Vitamin D Deficiency and Racial Disparities in Adverse Perinatal Outcomes Including Postpartum Depression

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Clinical Directors Network, Inc. (CDN)
Webinar
February 1st, 2018 ~ 12PM -1PM EST

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Lecture Outline

1. What is vitamin D and why is it important for physical and mental health?
   - Focus on perinatal mental health

2. Disparities in vitamin D, inflammation, and mental health

3. My published research study findings on prenatal vitamin D deficiency and postpartum depression

4. Ongoing and future research

Vitamin D & Physical and Mental Health

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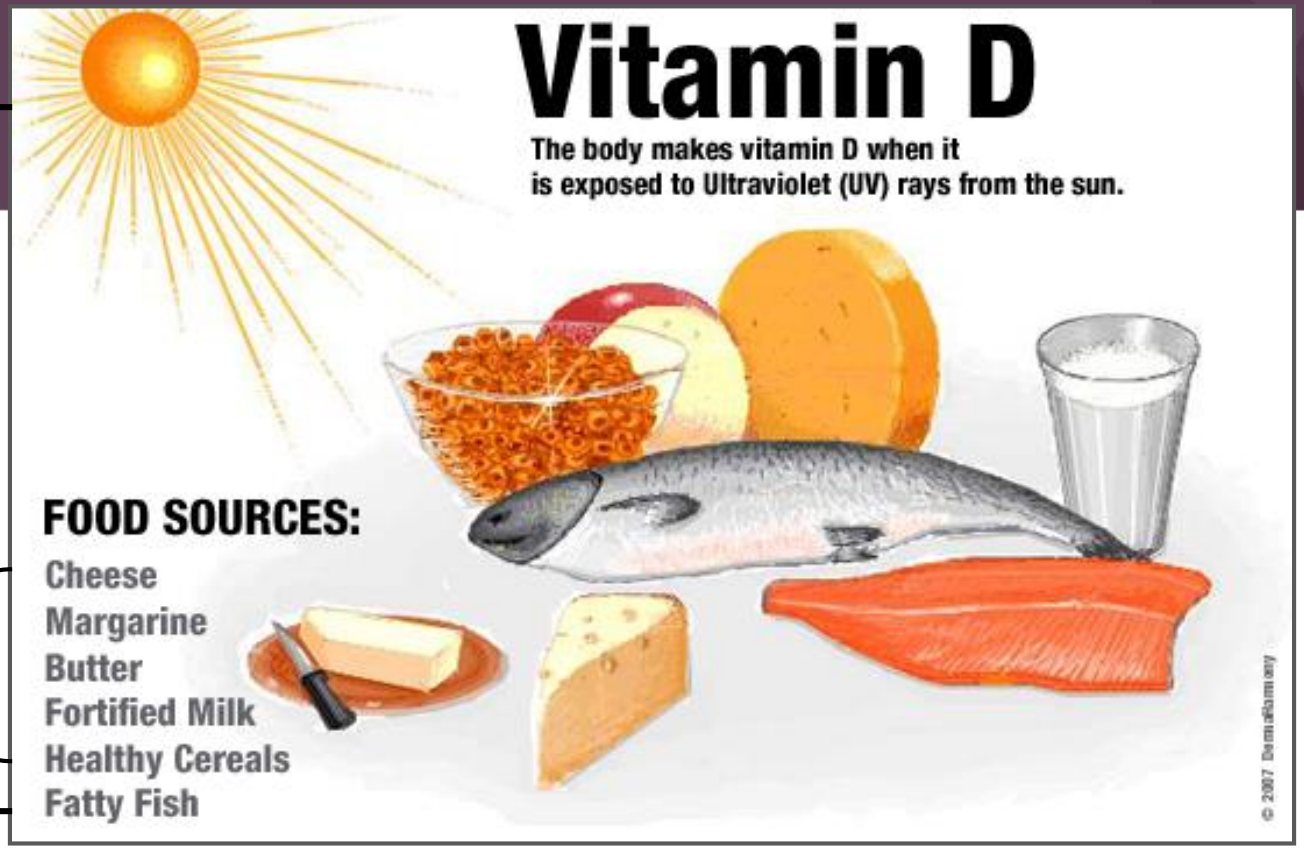
3000 IU
10min exposure

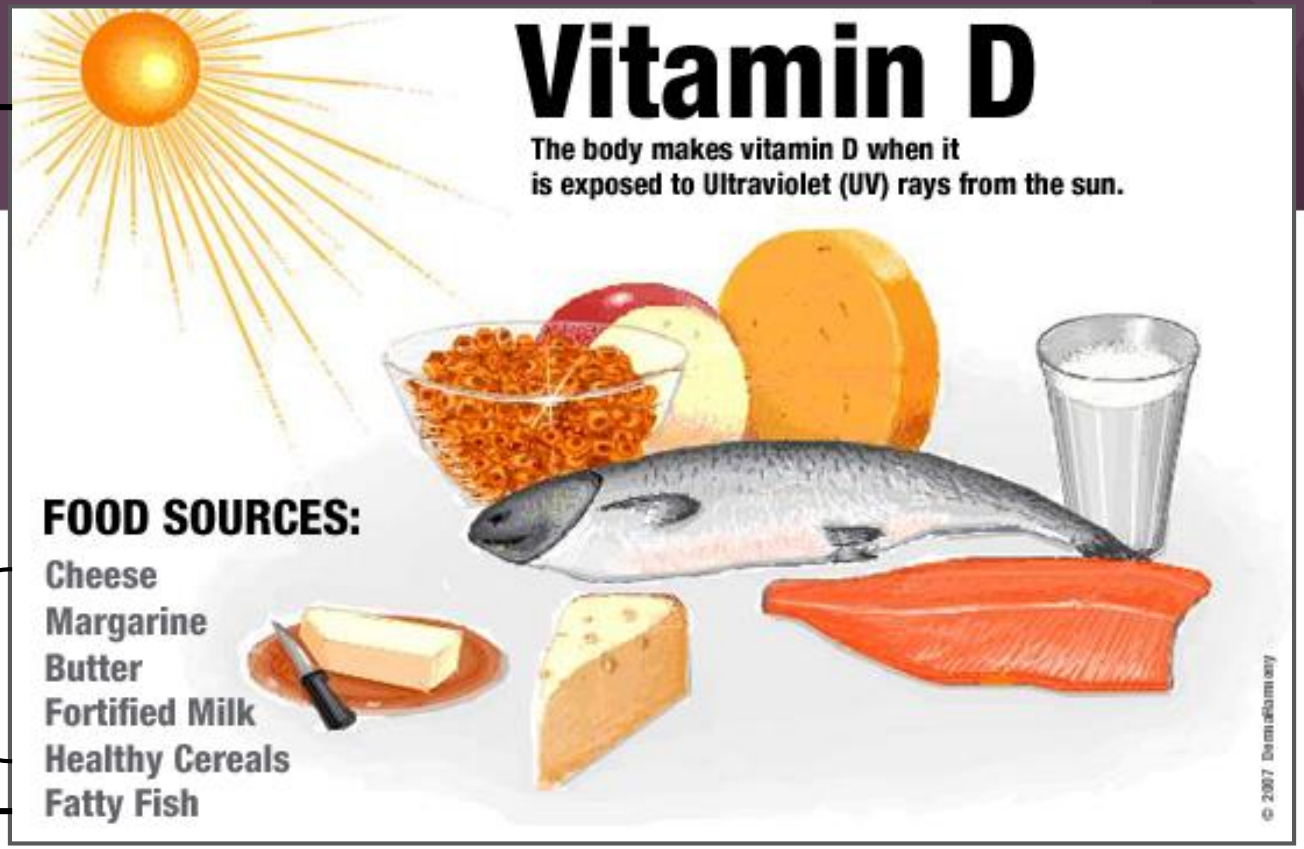


100-400 IU
3.5 oz

400-1000 IU
3.5oz

de Abreu et al., 2009; Penckofer et al., 2010; Zhang & Naughton, 2010

3000 IU
10min exposure



100-400 IU
3.5 oz

400-1000 IU
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- Required for normal brain homeostasis and development

- Vitamin D deficiency has been associated with a number of psychiatric conditions

