12 |
| | | | | 17 | | | 9.4±4.5 | | >13 |
| § Clavenna *et al.*(2017) [37] | Local maternal-child health centres | Milan | 2,706 | 126 | | | 4.7±0.8 | 60-90 days | ≥12 |
| Lucarini *et al.* (2017) [38] | Prenatal clinic, Hospital Santa Maria della Misericordia | Perugia | 54 | 3 | | | 5.5±6.3 | 1 week | 13-14 |
| | | | | 3 | | | 5.5±6.3 | | ≥15 |
| | | | | 16 | | | 30±14.5 | | 9-12 |
| | | | | 5 | | | 9.3±8.1 | 3 months | 13-14 |
| | | | | 4 | | | 7.4±7.3 | | ≥15 |
| | | | | 13 | | | 24.1±13.1 | | 9-12 |
| § Della Vedova *et al.* (2020) [39] | Vaccination centres | Brescia | 416 | 48 | | | 11.5±3.3 | 2-4 months | ≥10 |
| § Ferrari *et al.* (2020) [40] | Local Psychiatry Department Camposampiero | Padova | 3,102 | 454 | | | 14.6±1.2 | 6-8 weeks | ≥9 |
| Molgora *et al.* (2020) [41] | Online survey | | 389 | 133 | 34.2±5.8 | pregnancy | | | ≥13 |
| | | | 186 | 49 | | | 26.3±7.4 | 0-6 months | |
| Spinola *et al.* (2020) [42] | Online survey | | 243 | 108 | | | 44.4±8.4 | 1 year | >12 |
| § Zanardo *et al.* (2020) [43] | Abano Terme Hospital | Padova | 192 | 38 | | | 19.79% | 2 days | >12 |

*Continues*

**Table 1**
*Continued*

| Author (year) | Healthcare centre | Region/city | N. of women participants | N. of women at risk of depression | Before childbirth | | After childbirth | | Cut-off EPDS |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | % prevalence (CI 95%) | Screening time | % prevalence (CI 95%) | Screening time | |
| § Cena *et al.* (2021) [44] | 11 centres (local maternal-child health centres, Obstetrics and Gynaecology Unit) | Bergamo, Bologna, Brescia, Enna, Florence, Mantova, Milan, Novara, Rome, Turin | 2 | 0 | 0 | 1-13 weeks | | | ≥12 |
| | | | 129 | 16 | 12.4±6.1 | 14-26 weeks | | | |
| | | | 1,029 | 58 | 5.6±1.5 | 27-40 weeks | | | |
| | | | 1,160 | 74 | 6.4±1.4 | 1-40 weeks | | | |
| | | | 220 | 40 | | | 18.2±5.6 | 1-13 weeks | |
| | | | 66 | 14 | | | 21.2±11.1 | 14-26 weeks | |
| | | | 16 | 6 | | | 37.5±30.0 | 27-40 weeks | |
| | | | 1,462 | 133 | | | 9.2±1.5 | 1-40 weeks | |
| Della Corte *et al.* (2021) [45] | Local maternal-child health centres | Naples | 80 | 9 | | | 11.3±7.3 | 3 months | >10 |
| § Luciano *et al.* (2021) [46] | Obstetrics and Gynaecology Unit | Naples | 178 | 31 | | | 17.4±6.1 | 1 months | ≥10 |
| | | | 161 | 31 | | | 19.2±6.7 | 3 months | |
| | | | 109 | 18 | | | 16.5±7.6 | 6 months | |
| | | | 106 | 19 | | | 17.9±8.1 | 12 months | |
| § Molgora *et al.* (2022) [47] | Maggiore Hospital | Milan | 137 | 28 | | | 20.3±7.6 | 3 months | ≥12 |
| | | | | 29 | | | 21.3±7.7 | 6 months | |
| | | | | 30 | | | 21.9±7.8 | 12 months | |
| | | | | 56 | | | 40.9±10.7 | 3 months | ≥9 |
| | | | | 49 | | | 36.0±10.0 | 6 months | |
| | | | | 56 | | | 40.9±10.7 | 12 months | |
| Smorti *et al.* (2022) [48] | Santa Chiara Hospital | Pisa | 80 | 22 | 27.5±11.5 | 23-32 weeks | | | ≥10 |
| | | | 75 | 40 | 53.3±16.6 | | | | |

§ Studies included in the metanalysis.
CI: confidence interval. EPDS: Edinburgh Postnatal Depression Scale.

two studies enrolled women from northern, central and southern Italy.

