Factors Associated with Pregnancy-Related Anxiety: A Systematic Review and Meta-Analysis

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Abstract

The experience of general anxiety is common during pregnancy. However, research suggests that anxiety experienced during pregnancy is less generalised and more specific. This form of anxiety is known as Pregnancy-Related Anxiety (PrA). Research consistently supports the notion that PrA is a distinct anxiety disorder but poor conceptual understanding remains a challenge to the knowledge in this field. This comprehensive systematic review and meta-analysis aims to explore prevalence of PrA and pregnancy-related factors associated with levels of PrA. A systematic search of four electronic databases was conducted (PubMed, PsychINFO, CINAHL, and Embase). A total of 18 primary studies, consisting of 10,177 participants were included in the final analyses. Nine analyses were conducted including: prevalence of high rates of PrA by proportions, and standardised mean differences of pregnancy trimesters, parity, method of conception and history of pregnancy loss. Results found that 14.1% of women experienced high levels of PrA. They were also suggestive that nulliparous women and those with a history of pregnancy loss may be likely to experience higher levels of PrA. Further research is recommended to allow for better understanding of the prevalence of PrA and its associated factors, and to enable better support programs to be provided to women during the prenatal period.

Keywords: pregnancy-related anxiety; pregnancy-specific anxiety; parity; spontaneous conception; assisted reproduction; pregnancy loss

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DECLARATION:

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Amber Murray

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Chapter 1: Introduction

1.1 Overview

Conceiving a pregnancy is a time of excitement but can also be a time of apprehension and anxiety. It has been known for some time that women may experience anxiety whilst pregnant, but more recently it has been suggested that a specific anxiety disorder, unique to pregnancy, pregnancy-related anxiety (PrA), exists. Research consistently supports the existence of this form of anxiety during pregnancy, which has been shown to have negative impacts on the physical and psychological health of the mother and baby. However, with poor conceptual understanding and a lack of efficient screening methods, progression of knowledge about this form of anxiety faces great challenges. Further research is required in order to provide health care professionals with increased understanding about this form of anxiety, and in turn to ensure that better support is provided to pregnant women during the prenatal period.

1.2 Anxiety During Pregnancy

Anxiety disorders are the most prevalent form of psychiatric disorder, affecting approximately one in three people over the course of their lifetime (Bandelow & Michaelis, 2015). These disorders are associated with considerable impairment, resulting in high health care use and economic burden (Bandelow & Michaelis, 2015; Hoffman, Dukes, & Wittchen, 2006). Various categories of anxiety disorders, all presenting with distinct clinical manifestations, are recognised by the American Psychiatric Association (APA) in the Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-V; APA, 2013). It has been argued by some that this makes anxiety a multifaceted construct which is not always appropriately diagnosed or treated (Bandelow & Michaelis, 2015; Newham, Westwood, Aplin, & Wittkowski, 2012).

The experience of anxiety during pregnancy is common and widely reported in the literature. It has been suggested that 10-25% of all pregnant women experience mild to moderate levels of anxiety during pregnancy (Dayan, Creveuili, Marks, Conroy, Herlicoviez, Dreyfus, Tordjman, 2006; Madhavanprabhakaren, D/Sousa & Nairy, 2015). However, although pregnancy has been associated with higher rates of Generalised Anxiety Disorder (GAD), research indicates that a considerable amount of the variance between anxiety symptoms experienced during pregnancy cannot be explained by GAD or comorbidity with other mental disorders (Brunton, Dryer, Saliba and Kohlhoff, 2018; Huizink, Mulder, Robles De Medina, Visser, Buitelaar, 2004; Theut, Pedersen, Zaslow, Rabinovich, 1988). Therefore, researchers commenced investigations in an attempt to make sense of this unexplained variance.

Evidence suggesting the existence of a distinct anxiety disorder specific to pregnancy was first provided by Theut et al. (1988) when women with previous pregnancy loss were compared to those without prior loss. At that time, researchers were exploring 'parental anxiety'. Using the Pregnancy Outcome Questionnaire (POQ; Theut et al., 1988), developed to effectively measure aspects of parental anxiety, such as concerns regarding the pregnancy, wellbeing of the baby and general anxieties, and State Trait Anxiety Inventory (STAI; (Speilberger, 1968, 1977), Theut et al. (1988) surveyed 56 expectant women. They found that approximately half the women had experienced perinatal loss within the previous two years. Women with a history of perinatal loss scored significantly higher on the POQ than women who had not experienced loss; no differences were noted for the STAI (Theut et al., 1988). On this basis, it was concluded that women who had previous perinatal loss experienced pregnancy anxiety that was more specific, and less generalised, in comparison to those women who had not experienced loss (Theut et al., 1988).

It was not until nearly 20 years later, that Huizink and colleagues (Huizink et al., 2004) were influential in conceptualising PrA as a distinct form of anxiety. In 2004, key distinctions were found between anxiety symptoms during pregnancy and those of generalised anxiety. This was the first time that variations in anxiety experienced during pregnancy, could not be explained by other forms of anxiety or comorbidity (Huizink et al., 2004). This resulted in the term PrA being coined and postulated to describe a distinct anxiety disorder that is specific to pregnancy, expressly associated with pregnancy-related fears (Huizink et al., 2004).

PrA has been defined as worries, concerns and fears about pregnancy, childbirth, infant health, and future parenting (See Figure 1; Huizink et al., 2004). This type of anxiety differs from general anxiety that women may experience during pregnancy or other disorders that may be associated with pregnancy, such as tokophobia. Tokophobia has been classified as a pathological fear of pregnancy (Bhatia & Jhanjee, 2012), which can be primary or secondary (Hoffberg & Brockington, 2000). Primary tokophobia is morbid fear of childbirth in women who have no previous experience of pregnancy, while secondary tokophobia is defined as morbid fear of childbirth developing after a traumatic obstetric event in a previous pregnancy (Hoffberg & Brockington, 2000) Some argue that tokophobia is a symptom of depression and may develop in adolescence and prior to any pregnancy (Hoffberg & Brockington, 2000). For the purpose of the current research the construct of interest is specifically PrA as opposed to general anxiety in pregnancy or tokophobia.

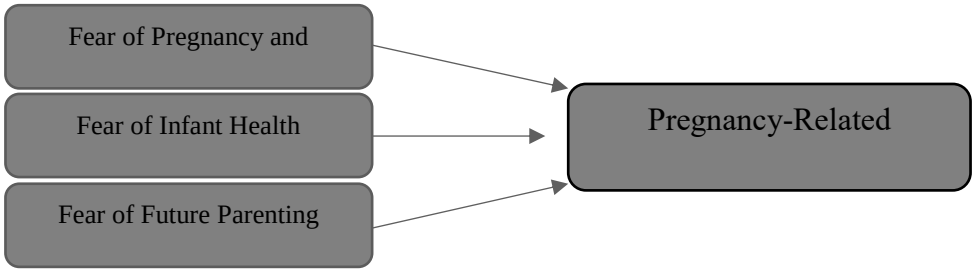

Figure 1. Model Conceptualising Pregnancy-Related Anxiety

Since the notion of PrA was suggested, much research has been undertaken in the area including the development of questionnaires to measure the construct. Common measures include the Pregnancy Outcome Questionnaire (POQ; Theut et al., 1988), Pregnancy Anxiety Scale (PAS; Levin, 1991), Pregnancy-Related Anxiety Questionnaire (PRAQ; Van Den Bergh, 1990; PRAQ-R; Sikkema, Robles De Medina, Schaad, Mulder, Bruinse, Buitelaar, Visser, Franx, 2001; PRAQ-R2; Huizink et al., 2004). Research in this field using such measures has consistently supported the idea that PrA is a distinct anxiety disorder. In addition, reviews conducted in the field also support PrA as a distinct disorder with clinical significance (Bayrampour, Ali, McNeil, Benzies, MacQueen, Tough, 2015; Brunton, Dryer, Saliba, & Kohlhoff, 2015; Schetter & Tanner, 2012).

1.3 Impact of PrA

PrA has been shown to have significant adverse impacts on the physical and psychosocial wellbeing of mothers and babies. A brief review of such impacts is provided below.

1.3.1 Physical Health Impacts

Reports consistently show an association between PrA and adverse outcomes for both mother and baby (Glover, 2014; Huizink et al., 2004; Huizink, Menting, Oosterman, Verhage, Kunseler, Schuengel, 2014; Westerneng, Witteveen, Warmelink, Spelten, Honig, De Cook, 2017). Adverse physical health outcomes of PrA have included increased risk of preterm birth (Dole et al., 2003; Kramer et al., 2009) and greater risk of emergency caesarian section (Fenwick, Gamble, Nathan, Bayes & Hauck, 2009; Madhavanprabhakaran et al., 2013). PrA has also been associated with low birth weight (Lobel, Cannella, Graham, Schneider, & Meyer, 2008).

