

Overview of Preterm Birth

Larry Rand, MD

Director, Perinatal Service, Fetal Treatment
Center

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Fetal Medicine

Principal Investigator, PTBi-CA

Preterm Birth
Initiative – California

UCSF



How big of a problem?

**15
Million/Year**

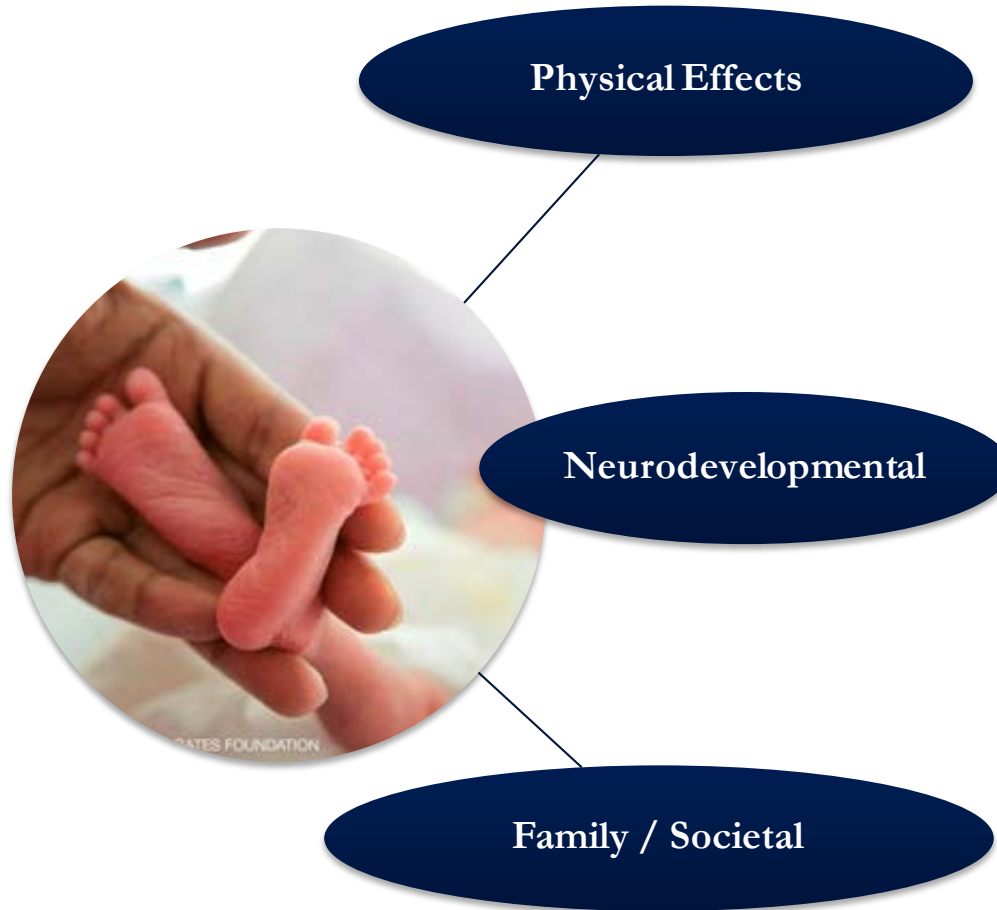
1 Million
Deaths

14 Million
Survivors

Global Epidemic

\$26 Billion/year
US (2006)

Every week matters: short and long term impact



- Visual Impairment
- Hearing Impairment
- Short Gut Syndrome
- Chronic Lung Disease/ Asthma
- High Blood Pressure
- Obesity/ Diabetes

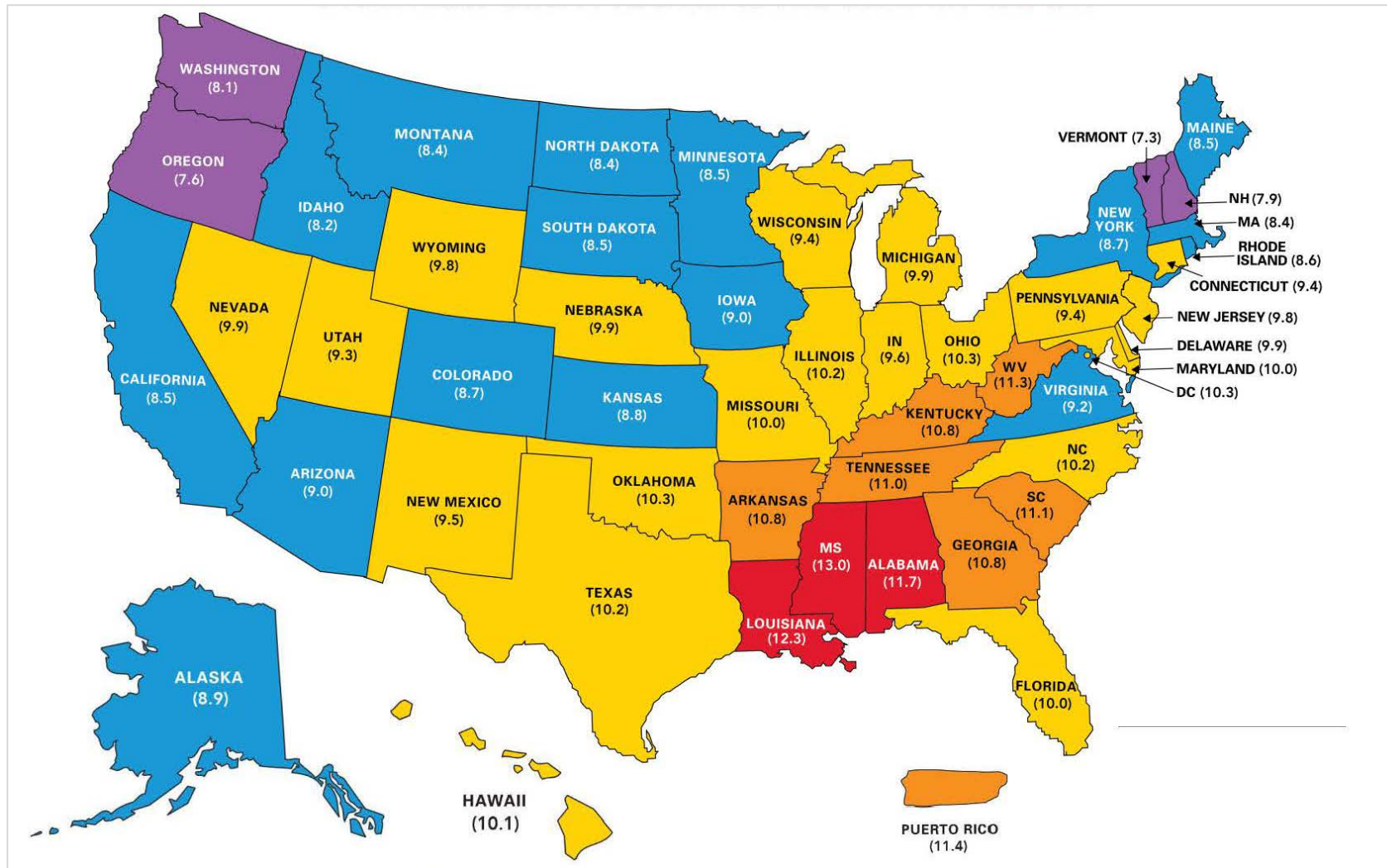
- Cerebral Palsy
- Cognitive Impairments
- Learning Impairments
- Dyslexia
- Academic Achievement
- ADHD
- Anxiety/ Depression

- Financial and Emotional Stress on Family
- Greater Health Costs
- Cross-generational Risks for Preterm Birth



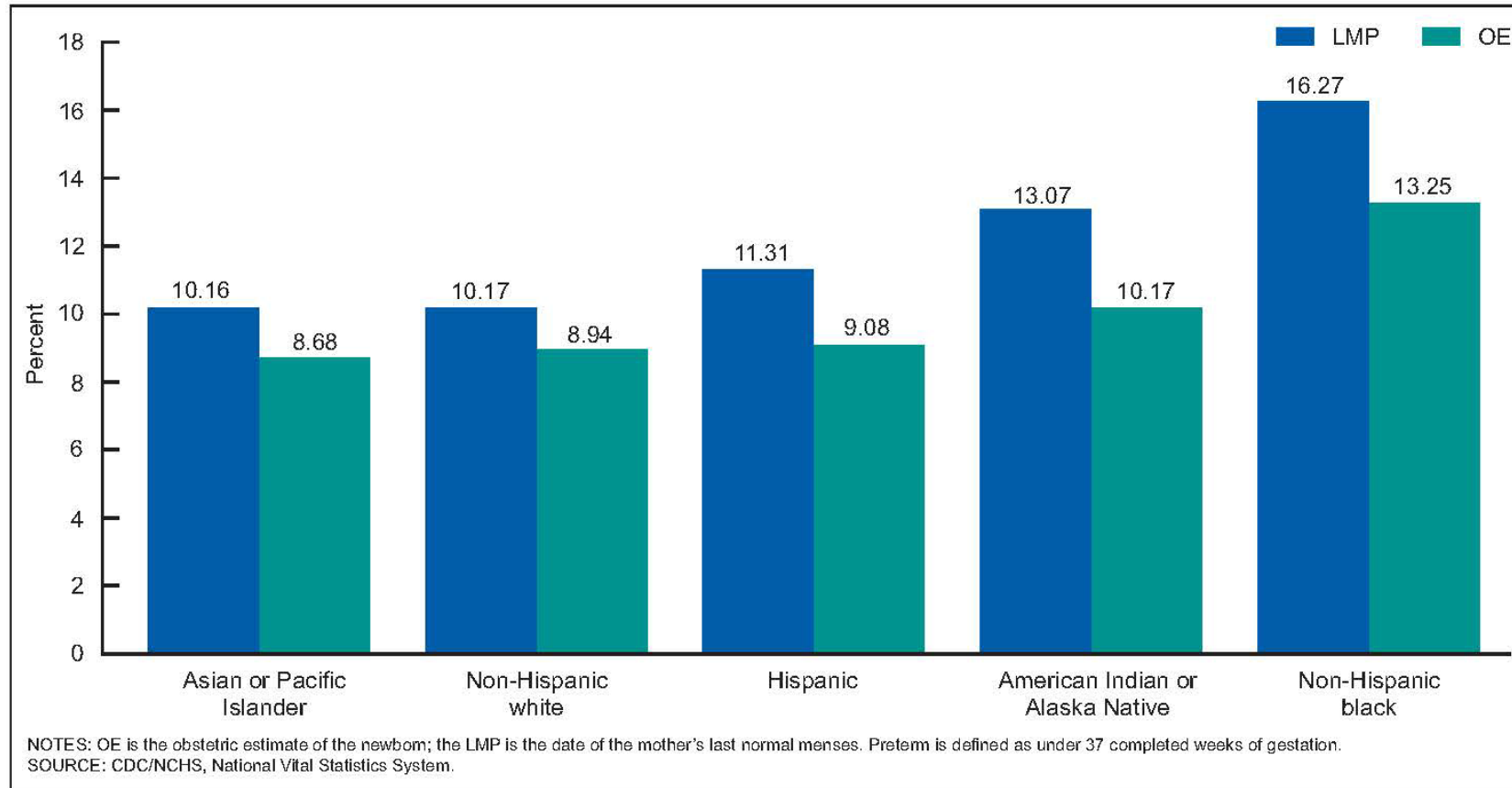
Burden of Preterm Birth: United States: 2015

FIRST INCREASE IN 7-YEARS

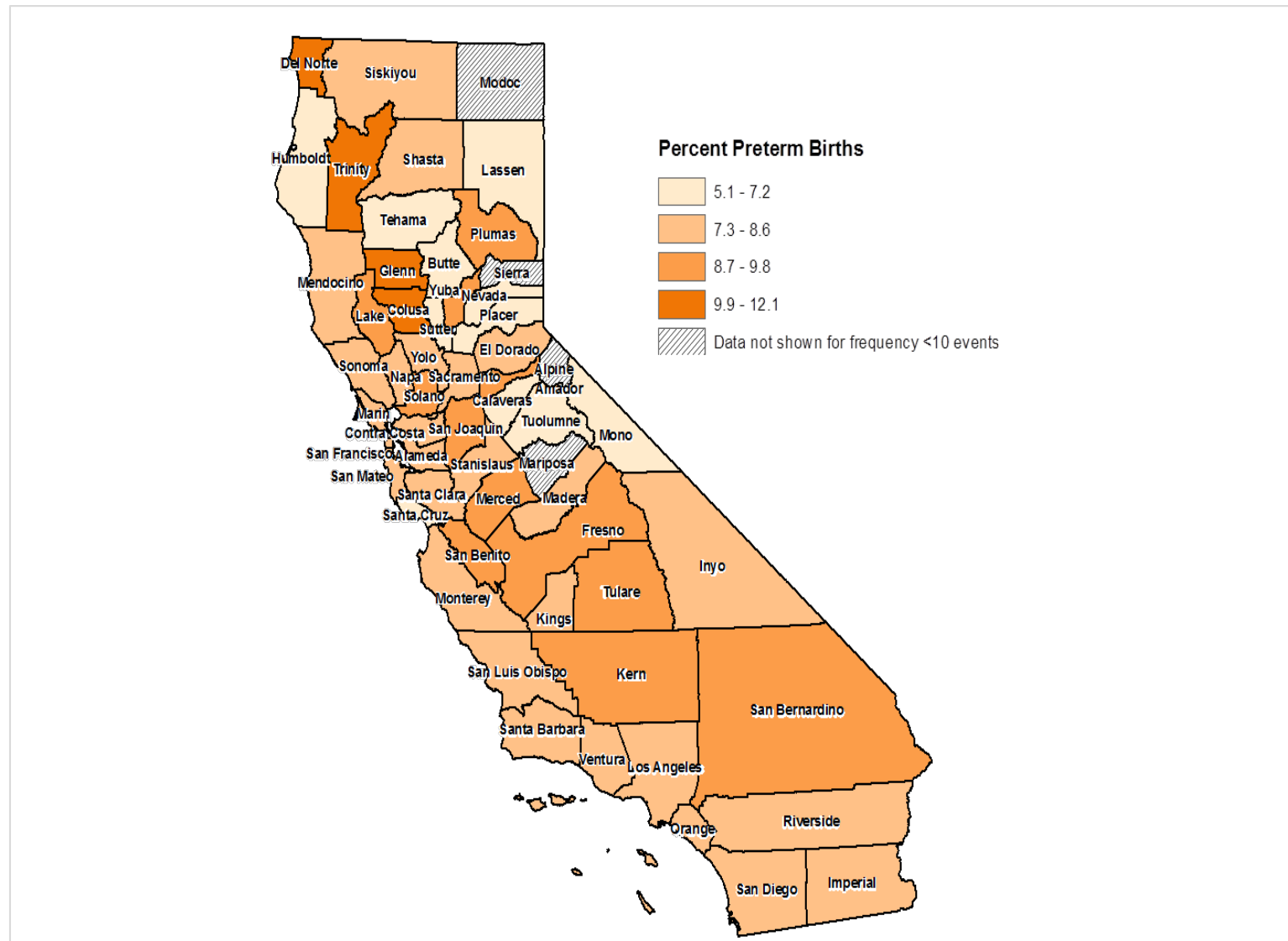


From March of Dimes Preterm Birth Report Card, 2016

US Rates of Preterm Birth by LMP versus OE (2015)

