Perinatal Depression: Impact, Detection, and Management

Ryan J Van Lieshout, MD, PhD, FRCPC

Albert Einstein/Irving Zucker Chair in Neuroscience

Canada Research Chair in Perinatal Mental Health

Professor, Dept of Psychiatry and Behavioural Neurosciences

McMaster University

John E Krzeczkowski, PhD

Assistant Professor, Dept of Health Sciences

Brock University

Disclosures

Ryan J Van Lieshout

-No relationships with financial sponsors to disclose

John E Krzeczkowski

-No relationships with financial sponsors to disclose

Agenda

Perinatal Depression:

- Prevalence and Scope
- Impact: Birthing Parents and Offspring
- Detection
- Diagnosis
- Management

JABFM.ORG
JABFM
JOURNAL OF THE AMERICAN BOARD OF FAMILY MEDICINE

Perinatal Depression: A Guide to Detection and Management in Primary Care

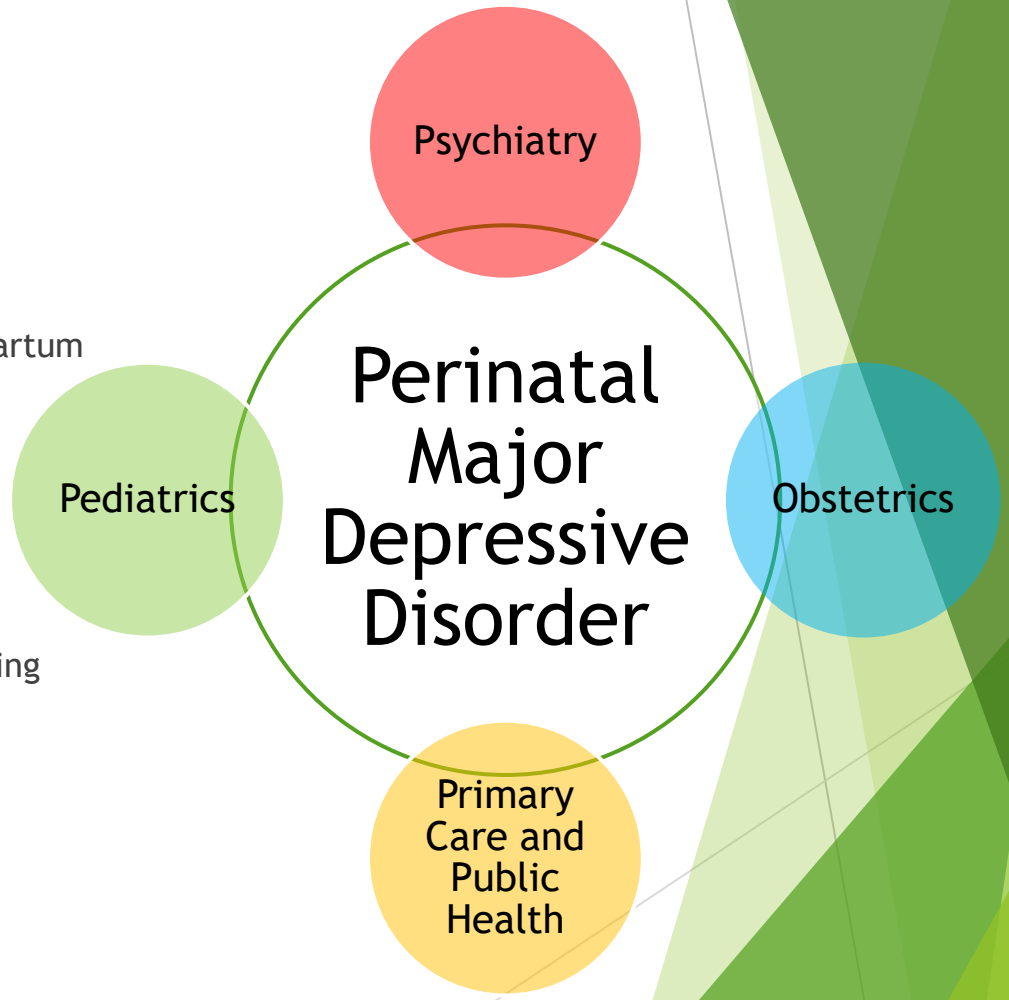
CLINICAL REVIEW

Manish H. Dama, MPH; Ryan J. Van Lieshout, MD, PhD, FRCP (C)

Corresponding Author: Manish H. Dama, MPH; School of Medicine - Trinity College Dublin - The University of Dublin
Email: damam@tcd.ie
DOI: 10.3122/jabfm.2023.230061R1
Keywords: Breast Feeding, Interpersonal Psychotherapy, Lactation, Postpartum, Psychosocial Intervention, Postpartum Depression, Pregnancy, Psychiatry, Selective Serotonin Reuptake Inhibitors, Surveys and Questionnaires
Dates: *Submitted:* 02/21/2023; *Revised:* 06-17-2023; *Accepted:* 06-26-2023
Status: In production for ahead of print.

Perinatal Depression

- Depression occurring during pregnancy and the 1st postpartum year
  - Most cases occur during gestation and the first 3 months postpartum
  - Increased levels of symptoms occur in up to 30% of individuals
- Formal Definition in DSM-5: Major depressive disorder (MDD) of peripartum onset:
  - MDD onset in pregnancy or first 4 postpartum weeks
  - Prevalence: 9.2 to 17.0%
- Adverse Outcomes for Mothers/Birthing Parents, Partners, and Offspring
  - Much more on offspring in a moment…
- Lifetime economic cost of one untreated case: $150,000 (CAD)
- Just 10% receive evidence-based treatment



Inspiration

My research program is inspired by my grandmother, who was a **public health nurse** for 25 years

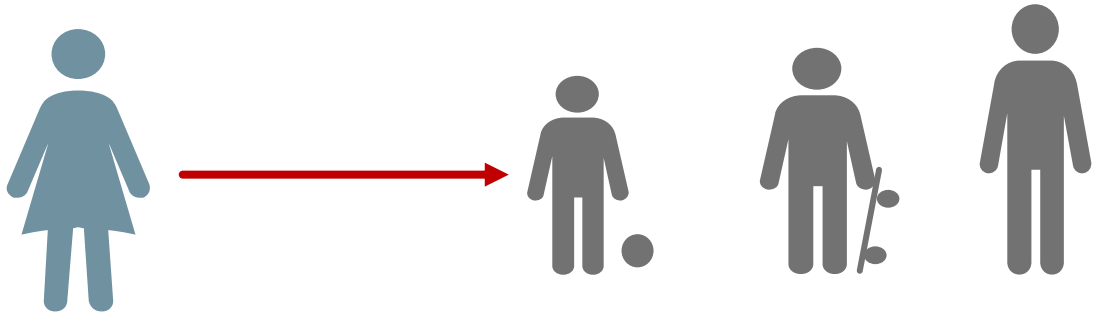
- In the late 1970s, she founded and led the Niagara Region's first postpartum depression support group

I wondered whether programs that support the health mothers/birthing parents also benefit children and families

ACEs Across Generations

Adverse Childhood Experiences (ACES)[1]

1. The experiencing/witnessing traumatic events (violence, abuse, neglect)
2. Environmental conditions that significantly disrupt child stability, safety, and bonding



Exposure to maternal PPD during the first postnatal year

Academic and behavioural problems in childhood

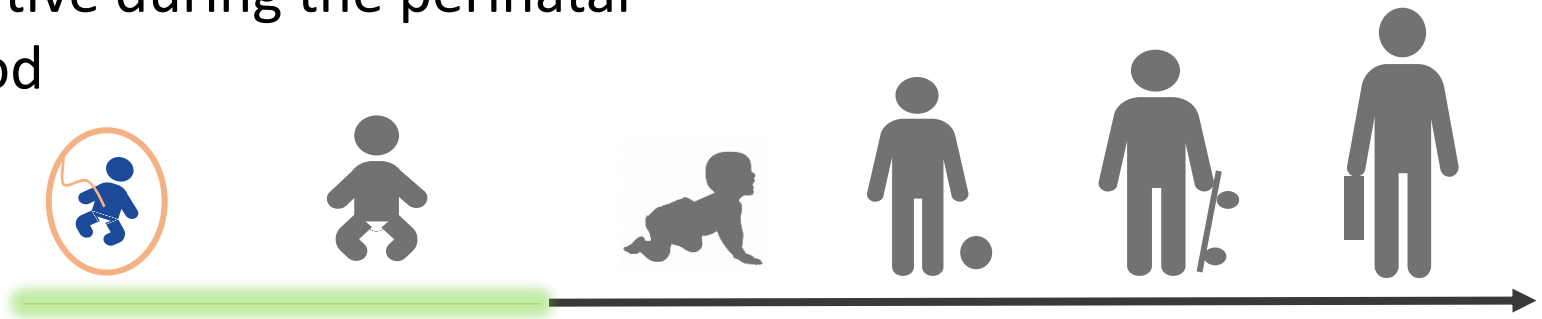
Increased risk for psychiatric disorders in adulthood

[1]Centre for Disease Control and Prevention. Adverse Childhood Experiences. June 2023. https://www.cdc.gov/violenceprevention/aces/index.html

(Krzeczkowski & Van Lieshout, 2018; Gluckman & Hansen, 2015)

ACEs Across Generations

The infant brain is very sensitive during the perinatal period



- Exposure to adversity during the prenatal and early postnatal period increases risk for multiple adverse health outcomes across the lifespan

If we can optimize early life conditions (i.e., get families off to a strong start) can we reduce or prevent adverse outcomes in children?

(Krzeczkowski & Van Lieshout, 2018; Gluckman & Hansen, 2015)

Postpartum Depression: A Common ACE

1 in 5 mothers experience postpartum depression

PPD has significant negative effects on mothers' health

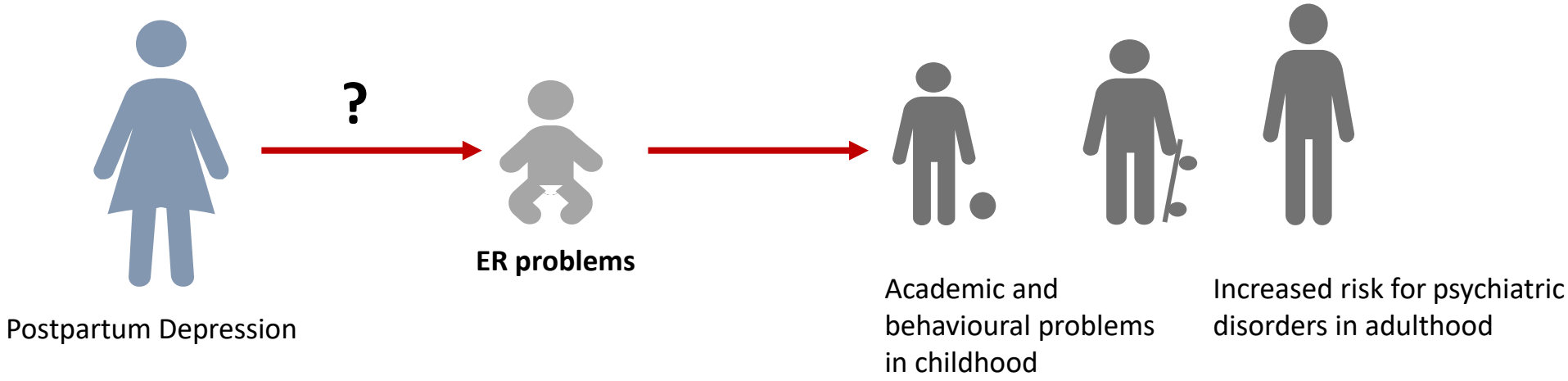
70%

Each case costs $150,000 over the lifespan, with 70% of these costs being due to problems in children

(Gavin, 2014; Goodman & Gottlieb, 2020)

The Impact of PPD on children

- Impacts of Postpartum Depression (PPD) on offspring can be detected as early as infancy
- Exposure to PPD disrupts infant emotion regulation (ER)
  - ER: the ability to modify emotions in the service of future goals



How does PPD disrupt infant ER?