de Abreu et al., 2009; Penckofer et al., 2010; Zhang & Naughton, 2010

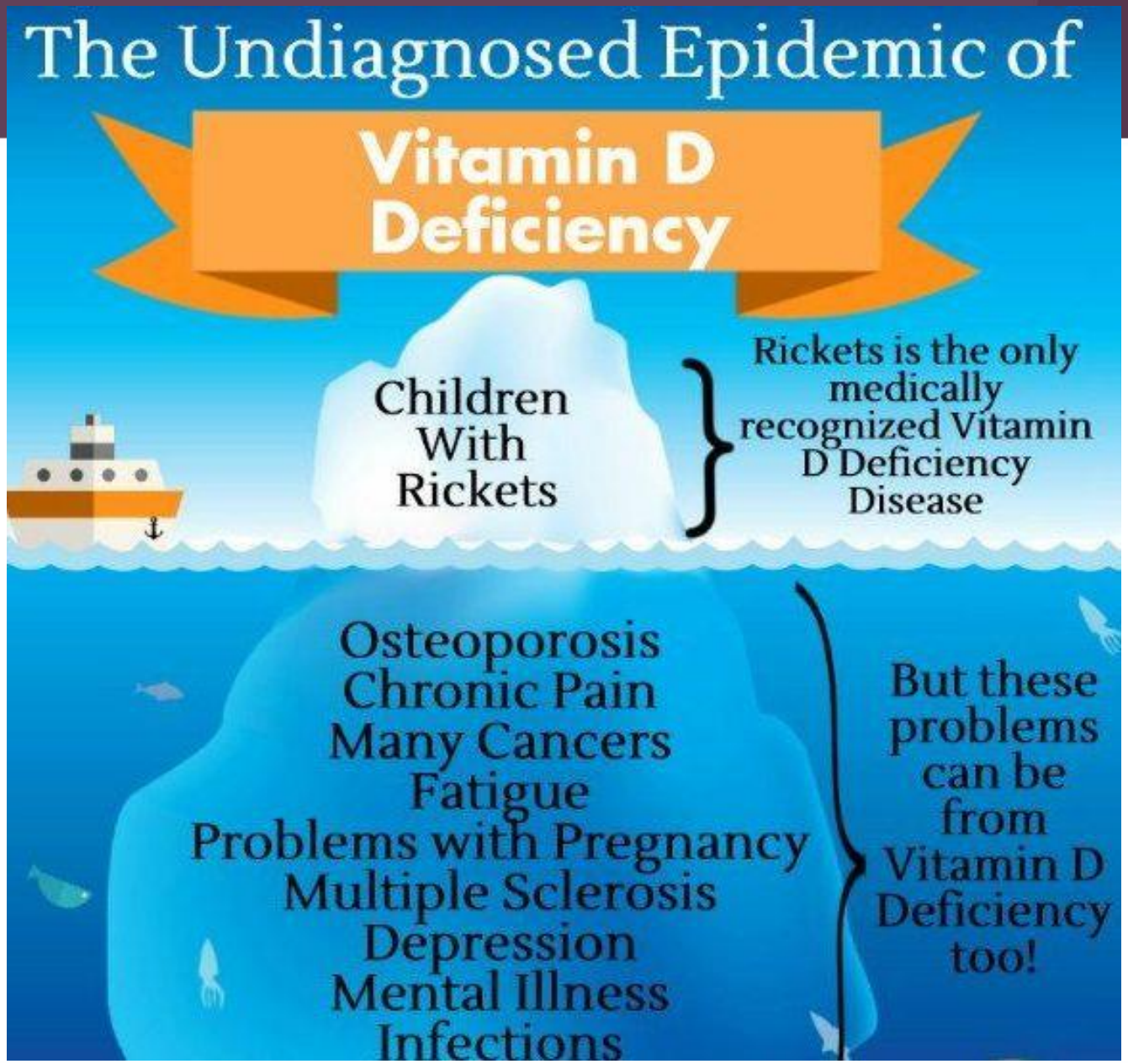
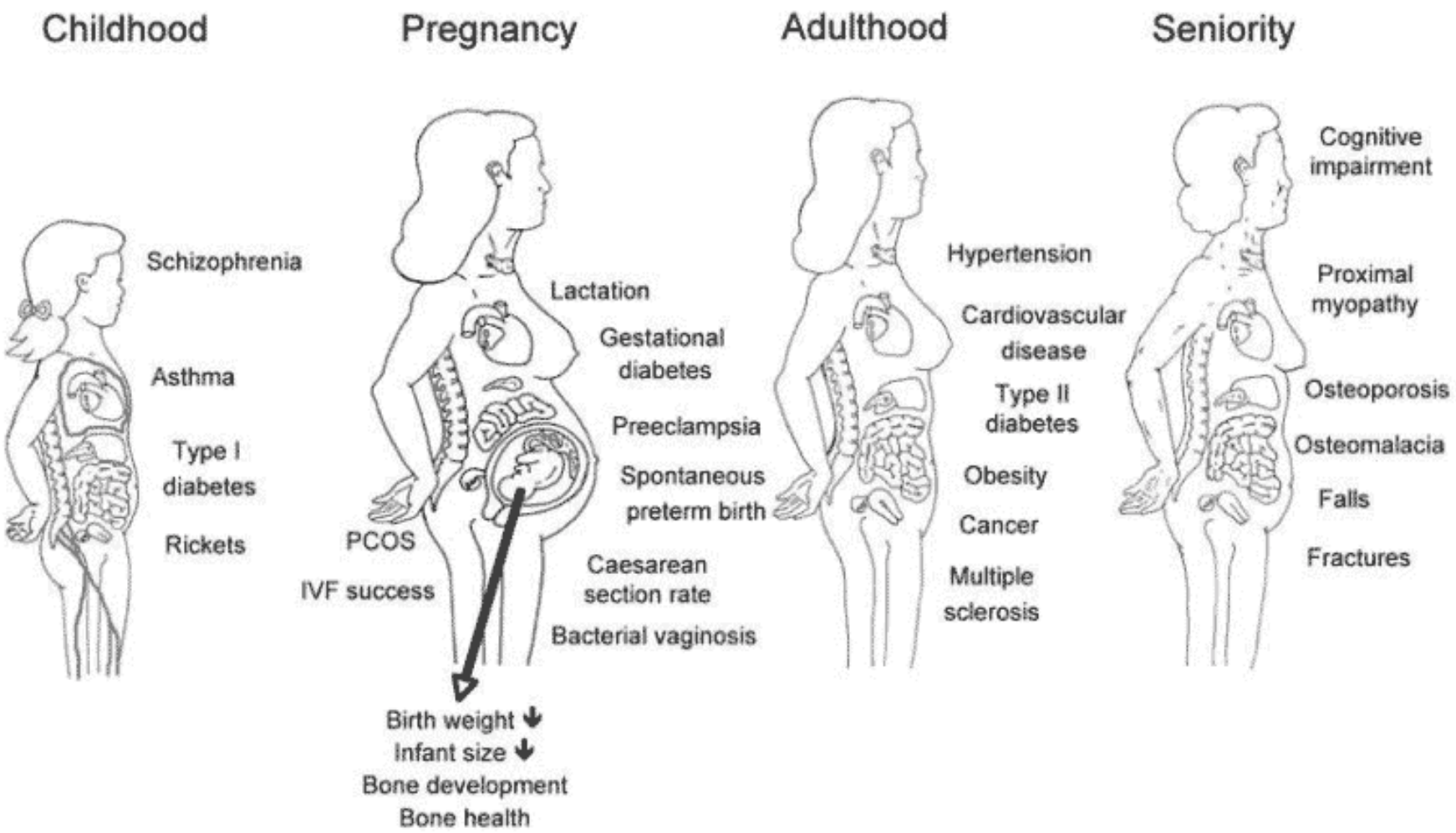


Image from Easy-Immune-Health.com

See Theodoratou et al.'s, 2014 Meta Analysis

Health Implications of Vitamin D Deficiency Across the Female Lifespan

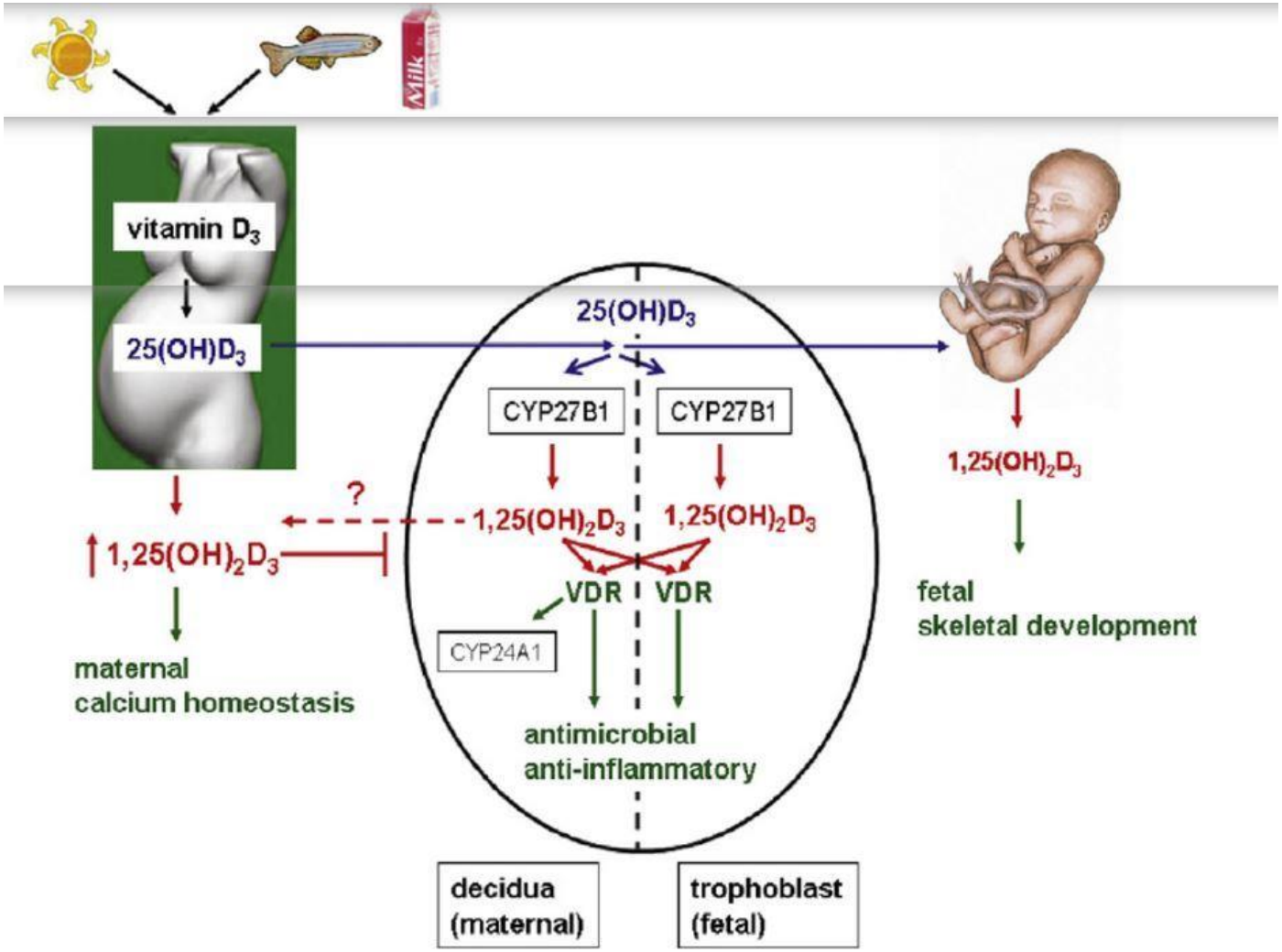


Grundmann, 2011; Aghajafari et. Al., 2013; Wei et al., 2013

Vitamin D Metabolism and Placental Function

Liu & Hewison, 2012

Vitamin D Metabolism and Placental Function



Liu & Hewison, 2012

Vitamin D and Depressive Symptoms

The British Journal of Psychiatry
BJPsych

Vitamin D deficiency and depression in adults: systematic review and meta-analysis

Rebecca E. S. Anglin, Zainab Samaan, Stephen D. Walter and Sarah D. McDonald

BJP 2013, 202:100-107.
Access the most recent version at DOI: 10.1192/bjp.bp.111.106666

Vitamin D and Depressive Symptoms

Depressive symptoms are associated with low vitamin D in a meta-analysis of 14 studies including 31,424 participants

RC PSYCH
ROYAL COLLEGE OF PSYCHIATRISTS

The British Journal of Psychiatry
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Perinatal Vitamin D and Depressive Symptoms

Prenatal depressive symptoms have been associated with low prenatal vitamin D levels in four published studies

Postpartum depressive symptoms have been associated with low postpartum vitamin D levels in two published studies

Images from Free vector clipart

Cassidy-Bushrow et al., 2012; Brandenbarg et al., 2012; Huang et al., 2014; Williams et al., 2016; Murphy et al., 2010; Fu et al, 2014