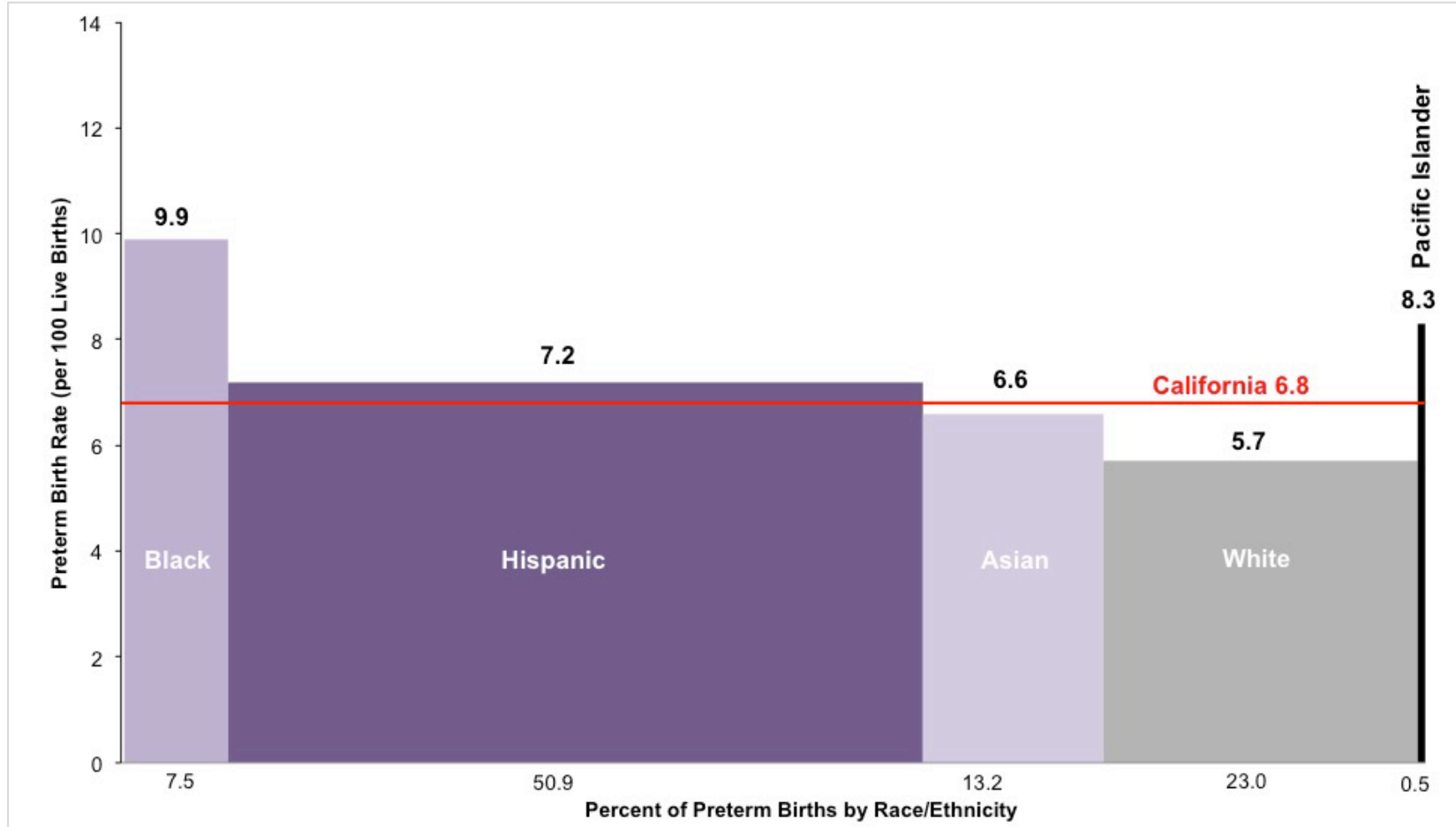


California: Rates of Preterm Birth Differ Greatly by Place



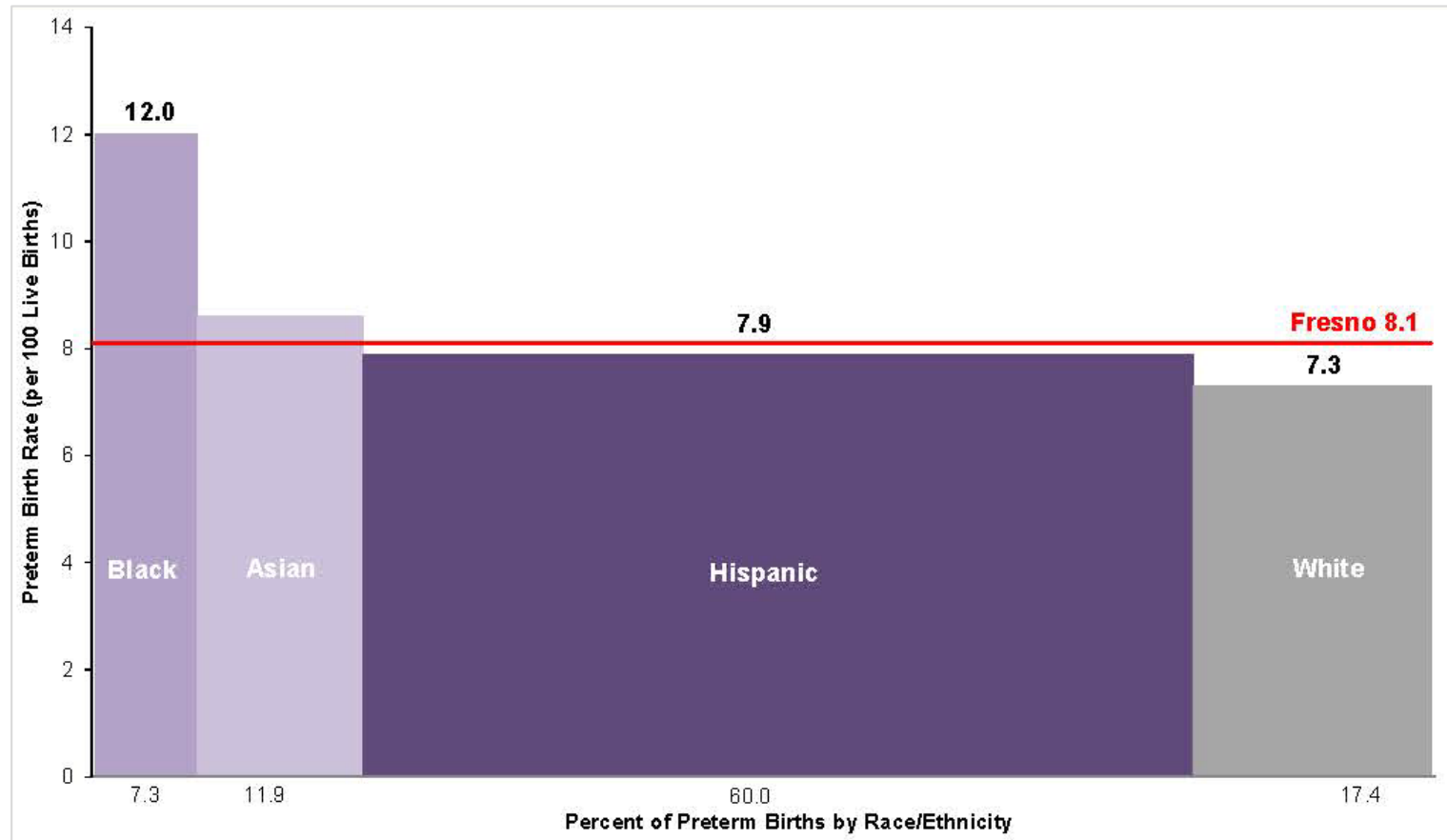
From California Summit on Preterm Birth, 2015

Preterm Birth in Singletons by Race/Ethnicity, California



From California Summit on Preterm Birth, 2015

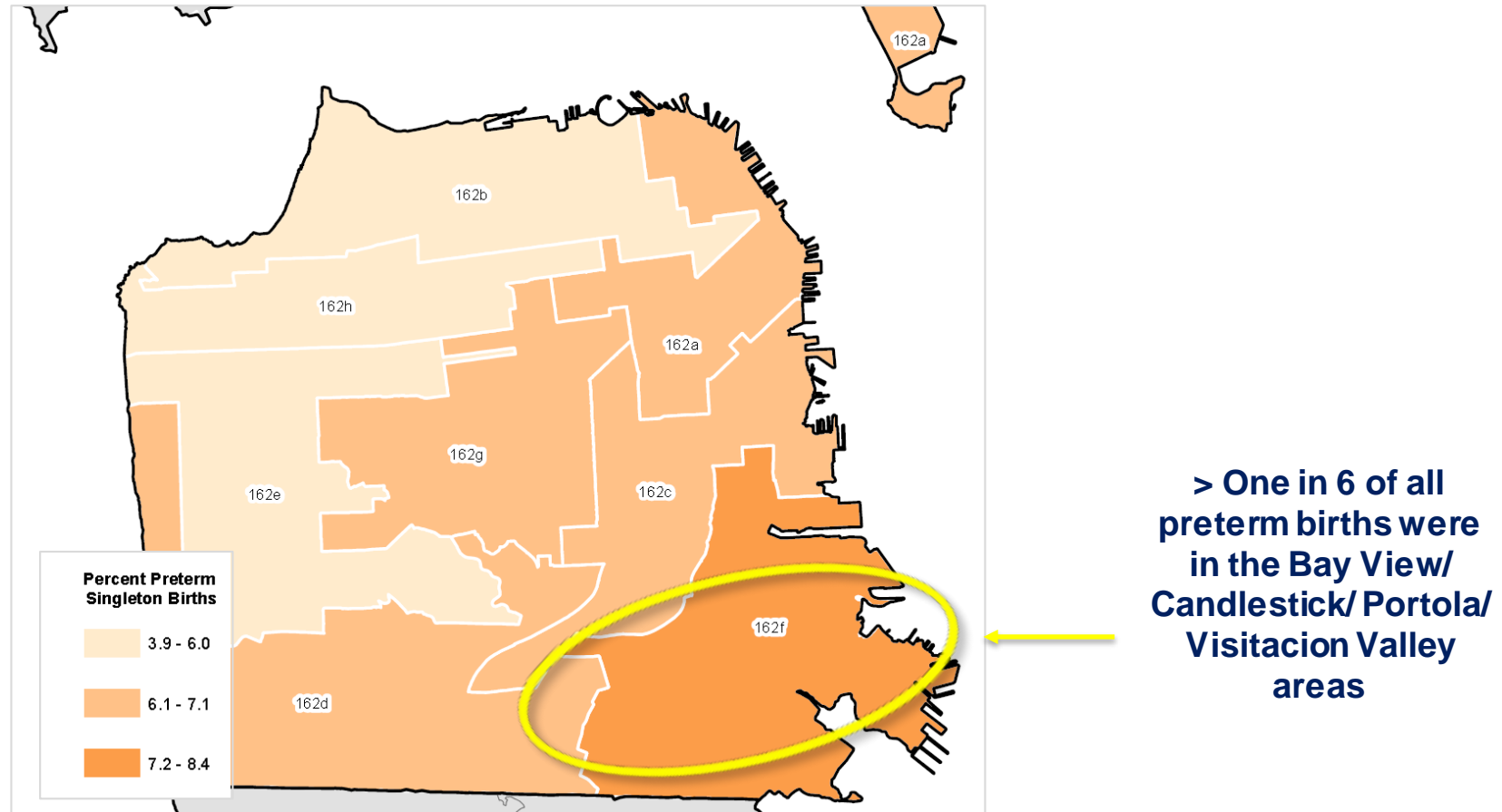
Preterm Birth in Singletons by Race/Ethnicity, Fresno



From California Summit on Preterm Birth, 2015

Disparities in Preterm Birth: Location Matters

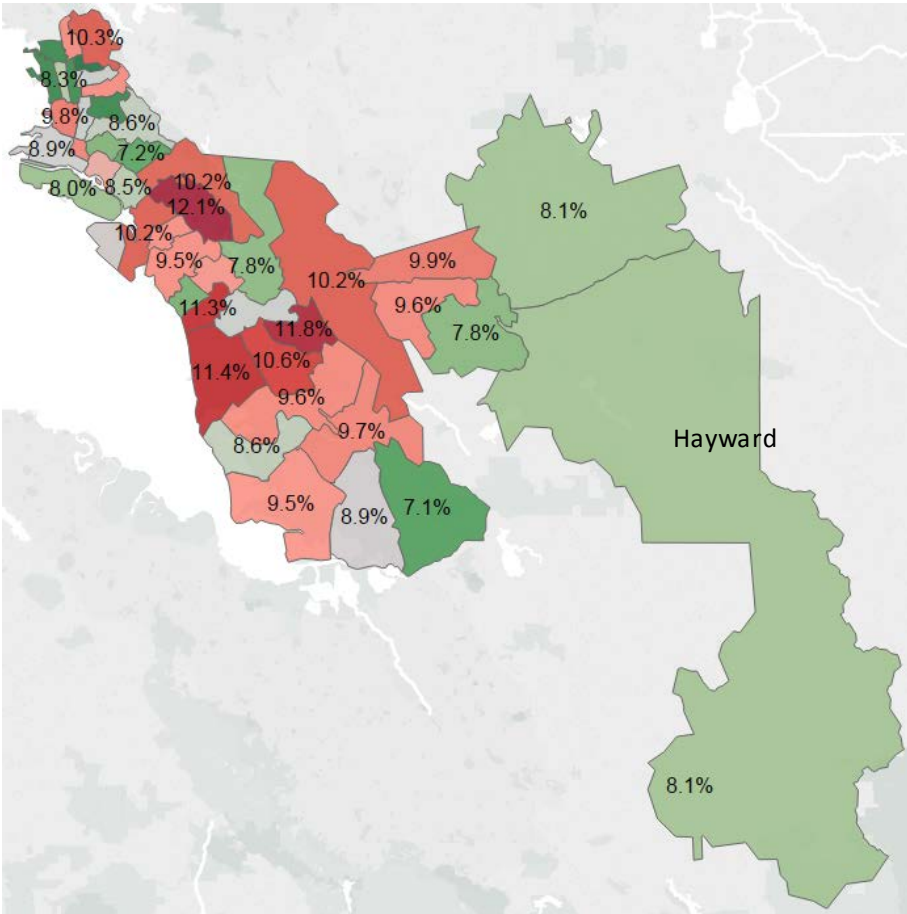
Rate of Preterm Birth in Singletons, (By MSSA/ Census Tract Groupings)