1.3.2 Psychosocial Impacts

The literature also suggests that PrA has significant psychosocial impacts. Some studies suggest that PrA increases the risk of postnatal mood disturbances such as postnatal depression, for mothers (Blackmore, Gustafsson, Gilchrist, Wyman, & O'Connor, 2016; Heron, O'Connor, Evans, Golding, & Glover, 2004; Robertson, Grace, Wallington & Stewart, 2004), while others report psychosocial implications for the baby (Huizink et al., 2004; Westerneng, et al., 2017). Researchers have found that experiencing anxiety during pregnancy is among the strongest risk factors for maternal postnatal depression (Heron et al., 2004; Robertson et al., 2004). Moreover, it has been suggested that postnatal mood disturbances still present at 6months post-partum, indicate that PrA is not resolved by the birth of the child (Blackmore, et al., 2016).

Furthermore, PrA has been found to have adverse outcomes for babies born to mothers who have experienced this condition during pregnancy. When mothers have experienced PrA, it has been reported that the children experience difficult temperament, and developmental delay, as well as emotional and behavioural difficulties (Huizink et al., 2014; Westerneng, et al., 2017). A recent review reported a 10–15% risk for childhood behavioural problems as a result of PrA (Glover, 2014). Additionally, evidence is suggestive that children of mothers who experienced PrA have lower heart rate variability and higher rates of fearful behaviour (Braeken, Kemp, Outhred, Otte, Monsieur, Van Den Bergh, 2013)

1.4 Prevalence of, and Factors Associated with, PrA

Varying estimates of PrA prevalence have been reported in the literature. Rates have been said to range from 14-54% (Dayan, Creveuil, Marks, Conroy, Herlicoviez, Dreyfus, & Tordjman, 2006; Kang, Yao, Dou, Guo, Li, Zhao, & Li, 2016; Khalesi & Bokhai, 2018; Matthey, Valenti, Souter, & Ross-Hamid, 2013; Rubertsson, Hellstrom, Cross, & Sydsjo, 2014; Wall, Premji, Letourneau, McCaffrey, & Nyanza, 2018). The wide variation in reported

prevalence rates of PrA may be explained by a number of confounding factors including current screening methods, the time point at which PrA is being assessed during pregnancy, and possibly not considering other factors that may contribute to symptoms experienced in PrA.

Some research in this field has begun to explore factors that may be associated with higher levels of PrA. For example, some research suggest that demographic factors may play a role. One study reported that women under the age of 25 years are at increased risk (Rubertsson et al., 2014), while others have explored pregnancy-related factors. This has included pregnancy trimester (Madhavanprabhakaran et al., 2015; Teixeira, Figueiredo, Conde, Pacheco, & Costa, 2009) with Madhavanprabhakaren et al. (2015) and Teixeira et al (2009) reporting highest levels of PrA in the first and third trimesters. Increased levels of PrA has also been associated with nulliparous women (Huizink, Delforterie, Scheinin, Tolvanen, Karlsson, & Karlsson, 2016; Khalesi & Bokhai, 2018; Tsartsara & Johnson, 2006). Additionally, method of conception also appears to be associated with levels of PrA with women who conceive naturally being reported to experience less PrA than those who conceived via assisted reproductive technology (ART; McMahon, Boivin, Gibson, Hammarberg, Wynter, Saunders, & Fisher, 2013). Finally, it has also been suggested that history of prior pregnancy loss may also be associated with PrA (Theut et al., 1988; Tsartsara & Johnson, 2006). From the research to date, it appears that rates and levels of PrA are highly varied and are often associated with a number of differing factors and contexts. Much is to be gained from a comprehensive evaluation of a wide range of factors that may be associated with higher levels of PrA.

1.5 Methodological Issues in the Field

While the literature on PrA has been developing for over a decade, currently knowledge related to PrA and its impact has been influenced by a number of limitations. In a

recent review, it was noted that poor conceptualisation of PrA remains a significant issue for the field (Brunton et al., 2018). Difficulties have arisen because PrA has often been investigated as part of a broader construct of maternal stress or insufficient questionnaire items have been used to comprehensively measure the PrA (Brunton et al., 2015). Consistent with this, others suggest difficulties in the measurement of PrA have arisen due to a possible overlap between measures of PrA and conventional measures of anxiety, worry and depression (Huizink et al., 2004; Brunton et al., 2018).

To date, as mentioned previously, a number of scales have been developed to specifically measure PrA. While such scales have made a valuable contribution by allowing researchers to begin to quantify PrA, it has been suggested that these scales do not sufficiently measure PrA in its entirety (Brunton et al., 2015). It has also been argued that such measures do not have sound theoretical and psychometric properties to sufficiently measure PrA as a construct (Bayranpour et al., 2018; Brunton et al., 2015).

In addition to limitations that may occur are a result of weaknesses in the measurement of PrA, issues also arise because a large number of studies use non-PrA scales such as the STAI (Speilberger, 1968, 1977) as a means to measure PrA. The STAI, developed to measure more general anxiety rather than PrA, has been shown to have poor reliability and validity when used to measure anxiety in pregnant women (Brunton et al., 2015). The use of varied and nonspecific measures creates challenges to further determining the prevalence of, and factors associated with PrA. These methodological implications demonstrate the necessity for further research in this field.

1.6 Current Research

Research supports the notion that PrA is a distinct anxiety disorder that is consistently associated with adverse pregnancy outcomes. However, to date it is not clear how common PrA is and whether PrA varies depending based on demographics or pregnancy-related

factors. A meta-analysis of existing studies will allow more accurate estimates of PrA prevalence to be determined and may encourage health professionals to take action to reduce these rates. The present study will systematically review the current literature on PrA to more accurately determine prevalence rates and to explore whether levels of PrA vary according to a number of pregnancy-related factors.

1.6.1 Research Aims of the Current Study

This comprehensive systematic review and meta-analysis examines the prevalence of PrA. Specifically, the current research aims to:

1. Determine the prevalence of PrA;
2. Examine whether PrA varies according to a range of pregnancy-related factors such as pregnancy trimester, parity, method of conception, and history of pregnancy loss;
3. Evaluate the quality of studies included in the meta-analysis.

Chapter 2: Method

2.1 Search Strategy

A comprehensive search of four electronic databases (PubMed, PsychINFO, Embase and CINAHL) was conducted for the period January 2004 to September 2018 to source studies that have examined PrA. The start date was selected as 2004 was the year in which PrA was first described. Search terms were customized to each individual database and comprised a range of extensive keywords, as listed in Table 1 (See Appendix A for detailed search strategies). To ensure accuracy, an expert research librarian was consulted when developing search terms and strategy. Given the nature of the search required, as advised by the research librarian, a stepped-approach was taken. First, for each database, 'pregnancy' and 'anxiety' were searched as indexing terms and as titles and abstracts and were then combined. Second, search terms such as 'PRAQ', 'pregnancy outcome questionnaire', 'post-partum anxiety', 'fetal anxiety' etc were searched (See Table 1). Finally, the results from the first and second stages of the search were combined using the "or" logic operator to ensure the most comprehensive search to identify relevant studies. Additionally, the reference lists of included studies were also examined to identify any relevant articles that may have been missed in the initial search.

Table 1

Search Terms and Boolean (Logical) Operators used in the Database Searches

AND ⇨

	Pregnancy	**Anxiety**
	Pregnancy – indexing and title and abstract	Anxiety – indexing and title and abstract
OR ⇩	PRAQ (pregnancy related anxiety questionnaire) pregnancy outcome questionnaire post-partum anxiety postpartum anxiety fetal anxiety foetal anxiety prenatal anxiety perinatal anxiety	

2.2 Eligibility Criteria

Studies were included in this meta-analysis if they satisfied the following criteria: (1) reported data about PrA; where (2) PrA was assessed using a validated, specific measure of PrA (e.g., PRAQ (multiple versions), POQ, PAS, PSAI); and studies had to (3) provide parametric data to enable the calculation of an effect size (i.e., means, *SDs*, exact *p* values), and (4) be published in the English language.

Studies that reported general anxiety in pregnancy rather than PrA were excluded. Additionally, commentaries, letters, opinions pieces, conference abstracts and reviews were also excluded. Finally, studies were excluded if they did not provide sufficient statistical information to be able to calculate effects sizes.

The initial literature search yielded 17,277 articles (See Figure 2). After screening for duplicates, 10,438 studies remained. Applying the selection criteria to the titles and abstracts, resulted in the removal of a further 9192 articles, leaving 1,247 for further evaluation. One additional study (Madhavanprabhakaren, Ramasubramaniam, & Akintola, 2013) was identified for possible inclusion through a manual search of reference lists. However, on further examination sample overlap was identified between Madhavanprabhakaren et al.(2013) and Madhavanprabhakaren et al. (2015). Therefore, the most relevant and detailed study was kept for inclusion in this review; Madhavanprabhakaren et al. (2015). The full-text versions of these remaining articles subsequently screened against the inclusion/exclusion criteria resulting in 18 studies eligible for inclusion.

Reliability of this article selection process was checked by a second reviewer (thesis supervisor, MO), who 180 screened titles and abstracts of potentially eligible studies, randomly chosen by the primary reviewer (AM). Inter-rater reliability was excellent, with agreement among raters achieved on 93% of occasions ($K = .83$, $p < .05$) (McHugh, 2012). Discrepancies were discussed and resolved by consensus.