Prospective Findings

Low Prenatal Vitamin D

Postpartum Depression

Nielson et al., 2013; Robinson et al., 2014; Gur et al., 2014

Prospective Findings

Low Prenatal Vitamin D

Postpartum Depression

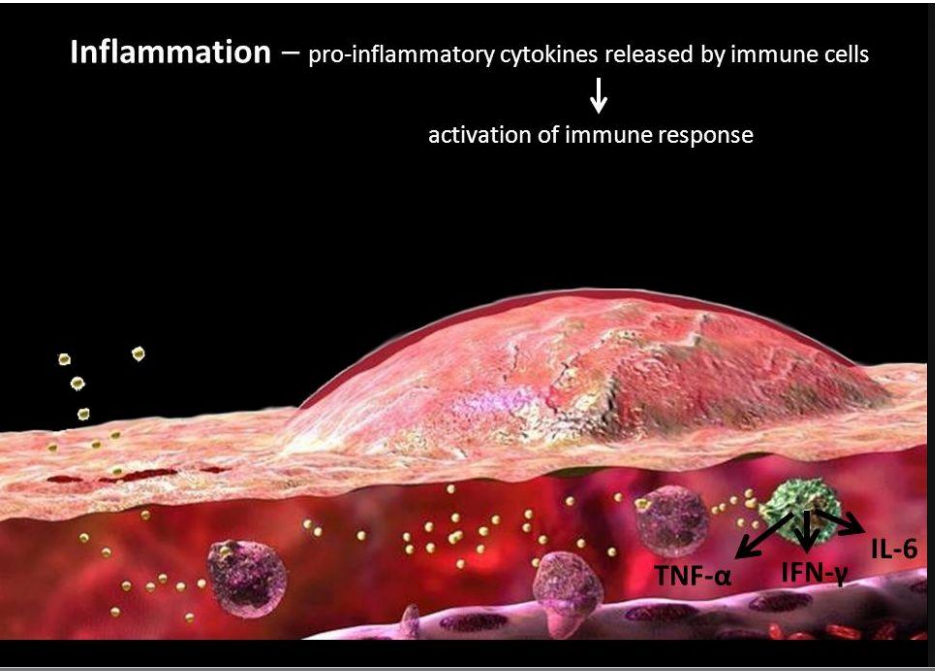
If low prenatal vitamin D leads to postpartum depressive symptoms, **are** inflammatory cytokines involved and **how**?

Nielson et al., 2013; Robinson et al., 2014; Gur et al., 2014

Inflammation & Depressive Symptoms

Depressive symptoms in general are associated with elevated inflammatory markers in men and women

Inflammation ⟷ Depression



Dolezal, 2015; Pexels free images

Inflammation & Depressive Symptoms

Associations of Depression With C-Reactive Protein, IL-1, and IL-6: A Meta-Analysis

M. Bryant Howren, MA, Donald M. Lamkin, MA and Jerry Suls, PhD

Inflammation & Depressive Symptoms

Associations of Depression With C-Reactive Protein, IL-1, and IL-6: A Meta-Analysis

M. Bryant Howren, MA, Donald M. Lamkin, MA and Jerry Suls, PhD

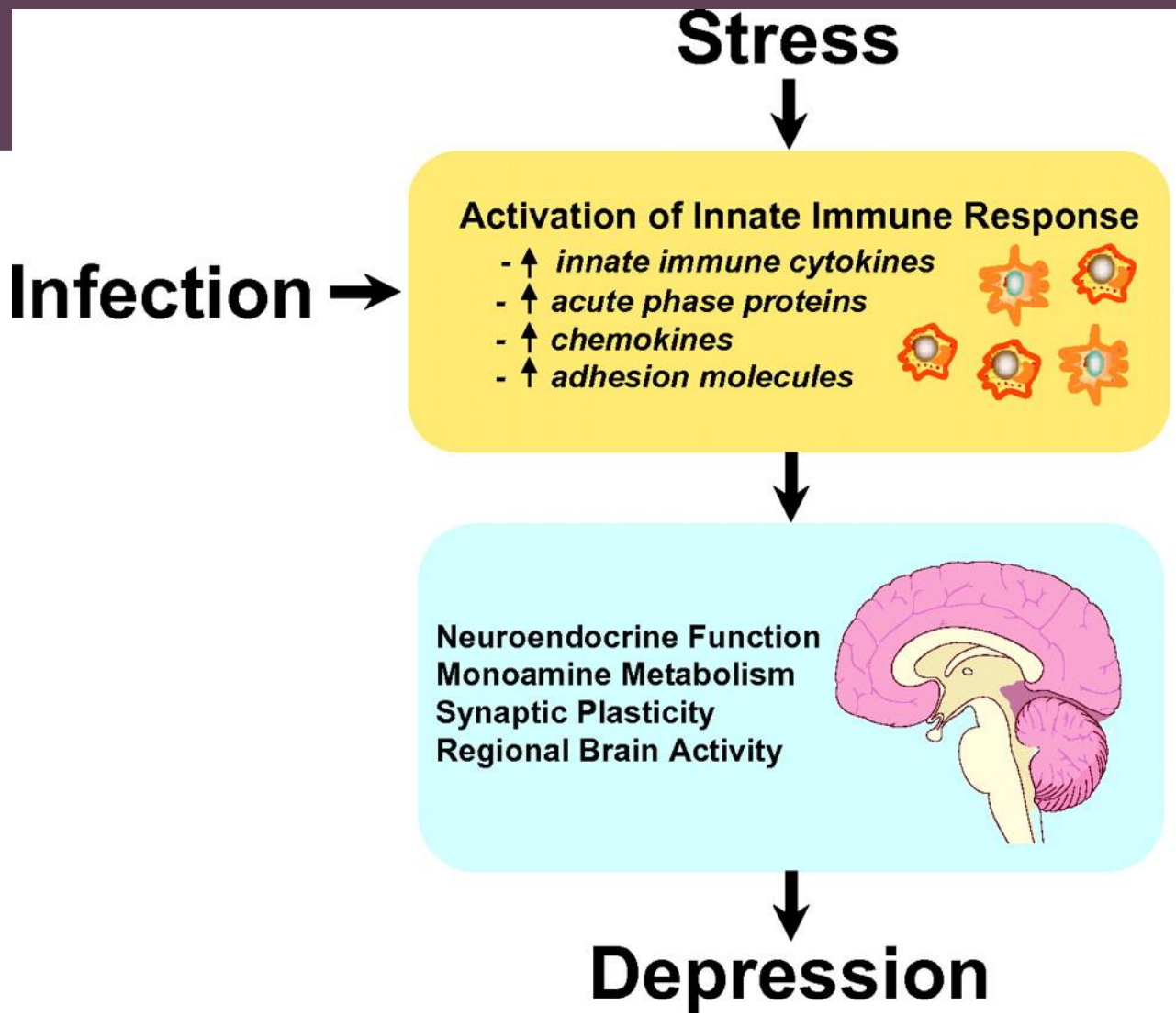
IL-6:	***d* 0.25, *p* < .001**	(62 studies)
CRP:	***d* 0.15, *p* < .001**	(51 studies)
IL-1:	***d* 0.35, *p* = .03**	(14 studies)
IL-1ra:	***d* 0.25, *p* = .02**	(9 studies)

Perinatal Inflammation and Depressive Symptoms

Prenatal depressive symptoms are associated with inflammatory markers in pregnant women in 5 out of 6 studies

Postpartum depressive symptoms are associated with inflammatory markers in 7 of 9 studies since 2000

Coussons-Read et al., 2007; Christian et al., 2009; Bushrow et al., 2012 ; Blackmore et al., 2014; Haeri et al., 2013; Roomruangwong et al., 2016; Yim et al., 2015; Liu et al., 2016



Adapted from Miller & Raison, 2008

Liu et al, 2006; McCann et al., 2008; Arora & Hobel, 2010; Chirumbolo et al., 2017

Stress

Infection →

Activation of Innate Immune Response
- ↑ *innate immune cytokines*
- ↑ *acute phase proteins*
- ↑ *chemokines*
- ↑ *adhesion molecules*

Adequate Vitamin D Reduced Inflammation

Deficient Vitamin D Unchecked Inflammation

Neuroendocrine Function
Monoamine Metabolism
Synaptic Plasticity
Regional Brain Activity

No Depression

Depression

Images from When the Bough Breaks & UC Davis Pediatrics

Liu et al, 2006; McCann et al., 2008; Arora & Hobel, 2010; Chirumbolo et al., 2017

Prenatal Depression

- Prenatal depression is quite common with rates ranging between 12 and 22%
- Associated with poorer maternal health behaviors and risk of postpartum depression
- Untreated prenatal depression has been associated with adverse birth outcomes

Bennett et al., 2004; McDonald et al., 2013; Zuckerman et al., 1989; Burt & Stein, 2002