From California Summit on Preterm Birth, 2015

Alameda: Distinct pockets of high PTB rates

Preterm birth rate by zip code



5.7% █ ← Low to high PTB rates → █ 12.1%

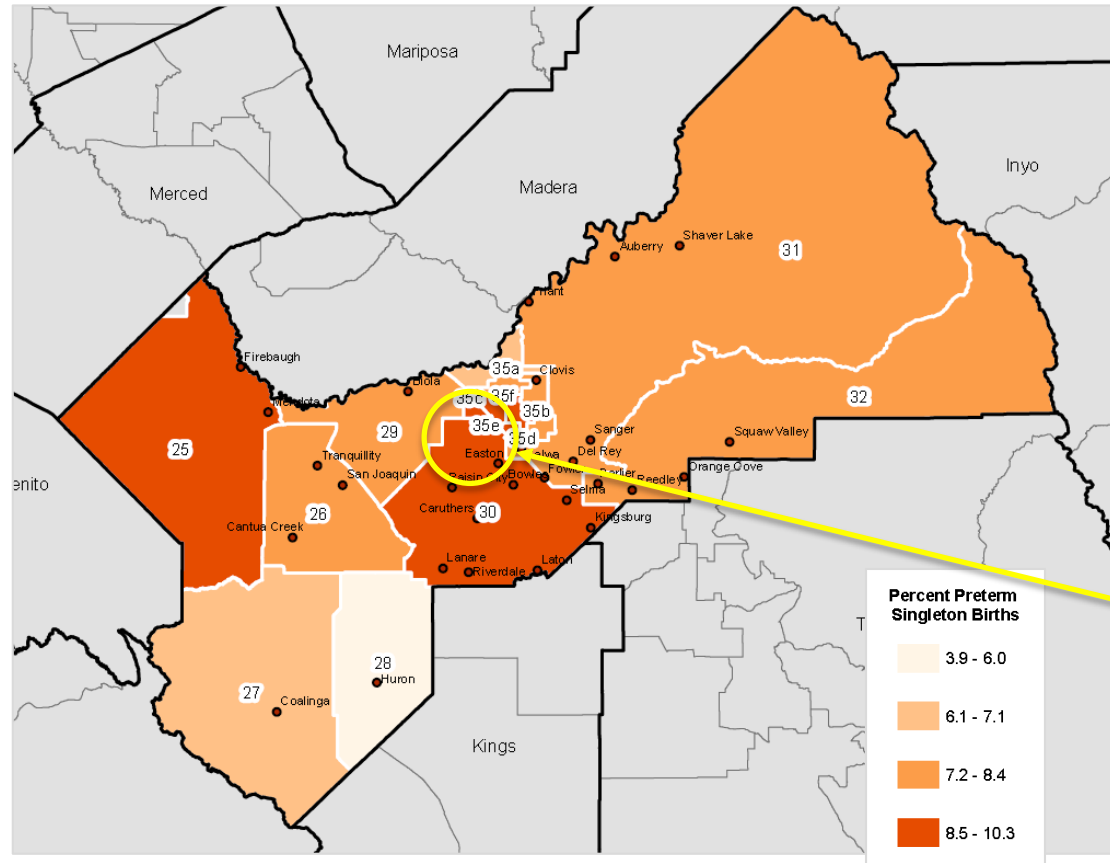
Risk among Black women in **Oakland** is not evenly distributed (potential inroads):

- Black women on Medical reporting some drug use:
 - 3 or more prenatal visits: 16.5% PTB
 - < 3 prenatal visits: 45.6%
- Black women with private insurance:
 - Hypertension is biggest driver of PTB
 - Gestational HTN: 18.3% PTB
 - Chronic HTN: 16.3% PTB
 - No hypertension: 7.1%
- Oakland inner harbor: as low as 6%
- Fruitvale area 8% overall

Slide adapted from FSG. Data source: Alameda County DPH, Percent of premature births by race and zip, Alameda County 2009-11

Disparities in Preterm Birth: Location Matters

Rate of Preterm Birth in Singletons, Fresno County (By MSSA/ Census Tract Groupings)



Rates can differ greatly within counties

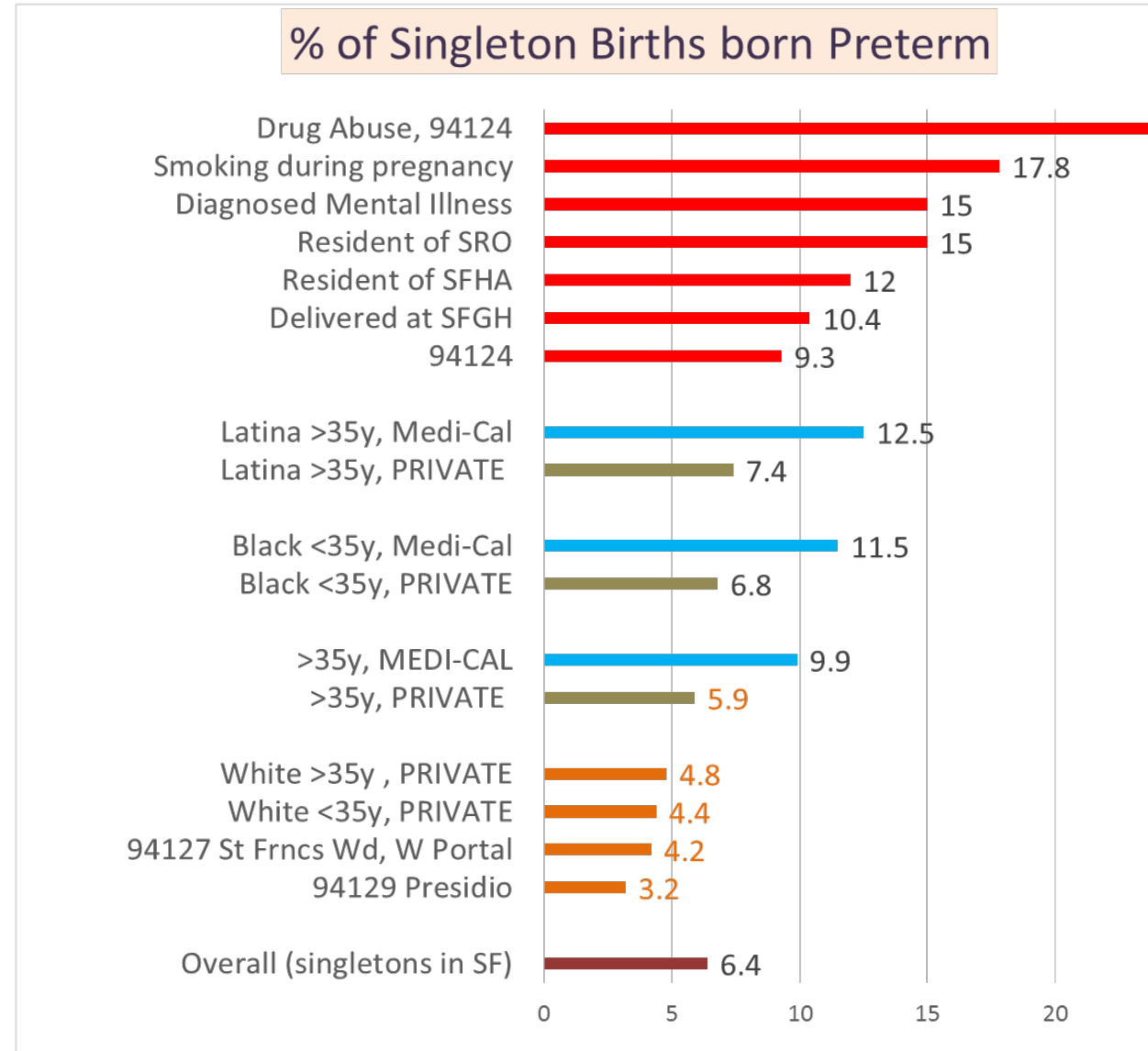
For example, in Fresno County, rates range from 6.0 to 9.9% for singletons

> 40% of all preterm births in three contiguous MSSAs in Urban Center

From California Summit on Preterm Birth, 2015

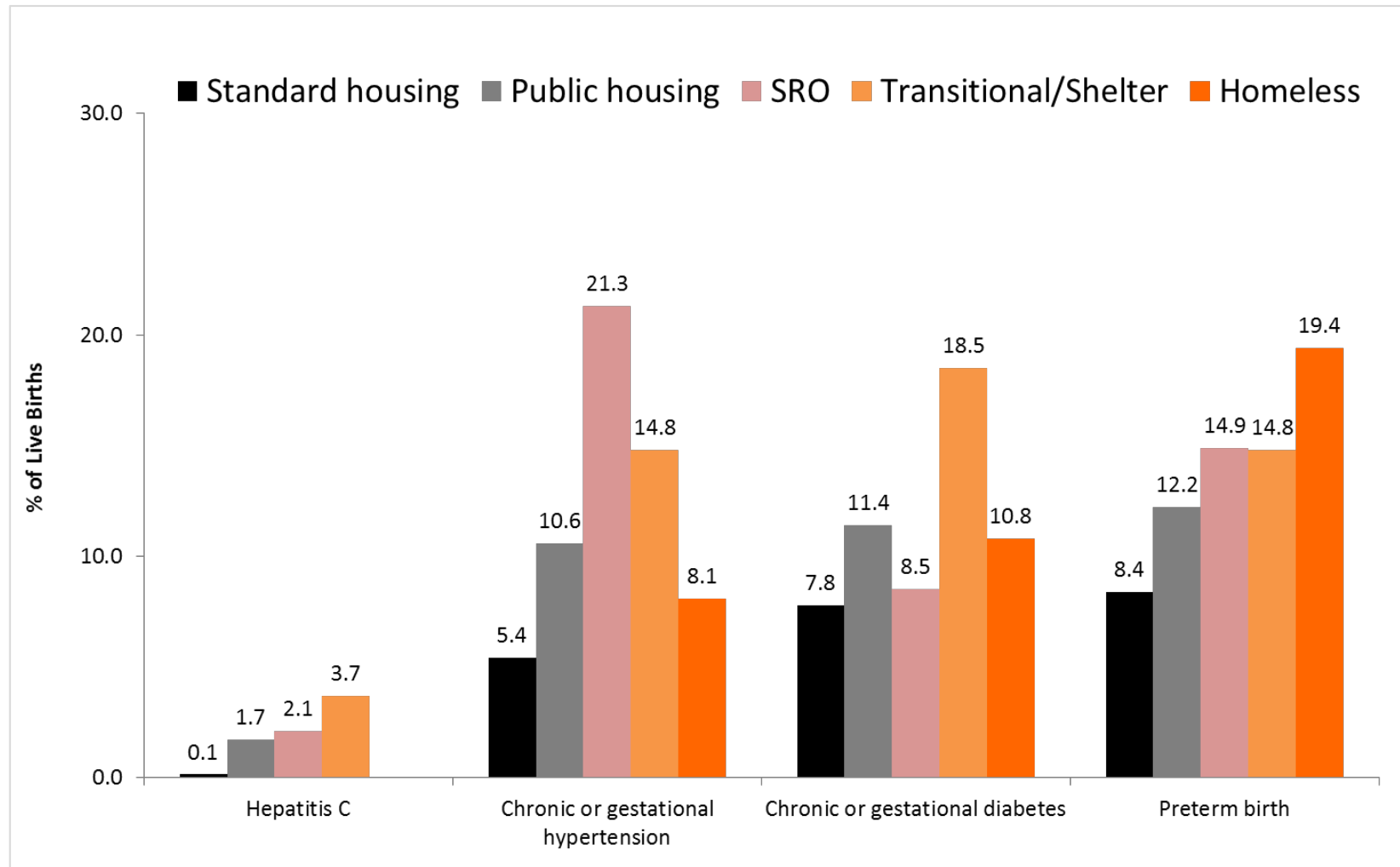
**Social
Determinants
of
Preterm
Birth**

in
San
Francisco



Data Source: Stookey, Jodi. CDPH Birth Statistical Master File for San Francisco, 2009-2012

Association of SF Housing Conditions with Maternal chronic disease and Preterm birth



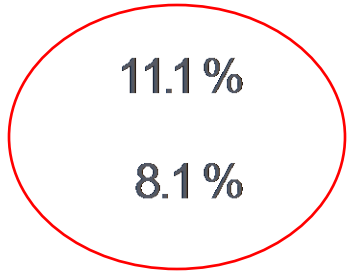
Data Source: Stookey, Jodi. CDPH Birth Statistical Master File for San Francisco, 2012

A Year in Fresno



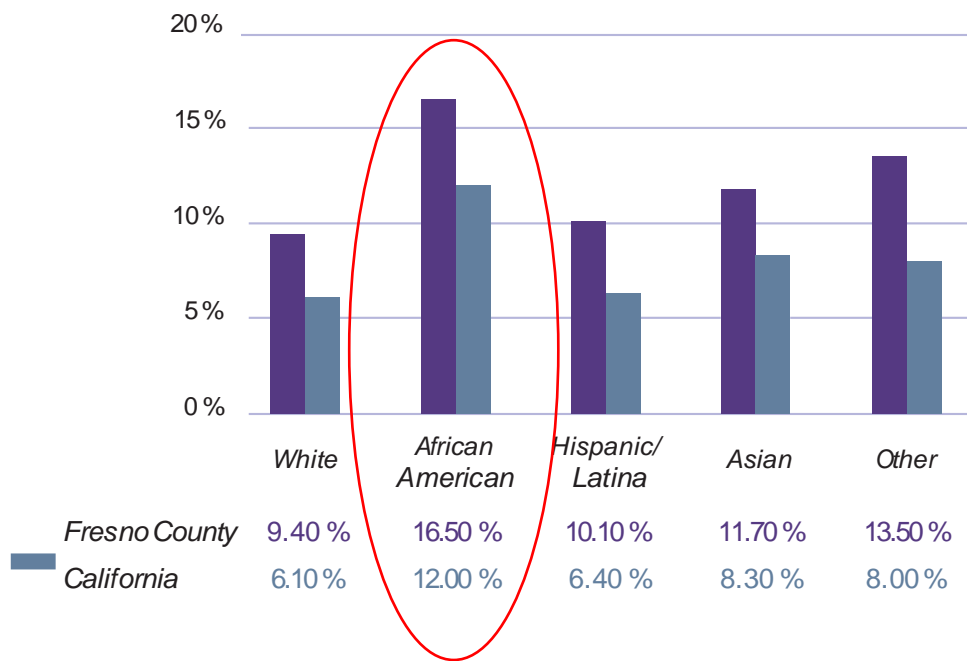
Fresno County Snapshot, 2015³

Total Population	956,749
All Births	15,357
Preterm Births (Born Before 37 Weeks)	1,702
Very Preterm (Born Before 33 Weeks)	453
Preterm Birth Rate	11.1%
California Preterm Birth Rate⁴	8.1%



