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# The presence of anxiety, depression and stress in women and their partners during pregnancies following perinatal loss: A meta-analysis

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**Short title:** Anxiety, depression and stress during pregnancies following perinatal loss

## Abstract

*Background* Research indicates perinatal loss is associated with anxiety, depression and stress in women and partners during subsequent pregnancies. However, there are no robust estimates of anxiety, depression and stress for this group. We meta-analytically estimated rates of anxiety, depression and stress in pregnant women and their partners during pregnancies after previous perinatal loss.

*Methods* Databases (Medline, PsychInfo, Embase, Cinahl Plus) and grey literature were searched from 1995 through to May 2016. Search terms included: depression, anxiety, or stress with perinatal loss (miscarry\*, perinatal death, spontaneous abortion, fetal death, stillbirth, intrauterine death, TOPFA) and subsequent pregnancy. Case-controlled, English-language studies using validated measures of anxiety, depression or stress in women or partners during pregnancy following perinatal loss were included. Data for effect sizes, study and demographic data were extracted.

**Results** We identified nineteen studies representing  $n=5114$  women with previous loss;  $n=30,272$  controls;  $n=106$  partners with previous perinatal loss; and  $n=91$  control men. Random effects modelling demonstrated significant effects of perinatal loss on anxiety ( $d=0.69$ , 95% CI=0.41–0.97) and depression ( $d=0.22$ , 95% CI=0.15–0.30) in women; but no effect on stress ( $d=-0.002$ , 95% CI=-0.0639–0.0605).

**Limitations** This study was limited by the quality of available studies, underpowered moderator analyses and an inability to examine additional covariates. Insufficient data were available to generate reliable effects for psychological distress in partners.

**Conclusions** Our findings confirm elevated anxiety and depression levels during pregnancies following perinatal loss. Further research on predictors of distress in women and their partners is required.

**Key words** Perinatal loss, anxiety, depression, stress, subsequent pregnancy

## Highlights

- Anxiety and depression are higher in women during pregnancies after perinatal loss.
- Psychological distress in partners at this time requires further investigation.
- Further research on predictors of distress in women and their partners is needed.
- Samples are biased by studies of miscarriage and more targeted studies by perinatal loss type are needed.

## Introduction

Each year in the UK, many women and their partners experience a perinatal loss (Manktelow et al., 2016; NISRA, 2016; NRS, 2016; ONS, 2016). Perinatal loss includes miscarriage (fetal death before 24 weeks' gestation), termination of pregnancy for fetal anomaly (TOPFA), stillbirth (when a baby is born dead after 24 weeks' gestation) and neonatal death. The majority of these women and their partners experience another pregnancy after their perinatal loss (Redshaw, 2014). Consequently, it is important to consider how perinatal loss may affect the well-being of these individuals and their babies during pregnancies subsequent to these losses.

Several studies (Armstrong, 2004; Bergner et al., 2008; Hughes et al., 1999; Robertson Blackmore et al., 2011) and a systematic review (Debackere et al., 2008) have reported an association between perinatal loss and anxiety, depression and stress in women during subsequent pregnancies. However, reliable estimates are hampered by considerable methodological variability in the literature due to small sample sizes (Armstrong, 2004; Gaudet, 2010; Hughes et al., 1999), self-selecting research participants (Armstrong and Hutti, 1998; Armstrong, 2002; Hutti et al., 2011), self-report measures (Bergner et al., 2008; Debackere et al., 2008; DeBackere et al., 2008; Robertson Blackmore et al., 2011) and variation across studies in terms of perinatal loss definitions, types of losses and types of anxiety measured.

That notwithstanding, research into support during pregnancies following perinatal loss has been prioritised by the James Lind Alliance (JLA, 2015). This is further underlined by the potential immediate and long-term implications of psychological distress after perinatal loss, including continued anxiety, depression and stress postpartum and lower parental attachment to their baby during pregnancies following perinatal loss (Armstrong and Hutti, 1998; Gaudet, 2010). Pregnancy-specific anxiety, depression, PTSD and grief intensity during pregnancies following perinatal loss have also been linked to poorer intimate partner relationships (Hutti et al., 2015).

Studies of women without previous perinatal loss experiences can be extrapolated to suggest that anxiety, depression and stress during subsequent pregnancies may also be associated with higher risks of pre-term birth, lower birth weight and poor infant development (Ding et al., 2014; Dunkel Schetter, 2012; Graignic-Philippe et al., 2014; Grigoriadis, 2013; Mulder et al., 2002). However, one study found that children born following stillbirth were not at risk of experiencing cognitive or health problems at 6 to 8 years of age (Turton et al., 2009a).

Although there has been a systematic review of this literature (Debackere et al., 2008), this included non-validated measures of anxiety, depression and stress; and did not quantify rates of common mental health difficulties.

Therefore, the current meta-analysis sought to generate effect sizes for the presence of anxiety, depression and stress for women and their partners in relation to control groups; and to model potential moderators of these effects. We hypothesized that anxiety, depression and stress would be significantly higher in women and their partners during pregnancy following perinatal loss than in controls.

## **Methods**

### **Search criteria**

This meta-analysis was conducted following MOOSE (Stroup et al., 2000) and PRISMA guidelines (BMJ, 2009). A comprehensive search was conducted using Ovid (Medline, PsychInfo and Embase) and EBSCOhost (Cinahl Plus) databases for research published between 1995 and May 2016. This search included studies published in the last 20 years when improved bereavement care following perinatal loss has been increasingly emphasised in many regions. A 'grey literature' search was performed using Open Grey, Virtual Health Library and Grey Literature Report. Reference lists of all included studies were checked. The search strategy used combinations of the following search terms: anxiety OR depression OR stress AND perinatal loss, perinatal death, miscarriage, spontaneous

abortion, stillbirth, neonatal death and termination of pregnancy for fetal anomaly AND subsequent pregnancy (see Appendix S1). The search was developed in consultation with a specialist librarian

## **Eligibility criteria**

Quantitative observational studies were included according to the following criteria: included women and/ or their partners during pregnancy following perinatal loss (including miscarriage, stillbirth, TOPFA and/ or neonatal death); had a control group with pregnant women and/ or their partners with no previous perinatal loss experience; used at least one validated anxiety disorder, depression or stress diagnostic tool; and published in English. No inclusion limits were imposed based on whether women and/ or their partners have other children or the time elapsed between perinatal loss experience and subsequent pregnancy.

## **Search results**

Two researchers (AH, LT) independently assessed all non-duplicate search for inclusion using Microsoft Excel 2010 and Endnote X7. Titles and abstracts were screened. Full-text manuscripts were assessed and reasons for exclusion or inclusion were recorded. When multiple records presented data for the same cohort, the record with the most comprehensive results was included. The authors of five studies were contacted as insufficient data were published. Where study inclusion could not be agreed the third researcher (AM) was consulted and a consensus agreement reached.

## **Data extraction**

Relevant data from included studies were extracted using Microsoft Excel. Data were extracted for study country, year, perinatal losses included, timing of assessment, psychological distress results and diagnostic tools used (see Appendix S2 for full details.).

## **Quality assessment**

Adapted versions of the Agency for Healthcare Research and Quality (AHRQ) checklist and related guidance notes were used by two independent researchers (AH, LT) to assess the quality of each study included (Williams and S., 2010) (see Appendices S3 and S4). Criterion 8 was excluded from the final scoring of the AHRQ checklists as longitudinal data were not analysed.

Independent quality assessments were compared and consensus scores reached for the purposes of the meta-analysis..

## **Analysis plan**

Analyses were completed using R Studio (V0.99.489). Independent group studies that reported mean scores and standard deviations for anxiety, depression or stress, effect sizes were calculated as Cohen's *d*. Odds ratios (ORs) were used where mean score and standard deviation data were unavailable. Where ORs were unreported but the numbers of participants with anxiety or depression were available, ORs and confidence intervals were calculated (Szumilas, 2010). All ORs were converted into standardised Cohen's *d* values and the standard errors of these effect sizes were calculated using the methods indicated by Borenstein *et al.* (Borenstein and Rothstein, 2009) and Chinn (Chinn, 2000).