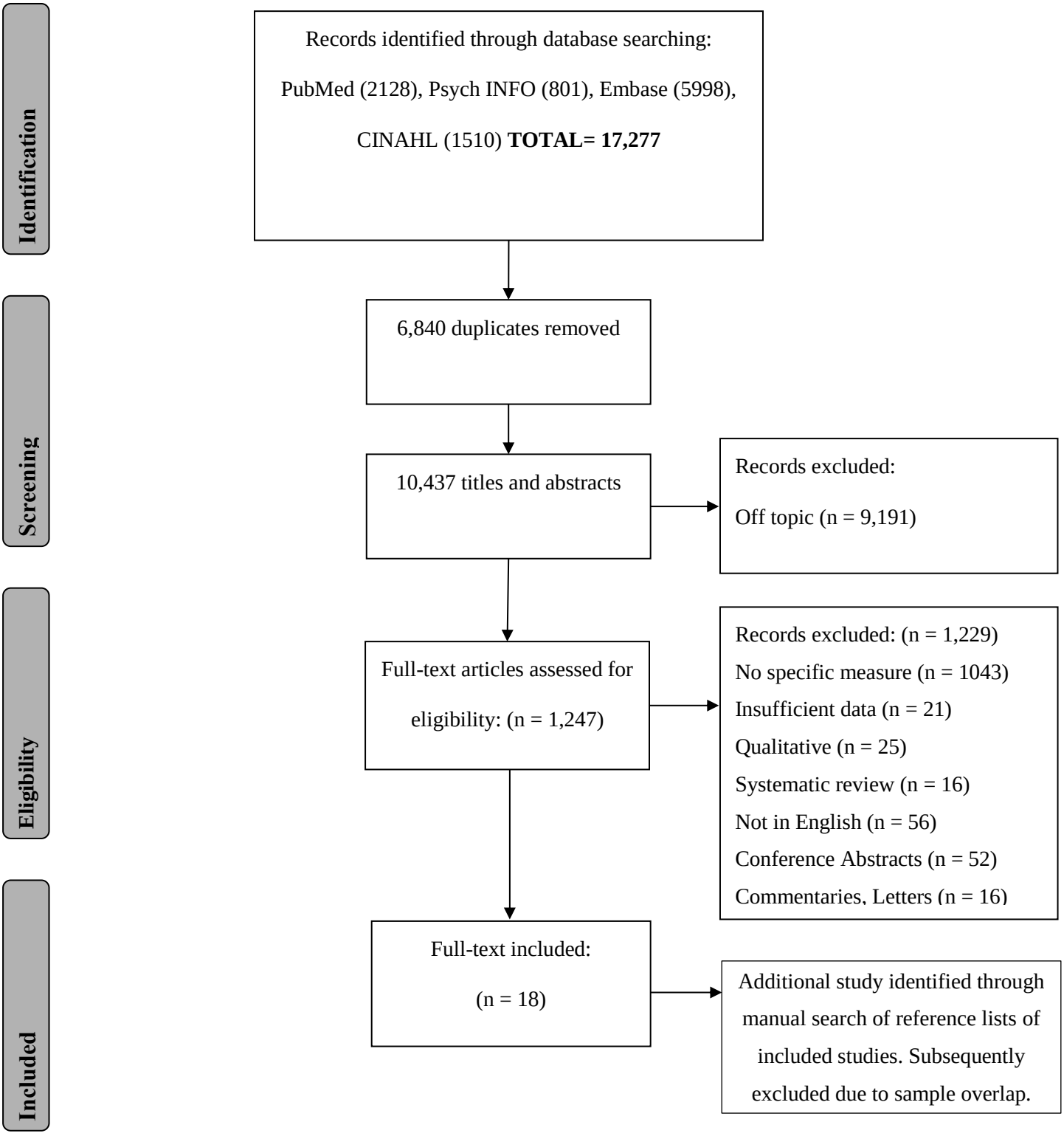

Figure 2. PRISMA flowchart of study selection process. Adapted from "Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement," by D. Moher, A. Liberati, J. Tetzlaff, D. G. Altman, The PRISMA Group, 2010, PLoS Medicine, 6(7): e1000097.

2.3 Data Collection and Preparation

In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher, Liberati, Tetzlaff, & Altman, 2010), and evidence-based recommendations for the reporting of systematic and meta-analytic reviews (Moher et al., 2010), key information for each study was summarised using a data extraction sheet (See Appendix B). This included information relating to: (1) sample recruitment and characteristics (e.g., recruitment source, sample size, age range and mean, ethnicity, marital status, education, pregnancy history and stage); (2) study characteristics (e.g., design, standardised outcome measures); and (3) effect size estimates (e.g., percentages, means, standard deviations).

2.4 Quality Assessment

Quality of included studies was evaluated using QualSyst (Kmet, Lee, & Cook, 2004). This 14-item scale examines items in relation to internal and external validity. Thus, studies were assessed and rated on critical aspects relevant to research (Pannucci & Wilkins, 2010), namely: internal validity (i.e., extent to which a study minimises systematic error by reducing biases in measurement and data collection), and external validity (i.e., extent to which the study findings can be generalised). For quantitative studies, each item is appraised and scored according to the degree to which the specific criteria are met ("yes" = 2, "partial" = 1, "no" = 0). If an item does not apply to a particular study it is marked "not applicable". A summary score for each study is obtained by summing scores to obtain a total score which is then divided by the total possible score (i.e., 28 – (number of "not applicable x 2)). It should be noted however, that ratings on the QualSyst may provide information more about the quality of the reporting of the studies rather than the actual quality of the research completed.

2.5 Statistical Analysis

Effect size data was entered into Comprehensive Meta-Analysis (CMA) software Version 3 (Borestein, Hedges, Higgins, & Rothenstein, 2009). A random-effects model of

meta-analysis was used. This model assumes that variation between observed effect sizes is due to subject-level sampling error and differences within individual study designs (Lipsey & Wilson, 2001)

Prevalence of high levels of PrA (defined in varying ways within included studies, i.e., high, severe, top 15% of scores or scores equal or greater than the 90th percentile) was calculated using proportions. For pregnancy-related factors associated with higher levels of PrA, such as pregnancy trimester, parity, method of conception, and history of pregnancy loss, effect sizes were calculated using Cohen's *d* effect size (Borenstein et al., 2009).

Effect sizes were computed primarily using means and standard deviations (SD). The PrA outcome measure scores were entered as continuous data, with the effect size calculated being the standardised mean difference (SMD; Cohen's *d*) between groups (i.e., one trimester versus another, nulliparous versus parous, assisted versus spontaneous conception, history of pregnancy loss versus no history of pregnancy loss) with 95% confidence intervals (CI) indicating the difference in means between groups, divided by the pooled SD. If studies reported PrA means and SDs by sub-scale (Winter, Van Acker, Bonduelle, Van Berkel, Belva, Liebaers, & Nekkebroeck, 2016) these were combined to determine an average mean effect size and standard error (SE) and a Cohen's *d* was calculated and used in subsequent pooled analyses to ensure consistency between effect size analyses. Similarly, if studies reported data via trimester (Huizink et al., 2016; Khalesi & Bokhai, 2018; Tsartsara & Johnson., 2006; Winter et al., 2016), parity (Khalesi & Bokhai., 2018), method of conception (Winter et al., 2016), birth preference (Witeveen et al., 2016), or gestation (Cole-Lewis, Kershaw, Earnshaw, Yonkers, Lin, & Ickovics 2014), if overall data was required these were combined to determine an average mean effect size and SE and a Cohen's *d* was calculated and used in subsequent pooled analyses to ensure consistency between effect size analyses. To calculate the mean effect size for a group of studies, individual effect sizes were pooled using a

random-effects model rather than a fixed-effect model as the included studies varied in design. Effect sizes were interpreted using Cohen's guidelines (0.2 = small, 0.5 = medium, and 0.8 = large effect) (Cohen, 1988).

To determine the accuracy of individual and weighted effect sizes, *p* values and 95% CIs were calculated. CIs reflect the range of values within which the true mean value lies. At the 95% level, there is a 5% chance that the actual effect size will lie beyond the range of values specified by the CI (Stratford, 2010). Effect sizes were deemed to be statistically significant when the CI did not include the value of zero.

Meta-analytic approaches may overestimate effects as they can be subject to a bias towards studies that report significant findings (Orwin, 1983). This problem arises when the results of published and unpublished studies are systematically different, and reviews like the current one, rely on data from published studies only (Orwin, 1983). Therefore, where possible, fail-safe Ns (N_{fs}) (Orwin, 1983) were calculated for effect size analyses to address possible publication bias which poses a potential threat to the validity of this meta-analysis (Rosenthal & DiMatteo, 2001).