Preterm Birth in Fresno County

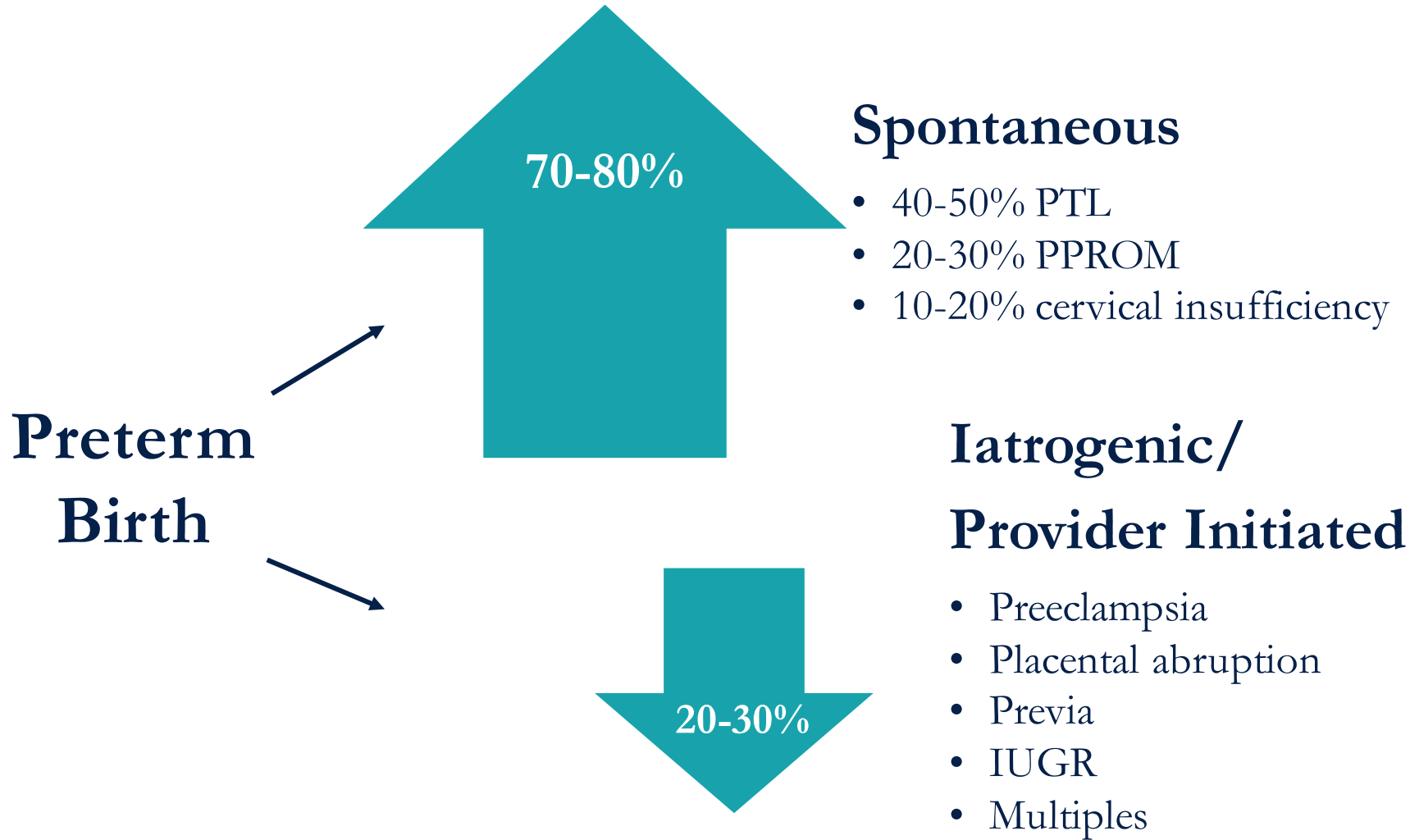
Fresno County and CA

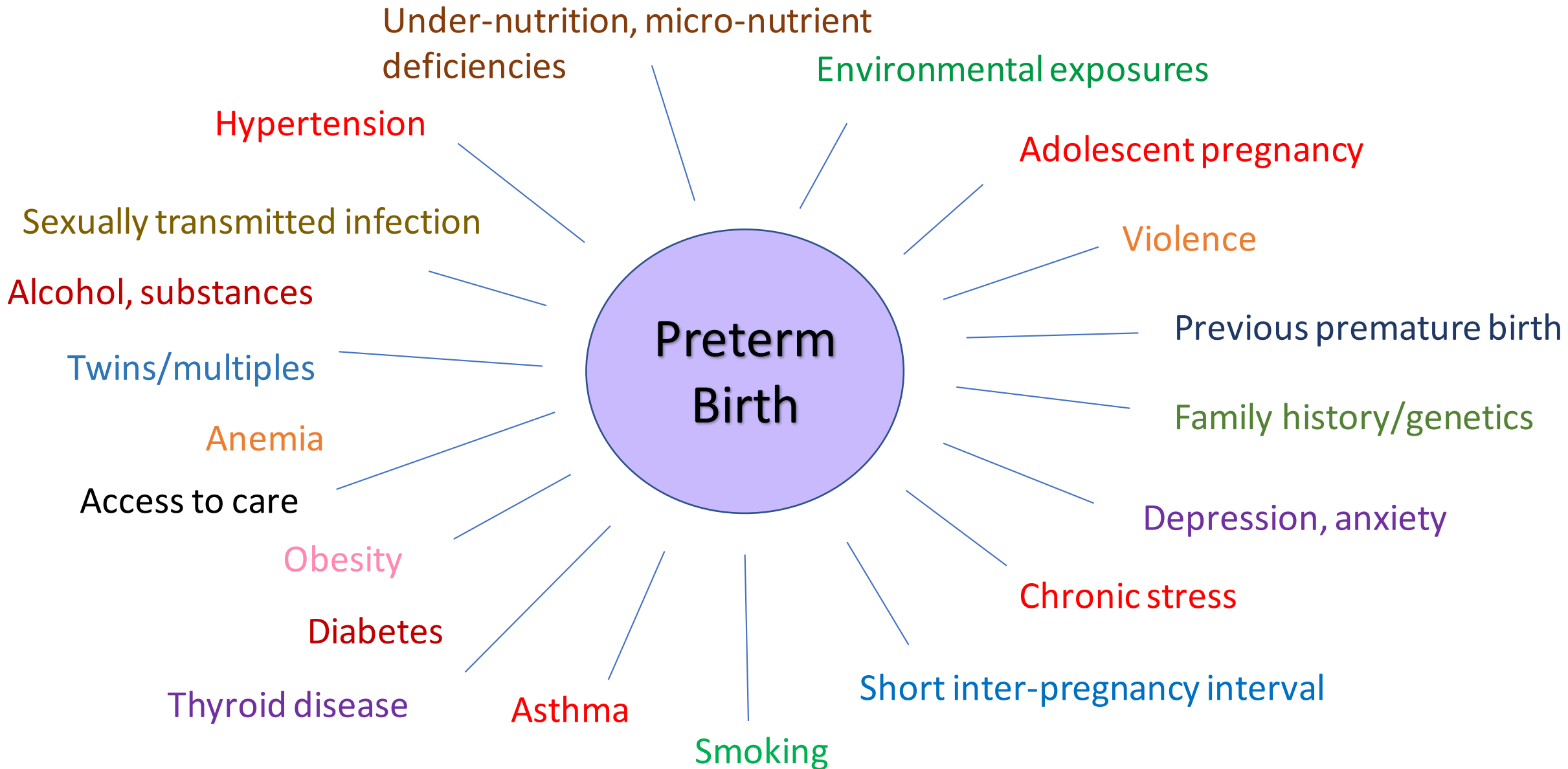


Pathogenesis of Preterm Birth

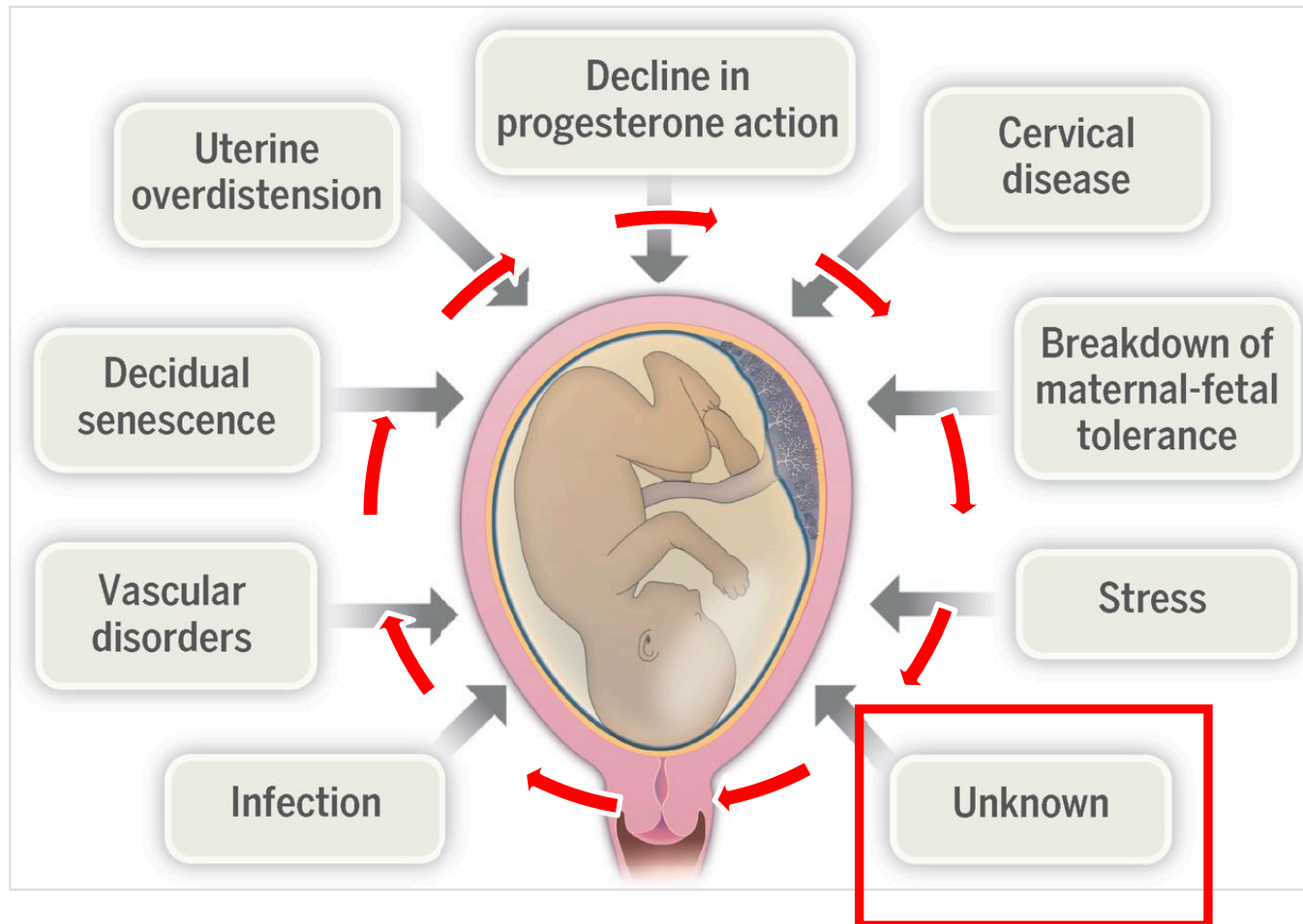


Clinical Subtypes of PTB





Suspected *Mechanisms* of Disease in Preterm Birth



4 Main Pathways

1. Infection/inflammation*
2. Decidual hemorrhage**
3. Uterine distention
4. Maternal or fetal stress

- *>40% have evidence of infection (chorioamnionitis)
- **Close to 40% of PTBs had evidence of occult decidual hemorrhage

Mechanistic differences seen by race/ethnicity

From Romero et al., 2014 Science

Pathogenesis of PTB

- Inflammation (good → bad)
- Disorders of innate immunity rather than specific bacteria
- State of normal vaginal flora at the start of pregnancy contributes to pregnancy outcome
- There is a significant racial disparity in inflammation-associated PTB, with African-Americans disproportionately affected
- Maternal psychological stress and distress has a pro-inflammatory effect (exaggerated inflammatory responses)

Risk Factors for Prematurity

- There are many risk factors for PTB
 - Some are actionable and reversible
 - Some are permanent
- **Timing:** important to identify risk factors for PTB in preconception period or early pregnancy to have chance at reducing risk (interventions across the reproductive lifecourse)
- **Public knowledge of risk factors and interventions is crucial**
 - PTB affects 1:10-12 pregnancies (vs Down syndrome, 1:300) but has remained a silent epidemic

Recurrence of PTB

Strongest risk factor for PTB is a previous PTB

- 30% recurrence after one sPTB; 60% recurrence after two
- Painless cervical dilatation (55% recurrence) vs PTL (27%) and PPROM (32%)
- Twin/multiple gestation w/ a previous history of sPTB: 67% risk of PTB (vs 20% if twins without previous PTB)
- iPTB → 25% recurrence rate (e.g., preeclampsia, growth restriction, fetal distress)
- After one PTB → risk of preE and IUGR *also* increase in next pregnancy

Interventions

- History of previous **sPTB** → weekly **17-OH Progesterone** injections (30% reduction)
- Follow cervical length → if shortens, consider **cerclage** (and switch to vaginal progesterone)
- History of previous **iPTB** → **aspirin** prophylaxis (decreases recurrent iPTB as well as sPTB)