Postpartum Depression

Gavin et al., 2005; Halbreich & Karkun, 2006

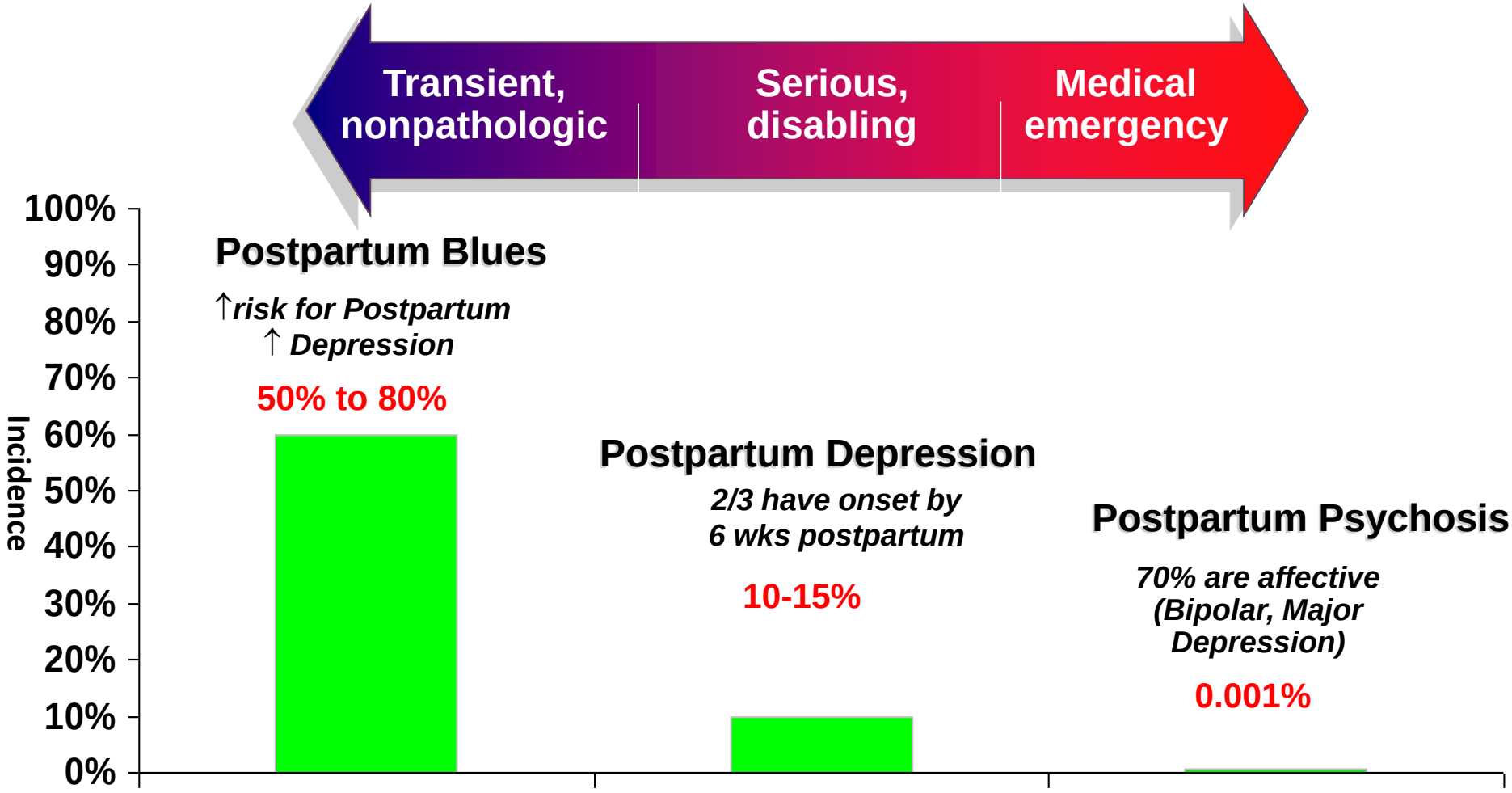
Postpartum Depression

- Approximately 10% of pregnant women in developed countries experience postpartum depression

- Prevalence rates can range as high as 60%

Gavin et al., 2005; Halbreich & Karkun, 2006

Spectrum of Postpartum Mood Changes



Nonacs & Cohen, 1998

Established **Psychosocial** Risk Factors for Postpartum Depression

- Low education
- Low income
- Single/no partner
- African American race
- Low social support
- High life stress
- History of depression
- Prenatal depressive symptoms

Beck et al., 2001; Skalkidou et al., 2012

Established **Biological** Risk Factors for Postpartum Depression

- Genetic and Epigenetic Studies
- Endocrine System
  - Reproductive Hormones
  - Stress Hormones
  - Thyroid Hormones
- Immune System

Yim et al., 2015, *Annual Review of Clinical Psychology*

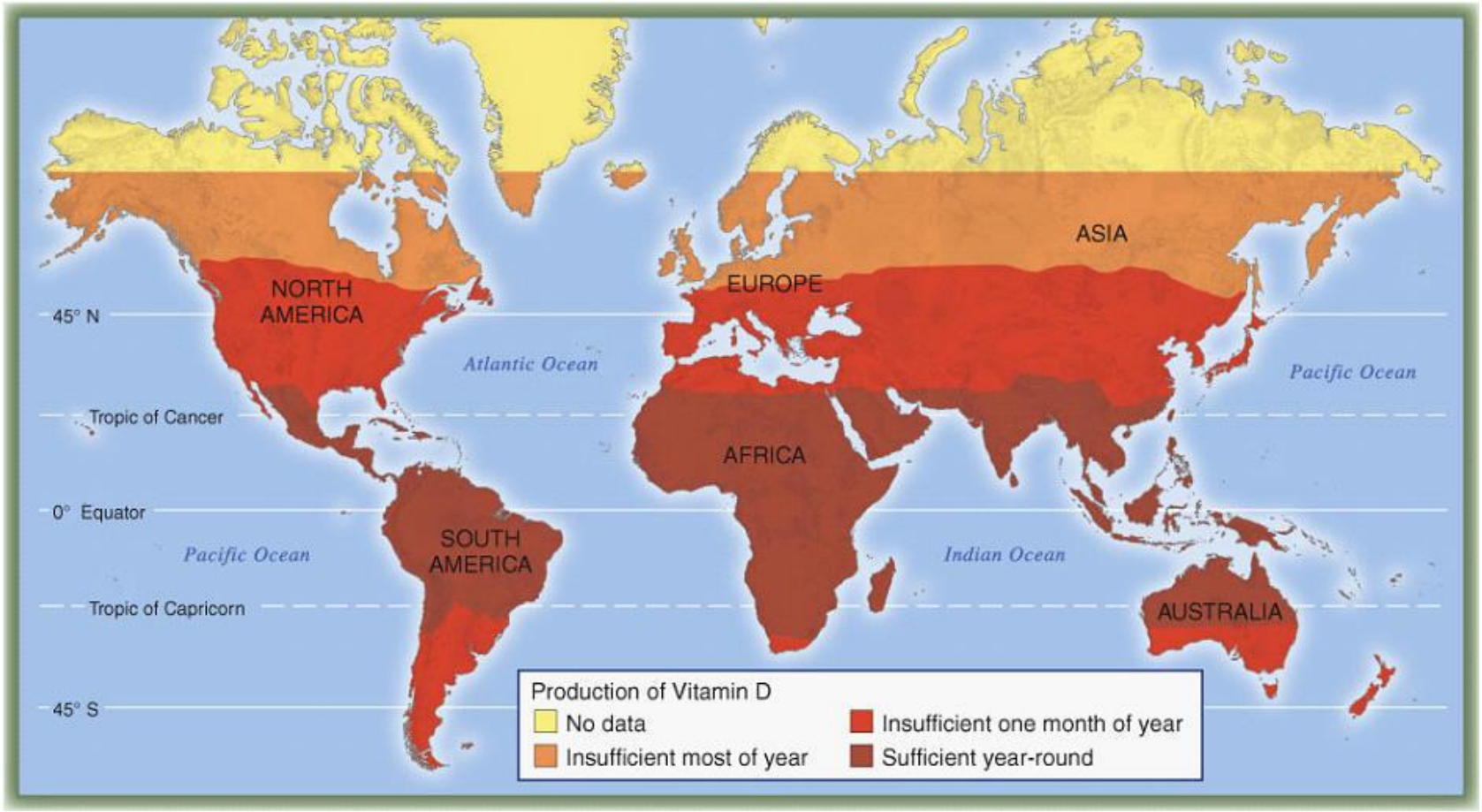
Disparities

In vitamin D, inflammation, and mental health

The Beauty of our Differences

PHOTOGRAPH BY SARAH LEEN, NATIONAL GEOGRAPHIC

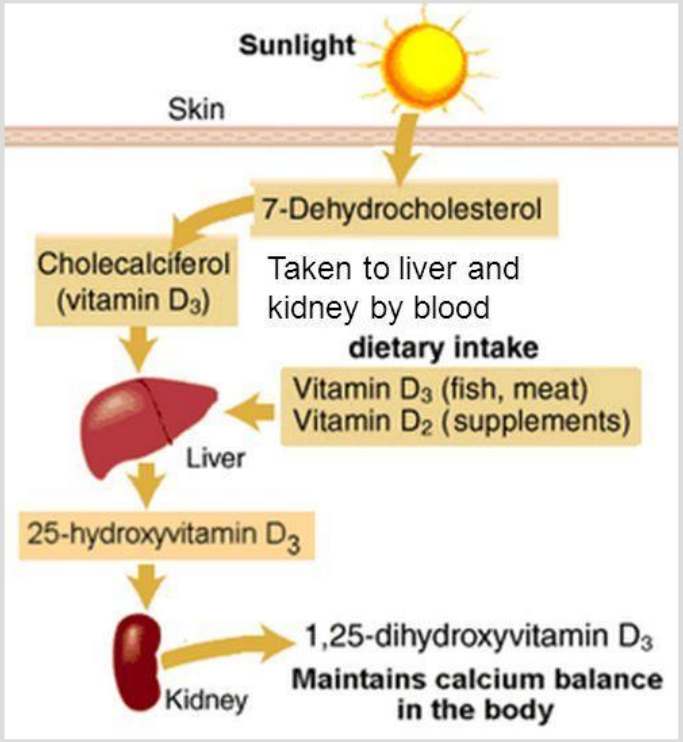
Skin Color and Vitamin D



Bonci et al., 2010

Skin Color and Melanin

Vitamin D Production



Exposure to UV light

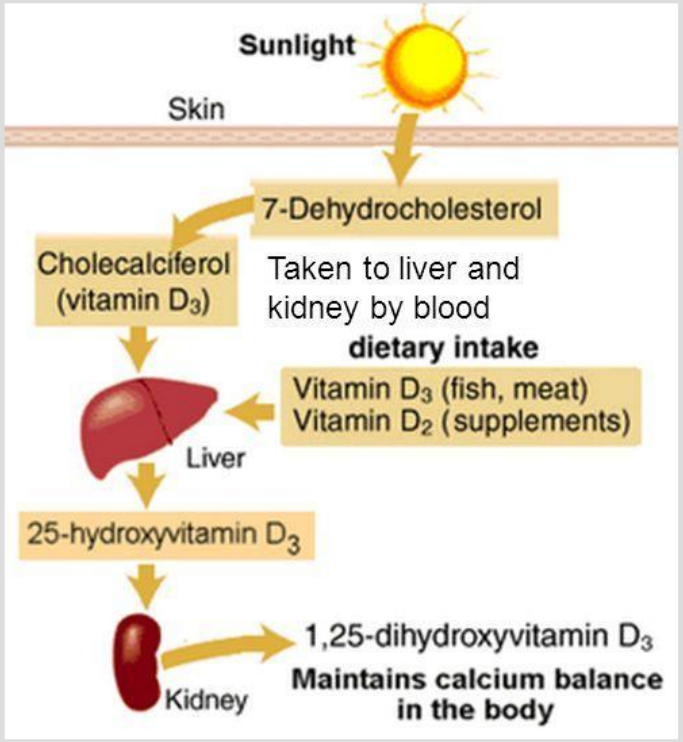
Active form of vitamin D

Too much melanin in skin can keep bodies from synthesizing vitamin D

Aranow, 2011; Hall et al., 2010, JN

Skin Color and Melanin

Vitamin D Production



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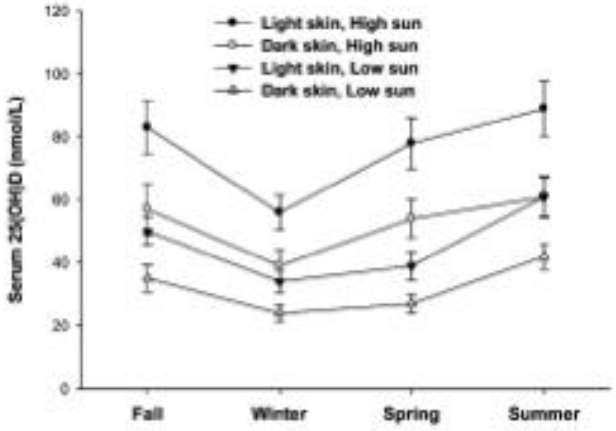