A random-effects model was used to weight studies and calculate a summary effect size as differences in sample sizes and covariates (e.g. different perinatal loss types or demographic characteristics) may create variations in effect sizes across studies (Borenstein and Rothstein, 2009). DerSimonian-Laird's method was used to calculate summary effects using fixed and random effects modelling with R packages 'meta' (Schwarzer, 2016), 'metafor' (Viechtbauer, 2010) and 'metagen' (Möbius, 2014). Confidence intervals of 95% and standard errors for each effect size were also calculated. *Z*-values and *p* values were computed to test the null hypotheses for each analysis. The *Q* and *I*<sup>2</sup> statistics were used to analyse heterogeneity and quantify observed variance. Influence analyses, publication bias and outlier biases were analysed using funnel plots and the Duval and Tweedie (Duval, 2000) "trim and fill" method (Varese *et al.*, 2012).

As most of the available data focused on women, the main analyses examined anxiety, depression and stress in women during subsequent pregnancies. Moderator analyses were conducted to determine whether the type of perinatal loss experienced, trimester when women were assessed for these conditions and country of study affected the results of the main analyses. Meta-regression was used to determine whether predictors of these conditions included the year of the study (based on the



assumption that bereavement care following perinatal loss has improved in the last 20 years in countries such as the UK) or quality rating of the study (assuming results were influenced by study quality). Separate random effects modelling was also used to examine the effect of perinatal loss on pregnancy-specific and trait anxiety. Secondary analyses of anxiety and depression data for men during pregnancies subsequent to perinatal loss were also performed.

## **Project registration**

The details of this study were registered on Prospero (CRD42016037951).

## **Results**

### **Study selection and characteristics**

Initial searches yielded 977 records with 756 non-duplicate results. In total, 697 records were excluded based on title and/ or abstract. Eligibility was assessed for 59 full-text manuscripts and reasons for excluding or including each study were recorded. Two records were excluded as insufficient data were available after contacting the authors of five articles. Anxiety data for two other studies (Hughes et al., 1999; Robertson Blackmore et al., 2011) were excluded although sufficient data were available to include these records in the depression analysis. Another paper (Côté-Arsenault and Dombek, 2001) was excluded as full results for the same cohort were confirmed to be published elsewhere (Côté-Arsenault, 2003). Two dissertations could not be accessed through library services or the authors. Nineteen records were included in the analysis (Figure 1). Table 1 reports study characteristics.

The total sample comprised  $n = 35,386$  pregnant women (age range 15-46 years) and  $n = 197$  partners of pregnant women. We identified  $n = 5114$  pregnant women who had experienced previous perinatal loss with  $n = 30,272$  control women without a perinatal loss history. Of the women who experienced perinatal loss, the majority of these women experienced miscarriage ( $n = 4446$ ). The sample also included women who experienced stillbirth ( $n = 229$ ), neonatal death ( $n = 4$ ) and perinatal loss resulting from severe fetal structural pathology ( $n = 44$ ). Several studies did not report the numbers of

women who experienced each type of perinatal loss separately. In these studies the numbers of women with previous miscarriages, stillbirths, neonatal death, TOPFA and termination of pregnancy experiences were combined ( $n = 382$ ). Three studies included  $n = 106$  men whose partner was pregnant following a previous perinatal loss with  $n = 91$  controls. Stillbirth was experienced by  $n = 38$  men in one study and the numbers of men who experienced miscarriage, stillbirth and neonatal death were combined in two studies ( $n = 68$ ).

## **Study quality**

Quality assessment measurements of included studies are shown in Table 2. AHRQ scores ranged from 9 to 18 from a possible score of 20. Only one study had a score  $>14$  (Bicking Kinsey et al., 2015).

No study reported whether the observers were blind to the assessments. The sample size was justified in six studies by power analyses (Armstrong, 2002; Bicking Kinsey et al., 2015; Couto et al., 2009; Côté-Arsenault, 2003; Huttu et al., 2011; Yilmaz and Beji, 2013) and one by calculating a post-hoc power analysis without reporting the percentage of the effect (Gaudet, 2010). Only seven studies adequately reduced recruitment bias for the perinatal loss cohort (Armstrong, 2002; Bergner et al., 2008; Bicking Kinsey et al., 2015; Gong et al., 2013; Hamama et al., 2010; Hunfeld et al., 1996; McCarthy et al., 2015) and baseline differences between the perinatal loss and control groups were sufficiently reduced in only four studies (Bicking Kinsey et al., 2015; Hughes et al., 1999; Turton et al., 2006; Woods-Giscombe et al., 2010). Variation in available demographic data made it difficult to compare study results with only five studies adequately reporting demographic data (Bicking Kinsey et al., 2015; Couto et al., 2009; Huttu et al., 2011; Turton et al., 2006; Woods-Giscombe et al., 2010).

The method for identifying previous perinatal loss experience was clearly stated in most studies, all studies used validated measures for anxiety, depression and/ or stress and most studies used robust statistical analyses and adequately reported data. Four studies had missing data  $>20\%$  (Franche and Mikail, 1999; Robertson Blackmore et al., 2011; Tsartsara and Johnson, 2006; Turton et al., 2006) and one of these studies used generalised estimating equations to determine the impact of missing data

(Robertson Blackmore et al., 2011). Two studies had drop-out rates of >20% post recruitment but no missing data for assessed participants (Hughes et al., 1999; Hunfeld et al., 1996). It was not possible to determine the rate of missing data for one study (Yilmaz and Beji, 2013). Three studies did not control for confounding variables (Armstrong and Hutti, 1998; Armstrong, 2002; Hughes et al., 1999).

### **Anxiety in women during pregnancy following perinatal loss**

Results suggested a significant medium effect of perinatal loss on increased anxiety levels in women during subsequent pregnancies ( $d = 0.69$ , 95% CI = 0.41–0.97,  $Z = 4.83$ ,  $p < 0.0001$ ,  $k = 13$ ) (Figure 2). The analysis was re-run without one outlier (Armstrong and Hutti, 1998) which decreased the effect although it was still significant ( $d = 0.59$ , 95% CI = 0.30–0.87,  $Z = 4.02$ ,  $p < 0.0001$ ,  $k = 12$ ), with continued significant heterogeneity ( $Q = 4056.32$ ,  $p < 0.0001$ ,  $I^2 = 99.7\%$ ) and asymmetry ( $p = 0.03$ ). Publication bias analysis indicated seven hypothetically missing effects for this analysis. A revised analysis including these effects suggested that these would render the anxiety effect non-significant ( $d = 0.15$ , 95% CI = -0.09–0.40,  $Z = 1.21$ ,  $p = 0.23$ ,  $k = 19$ ).

Moderator analyses showed there was no significant effect of type of perinatal loss previously experienced on anxiety ( $p = 0.13$ ) (Table 3). However, a significant difference was found in anxiety based on the trimester in which women were assessed ( $p = 0.0012$ ) (Table 3). Perinatal loss had a large significant effect on pregnancy-specific anxiety. The pregnancy-specific anxiety analysis also showed lower heterogeneity than all other anxiety analyses although heterogeneity continued to be significant in this analysis ( $p = 0.001$ ) (Table 3). Perinatal loss also had a significant medium effect on trait anxiety (Table 3).

There was no significant difference in anxiety levels between studies conducted in the USA and other countries ( $p = 0.80$ ) and high heterogeneity was found within both subgroups (Table 3). The year of study publication did not significantly affect the anxiety effect sizes observed ( $\beta = -0.04$ , SE = 0.03,  $p = 0.17$ ).

Meta-regression showed that study quality did not significantly affect the effect sizes observed for anxiety ( $\beta = -0.1485$ ,  $SE = 0.08$ ,  $p = 0.06$ ).

