Anxiety and Depression Are Risk Factors for Recurrent Pregnancy Loss: A Nested Case-control Study

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Abstract

Background: To evaluate the depression–anxiety interaction with the development of recurrent pregnancy loss (RPL).

Methods: A nested case–control study involving 2,558 participants was conducted with data from the prospective Miscarriage Woman Cohort study between 2017 and 2019 in the province of Gansu, China. The questionnaire data, the Self-Rating Anxiety Scale and the Self-Rating Depression Scale were collected after each participant’s first miscarriage. Information on RPL outcomes was obtained from the medical records within the subsequent two years. The logistic regression and the addition and multiplication interaction effects between anxiety and depression to RPL were analysed.

Results: The prevalence of anxiety (28.7% vs. 19.5%) and depression symptoms (48.6% vs. 41.3%) for the 1,132 RPL cases were higher than 1,426 non-RPL controls (P< 0.001). After adjustment for possible confounding variables, compared with the non-RPL participants without depression and anxiety symptoms, the odds ratio (OR) value, reflecting the multiplicative interaction, was 2.788 (95%CI: 1.511–5.144, P< 0.001) for cases with both anxiety and depression symptoms. Moreover, among these, the OR for cases with mild anxiety and severe depression was 5.369 (95%CI: 1.074–26.832, P< 0.001), and the OR for cases with severe anxiety and mild depression was 5.339 (95%CI: 1.033–27.590, P< 0.001). The relative excess risk of interaction value (RERI), reflecting the additive interaction between anxiety and depression to RPL was also 1.148 (95%CI: 0.316–4.212).

Conclusions: Either depression or anxiety alone could increase risk of subsequent RPL. There also was a synergistic effect of anxiety and depression after the first miscarriage that increased the development of subsequent RPL disease.

Background

Pregnancy loss (miscarriage) is a common disorder in women of child-bearing age. Two or more continuous pregnancy losses before the 24th week of gestation is defined as recurrent pregnancy loss (RPL)[1]. RPL has been reported to have a 0.8%–1.4% prevalence among women who experience more than two pregnancies[2]. RPL causes great physical and mental harm to couples, especially in terms of psychological stress, depression, anxiety about reproductive health and the viability of the next foetus. Nearly half of couples with RPL experience have been found to have psychological problems and could last for several months. Moreover, couples had to face the cumulative effect of RPL with an increase in exhaustion and pressure exerted by the subsequent pregnancy losses. Almost a third and a fifth of outpatients with RPL history are diagnosed as having depression and anxiety, respectively [3-6]. The maternal depression and anxiety problems after miscarriage possibly result in failure of the next pregnancy and adverse birth outcomes; however, the relevant literature is lacking in evidence to this effect [7-11].

There is not a effective preventive treatment for RPL in previous studies [2]. If we find the risk factors, we can prevent the occurrence of RPL. The opinion that depression / anxiety may be a cause and effect of RPL may be correct. However, we did not find data about the biological interaction of depression and anxiety as risk factors of RPL. Therefore, a nested case–control study with data from the prospective Pregnancy Woman Cohort study (PWC) in the province of Gansu was conducted to investigate the relationship between maternal depression and anxiety factors after a miscarriage and the development of RPL.

Methods

Study participants

A nested case–control study involving 2,558 study participants (1,132 RPL cases and 1,426 non-RPL controls) was conducted with data from the prospective PWC study between June 2017 and June 2019 in the Gansu province of China, which was implemented to explore the pregnant women’s weight management and other factors that affect pregnancy outcomes. Ethics approval for this study was obtained from the Gansu Provincial Maternity and Child-care hospital’s Ethics Committee.