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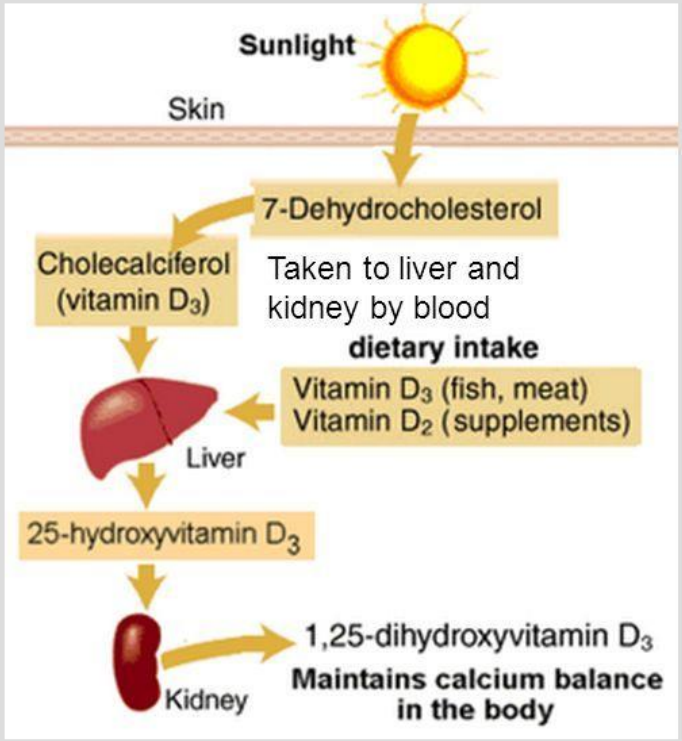

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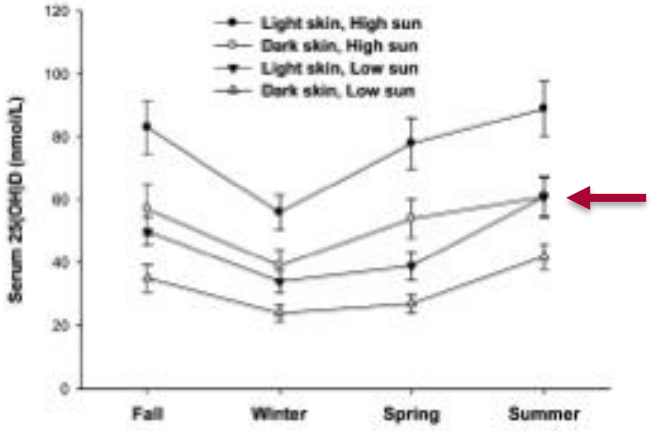

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The Role of Race/Ethnicity

Orr et al., 2006; Deverts et al., 2010; Nassar et al, 2011; Cassidy-Bushrow et al., 2012 ; Giurgescu et al., 2016

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African American women are at increased risk for:

- Prenatal and postpartum depression
- Prenatal vitamin D deficiency
- Higher levels of inflammatory biomarkers

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Vitamin D and Depression In Pregnancy and Postpartum

Low Prenatal Vitamin D

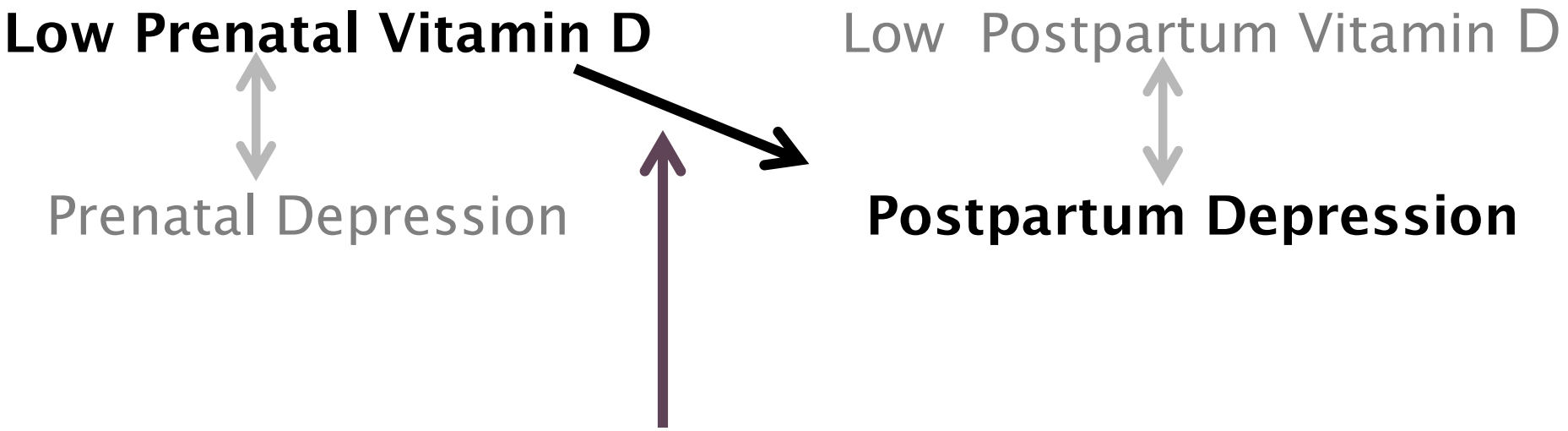
Low Postpartum Vitamin D

Prenatal Depression

Postpartum Depression

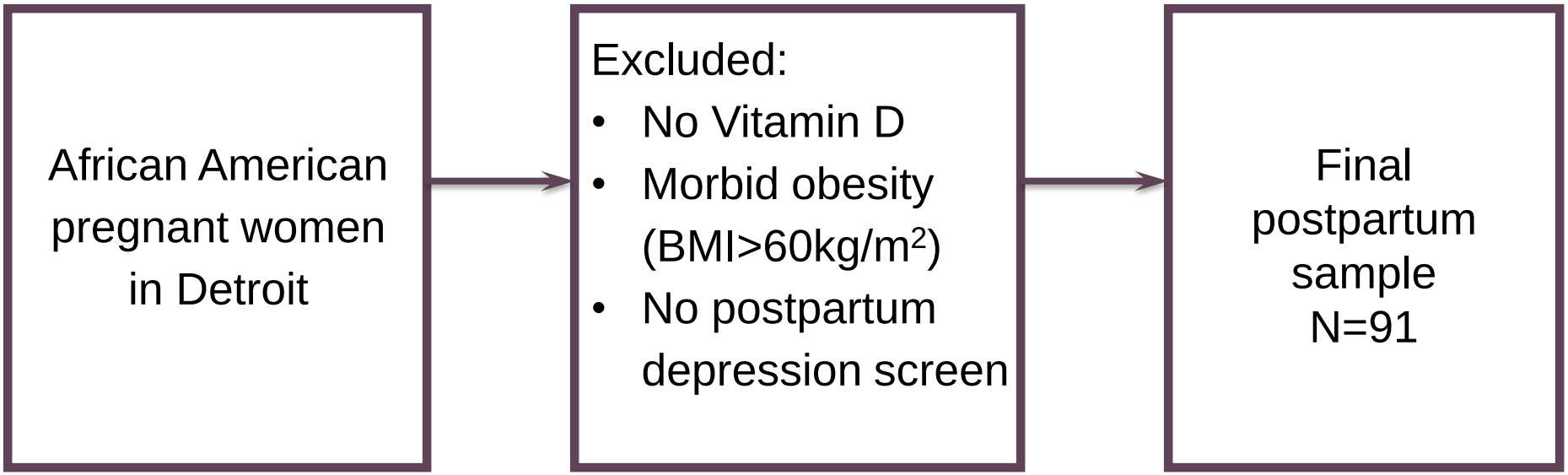
Hypotheses

I. Low levels of prenatal Vitamin D will predict postpartum depressive symptomatology:



II. This association will be moderated by prenatal inflammation

Henry Ford Health System Maternal Stress Study



Cassidy-Bushrow et al., 2012, *Journal of Women's Health*
Cassidy-Bushrow et al., 2012, *Journal of Reproductive Immunology*

Study Design

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Prenatal Visit (P1) N=178	Second Trimester (P2) N=178	Postpartum Period (PP) N=91
9-13 weeks gestation	13-28 weeks gestation	4-6 weeks postpartum
Vitamin D (25-OHD)		
	Inflammatory Markers	
		Depression Screen (EPDS)

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Descriptive Characteristics for Study Population Total Sample (N=91)

Maternal Age	27 ± 6
Married	25%
≥ High School Diploma	58%
Currently Employed	63%
Annual Income ($)	36,623 ± 34,609

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History of Preterm Birth	9%
Preterm Birth in this Pregnancy	7%
Nulliparous	47%
Smoking in Pregnancy	2%
Pre-Pregnancy BMI	29 ± 8

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VitD Season	
April-December	60%
January-March	40%
VitD ng/ml	13 ± 9
VitD≤ 20 ng/ml	85%

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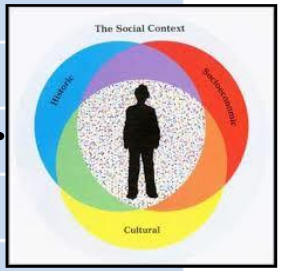

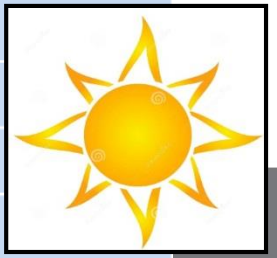

Hypothesis I Results

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An inverse association between prenatal log vitamin D and Postpartum depression symptomatology approached significance:

Prenatal Vitamin D ⟶ Postpartum Depression

$$\beta = -0.209,\ p = 0.058$$

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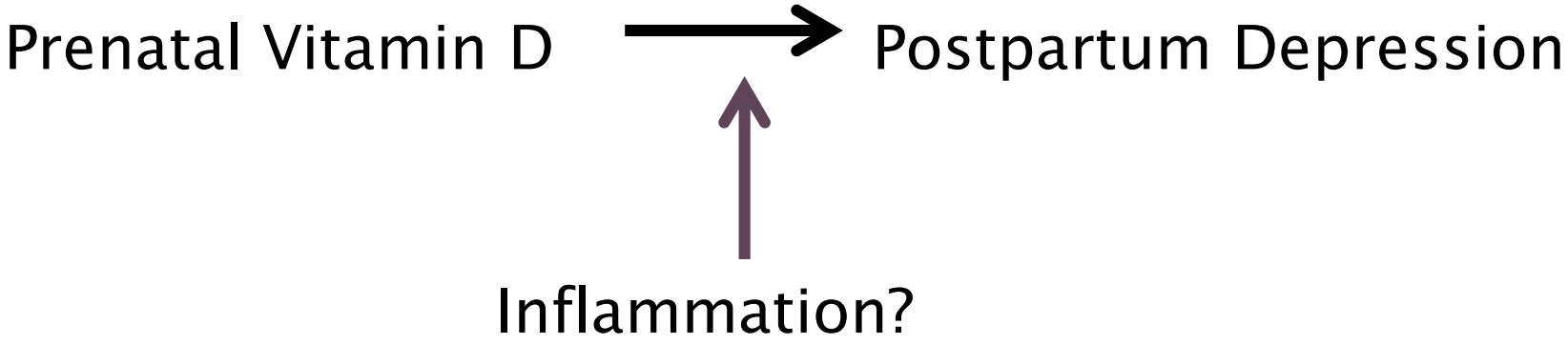
Controlling for maternal age, low education, marital status, prenatal depression, history of depression, season of vitamin D measurement, and pre-pregnancy BMI.

Hypothesis II Results



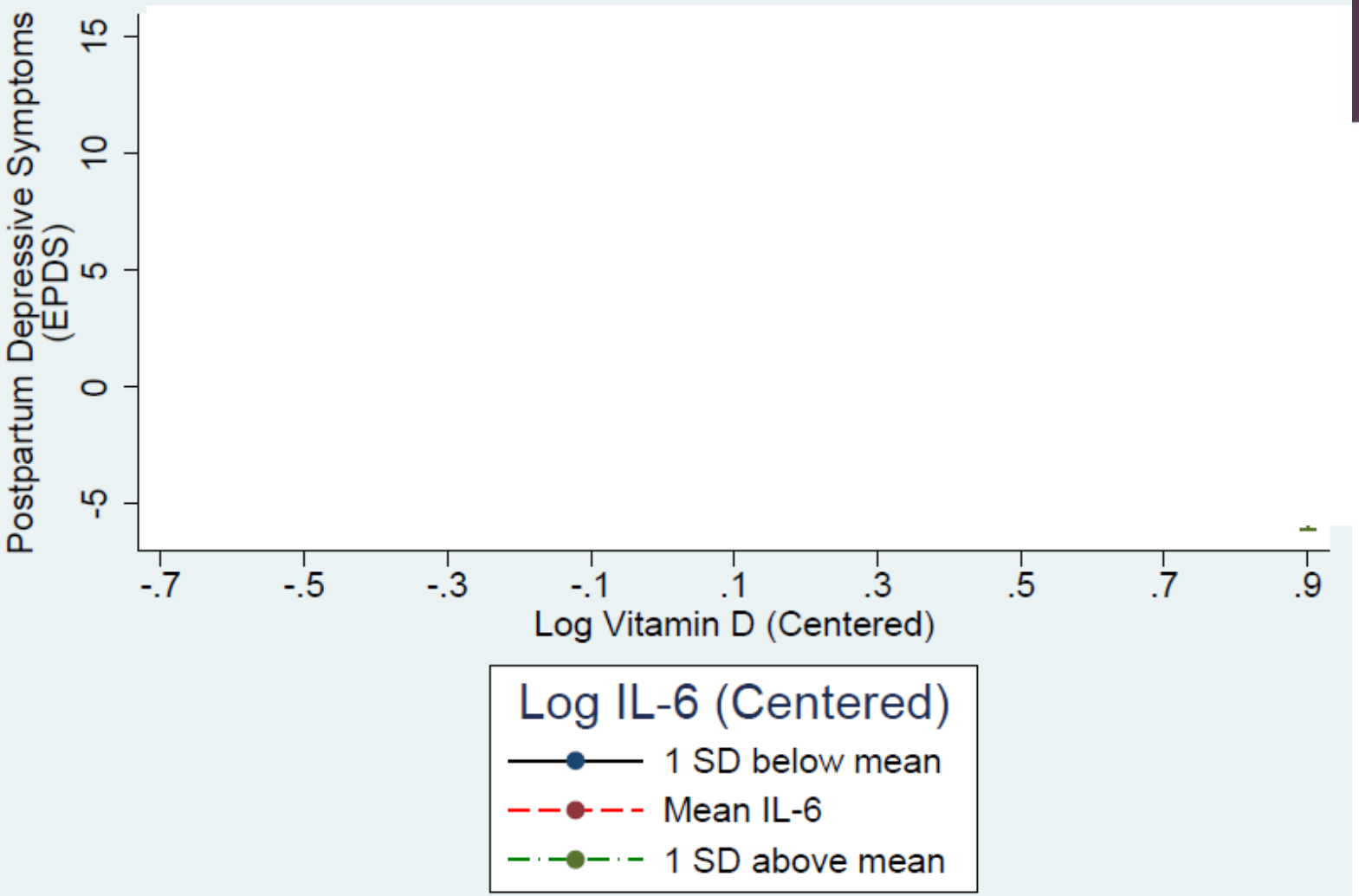
This association was moderated by prenatal inflammation:

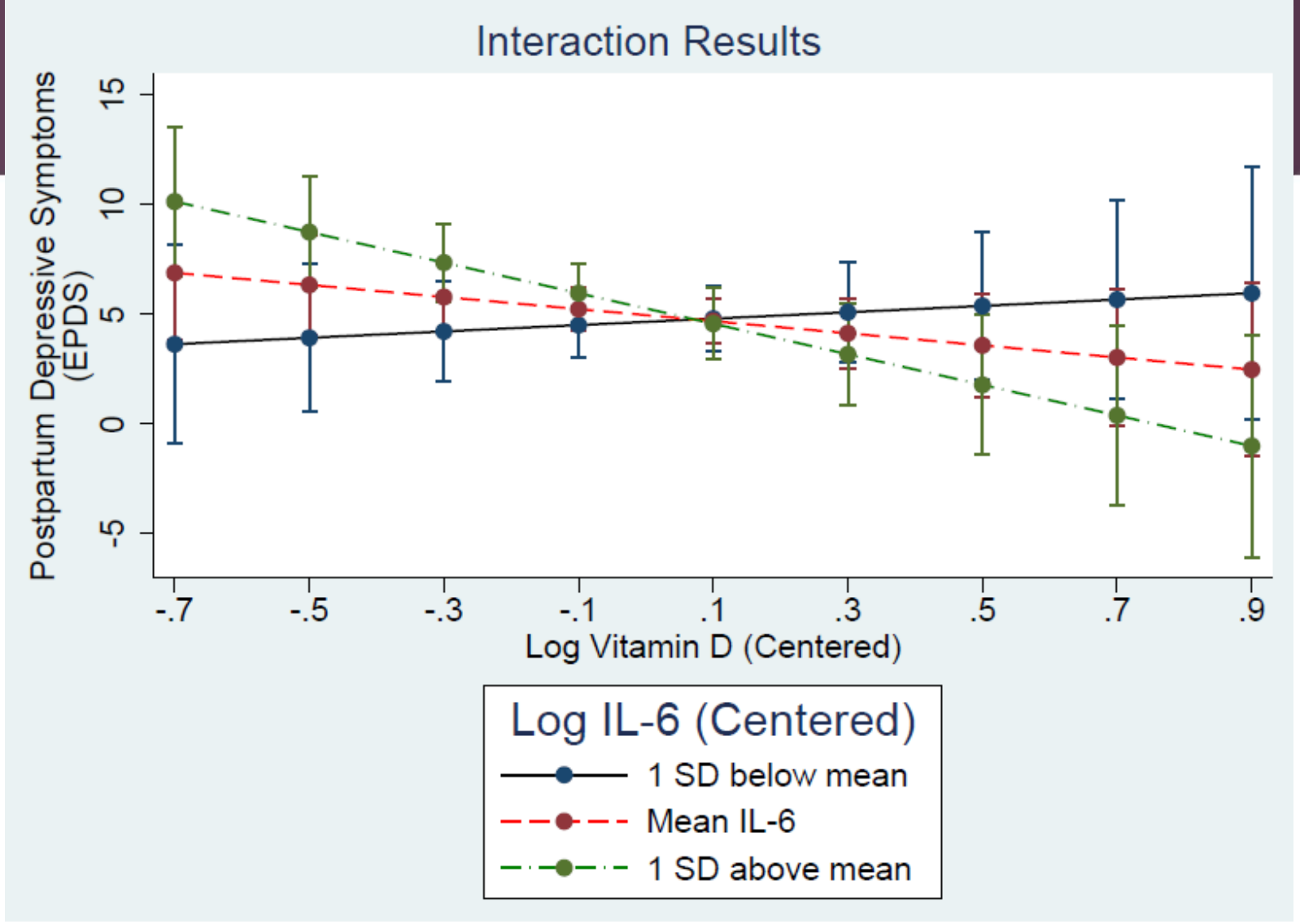
IL-6 significantly moderated the association.

$$\beta = -0.23,\ p = 0.025$$

Controlling for maternal age, low education, marital status, prenatal depression, history of depression, season of vitamin D measurement, and pre-pregnancy BMI

Interaction Results





When **IL6 is high** and Vitamin D is low, women have higher levels of predicted postpartum depressive symptomatology (EPDS).

Conclusion

Higher levels of vitamin D in early pregnancy may be protective against developing postpartum depressive symptoms, particularly in women with high levels of inflammatory markers

Ongoing & Future Research

Adverse Perinatal Outcomes

- Preterm Birth (PTB) = <37 weeks gestation
  - PTB is one of the leading causes of infant morbidity and mortality worldwide.
  - Rate of PTB in the U.S. is ~10%

- Low Birth Weight (LBW) = <2,500g birth weight (~5.5 lbs)
  - Rate of low birth weight (LBW) is ~8%

- Preeclampsia = New-onset hypertension (high BP) after 20 weeks of gestation accompanied by new-onset proteinuria
  - Rate of PE in the U.S. 2-5% of all births; 25% of preterm births

Martin et al., 2017: National Vital Statistics, final data for 2015

Ongoing Research I: Interconception Health

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Identifying Risk for Interconception Health Problems

1. Does an adverse perinatal outcome such as preterm birth, preeclampsia or a low birth weight baby lead to worsening health in between pregnancies?

