Environmental Contaminants in Pregnancy and Risk for Adverse Developmental Outcomes

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Air Pollution in Pregnancy and Early Life

- Pre-conception, gestation, and the first 2 years of postnatal life are periods of rapid development and growth shown to be especially vulnerable periods for exposures to environmental contaminants such as air pollution
- Ambient air pollutant exposures are associated with adverse perinatal outcomes, and later respiratory, cardiovascular, and neurodevelopmental outcomes in children

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Wildfires Events (WFE) are an Increasing Threat to Health

- Longer, more severe wildfire seasons, more smoke days
- Several of the largest and most destructive fires in last several years
- Air Quality Index (AQI) at hazardous levels for weeks with highest fine particulate matter ($PM_{2.5}$) concentrations ever recorded
- Wildfire smoke associated with significant respiratory and cardiovascular morbidity, and 339,000 premature deaths each year globally
- Urban wildfire smoke greater concern because in addition to combustion of organic material, building construction materials and interior furnishings (e.g. solvents, glues, metals, formaldehydes, and halogens) may release toxic volatile organic compounds during high temperature combustion
- Hundreds of thousands of pregnant women affected across CA

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Gestational Health Effects of Wildfires

- Smoke exposure leads to black carbon on fetal side of placenta (Bove et al 2019)
- Components of smoke (PM, PAH) can trigger inflammatory damage to the blood supply impairing placental development and function, and consequently compromising fetal growth
- Could be synergistic developmental effects of airborne pollutants when combined with material hardship and stress; affect overlapping pathways, e.g., pro-inflammatory cytokines
- Environmental impacts on epigenetic reprogramming during early pregnancy could have long-term effects
  Barker's 'fetal origins of adult disease' hypothesis

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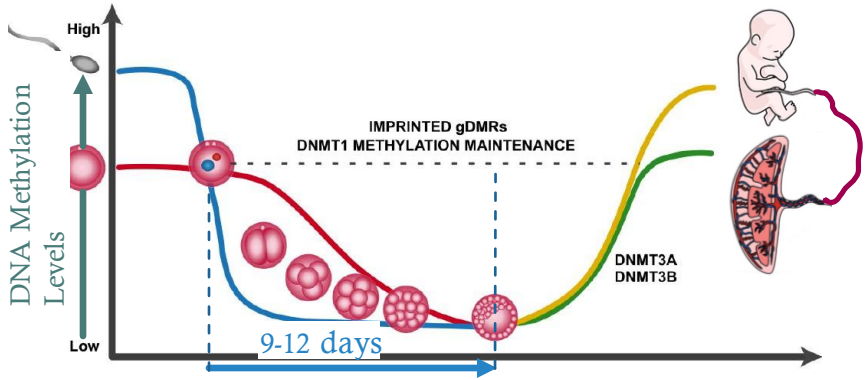
Dynamic Methylome Changes

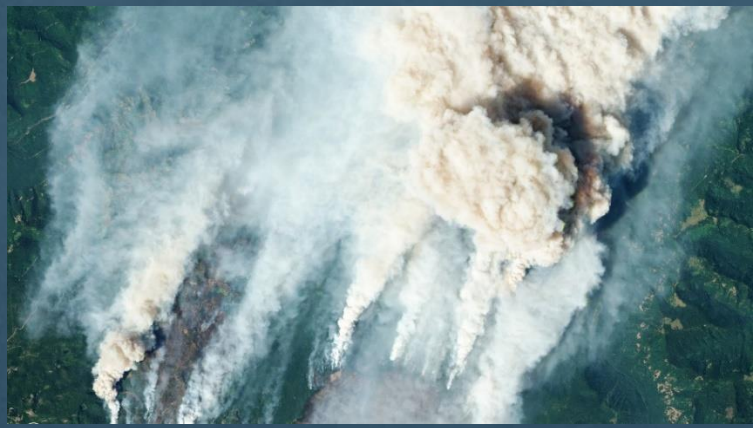
- Near conception, there are dynamic DNA methylation changes where methylome is erased and re-established
- Epigenetic reprogramming to prepare developing fetus for its environment
- Folate is a methyl-donor; critical timing of folic acid protective associations with developmental outcomes align
- Placenta epigenetic changes can serve as biomarkers of early gestational events and biologic pathways altered



Epigenetic Biomarkers
Reprogramming
Early Gestational Events
Altered Biologic Pathways

We Can Learn from Wildfire Events

- Wildfire smoke exposure reaches all SES groups (avoiding the confounding by SES in studies of ambient/traffic-related air pollution and other environmental contaminants
- Great variation in PM concentrations to examine dose-response/thresholds



- Can examine critical timing given shorter exposure windows than in ambient air pollution studies (where exposure is highly correlated over time)
- Can link exposure to WFE to biomarker measurements

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Wildfires & Pregnancy

- Reduced birth weight, esp. with 2nd trimester exposure to S. CA 2003 fires (Holstius et al 2012)
- 2009 bushfires in 2nd and 3rd trimesters associated with birth weight & preterm birth (O'Donnell et al 2013)
- Prolonged low-level exposure (CO 2007-2015) increased risk of pregnancy complications including gestational hypertension, low birth weight, and preterm birth (Abdo et al 2015)
- Wildfire smoke exposure in pregnancy (# days & intensity, esp. 2nd and 3rd trimesters) for CA 2008 fires associated with higher risk of preterm birth – especially for those w/low baseline smoke exposure (Heft-Neal et al 2021)
- Wildfire exposure CA 2007-2010 in 30 days before pregnancy and 1st trimester associated with higher risk of gastroschisis (Park et al 2013)
- None of above included more recent/severe wildfires with higher PM
- Brazil wildfire $PM_{2.5}$ 1st trimester associated with preterm birth (Requia et al 2022)

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Wildfires and Macaques

Non-human primate rhesus macaque studies

- Postnatal 2008 CA exposure associated with later immune dysregulation & compromised lung function that persisted into adulthood (Black et al 2017; Bassein et al 2019)
- Periconceptional exposure associated with pregnancy loss (Wilson et al 2021)
- Early pregnancy exposure 2018 CA Camp Fire associated with blunted cortisol, passive behavior, memory impairment in infant (Capitanio et al 2022)
- Early life 2008 CA wildfire exposure associated with long-term nasal methylome changes over nervous & immune system genes (Brown et al 2022)

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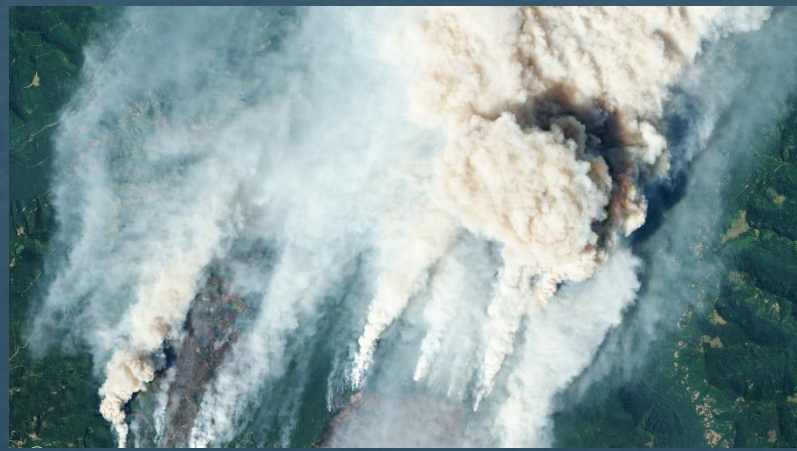
Remaining Questions Regarding Wildfire Events and Health

- WFEs impact all SES groups, but are exposures and associated health outcomes similar across groups?
- PM concentrations, exposure lengths vary greatly – can examine dose-response/thresholds



- What are the critical periods of exposure timing?
- What are the biological responses and mechanistic pathways impacted by wildfire smoke? Do they overlap with other types of air pollution?
- What long-term health outcomes are associated with exposure? With repeated exposures?

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B-SAFE Pregnancy Wildfire Study

Bio-Specimen Assessment of Fire Effects

OVERALL GOALS

- Establish cohort of women at different stages of pregnancy during the Northern California wildfires and their children
- Collect biospecimens and survey information that will be used in future studies to determine exposure loads, mechanistic responses, and health biomarkers

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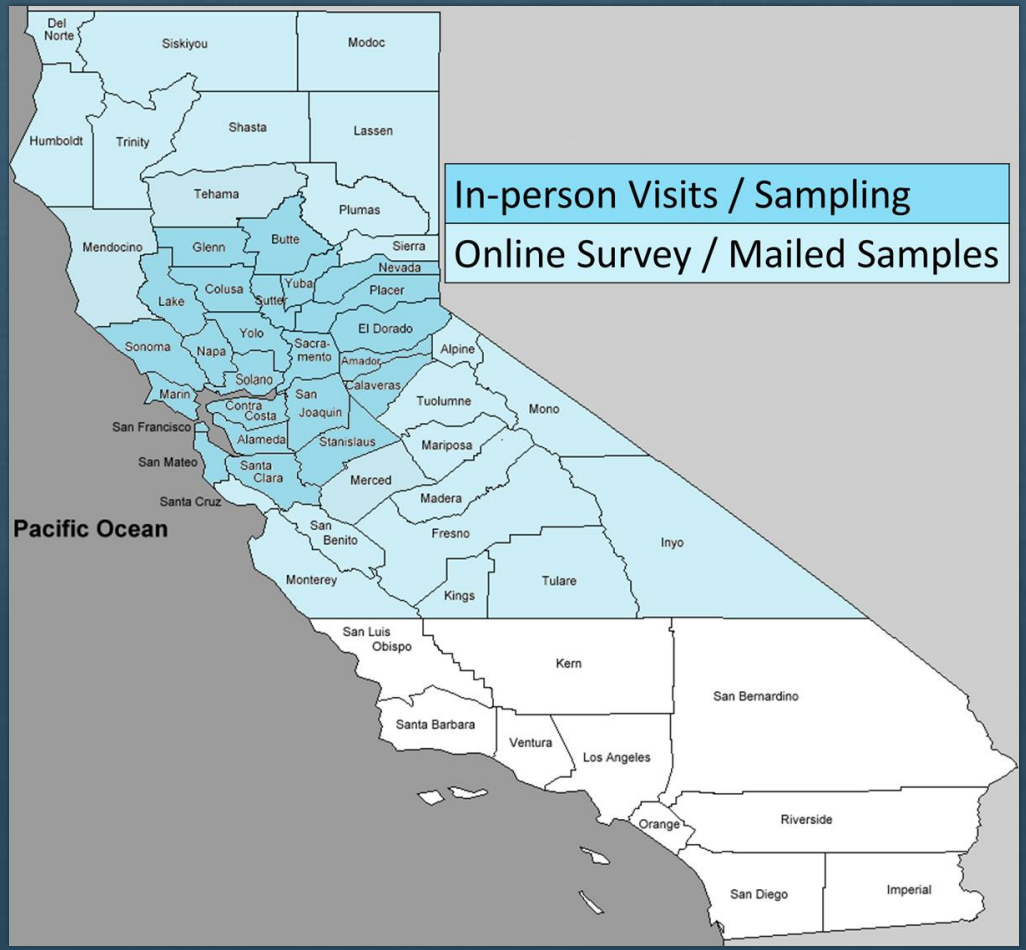
B-SAFE Wildfire Pregnancy Study

- Collect information on wildfire experience, stress, demographics, and pregnancy/delivery/postnatal health

- Collect Biospecimens:
  - Maternal blood, hair, urine, toenails, breast milk, MyExposome silicon wristbands
  - Placenta & umbilical cord blood at delivery
  - Baby's saliva, toenails, fecal sample, DBS, nasal swab
  - Older sibling nasal swabs

Recruitment Areas



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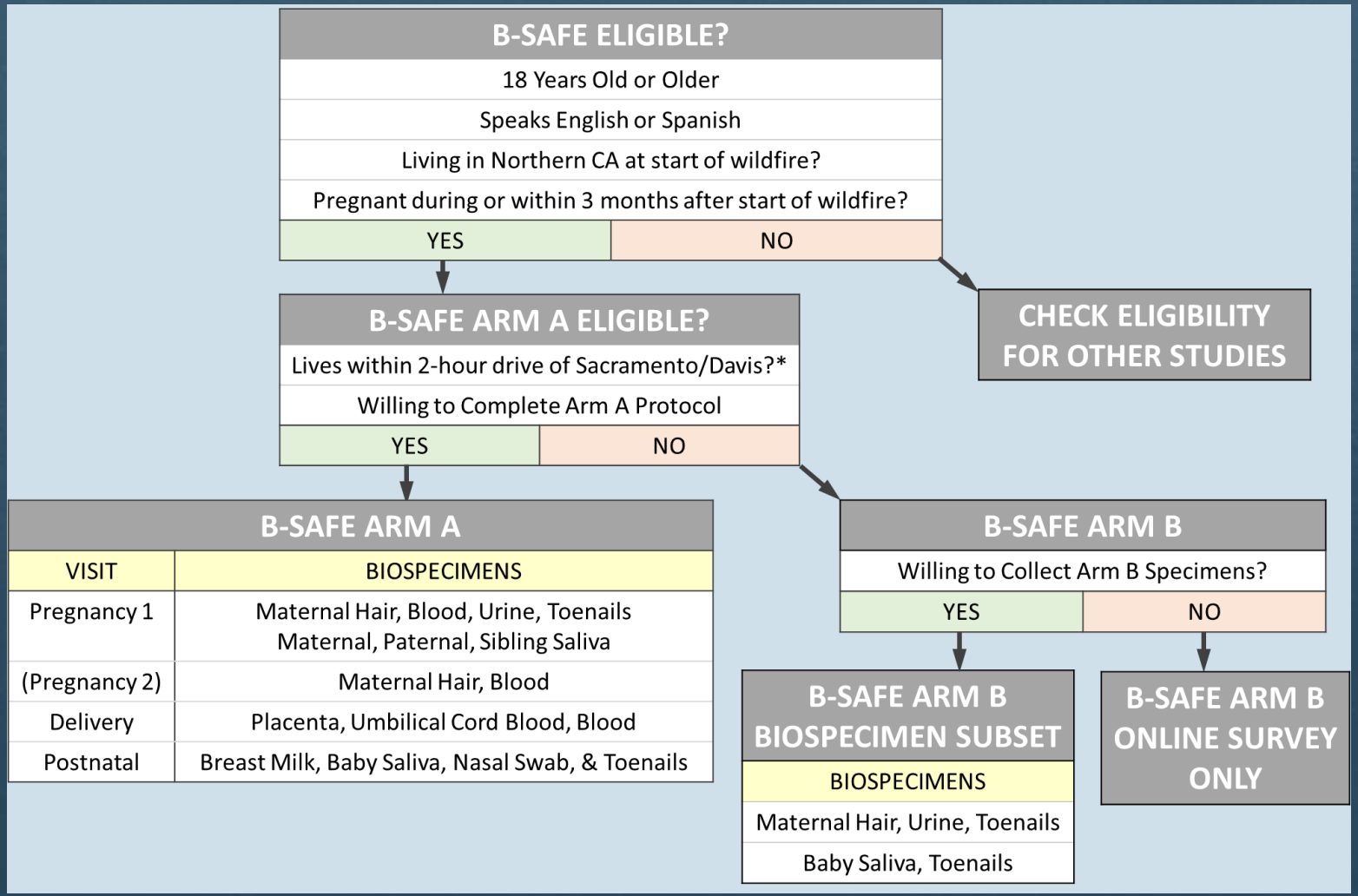
B-SAFE Protocol