(Gavin, 2014; Goodman & Gottlieb, 2020)

Postpartum depression, Child ER and Resilience

Emotion Regulation (ER) develops through mother-infant interactions

Interactions in healthy mother-infant pairs

Match → Mis-match → Match → Mis-match → Match

Infants learn
-Negative states can be repaired, challenges overcome
-Shapes ER brain development

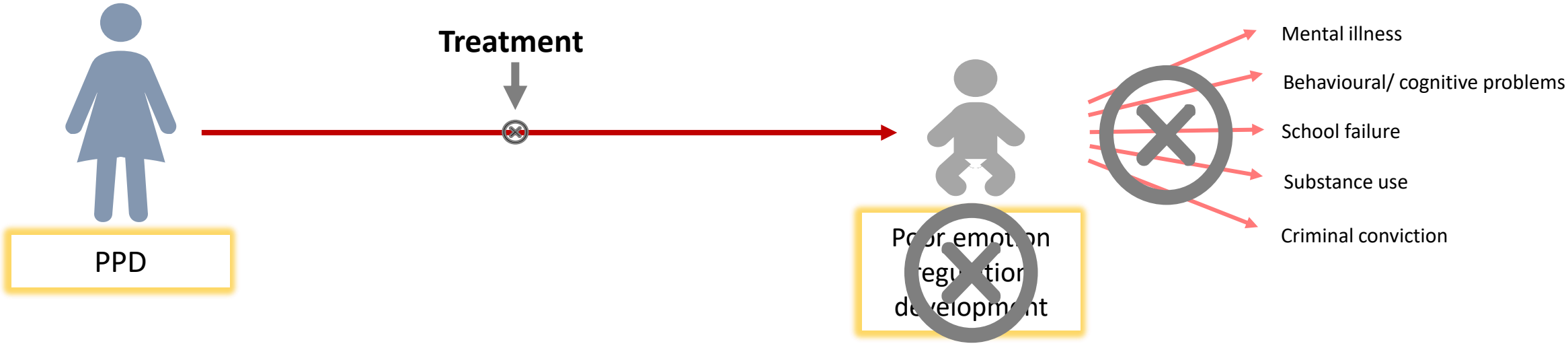
Interactions between mother-infant pairs affected by PPD

Match → Mis-match → Match → Mis-match

Infants learn
-Negative states are enduring
-Disrupts ER brain development

Treating PPD: Benefits for Parents and Children?

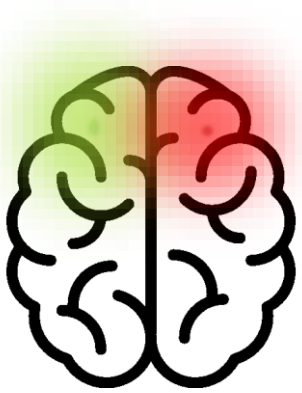
- Postpartum depression has a negative impact on offspring emotion regulation
- Brain regions involved in emotion regulation are sensitive to maternal inputs
- We have a tremendous opportunity, whereby treating PPD might alter brain-based systems underlying emotion regulation and optimize development across the lifespan



Assessing Emotion Regulation in Infants

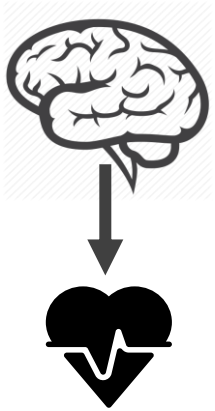
Frontal Brain Asymmetry (FA)

Greater Left FA: Better emotion regulation



Greater right FA: Poorer emotion regulation

Heart Rate Variability (HRV)



Higher HRV: Better emotion regulation

Lower HRV: Poorer emotion regulation

Does treating maternal postpartum depression improve infant emotion regulation?

PPD Intervention Studies

Study 1

Can treating PPD with group **Cognitive behavioural therapy (CBT) in a specialized women's mental health clinic** improve infant emotion regulation?

Study 2

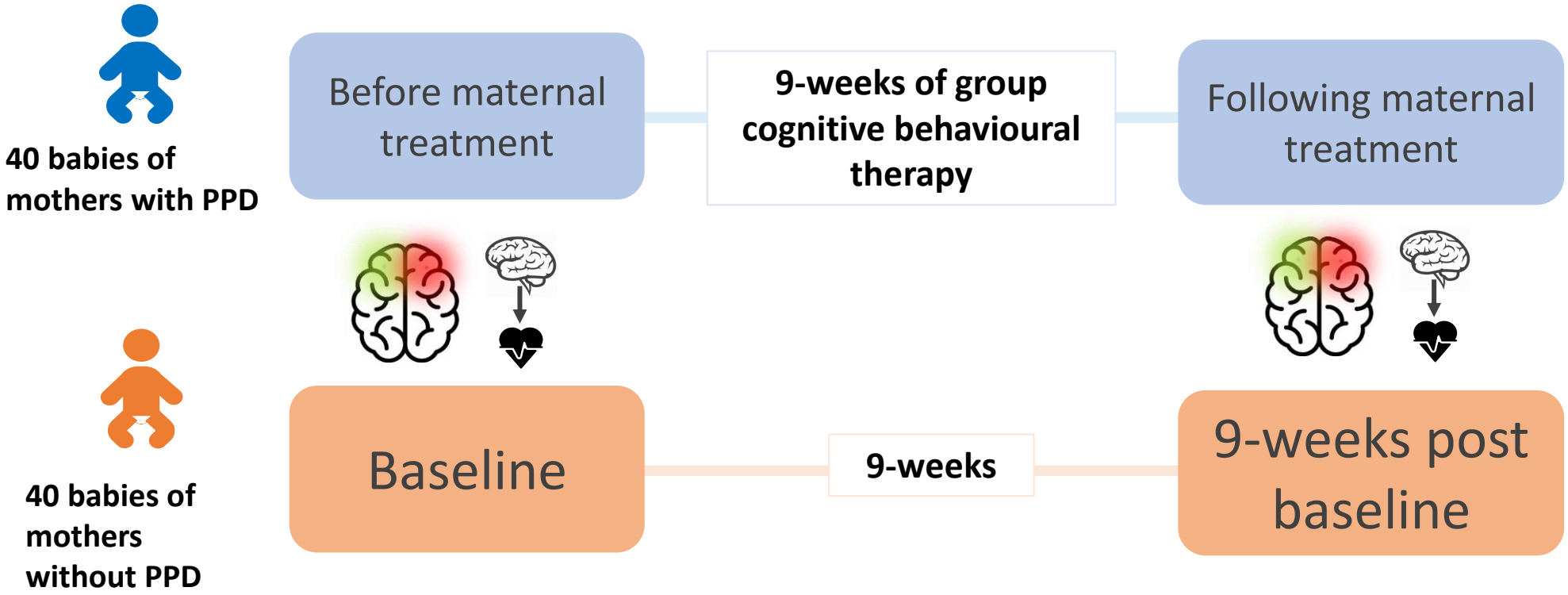
Does CBT **delivered by Peers** (people who have had and recovered from PPD) improve infant emotion regulation?

Study 3

Does **CBT delivered by public health nurses** improve infant emotion regulation?

Niagara Region
PUBLIC HEALTH

Study 1: Clinic-Delivered CBT



*referred to parents as “mothers” since all participants in all studies identified as a mothers and females

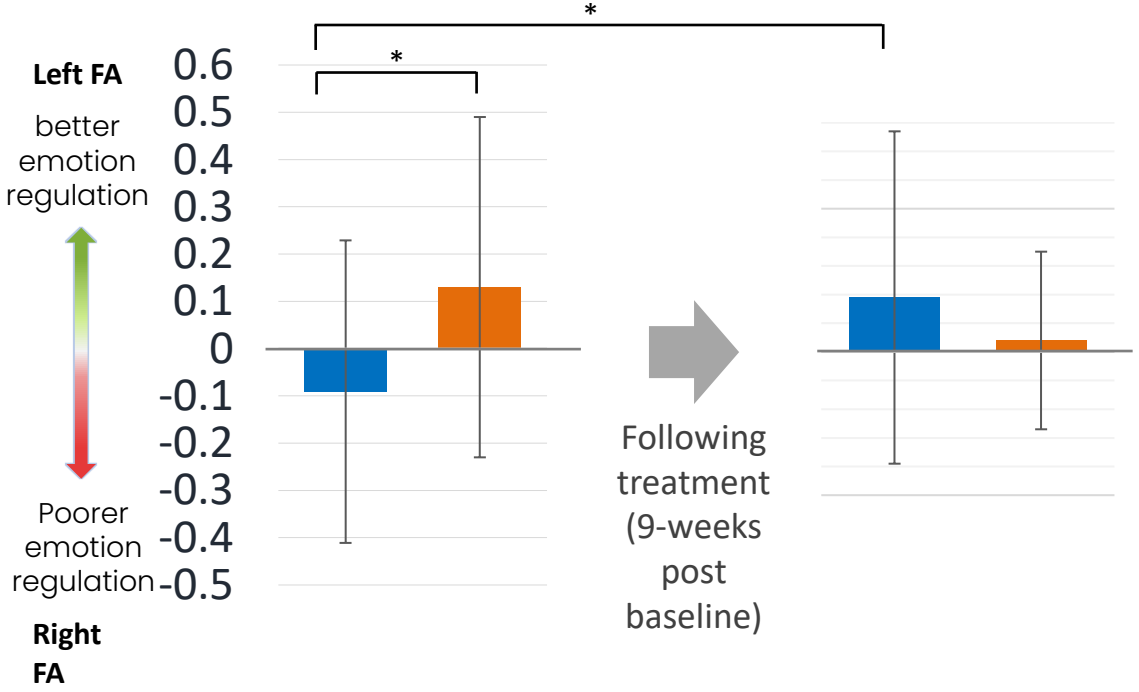
(Krzeczkowski et al., 2021. *Depression and Anxiety*)

Study 1: Clinic-Delivered CBT-Results

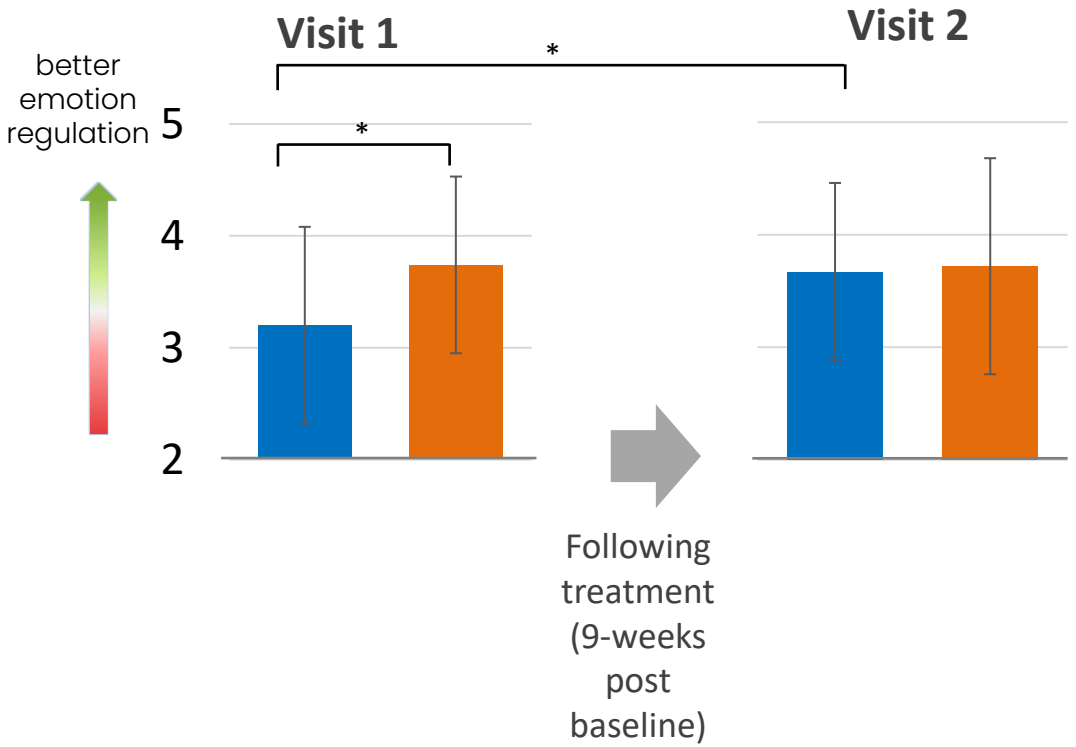
PPD babies

Control babies

Frontal EEG Asymmetry (FA)



Heart Rate Variability



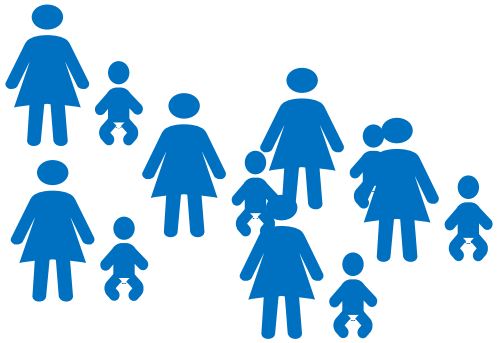
(Krzeczkowski et al., 2021)