### **Depression in women during pregnancy following perinatal loss**

There was a significant small magnitude effect for the association between perinatal loss and increased depression for women during subsequent pregnancies ( $d = 0.22$ , 95% CI = 0.15–0.30,  $Z = 5.81$ ,  $p < 0.0001$ ,  $k = 13$ ) (Figure 3). Excluding one outlier study (Couto et al., 2009) yielded a decreased but significant small effect size for increased depression during pregnancies following perinatal loss ( $d = 0.13$ , 95% CI = 0.08–0.18,  $Z = 5.39$ ,  $p < 0.0001$ ,  $k = 12$ ) and heterogeneity continued to be significant [ $Q = 799.25$ ,  $p < 0.0001$ ,  $I^2 = 98.6\%$  (95% CI = 98.3%–98.9%)] although no significant asymmetry was observed ( $p = 0.11$ ). By including five hypothetical missing studies in the analysis, it was estimated that there would be no significant effect for depression in women during pregnancy following perinatal loss ( $d = 0.02$ , 95% CI = -0.04–0.07,  $p = 0.56$ ,  $k = 17$ ).

Summary data for depression moderator analyses were run to identify potential causes of heterogeneity (Table 4). Type of previous perinatal loss ( $p < 0.01$ ) and the trimester of assessment for depression ( $p = 0.03$ ) showed significant effects on depression in women during subsequent pregnancies (Table 4). No significant difference in depression levels was observed between studies from the USA and other countries ( $p = 0.59$ ). However, year of study publication ( $\beta = -0.0224$ ,  $SE = 0.01$ ,  $p = 0.0004$ ) significantly affected the observed effect sizes. Meta-regression showed that study quality did not significantly affect the effect sizes for depression ( $\beta = -0.02$ ,  $SE = 0.04$ ,  $p = 0.65$ ) in women during pregnancy following perinatal loss.

### **Stress in women during pregnancy following perinatal loss**

Results suggested no significant effect for the association between previous perinatal loss and increased stress levels in women during subsequent pregnancy ( $d = -0.002$ , 95% CI = -0.0639–0.0605,  $Z = -0.05$ ,  $p = 0.96$ ,  $k = 3$ ), heterogeneity was not significant [ $Q = 0.58$ ,  $p = 0.75$ ,  $I^2 = 0.0\%$  (95% CI = 0.0%–64.0%)] and showed no significant asymmetry ( $p = 0.09$ ). The inclusion of one hypothetically missing study did not affect results ( $d = -0.0098$ , 95% CI = -0.0686–0.0489,  $p = 0.74$ ,  $k = 4$ ).

## **Anxiety and depression in men during pregnancy following perinatal loss**

A significant large effect was found for the association between previous perinatal loss and increased anxiety levels in men during subsequent pregnancies ( $d = 0.80$ , 95% CI = 0.5056–1.0968,  $Z = 5.31$ ,  $p < 0.0001$ ,  $k = 3$ ). Heterogeneity was not significant [ $Q = 0.50$ ,  $p = 0.78$ ,  $I^2 = 0.0\%$  (95% CI = 0.0%–58.0%)] and no significant asymmetry was observed ( $p = 0.09$ ).

A small significant effect was found for depression in men during pregnancy following perinatal loss ( $d = 0.30$ , 95% CI = 0.0135–0.5872,  $Z = 2.05$ ,  $p = 0.04$ ,  $k = 3$ ). No significant heterogeneity ( $Q = 0.14$ ,  $p = 0.93$ ,  $I^2 = 0.0\%$ ) or significant asymmetry ( $p = 0.75$ ) were found.

There were no hypothetically missing effects for the analyses of anxiety and depression in men during pregnancy following perinatal loss.

## **Discussion**

### **Main Findings**

Our meta-analysis results support an association between perinatal loss and increased anxiety and depression levels in during subsequent pregnancies. Stress levels in women were not significantly affected during pregnancies following perinatal loss. This analysis also suggests that perinatal loss has a larger effect on anxiety and depression in men than women during subsequent pregnancies, contradicting previous findings (Armstrong, 2002, 2004). However, the sample of men in this analysis was small and these results should be treated with caution.

Perinatal loss type did not affect women's anxiety levels during subsequent pregnancies, reiterating previous findings (Hutti et al., 2015; Robertson Blackmore et al., 2011), but did affect depression levels. Separate analyses of pregnancy-specific/state and trait anxiety suggested a large effect for previous perinatal loss experience on pregnancy-specific anxiety compared with a significant, medium effect on trait anxiety in women during subsequent pregnancies.

Additionally, perinatal loss type significantly affected depression, with miscarriage having no effect on depression during subsequent pregnancy.

### **Strengths and limitations**

The strengths of the current study relate to: the quantitative synthesis of data on psychological distress during pregnancy following perinatal loss, inclusion of only studies using validated psychological distress measures and the quality assessment of studies.

However, there are several limitations. Firstly, combining effect sizes may limit findings as individual studies may measure outcomes differently (Borenstein and Rothstein, 2009). We also were unable to examine additional covariates for anxiety and depression during pregnancy following perinatal loss, such as attachment (Armstrong and Hutti, 1998; Gaudet, 2010), PTSD (Hutti et al., 2015), participants' number of living children (Côté-Arsenault, 2003; Hunfeld et al., 1996; Robertson Blackmore et al., 2011; Woods-Giscombe et al., 2010) and time between the current pregnancy and previous perinatal loss (Robertson Blackmore et al., 2011).

The sample for this meta-analysis was also biased by the number of women who experienced miscarriage as compared to other types of perinatal loss. This may be significant as this analysis suggests that previous perinatal loss type may affect women's depression levels during subsequent pregnancies. Therefore, more targeted studies that examine the effect of specific perinatal loss experiences on subsequent pregnancies may be beneficial in terms of identifying variations in women's need for support during these pregnancies.

Methodological concerns are also relevant. Over half of the studies included primigravida women in control groups which may not reduce baseline differences as pregnancy rather than parenting is being examined in these analyses (Côté-Arsenault, 1999). Therefore, multigravida women may be more comparable controls than primigravida women (Côté-Arsenault, 1999). Additionally, perinatal loss definitions varied across studies and individual studies often excluded women with increased risks of experiencing perinatal losses (for example, women with multiple pregnancies, from ethnic minority backgrounds, living in poverty, experiencing health problems, who are obese or who are teenage

mothers) (Manktelow et al., 2015). Additionally, only five studies adequately reported demographic data (Bicking Kinsey *et al.*, 2015; Couto *et al.*, 2009; Hutti *et al.*, 2011; Turton *et al.*, 2006; Woods-Giscombé *et al.*, 2010). This limitation, added to variation in the available demographic data made it difficult to compare study results, and to control for the effect of demographic characteristics on psychological distress levels.

It is also the case that studies of the association between perinatal loss and subsequent distress do not control for baseline, pre-loss levels of anxiety, depression and stress in women and their partners. Though unlikely, it consequently cannot be ruled out that the results are confounded by higher base-rates of anxiety, depression and stress in the perinatal loss group.

The results of models using hypothetically missing results must be considered with great caution as this method ignores potential causes of asymmetry that are unrelated to publication bias (for example, trimester of assessment) and the adjusted model may not reflect actual population results (Borenstein and Rothstein, 2009; Higgins, 2011).

Moderator analysis results (excluding results for pregnancy-specific/state and trait anxiety analyses) were underpowered as some subgroups contained a single study, a small number of studies and/ or high levels of variance across studies (Borenstein and Rothstein, 2009). One subgroup in each moderator analysis included combined data for perinatal loss type or trimester of assessment which also limited the conclusions that could be drawn. Within the primary papers, data for women who experienced different types of perinatal losses were also often combined making it difficult to control for the effect of perinatal loss type on psychological distress levels. Further research focusing on women and their partners who have experienced specific types of perinatal loss may help improve our understanding of how different types of perinatal loss may affect women and their partners during subsequent pregnancies.

Meta-regression results included a relatively small number of studies, contained a low number of covariates for comparison and the associations between covariates and effects were small (Borenstein and Rothstein, 2009; Thompson and Higgins, 2002).

The analysis of partners of pregnant women with previous perinatal loss experience was limited by very small sample sizes and the lack of studies including same sex partners. Therefore, these results need to be considered with caution, particularly as they run contrary to previous findings suggesting perinatal loss has a greater effect on women than men in terms of psychological distress levels during subsequent pregnancies (Armstrong, 2002, 2004; Turton *et al.*, 2006).

