Research gaps in perinatal mental health disorders: perinatal depression

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Perinatal mental health disorders are common and increasing in prevalence

Perinatal mental health disorders (i.e., depression, anxiety disorders, OCD, PTSD, bipolar disorder) affect more than **1 in 5 perinatal individuals** and are among the most common complication of pregnancy and the year after delivery (Wisner KL et al, 2013; Fawcett EJ et al, 2019; Masters GA et al, 2022).

- number of births in US (2022): 3,661,220 (Hamilton BE et al, 2023 CDC National Vital Statistics System)
- estimated 500,000 pregnant women in the US to experience a mental disorder either prior to or during pregnancy, with unipolar depression and anxiety the most common diagnoses

Rates are higher in adolescents, disabled, military veterans and those marginalized by racism and socioeconomic disadvantage (Melville JL et al, 2010; Dinwiddie KJ et al, 2018).

The prevalence of perinatal mood and anxiety disorders (PMADs) has increased from 18.4 to 40.4 per 1,000 deliveries over 2006 to 2015 (McKee K et al, 2020).

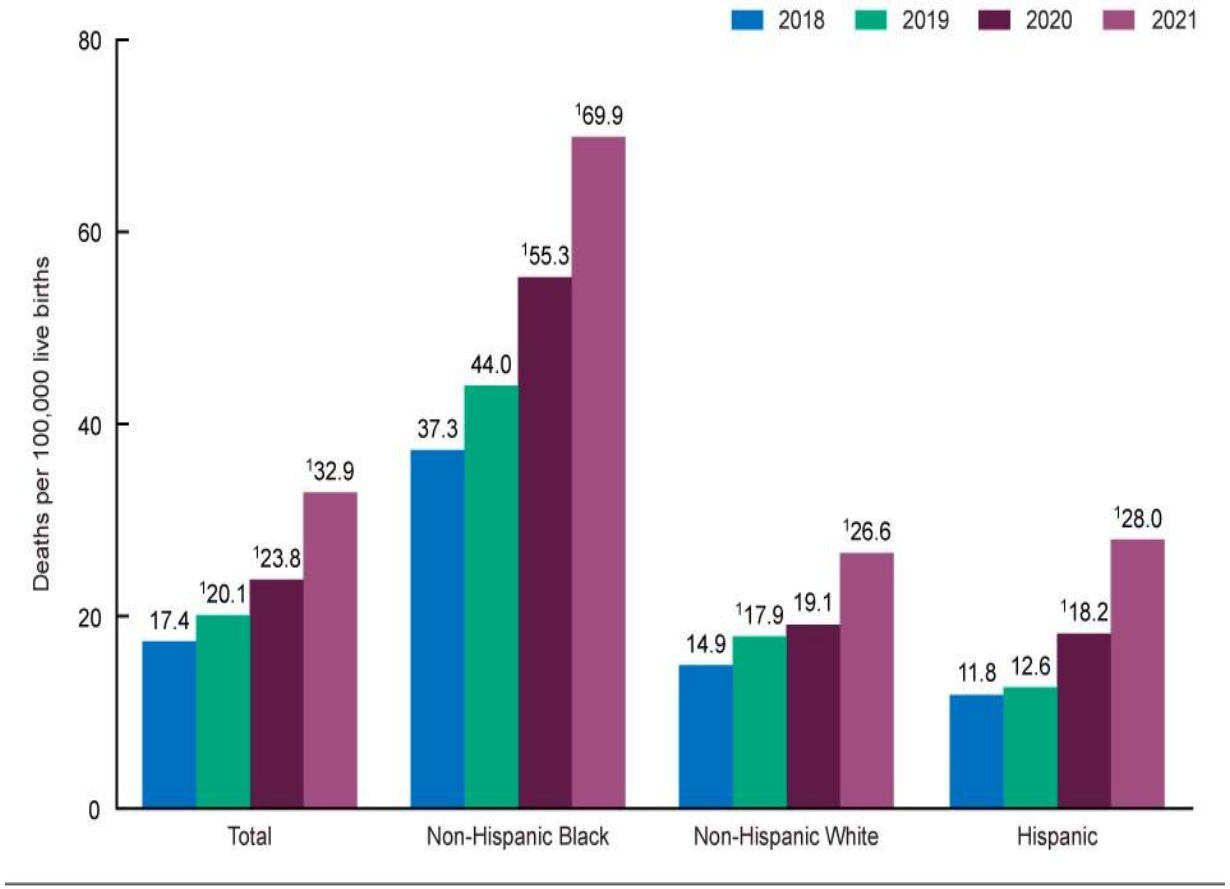
Prevalence of severe mental illness (bipolar and psychotic disorders) increased from 4.2 to 8.1 per 1000 deliveries over 2006 to 2015 (McKee K et al, 2020).