Women diagnosed with a miscarriage (a pregnancy loss) before they underwent treatment were enrolled from the Reproductive Medicine Center at Gansu Provincial Maternity and Child-Care hospital in the city of Lanzhou, which is located in the province of Gansu, China. A pregnancy loss (miscarriage) is defined as the spontaneous demise of a pregnancy before 24 weeks of gestation[2]. Information on RPL outcomes was obtained from the participants’ medical records within the subsequent two years. Women who experienced the losses of two or more pregnancies were defined as RPL cases. The non-RPL controls were randomly screened out and matched by maternal age. Potential cases and controls were excluded if the woman chose to induce abortion, faced infertility problems, suffered from chronic diseases or had a history of psychiatric disorders or addiction and was not available for analysis. 1:1 matched case control, re-checked and eliminated those who did not meet the admission criteria and lost follow-up, a total of 1,132 cases (RPL group) and 1,426 controls (non-RPL group) were included in this study.

Data collection

An in-person structured interview was undertaken with the participants after their first miscarriage by a specially trained nurse at the hospital. Information collected during the interview included socioeconomic characteristics (e.g., maternal age, ethnicity, education, occupation, family monthly income, time limit of past pregnancy loss and foetal abnormalities) and lifestyle habits before miscarriage (e.g., active or passive smoking status, alcohol consumption, sleep quality and level of physical exercise). Maternal menstrual and reproductive history (e.g., menstrual cycle, self-reported last menstrual period, gravidity and parity, multivitamin supplement use during pregnancy, gestational age and information on the birth outcomes) were obtained from the participants’ medical records. Follow-up data about the subsequent pregnancy outcomes (e.g., RPL, no pregnancy, or ≥24 gestational weeks) were obtained through outpatient department visits and telephone interviews until 30 June 2019. The follow-up rate was 88.2%.

Measurements

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We used the Self-Rating Anxiety Scale (SAS)[12] and the Self-Rating Depression Scale (SDS)[13], respectively (Chinese version) to ascertain the women’s true situations regarding depression and anxiety during the first few days after their first miscarriage. The SDS and the SAS both contain 20 items; they use a point score from the baseline of one. The point scores indicate the following: 1 = ‘none or a little of the time’; 2 = ‘some of the time’; 3 = ‘a good part of the time’; and 4 = ‘most or all of the time’. The original total scores of the SDS and SAS all ranged from 20 to 80. The SDS Index and SAS Index were obtained by multiplying the total score on each questionnaire by 1.25 and converting to a 100-point scale. According to the primary screening diagnostic criteria of Chinese anxiety and depression norms: SAS \( \geq 50 \) and SDS \( \geq 53 \) were defined, respectively, as anxiety and depression diagnoses[14].

**Statistical analysis**

We converted the quantitative variables (e.g., maternal age, SAS score, SDS score) to qualitative variables. The category ranges were age\((\leq 25, 26\text{–}30, 31\text{–}35)\); family monthly income\(\geq 2000, 2000\text{–}3000, 3000\text{–}4000\); anxiety: mild (score 50–59), moderate (score 60–69) and severe (score \( \geq 70 \)); depression: mild (score 53–62), moderate (score 63–72) and severe (score \( \geq 72 \))[15]. A chi-square test was used to evaluate the statistically significant differences between the RPL group and the control group.

We performed multiple logistic regression analysis to analyse the relationship between anxiety/depression symptoms from miscarriage and the incidence of subsequent RPL. The data entering the regression equation were derived from the statistically significant variables and clinically relevant reported data. Maternal age, ethnicity, family monthly income, education, times of miscarriage at baseline, whether they had a child, time limit of past pregnancy loss and foetal abnormalities were analysed as the potential confounding factors.