B-SAFE Study Recruitment To Date

- 544 mom-child pairs enrolled to date for 2017-2021 wildfires
  - 172 enrolled for 2017 Napa/Sonoma wildfires (Tubbs Fire)
  - 225 enrolled for 2018 Camp Fire
  - 18 for 2019 Kincade Fire
  - 95 for 2020 Complex Fires
  - 34 for 2021 Dixie/Caldor Fires
- Future Fires
  - Earlier prenatal recruitment including before fires
  - More diverse & Spanish -speaking participants

Exposure Measures

- Exposome silicone wristbands
- Air pollution modeling
- Metals in hair
- Blood analyses of internal contaminant metabolites

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Exposome Silicone Wristbands

- Collected MyExposome© wristbands worn by mothers for 1 week in MARBLES and B-SAFE pregnancy cohorts
- Quantifies 1500+ compounds – personal environmental monitoring
  - Flame retardants (PBDEs, OPFRs), PCBs, PAHs, pesticides, VOCs
  - Some validated with other measures, used in many studies, e.g., firefighters http://www.myexposome.com/
- Analyzing data to from MyExposome

Funded by EHSCC Pilot

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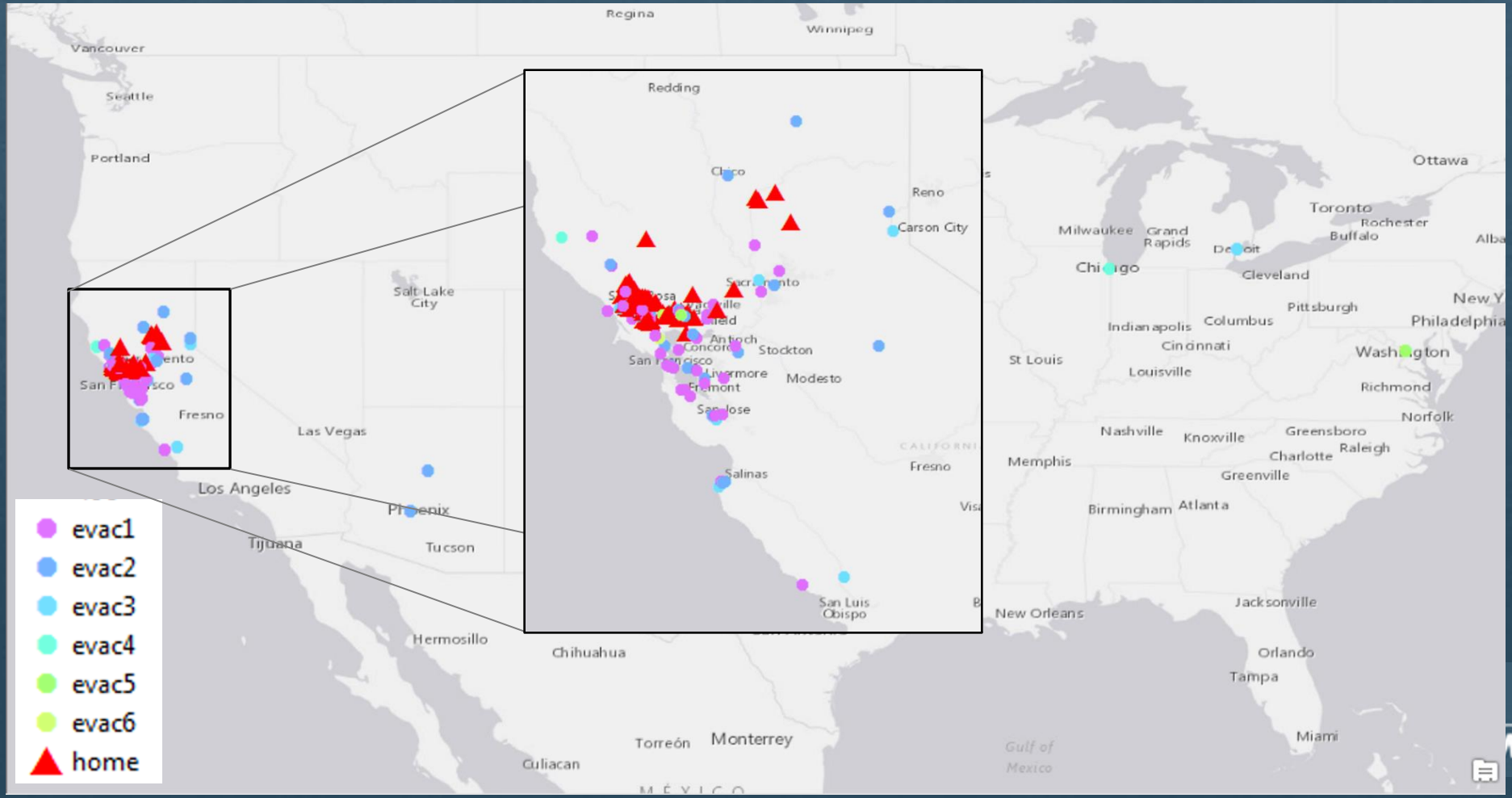
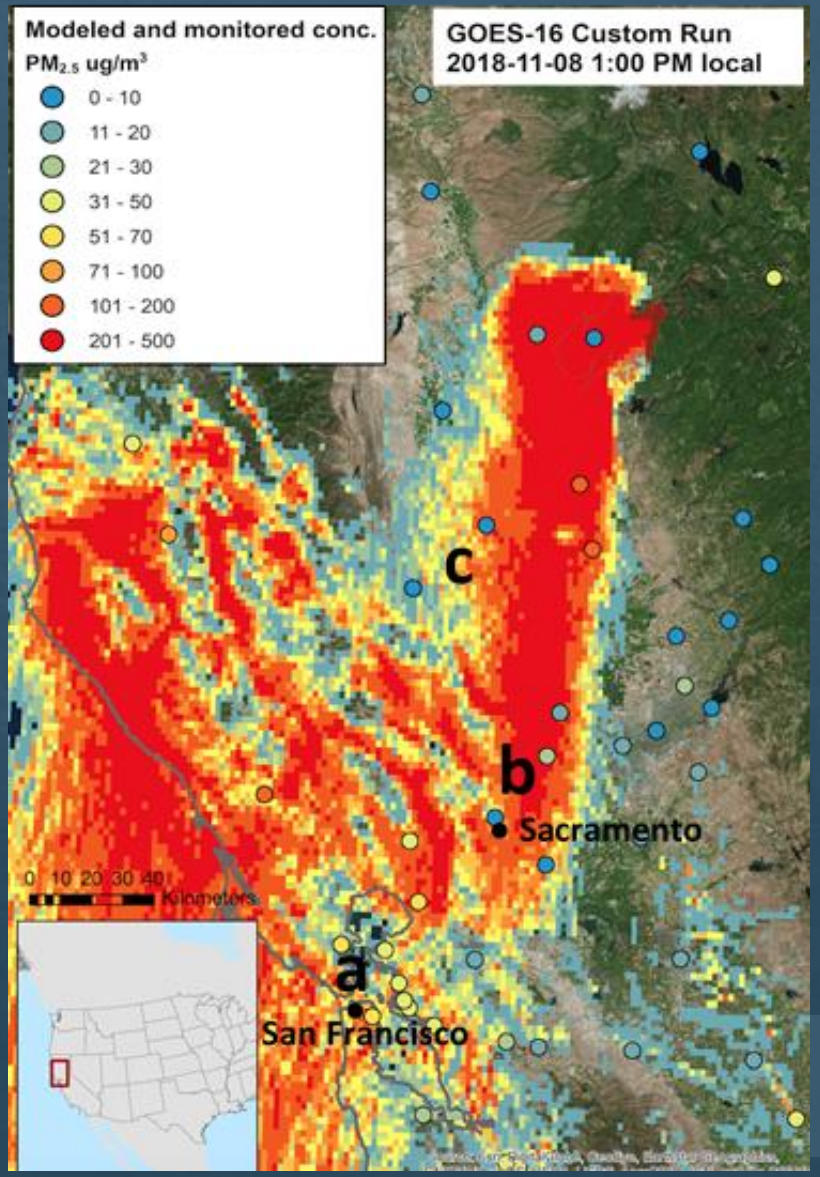
Home Locations at Start of Fires & Evacuation Locations 2017



Air Pollution Modeling

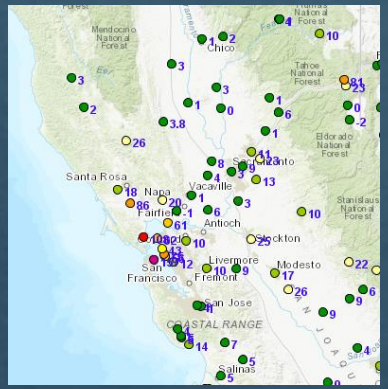
Collaborate with Sean Raffuse (UCD) on modeling of wildfire $PM_{2.5}$ exposure



Modeled near-surface $PM_{2.5}$ concentrations overlaid with measured $PM_{2.5}$ concentrations from monitoring stations (circles) at 1pm LT on 11/8/2018 for Northern California

Data Fusion Approach

Ground Monitors



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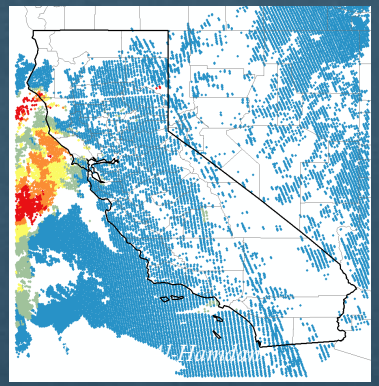
Satellite AOD



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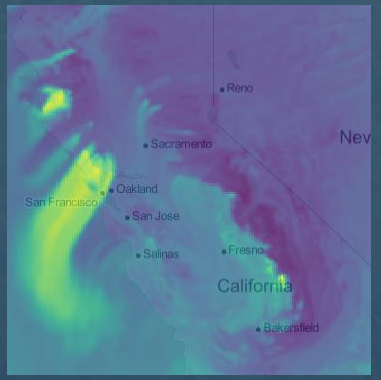
Air Quality Model



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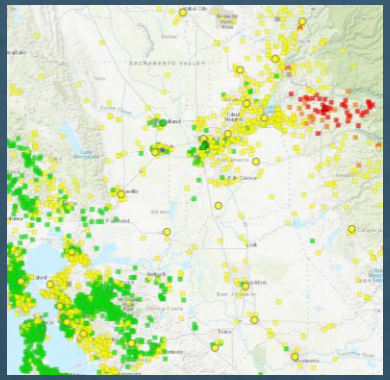
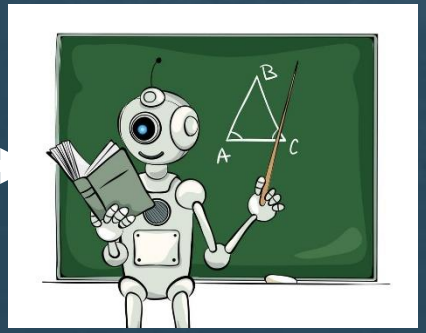
Sensor Network