The stress results for this analysis must be considered cautiously as they are derived from a relatively large sample size ( $n = 8240$ ) but a small number of studies ( $k = 3$ ) using different stress measures for women during pregnancy after perinatal loss (one of which was not pregnancy specific) (McCarthy *et al.*, 2015).

## **Interpretation**

Our findings support and extend previous reviews of the field (Debackere *et al.*, 2008). Further subanalyses suggested a difference in anxiety and depression levels in women depending on the trimester in which they are assessed for psychological distress.

Our study supports findings showing that pregnancy-specific anxiety may decrease after specific sources of pregnancy-related anxiety are diminished [for example, after ultrasound scanning for fetal anomalies (Tsartsara and Johnson, 2006) or the gestation of the previous loss (Debackere *et al.*, 2008; Hunter, 2016; Woods-Giscombe *et al.*, 2010)]. These findings may also reflect decreases in anxiety that are seen following the first trimester for pregnant women with no previous perinatal loss experience (Teixeira *et al.*, 2009; Theut *et al.*, 1988). The lower heterogeneity in the pregnancy-specific anxiety analysis may suggest that this provides a better model of anxiety in women during pregnancy following perinatal loss. However, some women may continue to have elevated anxiety levels after the first trimester and into the postpartum period (Brisch *et al.*, 2005; Robertson Blackmore *et al.*, 2011; Woods-Giscombe *et al.*, 2010).

No obvious explanation exists for the higher effect on depression suggested for assessments during the second trimester. Further research is needed to examine depression during pregnancy following perinatal loss.



The finding that miscarriage is not linked with depression during subsequent pregnancy offers support for Lok *et al.*'s (Lok *et al.*, 2010) finding that depression levels were not significantly elevated in women one year after miscarriage. Future research could examine depression in relation to the time period between miscarriage and the current pregnancy. Our depression findings cannot be generalised to include pregnant women with previous recurrent miscarriage (three or more consecutive miscarriages) experience as only one study in this subanalysis indicated the inclusion of these women (Bergner *et al.*, 2008).

Insufficient data were available to examine the effect of previous loss gestation and psychological assessment timing on levels of anxiety, depression and stress. However, future research should examine variations in anxiety and depression levels found in women during different trimesters of pregnancies following perinatal loss and control for the parity of previous losses. Future research could also examine mediating factors (such as parity and having other living children) that may predict persistence of elevated symptoms of anxiety and other types of psychological distress after a previous loss.

The high heterogeneity in this study may relate to differences in definitions of perinatal loss across studies. Additionally, some studies included women with previous experiences of abortion (Bergner *et al.*, 2008; Gaudet, 2010; Gong *et al.*, 2013; Hamama *et al.*, 2010; McCarthy *et al.*, 2015) or pre-term birth (Couto *et al.*, 2009) and it was not possible to separate data for two samples (Couto *et al.*, 2009; Gaudet, 2010) where abortion and pre-term birth data were combined with perinatal loss data. The inclusion of women with previous abortion experience may affect results as abortion is not generally a predictor for subsequent psychological distress (Foster *et al.*, 2015; Steinberg *et al.*, 2014), except in China [e.g. (Gong *et al.*, 2013)] where women experience higher levels of anxiety (but not depression) during pregnancies following abortion which is often used due to the country's one child policy (Huang *et al.*, 2012).

High heterogeneity across studies from different countries and those from the USA may indicate the need to examine how cultural factors, demographics, healthcare provisions and loss experiences may

relate to variations in anxiety and depression levels during pregnancy following perinatal loss (both across and within countries).

This analysis highlights the potential clinical importance of offering women and their partners appropriate assessments for psychological distress across all trimesters of subsequent pregnancies after perinatal loss, including assessments for pregnancy-specific and trait anxiety. Consideration should be given to the possibility that assessment and treatment may be required before women and their partners can access perinatal psychological support. Therefore presentation of distress may occur in primary care or general mental health settings. This has implications for broader awareness amongst mental health and primary care practitioners. Furthermore, the development of psychosocial interventions in response to perinatal loss remains at an early stage (Bennett et al., 2012; Brown-Bowers et al., 2012; Jones et al., 2015) and has not necessarily been targeted at reducing anxiety and depression, either immediately post loss or during a subsequent pregnancy following perinatal loss.

Effective care is important as perinatal loss experiences may have longer-term implications for women, their partners and their children (including those born following perinatal loss) in terms of attachment, familial relationships and emotional and physical well-being (Armstrong and Hutti, 1998; Gaudet, 2010; Hutti et al., 2015; Redshaw et al., 2014; Turton et al., 2009a; Turton et al., 2009b; Wojcieszek et al., 2016). In particular, some women who were pregnant following experiences of stillbirth and neonatal death highlighted the importance of: having continuity of care (sometimes from a professional with whom they had a previous relationship); good communication between professionals; labelling of their notes to indicate a previous experience of perinatal loss; carers carefully reading notes and medical records; having more frequent and easier access to antenatal care (including for their mental well-being); and health care professionals acknowledging that they may have the same experience of loss during these subsequent pregnancies (Redshaw et al., 2014). Additional studies examining the relationship between seeing and holding the baby following perinatal loss experiences and psychological well-being during subsequent pregnancies may also be important for making effective care recommendations (Redshaw et al., 2016). Pregnancies following perinatal loss may also be an opportune time to follow-up on the well-being of some individuals who

experience perinatal loss to help to reduce the higher mortality rates of individuals who experience stillbirth or the death of an infant (Halland et al., 2016; Harper et al., 2011), including complicating factors such as mental health and substance problems (Harper et al., 2011).

## **Conclusions**

This meta-analysis combines existing data and highlights the significant effect of perinatal loss on anxiety and depression in women during subsequent pregnancy, confirming previous review findings (Debackere et al., 2008). Limitations around moderators demonstrate the need for additional, more robust research investigating predictors of psychological distress during pregnancy following perinatal loss. Large maternity care cohort studies should collect longitudinal data during all trimesters of pregnancy and the postpartum period for psychological distress in women and their partners (including same-sex partners).

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## **Declaration of Interests**

AH was a previous employee and consultant for Sands (the Stillbirth and neonatal death charity). AM has been in receipt of funding from the Chief Scientists Office of the Scottish Government for research into pregnancy and major mental health difficulties. LT has no conflicts of interest to declare.

## **Details of Ethics Approval**

The meta-analysis did not involve the recruitment of participants and was not subject to external ethics review processes.

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## **Contributions to Authorship**

All authors provided substantial contributions to the conception and design of this research and were responsible for the final approval of the version of the article that is to be published. AM provided ongoing supervision and guidance to AH and LT who were responsible for the analysis and interpretation of data as part of their MSc research. AH drafted the article for submission. All authors contributed to the final submitted version. All authors agree to be accountable for all aspects of the work and will ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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## Figure and Table Caption List

**Figure 1** PRISMA flow diagram detailing the study selection process

**Figure 2** Forest plot of random effects model of effect sizes for studies of anxiety in women during pregnancy following perinatal loss

**Figure 2 Legend:** CI = Confidence interval; seTE = Standard error of treatment effect; SMD = Standardised mean difference; TE = Treatment effect; W = Weight.

**Figure 3** Forest plot of random effects model of effect sizes for studies of depression in women during pregnancy following perinatal loss

**Figure 3 Legend:** CI = Confidence interval; seTE = Standard error of treatment effect; SMD = Standardised mean difference; TE = Treatment effect; W = Weight.