We further analysed the effects of anxiety interaction with depression of different levels(no/mild/moderate/severe) on RPL by using addition or multiplication interaction statistical analysis models, which were taken from Andersson T’s literature report[16]. We used the odds ratios \((\text{OR}_{A*}B)\) and 95% confidence intervals \((\text{CI}_{A*}B)\) to analyse the multiplication interaction effect. Moreover, the relative excess risk of interaction \((\text{RERI, } \text{RERI} = \text{OR}_{A*}B \div \text{OR}_A \div \text{OR}_B \div 1\) value with 95%CI and attributable proportion \((\text{AP})\) was used to reflect the additive interaction effect, which was more likely to evaluate the biological interaction between risk factors and the disease. The results suggest a synergistic effect of anxiety or depression on the incidence of RPL when the RERI \( \geq 0 \) and the lower limit of 95%CI \( > 0 \).

The SPSS software (SPSS Inc., Chicago, IL, USA, version 19.0) and the Excel software from Andersson T. were used to perform the statistical analyses. A \( P \) value less than 0.05 was identified as being significant.

**Results**

**Sociodemographic Characteristics of Study Participants**

The sociodemographic features of the participants are summarised in Table 1. A total of 2,558 people were enrolled in the study. Among them, 93% of participants were of the Han nationality. The mean age (standard deviation, SD) of women with and without RPL were 32.6(3.9) and 32.9(4.8) years, respectively \((P=0.186)\). The number of participants with educational attainment beyond high or technical school was 53.6%. In terms of occupation, the number of employed participants and housewives were 79.9% and 20.1%, respectively. The family monthly incomes and the times of past pregnancy loss showed no significant differences between the two groups \((P=0.133)\). However, we found a significant difference in previous history of foetal abnormalities \((P=0.002)\).

**Depression and anxiety levels before RPL in the 2 Groups**

Table 2 shows the association between different depression and anxiety levels of participants and the development of RPL. The total prevalence of self-anxiety symptoms \((\text{SAS} \geq 50)\) were 28.7% and 19.5% in the RPL and control group, respectively. The total prevalence rates of self-depression symptoms \((\text{SDS} \geq 53)\) were 48.6% and 41.3% in the RPL and control group, respectively. The mild anxiety level \((19.30\% \text{ vs. } 14.10\% \text{, } P<0.001)\) after first miscarriage were significantly more common among women with subsequent RPL compared with the controls. After further adjustment for potential confounding variables (including maternal age, ethnicity, family monthly income, education, times of miscarriage at baseline, whether or not had a child, time limit of past pregnancy loss and foetal abnormalities), the adjusted OR \((95\%\text{CI})\) comparing anxiety levels of 50–59 (mild) with no anxiety as the reference were 3.105(1.644–5.863) in individuals who had subsequent RPL. Similarly, after further adjustment for potential confounding variables, the adjusted OR \((95\%\text{CI})\) for RPL comparing depression level of 53–62 (mild), 63–72 (moderate) and \( \geq 72 \) (severe) with a depression level:53 as the reference in the non-RPL group were 3.779 \((1.880–7.597)\), 2.382 \((1.626–3.489)\) and 2.143 \((1.223–3.753)\), respectively.