Machine Learning



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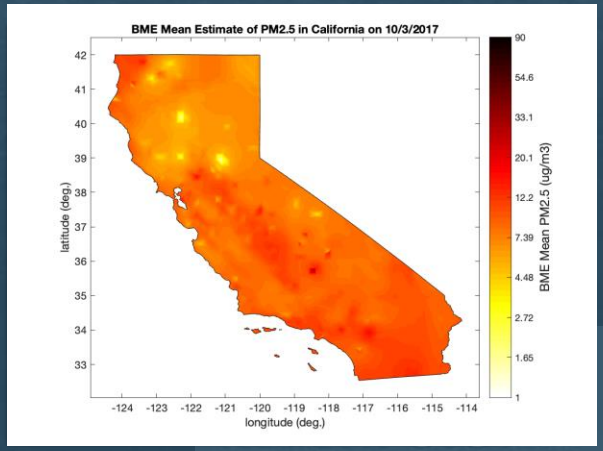
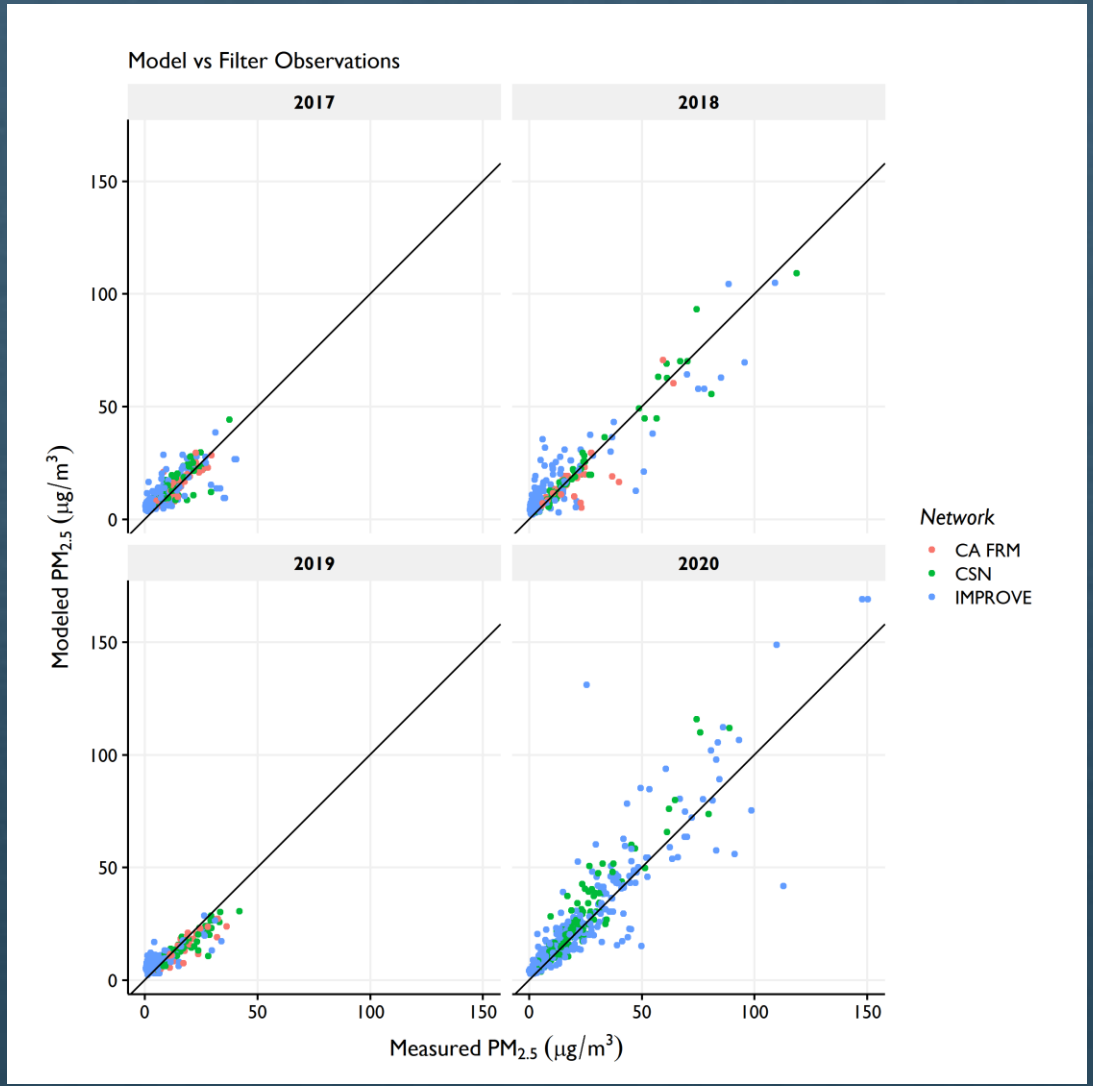
Estimates of daily mean $PM_{2.5}$ during the fire period for exposure assessment



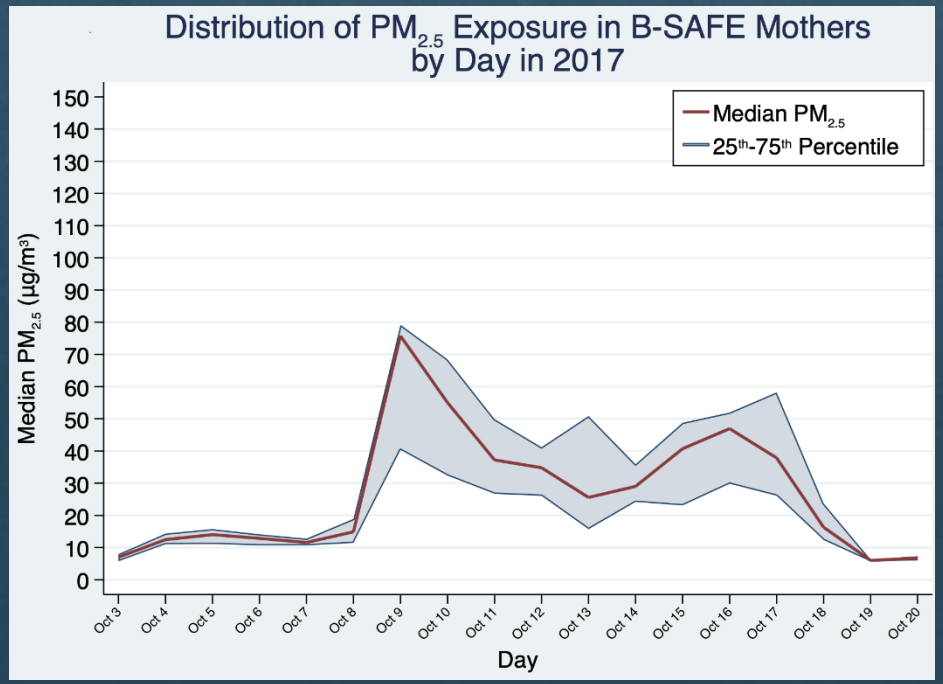
Fully independent evaluation against 24-hour filter-based measurements

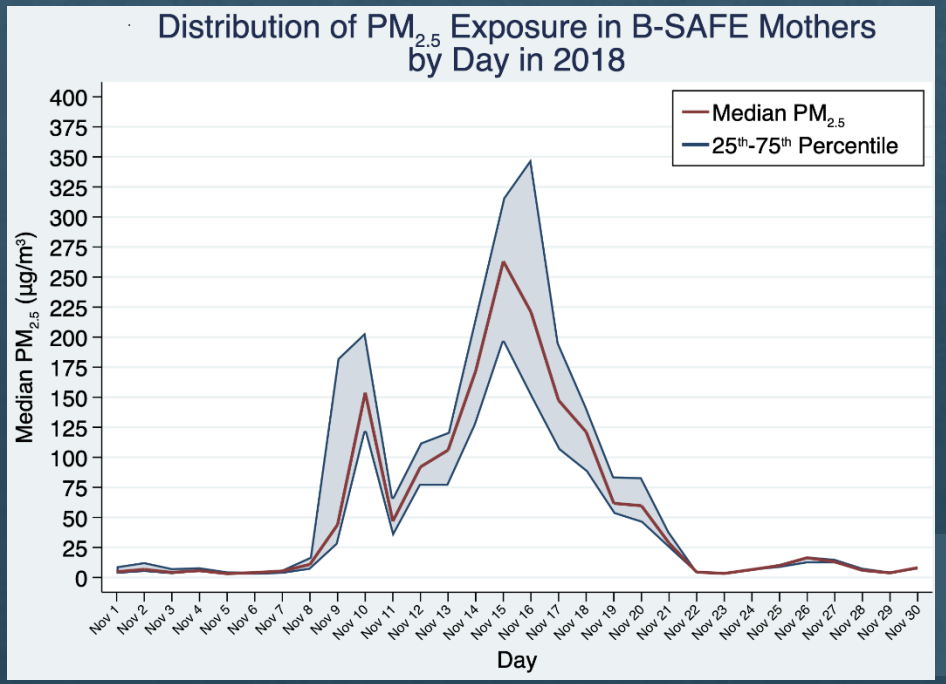
Rapidfire Methods *in submission*: Raffuse S, O'Neill S, Schmidt R. rapidfire – a model for rapid wildfire smoke exposure estimates using routinely-available data.

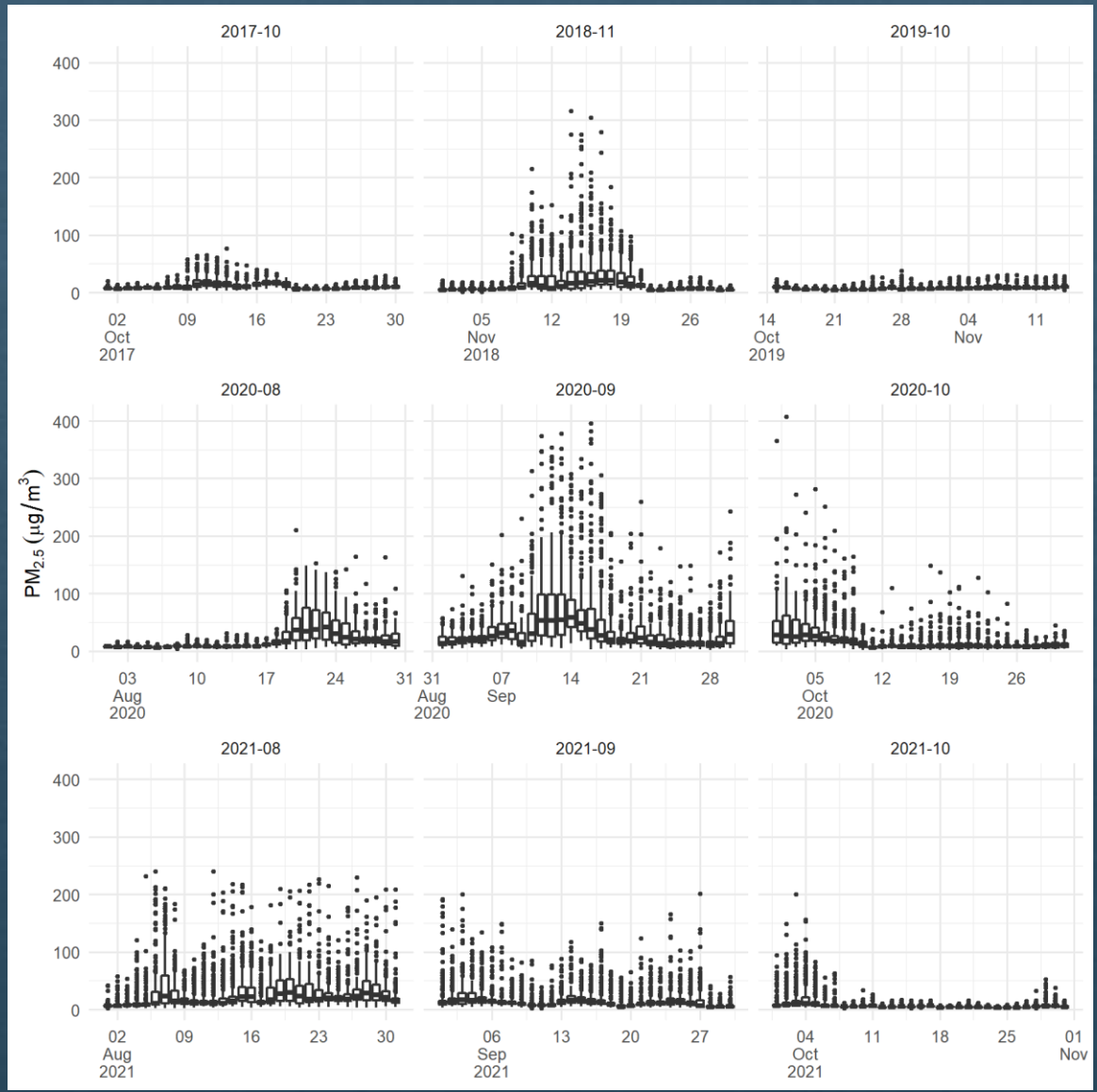


Fine Particulate Matter Exposure

- Median estimated $PM_{2.5}$ (25th-75th percentile range) based on ground air monitor data and satellite emissions models for B-SAFE mothers during wildfires based on reported addresses
- $PM_{2.5}$ higher during peak days for 2018 Camp Fire than for 2017 wildfires






2017-10
2018-11
2019-10
2020-08
2020-09
2020-10
2021-08
2021-09
2021-10
PM2.5 (μg/m3)
400
300
200
100
0
02 Oct 2017
09
16
23
30
05 Nov 2018
12
19
26
14 Oct 2019
21
28
04 Nov
11
03 Aug 2020
10
17
24
31
31 Aug 2020
07 Sep
14
21
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05 Oct 2020
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19
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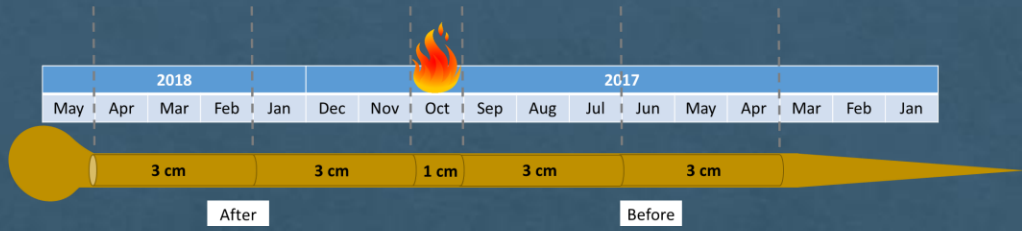
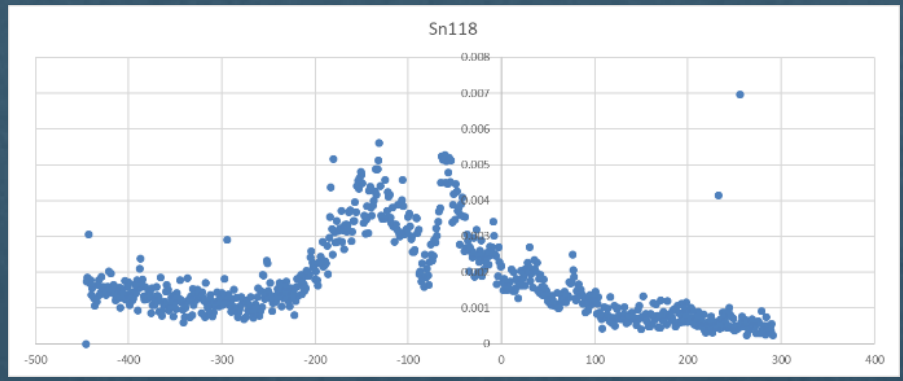
Metals in Hair