2. Does adding vitamin D deficiency improve identification of disease risk in our sample?

Ongoing Research I: Interconception Health

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Accortt et al, 2017 in *Maternal and Child Health*

Interconception Health

The Community Child Health Network (CCHN) assessed postpartum women at Cedars-Sinai and developed a composite of postpartum biomarkers from multiple biological systems, based on theories of **allostatic load (AL)**

Allostatic Load

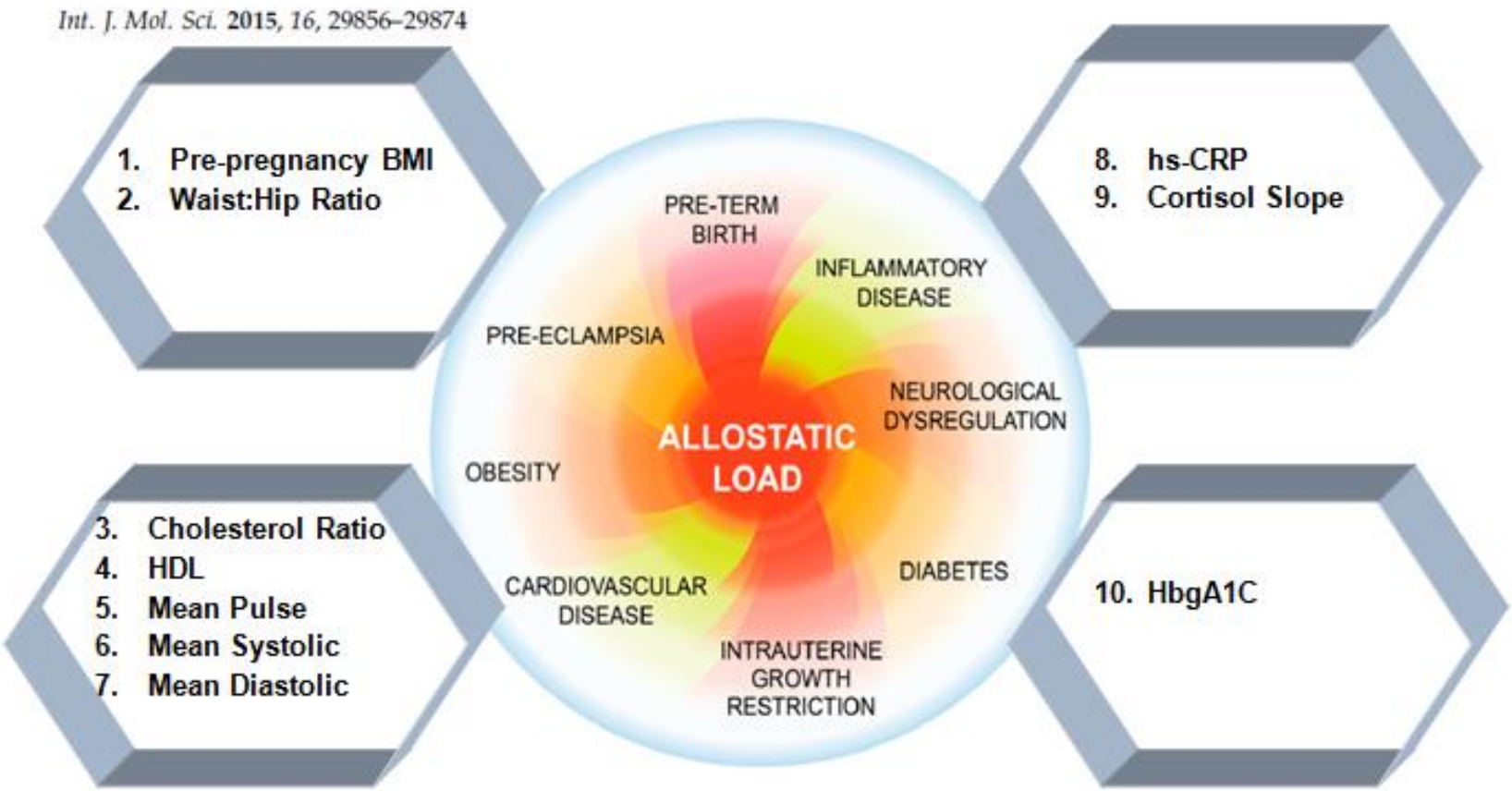
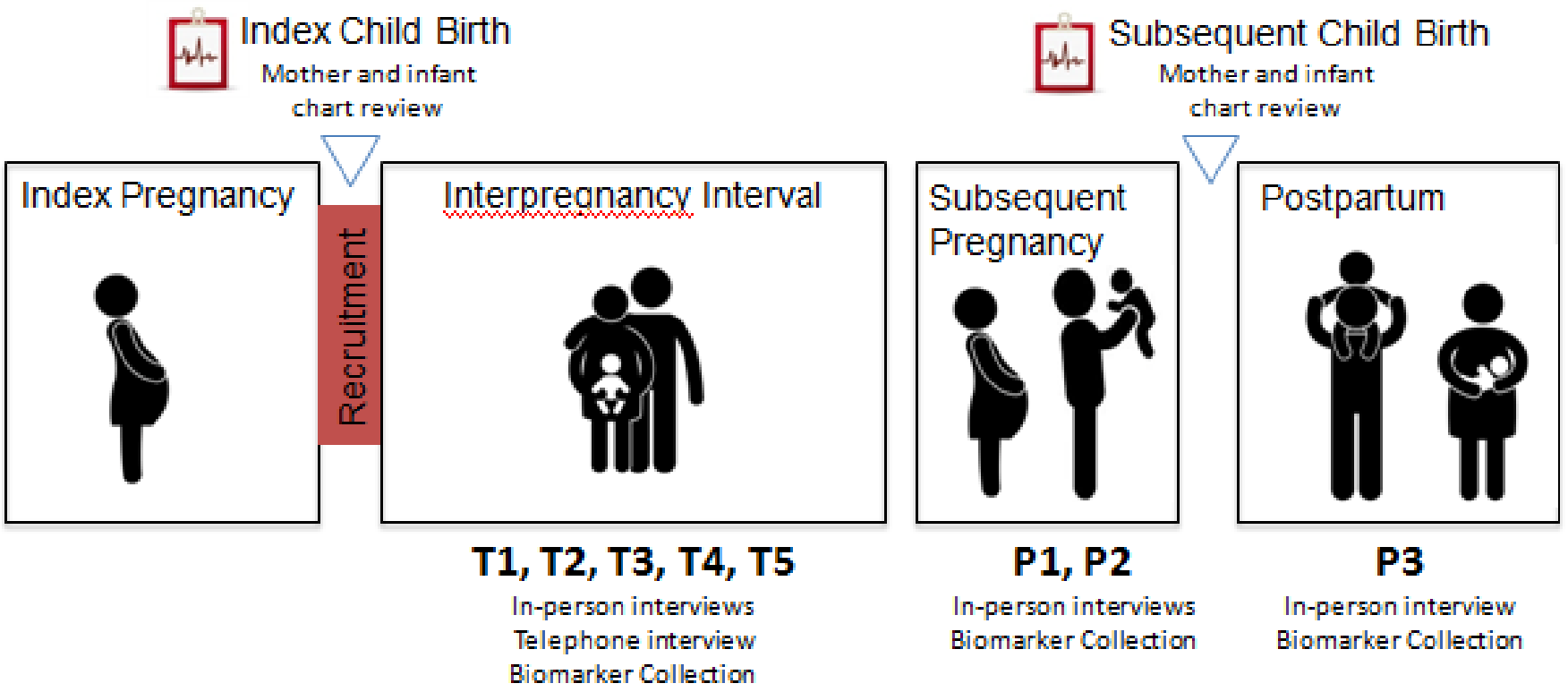


Figure 1. Allostatic load (AL) increases the risk for several perinatal and adult disease processes.

Olsen et al., 2015

CCHN Methods



Recruitment: 164 women from the Los Angeles site of the CCHN network recruited in hospital unit after delivery of index child, completed biomarker collection at **Times 2-3**. Average time of biomarker collection, since birth, was 263 days.

Data from other sites and subsequent pregnancies not presented here

Table 1 Demographic and clinical variables stratified by adverse perinatal outcome for descriptive purposes

	Total sample (N = 164)	Controls (N = 117, 71%)	Adverse outcome* (N = 47, 29%)	*p* value
Age (years)	27.8 ± 6.6	27.4 ± 6.7	28.9 ± 6.1	0.17
Married[a]	73(52%)	50/96 (53%)	23/45 (51%)	0.91
Employed (full or part-time)[b]	21(15%)	14/96 (15%)	7/45 (15%)	0.88
Education > high school diploma[c]	61(41%)	44/105 (42%)	17/45 (38%)	0.64
Poverty status[d]				0.75
Poor	71 (43%)	50 (43%)	21 (45%)	
Near poor	45 (27%)	34 (29%)	11 (23%)	
Not poor	48 (29%)	33 (28%)	15 (32%)	
Race/ethnicity				0.76
Caucasian	30 (18%)	20 (17%)	10 (21%)	
African American	42 (26%)	30 (26%)	12 (26%)	
Latina	90 (55%)	65 (56%)	25 (53%)	
Multiracial	2 (1.2%)	2 (1.7%)	0	
Days since delivery	316.1 ± 96.0	319.8 ± 98.6	307.0 ± 89.3	0.44
Primiparous	82 (50%)	56 (48%)	26 (55%)	0.38
Pre-pregnancy BMI	27.6 ± 6.4	26.8 ± 6.2	29.7 ± 6.6	0.01
Postpartum BMI	29.1 ± 6.9	28.2 ± 6.6	31.3 ± 7.1	0.01
Postpartum HBC Use[e]	29 (28%)	15/68 (22%)	14/34 (41%)	0.06
Postpartum multi-vitamin use[f]	14 (13%)	11/70 (16%)	3/35 (9%)	0.38
Breast feeding[f]	34 (32%)	27/70 (39%)	7/35 (20%)	0.08
Vitamin D ng/ml	20.2 ± 7.2	20.8 ± 7.7	18.9 ± 5.7	0.13
Vitamin D < 20 ng/ml	88 (54%)	56 (48%)	32 (68%)	0.02
Season of vitamin D measurement[g]				0.10
April–December	152 (93%)	111 (95%)	41 (87%)	
January–March	12 (7.3%)	6 (5%)	6 (13%)	