**Findings From the anxiety–depression interaction on the development of RPL**

The effect of the anxiety–depression interaction on the development of RPL by using addition or multiplication statistical analysis models is outlined in Table 3. The prevalence rates of comorbid anxiety and depression symptomology was 18.29% and 14.52% in the RPL and control group, respectively. First, we used multiplication interaction analysis models; after further adjustment for potential confounding variables, the adjusted OR \((95\%\text{CI})\) for RPL comparing comorbid anxiety and depression symptomology as the reference in the non-RPL group were 2.788(1.511–5.144). Second, we used addition interaction analysis models; the RERI value was 1.148(0.316–4.212), and the AP value was 0.253(0.038–0.823). The results suggest a synergistic effect of anxiety or depression on the incidence of RPL.
Table 4 shows the effects of anxiety interaction with depression of different levels (no/mild/moderate/severe) on RPL by using multiplication interaction analysis methods. After adjustment for all confounding variables, compared with the non-RPL participants without anxiety and depression conditions, the adjusted OR (95% CI) for RPL without anxiety but with mild, moderate or severe depression conditions were 1.737 (1.287–2.345), 1.837 (1.206–2.799) and 3.793 (1.179–12.200), respectively. Compared with the non-RPL participants without anxiety and depression conditions, the adjusted OR (95% CI) for RPL without depression but with mild, moderate or severe anxiety conditions were 1.657 (1.251–2.196), 2.174 (1.265–3.736) and 3.645 (1.378–9.643), respectively. Compared with the non-RPL participants with only mild depression conditions, the adjusted OR (95% CI) for RPL with mild depression but with mild, moderate or severe anxiety conditions were 1.461 (1.040–2.053), 2.430 (1.239–4.769) and 5.339 (1.033–27.590), respectively. Similarly, compared with the non-RPL participants with only mild anxiety conditions, the adjusted OR (95% CI) for RPL with mild anxiety but with mild, moderate or severe depression conditions were 1.461 (1.040–2.053), 1.739 (1.062–2.849) and 5.369 (1.074–26.832), respectively. However, no significant subgroup effect was identified for any outcomes.

Discussion

RPL has a remarkable emotional and psychological influence on women of child-bearing age and their families. Studies to date have focussed mainly on women and their partners’ anxiety or depression after pregnancy loss. However, there is scant epidemiological evidence to support negative psychology being a risk factor for RPL. Are psychological problems a risk factor for RPL? Do anxiety and depression have a biological interaction with RPL to induce miscarriage in women? The anxiety or depression status and the incidence of RPL are mutually causal, are they not?

There were many pathogeneses of RPL, including chromosomal abnormalities, autoimmune diseases, anti-phospholipid antibodies, endocrinological abnormalities, thrombophilia disorders and uterine abnormalities. Nearly half of these pregnancy loss reasons need to be explored as well as their psychological and psychiatric effects [2, 17]. Women with RPL commonly develop post-traumatic stress disorder, anxiety, depression and other negative psychological problems after pregnancy losses [18]. However, how the psychological factors affect RPL and whether the psychological problems of RPL could enter into the new pregnancy are not yet known. Therefore, we used a nested case–control study including the data of 1,132 RPL cases and 1,426 non-RPL controls from the prospective PWC study to explore the relationship between anxiety and depression status after a miscarriage and the incidence of subsequent RPL. We found that symptoms of anxiety or depression after a miscarriage are a risk factor for RPL at follow-up. The biological interaction between depression and anxiety symptoms increased the risk of developing RPL.

During the follow-up, we found the anxiety and depression levels after the first miscarriage were significantly more common among women with subsequent RPL compared with the non-RPL controls ($P < 0.001$). The prevalence of anxiety and depression symptoms being higher in a RPL group than a control group has been reported by previous literature. Nikcevic et al. [19] reported that almost all of the women had to face grief, anxiety and depression after experiencing a miscarriage and the physical recovery. Klier et al. [20] reviewed the related literature and reported that a variety of negative psychological problems would last almost six months after the loss event. M. Kagami et al. [21] reported that RPL-related negative psychology and the unhealthy marital relationship interacted on each other. Mevorach-Zussman et al. [22] found that compared with healthy women, women with RPL experience showed higher anxiety levels and lower quality of life; however, previous literature had not proved that anxiety was the cause of RPL. Kolte et al. [8] pointed out that a high stress level was more prevalent in women with RPL. Depression in women with RPL was more than five times higher than in healthy women. Koert et al. [7] reported that previous RPL might be a predictor of prenatal depression and postpartum depression. In conclusion, pregnancy loss disease interacts with negative psychological situations.