Perinatal mental health disorders are associated with adverse maternal, obstetrical, infant and child developmental outcomes (incomplete list)

- Decreased maternal functioning (Field, T, 2010)
- Psychosis, suicidal ideation, homicidal ideation and suicide attempt are psychiatric emergencies that lead to psychiatric hospitalization, maternal death (Rodriguez-Cabezas et al, 2019)
- Bidirectional relationship between depression and gestational diabetes mellitus (Fischer et al, 2023)
- Preterm labor (Bansil P et al, 2010) ,preterm birth (Grigoriadis S et al, 2013), stillbirth/neonatal death and hypertensive disorders of pregnancy (Staub et al, 2012, Thombre et al, 2015, Delanerolle et al, 2022)
- Increased requirement for surgical delivery interventions (Wang SY & Chen CH, 2010) and cesarean delivery (Bansil P et al, 2010)
- Inadequate maternal-infant bonding prenatally and post-delivery (Rossen et al, 2016; Betcher et al, 2020, Dagher et al, 2021)
- Lactation failure or unplanned weaning (Dennis CL & McQueen K, 2009; Stuebe AM et al, 2014)
- Impaired child cognitive development (Tuovinen S et al, 2018)
- Impaired child behavioral and emotional development (Leis JA et al, 2014; Pearson RM et al, 2013)
- Impaired child brain development/antenatal stress from mental illness is associated with accelerated development of offspring neural networks via fetal (developmental) programming (Schinost D et al, 2016; Rotem-Kohavi, N et al, 2020)

Cost of not treating perinatal mental health disorders (US, 2017) = $14.2 billion (Luca DL et al, 2020)

Maternal mortality rates continue to rise in the United States



Statistically significant increase from previous year ($p < 0.05$).
NOTE: Race groups are single race.
SOURCE: National Center for Health Statistics. National Vital Statistics System. Mortality.

Figure 1: Maternal mortality rates (deaths per 100,000 live births), by race and Hispanic origin: US 2018-2021

Based on data from the National Vital Statistics System

In 2021, 1,205 women died of maternal causes in the United States compared with 861 in 2020 and 754 in 2019

Perinatal mental health disorders are associated with severe maternal morbidity and are the leading cause of pregnancy-related death in the US

Women with PMADs and severe mental illness experience increased rates of severe maternal morbidity and mortality and increased hospital transfers, lengths of stay and delivery-related costs compared to other deliveries (McKee K et al, 2020).

The top three causes of pregnancy-related deaths include (Maternal Morbidity Review Committees (MMRC) in 36 states, 2017-2019; Trost SL et al, CDC 2022)

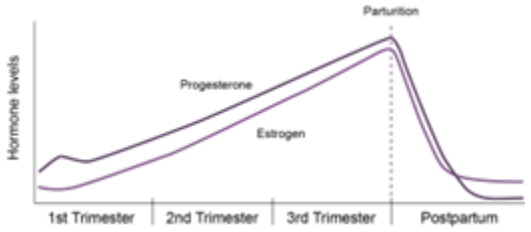
- mental health conditions: 22.7%
- hemorrhage: 13.7%
- cardiac and coronary conditions: 12.8%

Mental health conditions include deaths of suicide, overdose/poisoning related to substance use disorder, and other deaths determined by the MMRC to be related to a mental health condition, including substance use disorder.

Among those pregnancy-related deaths with a determination, 82/971 (8.4%) were determined to be a suicide.

Mental health conditions were the leading underlying cause of death among Hispanic and non-Hispanic White persons.