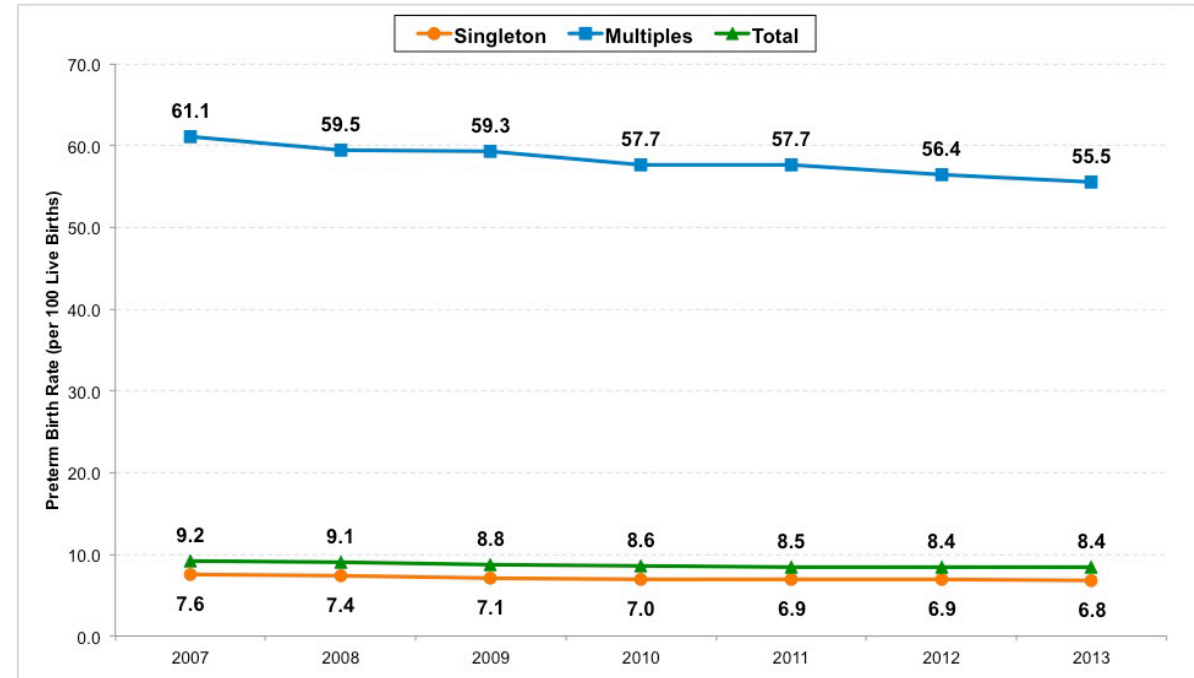
Cervical Length (ultrasound)

- The shorter the cervical length between 16-28 weeks, the higher the risk of PTB
- Cervical length screening:
 - No prior PTB (singleton) → **one-time** mid-trimester cervical length screening
 - If <25mm: start vaginal progesterone
 - (+) history of PTB (singleton) → **serial** cervical length exams (every 1-2 weeks)
 - If cervix shortens further while already on progesterone → consider **cerclage**
- If cervix is prematurely **dilated** (>1cm) → **emergency cerclage** helps increase gestation and neonatal survival



Multiple gestations

- Account for 2-3% of all births but 20% of preterm births
- ART has increased incidence of multiples → increase risk of both sPTB and iPTB
- Thought due to greater uterine distention and higher hormone levels
- **Progesterone, pessary, cerclage and bedrest** do NOT prolong gestation for twins (may make it worse!)
- Critical to **prevent and reduce** multi-fetal pregnancies, especially higher order
- **Single embryo transfer (SET)** policies have had huge impact



Chronic Disease

- Hypertension (3x), diabetes (2x)
- Renal insufficiency, autoimmune disease, anemia
- STIs and other infections
- Depression and use of SSRIs
- Smoking or substance use
- **Preconception identification and optimization (takes time) → improving maternal health before entering into pregnancy will improve pregnancy outcomes**



Interpregnancy Interval (IPI)

- Short IPI of <6 months triples risk of PTB (<34wks)
 - If previous pregnancy was preterm → even higher risk
- Spacing to at least 12 months reduces risk of PTB substantially
- MOD recommends 18 months
- **Postpartum contraceptive coverage is protective against PTB**



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Depression, anxiety, and PTSD

- Doubles risk of PTB
- Dose:Response relationship (the worse the symptoms, the higher the PTB risk)
- IPV

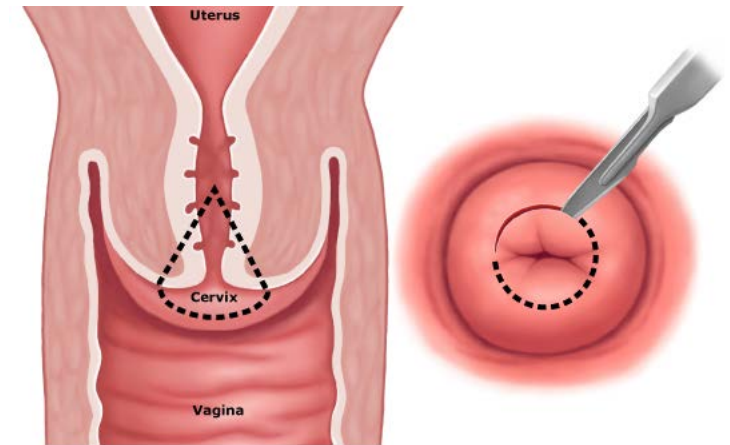
Sleep

- Nearly doubles the risk of PTB (insomnia, sleep apnea)



Previous cervical surgery (LEEP/loop excision or cold-knife cone biopsy):

- ↓ tensile strength, ↑ susceptibility to infection, ↓ cervical plasticity, ↑ scarring
- Found same increased risk of PTB among women with CIN 3 vs without CIN.
 - Suggests that it's the immunological, clinical, and social risk factors associated with CIN that put the woman at increases risk of PTB rather than the cervical surgery itself



Asymptomatic Bacteruria

- Undetected/untreated UTIs can result in pyelonephritis, bacteremia, and PTB
- For patient with sickle cell trait, recurrent UTIs, diabetes, or renal disease, important to check first trimester urine culture and repeat culture each trimester



Periodontal Disease

- Epidemiologically linked but not causally related (yet)
- Periodontal disease also a marker of people with genetic predisposition to exaggerated local or systemic inflammatory response to bacteria
 - Vaginal bacteria may similarly stimulate an enhanced production of cytokines → PTB
 - However, periodontal therapy not shown to decrease PTB rates (may be an issue of timing and choice of therapy)

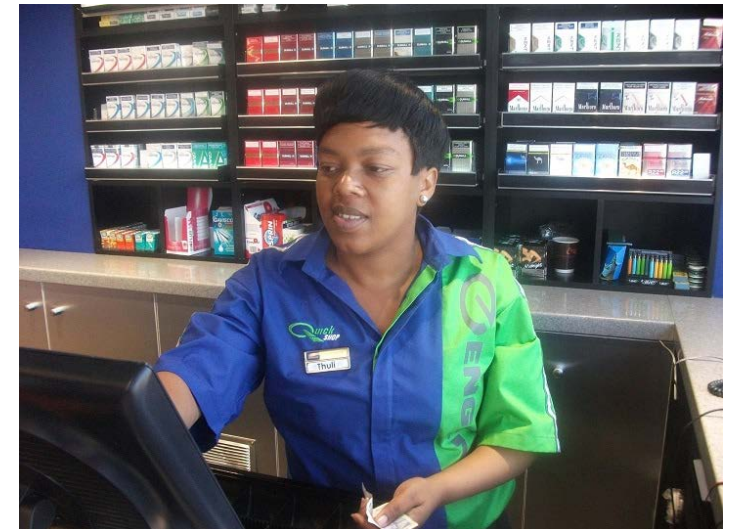


STIs

- Bacterial Vaginosis (BV): asymptomatic women who are screened for BV and treated show a modest effect of PTB reduction
- Studies flawed: confounded by insufficient treatment course, non-protocol antibiotics, recolonization after treatment, failure to culture fastidious bacteria

Occupational

- European study showed women working $>42\text{h}/\text{week}$, stood $>6\text{hr}/\text{day}$, or had low job satisfaction were all at increased risk of PTB
- Never been studied in RCTs
- Very dependent on mother's ability to handle stress & fatigue (resilience)
- “Healthy worker” effect: someone who is in better health at preconception is more likely to withstand harder work conditions
- **Do consider workplace conditions among women at high risk for PTB**
- **Stress reduction (& desirable societal goals):**
 - Paid maternity leave
 - Guaranteed job protection
 - Regulation of hazardous work conditions



Smoking

- Direct effect on PTB risk
- Also increases complications of pregnancy including abruption, placenta previa, and IUGR, all of which may lead to iPTB.
- **Medicaid programs** are required to cover smoking cessation counseling and drug therapy for pregnant women without cost sharing, in the hopes of increasing utilization of services (policy as intervention)



Substance misuse

- Higher rate of (+)urine tox screens among patients w/ PTB (17% vs 2.8% in term births)
- Cocaine most significantly increases PTB risk
- 60% of (+)tox screens are due to cocaine
- With use of multiple substances, risk of PTB increases by 30-60%
- Substance abuse programs and behavioral health services critical & most optimal in **preconception period**



Diet

- Undernutrition/malnutrition **at time of conception** is most important in terms of PTB risk
 - Accelerates Hypothal-pituitary-adrenal axis → results in precocious fetal cortisol surge (→PTB)
- Insufficient (or too much) weight gain in pregnancy increases risk of PTB
- Obese pregnant women tend toward higher iPTB rates due to maternal complications
- Weight loss in preconception has high ROI for pregnancy and health overall
- **WIC shown to be protective for PTB (20% risk reduction)**



Stress

- Maternal or fetal stress activates placenta to produce more CRH → ↑prostaglandin production (→ contractions)
- **Maternal psychosocial stress doubles risk of PTB**
- Challenging to study:
 - Difficult to define and measure maternal stress
 - Assessed at different time points throughout the pregnancy
 - No differentiation b/w acute and chronic stressors
 - Discordant baseline characteristics in populations studied

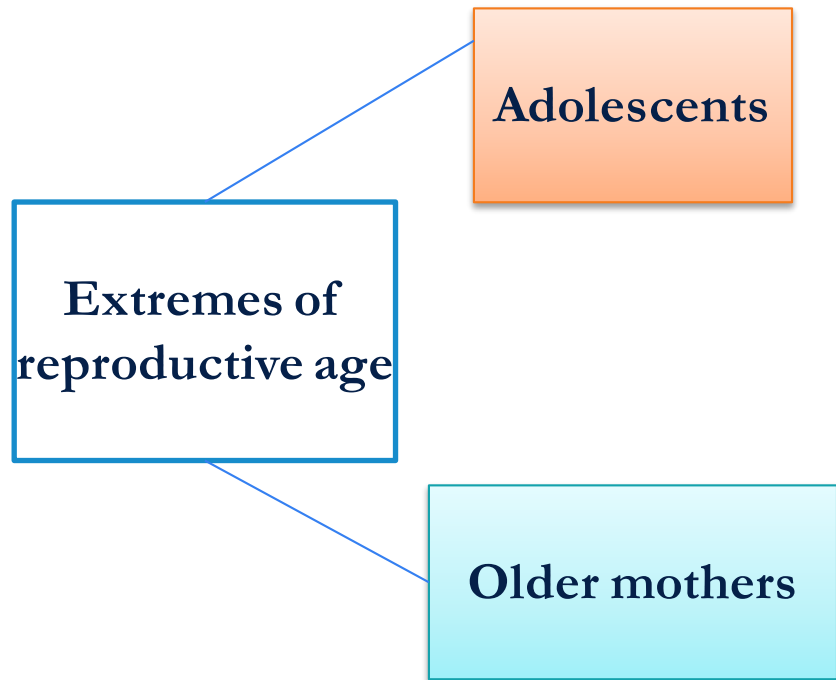


Suboptimal Prenatal Care

- Consistent risk factor for PTB : causal or a marker for other factors that could increase risk of PTB?
- Unethical to do RCT of PNC vs no PNC (can only compare *standard* care with *enhanced care* models)
- Highly dependent on **perceived** quality of care and sense of respect and trust/authentic relationships—**respectful maternity care**
- Dose: Response relationship
- **Nurse Family Partnership protective** (8.7% clients vs 12.3% matched controls)
- **Group prenatal care: profound effects**
 - 33% reduction in PTB among ALL women (not just those who have had a previous PTB)
 - 42% reduction in PTB among Black women participants
 - At one year postpartum, 15 lb weight-loss maintained; doubled rate of breastfeeding, halved rates of postpartum STIs & depression/anxiety – major markers of future health and impact on **NEXT** pregnancy (not yet studied...)
 - What's the secret sauce?



Age



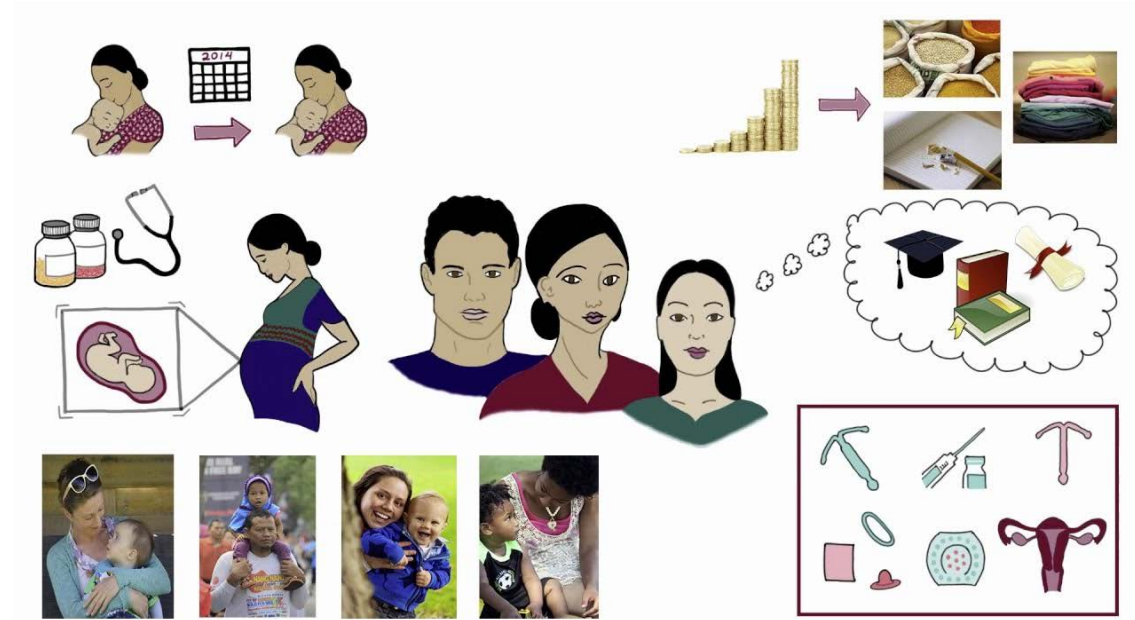
- Physiologic immaturity
- SES factors

Both have high rates of unintended pregnancy

- More chronic diseases
- More obesity

Family Planning

- >40% of PTBs in the US are the result of an unintended pregnancy
- Esp important among mothers experiencing significant stress
- CO showed an historic 12% ↓ PTB rates after implementation of statewide LARC program
- **Reproductive justice lens critical:** focus should not be on “increasing LARC implementation” but on increasing access to and uptake of quality, personalized family planning counseling



Genetics of PTB

- Genetic polymorphisms have been discovered that contribute to length of gestation and likelihood of PTB
- If mom herself born preterm, higher likelihood she'll deliver preterm
- If your sister delivers preterm, your risk of PTB increases by 80%
- Identical twins have higher PTB concordance than fraternal twins
- **Although PTB-susceptibility genes identified, epigenetic/gene-environment interactions more important**