- Piloted novel methods for measuring metals by laser ablation ICPMS in Dr. Manish Aurora's laboratory along the length of the hair to capture fine-grain timing of before and after the wildfires
- Analyzed 26 metal element concentrations from first 6 samples with high Oct 2017 wildfire smoke exposure
- Found peak in tin (Sn) concentrations near the middle of the strand timeline
- Analyzing additional hair samples from 2017, 2018 and 2020 fires w/Sean Raffuse & Dr. Bennett

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Blood Contaminant Markers

- Dr. Ameer Taha's laboratory measured 55 chemical compounds in maternal serum
  - Flame retardants (PBDEs), PCBs, PAHs, fatty acids and oxylipins (markers of immune activation)
- 165 B-SAFE mothers from 2017 wildfire and 25 CHARGE study typical control mothers collected pre-fire (2016)
- Measured 44 of 55 chemotypes in the majority (70+%)
- Contaminant concentrations not higher in B-SAFE high-exposed vs. low exposed
- Found upregulation in oxylipins involved in inflammation resolution in wildfire-exposed

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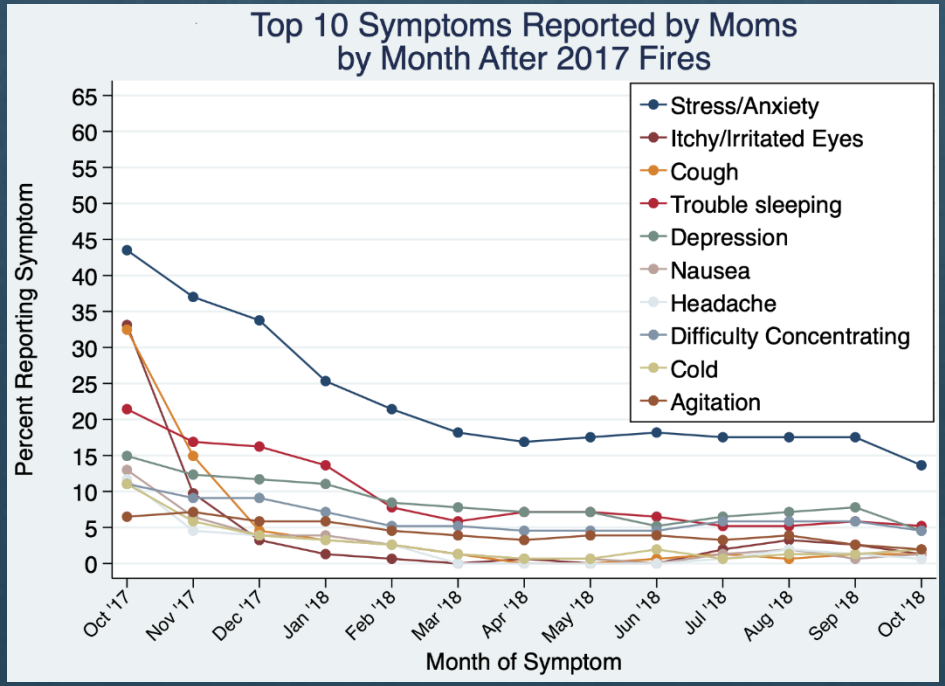
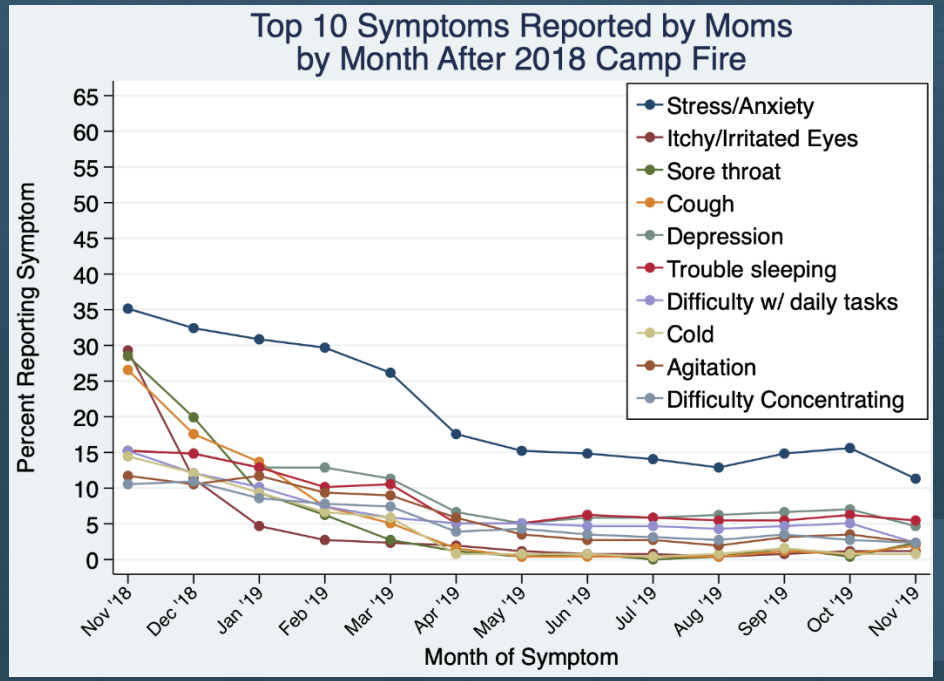
Symptoms Reported by Mothers

- ~50% reported any symptoms after both 2017 wildfires (49%) & 2018 Camp Fire (56%)
- Most commonly reported symptom both years was Stress/Anxiety, persisted for many
- Top respiratory symptoms, like itchy/irritated eyes, cough, and sore throat, reported in over 25-32% initially, but dropped steeply after the first month
- Trouble sleeping was reported for 10-22% in the first several months





B-SAFE Future Directions

- **On-going Work**
  - B-SAFE PM and Stress in relation to birth outcomes
  - Nasal epigenetics pilot study (older siblings to replicate NHP findings) – Dr. Hong Ji
  - Follow-up survey for child respiratory/CBCL – EHSC Pilot – Anh Nguyen
  - Cytokines in maternal blood samples (JVW)
  - Placenta Epigenetics (w/LaSalle Lab)
  - Non-human primate studies – CNPRC Pilot
  - EPA Grant – linkage study & communication
  - Wildfire Impacts in MARBLES Cohort
- **Future Studies**
  - Follow-up of children's neurodevelopmental and respiratory health
  - Examine mechanistic biomarkers (e.g., epigenetic, immune, metabolomics)
  - Intervention studies

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CNPRC NHP WFE Pilot Study

w/Erin Kinnally, Sean Raffuse, Janine LaSalle, Logan Williams, Hong Ji, Dan Tancredi

1) Compare biobehavioral assessment data for ~400 rhesus macaques at 90-120 days old exposed to wildfire smoke at different perinatal times to ~3900 unexposed macaques

   Examine biomarkers and behavior by wildfire air pollutant concentrations, days exposed, and timing in gestation for WFE over past 20 years

2) Whole genome bisulfite sequencing (WGBS) on blood of 85 exposed macaques (59 highly exposed, 28 near conception) and 65 unexposed maternal siblings to identify DNA methylation changes in gene pathways associated with wildfire exposure

   Examine overlap with gene pathways implicated in neurodevelopmental conditions

3) Relate wildfire-associated epigenetic changes in blood to macaque behavioral and developmental outcomes

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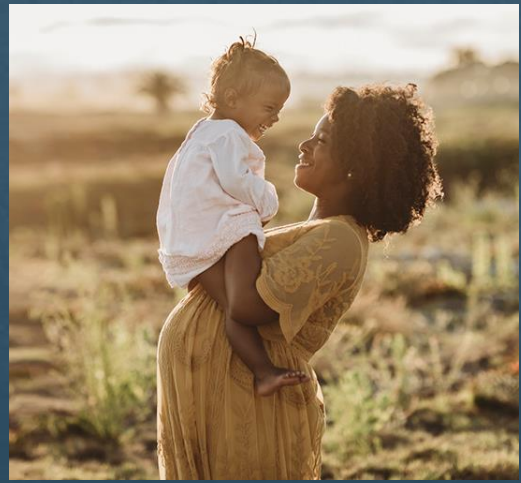
CALIFORNIA NATIONAL PRIMATE RESEARCH CENTER

EPA Grant - Early Life Vulnerability to Climate-driven Wildfire Events on Pregnancy and Child Developmental Health Outcomes in Underserved Populations

UCD: Miriam Nuno (Co-PI), Kathryn Conlon, Michael Kleeman, Sean Raffuse, Debbie Bennett, Irva Hertz-Picciotto, Richard Corsi, Tanya Khemet Taiwo
UCLA: Beate Ritz



- Determine who is most impacted by wildfire smoke in California (2000-2021) and how exposures relate to pregnancy and child neurodevelopmental outcomes (linking to CA birth records and DDS records)
- Community-engaged education sessions to inform communities on how to protect themselves from smoke exposures

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

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EPA Star Grant - Early Life Vulnerability to Climate-driven Wildfire Events on Pregnancy and Child Developmental Health Outcomes in Underserved Populations

Vulnerable Populations:

- Pregnant people and their developing children are vulnerable to wildfire smoke
- Black and brown pregnant people at higher risk for preterm birth and low birthweight, outcomes previously associated with prenatal wildfire exposures
- Low SES and underserved people are more exposed to background ambient air pollution

Non-chemical Stressors:

Environmental, neighborhood, and contextual factors that could increase vulnerability including individual and community-level factors: prenatal care, immigration status, SES, demographics, access to greenspace, walkability, child opportunity index, neighborhood deprivation index, background air pollution

Health Outcomes: Birth weight, gestational age/preterm birth, autism, developmental delay

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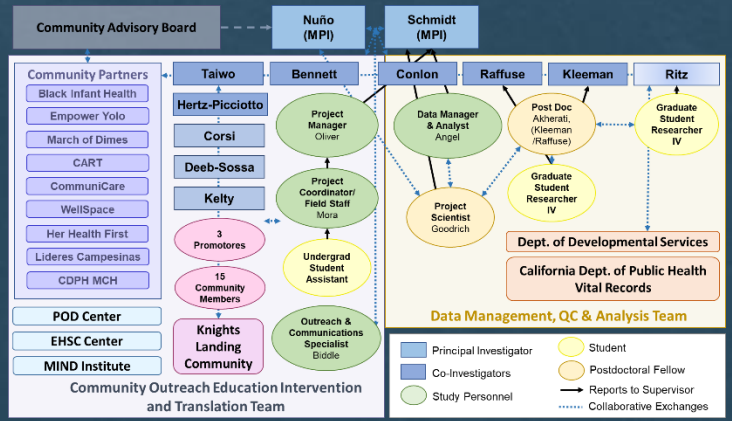
Impact: Determine whom and when to focus educational campaigns and exposure mitigation tools for the greatest exposure reduction and improvement of child health outcomes; Find ways to improve acceptance of educational training on exposure mitigation among the most vulnerable



Wildfire Impacts in MARBLES Cohort

Placenta Epigenetics – Logan Williams

Maternal Cytokines – Amanda Goodrich

MARBLES

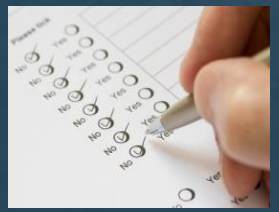
_M_arkers of _A_utism _R_isk in _B_abies:
_L_earning _E_arly _S_igns

~550 Mothers of a child with autism planning pregnancy or pregnant with another child

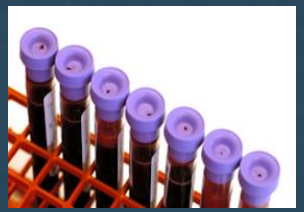
- **ASD Recurrence rate is ~ 1 in 5**
- **~15% Non-Typical Development**
- **At risk for pregnancy complications**

Pregnancy → **Child Neurodevelopment** → **Dx Outcome**

EEQ, FFQs



Biologic Samples



Parent Forms & Clinical Assessments

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Risk Factors for Autism and Other Neurodevelopmental Disorders

- High Heritability / Genetic Contributions
  - Twin studies: H = 38% - 83%; Most recent study of over 2 million twin/sib pairs including 22,156 diagnosed with ASD: H=81%
  - Higher risk if in the family; Siblings 1/5 (10 times higher)
  - Many de novo and rare gene variants linked
- Advance Parental Age
- Prenatal Infections (Rubella) & Fever
- Medications (Thalidomide, Valproate, SSRIs)
- Air Pollution
- Maternal Stress
- Maternal Obesity, Diabetes other Metabolic Conditions
- Month/Season of Conception
- Closely Spaced Pregnancies
- Early Anemia
- Not taking prenatal vitamins early in pregnancy
- Pesticides
- Per-and polyfluoroalkyl substances (PFAS)

Wildfire Impacts in MARBLES

- Use longitudinally-collected biospecimens and data to evaluate associations with wildfire events
- Prenatal WFE with birth weight – Arriel Alvarez
- Existing placenta WGBS and maternal blood cytokine measures relating to 2008 wildfire season (not yet for more severe 2017-2021 WF)
  - Placenta Epigenetics – Logan Williams, Janine LaSalle
  - Maternal Cytokines – Amanda Goodrich, Judy Van de Water