Most of the screenings took place during prenatal checks at the health facilities to which the women regularly belonged and during childbirth preparation courses.

The prevalence values observed in the 4 prenatal studies and the 15 studies relating to the postpartum period are highly variable and depend, as already mentioned, on the type of centre that carried out the screening, and consequently on the women who refer to it, on the cut-off used, and on the sample size (*Tables 2, 3, 4*).

As *Figure 2* shows, the pooled prevalence estimate was 20.2% (95% CI 15.3-24.5) for the 4 prepartum studies with cut-off scores ≥10. Significant heterogeneity was observed between studies ($I^2$=0.97; p<0.001). Observation of the funnel plot shows the presence of a significant publication bias, determined by the presence of a small study with a low prevalence and a large study with a high prevalence. The small number of studies included in this meta-analysis does not allow for a sensitivity analysis.

Regarding the studies relating to postpartum, after a preliminary analysis that showed significant heterogeneity, a sensitivity analysis was conducted, distinguishing the studies that used a cut-off ≥9 from those with a cut-off ≥12.

*Figure 3* of postpartum studies using cut-off scores ≥9 shows an overall prevalence estimate of 27.5% (95% CI 17.8-37.3). However, significant heterogeneity was observed between the studies ($I^2$=0.98; p<0.001).

*Figure 4* of postpartum studies using cut-off scores ≥12 shows an overall prevalence estimate of 11.1% (95% CI 6.0-16.2). In addition, in this case, significant heterogeneity is observed ($I^2$=0.95; p<0.001).

## DISCUSSION

To our knowledge, this is the first systematic review that intends to summarise prevalence estimates of

**Table 2**
Prevalence studies during the prepartum period included in the meta-analysis

| Authors (year) | N. of women participants | N. of women at risk of depression | % prevalence (CI 95%) | Screening time | Cut-off |
|---|---|---|---|---|---|
| Aceti *et al.* (2012) [30] | 253 | 49 | 19.3±5.1 | 3 months | ≥12 |
| Balestrieri *et al.* [31] | 1,608 | 383 | 23.8±2.4 | 12-15 weeks | ≥10 |
| Giardinelli *et al.* [32] | 590 | 129 | 21.9±3.8 | 28-32 weeks | ≥10 |
| Cena *et al.* [44] | 129 | 16 | 12.4±6.1 | 14-26 weeks | ≥12 |

**Table 3**
Prevalence studies (with EPDS ≥9) during the post-partum period included in the meta-analysis

| Authors (year) | N. of women participants | N. of women at risk of depression | % prevalence (CI 95%) | Screening time | Cut-off |
|---|---|---|---|---|---|
| Currò *et al.* (2009) [25] | 1,122 | 298 | 26.6±2.5 | 15-20 days | ≥10 |
| Gremigni *et al.* (2011) [29] | 70 | 39 | 55.7±17.5 | 3 months | ≥9 |
| Giardinelli *et al.* (2012) [32] | 590 | 78 | 13.2±2.48 | 12 weeks | ≥10 |
| Elisei *et al.* (2013) [33] | 85 | 34 | 40.0±13.4 | 3 months | ≥9 |
| Lucarini *et al.* (2017) [38] | 54 | 22 | 40.7±17.0 | 3 months | ≥9 |
| Della Vedova *et al.* (2020) [39] | 416 | 48 | 11.5±3.3 | 2-4 months | ≥10 |
| Ferrari *et al.* (2020) [40] | 3,102 | 454 | 14.6±1.2 | 6-8 weeks | ≥9 |
| Luciano *et al.* (2021) [46] | 161 | 31 | 19.2±6.7 | 3 months | ≥10 |
| Molgora *et al.* (2022) [47] | 137 | 56 | 40.9±10.7 | 3 months | ≥9 |

EPDS: Edinburgh Postnatal Depression Scale.