Race/ethnicity

- **Black women at double the risk** of PTB overall
- Recurrence rates are 60% higher among Black women
- Mechanistically, we see more **decidual hemorrhage/abruption** among whites vs higher state of **inflammation/reactivity** among Blacks
- Polymorphisms for genes regulating **innate immunity** appear to play a role
 - Race/ethnicity influences a woman's microbiome and the impact of her vaginal bacteria on risk of PTB
- **RACISM, CHRONIC STRESS: epigenetic, environmental, structural, local and societal factors** (MIHA, Braveman 2017)

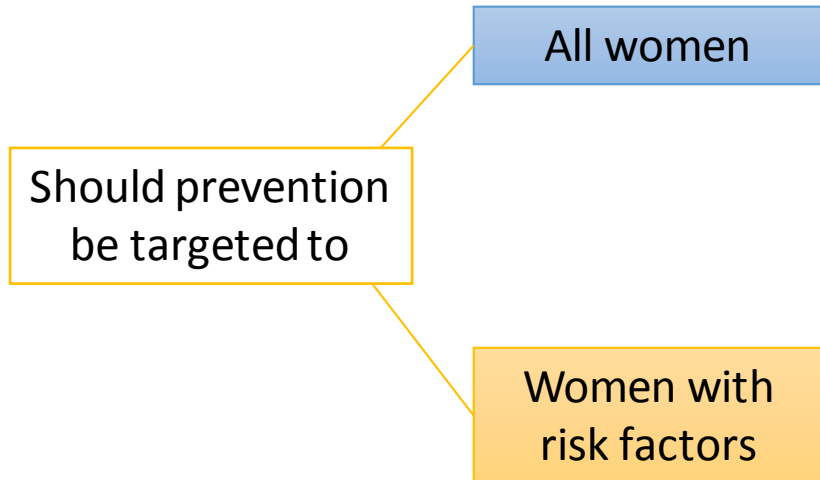


Prevention of PTB has been elusive:

- 60% of preterm births occur in women with no risk factors
- Mechanisms remain unclear
- No adequate animal model for PTB

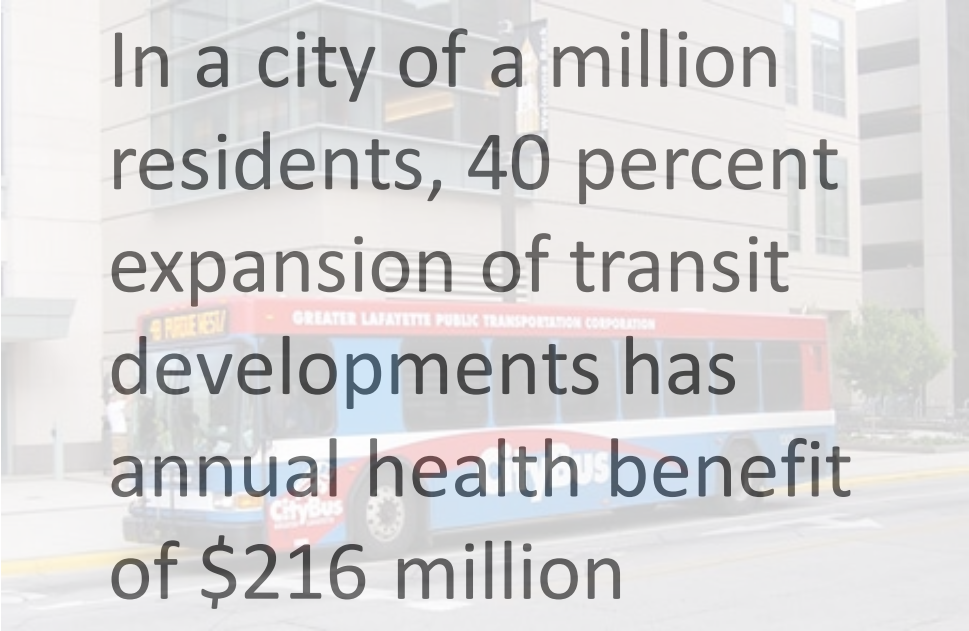


Interventions

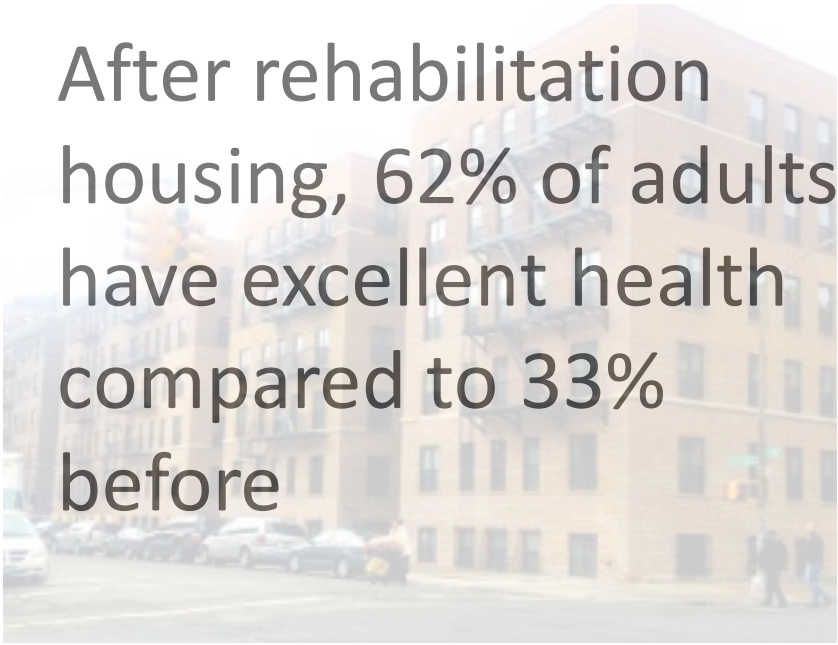


- Community mobilization and education
- Smoking cessation
- Early diagnosis of HTN, DM, infections, etc

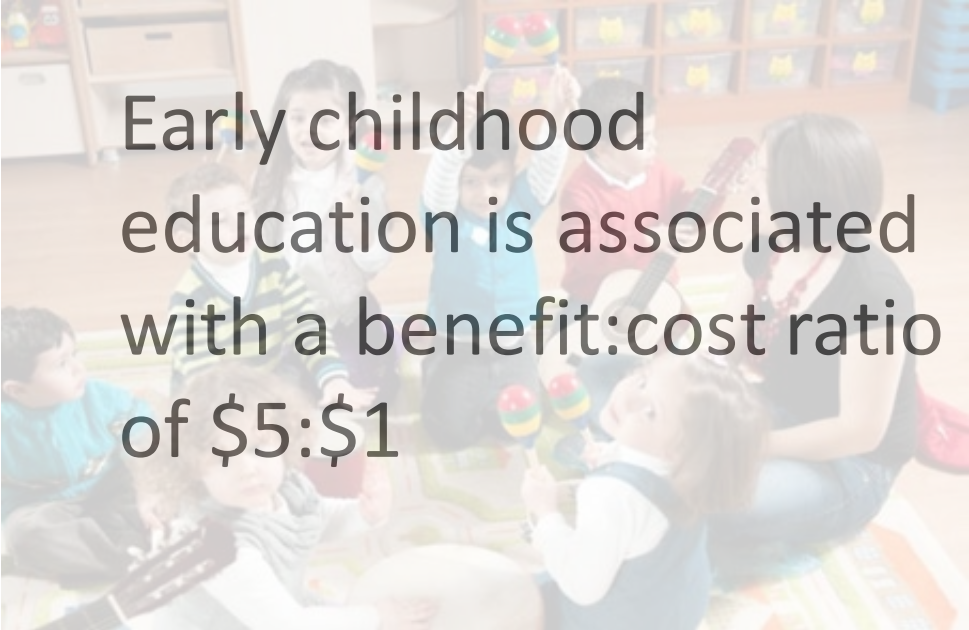
- Previous PTB
- Short cervix
- Smoker, substance use
- Multiple gestation
- HTN, DM
- Short IPI
- Women of color



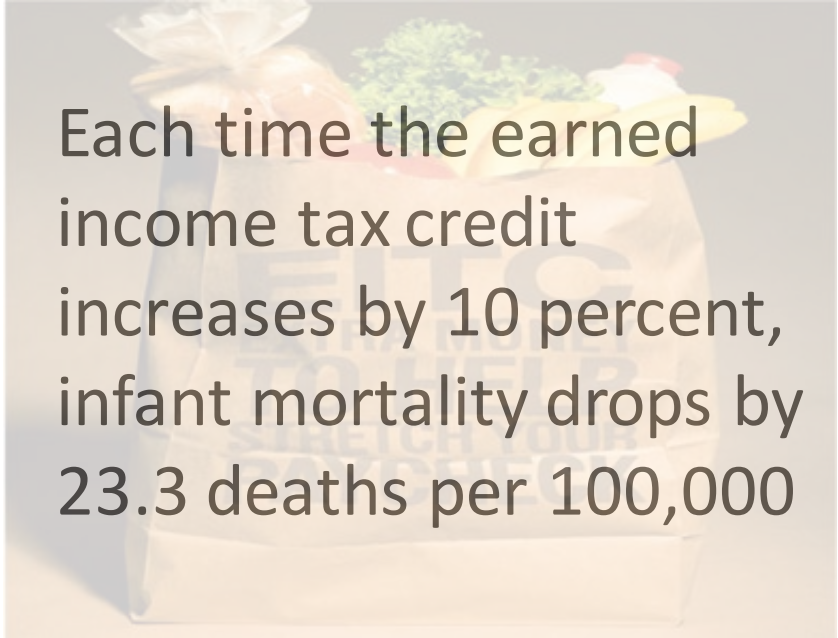
In a city of a million residents, 40 percent expansion of transit developments has annual health benefit of \$216 million



After rehabilitation housing, 62% of adults have excellent health compared to 33% before



Early childhood education is associated with a benefit:cost ratio of \$5:\$1



Each time the earned income tax credit increases by 10 percent, infant mortality drops by 23.3 deaths per 100,000

Examples of policy opportunities to reduce the burden of preterm birth

- MediCal-covered pregnancy Doula program
- Ensure access to high quality family planning services (e.g., FQHCs, same-day, etc)
- Focus on adolescents (preconception health, education, quality FP)
- Prioritize emergency housing for pregnant women experiencing housing instability
- Expanding paid parental leave
- Better breastfeeding support policies and investment in breast milk banks
- Improve access to mental health services for pregnant women and early parenting education/support services

Policy
Advocacy



The California Preterm Birth Initiative (PTBi-CA)