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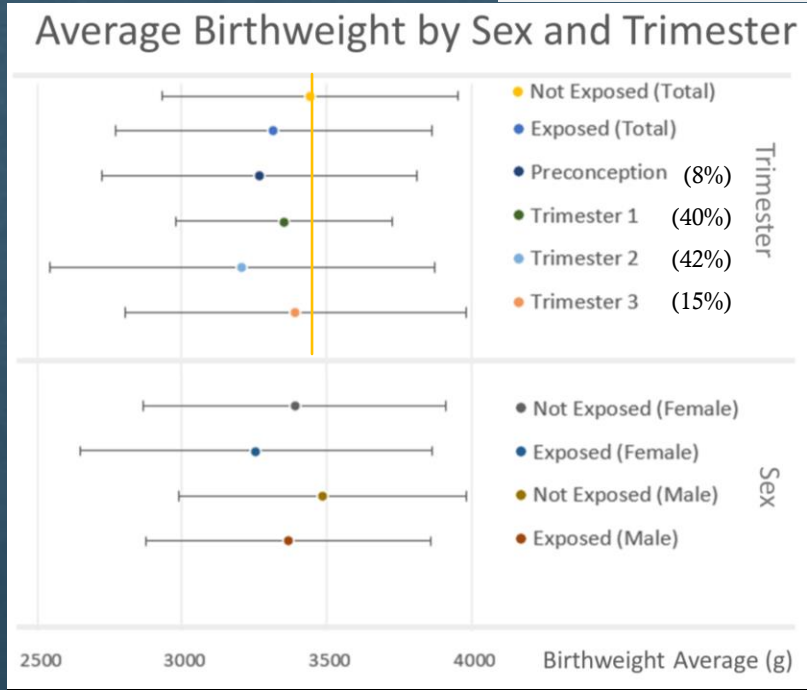
Prenatal WF Smoke and BW & GA

Arriel Alvarez, UC LEADS Graduate Studies Summer Research Program

Wildfire Years	
2008	36 (55%)
2017	12 (18%)
2018	16 (25%)
2019	1 (2%)

- Associated prenatal exposure 2006-2019 wildfires with birthweight and gestational age in MARBLES
- Birthweight was lower in WF-exposed compared to unexposed
- 2nd trimester exposure associated with greatest reduction in birthweight
- Less of a difference in GA, but greater % preterm in WF-exposed
- Results in MARBLES high-familial risk cohort similar to those in population-based studies
- Examine mechanistic responses



		Exposed N= 65		Not Exposed N= 356	
		Average	St. Deviation	Average	St. Deviation
Birth Weight		3316	546.51	3442.17	509.87
Gestational Age		38.78	1.77	38.97	1.56
		n	%	n	%
Low Birth Weight	No	61 (93.85%)		344 (96.63%)	
	Yes	4 (6.15%)		12 (3.37%)	
Preterm	No	59 (90.77%)		337 (94.66%)	
	Yes	6 (9.23%)		19 (5.34%)	

Image of Atlas Fire by Michael Short, 2017.

Prenatal wildfire exposure associates with differential placental DNA methylation and pregnancy traits

Logan A. Williams and **Rebecca J. Schmidt**

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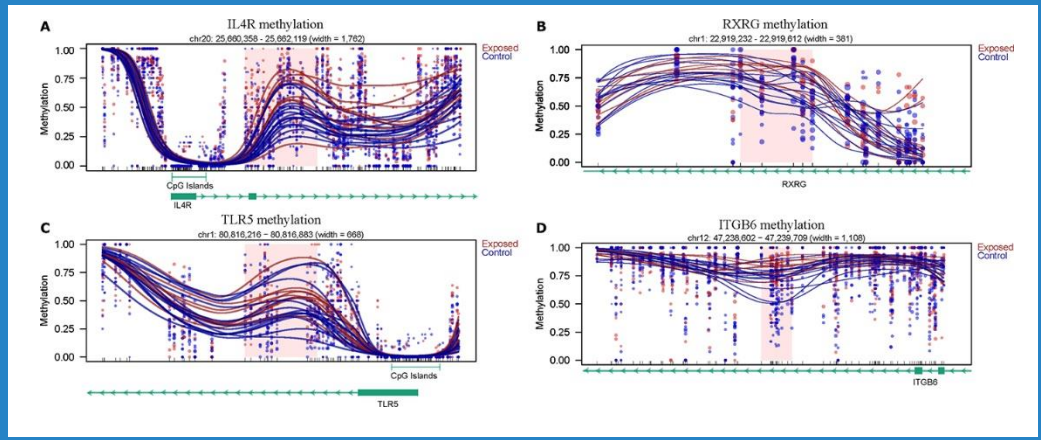
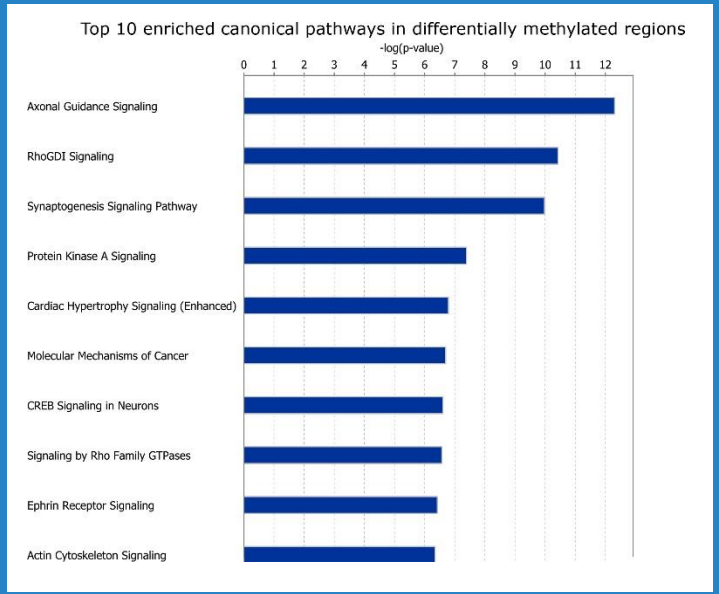
Wildfire smoke exposure has been shown to associate with developmental outcomes in macaques, and epigenetic changes may be involved

- Early pregnancy exposure 2018 CA Camp Fire associated with blunted cortisol, passive behavior, memory impairment in infant (Capitanio et al 2022)
- 3370 differentially methylated regions (DMRs) were identified between 2008 wildfire exposed (WFE) and non-wildfire exposed macaque nasal epithelium
- DMRs were significantly enriched for synaptogenesis, protein kinase A signaling, and immune processes (Brown et al 2022)





Figures from Brown et. al 2022

Hypothesis: Prenatal WFE is associated with placental epigenetic markers of dysregulation during gestation, with that dysregulation being enriched for genes relevant to ASD/neurodevelopment

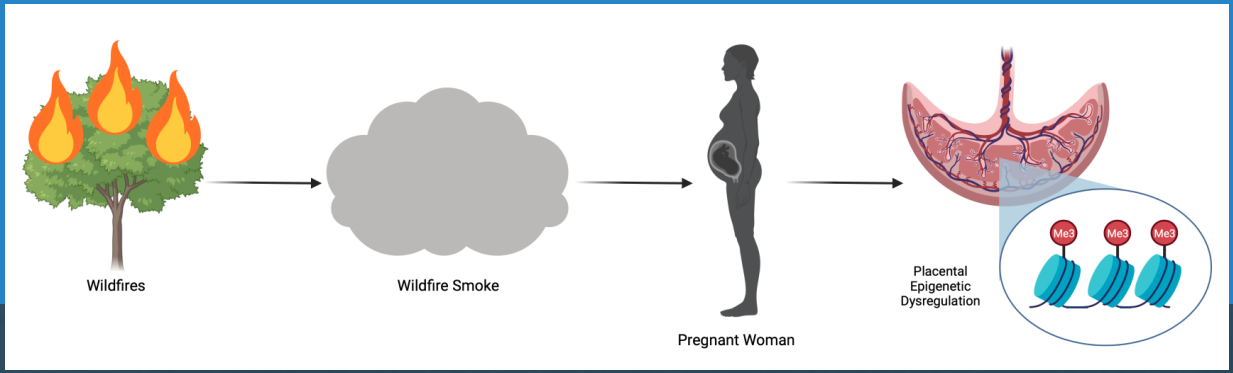


Figure made in Biorender

Placenta Samples Collected and Classified by WFE

- Placenta is essential to early development
- Collect placenta samples in the MARBLES cohort
- Classified WFE by whether the mother was pregnant during and resided in an area with high smoke exposure during 2008 wildfire season
- WGBS DNA methylation in n=136 (124 non-WFE, 12 WFE)

MARBLES

Markers of Autism Risk in Babies - Learning Early Signs

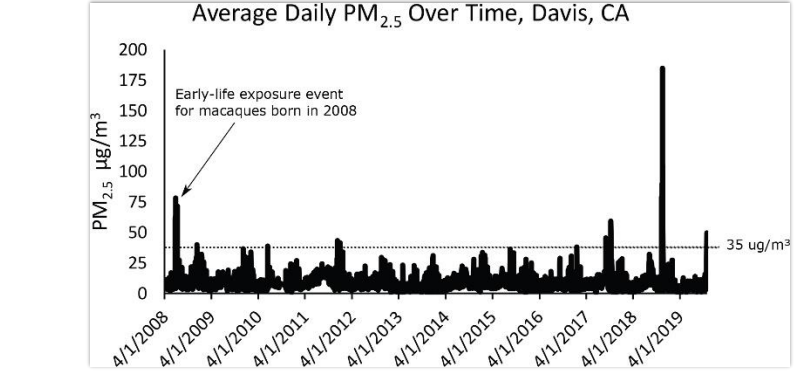


Figure from Brown et. al 2022

Placenta DNA Methylation Profiled and Categorized Into Comethylation Modules

- Placental DNA extracted and used for WGBS
  - Methylation genomically encoded into DNA, then sequenced
- WGBS data used to identify comethylation modules
  - Identifies clusters of comethylated regions
  - Can be examined for associations with sample traits/exposures
  - Examined WFE and ND outcomes