The N_{fs} reflects the number of unidentified or unpublished studies reporting no effect (i.e., no relationship) that would need to exist to produce a small effect size, defined in this review as an effect size of 0.20, as suggested by Orwin (1983). Fail-safe N was calculated using Orwin (1983) fail-safe N formula (Eq. (11)):

$$N_{fs} = \frac{N\,(d - d_c)}{d_c}$$

where N = the number of studies in the meta-analysis, d = the average effect size for the studies synthesized, and d_c = the criterion value selected that d would equal when some knowable number of hypothetical studies (N_{fs}) were added to the meta-analysis. The value for d_c was set at 0.2 (small effect). Generally, the higher the N_{fs} value the greater confidence can be held in the finding as it is more unlikely that there are unidentified or unpublished

studies that would contradict the findings (Ellis, 2010). This meta-analysis employed a conservative approach whereby, findings were considered robust when the N_{fs} value exceeded the number of studies contributing to an effect size estimate (i.e., $N_{fs} > N_{studies}$). This differs from other N_{fs} formula, which rely on the total number of studies undergoing meta-analysis (Zakzanis, 2001).

Heterogeneity was also assessed. Heterogeneity tests the variation in study outcomes between studies (Borenstein et al., 2009). This study used the I^2 statistic to evaluate the degree of consistency in the pooled effect size estimates (Higgins & Green, 2011). The value of I^2 denotes the percentage of observed between-studies variance that can be credited to real differences in effect sizes (heterogeneity) instead of chance (Higgins & Thompson, 2002; Higgins, Thompson, Deeks, & Altman, 2003). I^2 values of 2% are considered low; 50% considered moderate; and greater than 50% indicate considerable heterogeneity across individual effect size estimates (Higgins et al., 2003).

In combination, these statistics were used to assess the pregnancy-related factors associated with levels of PrA. Factors were deemed to have to have an important effect on PrA levels if the factor was: (1) associated with a small (Cohen's $d \geq .20$) to medium (Cohen's $d \geq .50$) effect; (2) that was statistically significant (i.e., 95% CIs $\neq 0$; $p < .05$); and (3) the *Nfs* was greater than the number of studies which contributed to the pooled effect size.

Chapter 3: Results

3.1 Study Characteristics

A total of 18 studies, published in peer review journal articles between 2004 and 2019, were included in this meta-analysis (See Table 2). Data originated from diverse countries including the United States of America, Switzerland, Finland, Iran, Australia, Germany, The Netherlands, the United Kingdom and Tanzania. Sample sizes ranged from 24 (Tsartsara & Johnson., 2006) to 2,854 (Witteveen et al., 2016). Study designs included longitudinal and cohort, although the majority were cross-sectional in nature; and one was a randomised control trial (Cole-Lewis et al., 2015).

A total of 10 scales that specifically measure PrA were used across the 18 studies. The majority of studies used a form of the PRAQ (PRAQ, PRAQ-R, PRAQ-R2) ($N_{studies}$ = 11). Two studies used the PDQ (Cole-Lewis et al., 2015; Pleuss, 2009). Other measures were used in only one study; POQ (Tsartsara & Johnson, 2006), PSAI (Madhavanprabhakaran et al., 2015), PAS (Poikkeus et al., 2006), Anxiety for Pregnancy Scale (Mortazavi et al., 2017), Pregnancy-Specific Anxiety Scale P-SA scale (Khalesi & Bokhai, 2018) and Anxiety Concerning Health and Defects in the Child Scale (ACHD; McMahon, 2013). Majority of studies recruited participants from health clinics. This included hospitals, midwife clinics and in vitro fertilisation (IVF) clinics, while three studies used a dataset (Cole-Lewis et al., 2015; Huizink et al., 2015; Kataja et al., 2018).

Table 2
Descriptive Characteristics of included studies (N- $18_{studies}$)

Lead Author	Country	Sample Size	Recruitment	Parous or Nulliparous	Trimester	Study Design	PrA Measure
Bakker, 2013	The Netherlands	217	Midwifery practice	NA	1, 2, 3	Cohort	PRAQ
Cole-Lewis, 2015	USA	920	Dataset	NA	2,3	RCT	PDQ
Darwiche, 2014	Switzerland	105	Hospital	N	1		PRAQ-R
Huizink, 2016	Finland	1144	Finn Brain Birth Cohort study	P / N	2, 3	Cohort Study	PRAQ
Huizink, 2017	The Netherlands	1073	Midwifery practice	N	1, 2, 3	Longitudinal Cohort	PRAQ-R
Kataja, 2017	The Netherlands	230	Finn Brain Birth Cohort study	P / N	2, 3	Cohort	PRAQ-R2
Khalesi, 2018	Iran	208	Hospital	P / N	2, 3	Cohort	P-SA Scale
Madhavanprabhakaran, 2015	Oman	500	Hospital	P / N	1, 2, 3	Cohort	PSAI
Matthey, 2012	Australia	391	Hospital	P / N	1, 2, 3		PRAQ
McMahon, 2013	Australia	512	ART Clinic and Hospitals	NA	2, 3	Longitudinal	ACHDCS
Mortazavi, 2017	Iran	400	Health Clinic	NA	3	Cross-sectional	APS
Pleuss, 2009	Germany	66	Health Clinic	P / N	NA	Longitudinal	PDQ
Poikkeus, 2006	Finland	746	ART Clinic/ Hospitals	P	1	Longitudinal	PAS
Tsartsara, 2006	UK	24	Hospitals	P / N	3	Longitudinal	POQ
Van Bussell, 2008	UK	390	Hospital	P / N	1,2,3	Longitudinal	PRAQ
Wall, 2017	Tanzania	212	Hospitals	P / N	1, 2, 3	Cross sectional	PRAQ
Winter, 2016	The Netherlands	185	Health Centers	P / N	1, 2, 3	Longitudinal	PRAQ
Witeveen, 2016	The Netherlands	2854	Midwife Center	P / N	1, 2, 3	Cohort	PRAQ

Note: NA= Not applicable Measure Abbreviations: ACHDCS= Anxiety Concerning Health and Defects in the Child Scale; APS = Anxiety for Pregnancy Scale; PAS = Pregnancy Anxiety Scale; PDQ= Pregnancy Distress Scale; POQ = Pregnancy Outcome Questionnaire; PRAQ= Pregnancy-Related Anxiety Questionnaire; PRAQ-R= Pregnancy-Related Anxiety Questionnaire-Revised; PRAQ-R2= Pregnancy-Related Anxiety Questionnaire-Revised-2; P-SA= Pregnancy-Specific Anxiety Scale; PSAI= Pregnancy-Specific Anxiety Inventory.

3.2 Participant Characteristics

A total of 10,177 pregnant women were included in this meta-analysis. The age range was 14-44 years with a mean age of 29.06 years (*SD*=6.50). The majority of studies included both nulliparous (first time pregnancy) and parous (previous pregnancy) women in their sample (61.11%). However, one study recruited only nulliparous women (Darwiche et al., 2014) and another study recruited only parous women (Poikkeus et al., 2006). Parity was not specified in four studies (Bakker, Van Nimwegen-Matzinger, Ekkel-Van Der Voorden, Nijkamp, & Vollink, 2013; Cole-Lewis., 2015; Mortazavi & Akaberi, 2017; McMahon et al., 2013). Partnered and non-partnered women were included in the studies. Participants were sourced from a diverse range of ethnic backgrounds. Participant education included low, middle and high levels and included both employed and unemployed women. However, it must be noted that not all information was provided for participant characteristics. Refer to Table 3.

Table 3

*Participant Sociodemographic and Pregnancy Characteristics ($N_{studies}$ = 18)**

Variable	*N Studies* [a]	*N Participants (%)*[a,b]	*M (SD)*	Range
Age (y)	14	6611(64%)	29.06 (6.50)	14-42
	4	3,556(34%)		16-44
Ethnicity				
Latina	1	125 (0.1%)		
Dutch	5	4,810 (47%)		
Iran	2	608 (0.5%)		
Caucasian	2	99 (0.09%)		
Black	1	720 (0.7%)		
Indian	1	500 (0.4%)		
Tanzanian	1	212 (0.02%)		
Education				
Low	5	334 (0.03%)		
Middle	6	724 (0.07%)		
High	4	537 (0.05%)		
Employment				
Yes	3	494 (0.04%)		
No	2	340 (0.03%)		
Marital Status				
Partnered/ Married	5	1,907 (1.8%)		
Single	1	6 (0%)		
Parous				
Children	4	742 (0.07%)		
No children	5	1,860 (1.8%)		
Conception				
ART	4	786 (0.07%)		
Spontaneous	4	764 (0.07%)		
Past Pregnancy Loss				
Yes	3	327 (0.03%)		
No	1	332 (0.03%)		

Note: $N_{studies}$ = number of studies providing data; $N_{participants}$ = number of participants in which the data was provided. [a] Number varies within columns because not all studies reported this information. [b] Percentage (%) of participants that fulfill that category in relation to the total sample size of the studies that reported the data.