Studies 2 and 3

Study 2: Peer delivered CBT

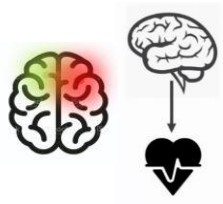
Study 3: Public Health Nurse CBT

Treatment group



Study Visit 1

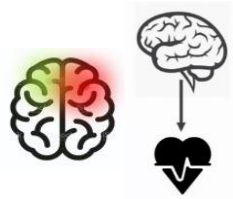
Before treatment



9-weeks of group CBT
Study 2- Delivered by PEERS
Study 3-Delivered by PH Nurses

Study Visit 2

Following treatment



At baseline

9 weeks

9-weeks post-baseline

Wait-list control

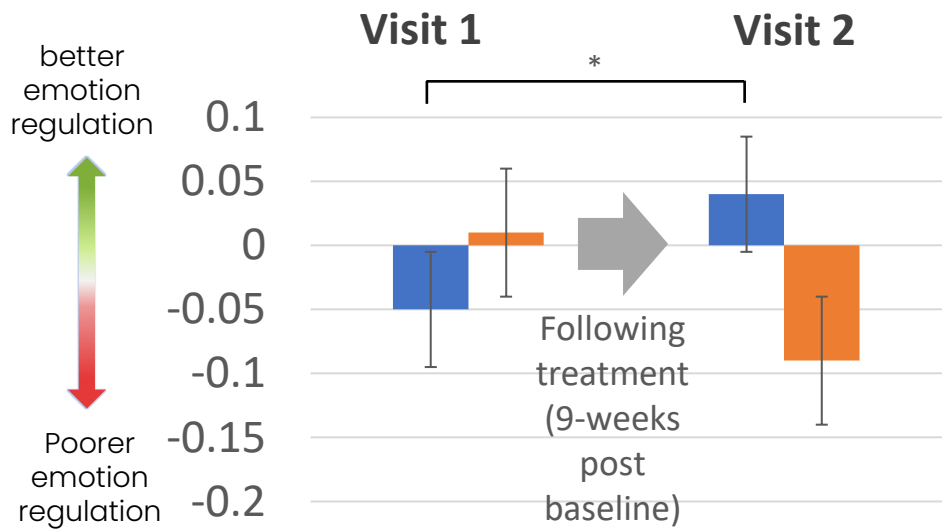
(Amani, Krzeczkowski et al., *Development and Psychopathology, 2024;* Amani, Krzeczkowski et al., *J Affect Disord, 2024*)

Study 2: Peer Delivered CBT

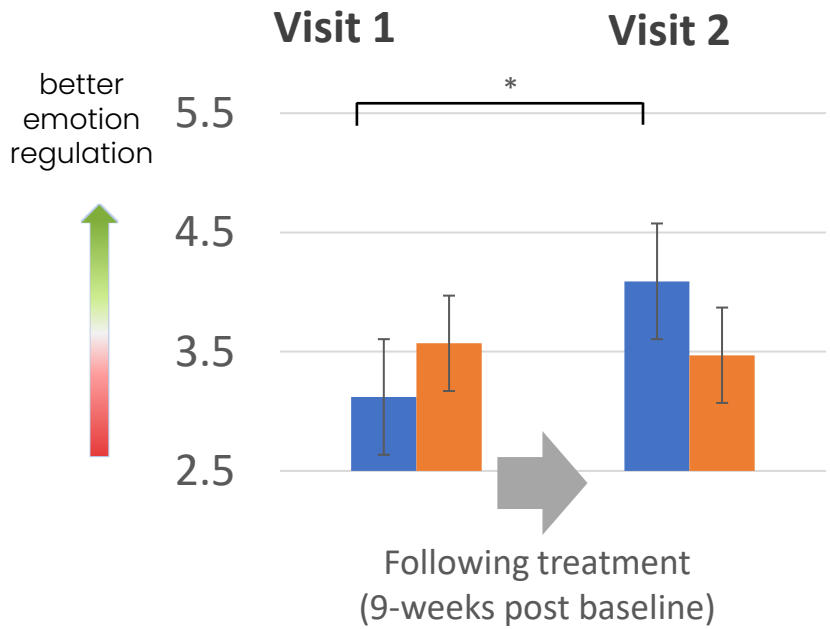
Treatment group babies (n=15)

Wait list control babies (n=15)

Frontal EEG Asymmetry



Heart Rate Variability



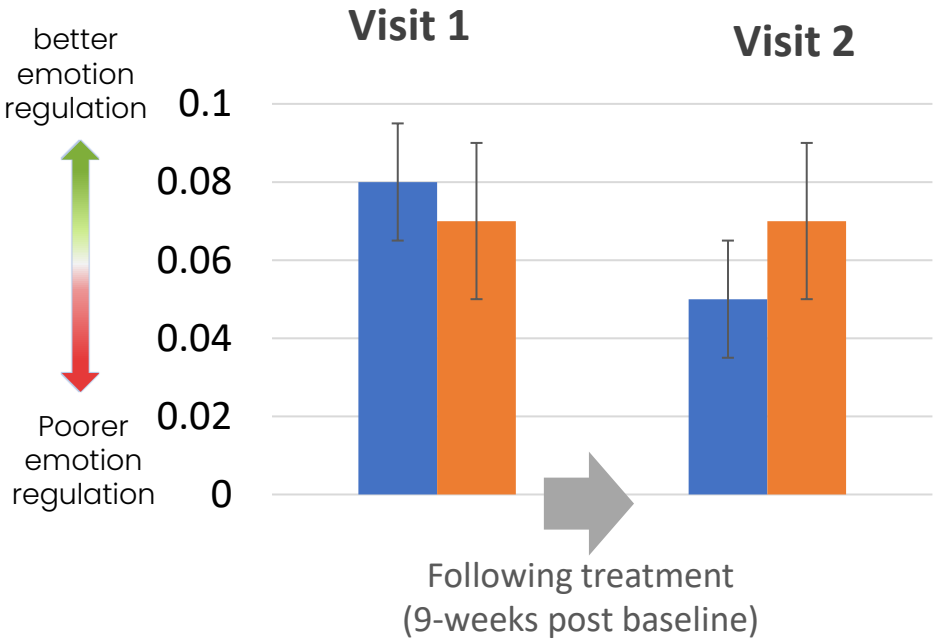
(Amani, Krzeczkowski et al., *Development and Psychopathology, 2024*)

Study 3: Nurse Delivered CBT

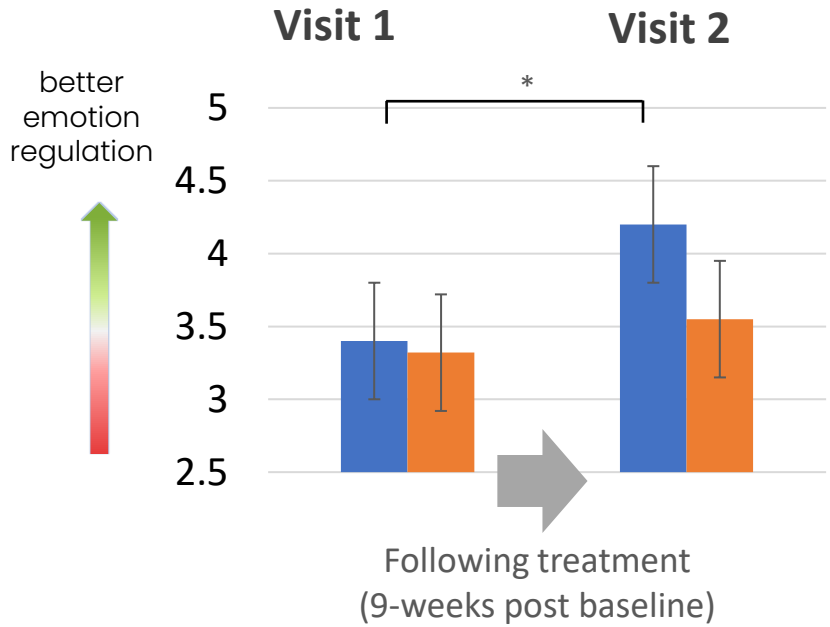
Treatment group babies (n=35)

Wait list control babies (n=35)

Frontal EEG Asymmetry



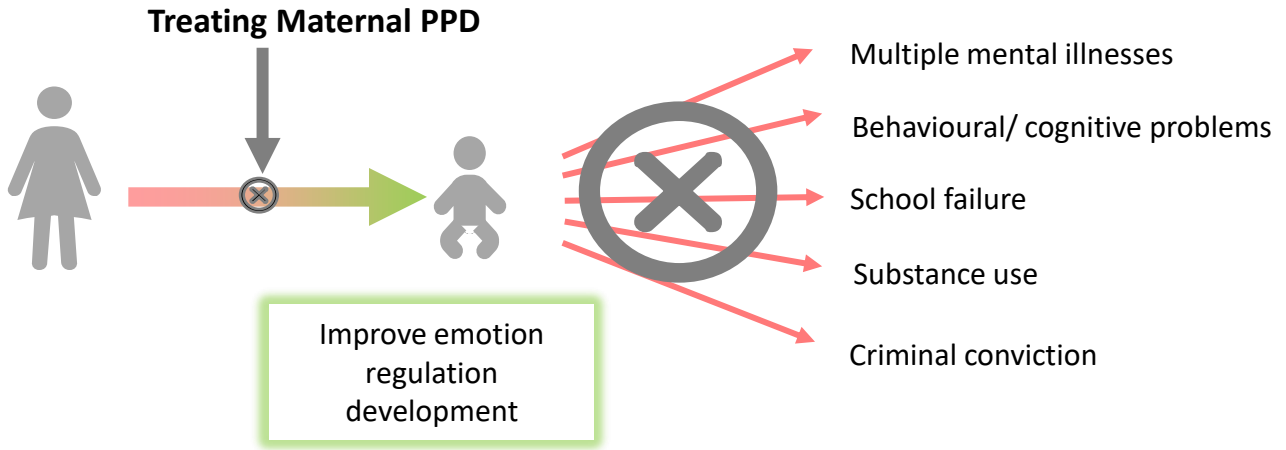
Heart Rate Variability



(Amani, Krzeczkowski et al., *Development and Psychopathology, 2024;* Amani, Krzeczkowski et al., J *Affect Disord, 2024*)

Summary

- In 3 different studies and samples using 3 different forms of CBT deliver, we showed that treating PPD improves infant emotion regulation



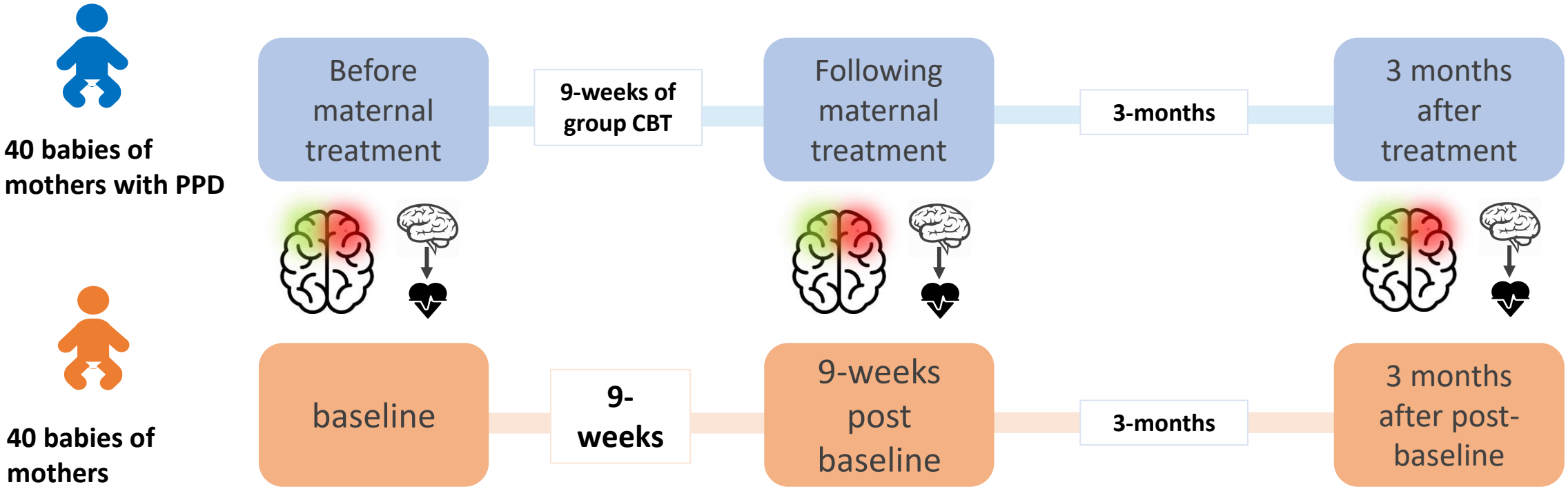
- Treating PPD may optimize the development of the infant brain

(Akil, 2020; Gatz-Kopp, 2018)

Do benefits last beyond acute treatment?