Comethyl: Mordaunt et al 2022
https://doi.org/10.1093/bib/bbab554

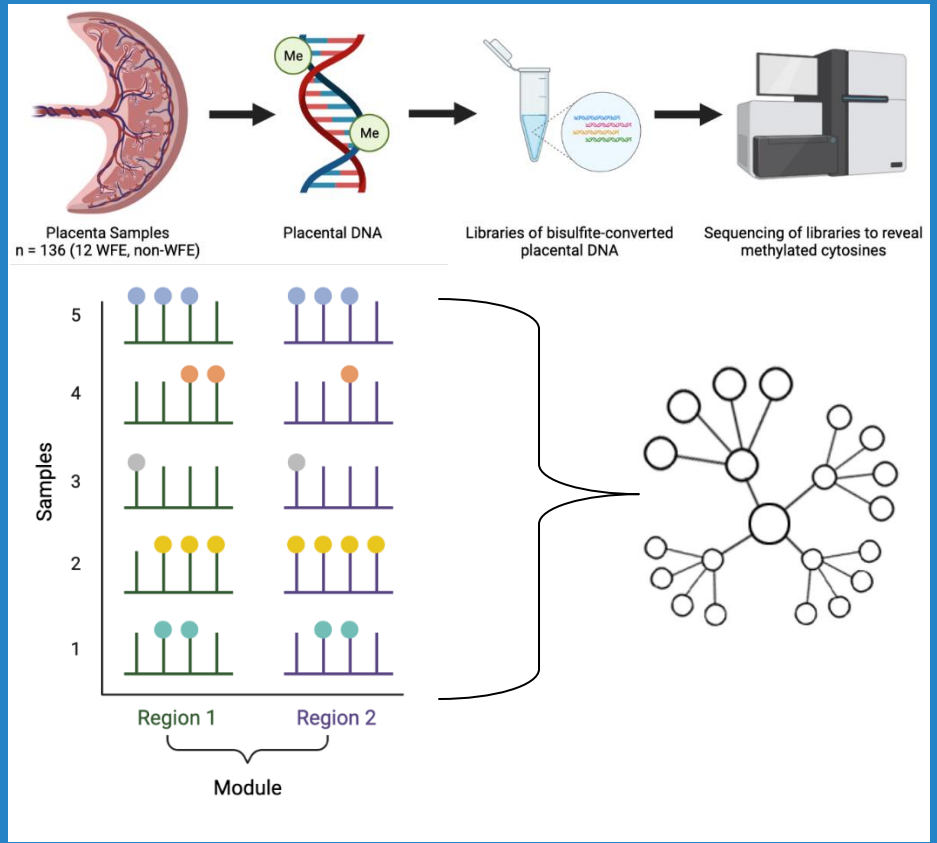
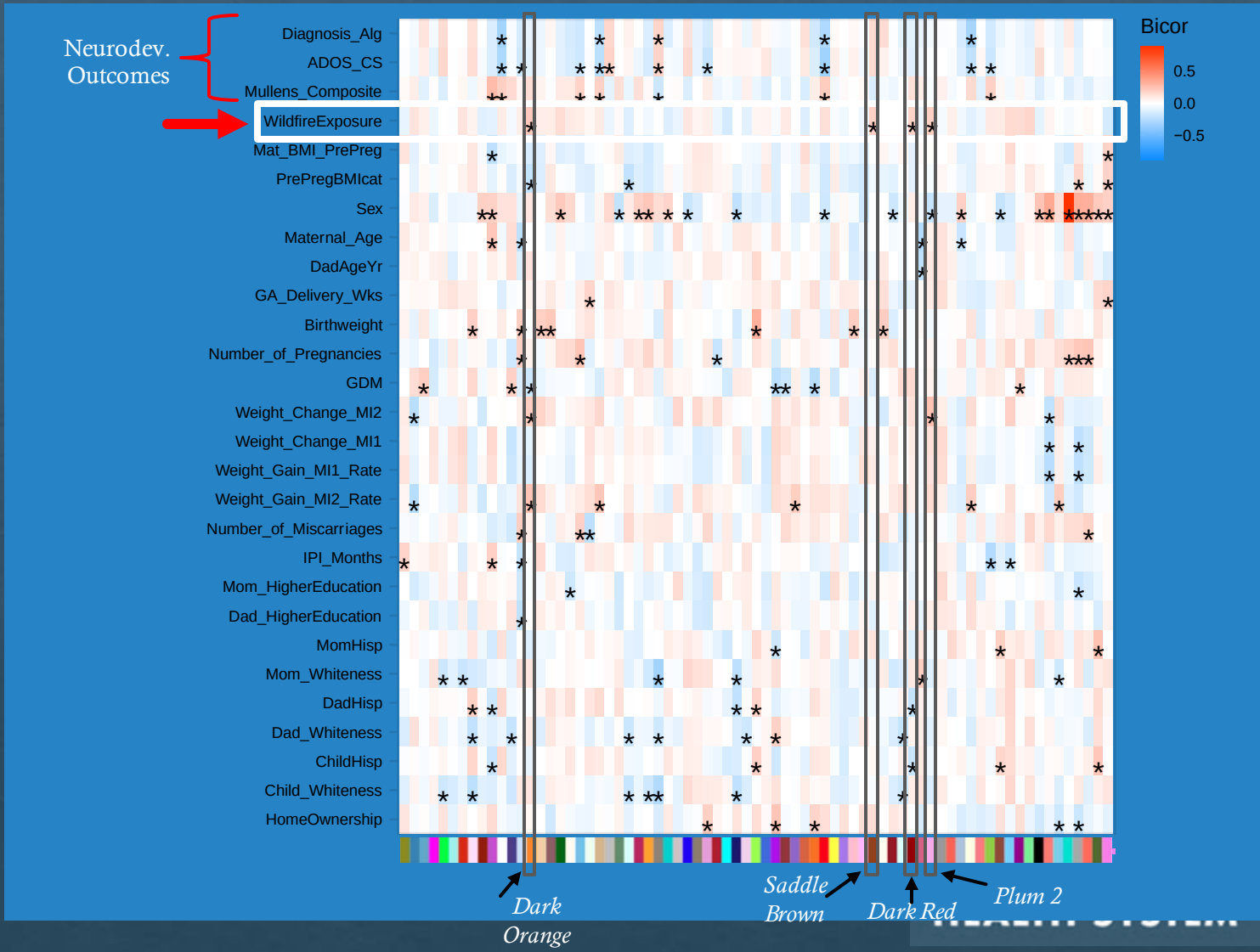
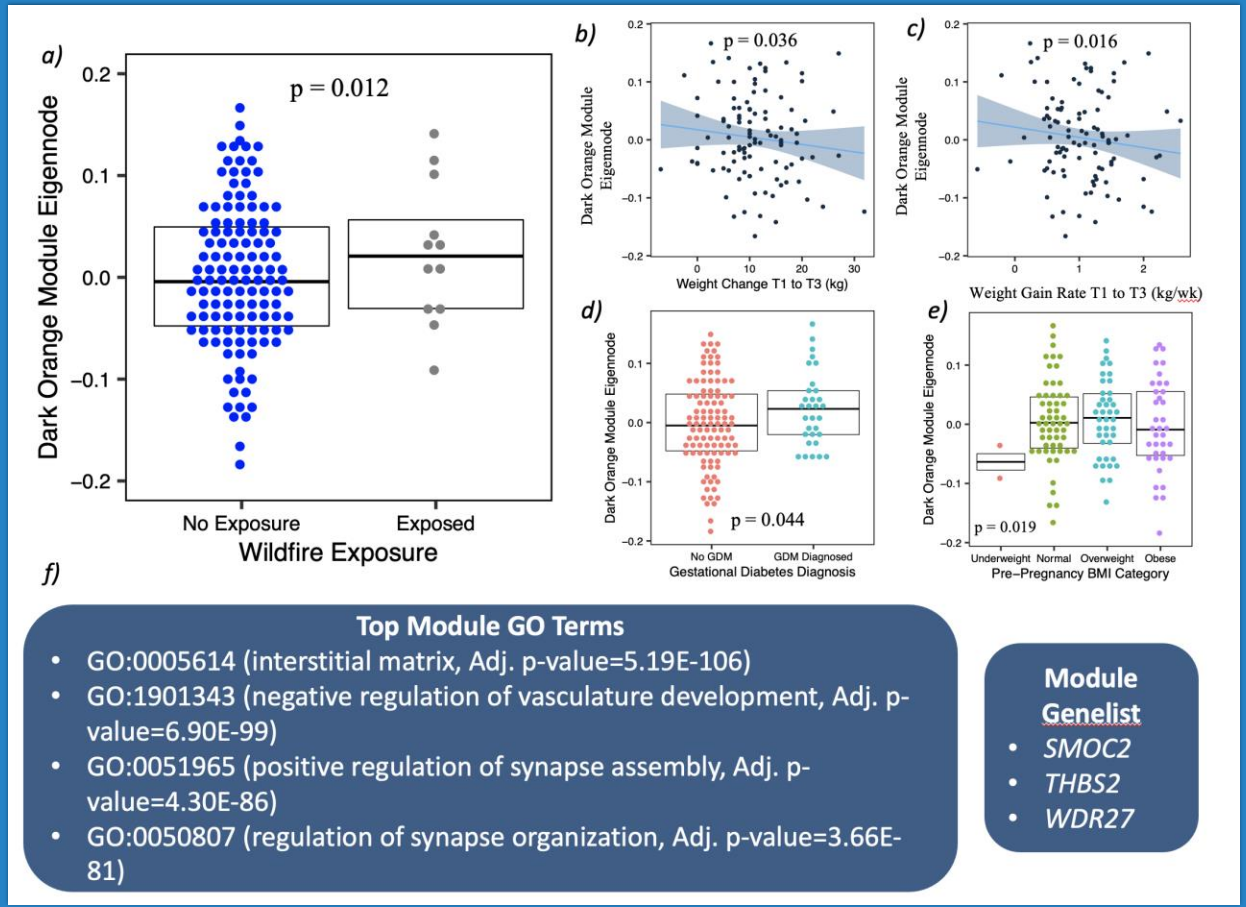


Figure made in Biorender.

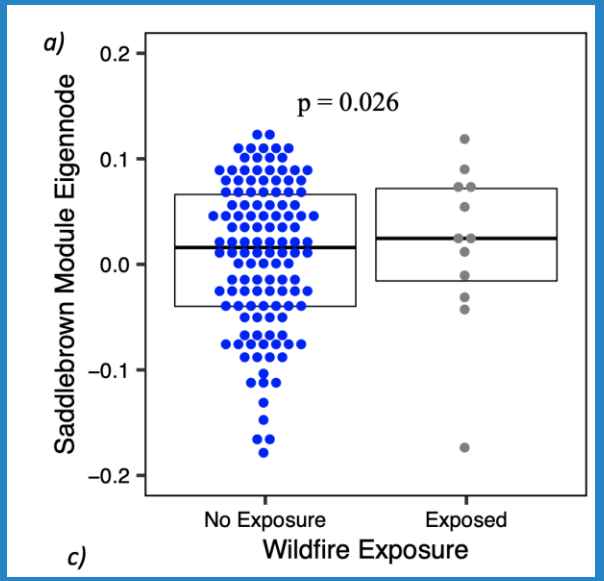
Associations between comethylation modules and prenatal WFE

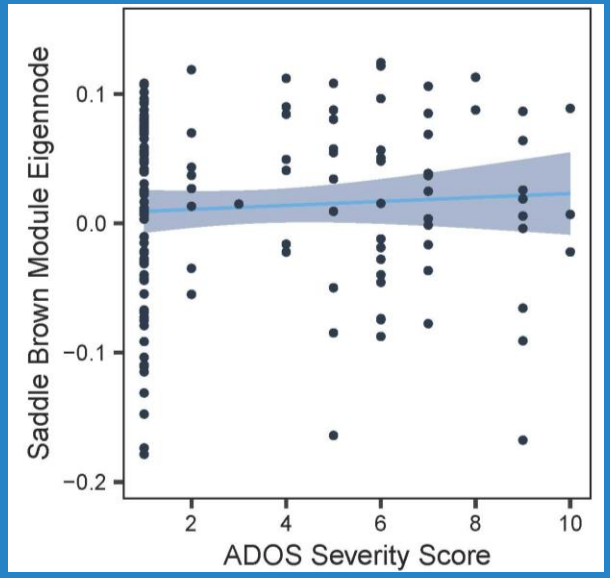


***Dark Orange* module** associates with metabolic covariates, and is enriched for ASD-relevant gene pathways



***Saddle Brown* module** is also enriched for neurologically relevant genes, and is approaching significance with ADOS





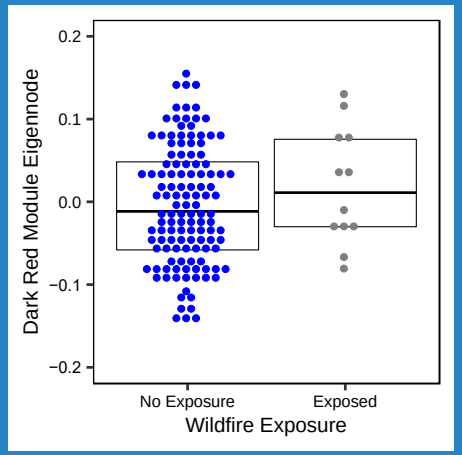
Top Module GO Terms

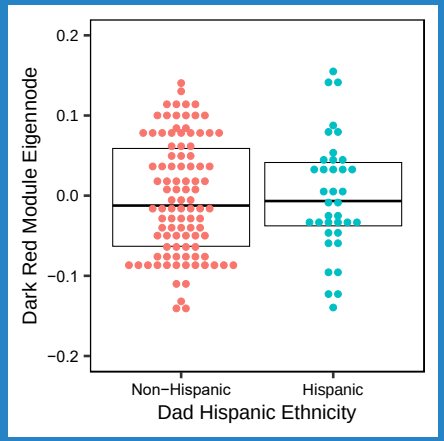
- GO:0005834 (heteromeric G-protein complex, Adj. p-value=1.38E-107)
- GO:0071565 (nBAF complex, Adj. p-value = 2.62E-107)
- GO:0070603 (SWI/SNF superfamily-type complex, Adj. p-value=5.44E-89)
- GO:0031234 (extrinsic component of cytoplasmic side of plasma membrane, Adj. p-value = RGS6)

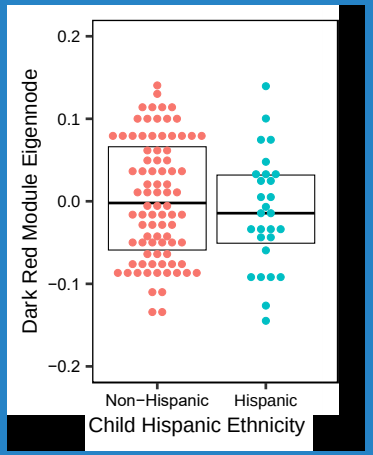
Module Genelist

- *DPF3*
- *RGS6*
- *SIPA1L1*

***Dark red* module** was enriched for mitochondrial and metabolic pathways







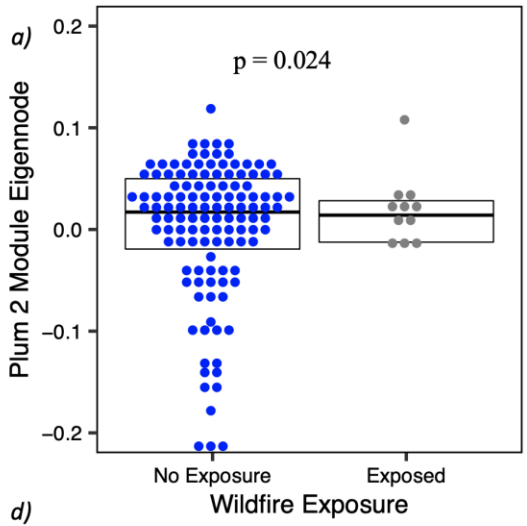
Top Module GO Terms

- GO:0008121 (ubiquinol-cytochrome-c reductase activity, Adj. p-value=6.09E-168)
- GO:0016679 (oxidoreductase activity acting on diphenols and related substances as donors, Adj. p-value=1.89E-167)
- GO:0051537 (2 iron 2 sulfer cluster binding, Adj. p-value=4.31E-158)
- GO:0042775 (mitochondrial ATP synthesis coupled electron transport, Adj. p-value=5.07E-135)

Module Genelist

- *UQCRFS1*

Plum 2 module associates with lower weight gain and sex, and is enriched for DNA maintenance



Top Module GO Terms

- GO:0072757 (cellular response to camptothecin, Adj. p-value=8.17E-27)
- GO: 0070202 (regulation of establishment of protein localization to chromosome, Adj. p-value=2.04E-26)
- GO: 0072711 (cellular response to hydroxyura , Adj. p-value=3.26E-26)
- GO:0010569 (regulation of DSB repair via homologous recombination , Adj. p-value=2.87E-20)

Module Genelist

- *SPIDR*

Prenatal WFE are associated with placental epigenetic differences that could have implications for fetal growth & neurodevelopment

- More investigation needed into potential neurodevelopmental links
  - Lack of WFE and ASD association limits findings
  - Small sample of WFE placentas and timing of WFE at any time in pregnancy
  - 2008 WF $PM_{2.5}$ concentrations orders of magnitude lower than recent fires
- Expanding this study to include more WFE placentas, incl. from BSAFE study
  - Seek to replicate these findings

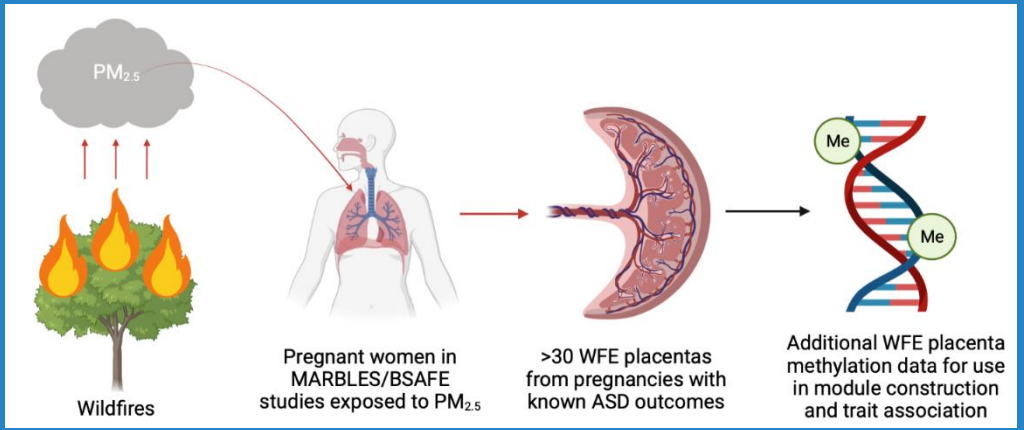


Figure made in Biorender.