**Table 1** Study characteristics and demographic details

**Table 2** Quality assessment ratings based on the AHRQ Checklist

**Table 3** Results of moderator analyses for anxiety in women during pregnancy following perinatal loss

**Table 4** Results of moderator analyses for depression in women during pregnancy following perinatal loss

## Appendix S1: Search terms

The full list of search terms that was used in all possible combinations to search each database as part of this meta-analysis includes:

1. anx\* OR depress\* OR stress\*
2. "subsequent pregnanc\*" OR "next pregnanc\*" OR "following pregnanc\*" OR "pregnanc\* after"
3. "miscarri\*" OR "perinatal death\*" OR "perinatal loss\*" OR "pregnancy loss\*" OR "childbearing loss\*" OR "abortion\* N2 spontaneous" OR "habitual\* N2 abortion" OR "stillbirth\*" OR "still-birth\*" OR "fetal death\*" OR "foetal death\*" OR "intrauterine death\*" OR "intra-uterine death\*" OR "IUFD" OR "neonatal death\*" OR "baby death\*" OR "infant death\*" OR "newborn death\*" OR "new born death\*" OR "termination of pregnanc\* for fetal anomal\*" OR "termination of pregnanc\* for foetal anomal\*" OR "termination of pregnanc\* for fetal abnormalit\*" OR "termination of pregnanc\* for foetal abnormalit\*" OR "termination of pregnanc\* for fetal malformation\*" OR "termination of pregnanc\* for foetal malformation\*" OR "termination of pregnanc\* for fetal deformit\*" OR "termination of pregnanc\* for foetal deformit\*" OR "termination of pregnanc\* for fetal irregularit\*" OR "termination of pregnanc\* for foetal irregularit\*" OR "TOPFA" OR "termination of pregnanc\* for congenital anomal\*" OR "termination of pregnanc\* for congenital abnormalit\*" OR "termination of pregnanc\* for congenital malformation\*" OR "termination of pregnanc\* for congenital deformit\*" OR " termination of pregnanc\* for congenital irregularit\*"

Combined terms: 1 AND 2 AND 3.

ADJ2 was used instead of N2 for databases that were searched using Ovid.

## **Appendix S2: Extracted data**

The data for the following variables was extracted from all studies included in the review:

- author names and location;
- title;
- country of study;
- year of publication;
- study design (longitudinal, cross-sectional, analysis of secondary data);
- sample sizes for perinatal loss and control groups;
- demographic details of participants (where reported), including age, marital status, employment, socioeconomic status, education, ethnicity, perinatal losses experienced, number of perinatal losses and/ or timing of assessment for psychological distress;
- data required to calculate effect sizes (sample size, mean scores for anxiety/ depression/ stress, standard deviations, odds ratios (ORs), confidence intervals and/ or the numbers of participants with anxiety, depression or stress in the perinatal loss and control groups);
- and the diagnostic tool(s) used by each study (Dykiert, n.d.).

**Table 1** Study characteristics and demographic details

<i>Author(s) (Year)</i>	<i>Location of study</i>	<i>Sample size (Perinatal loss/ control group- Female participants unless specified)</i>	<i>Number of assessments/ Time when assessed</i>	<i>Perinatal loss experience</i>	<i>Measures of anxiety, depression and/ or stress used</i>	<i>Mean age in years (Perinatal loss/ control group unless specified)</i>	<i>Ethnicity (%)</i>	<i>Relationship status (%)  (Married or in a relationship)<sup>d</sup></i>	<i>Education (Mean number of years unless specified)<sup>d</sup></i>
<b>Armstrong &amp; Hutti (1998)</b>	USA	31 (16/15)	One/ Second or third trimester	Late miscarriage, stillbirth, neonatal death	POQ	31.5/26	Unreported	<i>Perinatal loss group:</i> 100  <i>Control group:</i> 93.33	<i>Perinatal loss group:</i> 15.69 years  <i>Control group:</i> 14.67 years
<b>Armstrong (2002)</b>	USA	70 (40/30) <sup>a</sup> women  70 (40/30) <sup>a</sup> men	One/ Second or third trimester	Miscarriage, stillbirth, neonatal death	POQ; CES-D	32.7/29.5	<i>Perinatal loss group:</i>  White: 90; Unreported: 10   <i>Control</i>	100	Unreported

							<i>group:</i>		
							Unreported		
<b>Bergner et al. (2008)</b>	Germany	131 (62/69) <sup>b</sup>	One/ First trimester	Miscarriage (before 16 weeks' gestation)	STAI (German version); PSA Scale; The Depression Scale	32.06 <sup>d</sup>	Unreported	97.1	62% high school, advanced technical or university degree; 30.7% secondary school; 5% primary or lower vocational school degree
<b>Bicking Kinsey et al. (2015)</b>	USA	2791 (448/2343)	Four/ Third trimester and 1, 6 and 12 months postpartum	Miscarriage (before 20 weeks' gestation)	EPDS; Psychological Hassles Scale	28.2/27.1	<i>Perinatal loss group:</i> White: 85.7; Black: 7.1; Hispanic: 3.8; Other: 3.3	72.1	16.2% high school, GED or less; 26.0% some college or vocational programs; 57.8% completed 4 year degree or higher
							<i>Control group:</i>		
							White: 84.6; Black: 6.3; Hispanic:		

5.4;  
Other: 3.7

<b>Côté-Arsenault (2003)</b>	USA	170 (74/96)	One/ Second or third trimester	Miscarriage, stillbirth, neonatal death	STAIS; POQ	32.8 <sup>d</sup> (Age range 19-44)	White: 91; Other: 9	92.9	15.1 years
<b>Couto et al. (2009)</b>	Brazil	240 (120/120)	One/ Second trimester	Miscarriage, stillbirth, neonatal death	HADS; SF-36	30.3/27.6	<i>Perinatal loss group:</i>  White: 73; Other: 27	<i>Perinatal loss group:</i>  88	<i>Perinatal loss group:</i>  >10 = 32%
							<i>Control group:</i>  White: 70; Other: 30	<i>Control group:</i>  75	<i>Control group:</i>  >10 = 46%

<b>Franché &amp; Mikail (1999)</b>	Canada	62 (31/31) women 51 (28/23) men	One/ First or second trimester	Miscarriage, stillbirth, neonatal death	STAI; POQ; BDI	29.83 <sup>d</sup> (Age range 19-40)  <i>Couples:</i> 32.76 <sup>d</sup> (Age range 20-46)	Born in Canada: 91 Not born in Canada: 9	100	14.97
<b>Gaudet et al. (2010)</b>	France	170 (96/ 74)	One/ First, second or third trimester	Termination of pregnancy, miscarriage, TOPFA, stillbirth, neonatal death	HADS	29.8 (Age range 24-41)/ 27  (Age range 20-36)	Unreported	<i>Perinatal loss group:</i> 99  <i>Control group:</i> Unreported	Unreported
<b>Gong et al. (2010)</b>	China	11828 (861/ 10967) <sup>c</sup>	One/ First or second trimesters	Miscarriage	SAS; CES-D	26.49 <sup>d</sup> (Age range 17-46)	Unreported	Unreported	<i>Perinatal loss group:</i> <9 years (n=220); 10~ (n=223); ≥13 (n=418)  <i>Control group:</i>

									<9 years (n=2957); 10~ (n=2438); ≥13 (n=5572)
<b>Hamama et al. (2010)</b>	USA	1360 (184/1176) <sup>c</sup>	One/ Unspecified	Miscarriage	CIDI Short Form	26 <sup>d</sup>	White: Unreported; Black: 45; Hispanic: 4.2; Asian: 7.1; Native American/ Alaskan: 1.5; Native Hawaiian/ Pacific Islanders: 0.4; Other: 3.2	<i>Perinatal loss group:</i>  57.6          <i>Control group:</i> 63	<i>Perinatal loss group:</i>  56.8% secondary education or less          <i>Control group:</i> 43.5% secondary education or less
<b>Hughes et al. (1999)</b>	UK	120 (60/60)	Two/ Third trimester and one year postpartum; 6 and 26 weeks postpartum for depression only	Stillbirth	STAI; EPDS; BDI	30 (Age range 20- 46)/ 29 (Age range 20- 43)	<i>Matched pairs (perinatal loss/ control group:</i>  White: 39; Black: 11; Asian: 1; Indian or Pakistani: 9	Unreported	Unreported
<b>Hunfeld et al. (1996)</b>	The Netherlands	44 (18/26) <sup>b</sup>	Four/ Second and third trimesters (2 weeks	Perinatal loss resulting from severe fetal	STAI (Dutch Adaptation); POQ (Adapted by	32.8 (Age range 21-	Unreported	Unreported	Unreported



			before, 1 day before, 1 day after and 4 weeks after 18-21 week anomaly scan)	structural pathology	their research group)	39)/ 33.3  (Age range 26-38) <sup>e</sup>			
<b>Hutti et al. (2011)</b>	USA	68 (36/32) <sup>a</sup>	One/ Third trimester	Miscarriage, stillbirth, neonatal death	STAI; CES-D	31.3/30.1	<i>Perinatal loss group:</i>  White: 93.1; Black: 2.8; Hispanic: 2.8; Asian: 1.4	<i>Perinatal loss group:</i>  33.6	<i>Perinatal loss group:</i>  high school - 7.0%; college graduate - 25.0%; advanced degree - 68.0%
							<i>Control group:</i>  White: 98.8; Hispanic: 1.2	<i>Control group:</i>  35.5	<i>Control group:</i>  high school - 12.2%; college graduate - 13.4%; advanced degree - 74.4%
<b>McCarthy et al. (2015)</b>	Multi-site (New Zealand/ Australia/ Ireland/ UK)	4890 (559/4331) <sup>b</sup>	One/ Second trimester	Miscarriage (before 20 weeks' gestation)	STAI (Short Form); EPDS; Perceived Stress Scale	29.6/28.4	<i>Perinatal loss group:</i>  White: 92; South Asian: 2; Other: 6	<i>Perinatal loss group:</i>  94	Unreported