After further adjustment for potential confounding variables, we used logistic regression and addition interaction analysis models and found the adjusted OR (95% CI) for RPL comparing comorbid anxiety and depression symptomology with no anxiety and depression symptomology as the reference in the non-RPL group were 2.788 (1.511–5.144). The RERI value was 1.148 (0.316, 4.212); AP value was 0.253 (0.038, 0.823). The results suggest a synergistic effect of anxiety or depression on the development of RPL. A reciprocal link between anxiety and distress during the pregnancy period has been reported only in a few observational studies. Ramakrishna S et al. [23] reported that the prevalence of comorbid anxiety and depression symptomology for women was 13.4% during the postpartum period. Related studies identifying the psychological status correlated with RPL comorbidity are rare. We further found that the longer the higher levels of comorbid anxiety and depression persisted after the pregnancy loss event, the higher the incidence of recurrence of the disease. There was a multiplication interaction between anxiety and depression to different degrees. In other words, the women who had had miscarriages, with both depression and anxiety, had an excess risk of RPL. This means that a considerable number of RPL cases may be due to the presence of depression and anxiety in the same causal mechanism. Further research should continue to investigate the underlying mechanistic implications of this interaction.

The potential limitations of this study were as follows. The anxiety and depression symptom data were collected only once after the miscarriage and before the symptomatic treatment. The level measured at one point in time may not accurately reflect long-term psychology adjustment. The reliability of the psychological scales was also limited. Due to the limited sample size, the effect of severe anxiety combined with severe depression on RPL was not truly reflected. The second challenge was the sensitivity and specificity of the SAS and the SDS compared with using ‘Hospital Anxiety and Depression Scale’ (HADS) as a screening tool to capture symptoms of anxiety and depression [4]. To comprehensively consider the feasibility of implementation, we strengthened the quality control of the process to enhance the credibility of our results.

In summary, we evaluated the depression–anxiety interaction to the development of RPL by using consistently approved statistical interaction analysis tools. During the follow-up, we found that the anxiety and depression conditions after first miscarriage increased the development of subsequent RPL disease. There was a synergistic effect of anxiety and depression for miscarriage women on the incidence of RPL. The findings of our study can enrich the risk factor data on psychological status in recurrent spontaneous abortion in women and may be evidence that progressive aggravation of anxiety and depressive symptoms may accelerate the deterioration of RPL. Care providers should take steps to help couples who have suffered miscarriage to relieve the distress and anxiety.
conditions when they encounter a pregnancy loss[24]. Further research should focus on the underlying mechanisms between psychological changes and the development of RPL.

**Abbreviations**

RPL: recurrent pregnancy loss;
SAS: the Self-Rating Anxiety Scale;
SDS: the Self-Rating Depression Scale;
RERI: the relative excess risk of interaction;

**Declarations**

**Ethics approval and consent to participate**

Ethics approval for this prospective cohort study was obtained from the Gansu Provincial Maternity and Child-care hospital's ethics committee (File NO.[2017] GSFY (16). The standard informed consent form and the confidentiality agreement for all participants were signed and preserved after they had been introduced to the purpose of the study and informed about their right to interrupt the interview at any time or decline to be interviewed without any future prejudice. Collected data were anonymous and could not be linked to any particular respondent. No payments were made for participation in the studies.

**Consent for publication**

Not applicable

**Availability of data and materials**

A minimal set of data is available from the corresponding author on request.

**Competing interests**

The authors declare that they have no competing interests.

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**Authors' contributions**

Yanxia Wang performed the statistical analyses and draughted the first draught; Zhaoyan Meng improved the final manuscript; Jianyin Pei, Liu Qian contributed to the study design; Baohong Mao and Cao Jianing analysed the data. Yamei Li, Jing Li, Zhirong Dai, Chunhua Zhang, Lina Chen, Yuxia Jin collected clinical data and interpretation. Bin Yi were revised the manuscript and gave the final approval for publication. All authors approved the final version.