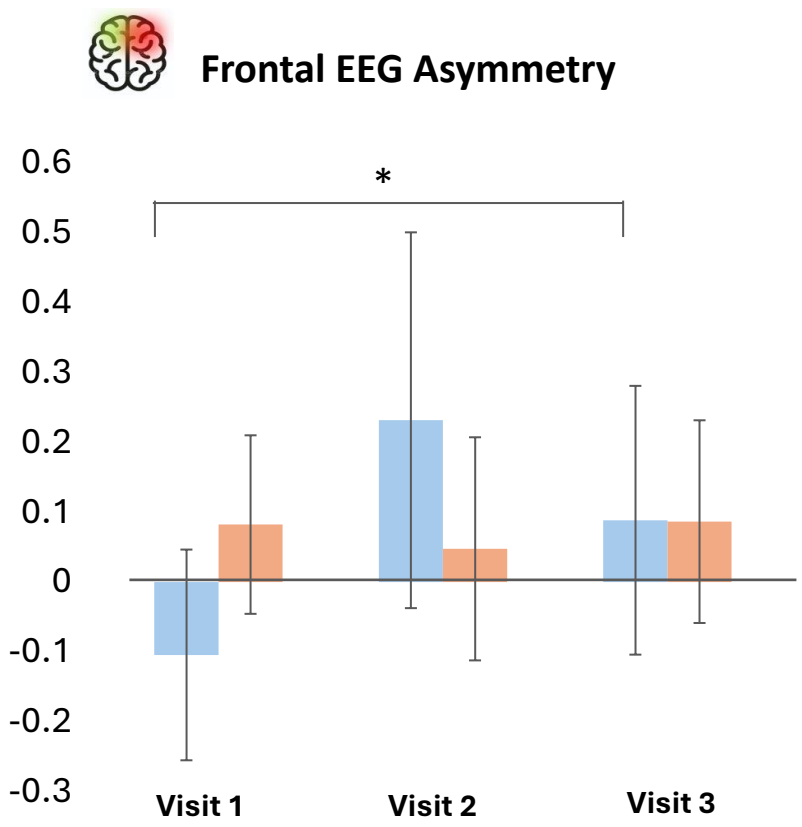
- Benefits observed immediately following interventions may decrease over time
- Does treating PPD with 9-weeks of CBT set the infant brain on a new, more adaptive trajectory (i.e., greater ER capacity, resilience, and lower risk for mental health problems)?
- **We aimed to investigate if changes in infant ER abilities persisted three months after the treatment was completed (6 months post-baseline)**

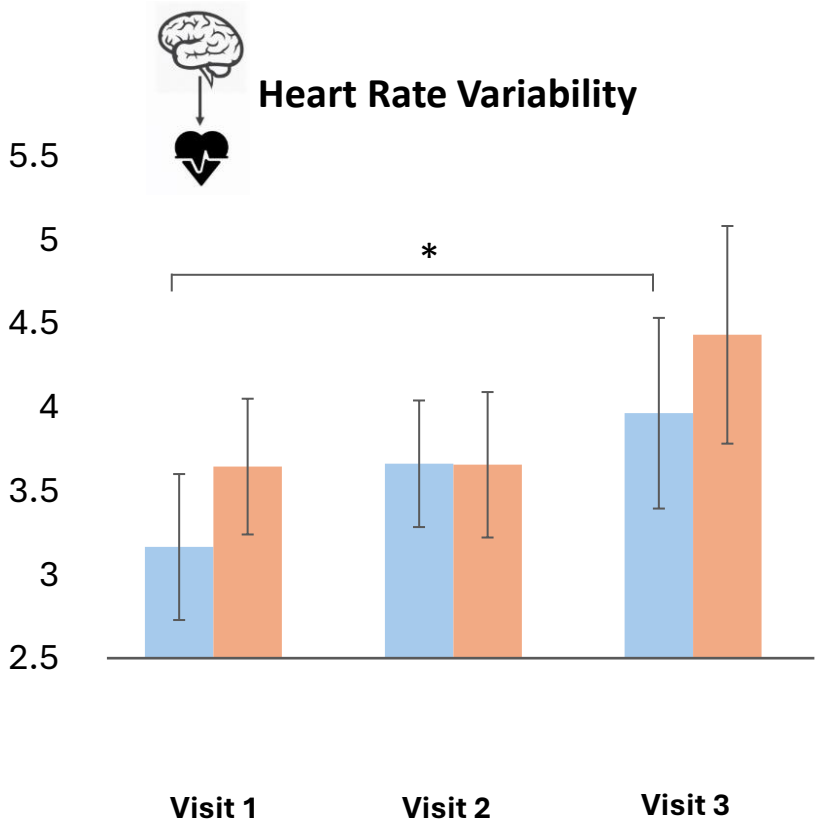
Study 1: Longer-Term Effects of PPD Treatment



(Krzeczkowski et al., *Under review Developmental Science)*

Study 1: Longer-Term Infant Outcomes





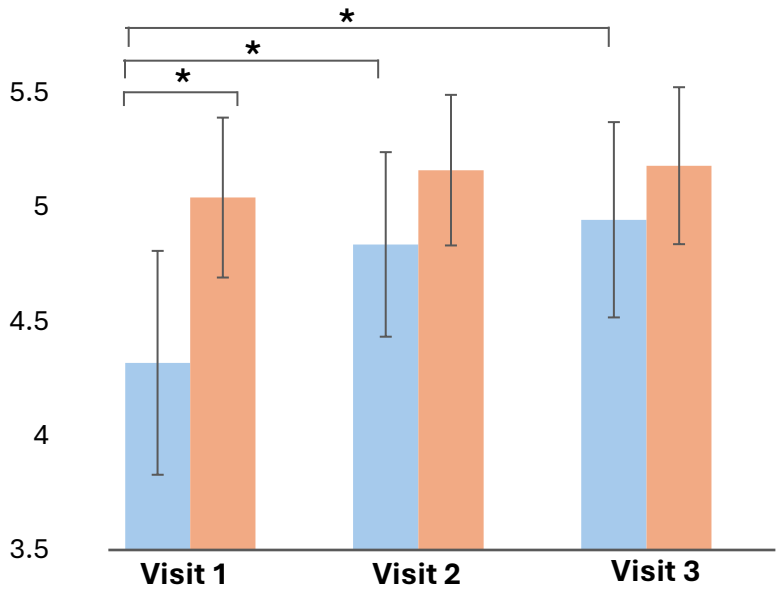
Beneficial changes in both frontal EEG asymmetry and heart rate variability persisted 3 months after treatment ended

Changes in Infant Temperament?

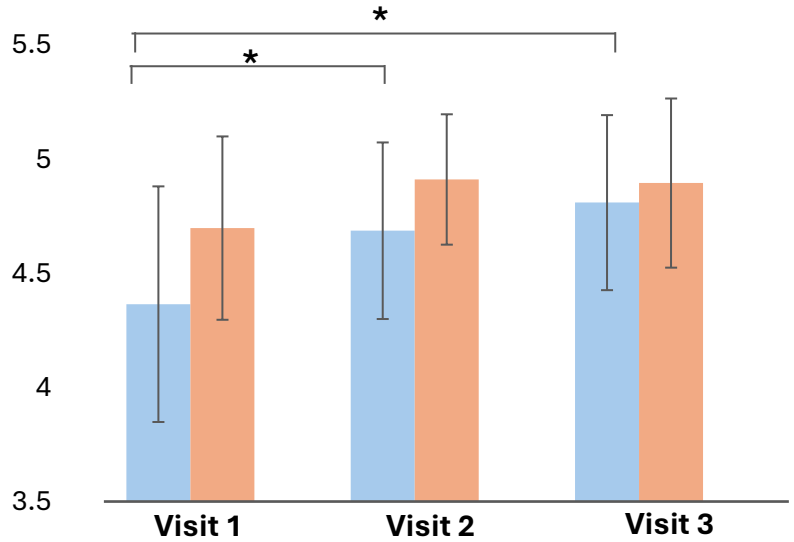
- ***Infant Temperament:*** Pattern of characteristics consistently displayed by an infant
- **Positive affect:** smiling, laughing, soothability and how long infants attend to activities

Did mothers and their partners observe chance in their infants' temperament after treatment?

Mother reported infant positive affect



Partner reported infant positive affect

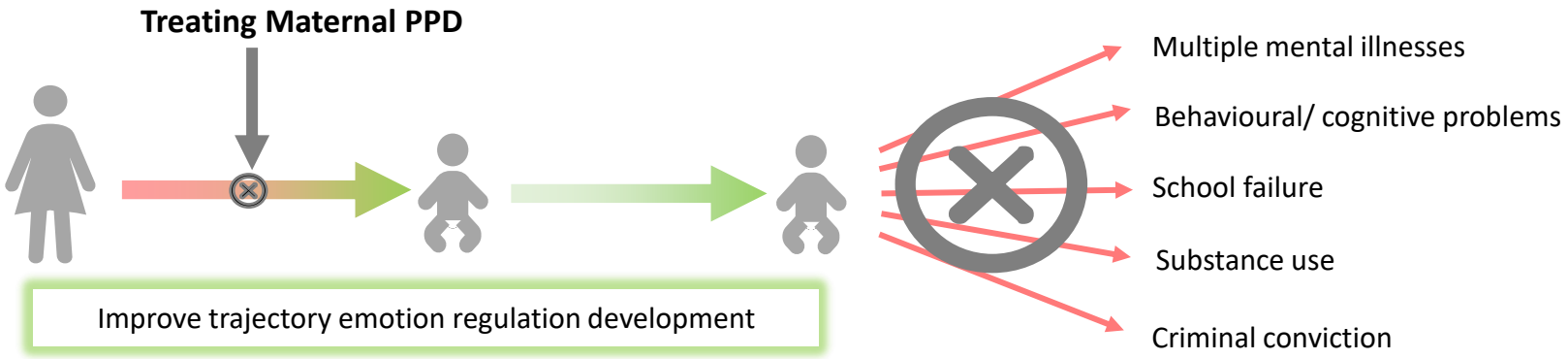


Long term changes are also observed in infant positive affect

(Krzeczkowski et al., Under Review, *Development and Psychopathology*)

Summary

- Following 9 weeks of CBT for PPD, adaptive changes across 3 measures of ER persisted
- These continued for 3 months post-treatment, a period corresponding to 1/3 of the infant's entire life



Treating PPD may set infants on a new, more adaptive developmental trajectory

Why These Changes?

- Infants rely on mothers to soothe them when distressed. Mothers with PPD can struggle to do this

The Still-face Paradigm

Play
(2 minutes)

Still-face
(2 minutes)

Reunion
(2 minutes)

HRV underlies emotion regulation in mothers and children, does mother-infant HRV synchrony play a role in how mothers soothe infants and does this improve following PPD treatment?