							<i>Control group:</i>		
							White: 90; South Asian: 3; Other: 7	<i>Control group:</i> 90	
<b>Roberston Blackmore et al. (2011)</b>	USA	12408 (2158/ 10250) <sup>b</sup>	Six/ Second and third trimesters and 2, 8, 21 and 33 weeks postpartum		CCEI; EPDS	27.78*  (Age range 15-45)	White: 97.39; Ethnic minority: 2.61	76.17	None or certificate of secondary education - 20.20%; vocational - 9.84%; ordinary level/ general certificate of secondary education - 34.64%; advanced Level - 22.45; degree - 12.87%
<b>Tsartsara &amp; Johnson (2006)</b>	UK	Trimester 1: 35 (10/25); Trimester 2: 23 (5/18)	Two/ First and third trimesters	Miscarriage, stillbirth	POQ	30.4*  (Age range 19-44)	Unreported	85.6	Unreported
<b>Turton et al. (2006)</b>	UK	76 (38/38) men	Two/ Third trimester and one year postpartum; Also 6 weeks and 6 months postpartum for depression	Miscarriage	STAI; BDI	34.84/35.58	<i>Perinatal loss group:</i>  White: 72.4; Black: 14.4; South Asian: 10.5; Other: 2.6	100	<i>Perinatal loss group:</i>  No examinations - 0%; O level - 22.4%; A level - 26.3%; university - 51.3%  <i>Control group:</i>
							<i>Control</i>		

				only				<i>group:</i>	No examinations - 3.9%; O level - 14.5%; A level - 23.7%; university - 57.9%
<b>Woods-Giscombé et al. (2010)</b>	USA	363 (113/250)	Three/ First, second and third trimesters	Stillbirth	State Anxiety Subscale of the STPI; PDQ	28.2/26.5	<i>Perinatal loss group:</i> White: 56.6; Black: 15; Hispanic: 12.4; Asian: 1.8; Native Americans: 0.9; Other: 12.4	<i>Perinatal loss group:</i> 69	<i>Perinatal loss group:</i> Junior high school - 2.7%; some high school - 16.8%; graduated high school - 34.5%; some college - 37.2%; graduated college - 8.0%; graduate degree - 0.9%
							<i>Control group:</i> White: 69.6; Black: 10.8; Hispanic: 10.8; Asian: 2.0; Native Americans: 0.4; Other: 6.8	<i>Control group:</i> 67.2	<i>Control group:</i> Junior high school - 0.40%; some high school - 12.2%; graduated high school - 39.3%; some college - 38.1%; graduated college - 7.7%; graduate degree - 2.4%
<b>Yilmaz &amp; Beji (2013)</b>	Turkey	342 (128/214)	One/ Third trimester	Miscarriage	CES-D	29.93/28.02	Unreported	100	<i>Perinatal loss group:</i> Literate - 2.3%; primary school - 57.7%; secondary

school - 25.8%; college - 14.8%

*Control group:*

Literate - 1.4%; primary school - 44.4%; secondary school - 30.4%; college - 23.8%

*Note.* BDI = Beck Depression Inventory; CCEI = Crown-Crisp Experiential Index; CES-D = Center for Epidemiological Studies - Depression Scale; CIDI = Composite International Diagnostic Interview; EPDS = Edinburgh Postnatal Depression Scale; HADS = Hospital Anxiety and Depression Scale; PDQ = Prenatal Distress Questionnaire; POQ = Pregnancy Outcome Questionnaire; PSA = Pregnancy-Specific Anxiety; SAS = Self-rating Anxiety Scale; SF-36 = Short Form-36 Quality of Life Questionnaire; STAI = State Trait Anxiety Inventory; STAIS = STAI State Anxiety Scale; STPI = State-Trait Personality Inventory.

<sup>a</sup>More than one control group sample was available for these studies and the multigravida control group was selected over primigravidae controls.

<sup>b</sup>More than one perinatal loss group sample was available. The larger sample was selected for inclusion in this study as it is more likely to be representative of a larger sample.

<sup>c</sup>Case groups which included women with previous abortion experiences were available but excluded from this analysis.

<sup>d</sup>Perinatal loss and control group data combined.

<sup>e</sup>Median age reported instead of mean age.

**Table 2** Quality assessment ratings based on the AHRQ Checklist. Quality assessment grades were compared by two independent researchers and a consensus was reached for all grades (see *Study quality* above for details). Assessment grades were scored using the following values: Yes = 2; Partially = 1; No/ Can't tell = 0.

<i>Author(s) (Year)</i>	<i>Unbiased selection of the perinatal loss cohort?</i>	<i>Selection minimizes baseline differences in prognostic factors?</i>	<i>Sample size calculated ?</i>	<i>Adequate description of the cohort?</i>	<i>Identification of perinatal loss experience?</i>	<i>Validated method for ascertaining depression, anxiety and/or stress?</i>	<i>Outcome assessment blind to exposure?</i>	<i>Missing data/drop- out (acceptable amount)?</i>	<i>Analysis controls for confounding mental health predictors/ correlates in subsequent pregnancy?</i>	<i>Analytic methods appropriate?</i>	<i>Total AHR Q Score</i>
<b>Armstrong &amp; Hutti (1998)</b>	Partially	Partially	No	Partially	No	Yes	Can't tell	Yes	No	Yes	9
<b>Armstrong (2002)</b>	Yes	Partially	Yes	Partially	Partially	Yes	Can't tell	Yes	No	Yes	13
<b>Bergner <i>et al.</i> (2008)</b>	Yes	Partially	No	Partially	Yes	Yes	Can't tell	Yes	Yes	Yes	14
<b>Bicking Kinsey <i>et al.</i> (2015)</b>	Yes	Yes	Yes	Yes	Yes	Yes	Can't tell	Yes	Yes	Yes	18
<b>Côté- Arsenault (2003)</b>	Partially	Partially	Yes	Partially	Yes	Yes	Can't tell	Yes	Partially	Partially	13
<b>Couto <i>et al.</i></b>	Partially	Partially	Yes	Yes	Yes	Yes	Can't tell	Yes	Partially	Partially	14

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<b>(2009)</b>											
<b>Franche &amp; Mikail (1999)</b>	Partially	Partially	No	Partially	Yes	Yes	Can't tell	No	Yes	Yes	11
<b>Gaudet et al. (2010)</b>	No	No	Partially	No	Yes	Yes	Can't tell	Yes	Yes	Partially	10
<b>Gong et al. (2010)</b>	Yes	Partially	No	Partially	Can't tell	Yes	Can't tell	Yes	Yes	Yes	12
<b>Hamama et al. (2010)</b>	Yes	No	No	Partially	Yes	Yes	Can't tell	Yes	Yes	Partially	12
<b>Hughes et al. (1999)</b>	Partially	Yes	No	Partially	Yes	Yes	Can't tell	Partially	No	Yes	11
<b>Hunfeld et al. (1996)</b>	Yes	No	No	No	Yes	Yes	Can't tell	Partially	Partially	Yes	10
<b>Hutti et al. (2011)</b>	Partially	Partially	Yes	Yes	Partially	Yes	Can't tell	Yes	Partially	Yes	14
<b>McCarthy et al. (2015)</b>	Yes	Partially	No	Partially	Can't tell	Yes	Can't tell	Yes	Yes	Yes	12
<b>Roberston Blackmore et al. (2011)</b>	Partially	Can't tell	No	Partially	Yes	Yes	Can't tell	Partially	Yes	Yes	11
<b>Tsartsara &amp; Johnson (2006)</b>	Partially	Can't tell	No	No	Yes	Yes	Can't tell	No	Partially	Yes	8

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<b>Turton <i>et al.</i> (2006)</b>	Partially	Yes	No	Yes	Yes	Yes	Can't tell	No	Yes	Yes	13
<b>Woods-Giscombé <i>et al.</i> (2010)</b>	Partially	Yes	No	Yes	Partially	Yes	Can't tell	Yes	Yes	Partially	13
<b>Yilmaz &amp; Beji (2013)</b>	Partially	Partially	Yes	Partially	Yes	Yes	Can't tell	Can't tell	Partially	Partially	11

*Note.* Scored using the following values: Yes = 2; Partially = 1; No/ Can't tell = 0.