Research into pathophysiological mechanisms of perinatal depression

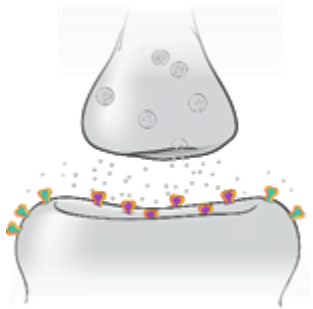


Endocrine Mechanisms

A subset of women with PPD are susceptible to fluctuating reproductive hormone levels during the peripartum period.[1]

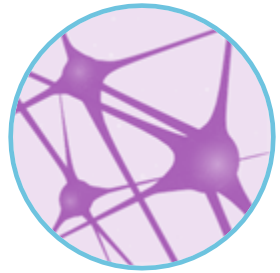
Epigenetic Mechanisms

Estradiol-mediated epigenetic mechanisms may be associated with PPD risk.[2]



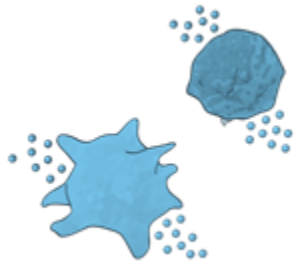
Synaptic Transmission Mechanisms

Alterations in serotonin receptors and GABA receptors have been implicated in PPD.[6,7]



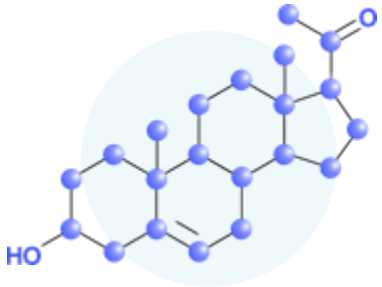
Neural Network Mechanisms

Imaging studies have demonstrated altered activity in the amygdala, prefrontal cortex, cingulate cortex, and insula in PPD.[10,11]



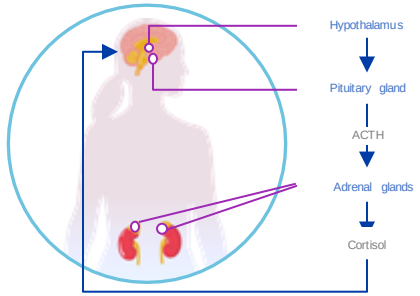
Inflammatory Mechanisms

Altered levels of immune system factors have been associated with PPD.[3]



Neurosteroid Mechanisms

Altered levels of allopregnanolone and dysfunction in NAS signaling have been observed in PPD.[4,5]



Stress Mechanisms

Dysfunction of the HPA axis has been implicated in women with PPD and animal models of PPD, particularly overactivity.[8,9]

1) Schiller CE, et al. 2015 2) Guintivano J, et al. 2014 3) Osborne LM, et al. 2013. 4) Deligiannidis KM et al, 2020 5) Antonoudiou P et, 2022 6) Thompson SM et al 2024 7) Moses-Kolko EL, et al. 2008. 8) Bloch M, et al. 2003 9) Melón LC, et al. 2018 10) Deligiannidis KM et al, 2019 11) Fiorelli M, et al. *Behav Neurol.* 2015.

Research into prevention of perinatal depression

***US Preventive Services Task Force recommended**

***Mothers and Babies program** (CBT-based): to create a healthy physical, social and psychological environment (McFarlane et al, 2017)

***Reach Out, Stand Strong Essentials for New Mothers (ROSE):** IPT-based, stress-management, developing a social support system, managing role transitions and associated changes and addressing interpersonal conflicts (Berry et al, 2021), effective in at-risk populations and those from disadvantaged backgrounds

***Practical Resources for Effective Postpartum Parenting (PREPP) program:** maternal well-being, infant behavior and maternal infant bonding (Werner et al, 2016), effective in at-risk populations and those from disadvantaged backgrounds

Other areas of investigation:

- Doulas
- Digital interventions
- Big data (EMR) machine learning approaches to identify at-risk individuals
- Home visiting programs

Therapeutics in perinatal depression

Psychotherapies: monotherapy for mild-moderate unipolar perinatal depression

- Interpersonal psychotherapy (IPT) (Reay R et al, 2012; Grote NK et al, 2010; Spinelli MG & Endicott J 2003; O'Hara MW et al, 2000; Klier CM et al, 2001; Stuart S & O'Hara MW 1995)
- Cognitive behavioral therapy (CBT) (Milgrom J et al, 2016; Milgrom J et al, 2015; Ammerman RT et al, 2013; Le HN et al, 2011)
- Mindfulness-based CBT (Dimidijian S et al, 2016; Dimidijian S et al, 2014; Goodman JH 2014)
- Peer support and group psychotherapies (Dennis CL et al 2009; Dennis CL 2003; Chen CH et al 2000; Honey KL 2002; Milgrom et al 2005)