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**Tables**
| Characteristics                  | RPL Group (n=1132) | Control Group (n=1426) | P value |
|----------------------------------|--------------------|------------------------|---------|
| Age (year)                       |                    |                        |         |
| ≤ 25                             | 38 (3.4%)          | 59 (4.1%)              | 0.186   |
| 26–                              | 324 (28.6%)        | 422 (29.6%)            |         |
| 30–                              | 358 (31.6%)        | 481 (33.7%)            |         |
| ≥ 35                             | 412 (36.4%)        | 464 (32.5%)            |         |
| Ethnicity (%)                    |                    |                        | 0.198   |
| The Han nationality             | 1045 (92.7%)       | 1335 (93.6%)           |         |
| Other                            | 87 (7.7%)          | 91 (6.4%)              |         |
| Education                        |                    |                        | 0.092   |
| ≤ primary school                | 59 (5.2%)          | 64 (4.5%)              |         |
| middle school                    | 418 (36.9%)        | 473 (33.2%)            |         |
| High or technical school         | 618 (54.6%)        | 827 (58%)              |         |
| ≥ College graduate              | 37 (3.3%)          | 62 (4.3%)              |         |
| Occupation                       |                    |                        | 0.566   |
| Employed                         | 901 (79.6%)        | 1148 (80.5%)           |         |
| Housewife                        | 231 (20.4%)        | 278 (19.5%)            |         |
| Monthly income (RMB, Yuan)       |                    |                        | 0.133   |
| ≤ 2000                           | 333 (29.4%)        | 360 (25.2%)            |         |
| 2000–                            | 468 (41.3%)        | 620 (43.5%)            |         |
| 4000–                            | 104 (9.2%)         | 139 (9.7%)             |         |
| ≥ 6000                           | 227 (20.1%)        | 307 (21.5%)            |         |
| Time limit of past pregnancy loss|                    |                        | 0.762   |
| First trimester                 | 1041 (92.0%)       | 1316 (92.3%)           |         |
| Second trimester                | 91 (8.0%)          | 110 (7.7%)             |         |
| Fetal abnormalities              |                    |                        | 0.002   |
| Yes                              | 1109 (98.0%)       | 1417 (99.4%)           |         |
| No                               | 23 (2.0%)          | 9 (0.6%)               |         |

*All P values derived from Chi-square test.
### Table 2 Anxiety or depression symptoms at baseline in association with incident RPL

| Symptoms<sup>a</sup> | Total | RPL group (n=1132) | Control group (n=1426) | P value | Crude OR (95%CI) | Adjusted OR<sup>b</sup> (95%CI) |
|----------------------|-------|--------------------|-------------------------|---------|------------------|-------------------------------|
|                      |       | n.     | %       | n.     | %       |                  |                                    |
| SAS, scores          | 2558  | 1955   | 71.30   | 1148   | 80.50   | 1.00             | 1.000                              |
| ≥50                  | 1955  | 807    | 41.30   | 201    | 14.10   | 1.227(1.103-1.365)| 3.105(1.644-5.863)               |
| 50-59                | 420   | 219    | 52.60   | 201    | 14.10   | 1.426(1.163-1.749)| 0.685(0.286-1.638)               |
| 60-69                | 136   | 80     | 59.70   | 56     | 3.90    | 1.314(0.954-1.810)| 1.332(0.677-2.620)               |
| ≥70                  | 47    | 26     | 55.30   | 21     | 1.47    | 1.314(0.954-1.810)| 1.332(0.677-2.620)               |
| Mean ± SD            | 42.31±9.73 | 45.49±10.17 | 1.00 | 1.00 | 1.000 | 1.000 |
| SDS, scores          | 2558  | 1419   | 55.20   | 837    | 58.70   | 1.00             | 1.000                              |
| ≥53                  | 1419  | 582    | 41.10   | 395    | 27.70   | 1.101(1.016-1.192)| 3.7791.880-7.597)               |
| 53-62                | 737   | 342    | 46.50   | 395    | 27.70   | 1.203(1.074-1.347)| 2.382(1.626-3.489)               |
| 63-72                | 365   | 186    | 51.20   | 179    | 12.60   | 1.455(0.983-2.155)| 2.143(1.223-3.753)               |
| ≥72                  | 37    | 22     | 60.50   | 15     | 1.10    | 1.455(0.983-2.155)| 2.143(1.223-3.753)               |
| Mean ± SD            | 49.59±12.04 | 51.96±11.52 | 1.00 | 1.00 | 1.000 | 1.000 |

Note. SAS, Self-Anxiety Scale; SDS, Self-Depression Scale; OR, odds ratio; CI, confidence interval.