Cytokines/Chemokines

In MARBLES

Cytokines/Chemokines

- Immune molecules such as cytokines and chemokines are critical for normal brain development
- Induction of maternal cytokine response and the cascade of downstream cellular and molecular events implicated in disrupted brain development and resultant behavioral changes
- Critical timing and mechanisms involved remain unestablished
- Previous study showed $PM_{2.5}$ exposure associated with changes in prenatal maternal cytokine profiles

UCDAVIS HEALTH SYSTEM

Methods

- 29 cytokines/chemokines quantified in maternal plasma, from each trimester, for 148 MARBLES participants using Luminex multiplex assay
- Cytokines from blood collected between 4/2003 to 4/2015
- Examined mothers exposed to 2008 wildfires
  - Occurred Jun – Aug 2008 (Mostly Jun and July)
  - Conception date $\leq$ 9/30/08 and child DOB $\geq$ 1/6/2008
    - These dates allowed for exposure in 3 months before pregnancy through birth
  - All others considered "un-exposed"

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Methods

- Sample sizes (Exposed/Unexposed):
  - Trimester 1: 17/61
  - Trimester 2: 24/111
  - Trimester 3: 18/98
- Linear Regression
  - All cytokines/chemokines natural log transformed due to heavy right skew
  - Adjusted for gestational age at time of sample (days)

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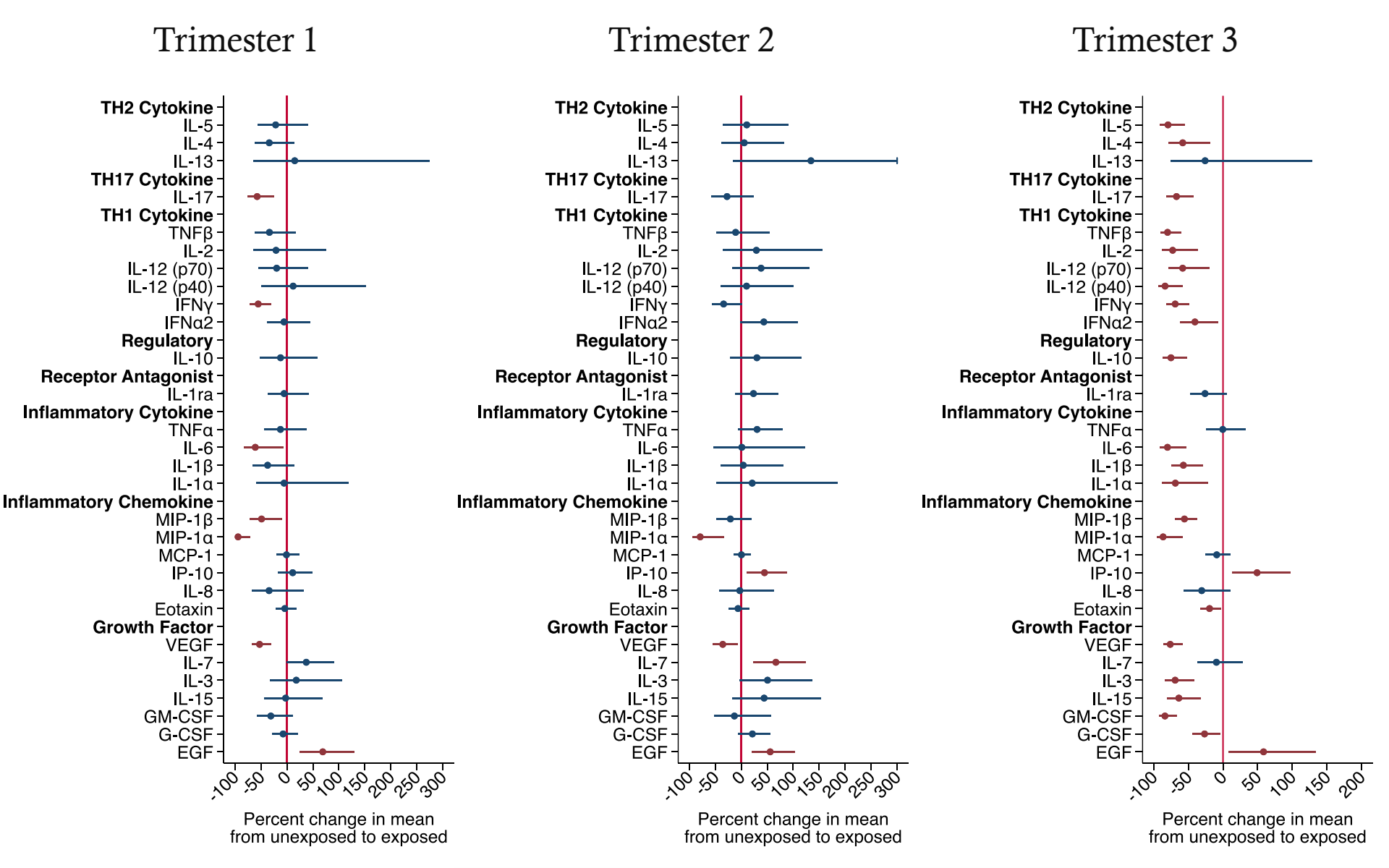
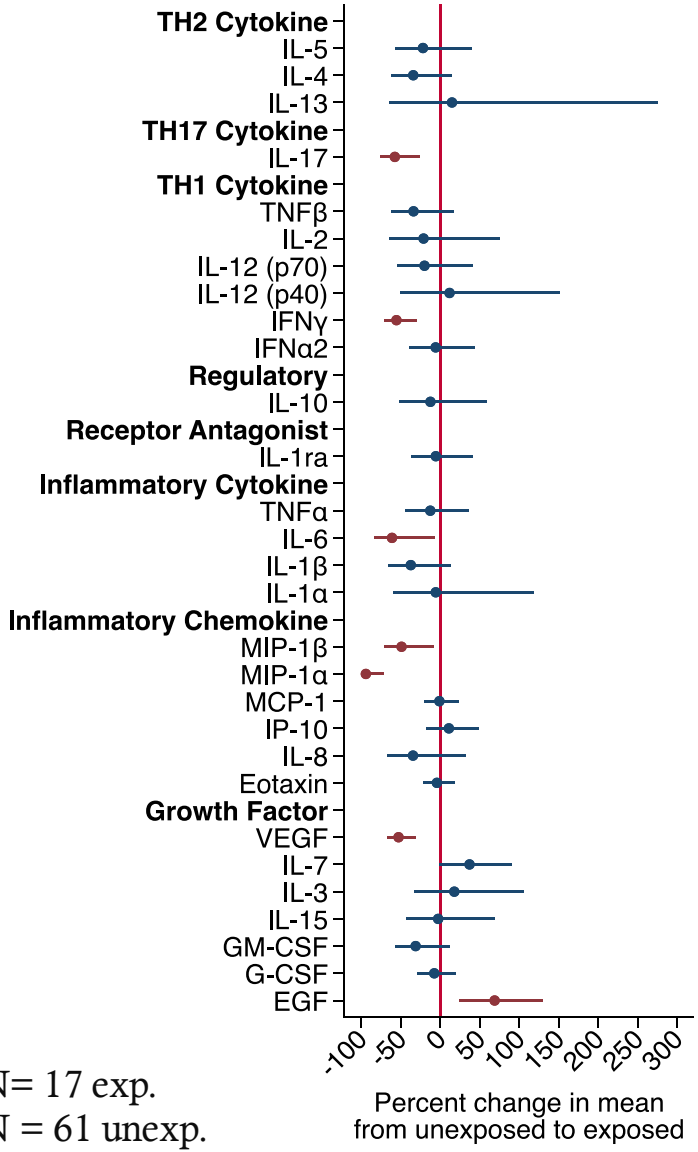
Results


Trimester 1
Trimester 2
Trimester 3
TH2 Cytokine
IL-5
IL-4
IL-13
TH17 Cytokine
IL-17
TH1 Cytokine
TNFβ
IL-2
IL-12 (p70)
IL-12 (p40)
IFNγ
IFNα2
Regulatory
IL-10
Receptor Antagonist
IL-1ra
Inflammatory Cytokine
TNFα
IL-6
IL-1β
IL-1α
Inflammatory Chemokine
MIP-1β
MIP-1α
MCP-1
IP-10
IL-8
Eotaxin
Growth Factor
VEGF
IL-7
IL-3
IL-15
GM-CSF
G-CSF
EGF
-100 -50 0 50 100 150 200 250 300
Percent change in mean
from unexposed to exposed

Results - Trimester 1

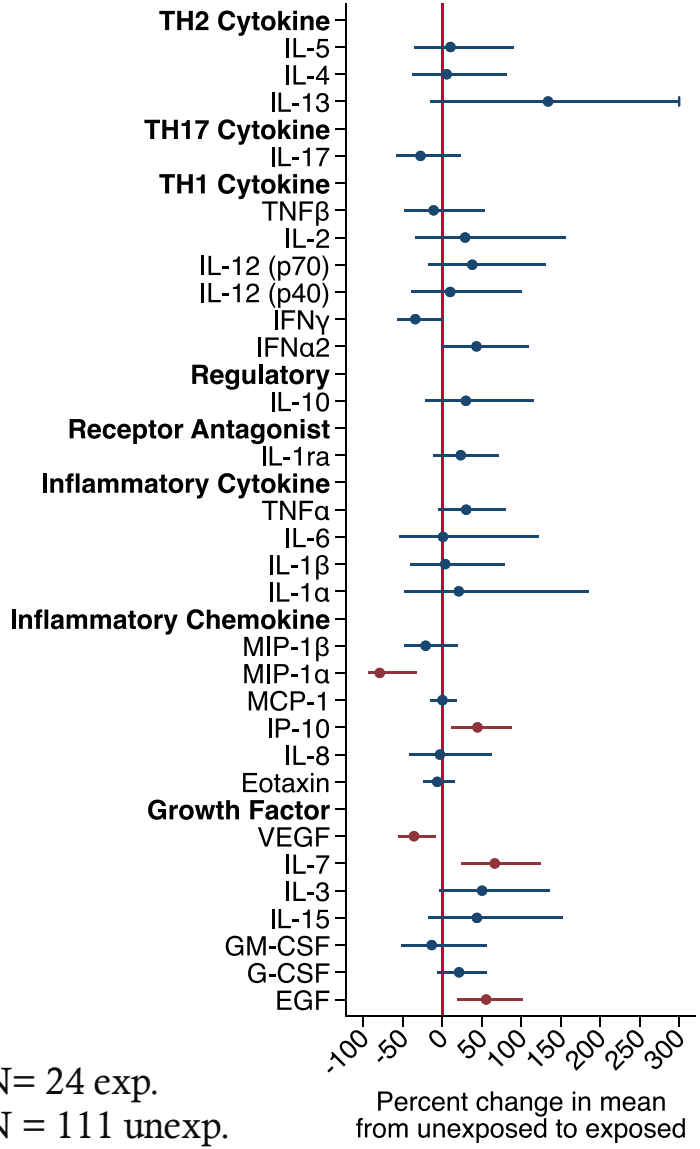
- Th17 (IL-17) cells induce protective immunity against extracellular microbes
- IFNγ involved in initiation of endometrial vasculature remodeling, angiogenesis at implantation sites, and maintenance of the maternal component of the placenta
- IL-6 - pro- and anti-inflammatory cytokine critical for relaying the effects of maternal inflammation to the developing fetus, which can then lead to altered social and cognitive behaviors in affected offspring. Also needed for healthy brain development. Balance is key- Goldilocks effect
- MIP-1α & MIP-1β attract macrophages/NK cells- **placental health**
- VEGF has important function in implantation process and in vascular formation in the placental growth process during the entire pregnancy period
- EGF stimulates cell proliferation and production of important placental hormones, such as HCG



N= 17 exp.
N = 61 unexp.

Results - Trimester 2

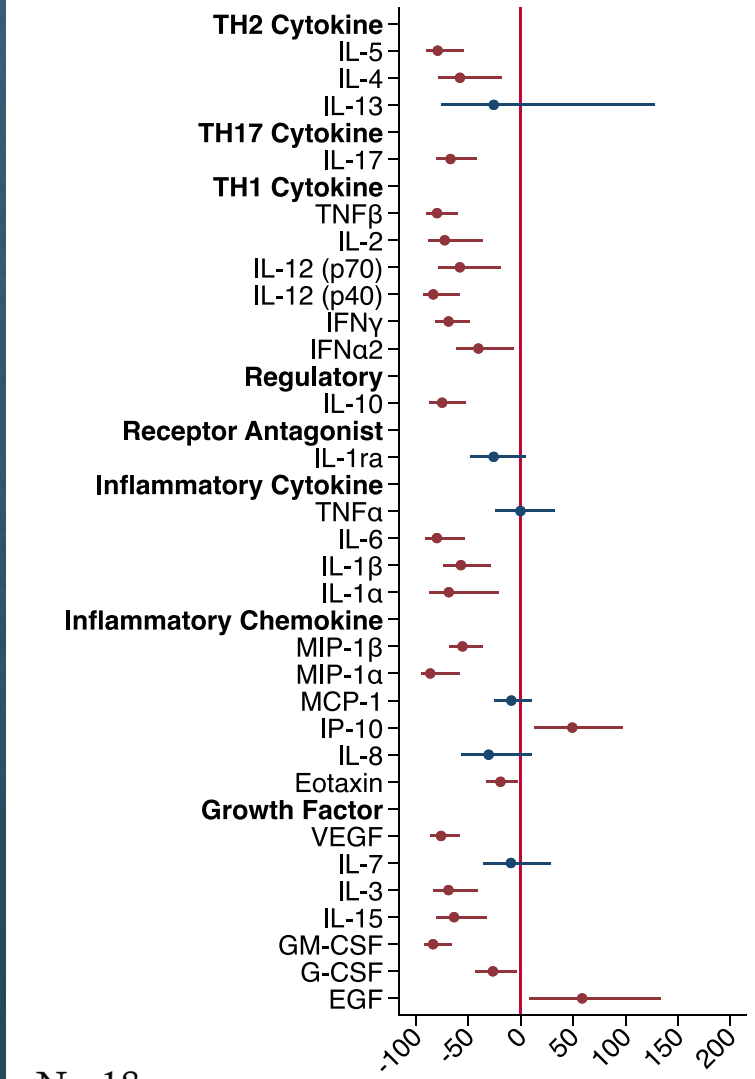
- MIP-1α & MIP-1β attract macrophages/NK cells
- IP-10 participates in formation of the pro-inflammatory immune microenvironment during early pregnancy by regulating the distribution of immune cells and promoting the production of pro-inflammatory cytokines
- IL-7 plays a key role in T- and B- cell maturity and homeostasis in humans. An overexpression of IL-7 could result in early pregnancy loss by inducing a pro-inflammatory environment
- VEGF has important function in implantation process and in vascular formation in the placental growth process during the entire pregnancy period
- EGF stimulates cell proliferation and production of important placental hormones, such as HCG



N= 24 exp.
N = 111 unexp.