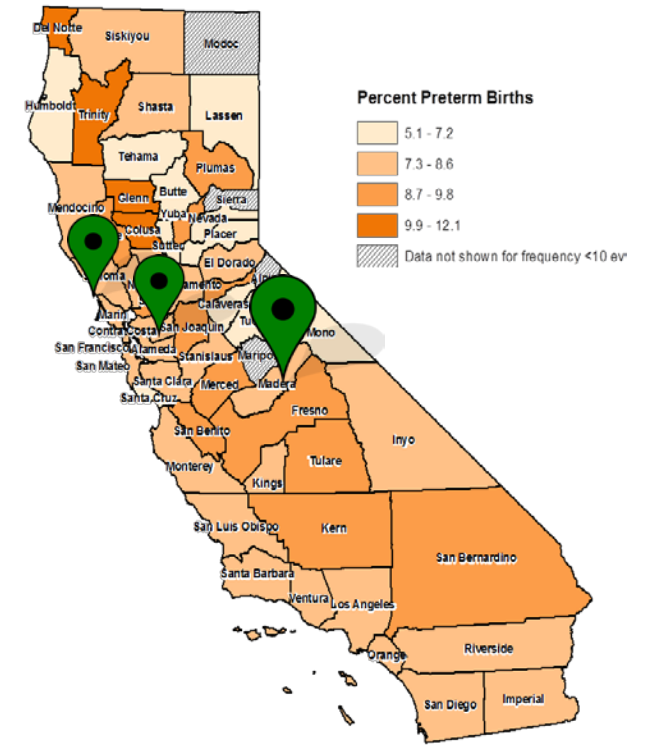


California

Preterm Birth Initiative



University of California
San Francisco



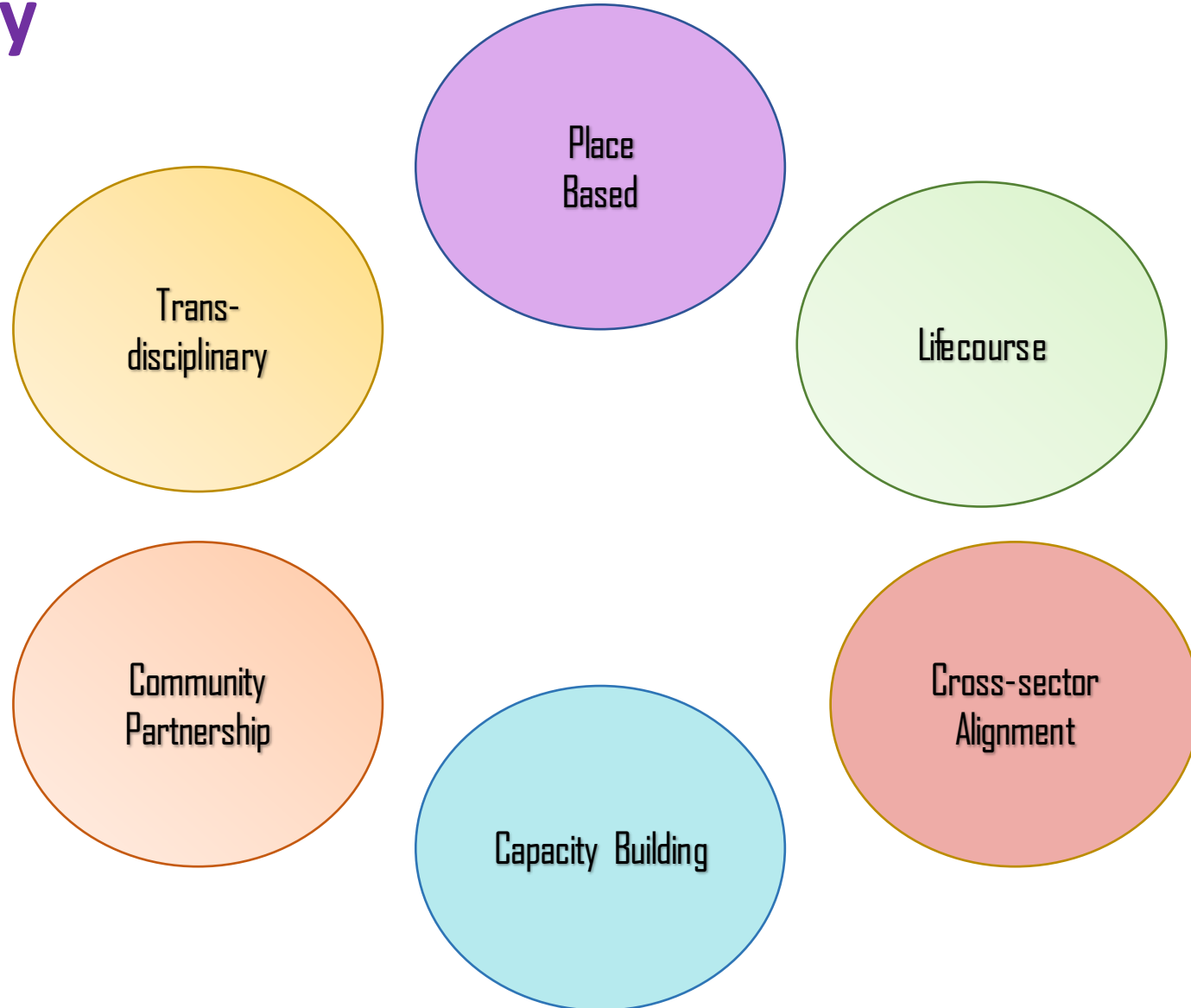
PTBi-California: Goals

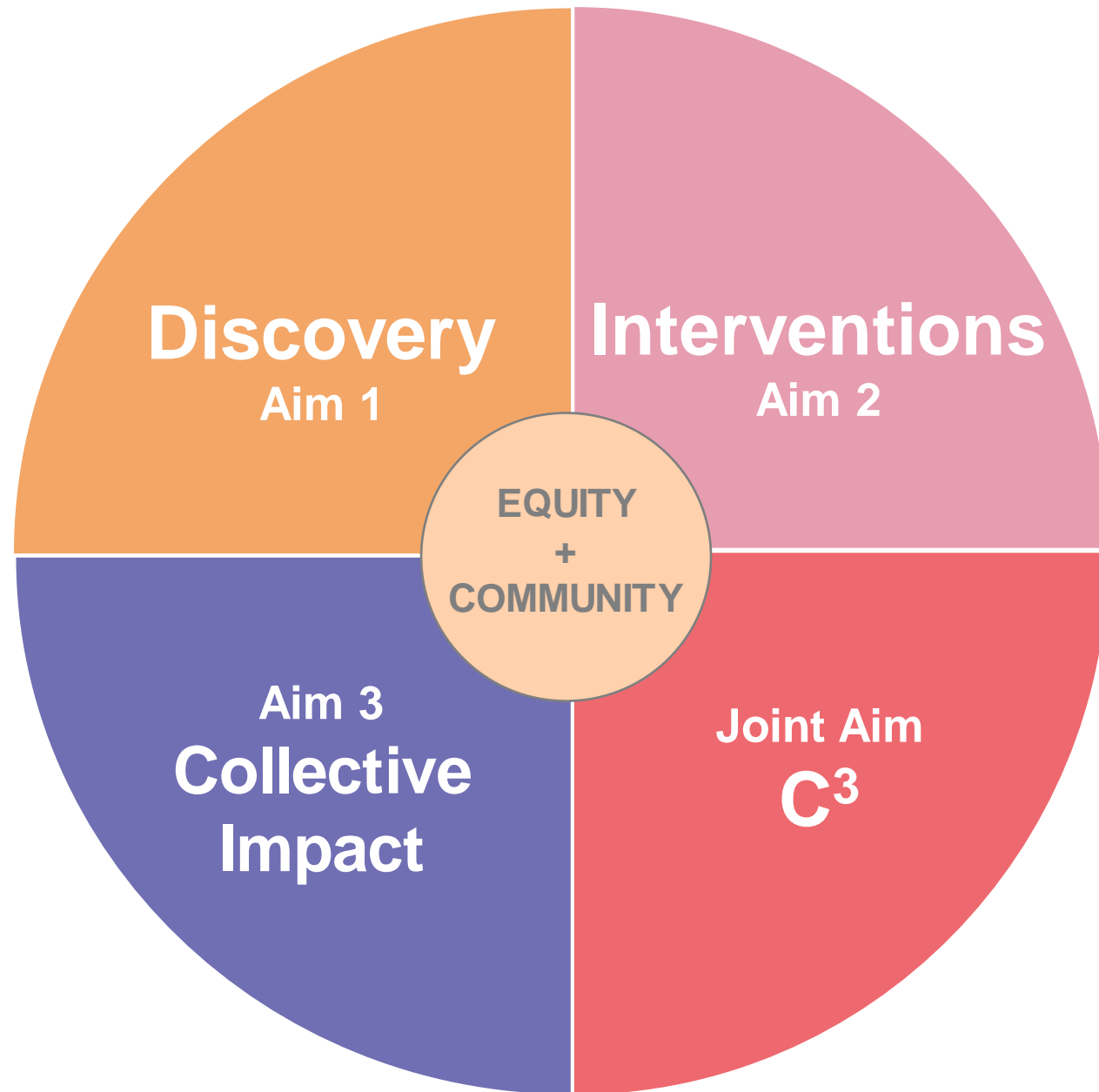


- To develop an **infrastructure** that can support and catalyze **transdisciplinary thinking** (cell-to-society) to support innovation in the preterm birth field
- To **transform the research enterprise** through a **place-based, community-engaged and patient-centered approach**, accounting for real-world contexts and “users”



Doing Research Differently





California

Preterm Birth
Initiative



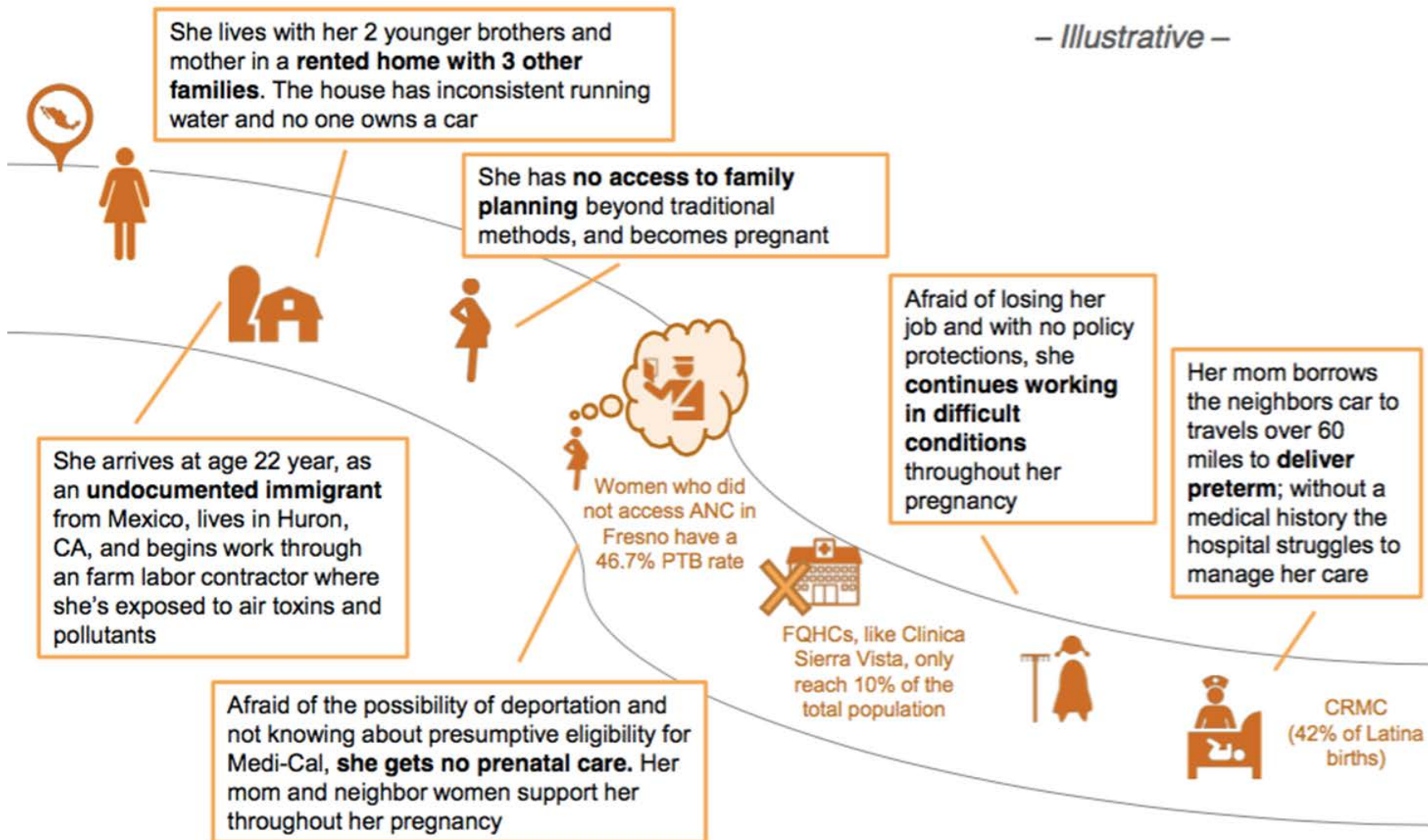
University of California
San Francisco

EQUITY
+
COMMUNITY

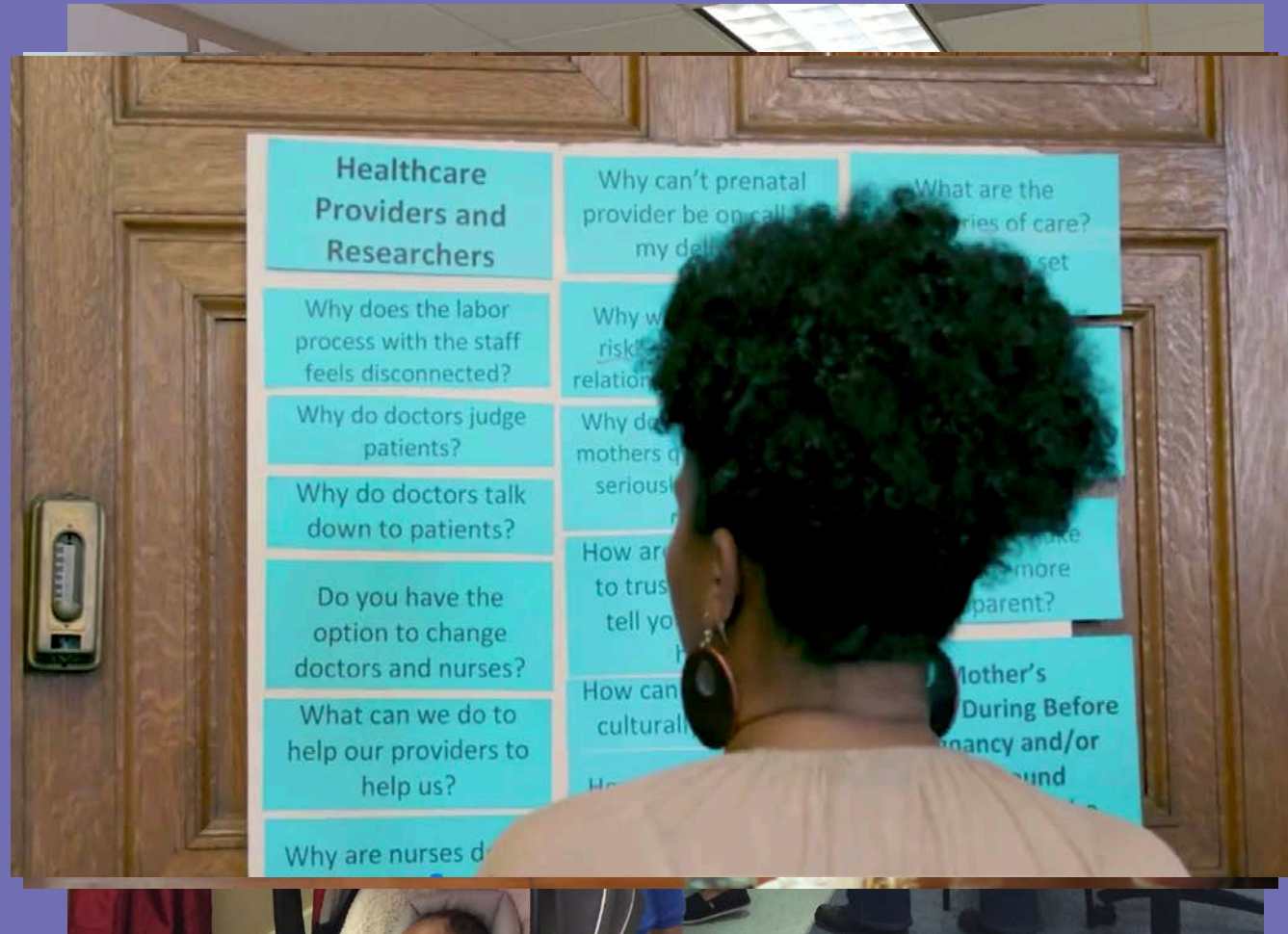


The journey of a woman at risk in Fresno

– Illustrative –



Research Prioritization



Healthcare Providers and Researchers

Why does the labor process with the staff feels disconnected?

Why do doctors judge patients?

Why do doctors talk down to patients?

Do you have the option to change doctors and nurses?

What can we do to help our providers to help us?

Why are nurses d

Why can't prenatal provider be on call my del

Why w risk relation

Why do mothers d serious

How ar to trust tell yo

How can cultural

What are the series of care? set

How can we make more parent?

Mother's During Before pregnancy and/or

How can we



LEAST IMPORTANT

LEAST IMPORTANT

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IMPORTANT

HIGH EXCU
Speak up





Research Abstracts

Summaries of ongoing research projects across the Preterm Birth Initiative.

PRECONCEPTION

Perceptions and the availability of postpartum contraception following preterm birth

H. Thiel de Bocanegra¹, K. Saylor¹
¹Department of Obstetrics, Gynecology & Reproductive Sciences, UCSF

Plain Language Summary: We have conducted in-depth interviews with women in San Francisco, Oakland, and Fresno who have had a preterm birth to identify their preferences for contraception services and referrals after delivering preterm. These data will be accompanied by an assessment of the challenges and barriers to effective contraception counseling, in order to make recommendations to providers and maternity facilities.

Background: Short inter-pregnancy intervals lead to adverse maternal and

discharge from the maternity ward and transition to postpartum care to meet a woman's contraceptive preferences.

Methods: In this mixed method approach, we used data from the California Medical Quality Care Collaborative to describe 2015 hospital characteristics, mother's demographics and medical conditions, and birth outcomes of all maternity wards. We conducted provider surveys with 18 medical directors and nurse managers about hospital protocols and clinician practices. Finally, we interviewed women who had a preterm birth. We will report findings of the first 20 interviews. Interviews were audio recorded, transcribed and analyzed using AtlasTi8 software.