Serotonergic antidepressants: moderate/severe unipolar perinatal depression

- *No* randomized, placebo-controlled trials (RCT) of antidepressants for antenatal depression
- Limited RCT-level evidence for the use of serotonergic antidepressants in postpartum depressed patients (Yonkers KA et al, 2009; Brown JVE et al, Cochrane Database Syst Rev, 2021; Molenaar NM et al 2018)
- Use is associated with different risks: pregnancy or during lactation
- Treatment approach: titrate until efficacy/tolerability then treat acute episode at that dose -> once reach euthymia, continue treatment (continuation phase) for 4-9mo to prevent relapse.
- Often best to combine with psychotherapies

Therapeutics in perinatal depression (postpartum admin only)

Decades of research into the role of neurosteroids/neuroactive steroids in brain functioning

- discovery of allopregnanolone in adrenal glands (1938) by Beall & Reichstein
- neurosteroid: introduced in 1981 by French physiologist Étienne-Émile Baulieu
- neuroactive steroid: in 1992 characterized by Steven Paul (NIMH) and Robert Purdy; "natural or synthetic steroids that rapidly alter the excitability of neurons by binding to membrane-bound receptors such as those for inhibitory and excitatory neurotransmission"
- **86 years of research from 1938-2024** (Paul SM et al, 2020)

epilepsy and anesthetics -> anxiolytic effects ->role in stress response->role in perinatal physiology->effects of SSRIs on allopregnanolone in depression ->role in PTSD -> role in PPD pathophysiology ->therapeutic effects in PPD

Brexanolone: IV administered, exogenous version of allopregnanolone, binds GABA-A receptors

- First FDA-approved PPD treatment (2019) and first-in-class neuroactive steroid antidepressant
- Administered as a 60-hour peripheral infusion with rapid-acting antidepressant effects

Zuranolone: synthetic analog of allopregnanolone, binds GABA-A receptors

- First oral FDA-approved PPD treatment (2023)
- Once daily oral dosing (50mg) x 14 days with rapid-acting antidepressant effects

Neurostimulation therapeutics in perinatal depression

Transcranial magnetic stimulation (TMS): (Kim DR et al, 2019; Miuli A et al, 2023; Myckowski ML et al, 2012; Garcia KS et al, 2010)

- Very limited research, signal for efficacy and good safety for patient and fetus/newborn

Transcranial direct current stimulation (tDCS): (Vigod S et al 2019; Sun W et al, 2023)

- Very limited research

Electroconvulsive therapy (ECT): (Bulbul F et al, 2013; Focht A & Kellner CH, 2012; Pomlili M et al, 2014)

- Limited rigorous research
- Most common complication is premature uterine contractions, preterm labor, fetal bradyarrhythmia
- Option for perinatal women with
  - Severe mood episode that does not respond to pharmacotherapy
  - Catatonia, food refusal, psychosis
  - High risk of suicide

Magnetic seizure therapy (MST): no published studies

Transcutaneous auricular vagus nerve stimulation (taVNS): (Deligiannidis KM et al, 2022)

- One study, lacked sham-control

Therapeutics in perinatal depression

Bright light therapy/chronotherapies: (Wirtz-Justice et al, 2011; Crowley SK & Youngstedt SD, 2012, Corral et al, 2007)

- Low cost, home-based, tolerability
- Few efficacy or effectiveness trials

Complementary or integrative health practices

- May include mind-body practices, traditional healing practices, natural products or nutraceuticals
- Limited rigorous research; lack of validated tool use, lack of adequate controls
- Approximately 1/3 of perinatal individuals use a complementary intervention to manage their symptoms (Birdee et al, 2014)

Research and funding gaps in perinatal mood and anxiety disorders

Pathophysiology (1/2)

- What are the best preclinical models to study perinatal psychiatric illness development and test developing therapies?
- How do we dually fund extramural preclinical and clinical investigators to do translational research together? Is there a similar program to the NIH bench-to-bedside (BtB) and back program linking intramural (1999) and intramural with extramural scientists (2006) for extramural scientists, in perinatal psychiatric disorder research?
- How does maternal brain physiology/circuitry change across the perinatal period in health and psychiatric illness?
- What are the mechanisms for antepartum and postpartum triggering of onset for each psychiatric illness, are there shared mechanisms across perinatal psychiatric diseases, e.g. depression, anxiety, OCD

Research and funding gaps in perinatal mood and anxiety disorders

Pathophysiology (2/2)