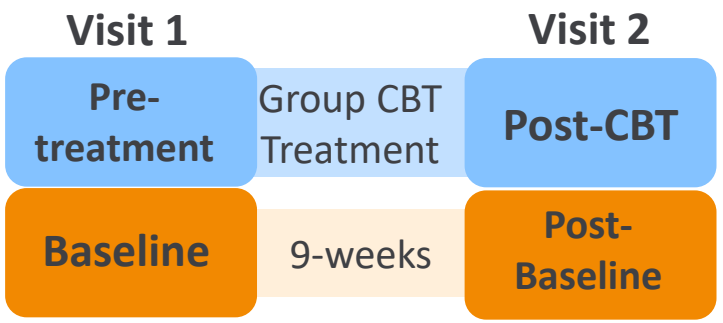
(Akil, 2020; Gatz-Kopp, 2018)

Study 1: Methods

Sample and Design

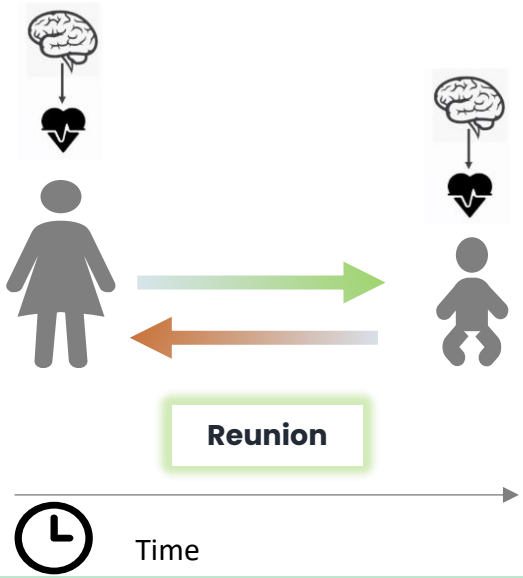
- **Cases:** n=40 dyads diagnosed with maternal PPD
- **Controls:** n=40 healthy controls without PPD

Matched on age, sex, SES



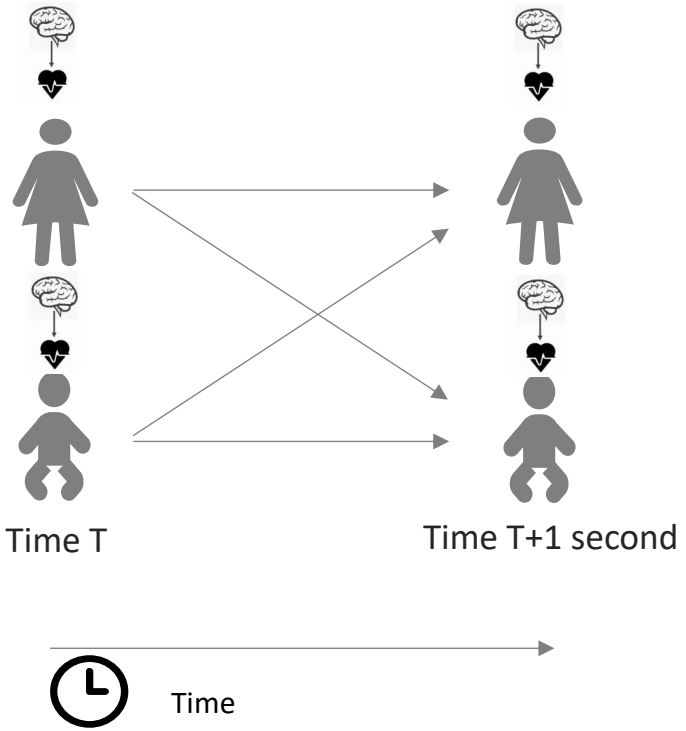
Variables

Reunion



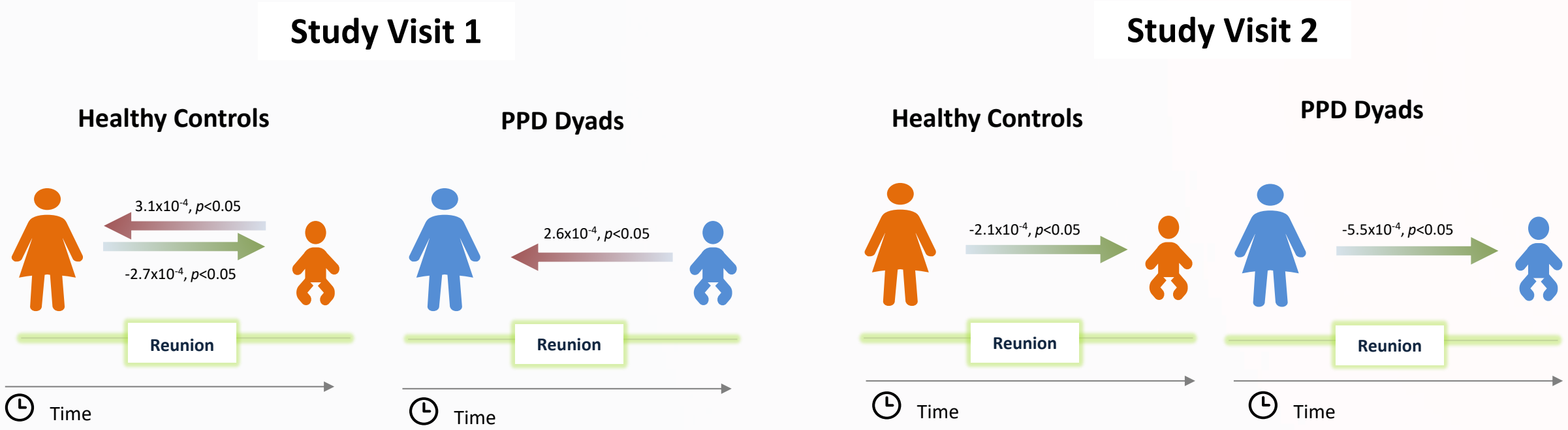
Statistical analyses

Stability and Influence model



(Krzeczkowski et al., 2022; Thorson & West, 2020)

Study 1: Results and Interpretation



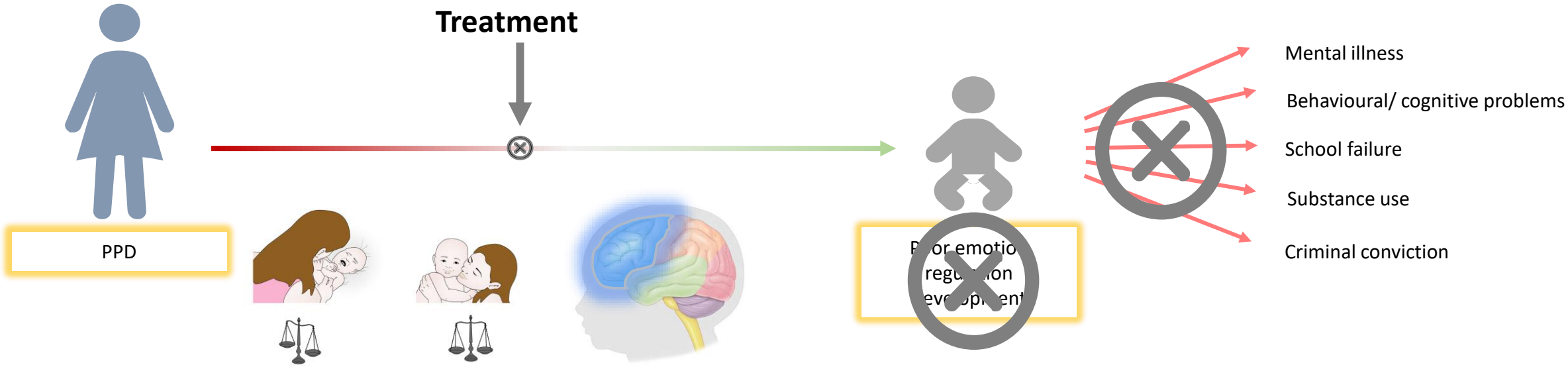
Interpretation

- Adaptive changes in a mechanism though which mothers may actively regulate infant distress in real time
- Treating PPD may enable the mother to better respond to infant cues and provide support

(Krzeczkowski et al., J Psychopathol & Clin Sci, 2022)

Overall Implications

This work suggest that **<u>treating</u>** an ACE (PPD) may alter brain-based and temperament systems underlying emotion regulation and could optimize mental health across the lifespan



SCREENING
Should we Screen for Perinatal Depression?

Yes. USPSTF 2023 guidelines (and most others) recommend screening for depression in pregnant and postpartum persons

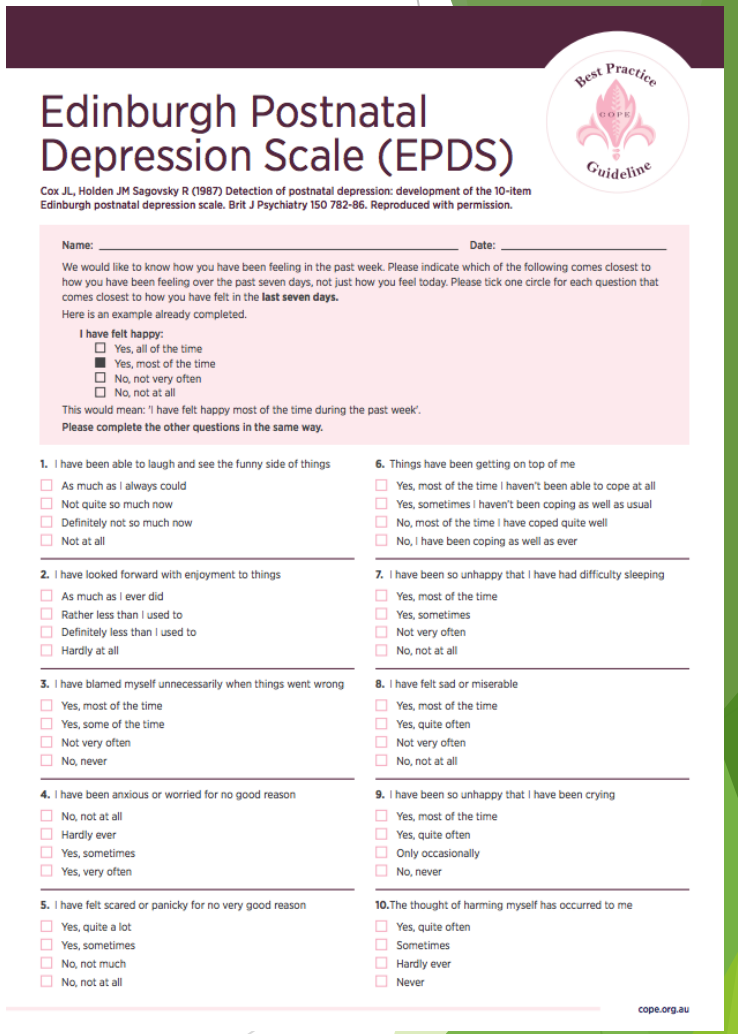
- 2016 systematic review (5 RCTs and 1 controlled clinical trial, 11,869 participants)
- Absolute risk reduction of 2.1% to 9.1% in depression prevalence at follow-up (3-5 months)

How to Screen?

1) Edinburgh Postnatal Depression Scale (EPDS)

- Supported by COPE 2023, ACOG 2023, USPSTF 2023, NICE 2020, and AAP 2019 guidelines
- 10-item self-reported questionnaire
- Affective and cognitive focus
- **Total EPDS score ≥ 11 to screen for perinatal MDD**
  - 2020 IPD meta-analysis (58 studies, 15,557 participants)
  - Reference: Semi-structured diagnostic interview (36 studies, 9066 participants)
  - Sensitivity: 0.81, 95%CI: 0.75-0.87
  - Specificity: 0.88, 95%CI: 0.85-0.91

***Total PHQ-9 score ≥ 10 if you're so inclined…**



Edinburgh Postnatal Depression Scale (EPDS)

Best Practice COPE Guideline

Cox JL, Holden JM Sagovsky R (1987) Detection of postnatal depression: development of the 10-item Edinburgh postnatal depression scale. Brit J Psychiatry 150 782-86. Reproduced with permission.

Name: _____ Date: _____

We would like to know how you have been feeling in the past week. Please indicate which of the following comes closest to how you have been feeling over the past seven days, not just how you feel today. Please tick one circle for each question that comes closest to how you have felt in the **last seven days.**

Here is an example already completed.

I have felt happy:
- ☐ Yes, all of the time
- ■ Yes, most of the time
- ☐ No, not very often
- ☐ No, not at all

This would mean: 'I have felt happy most of the time during the past week'.

Please complete the other questions in the same way.