Data are N (%) or mean ± standard deviation

Comparison was tested with t-tests, chi square, or Fisher's exact test

Controls were women who did not have any of the adverse perinatal complications of interest in the study

Adverse perinatal outcome includes one or more of the following: low birth weight, preterm birth, preeclampsia or gestational diabetes

*Nineteen (of 47) women experienced more than one adverse outcome (see supplementary table). This subgroup did not statistically differ (from 117 controls) on pre-pregnancy or postpartum BMI, vitamin D levels, or the demographic factors listed above. They did differ on vitamin D deficiency (20% of women who had more than one outcome were vitamin D deficient compared to 8% who were not deficient) and season of vitamin D measurement (40% of women who had more than one outcome delivered in Jan–March compared to 12% who delivered in April–December)

[a]Marital data available for N = 141

CCHN Results

- In line with rates of adverse perinatal outcomes reported in the US, 29% (N = 47) experienced one or more outcome:
  - Fifteen percent (N = 24) had PTB, 12% (N = 20) had LBW, 10% (N = 17) had GDM, and 8% (N = 13) had preeclampsia

- Half met criteria for vitD deficiency (vitamin D ≤ 20 ng/ml).
  - The adverse outcome group had higher rates of 25(OH)D deficiency than those who didn't (68% vs. 48%, p = 0.02)

- Logistic regression results, adjusting for maternal age and race, showed that an adverse perinatal outcome was associated with higher postpartum AL:

  OR 1.53 for a 1-unit increase in AL, 95% CI 1.24–1.89

Creanga et al. 2014; Accortt et al, 2017

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CCHN Results

Does adding vitamin D deficiency improve identification of disease risk in our sample?

YES – and two different statistical approaches confirm

- Adding 25(OH)D deficiency as a separate variable to the logistic regression model improved model fit:

  Delta (-2LogL) = 5.667, *p = 0.017*

- *Adding 25(OH)D deficiency as an 11th component* to the AL index improved the model fit compared to the 10 component AL index (Delta (−2LogL) = 3.955, *p = 0.047), and the AIC improved from 184.27 for the* 10-biomarker AL model to 180.32 for the 11-biomarker AL model

CCHN Conclusions

Results suggest that including Vitamin D (25(OH)D) in the AL composite score is a valuable addition to better identify women at risk for future health problems including adverse pregnancy outcomes

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Ongoing Research II: The DAVID Study

Depression **A**nd **Vi**tamin **D** (DAVID) Study: 101 women from obstetric clinics at Cedars-Sinai completed biomarker collection and depression screening (EPDS) at 3 times

A composite of four adverse pregnancy complications and outcomes was created: preterm birth (PTB), low birth weight (LBW), small for gestational age (SGA), and preeclampsia (PE)

Question: Is low prenatal vitamin D associated with APOs and what role does prenatal depression play?

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Accortt et al, Accepted in Journal of Behavioral Medicine, Special Postpartum Depression Edition

The DAVID Study

- Women with **prenatal** (14 wks) vitamin D deficiency had 3.43 times the risk of developing an adverse outcome compared to those vitamin D sufficient

Relative Risk = 3.43; 95% CI 1.60 – 7.34, $p = 0.004$

- 60% percent with **both** prenatal risk factors, vitamin D deficiency & minor depression (EPDS ≥10,) had adverse perinatal outcomes VS 17% with only 1 or neither risk factor

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Ongoing Research III: The Postpartum Heart Health Registry & Biorepository

- Adverse perinatal outcomes are associated with future cardiovascular disease

- Our **goal** is to study the association between adverse pregnancy outcomes, mental health, and cardiovascular health

Image from US News and World Health Report

Rich-Edwards et al., 2014; Catov et al., 2016

The Postpartum Heart Health Registry & Biorepository

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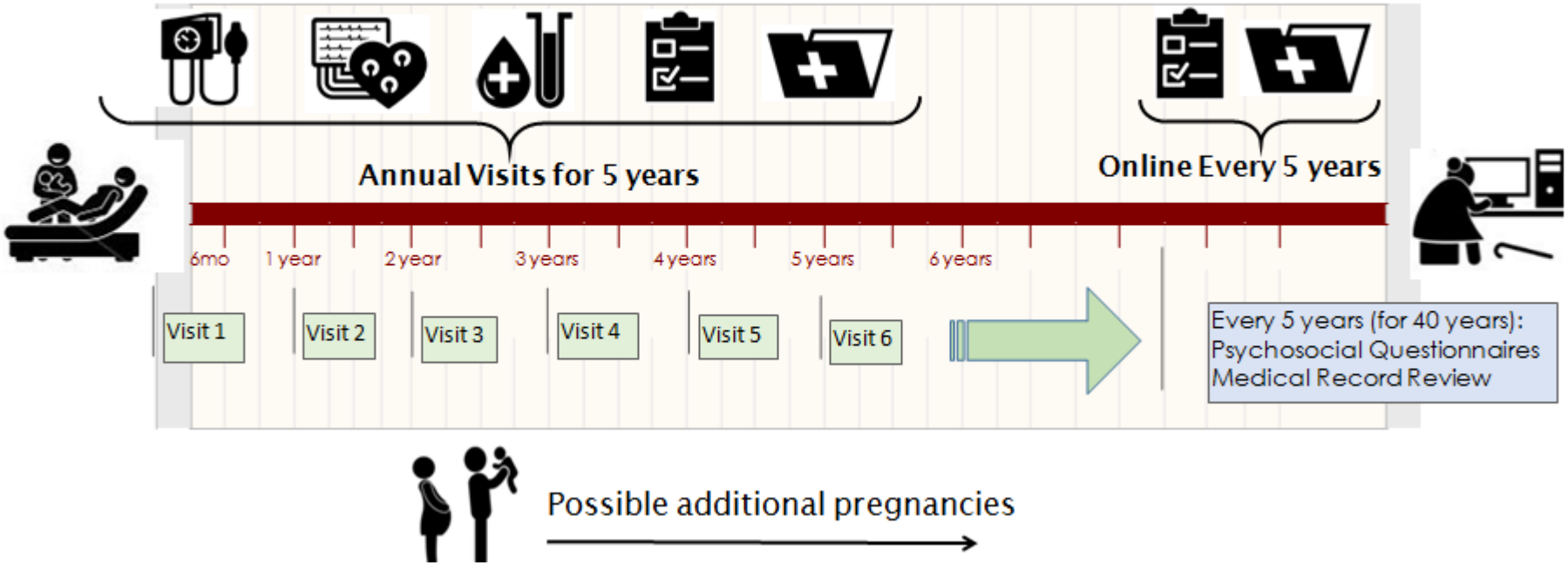
Precise Longitudinal Screening & Monitoring for CVD risk

The Postpartum Heart Health Registry & Biorepository

Precise Longitudinal Screening & Monitoring for CVD risk



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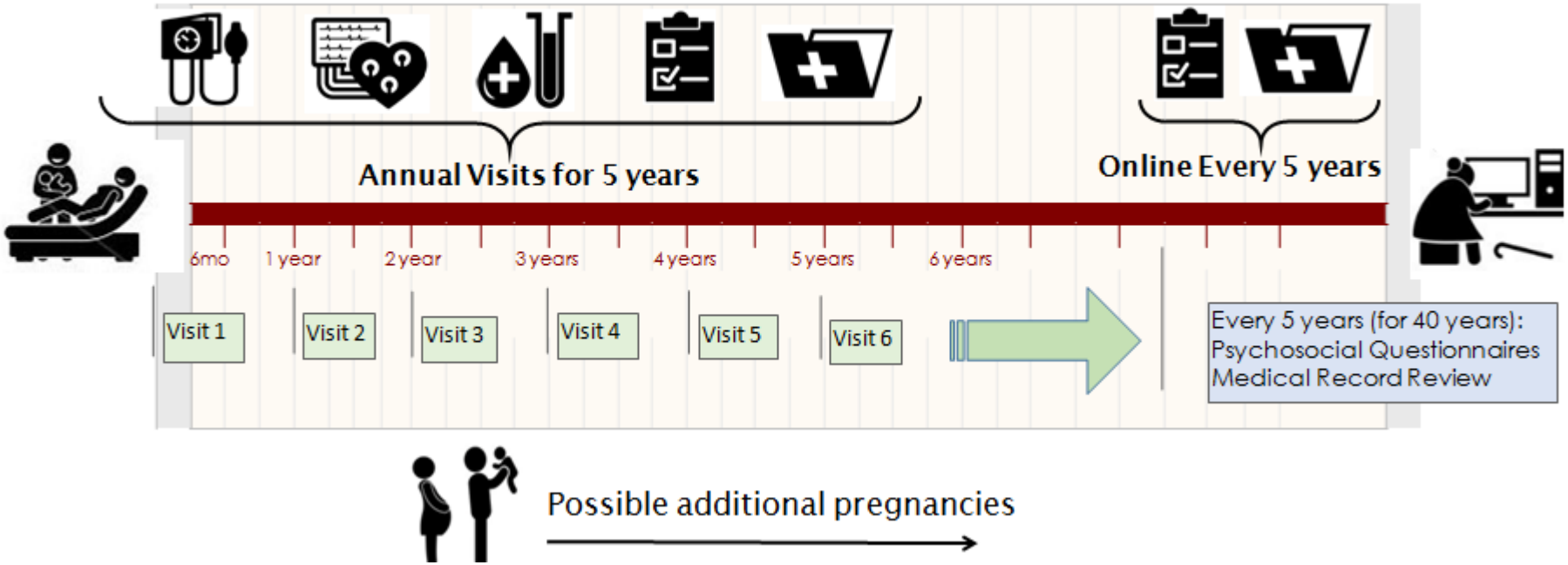

To date: 40 women enrolled, 30 with preeclampsia
And 15 already completed 1 year follow-up

Project Rationale

Women with preeclampsia or spontaneous preterm delivery, compared to term delivery, will demonstrate dysfunction in their:

1. **Physiology**

   More adverse peripheral vascular augmentation index & pulse wave velocity, and higher blood pressure

2. **Biology**

   Higher serum lipids, interleukin [IL]-6, high sensitive C-reactive protein [hs-CRP], brain natriuretic peptide [BNP], lower vitamin D, & telomere shortening

3. **Psychology**

   Increased self-reported depression, anxiety & stress

Future Directions

Vaziri et al., 2016

Future Directions

Future Intervention Study

- Investigate whether increased prenatal vitamin D supplementation would decrease postpartum depression, and for whom this intervention might work best

Image from Nature Made

Thank you

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Questions?

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