3.3 Quality Assessment

Study quality was examined using the QualSyst (see Appendix D). Results yielded study quality scores ranging from 16 to 20 (M = 18.66, SD = 1.49), indicating moderate quality studies (See Table 4). Level of reporting in the included studies was sound in some aspects and not sufficient in others. Research questions were sufficiently described and for the majority, outcome measures were well described and reported. For the studies reporting high prevalence of PrA by proportions(Khalesi and Bokhai, 2018; Matthey et al., 2018; Poikkeus et al., 2006; Wall et al., 2018), a lack of cut offs to define 'high levels' of PrA was noted. Only two studies Poikkeus et al (2006) and Matthey et al (2013) adequately defined this. Research designs of included studies were appropriate and well defined with only one study, Matthey et al (2013) not clearly defining this (Matthey et al., 2013). Where random allocation and blinding of investigators and participants was possible, it was reported (Cole-Lewis et al., 2014) All studies used specific measures to assess PrA levels and adopted appropriate methods of statistical analysis. Recruitment of participants was provided by all studies with clear inclusion and exclusion criteria described. External validity of included studies was increased as participants were sourced from a wide array of countries. However, a large number of the studies only partially reported participant characteristics with sufficient detail (see Table 3). The majority of studies demonstrated good power by satisfying the minimum sample size to achieve a large and statistically significant effect. One study (Tsartsara & Johnson, 2006) was underpowered as it failed to meet the minimum sample size recommended by Cohen (1992) (i.e., $N_{participants}$ = 26, power at .80, α = .05).

Table 4

Quality Assessment ($N_{studies}$ = 18)

	1. Question sufficiently described?	2. Design evident and appropriate?	3. Method of subject/comparison group selection or source of information/input variables described and appropriate?	4. Subject characteristics sufficiently described?	5. If interventional and random allocation was possible, was it described?	6. If interventional and blinding of investigators was possible, was it reported?	7. If interventional and blinding of subjects was possible, was it reported?	8. Outcome measure well defined? Means of assessment reported?	9. Sample size appropriate?	10. Analytic methods described/justified and appropriate?	11. Some estimate of variance is reported for the main results?	12. Controlled for confounding?	13. Results reported in sufficient detail?	14. Conclusions supported by the results?	**Total Quality Score**
Bakker, 2013	●	●	●	◗	NA	NA	NA	◗	●	●	●	●	●	●	20/28
Cole-Lewis, 2014	●	●	◗	◗	●	●	○	◗	●	◗	◗	●	◗	●	19/28
Darwiche, 2014	●	◗	●	●	NA	NA	NA	●	◗	◗	○	●	●	●	17/28
Huizink, 2016	●	●	◗	●	NA	NA	NA	●	●	●	○	○	●	●	17/28
Huizink, 2017	●	●	●	●	NA	NA	NA	●	●	●	◗	◗	●	●	20/28
Kataja, 2017	◗	●	●	◗	NA	NA	NA	●	●	●	○	◗	●	●	17/28
Khalesi, 2018	●	●	●	◗	NA	NA	NA	●	●	◗	○	○	●	●	16/28
Madhavanprabhakaran, 2015	●	●	●	◗	NA	NA	NA	●	●	●	○	◗	●	●	19/28
Matthey, 2013	●	○	●	◗	NA	NA	NA	●	●	◗	◗	◗	●	●	16/28
McMahon, 2013	●	●	●	◗	NA	NA	NA	◗	●	●	○	●	●	●	18/28
Mortazavi, 2017	●	●	●	◗	NA	NA	NA	●	●	●	◗	●	◗	●	20/28
Pleuss, 2010	●	●	◗	◗	NA	NA	NA	●	◗	●	●	●	●	●	20/28
Poikkeus, 2006	●	●	●	●	NA	NA	NA	●	●	●	○	○	●	●	19/28
Tsaratsara, 2009	●	●	●	●	NA	NA	NA	●	○	●	◗	●	●	●	20/28
Van Bussell, 2008	●	●	●	◗	NA	NA	NA	●	●	●	◗	◗	●	●	20/28
Wall, 2018	●	●	●	◗	NA	NA	NA	●	●	●	◗	◗	●	●	20/28
Winter, 2016	●	●	●	●	NA	NA	NA	●	●	●	○	●	◗	●	20/28
Witeveen, 2016	●	●	●	◗	NA	NA	NA	●	●	◗	◗	●	◗	●	18/28

Note. ●*= yes,* ○*= no,* ◗ *= partial, NA= not applicable*

3.4 Effect Size Estimates

Comprehensive meta-analysis was used to measure effect sizes in a total of nine analyses related to PrA; one analysis in relation to prevalence of high levels of PrA and eight in relation to pregnancy-related factors associated with higher levels of PrA. Specifically, this included analyses of: prevalence of high levels of PrA by proportions, and SMD (Cohens *d*) in relation to pregnancy-related factors associated with PrA such as pregnancy trimester (Trimester 1 vs Trimester 2, Trimester 2 Vs Trimester 3 and Trimester 1 Vs Trimester 3), parity (nulliparous versus parous women overall and then in Trimester 2 and Trimester 3), method of conception (spontaneous versus assisted reproduction), and history of pregnancy loss.

Of these nine analyses, none were found to be significant in accordance to the criteria used for this review (i.e., Cohen's $d \geq .20$; $N_{fs} > N$; CIs $\neq 0$; $p < .05$). A small to medium statistically significant effect size was found for the relationship between parity and PrA however the N_{fs} was less than the number of studies included in the analysis. Similarly, a medium effect size with the N_{fs} greater than the number of included studies was found for history of pregnancy loss, however this was not statistically significant.

3.4.1 PrA Prevalence

Four studies contributed to a prevalence estimate providing information on the proportion of women experiencing high levels of PrA. Effect size estimates (See Figure 3) suggested that 14.1% of women experienced high levels of PrA ($N_{studies} = 4$, Event rate = 0.141, 95% CIs [0.067, 0.271]; $p = .000$). However, substantial heterogeneity was noted ($I^2 = 95.39\%$).

Lead Author	PRA Measure	$N_{studies}$	Event Rate	95% CI		*p*
				Lower	Upper	
Khalesi, 2018	P-SA Scale		0.324	0.264	0.391	0.000
Matthey, 2018	PRAQ		0.144	0.094	0.215	0.000
Poikkeus, 2006	PAS		0.113	0.092	0.138	0.000
Wall, 2018	PRAQ		0.061	0.036	0.102	0.000
Overall		**4**	**0.141**	**0.067**	**0.271**	**0.000**

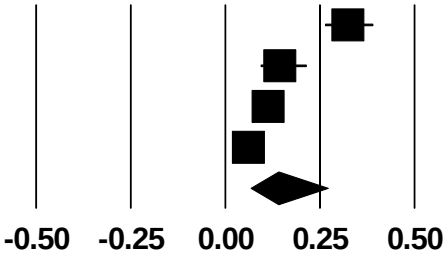

Figure 3. Prevalence of High Level of PrA. A positive and significant effect indicates the portion of women who reported high levels of PrA.

3.4.2 PrA According to Pregnancy Trimester

Differences between PrA according to trimester were explored. Comparisons were made between Trimesters 1 and 2 (Figure 4), Trimesters 2 and 3 (Figure 5), and Trimesters 1 and 3 (Figure 6).

3.4.2.1 Trimester 1 versus Trimester 2

Six studies explored differences in PrA between first and second trimesters. Effect size estimates suggested that PrA is higher in the first trimester than the second trimester ($N_{studies}$ = 6, Cohen's d = 0.154, 95% CIs [-.303, .612]; *Nf*s < $N_{studies;}$ p = .508) however the difference was not statistically significant. Also, substantial heterogeneity was noted (I^2 = 98%). The *Nfs* of 1.38 suggests this finding is not robust.

3.4.2.2 Trimester 2 versus Trimester 3

Eight studies explored differences in PrA between second and third trimesters. Effect size estimates suggested that PrA is higher in the third trimester than the second trimester ($N_{studies}$ = 8, Cohen's d = 0.242, 95% CIs [-0.714, 0.229]; *Nf*s < $N_{studies;}$ p = 0.314) however the difference was not statistically significant. Also, substantial heterogeneity was noted (I^2 = 99%). The *Nfs* of 1.68 indicates that this finding is not robust.

3.4.2.3 Trimester 1 versus Trimester 3

Eight studies explored differences in PrA between first and third trimesters. Effect size estimates suggested that PrA is higher in the third trimester than the first trimester ($N_{studies}$ = 8, Cohen's d = 0.121, 95% CIs [-0.366, 0.125]; *Nf*s < $N_{studies;}$ p = .366) however the difference was not statistically significant. Also, substantial heterogeneity was noted (I^2 = 93%). The *Nfs* of 3.16 indicates that this finding is not robust.

Lead Author	PrA Measure	$N_{studies}$	Cohen's *d*	95% CI Lower	95% CI Upper	*p*	*Nfs*
Bakker, 2013	PRAQ		0.234	-0.005	0.473	0.055	
Huizink, 2017	PRAQ		0.023	-0.062	0.108	0.594	
Kataja, 2017	PRAQ-R2		-0.261	-0.587	0.065	0.116	
Madhavanprabhakaren, 2015	PSAI		1.138	1.004	1.271	0.000	
Van Bussell, 2009	PRAQ		-0.266	-0.412	-0.120	0.000	
Winter, 2016	PRAQ		0.032	-0.170	0.234	0.759	
Overall		**6**	**0.154**	**-0.303**	**0.611**	**0.508**	**1.38**

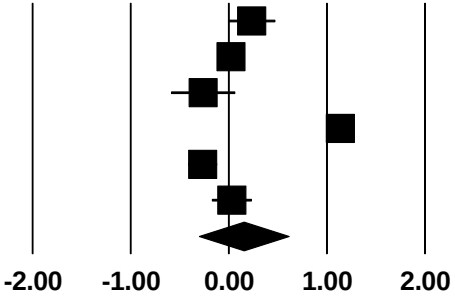

Figure 4. PrA by Pregnancy Trimester 1 versus Trimester 2. A positive and significant effect would indicate that PRA was higher in Trimester 1 compared with Trimester 2.