- Are mechanisms of risk for perinatal triggered psychiatric illness similar/dissimilar to other reproductive mood disorders (premenstrual, perimenopausal) and how?
- How does the pathophysiology (not just the trigger) differ between perinatal-onset psychiatric illness vs. non perinatal onset illness? Are they the same but just have a different trigger, or are they distinct?
- What is the underlying biology of the heterogeneous clinical phenotypes of perinatal psychiatric disorders? How many phenotypes are there?
- What are the shared or distinct mechanisms between perinatal mental health pathophysiology and obstetrical complications leading to severe maternal morbidity (e.g. preeclampsia, gestational diabetes, hemorrhage, placental abruption, stillbirth)
- Mechanisms of fetal programming, how is psychiatric illness risk passed to the offspring in utero, role of placenta, epigenetics, stress-related mechanisms, maternal immune activation, etc. on altered child neurodevelopment, etc.

Research and funding gaps in perinatal mood and anxiety disorders

Prevention and Treatment (1/2)

- Translation of preclinical findings to clinical findings- are the preclinical models accurate or do we just base our clinical studies on them without knowing? e.g. the mechanism of how a drug works to prevent/treat in a postpartum mouse, is that how it works in postpartum human subjects?
- Research into how current perinatal mental health treatments impact fetal/child development, what are the risks, and are there benefits for the developing child? What are they?
- Randomized controlled trials to test efficacy and safety of new (and current) treatments in pregnancy and in lactation- *we lack efficacy data on most medications* used in pregnancy and during lactation
  - Pharmacotherapies
  - Neuromodulation
  - Digital therapies
  - Complementary/integrative
- Intervention studies in perinatal patients require a unified battery of outcome measures to increase rigor and to ensure comparability of results in future research. Are currently used psychometrics, which were developed in non-perinatal populations, accurate and precise enough for efficacy research?

Research and funding gaps in perinatal mood and anxiety disorders

Prevention and Treatment (2/2)

- Obstetric research should include better measures of perinatal mental health to investigate whether mental health status affects treatment efficacy and safety (e.g. smoking cessation in pregnancy RCTs, not only measure smoking and infant development outcomes but also maternal mental health outcomes)
- Research to improve access to treatment for women with difficulties due to poverty, racism, stigma and interpersonal violence
- Comparative effectiveness research (T4) in treatment of perinatal psychiatric disorders
  - Are treatments effective if delivered by non-specialists?
- Which treatments for which perinatal patients? Who will do best with which psychotherapy vs. which pharmacotherapy vs. which form of neuromodulation? Do different phenotypes respond differently to different treatments?
- Which integrated treatments are best for perinatal individuals with comorbid psychiatric illness (e.g., perinatal depression plus generalized anxiety disorder plus PTSD?)
- We have no biomarkers of treatment prediction.

Barriers to research progress, addressing the inequities in perinatal psychiatric disorder research

Inadequate numbers of trained and NIH-funded perinatal mental health investigators across disciplines and disorders

- Psychiatry, psychology, epidemiology, advanced practice nursing, mental health counseling, social work, etc.

Inadequate number of NIH-funded basic science investigators focused on perinatal mental health research

Inadequate coordinated funding mechanisms and research for T1 and T2 research

RFAs may be of limited duration, is there a way to sustain funding priorities over time and thus sustain the biomedical research workforce reliant on NIH funding to support research progress? Do we lose investigators interested and trained in this area of research who choose other “more fundable” areas of research?

Some perinatal psychiatric research requires study of both the pregnant individual and fetus/infant, do current funding mechanisms support research that cross institute priorities, e.g. NIMH, NICHD, NIDA, NIAAA?

Many early career investigators may not be affiliated with one of the 11 SCORE programs or 19 active BIRCWH programs so not have access to these funding streams

Barriers to research progress, addressing the inequities in perinatal psychiatric disorder research

Does the NIH Center for Scientific Review have sufficient resources to recruit qualified grant reviewers in this still limited research area? Do proposals involving disorders that are more well known (e.g., schizophrenia), have an advantage of the familiarity of the review panel, making it more challenging for proposals involving disorders whose knowledge base is less mature to be funded?

Do women's perinatal mental health grant applications have the same funding level of success as non-women's mental health grant applications? Is there bias against funding of *women's* or *reproductive* mental health research?