1. I have been able to laugh and see the funny side of things
- ☐ As much as I always could
- ☐ Not quite so much now
- ☐ Definitely not so much now
- ☐ Not at all

2. I have looked forward with enjoyment to things
- ☐ As much as I ever did
- ☐ Rather less than I used to
- ☐ Definitely less than I used to
- ☐ Hardly at all

3. I have blamed myself unnecessarily when things went wrong
- ☐ Yes, most of the time
- ☐ Yes, some of the time
- ☐ Not very often
- ☐ No, never

4. I have been anxious or worried for no good reason
- ☐ No, not at all
- ☐ Hardly ever
- ☐ Yes, sometimes
- ☐ Yes, very often

5. I have felt scared or panicky for no very good reason
- ☐ Yes, quite a lot
- ☐ Yes, sometimes
- ☐ No, not much
- ☐ No, not at all

6. Things have been getting on top of me
- ☐ Yes, most of the time I haven't been able to cope at all
- ☐ Yes, sometimes I haven't been coping as well as usual
- ☐ No, most of the time I have coped quite well
- ☐ No, I have been coping as well as ever

7. I have been so unhappy that I have had difficulty sleeping
- ☐ Yes, most of the time
- ☐ Yes, sometimes
- ☐ Not very often
- ☐ No, not at all

8. I have felt sad or miserable
- ☐ Yes, most of the time
- ☐ Yes, quite often
- ☐ Not very often
- ☐ No, not at all

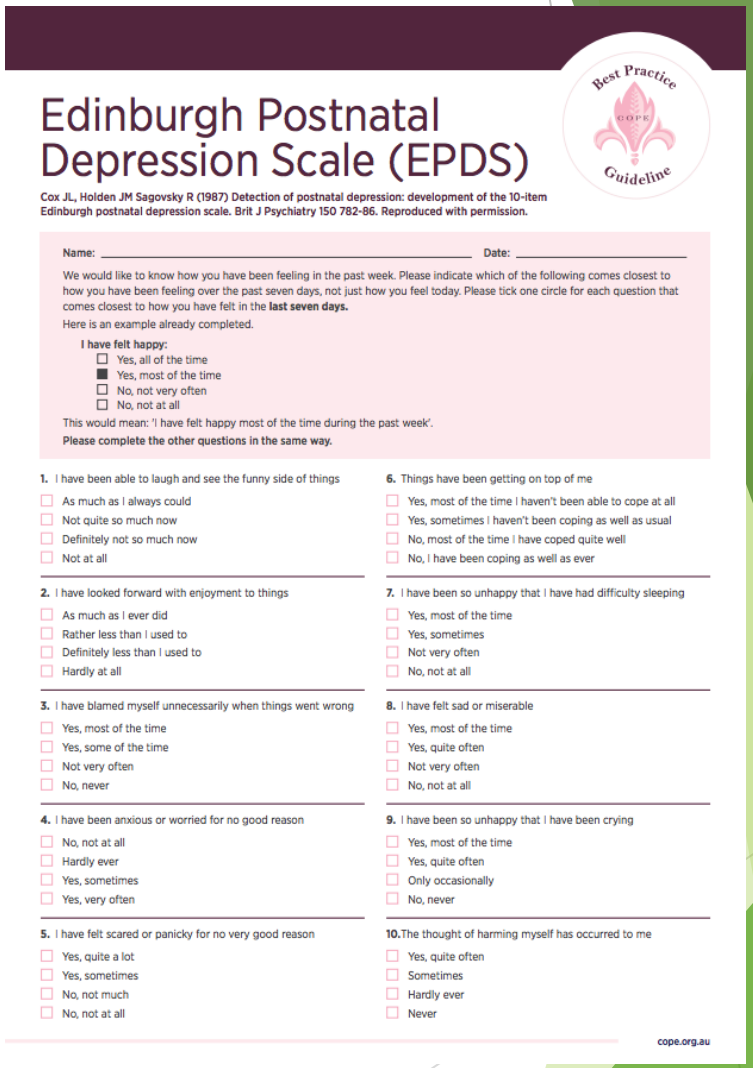
9. I have been so unhappy that I have been crying
- ☐ Yes, most of the time
- ☐ Yes, quite often
- ☐ Only occasionally
- ☐ No, never

10. The thought of harming myself has occurred to me
- ☐ Yes, quite often
- ☐ Sometimes
- ☐ Hardly ever
- ☐ Never

cope.org.au

https://www.cope.org.au/health-professionals/clinical-tools-health-professionals/epds-questionnaire-screenshot-2/

- **EPDS Severity ranges (for guiding treatment)**
  - 0 to 6 – none to minimal depression
  - 7 to 14 – mild depression
  - 15 to 19 – moderate depression
  - 19 to 30 – severe depression
- **4-point reduction = clinically significant improvement**



Edinburgh Postnatal Depression Scale (EPDS)

Best Practice COPE Guideline

Cox JL, Holden JM Sagovsky R (1987) Detection of postnatal depression: development of the 10-item Edinburgh postnatal depression scale. Brit J Psychiatry 150 782-86. Reproduced with permission.

Name: _____ Date: _____

We would like to know how you have been feeling in the past week. Please indicate which of the following comes closest to how you have been feeling over the past seven days, not just how you feel today. Please tick one circle for each question that comes closest to how you have felt in the **last seven days.**

Here is an example already completed.

I have felt happy:

- ☐ Yes, all of the time
- ■ Yes, most of the time
- ☐ No, not very often
- ☐ No, not at all

This would mean: 'I have felt happy most of the time during the past week'.

Please complete the other questions in the same way.

1. I have been able to laugh and see the funny side of things
- ☐ As much as I always could
- ☐ Not quite so much now
- ☐ Definitely not so much now
- ☐ Not at all

2. I have looked forward with enjoyment to things
- ☐ As much as I ever did
- ☐ Rather less than I used to
- ☐ Definitely less than I used to
- ☐ Hardly at all

3. I have blamed myself unnecessarily when things went wrong
- ☐ Yes, most of the time
- ☐ Yes, some of the time
- ☐ Not very often
- ☐ No, never

4. I have been anxious or worried for no good reason
- ☐ No, not at all
- ☐ Hardly ever
- ☐ Yes, sometimes
- ☐ Yes, very often

5. I have felt scared or panicky for no very good reason
- ☐ Yes, quite a lot
- ☐ Yes, sometimes
- ☐ No, not much
- ☐ No, not at all

6. Things have been getting on top of me
- ☐ Yes, most of the time I haven't been able to cope at all
- ☐ Yes, sometimes I haven't been coping as well as usual
- ☐ No, most of the time I have coped quite well
- ☐ No, I have been coping as well as ever

7. I have been so unhappy that I have had difficulty sleeping
- ☐ Yes, most of the time
- ☐ Yes, sometimes
- ☐ Not very often
- ☐ No, not at all

8. I have felt sad or miserable
- ☐ Yes, most of the time
- ☐ Yes, quite often
- ☐ Not very often
- ☐ No, not at all

9. I have been so unhappy that I have been crying
- ☐ Yes, most of the time
- ☐ Yes, quite often
- ☐ Only occasionally
- ☐ No, never

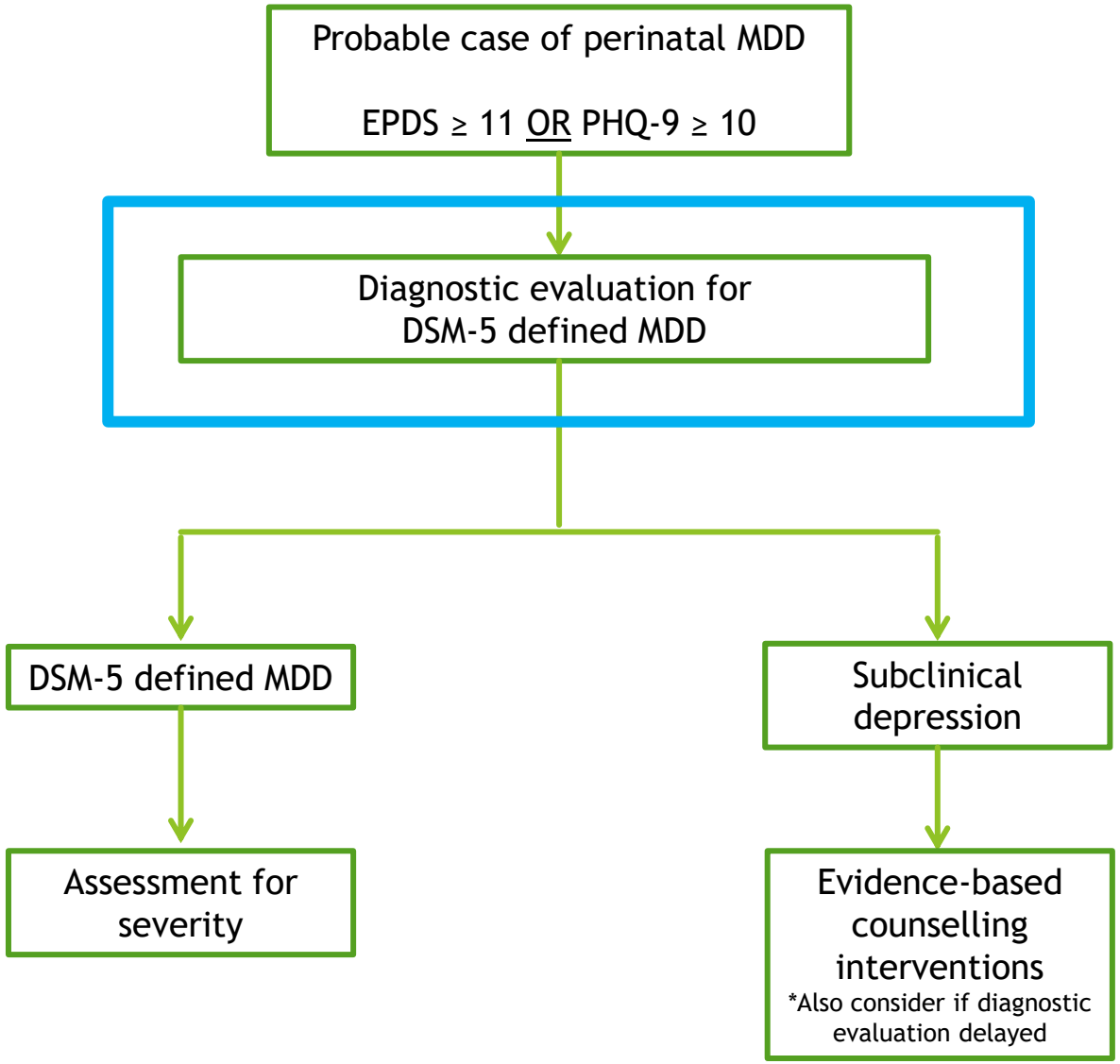
10. The thought of harming myself has occurred to me
- ☐ Yes, quite often
- ☐ Sometimes
- ☐ Hardly ever
- ☐ Never

cope.org.au

https://www.cope.org.au/health-professionals/clinical-tools-health-professionals/epds-questionnaire-screenshot-2/

When Should I Screen? Recommendations:

- **Pregnancy Screening**
  - COPE 2023 and ACOG 2023 guidelines
  - At least 1st trimester (e.g., 1st antenatal visit) and 3rd trimester (e.g., at or around 30 weeks)
  - Consensus based recommendation; no empirical evidence to support this recommendation
- **Postnatal Screening** AAP 2019 guideline
  - At least 1-, 2-, 4-, and 6-months postpartum
  - Consensus based recommendation; no empirical evidence to support this recommendation


Probable case of perinatal MDD
EPDS ≥ 11 OR PHQ-9 ≥ 10
Diagnostic evaluation for DSM-5 defined MDD
DSM-5 defined MDD
Assessment for severity
Subclinical depression
Evidence-based counselling interventions
*Also consider if diagnostic evaluation delayed