Lead Author	PrA Measure	$N_{studies}$	Cohen's *d*	95% CI Lower	95% CI Upper	*p*	*Nfs*
Bakker, 2013	PRAQ		-0.265	-0.514	-0.015	0.037	
Cole-Lewis, 2014	PDQ		0.187	0.096	0.279	0.000	
Huizink, 2017	PRAQ		0.023	-0.062	0.108	0.594	
Kataja, 2017	PRAQ-R2		-0.002	-0.326	0.323	0.992	
Khalesi, 2018	P-SA Scale		-0.034	-0.225	0.158	0.730	
Madhavanprabhakaren, 2015	PSAI		-1.846	-1.994	-1.698	0.000	
Van Bussell, 2009	PRAQ		-0.012	-0.168	0.145	0.883	
Winter, 2016	PRAQ		0.020	-0.183	0.222	0.850	
Overall		**8**	**0.242**	**-0.714**	**0.229**	**0.314**	**1.68**

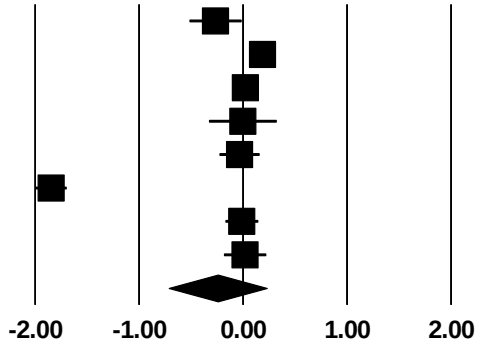

Figure 5. PrA by Pregnancy Trimester 2 versus Trimester 3. A negative and significant effect would indicate that PRA was higher in Trimester 2 compared with Trimester 3.

Lead Author	*PrA Measure*	$N_{studies}$	Cohen's *d*	95% CI Lower	Upper	*p*	*Nfs*
Bakker, 2013	PRAQ		-0.029	-0.229	0.171	0.777	
Huizink, 2017	PRAQ		0.047	-0.038	0.131	0.281	
Kataja, 2017	PRAQ-R2		-0.270	-0.596	0.056	0.104	
Madhavanprabhakaren, 2015	PSAI		-0.692	-0.820	-0.564	0.000	
Pleuss, 2010	PDQ		0.015	-0.326	0.356	0.931	
Tsartsara, 2006	POQ		0.395	-0.130	0.919	0.140	
Van Bussell, 2009	PRAQ		-0.279	-0.430	-0.129	0.000	
Winter, 2016	PRAQ		0.050	-0.152	0.252	0.626	
Overall		**8**	**0.121**	**-0.366**	**0.125**	**0.336**	**3.16**

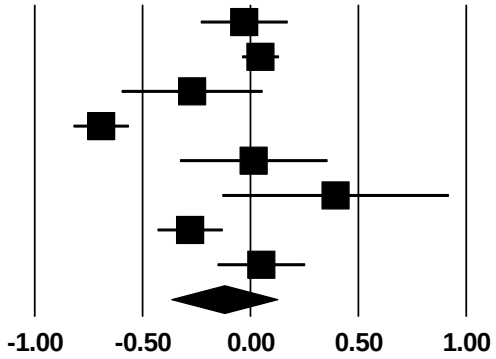

Figure 6. PrA by Pregnancy Trimester 1 versus Trimester 3. A negative and significant effect would indicate that PRA was higher in Trimester 1 compared with Trimester 3.

3.4.3 PrA According to Parity

Four studies examined whether PrA was related to parity across pregnancy (all trimesters combined; Figure 7). Effect size estimates suggest a significant difference between nulliparous and parous women ($N_{studies}$ = 4, Cohen's d = 0.461, 95% CIs [0.178, 0.745]; *Nf*s > $N_{studies;}$ p = .001), indicative that nulliparous women experience higher levels of PrA than parous women. However, high heterogeneity was noted (I^2 = 90.64%), and the *Nfs* of 5.22 indicates that this finding is robust.

3.4.3.1 Parity in Trimester 2

Two studies examined whether PrA was related to parity in the second trimester (Figure 8). Effect size estimates indicate no significant difference in PrA according to parity in Trimester 2 ($N_{studies}$ = 2, Cohen's d = 2.114, 95% CIs [-1.528, 5.756]; *Nf*s >$N_{studies;}$ p = .255). The *Nf*s of 19.14 suggests that the finding is robust.

3.4.3.2 Parity in Trimester 3

Two studies examined whether PrA was related to parity in the third trimester (Figure 9). Effect size estimates indicate no significant difference in PrA according to parity in Trimester 3 ($N_{studies}$ = 2, Cohen's d = 3.376, 95% CIs [-2.721, 9.472]; *Nf*s > $N_{studies;}$ p = 0.278). The *Nf*s of 31.76 suggests that the finding is robust.

Lead Authors	PrA Measure	$N_{studies}$	Cohen's *d*	95% CI		*p*	*Nfs*
				Lower	Upper		
Huizink, 2016	PRAQ		0.269	0.187	0.351	0.000	
Khalesi, 2018	P-SA Scale		5.225	2.773	7.677	0.000	
Tsartsara, 2006	POQ		1.809	1.017	2.602	0.000	
Witeveen, 2016	PRAQ		0.209	0.135	0.283	0.000	
Overall		**4**	**0.461**	**0.178**	**0.745**	**0.001**	**5.22**

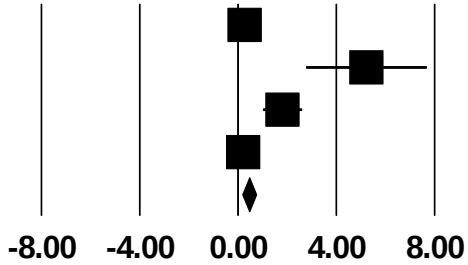

Figure 7. PrA by Nulliparous versus Parous Women. A positive and significant effect indicates that PrA was higher in nulliparous women compared to parous women.

Lead Authors	*PrA Measure*	$N_{studies}$	Cohen's *d*	95% CI		*p*	*Nfs*
				Lower	Upper		
Huizink, 2016	PRAQ		0.263	0.146	0.380	0.000	
Khalesi, 2018	P-SA Scale		3.979	3.510	4.448	0.000	
Overall		**2**	**2.114**	**-1.528**	**5.756**	**0.255**	**19.14**

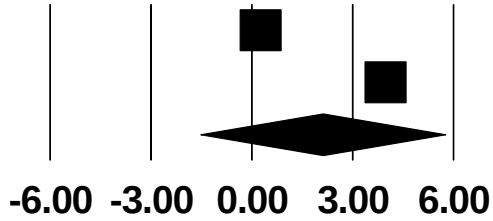

Figure 8. PrA by Nulliparous versus Parous Women in Trimester 2. A positive and significant effect would indicate that PrA was higher in nulliparous women compared to parous women in the second trimester.

Lead Authors	PrA measure	$N_{studies}$	Cohen's *d*	95% CI Lower	Upper	*P*	*Nfs*
Huizink, 2016	PRAQ		0.275	1.58	0.391	0.000	
Khalesi, 2018	P-SA Scale		6.496	5.815	7.176	0.000	
Overall		**2**	**3.376**	**-2.721**	**9.472**	**0.278**	**31.76**

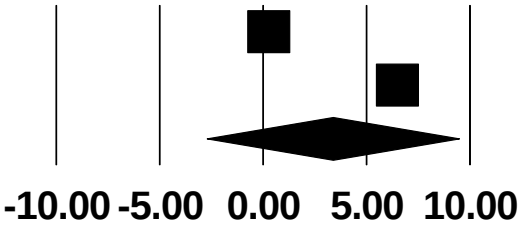

Figure 9: PrA by Nulliparous versus Parous Women in Trimester 3. A positive and significant effect would indicate that PRA was higher in nulliparous women compared to parous women in the third trimester

3.3.4 PrA According to Method of Conception

Three studies examined whether PrA was related to method of conception (Figure 10). When examining levels of PrA according to how women conceived, effect size estimates suggest a non-significant relationship ($N_{studies}$ = 3, Cohen's d = 0.061, 95% CIs [-0.166, 0.289]; *Nf*s < $N_{studies;}$ p = 0.597), indicating that method of conception was not related to higher levels of PrA. However, moderate heterogeneity was noted (I^2 = 50.64%), and the *Nfs* of 2.08 indicates that this finding is not robust.