**Table 3** Results of moderator analyses for anxiety in women during pregnancy following perinatal loss

Moderator	<i>k</i>	<i>d</i> (95% CI), <i>p</i> value	<i>Q</i> test	<i>I</i> <sup>2</sup> (%)
<b><i>Perinatal loss type</i></b>				
Combined perinatal loss types <sup>a</sup>	7	0.85 (0.52–1.19), <i>p</i> < 0.0001	909.62	99.3
Miscarriage	5	0.45 (0.18–0.72), <i>p</i> < 0.0001	282.22	98.6
Anomaly-related	1	0.50 (0.3088–0.6882)	0.00	-
<b><i>Trimester of anxiety assessment</i></b>				
First trimester	4	0.61 (0.26–0.95), <i>p</i> < 0.0001	57.39	94.8
Second trimester	5	0.44 (-0.01–0.90), <i>p</i> < 0.0001	2303.21	99.8
Third trimester	1	0.26 (0.15–0.38)	0.00	-
Combined trimester data <sup>a</sup>	4	1.12 (0.67–1.56), <i>p</i> < 0.0001	153.71	98.0
<b><i>Type of anxiety assessed</i></b>				
Pregnancy-specific anxiety	9	0.83 (0.53–1.13), <i>Z</i> = 5.41, <i>p</i> < 0.0001	26.13	69.4 (95% CI 38.9–84.7)
Trait anxiety	8	0.53 (0.14–0.92), <i>Z</i> = 2.66, <i>p</i> = 0.0078	3765.64	99.8
<b><i>Country of study</i></b>				
USA	5	0.73 (0.35–1.10), <i>p</i> < 0.0001	222.61	98.2
All other countries combined	8	0.65 (0.25–1.06), <i>p</i> < 0.0001	3809.74	99.8

<sup>a</sup>Where separate data were unavailable for different perinatal loss types or trimesters of assessment.