<sup>a</sup> Normal SAS<50, Case SAS≥50; Normal SDS<53, Case SDS≥53.
<sup>b</sup> Adjusted for age, ethnicity, family monthly income, education, times of miscarriage at baseline, whether or not have a child, time limit of past pregnancy loss, whether or not have fetal abnormalities.

### Table 3 The joint association of anxiety and depression at baseline with incident RPL

| Anxiety | Depression | RPL group(n=1132) | Control group(n=1426) | P value | OR(95%CI)<sup>a</sup> |
|---------|------------|--------------------|------------------------|---------|------------------------|
|         |            | n.     | %       | n.     | %       |                  |                                    |
| No      | No         | 464    | 40.99   | 703    | 49.30   | 1.133(1.001-1.284)|                                    |
| Yes     | No         | 118    | 10.42   | 134    | 9.40    | 1.000              |                                    |
| No      | Yes        | 343    | 30.30   | 343    | 24.05   | 1.067(0.988-1.152)|                                    |
| Yes     | Yes        | 207    | 18.29   | 207    | 14.52   | 1.067(0.988-1.152)|                                    |

Note. RPL, recurrent pregnancy loss; CI, confidence interval; OR, odds ratio; RERI, relative excess risk due to interaction.

<sup>a</sup> Adjusted for age, ethnicity, family monthly income, education, times of miscarriage at baseline, whether or not have a child, time limit of past pregnancy loss, whether or not have fetal abnormalities at baseline.

### Table 4 Adjusted odd ratios (95% CI) with incident RPL by joint effects of maternal anxiety and distress
### Interaction effect of Psychological anxiety and distress

| Anxiety | No depression | Mild depression | Moderate Depression | Severe Depression |
|---------|---------------|-----------------|---------------------|------------------|
|         | case/controls | OR^a (95% CI)   | case/controls | OR^a (95% CI) | case/controls | OR^a (95% CI) |
| Normal  | 464/703       | 1.00            | 213/299          | 1.737 (1.287, 2.345) | 121/135       | 1.837 (1.206, 2.799) | 9/11     | 3.793 (1.179, 12.200) |
| Mild    | 85/86         | 1.657 (1.251, 2.196) | 85/80            | 1.461 (1.040, 2.053) | 42/33         | 1.739 (1.062, 2.849) | 7/2       | 5.369 (1.074, 26.832) |
| Moderate| 27/33         | 2.174 (1.265, 3.736) | 36/14           | 2.430 (1.239, 4.769) | 14/9          | 1.462 (0.570, 3.750) | 3/0       | ——                |
| Severe  | 6/15          | 3.645 (1.378, 9.643) | 8/2             | 5.339 (1.033, 27.590) | 9/2           | 4.457 (0.894, 22.387) | 3/2       | 1.378 (0.210, 9.047) |
| P for trend | 0.40       | <0.001          | <0.001          | <0.001            | <0.05         | 1.00          | 1.234 (1.024, 1.487) | 1.450 (1.141, 1.842) | 1.878 (1.017, 3.807) |

Note: RPL, recurrent pregnancy loss; CI, confidence interval; OR, odds ratio; a: Adjusted for age, ethnicity, family monthly income, education, times of miscarriage at baseline, whether or not have a child, time limit of past pregnancy loss, whether or not have fetal abnormalities at baseline.

### Supplementary Files

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