**Table 4**
Prevalence studies (with EPDS ≥12) during the post-partum period included in the meta-analysis

| Authors (year) | N. of women participants | N. of women at risk of depression | % prevalence (CI 95%) | Screening time | Cut-off |
|---|---|---|---|---|---|
| Monti *et al.* (2008) [24] | 234 | 31 | 13.2±4.7 | 3 months | ≥13 |
| Piacentini *et al.* (2009) [26] | 509 | 38 | 7.5±2.3 | 8-12 weeks | ≥12 |
| Mirabella *et al.* (2014) [34] | 567 | 42 | 7.4±1.87 | 6-12 weeks | ≥12 |
| Clavenna *et al.* (2017) [37] | 2,706 | 126 | 4.7±0.8 | 60-90 days | ≥12 |
| Cena *et al.* (2021) [44] | 66 | 14 | 21.2±11.1 | 14-26 weeks | ≥12 |
| Molgora *et al.* (2022) [47] | 137 | 28 | 20.3±7.6 | 3 months | ≥12 |

EPDS: Edinburgh Postnatal Depression Scale.

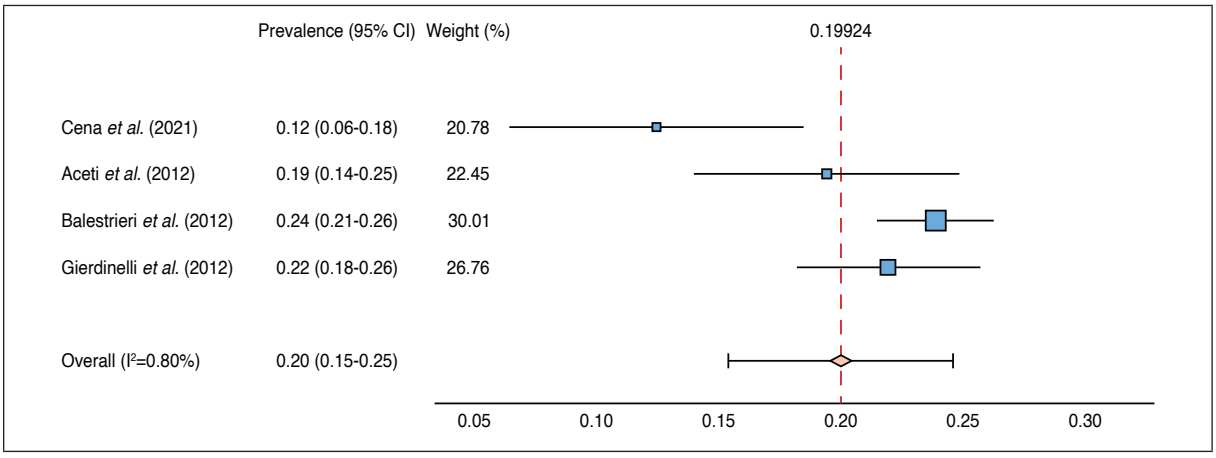


**Figure 2**
Forest plot of prevalence studies during the prepartum period.

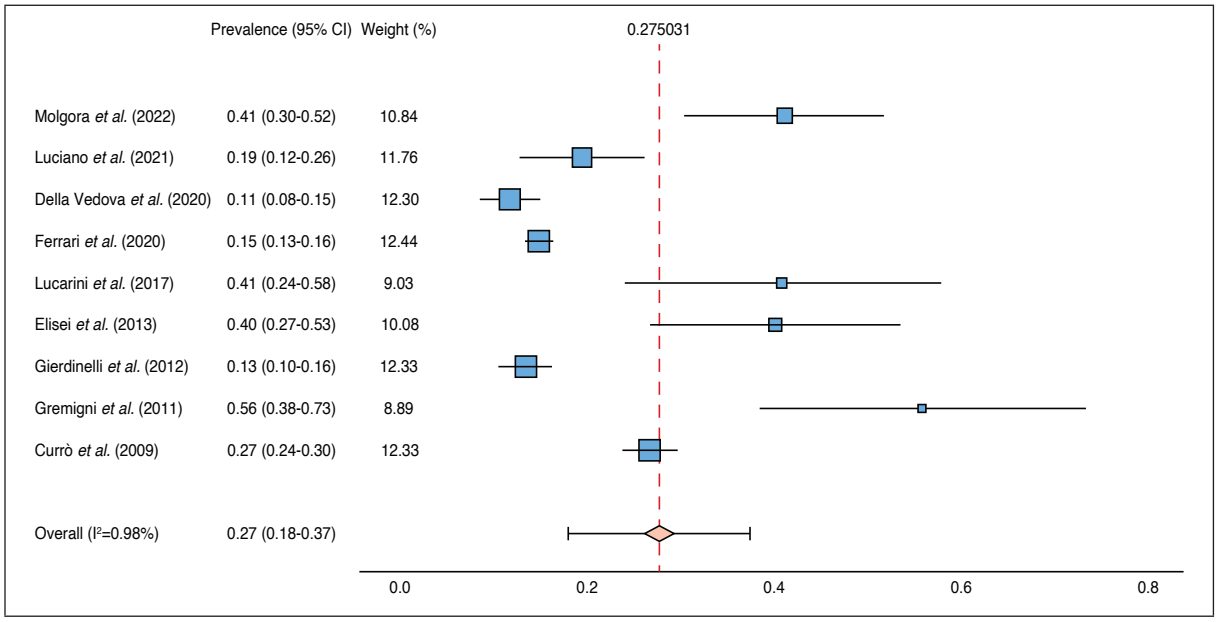


**Figure 3**
Forest plot of prevalence studies (with EPDS ≥9) during the post-partum period.
EPDS: Edinburgh Postnatal Depression Scale.

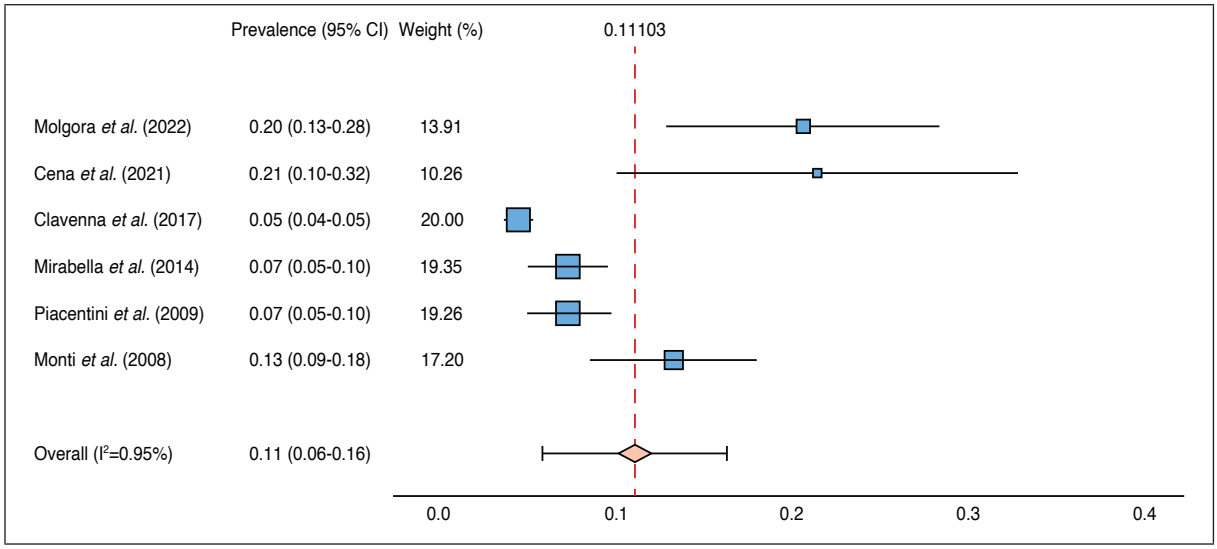


**Figure 4**
Forest plot of prevalence studies (with EPDS ≥12) during the post-partum period.
EPDS: Edinburgh Postnatal Depression Scale.

depression in the perinatal period in Italy, taking into consideration the studies that used the same screening tool.