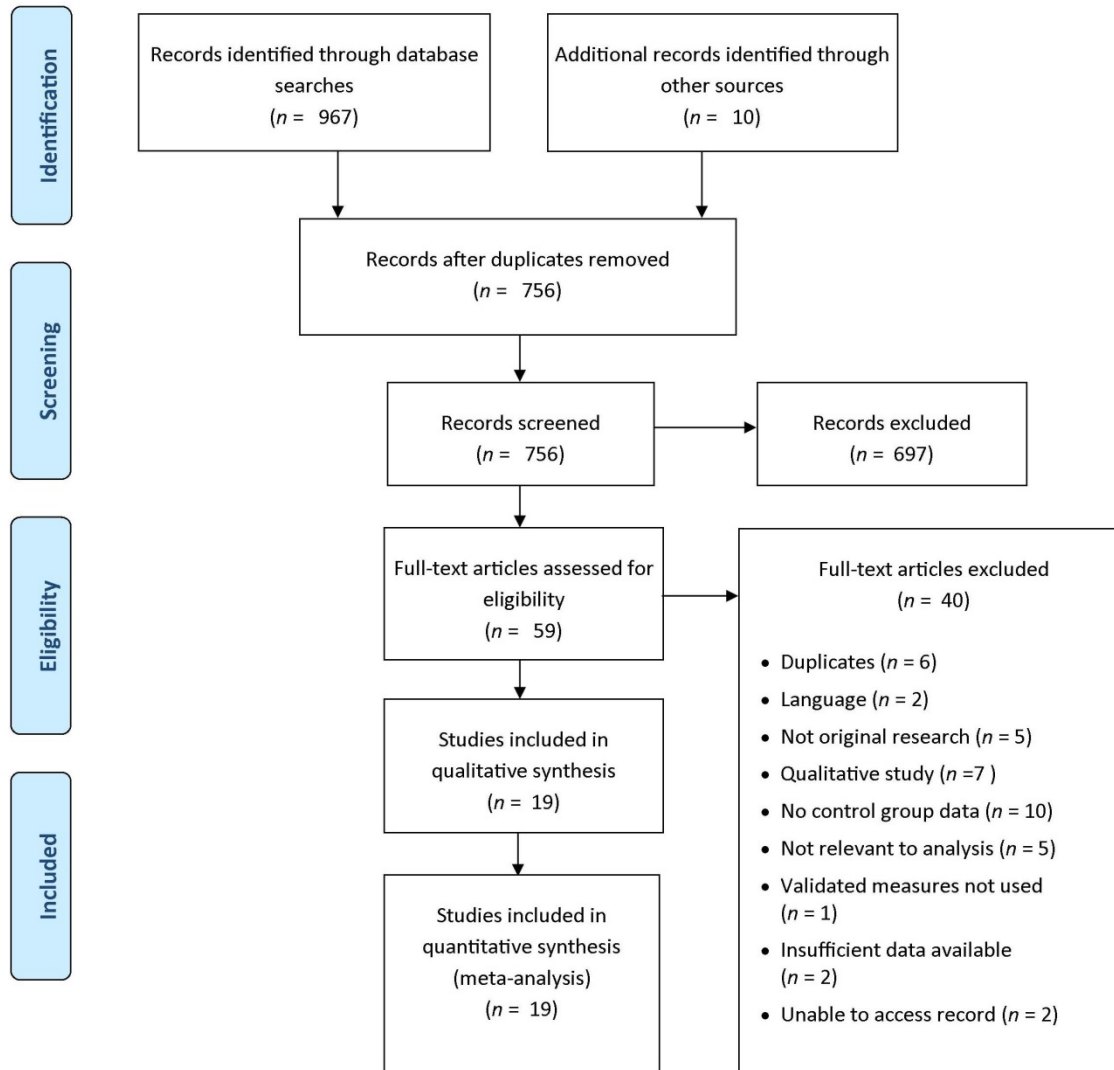


**Table 4** Results of moderator analyses for depression in women during pregnancy following perinatal loss

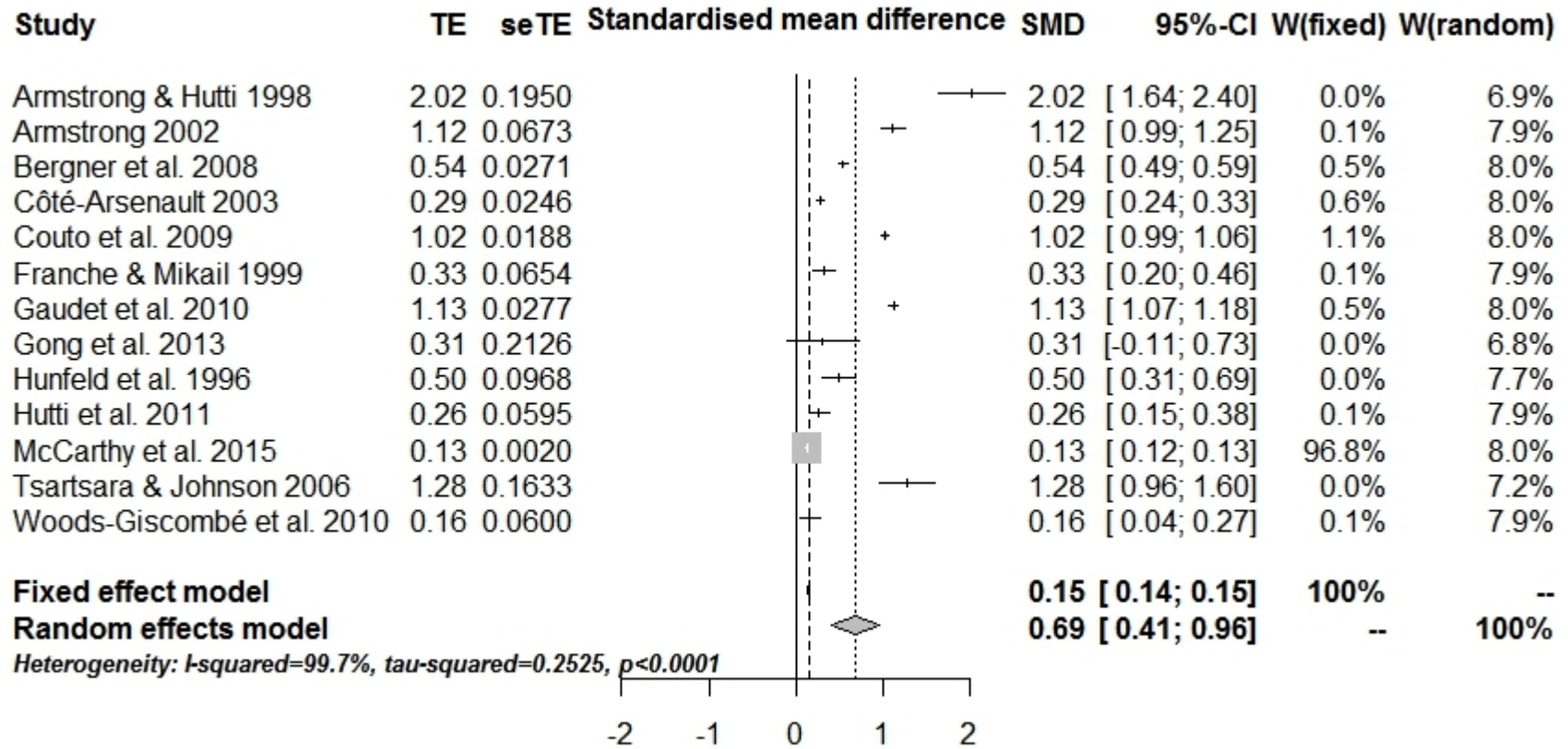
Moderator	<i>k</i>	<i>d</i> (95% CI), <i>p</i> value	<i>Q</i> test	<i>I</i> <sup>2</sup> (%)
<b>Perinatal loss type</b>				
Combined perinatal loss types <sup>a</sup>	7	0.32 (0.08–0.55), <i>p</i> < 0.0001	755.32	99.2
Miscarriage	5	-0.01 (-0.02–0.01), <i>p</i> = 0.0001	22.78	82.4
Stillbirth	1	0.81 (-0.26–1.88)	0.00	-
<b>Trimester of depression assessment</b>				
First trimester	2	-0.03 (-0.28–0.22), <i>p</i> = 0.19	1.70	41.3
Second trimester	3	0.32 (-0.33–0.98), <i>p</i> < 0.0001	2000.26	99.9
Third trimester	4	0.06 (-0.04–0.16), <i>p</i> < 0.05	8.05	62.7
Combined trimester data <sup>a</sup>	5	0.29 (0.15–0.45), <i>p</i> < 0.0001	84.19	95.2
<b>Country of study</b>				
USA	4	0.18 (-0.02–0.39), <i>p</i> < 0.0001	43.97	93.2
All other countries combined	9	0.27 (0.04–0.49), <i>p</i> < 0.0001	2708.86	99.7

<sup>a</sup>Where separate data were unavailable for different perinatal loss types or trimesters of assessment.

Figure 1: PRISMA flow diagram detailing the study selection process

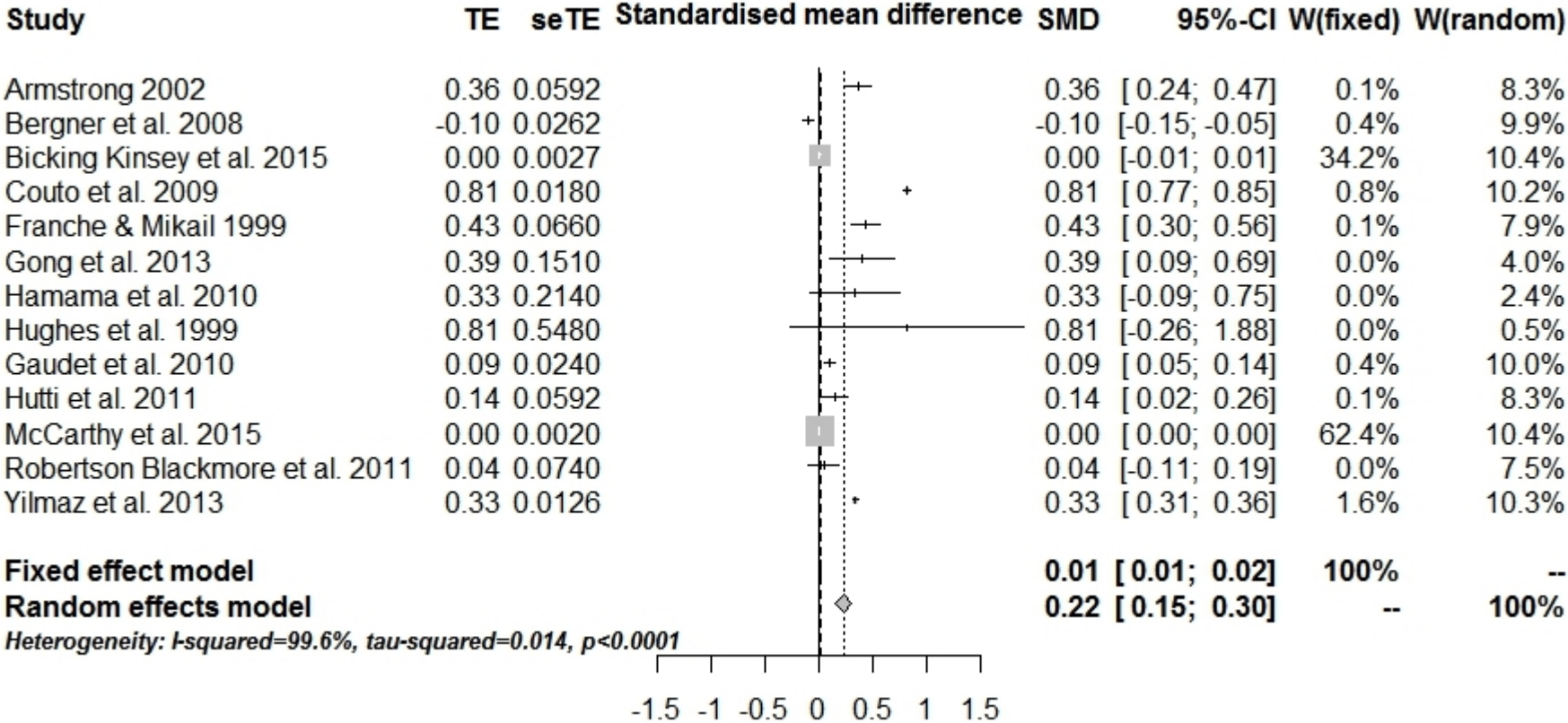


**Figure 2** Forest plot of random effects model of effect sizes for studies of anxiety in women during pregnancy following perinatal loss



Notes: CI = Confidence interval; seTE = Standard error of treatment effect; SMD = Standardised mean difference; TE = Treatment effect; W = Weight.

Figure 3: Forest plot of random effects model of effect sizes for studies of depression in women during pregnancy following perinatal loss



Notes: CI = Confidence interval; seTE = Standard error of treatment effect; SMD = Standardised mean difference; TE = Treatment effect; W = Weight.