Results: Hospitals vary widely in their administrative structures, volume of births and mother's medical characteristics. Women suggested that presenting contraceptive health education over several prenatal visits, framing the discussion on

PRECONCEPTION

What do women want to know about contraception after childbirth, and how do they want to receive this information? Providing patient-centered care to support informed decision making

W. Wilson¹, J. Fitzpatrick¹, S. Azam², K. Holt¹, C. Dehlendorf^{1,2,4}

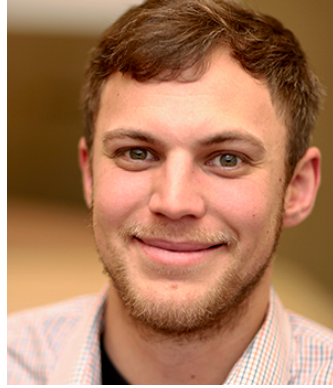
¹Department of Family and Community Medicine, UCSF; ²ACCESS Women's Health Justice; ³Department Obstetrics, Gynecology & Reproductive Sciences, UCSF; ⁴Department of Epidemiology & Biostatistics, UCSF

Plain Language Summary: This project seeks to understand women's experiences and preferences related to contraceptive counseling before and after giving birth.



Research with the Community





Discovery
Aim 1

Joint
Aim
C3

Persistent Pulmonary Hypertension of the Newborn in Late Preterm and Term Infants in California

Original Article


... PhD, MS,^{b,c} Rebecca J. Baer, MPH,^{c,d}

Risk of preterm birth among women using drugs during pregnancy with elevated α -fetoprotein

R J Baer , C D Chambers, K K Ryckman

RESEARCH

Preterm birth: the role of knowledge transfer and exchange

Hacsi Horvath^{1,2,3*} , Claire D. Brindis^{2,4}, E. Michael Reyes⁵, Gavin Yamey^{3,6}, L...
Transfer and Exchange (KTE) Working Group

Original Research

Recurrence of Preterm Birth and Early Term Birth

Juan Yang, PhD, Rebecca J. Baer, MPH, Vincenzo Paul Chung, MD, Tumaini Coker, MD, Robert J. Miriam Kuppermann, PhD, Louis J. Muglia, MD, Kelli Ryckman, PhD, Gary M. Shaw, DrPH, Davi...

Risk of recurrent preterm birth among women according to change in partner

Rebecca J. Baer , Juan Yang / Christina D. Chambers / Kelli K...
Audrey F. Saftlas / Vincenzo Bernholte...
David K...

Genetic Associations with Gestational Duration and Spontaneous Preterm Birth

G. Zhang, B. F...
N. Litterman, P...
A.R. Chavan, G.P...
M. Rämet, V. S...
K.K. Ryckman, J...
E.A. Nohr,

Original Research

Sleep Disorder Diagnosis During Pregnancy and Risk of Preterm Birth

Jennifer N. Felder, PhD, Rebecca J. Baer, MPH, Larry Rand, MD, Laura L. Jelliffe-Pawlowski...
and Aric A. Prather, PhD

Risk of preterm birth by subtype among Medi-Cal participants with mental illness

An abstract of these findings was presented as a poster at the 36th annual pregnancy meeting of the Society of...
...Fetal Medicine, Feb. 1-4, 2016, Atlanta, GA.

Original Article

Inflammatory biomarkers and spontaneous preterm birth among obese women

Matthew B. Wallenstein, Laura L. Jelliffe-Pawlowski, Wei Yang, Suzan L. Carmichael, David K. Stevenson,
Kelli K. Ryckman & ...show all

Pages 3317-3322 | Received 15 Sep 2015, Accepted 20 Nov 2015, Published online: 23 Dec 2015

ORIGINAL ARTICLE

Genetic Associations with Gestational Duration and Spontaneous Preterm Birth

Survival and Major Morbidity of Extremely Preterm Infants: A Population-Based Study

James G. Anderson, MD,^a Rebecca J. Baer, MPH,^b J. Colin Partridge, MD, MPH,^a Miriam Kuppermann, PhD, MPH,^c
Linda S. Franck, RN, PhD,^d Larry Rand, MD,^c Laura L. Jelliffe-Pawlowski, PhD, MS,^e Elizabeth E. Rogers, MD^a



SOLARS



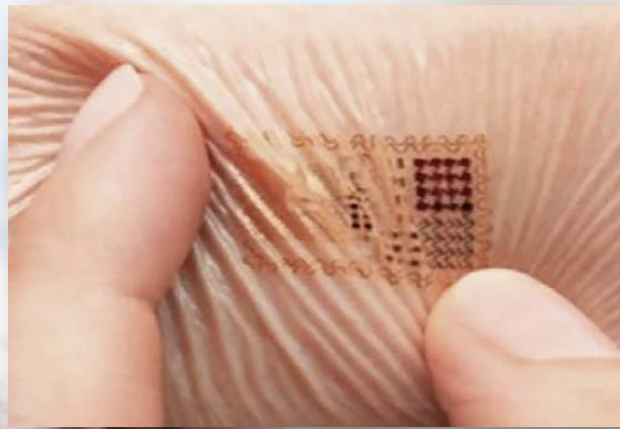
Discovery
Aim 1

Preconception & Prenatal



Interventions
Aim 2

Postnatal



Interventions
Aim 2

Family Integrated Care Model



THE WALL STREET JOURNAL.







HEALTH & WELLNESS

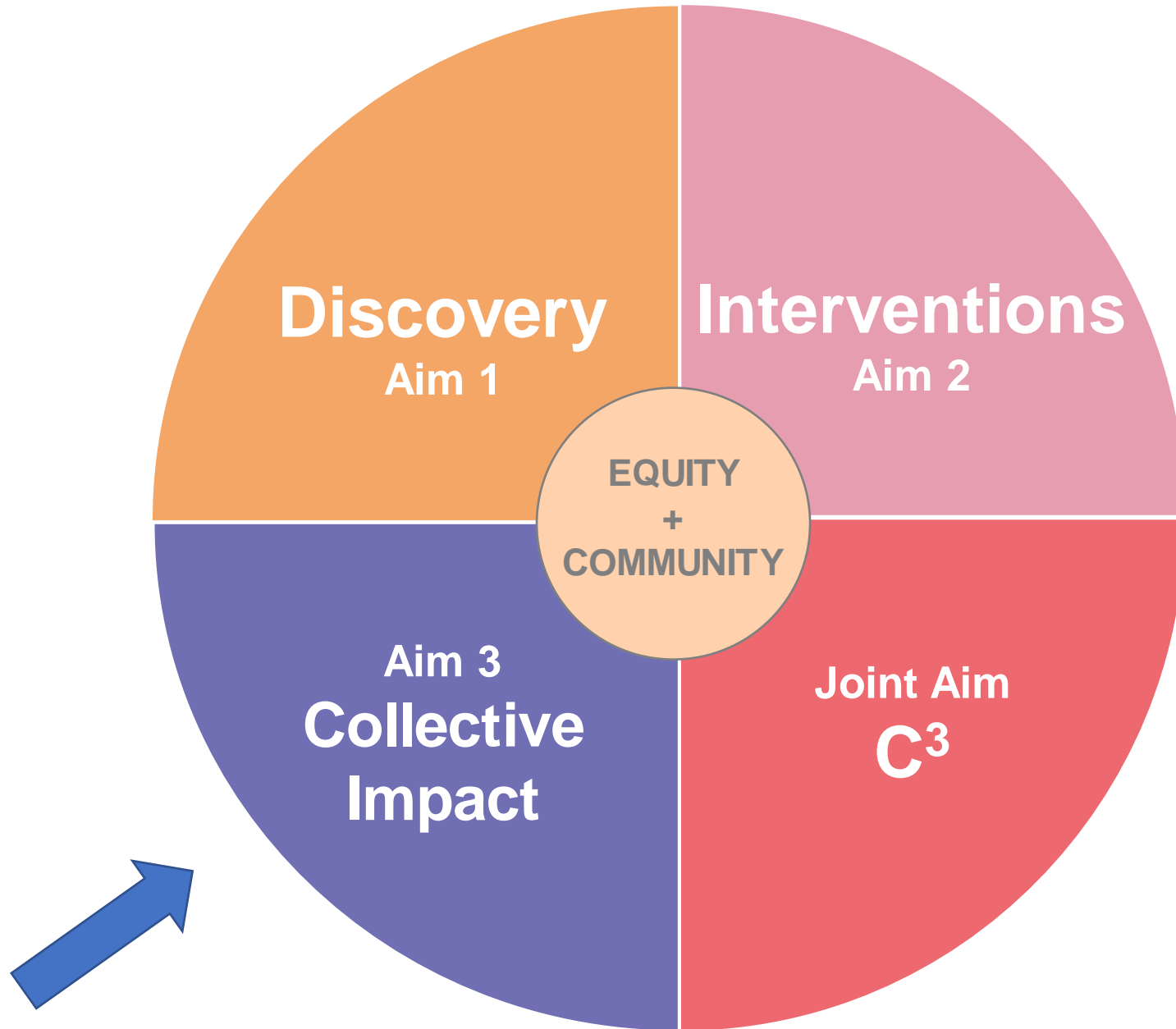
What Parents Can Do to Help Premies

Hospitals are enlisting moms and dads to work full-time with their premature babies in the NICU

<http://www.wsj.com/articles/what-parents-can-do-to-help-preemies-1428940972>

Potential outcomes

For the Baby	For the Parent	For the Hospital
 Weight gain	 Stress	 Length of stay by 2 days
 Complications at discharge	For the Care Team  Satisfaction	 Est. \$400M in hospital costs/yr



California

Preterm Birth
Initiative



University of California
San Francisco

Fresno PTBi Collective Impact: Leaders at the Table



Faith in the Valley

Mothers With Lived Experience



Nicole Hutchings



Niecia Harris



Kristi Hernandez-Barrientez



Andrea Powell



reclaim. restore. equip. repeat.



Achieving large-scale change through Collective Impact

Common Agenda	<ul style="list-style-type: none">• Common understanding of the problem• Shared vision for change	
Shared Measurement	<ul style="list-style-type: none">• Collecting data and measuring results• Focus on performance management• Shared accountability	
Mutually Reinforcing Activities	<ul style="list-style-type: none">• Differentiated approaches• Willingness to adapt individual activities• Coordination through joint plan of action	
Continuous Communication	<ul style="list-style-type: none">• Consistent and open communication• Focus on building trust	
Backbone Support	<ul style="list-style-type: none">• Separate organization(s) with staff• Resources and skills to convene and coordinate participating organizations	



Healthy Babies, Strong Families

Fresno County Preterm Birth Initiative · Strategic Blueprint 2017/2018

November 17, 2017

PTBiFresno.org



7% by
2025

Fresno County Preterm Birth Initiative
in partnership with
UCSF California Preterm Birth Initiative

Thank You!

- It definitely takes a village!
- Every child deserves an equal chance at a healthy start

www.pretermbirth.ucsf.edu

www.PTBiFresno.org

#HealthyBabiesStrongFamilies







Focus areas and cross-cutting strategies

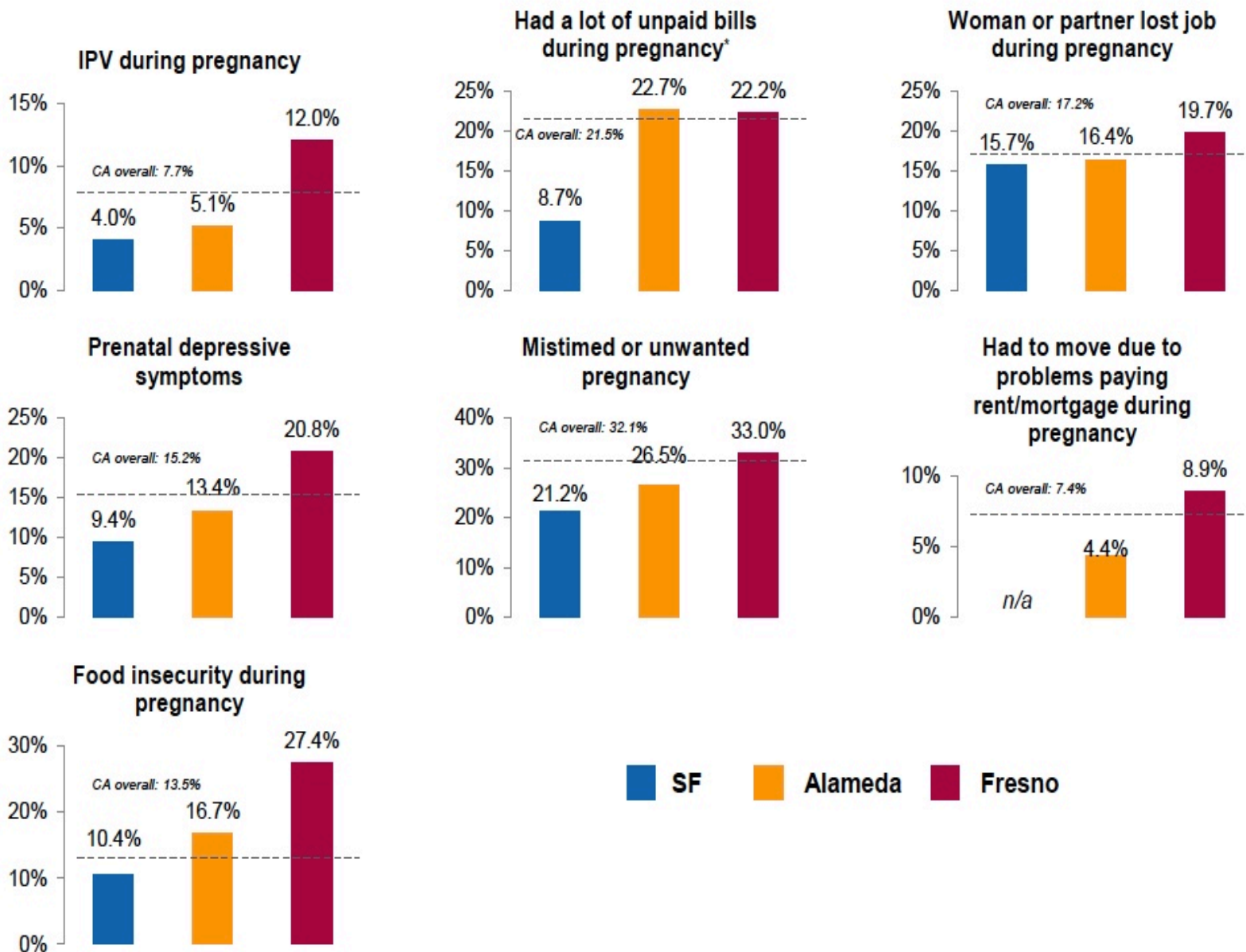
Focus areas:



Cross-cutting strategies:



Prenatal data from the MIHA survey reaffirms the high levels of risk factors in Fresno in particular



Postnatal data from the MIHA survey reaffirms the high levels of risk factors in Fresno in particular