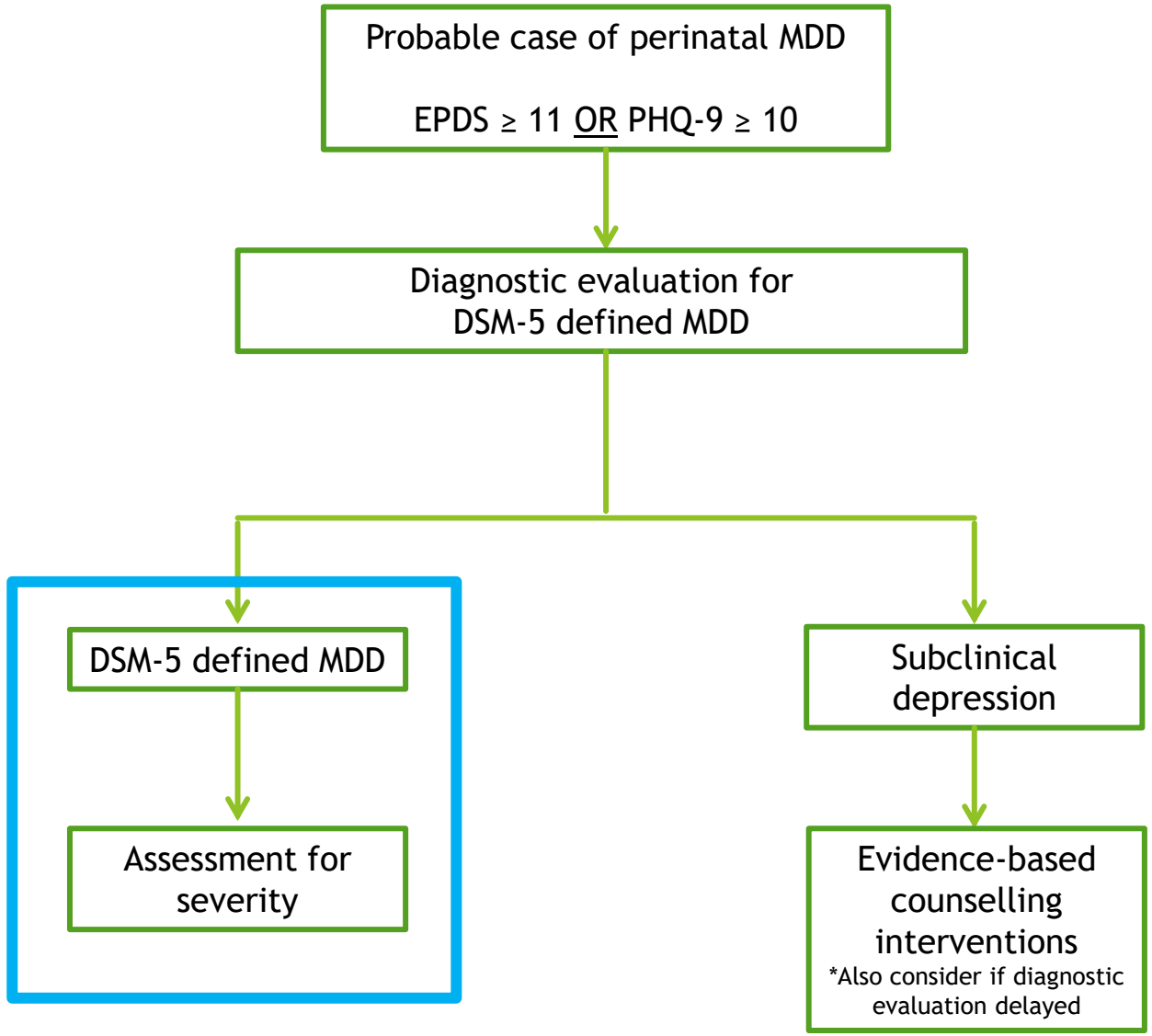
Diagnosing DSM-5 defined Perinatal MDD

M SIG E CAPS Mnemonic (5 or more symptoms)

Specific features of MDD in perinatal period

- Sadness and anhedonia may not be as prominent
- Less suicidality
- More:
  - Anxiety
  - Restlessness/agitation
  - Impaired concentration/decision making/confidence
  - Obsessional thoughts (e.g., harm coming to fetus/infant)
- Physical complaints related to physiological changes in perinatal period may resemble somatic symptoms of MDD
  - Changes in appetite and/or weight
  - Changes in sleep duration and/or quality
  - Changes in energy levels (e.g., fatigue)

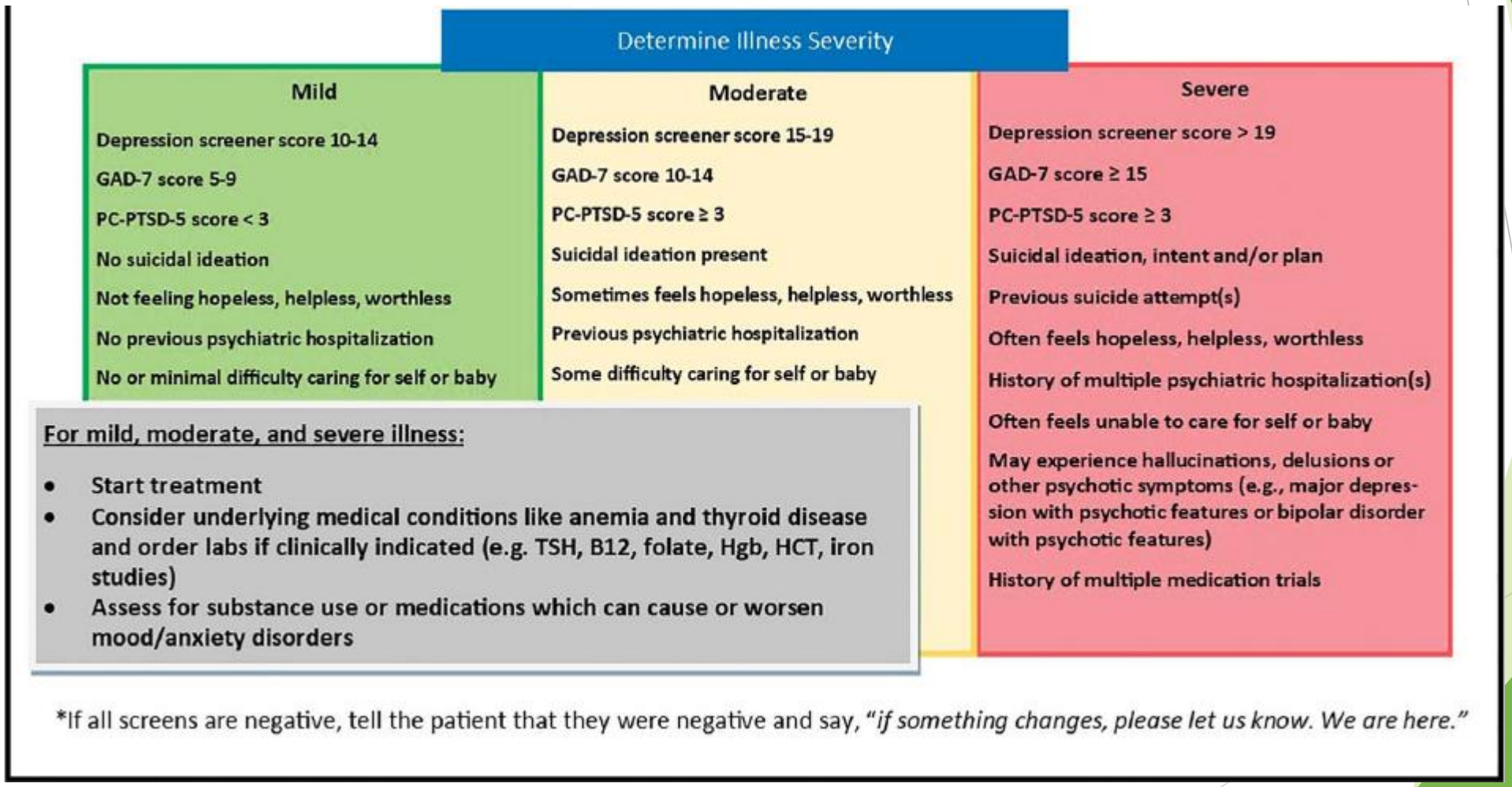
Table 1. Mental Health Conditions and Associated Diagnostic Criteria*
Major Depressive Disorder
A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure
Note: Do not include symptoms that are clearly attributable to another medical condition
1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (eg, feels sad, empty, hopeless) or observation made by others (eg, appears tearful). (Note: In children and adolescents, can be irritable mood) 2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation) 3. Significant weight loss when not dieting or weight gain (eg, a change of more than 5% of body weigh in a month), or decrease or increase in appetite nearly every day. (Note: In children, consider failure to make expected weight gain) 4. Insomnia or hypersomnia nearly every day 5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down) 6. Fatigue or loss of energy nearly every day 7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick) 8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others) 9. Recurrent thoughts of death (not just fear of dying); recurrent suicidal ideation without a specific plan; a specific suicide plan; or a suicide attempt
B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
C. The episode is not attributable to the physiological effects of a substance or another medical condition
Note: Criteria A-C represent a major depressive episode Note: Responses to a significant loss (eg, bereavement, financial ruin, losses from a natural disaster, a serious medical illness or disability) may include the feelings of intense sadness, rumination about the loss, insomnia, poor appetite, and weight loss noted in Criterion A, which may resemble a depressive episode. Although such symptoms may be understandable or considered appropriate to the loss, the presence of a major depressive episode in addition to the normal response to a significant loss should also be carefully considered. This decision inevitably requires the exercise of clinical judgement based on the individual's history and the cultural norms for the expression of distress in the context of loss.
D. At least one major depressive episode is not better explained by schizoaffective disorder and is not superimposed on schizophrenia, schizophreniform disorder, delusional disorder, or other specified or unspecified schizophrenia spectrum and other psychotic disorders
E. There has never been a manic episode or a hypomanic episode
Note: This exclusion does not apply if all of the manic-like or hypomanic-like episodes are substance-induced or are attributable to the physiological effects of another medical condition


Probable case of perinatal MDD
EPDS ≥ 11 OR PHQ-9 ≥ 10
Diagnostic evaluation for DSM-5 defined MDD
DSM-5 defined MDD
Assessment for severity
Subclinical depression
Evidence-based counselling interventions
*Also consider if diagnostic evaluation delayed

Assessing Severity Using DSM-5 MDD

MILD	MODERATE	SEVERE
Around 5 symptoms (distressing but manageable with little impairment in social/occupational functioning)	Number and intensity of symptoms as well as functional impairment between “mild” and “severe” specifiers	Substantially more than 5 symptoms (distressing to unmanageable with marked interference with functioning)

Severity of DSM-5 defined Perinatal MDD (ACOG 2023 guideline)



Treatment (Mild to Moderate): 1st Line

Therapist-delivered online or in-person CBT or IPT (Individual or Group)

- Supported by COPE 2023, ACOG 2023, and CANMAT 2016 guidelines
- Moderate to large effect in reducing perinatal depressive symptoms
- 2021 Meta analysis (43 RCTs, 6270 participants)
  - Overall: Hedges' g = 0.67, 95%CI: 0.45-0.89, NNT = 4.4
  - Pregnancy: Hedges' g = 0.83, 95%CI: 0.19-1.47, NNT = 3.4
  - Postpartum: Hedges' g = 0.61, 95%Cl: 0.49-0.73, NNT = 4.9

Treatment (Mild to Moderate): 2nd Line

SSRI monotherapy (1st Line for Severe)

- Supported by COPE 2023, ACOG 2023, and CANMAT 2016 guidelines
- **Pregnancy**
  - Based on data from RCTs testing the efficacy of SSRIs for treating MDD in the general population
  - No RCTs exist in testing antidepressants among pregnant individuals
- **Postpartum**
  - 2021 Cochrane Review (11 RCTs, 1016 participants)
  - Modest effect in reducing postnatal depressive symptoms
  - SMD: -0.30, 95%CI: -0.55 to -0.05 at 5-to-12-week follow-up

Preferred Perinatal SSRIs

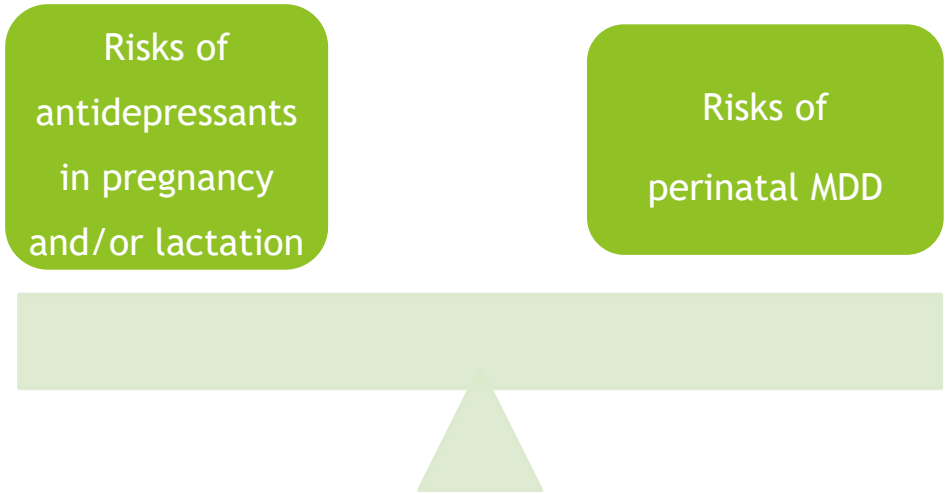
Sertraline, Escitalopram, or Citalopram

- Based on their efficacy for treating MDD in the general population and their relatively safer profile during gestation and lactation compared to other antidepressants
- RCT data exist to support the use of sertraline for managing PPD
- Support for sertraline: ACOG 2023, AHRQ 2021, and CANMAT 2016 guidelines
- Support for escitalopram: ACOG 2023 and CANMAT 2016 guidelines
- Support for citalopram: CANMAT 2016 and Danish 2014 guidelines
- *Previously effective medication(s) should also be considered
- *Switching doesn’t necessarily lead to better outcomes