Lead Authors	PrA Measure	$N_{studies}$	Cohen's *d*	95% CI		*p*	*Nfs*
				Lower	Upper		
Darwiche, 2014	PRAQ-R		-0.042	-0.425	0.341	0.829	
McMahon, 2013	ACHD Scale		0.219	0.045	0.393	0.014	
Winter, 2016	PRAQ		-0.108	-0.415	0.199	0.490	
Overall		**3**	**0.061**	**-0.166**	**0.289**	**0.597**	**2.08**

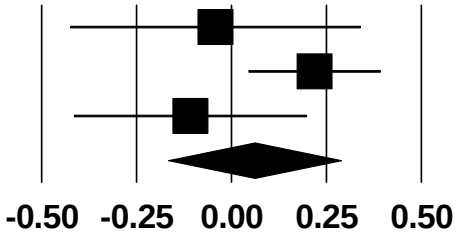

Figure 10. PrA by Method of Conception. A positive and significant effect would indicate that PrA was higher in women who conceived using fertility treatment compared to women who conceived spontaneous.

3.4.5 PrA by History of Pregnancy Loss

Two studies examined whether higher levels of PrA was associated with history of pregnancy loss (Figure 11). Effect size estimates suggest no statistically significant difference in PrA between women who have had prior loss compared to women who have not ($N_{studies}$ = 2, Cohen's d = 0.470, 95% CIs [-0.014, 0.953]; *Nf*s > $N_{studies;}$ p = 0.057). This result, however produced a large effect size that was very close to statistical significance. The *Nf*s of 2.7 suggests that the finding is sound.

Lead Author	PrA Measure	$N_{studies}$	Cohen's *d*	95% CI Lower	95% CI Upper	*p*	*Nfs*
Mortazavi, 2018	Anxiety for Pregnancy Scale		0.200	-0.121	0.521	0.223	
Tsartsara, 2006	POQ		0.695	0.559	0.831	0.000	
Overall		**2**	**0.470**	**-0.014**	**0.953**	**0.057**	**2.7**

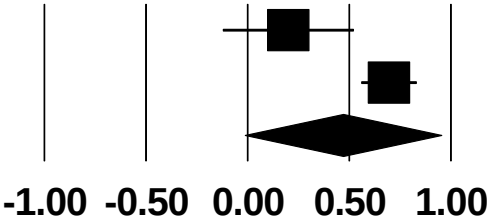

Figure 11. PrA by History of Pregnancy Loss. A positive and significant effect would indicate that PrA was higher in women who experienced previous pregnancy loss compared to women who did not have a pregnancy loss history.

Chapter 4: Discussion

4.1 Key findings

This comprehensive systematic review and meta-analysis initially aimed to determine the overall prevalence of PrA and whether prevalence varied according to pregnancy-related factors. However, when reviewing the literature on this topic, it became apparent that poor conceptualization has hindered progression of knowledge regarding PrA as a distinct anxiety disorder. The number of studies reporting prevalence is limited, with a larger number of studies investigating factors that are associated with higher levels of PrA as opposed to reporting a prevalence rate. Additionally, among the studies that do report PrA prevalence, the use of non-specific anxiety measures to assess PrA is observed (Dayan et al., 2006; Kang et al., 2016; Rubertsson et al., 2014). Furthermore, Of the studies that did report prevalence, only prevalence of high levels of PrA were reported. Limited reporting of prevalence in primary studies may be due to a number of confounding factors. This could include the poor conceptualisation of PrA that remains, or the lack of cut off scores to determine presence or absence of PrA in current scales used to assess instances of PrA. Taking this into consideration, to assess PrA for the purpose of this review, nine analyses were conducted to explore prevalence of high levels of PrA and pregnancy-related factors associated with higher levels of PrA.

The nine analyses included: prevalence of high levels of PrA by proportions in the studies that report percentages of PrA (Khalesi & Bokhai, 2018; Matthey et al., 2013; Poikkeus et al., 2006; Wall et al., 2018). Standardized mean differences were examined using Cohen's *d* in relation to pregnancy-related factors associated with PrA such as pregnancy trimester (Bakker et al., 2013; Van Bussell, Spitz & Demyttenaere, 2008; Cole- Lewis et al., 2014; Huizink et al., 2017; Khalesi & Bokhai, 2018; Kataja et al., 2018; Madhavanprabhakaran et al., 2015; Pluess et al., 2010; Tsartsara & Johnson., 2006; Winter et

al., 2016), parity (Huizink et al., 2016; Khalesi & Bokhai, 2018; Tsartsara & Johnson, 2006; Witeveen et al., 2016), method of conception (Darwiche et al., 2014; McMahon et al., 2013; Winter et al., 2016), and history of pregnancy loss (Mortazavi et al., 2018; Tsartsara & Johnson, 2006). Of these nine analyses, none were found to be significant in accordance to the criteria used for this meta-analysis (Cohen's $d \geq .20$; $N_{fs} > N$; CIs $\neq 0$; $p < .05$). However, the results of the present study yield important findings for the knowledge that is known of PrA.

Using the four studies reporting prevalence of PrA, findings suggest that overall, 14.1% of women experience high levels of PrA during pregnancy. This rate varies widely from some previous reports of PrA prevalence, and is on the lower end of the 14-54% range that has previously been reported in this field (Henderson & Maggie, 2013; Kang et al., 2016; Rubertsson et al., 2014). This may be due to the studies included in this analysis only looking at high levels of PrA. Another possible explanation for this may be the use of non-specific measures of PrA in the studies reporting prevalence that are not included in this review. However, it must be noted that only four studies were included in the current analysis and rates reported have varied so widely. Therefore, it is important that further research is conducted. Research to determine appropriate cut offs for presence or absence to define levels of PrA will be beneficial to this field to further establish the true prevalence of PrA.

For pregnancy trimesters, three analyses were conducted, comparing each trimester against the other (Trimester 1 versus 2, Trimester 2 versus 3, and Trimester 1 versus Trimester 3), no clinically significant differences were found. This is inconsistent with one study in the literature which found higher prevalence in the first and third trimesters (Teixeira et al., 2009). The use of general measures of anxiety rather than PrA specific measures, as used by Teixeira et al (2009) may explain this. However, this finding is also inconsistent with three primary studies that were used in this meta-analysis who all found statistically

significant differences (Cole-Lewis et al., 2014; Madhavanprabhakaren et al., 2015; Van Bussell et al., 2018). Inconsistencies observed in the research exploring the relationship between PrA levels and pregnancy trimester may be due to a number of confounding factors. Factors such as sample sizes, when in pregnancy PrA levels were assessed, or demographic factors may explain this. Nonetheless, further research is required to further explore this relationship.

A small to medium effect size was found when examining the relationship between PrA and parity, indicating that nulliparous women (those without children) are likely to experience higher levels of PrA as opposed to parous women (those with children). The *Nfs* suggest that this is a robust findings. This is not surprising as there are a number of studies that have reported higher levels of PrA in first time mothers (Huizink et al., 2015; Khalesi & Bokhai, 2018; Tsartsara & Johnson, 2006; Witteveen et al., 2016). Therefore, the field would benefit from future research exploring PrA in nulliparous women in greater detail as research is consistently reporting higher levels in nulliparous women. This will ensure that appropriate care can provided to first time mothers who may be experiencing symptoms of PrA.

Furthermore, the analysis regarding method of conception found no significant difference between women who conceived via assisted reproductive therapy (ART) and those who conceived naturally. This is inconsistent with some primary research that has reported higher levels of PrA among women conceiving through ART (McMahon et al., 1997, 2013). However, the current analysis is not alone in this conclusion. Poikkeus et al (2006) also concluded that there was no significant difference between a population of people conceiving through ART and those who conceived naturally (Poikkeus et al., 2006). Nonetheless, as with other analyses in the current review, inconsistencies in the research investigating this relationship necessitate the need for further research.

Finally, for the analysis regarding history of pregnancy loss, a medium to large effect was found and the fail-safe *N* suggested the analysis was robust, however this result was just outside statistical significance ($p = 0.57$). Although not statistically significant, the finding is consistent with previous findings which suggest an relationship between conception following perinatal loss and increased anxiety (Tsartsara & Johnson, 2006).

In light of these findings, it would be beneficial to conduct further research to advance the knowledge that is known about PrA. It is evident that PrA is a complex construct with a number of confounding factors influencing its occurrence and impact. Inconsistencies in the research investigating PrA and its associated factors necessitates the need for further research to be conducted. Knowing what causes PrA presence and severity will provide health care professionals with greater understanding of the disorder, as well as to allow for better support to be provided to pregnant women during the prenatal period.

4.2 Quality findings

The results of this meta-analysis should be interpreted in reference to the quality of the studies included in the final analyses. Quality of included studies was assessed using the QualSyst checklist (Kmet et al., 2004). Studies were assessed in relation to critical aspects relevant to research including both internal and external validity. That is, the level to which a study minimises systematic error by reducing biases (internal validity) and the extent to which the study findings can be generalised (external validity). The results of the QualSyst checklist indicated moderate quality of included studies. Overall, some aspects of reporting were found to be sound, while others were found to be limited. Specifically, in the studies reporting prevalence of PrA, a lack of cut offs to define what was meant by ‘high levels’ of PrA was noted in some studies. Furthermore, participant characteristics were only partially reported in a number of the included studies. Therefore, level of reporting was somewhat compromised which weakens the internal and external reliability. However, the QualSyst

checklist may provide information more about the quality of reporting as opposed to the actual quality of the research that was completed (Kmet et al., 2004). Therefore, this must be taken into consideration.