Do investigators conducting perinatal mental health research have to shape their grant applications to fit current funding priorities (or biases) to increase their odds of funding, rather than submit the science that should be funded? Are the funding priorities of NIH in alignment with the research needs of the people it serves?

How to best recruit and retain perinatal individuals with psychiatric and often comorbid medical illness or substance use disorders in research? Minoritized populations?

Perinatal mental health receives limited federal research dollars in comparison to other women's health issues with a similar population prevalence

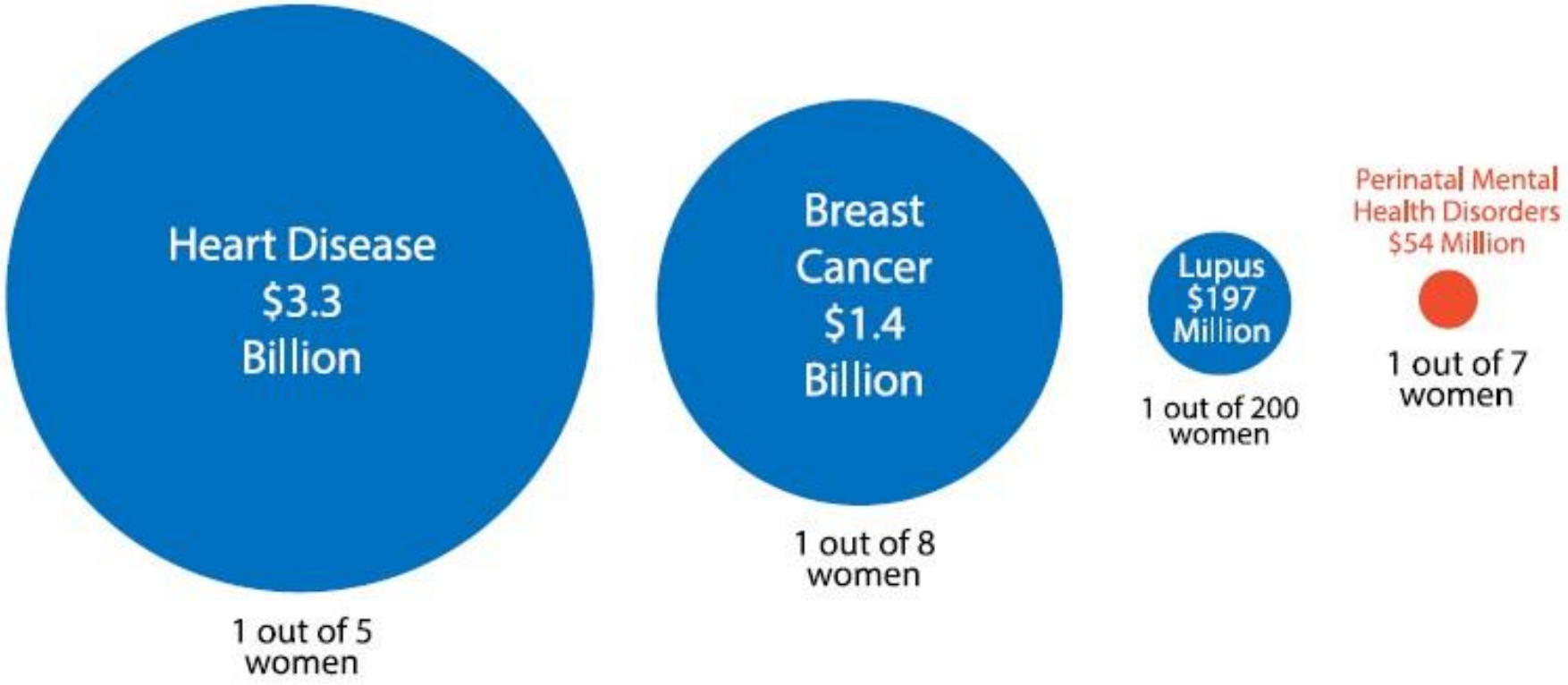


Figure 3: Perinatal mental health funding does not match the crisis today. Total grant funding by the National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC) for fiscal year 2017 for heart disease, breast cancer, lupus, and perinatal mental health is compared above, with the prevalence information. Federal RePORTER database information was used by The Reilly Group to conduct the funding analysis.

Mind the Gap: A Strategic Roadmap
to Address America's Silent Health Crisis: Untreated and Unaddressed Perinatal Mental Health Disorders, Led by Postpartum Support International

Thank you