Less Preferred SSRIs

- **Paroxetine and fluoxetine**
  - **Paroxetine**
    - Its use in pregnancy has been linked to congenital cardiac malformation in several individual observational studies
  - **Fluoxetine**
    - Longer half-life may lead to accumulation in breastmilk and increase risk of adverse events in breastfed infant
  - **However, if a patient has a good past response or are severe, these may be considered**

Balancing the Risks and Benefits of Antidepressant Therapy in Perinatal MDD



Methodological Limitations of Research Examining Pregnancy Antidepressant Risk

- **Confounding by Indication**
- **Most meta-analyses of observational studies have not adjusted for confounders**
  - Pre-pregnancy obesity
  - Gestational alcohol and/or tobacco use
  - Gestational substance misuse (e.g., cannabis)
  - Antenatal medical comorbidities (e.g., gestational diabetes)
  - **Psychiatric problems**
- **Magnitude of reported risks are often small and are generally not considered as clinically significant at an individual patient level**
  - Relative risk (risk ratio or odds ratio) of two-fold or more (i.e., Risk ≥ 2.0) is generally considered clinically significant at the patient level in perinatal psychiatric practice

Congenital Malformations: 1st-trimester SSRI use

Outcome	Risk	RCT study design	Comparator group with indication for antidepressant (e.g., depression)	Statistical adjustment for other potential confounds
Any congenital malformation	Relative risk ~ 1.1	X	X	X
Cardiovascular congenital malformations	Relative risk ~ 1.2 to 1.3	X	X	X

2018 Meta-analysis of observational studies (29 studies, 9,085,954 participants)

- Associations no longer statistically significant when examined only among pregnant individuals with a psychiatric diagnosis
- Same findings for individual SSRIs: sertraline, escitalopram, citalopram, and fluoxetine

Congenital Malformations: 1st-trimester SNRI use

Outcome	Risk	RCT study design	Comparator group with indication for antidepressant (e.g., depression)	Adjustment for other potential confounds
Any congenital malformation	-	-	-	-
Cardiovascular congenital malformations	Relative risk ~ 1.3 to 1.7	X	X	X

2022 Meta-analysis of observational studies (8 studies, > 5,000,000 participants)

- Association with cardiovascular congenital malformations was no longer statistically significant when examined only among pregnant individuals with a clinical indication for SNRI use
- Same findings for individual SNRIs: venlafaxine and duloxetine

Spontaneous Abortion and Stillbirth

Outcome	Class of antidepressant	Risk	RCT study design	Comparator group with indication for antidepressant (e.g., depression)	Adjustment for other potential confounds
Spontaneous abortion	-	Relative risk ~ 1.5	X	X	X
Stillbirth	-	Relative risk ~ 1.2	X	X	X

Additional notes on spontaneous abortion and stillbirth

- Spontaneous abortion risk may be lower for: sertraline, escitalopram, citalopram, and paroxetine
- Spontaneous abortion risk may be higher for: fluoxetine and venlafaxine
- Association with stillbirth may be limited to 1st trimester antidepressant use; not 2nd or 3rd trimester
- Risk of stillbirth with gestational depression ~ 1.5

Pre-Eclampsia

Outcome	Class of antidepressant	Risk	RCT study design	Comparator group with indication for antidepressant (e.g., depression)	Adjustment for other potential confounds
Pre-eclampsia	SSRIs	Relative risk ~ 1.4	X	X	X

Additional notes on preeclampsia

- Risk of preeclampsia with gestational depression ~ 1.5
- Risk of any gestational hypertensive disorder with gestational depression ~ 1.3

Low Birthweight and Preterm Birth

Outcome	Class of antidepressant	Risk	RCT study design	Comparator group with indication for antidepressant (e.g., depression)	Adjustment for other potential confounds
Low birthweight	-	Relative risk ~ 1.4 (~70 grams)	X	✓	X
Preterm birth	SSRIs	Relative risk ~ 1.1 Mean difference: -0.36 weeks (~ 3 days earlier)	X	✓	✓ (Race/ethnicity, parity, and gestational tobacco use)

Risk of low birthweight with gestational depression ~ 1.7 to 2.0

Risk of preterm birth with gestational depression ~ 1.4 to 2.4

Persistent Pulmonary Hypertension of Newborn

Outcome	Class of antidepressant	Risk	RCT study design	Comparator group with indication for antidepressant (e.g., depression)	Adjustment for other potential confounds
Persistent pulmonary hypertension of newborn	SSRIs or SNRIs	Relative risk ~ 1.5 to 1.8	X	X	X

Absolute risk is very low:

- Absolute risk to infants exposed to serotonergic antidepressants in-utero: 0.6-3.0/1000 live births
- Absolute risk to infants unexposed to serotonergic antidepressants in-utero: 2.0/1000 live births

Number needed to harm: 1000 to 1615

Potential risk of PPHN among individual SSRIs (highest to lowest risk):

- fluoxetine > citalopram > paroxetine > escitalopram > sertraline

Postpartum Hemorrhage

Outcome	Class of antidepressant	Risk	RCT study design	Comparator group with indication for antidepressant (e.g., depression)	Adjustment for other potential confounds
Postpartum hemorrhage	SSRIs	Relative risk ~ 1.2	X	X	X

Additional notes on postpartum hemorrhage

- Risk may be higher for SNRIs than SSRIs
  - 2016 Meta-analysis of observational studies (8 studies, 40,000 participants)
  - SNRI risk – RR: 1.62, 95%CI: 1.41-1.85
  - SSRI risk – RR: 1.20, 95%CI: 1.04-1.38

Poor Neonatal Adaption Syndrome

- PNAS: either or a combination of autonomic dysfunction, neuromuscular problems, poor feeding, and/or hypoglycemia
- Incidence: 0-30% of neonates exposed to antidepressants late in-utero
- ?Dose-Dependent
- Presentation: Mild and transient, can last 2-14 days post-delivery, and resolves with supportive care
  - Can last longer if benzodiazepines are concurrently used during late gestation
- Antidepressants with possibly highest risk of PNAS: **fluoxetine, paroxetine, and venlafaxine**

Offspring Neurodevelopment

- **Minimal to no risk for either short or long-term neurodevelopmental and neurobehavioral outcomes in offspring with antidepressant exposure**
- **Risk of neurodevelopmental disorders in offspring (e.g., ASD or ADHD) NOT INCREASED**
  - Meta-analyses of observational studies have demonstrated **no** consistent statistically significant associations between gestational antidepressant use and offspring neurodevelopmental disorders
  - A recent individual observational study suggest that untreated gestational psychiatric disorders and **not** SSRI use in pregnancy may be linked to neurodevelopmental disorders in offspring
    - See: Ames JL, et al. Maternal psychiatric conditions, treatment with selective serotonin reuptake inhibitors, and neurodevelopmental disorders. Biol Psychiatry 2021;90(4):253-262.

Lactation and Antidepressant Use

- **Most antidepressants have a relative infant dose < 10% among healthy infants**
  - Threshold used to determine whether medication is safe to use during breastfeeding
- **Systematic review evaluating multiple safety parameters suggest the safest antidepressants to use when breastfeeding**
  - Sertraline
  - Paroxetine
  - Fluvoxamine
  - Citalopram
  - Escitalopram
- **Adverse events reported are non-specific and often resolve spontaneously with cessation of medication and/or breastfeeding**
- **<u>Beware Doxepin</u>**

Adverse Effects During Lactation

- Data from a 2015 systematic review of observational research examining adverse events among breastfed infants

Individual SSRI	Prevalence rate	Reported adverse events
Sertraline	2/280 cases (~0.7%)	Agitation, restlessness, poor feeding, insomnia
Paroxetine	2/228 cases (~0.9%)	Agitation, lethargy, poor weight gain, hypotonia

Adverse events among breastfed infants exposed to SSRIs during lactation

- Data from a 2015 systematic review of observational research examining adverse events among breastfed infants

Individual SSRI	Prevalence rate	Reported adverse events
Citalopram	6/112 cases (~5.4%)	Colic, decreased feeding, irritability/restlessness, sleep disturbance, hypo/hypertonia, irregular breathing
Fluoxetine	11/280 cases (~3.9%)	Colic, seizures, irritability/restlessness, somnolence, lethargy, fever, unresponsiveness, watery stool, uncontrollable crying, vomiting, poor sleep

Adverse events among breastfed infants exposed to SSRIs during lactation

- Data from a 2015 systematic review of observational research examining adverse events among breastfed infants

Individual SSRI	Prevalence rate	Reported adverse events
Escitalopram	1/37 cases (~2.7%)	Colic, decreased feeding, irritability/restlessness, sleep disturbance, hypo/hypertonia, irregular breathing
Fluvoxamine	1/18 cases (~5.6%)	Colic, decreased feeding, irritability/restlessness, sleep disturbance, hypo/hypertonia, irregular breathing

Forget the Meds, what about gestational MDD: MDD Risks for Pregnancy and Delivery Complications

Adverse outcome	Magnitude of Risk
Preterm birth	Relative risk ~ 1.4 to 2.4
Low birthweight	Relative risk ~ 1.7 to 2.0
Intrauterine growth restriction	Relative risk ~ 4.4
Head growth	Mean difference: -0.08 mm/week
Body growth	Mean difference: -4.4 g/week
Low 5-minute APGAR score	Relative risk ~ 1.5

Postpartum Complications of MDD

Adverse outcome	Magnitude of Risk
Infant malnutrition	Relative risk ~ 1.4
Infant physical illness	Relative risk ~ 1.7 to 2.6
Infant hospitalization	Relative risk ~ 1.4
Exclusively breastfed	Relative risk ~ 0.5 to 0.8

- **Other postpartum complications with postpartum MDD**
  - Poorer maternal-infant attachment
  - Less optimal parenting practices

More Postpartum Complications

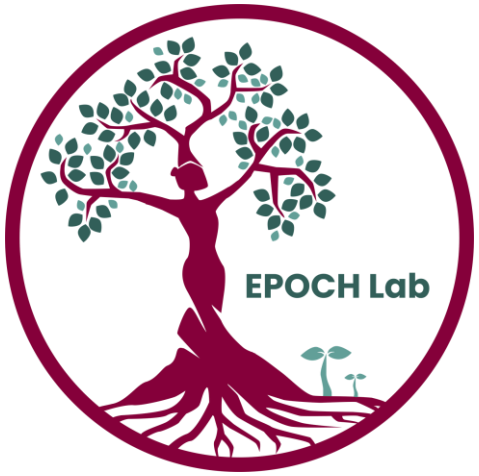
Adverse outcome	Magnitude of Risk
Childhood maltreatment	Relative risk ~ 3.0
Partner depression	Relative risk ~ 1.2 to 1.7
Offspring depression in adolescence and adulthood	Relative risk ~ 1.7

- **1/4th of cases with postpartum MDD will have symptoms for up to 3 years**
  - Putnick DL, et al. Trajectories of maternal postpartum depressive symptoms. Pediatrics 2020;146(5):e20200857.
- **STAR*D trial demonstrates remission of maternal depression reduces rates of offspring mental health problems**
  - Weissman MM, et al. Remissions in maternal depression and child psychopathology: a STAR*D-child report. JAMA 2006;295(12):1389-1398.
  - Wickramaratne P, et al. Children of depressed mothers 1 year after remission of maternal depression: findings from the STAR*D-Child study. Am J Psychiatry 2011;168(6):593-602.

Conclusion and Key Points to Consider for Clinical Practice

- Perinatal MDD is common and screening with the EPDS (EPDS score ≥11) followed by diagnostic evaluation for enhances perinatal MDD detection
- Treating Perinatal Depression helps mothers and their offspring
  - Those with perinatal MDD (mild-moderate) should be referred to therapist delivered CBT or IPT (training available)
  - Moderate-severe perinatal MDD should receive SSRI monotherapy, with sertraline, escitalopram, or citalopram being preferred first-line agents (these are 1st line of psychotherapy not available)
  - Discussions about medications and the consequences of perinatal MDD can aid patient decision-making

Thank You



STRONG STARTS
Research Program
John Krzeczkowski, PhD