4.3 Clinical Implications and Future Research

Findings from this meta-analysis have important implications for the knowledge that is known of PrA. Previous research consistently supports PrA as a distinct anxiety disorder that is specific to pregnancy, which has been shown to have adverse outcomes for both mother and baby (Glover, 2013; Huizink et al., 2004; Huizink et al., 2014; Westerneng et al., 2017). However, as suggested by a recent review on this topic (Brunton et al., 2015), a lack of conceptual understanding remains a large limitation to the progression of classifying PrA as a distinct disorder. The continued use of non-specific screening methods to assess PrA makes the detection and treatment of this disorder an ongoing challenge for researchers and clinicians in the field. In addition to this, a recent review has suggested that even current scales that specifically measure PrA do not adequately assess PrA in its entirety (Brunton et al., 2015), suggesting that improvement of screening measures is essential.

Although the findings of the current analyses were not found to be significant, they provide important information for researchers, as well as health care professionals in this field. The key findings tell us that overall, 14.1% of pregnant women experience high levels of PrA. Findings from the current analyses suggest that PrA is a complex structure that may be impacted by a number of factors. The results indicate that levels of PrA are not affected by factors such as method of conception or trimester, however, do indicate that first time mothers and those who have a history of pregnancy loss may be at an increased risk of experiencing symptoms of PrA. However, inconsistent findings suggests that further research is required to ensure that improved understanding of PrA and its impact is developed.

4.4 Study limitations

The results of this meta-analysis must be considered in light of possible limitations. Firstly, poor conceptualisation of PrA remains apparent and is a large limitation to research conducted on this topic. Researchers in the field note that current scales, even those specific to PrA, fail to sufficiently measure PrA in its entirety (Brunton et al., 2015). This makes the measurement and distinction of PrA from other forms of anxiety a challenge for researchers and clinicians. In addition to this, the majority of current scales used to measure PrA rely on self-report methods and are subject to self-report biases (Paullhus & Vazire, 2007). Therefore, it can be said that future research will benefit from the development of validated scales with sound construct validity to measure and further develop understandings of PrA.

Secondly, of the nine analyses explored in this meta-analysis, some included a small number of studies. This in turn limits the conclusions that can be drawn from the results and may explain some of the non-significant findings. Furthermore, a large number of studies were excluded from inclusion of this review due researchers' use of non-specific scales to measure PrA.

While there are possible limitations that must be considered, this meta-analysis also holds strengths. The present study involved a comprehensive search of the literature on PrA. Consulting a research librarian ensured that efficient search terms were formulated specific to the topic of interest. A total of 10,438 journal articles were screened for inclusion with the final analyses including 18 primary studies and 10,177 participants. Also, *Nfs* were calculated to assess the possible limitation of publication bias. Finally, the findings of the current review have important implications for both researchers and health care professionals as they highlight and contribute to what is so far known about PrA and pregnancy-related factors that may influence levels of PrA.

4.5 Conclusion

This comprehensive systematic review and meta-analysis highlights important findings on PrA and provides important information for researchers and health care professionals assisting women that may be experiencing symptoms of PrA. It is clear that PrA is a complex structure and poor conceptualisation remains a limitation to knowledge that is known about PrA as a distinct anxiety disorder. The use of non-specific measures in assessing prevalence of PrA, as well as the lack of cut off scores to indicate presence or absence holds challenges for the estimation of prevalence and diagnosis of PrA. The current research supports that PrA and its impact may be influenced by a number of confounding factors. Factors such as pregnancy trimesters and method of conception were found to have no effect on PrA levels while other factors such as parity (nulliparity) and history of pregnancy loss were found to have some impact on PrA levels. However, inconsistencies can be observed in the research investigating these relationships which precipitates the need for further research to be conducted. Therefore, further research is recommended to increase understanding of PrA for both researchers and health care professionals. This will allow for improved and appropriate prenatal programs to be provided to women during the prenatal period.

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Appendices

Appendix A: Final Search Terms

Search Process 1

PubMed

Pregnancy	Anxiety
Pregnancy[mh] OR pregnancy[tiab]	Anxiety[mh] OR Anxiety[tiab]

Psych info

Pregnancy	Anxiety
Pregnancy.sh OR pregnancy.tw	Anxiety.sh OR anxiety.tw

CINAHL

Pregnancy	Anxiety
MH Pregnancy OR TI pregnancy or AB pregnancy	MH Anxiety OR TI anxiety or AB anxiety

Embase

Pregnancy	Anxiety
Pregnancy/de OR pregnancy:ti,ab	Anxiety/de OR anxiety:ti,ab

Search Process 2

PubMed

Terms
praq[tiab] OR pregnancy outcome questionnaire[tiab] OR post-partum anxiety[tiab] OR postpartum anxiety[tiab] OR fetal anxiety[tiab] OR foetal anxiety[tiab] OR prenatal anxiety[tiab] OR perinatal anxiety[tiab]

PsycINFO

Terms

praq.ti,ab OR pregnancy outcome questionnaire.ti,ab OR post-partum anxiety.ti,ab OR postpartum anxiety.ti,ab OR fetal anxiety.ti,ab OR foetal anxiety.ti,ab OR prenatal anxiety.ti,ab OR perinatal anxiety.ti,ab

CINAHL – TI /AB

Terms
TI praq OR AB praq OR “pregnancy outcome questionnaire” OR AB “pregnancy outcome questionnaire” OR TI “post-partum anxiety” or AB “post-partum anxiety” OR TI “postpartum anxiety” OR AB “postpartum anxiety” OR TI “fetal anxiety OR AB “fetal anxiety” OR TI “foetal anxiety” OR AB “foetal anxiety” OR TI “prenatal anxiety” OR AB “prenantal anxiety” OR TI “perinatal anxiety” OR AB “perinatal anxiety”

Embase

Terms
praq:ti,ab OR “pregnancy outcome questionnaire”:ti,ab OR “post-Partum anxiety”:ti,ab OR “postpartum anxiety”:ti,ab OR “fetal anxiety” OR “foetal anxiety”:ti,ab OR “prenatal anxiety”:ti,ab OR “perinatal anxiety”

Appendix B: Data Extraction Sheet

<table>
<tr><td colspan="3">Article title:
Author:
Study Country:
Year:
Study design:
Sample characteristics</td></tr>
<tr><td>Sample size:
(N =)
Comparison group:
(N =)

Sample recruitment:
_____

Age
At time of assessment:
Range:
Mean:
SD:

Ethnicity (% or N)
European/Caucasian:
Asian:
African:
Other:
_____
Marital Status
[ ] Married/ defacto
[ ] Divorced/ single
[ ] Not specified
Education
[ ] High School
[ ] Tertiary
[ ] Other:
_____</td><td>Employment:
[ ] Full-time
[ ] Part-time
[ ] Unemployed
[ ] Other: _____

Previous pregnancies
[ ] Yes [ ] No
Number of pregnancies:
Number of children:

Pregnancy loss
[ ] Yes [ ] No

Fertility treatment
[ ] Yes [ ] No

Pregnancy Trimester
[ ] First Trimester:
[ ] Second Trimester
[ ] Third Trimester:

Pregnancy-related anxiety measure:
_____

Anxiety rate:
Range:
Mean:
SD:</td><td>Data collection:
[ ] From subject
[ ] Medical records
[ ] Other

Random Selection
[ ] Yes
[ ] No

Eligibility Criteria Specified
[ ] Yes [ ] No
[ ] Partially

Missing Data explained
[ ] Yes [ ] No
[ ] Partially

Sample recruitment
[ ] Not specified
[ ] Database
[ ] Fertility Clinic
[ ] Medical centre/GP
Other:
_____</td></tr>
<tr><td colspan="3"><u>Effect size data</u>
Outcome measure: _____
Method of administration: [ ] Self-administration [ ] Clinical interview [ ] Other _____
Cut-off score (if applicable):
Prevalence estimate:</td></tr>
<tr><td colspan="3"><u>Other data</u>
(medications prescribed, psychiatric history, exclusion, etc)</td></tr>
</table>

Appendix C: Quality Assessment

Criteria		Yes (2)	Partial (1)	No (0)	N/A
1	Question/ objective sufficiently described?				
2	Study design evident and appropriate?				
3	Method of subject/ comparison group selection or source of information/ input variables described and appropriate?				
4	Subject characteristics sufficiently described?				
5	If interventional and random allocation was possible, was it described?				
6	If interventional and blinding of subjects was possible, was it reported?				
7	If interventional and blinding of subjects was possible was it reported?				
8	Outcome and exposure measure(s) well defined and robust to measurement / misclassification bias? Means of assessment reported?				
9	Sample size appropriate?				
10	Analytic methods described/ justified and appropriate?				
11	Some estimate of variance is reported for the main results?				
12	Controlled for confounding?				
13	Results reported in sufficient detail?				
14	Conclusions supported by the results?				