The different cut-off scores used help to explain the variability of prevalence estimates: lower cut-off scores correspond to higher prevalence estimates, and vice versa.

The results of the meta-analysis show that in the prepartum period, about one in five women shows a risk of depression, while in the postpartum period, more than one in four women shows a risk of depression if we consider the EPDS with a cut-off ≥9, and about one in ten when a cut-off ≥12 is considered.

Our estimates of the risk of prepartum depression are similar to those observed in other systematic reviews. In particular, the review of Nisar [49] which includes only studies conducted in China, shows prenatal depression values of 19.7%. While the review by Gavin [50] which also included studies conducted in Western countries, reports an estimate of prenatal depression prevalence of 18.4%.

Furthermore, our data are in line with the review by Underwood [51] which found a prevalence of depression of 17.2% during pregnancy for EPDS cut-off values ≥10 and ≥12.

Regarding the postpartum period, other systematic reviews show an overall estimate ranging from 14 to 17% [49, 52, 53]. It should be noted, however, that the studies included in these reviews also used other screening tools (CES-D, BDI, PHQ-9) in addition to the EPDS to calculate overall prevalence. Also, where EPDS was used, no differentiation was made for the cut-off scores used or for the periods in which screening was performed.

The estimates found in our country are consistent with those of another recent Italian study in which the EPDS was used (11-24%) during the perinatal period [54].

Concerning the general population, the only epidemiological study conducted in Italy on the prevalence of common mental disorders in a representative sample of the adult population and performed with a highly reliable diagnostic tool (Composite International Diagnostic Interview, CIDI) is the European Study of the Epidemiology of Mental Disorders (ESEMeD) study [55] which showed estimates of lifetime major depression in the female population equal to 13.4% (95% CI 11.0-15.0). Importantly, the sample of this survey suffers from depression, not the risk of depression that our systematic review refers to. Our overall estimate is therefore consequently higher because it refers to a more vulnerable population and to a probability of depression that, if confirmed with an appropriate diagnostic tool, would probably have lower values.

Finally, this systematic review shows that the risk of depression is also high during pregnancy and underlines the need to monitor women during this period, given that prenatal depression has always been recognised as one of the major risk predictors for depression during pregnancy and the postpartum period [56, 57]. Very often, prenatal depression is not recognised as such, partly due to its insidious onset and partly because many women do not recognise the disorder as such or are afraid to seek help from a specialist. A timely diagnosis is instead essential because it allows effective treatments to be undertaken, not only to reduce women's suffering but also to limit the consequences for children and family relationships in general [58, 59].

## CONCLUSION

This review and meta-analysis attempted to summarise the principal screening studies on the risk of depression for women in the perinatal period. The studies analysed are methodologically very different from each other and not always comparable. The reported prevalences are not always clearly referable to a clear cut-off score used, the screening periods are highly variable, and the centres where screening is performed have, by their very nature, a very different reference population as regards the risk of depression.

However, the data appear to tend towards values that are not too far apart when considering cut-off scores and uniform screening periods.

Monitoring the frequency of depression in the perinatal period is essential from a public health point of view to identify early women to be referred to a treatment that is easy to implement and of proven efficacy to reduce major complications for the woman and for the child.

### *Authors' contributions*

LC and FM developed the outline of this review, performed the statistical analysis, and contributed to the writing of the manuscript; GG and EP searched the literature and performed the quality analysis; AG contributed to the final version of the manuscript and supervised the whole study. All the Authors have read and approved the final manuscript.

### *Conflict of interest statement*

We declare no competing interests.

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