Results - Trimester 3

- Nearly all cytokines/chemokines statistically significantly reduced
- IP-10, EGF statistically significantly increased



N= 18 exp.
N = 98 unexp.

Summary of WFE and Cytokines

- Prenatal exposure to WFE associated with:
  - Decreased TH1 (IFNγ), TH17 (IL-17, pro-inflammatory cytokines and chemokines, and growth factors in Trimester 1
    - Reduced VEGF could have global implications regarding placental and fetal vascular health. This finding consistent in all 3 trimesters with WF exposure
    - Other chemokines necessary for placental health and resistance to infection also reduced in WF-exposed women
  - Decreases in most cytokines and chemokines in Trimester 3
    - Fewer people exposed in this group, and cytokines/chemokines less stable during this time point, so, these results are somewhat less conclusive
- Larger studies, with better exposure assessment for PM from more recent, severe WFEs needed

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Take-Aways

- Birth and developmental outcomes have overlapping risk factors and potentially overlapping etiologies
- Extreme wildfire events are a examples of contaminant and stress events
- New and existing cohorts with biospecimens are useful to help understand exposures, biological responses, and downstream developmental (and other) health consequences associated
- There is much to learn!
- Meanwhile, best to mitigate exposure to smoke as much as possible in potentially susceptible developmental periods

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How To Reduce Wildfire Smoke Exposures

Corsi-Rosenthal Air Filter Box

- Stay indoors as much as possible
- Use air purifier if possible
  - Corsi-Rosenthal Air Filter Boxes
  - Air conditioner or house fan with Merv 13+ filters
- Wear N-95 or KN-95 Masks when outdoors
- Evacuate wildfire-smoke affected areas if possible

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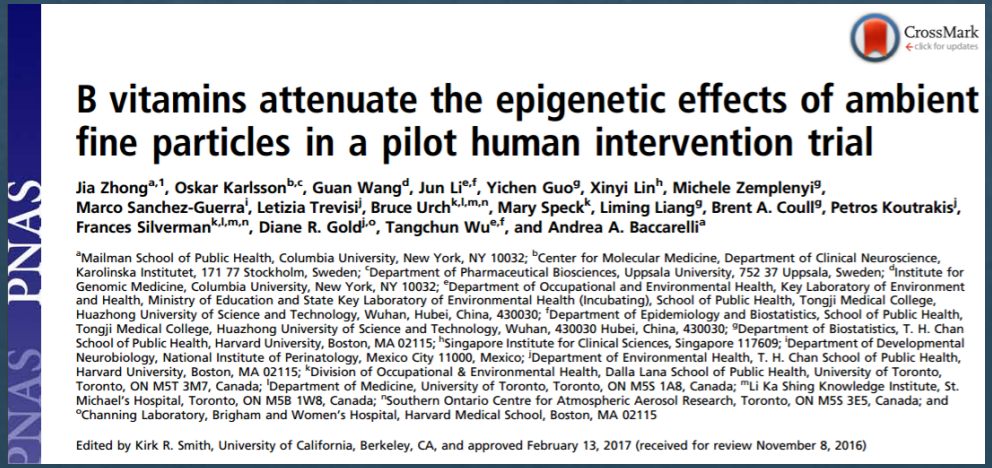
Folic Acid Can Counter Contaminant Effects

- In both human and animal experimental studies:
  - Environmental contaminants → DNA methylation changes
  - Supplemental folic acid reversed the DNA methylation changes
- In mice, this also countered the health effects in offspring



PNAS PNAS

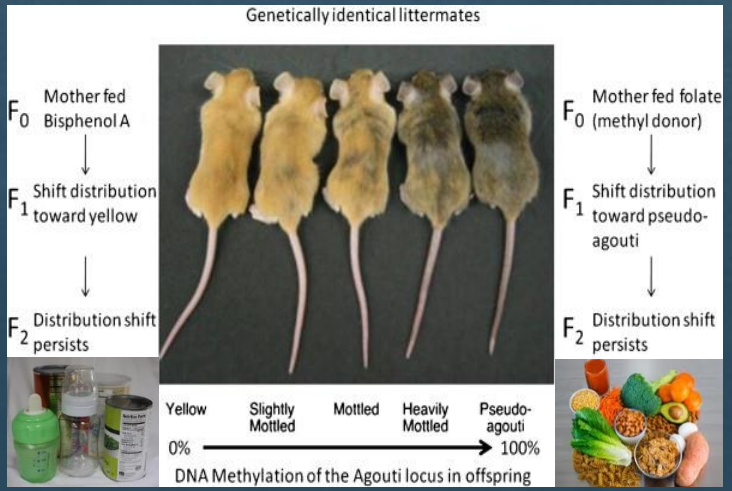
CrossMark click for updates

B vitamins attenuate the epigenetic effects of ambient fine particles in a pilot human intervention trial

Jia Zhong[a,1], Oskar Karlsson[b,c], Guan Wang[d], Jun Li[e,f], Yichen Guo[g], Xinyi Lin[h], Michele Zemplenyi[g], Marco Sanchez-Guerra[i], Letizia Trevisi[j], Bruce Urch[k,l,m,n], Mary Speck[k], Liming Liang[g], Brent A. Coull[g], Petros Koutrakis[j], Frances Silverman[k,l,m,n], Diane R. Gold[j,o], Tangchun Wu[e,f], and Andrea A. Baccarelli[a]

[a]Mailman School of Public Health, Columbia University, New York, NY 10032; [b]Center for Molecular Medicine, Department of Clinical Neuroscience, Karolinska Institutet, 171 77 Stockholm, Sweden; [c]Department of Pharmaceutical Biosciences, Uppsala University, 752 37 Uppsala, Sweden; [d]Institute for Genomic Medicine, Columbia University, New York, NY 10032; [e]Department of Occupational and Environmental Health, Key Laboratory of Environment and Health, Ministry of Education and State Key Laboratory of Environmental Health (Incubating), School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China, 430030; [f]Department of Epidemiology and Biostatistics, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 430030 Hubei, China, 430030; [g]Department of Biostatistics, T. H. Chan School of Public Health, Harvard University, Boston, MA 02115; [h]Singapore Institute for Clinical Sciences, Singapore 117609; [i]Department of Developmental Neurobiology, National Institute of Perinatology, Mexico City 11000, Mexico; [j]Department of Environmental Health, T. H. Chan School of Public Health, Harvard University, Boston, MA 02115; [k]Division of Occupational & Environmental Health, Dalla Lana School of Public Health, University of Toronto, Toronto, ON M5T 3M7, Canada; [l]Department of Medicine, University of Toronto, Toronto, ON M5S 1A8, Canada; [m]Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, ON M5B 1W8, Canada; [n]Southern Ontario Centre for Atmospheric Aerosol Research, Toronto, ON M5S 3E5, Canada; and [o]Channing Laboratory, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115

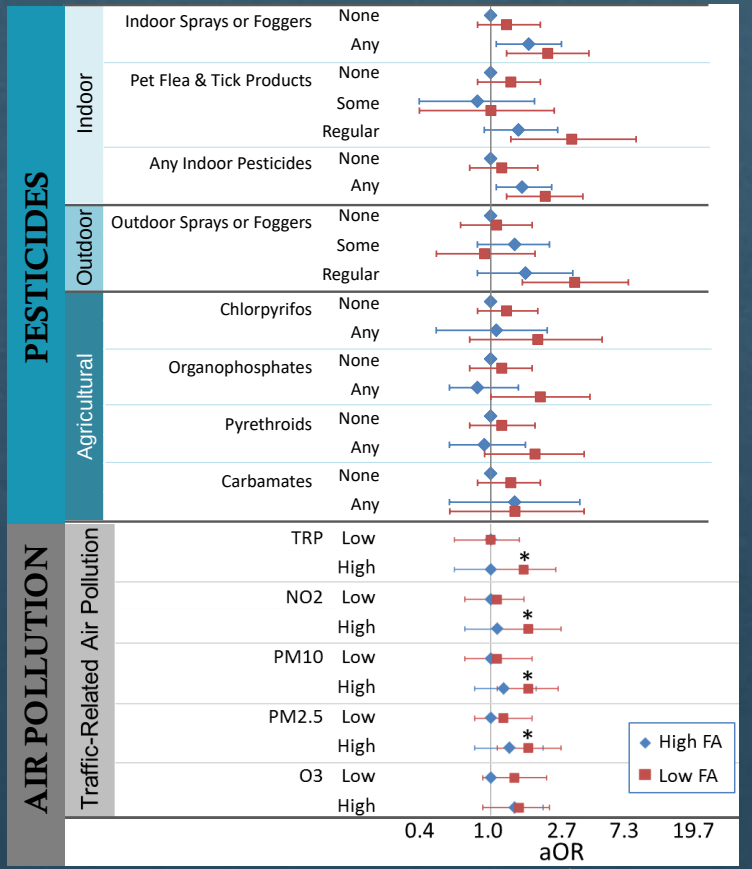
Edited by Kirk R. Smith, University of California, Berkeley, CA, and approved February 13, 2017 (received for review November 8, 2016)



Dolinoy et al, 2007

Supplemental Folic Acid x Environmental Contaminant Interactions

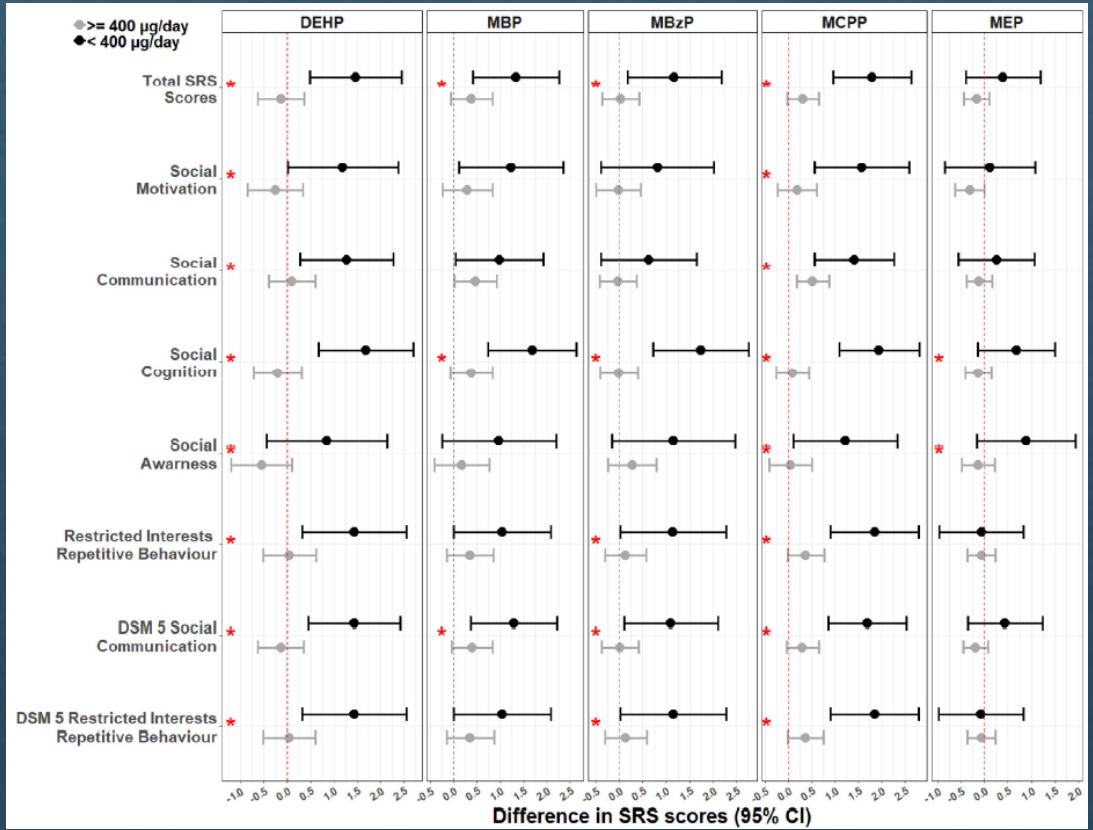
- ASD ORs for pesticides and air pollution higher when mothers had low periconceptional folic acid
  (Schmidt et al. 2017; Goodrich et al. 2018)
- Effect modification of associations between phthalates and periconceptional folic acid supplements in MARBLES
  (Shin et al. 2018)
- Effect modification of associations between phthalates and prenatal folic acid in MIREC
  (Oulhote et al. 2020)
- Folic acid might attenuate associations between contaminants & ASD



Folic Acid x Phthalate Interactions with ASD Traits in MIREC

SRS scores highest (more ASD traits) for those with both high phthalates and low prenatal FA (<400 µg/d)

(Oulhote et al 2020)



* Significant EM by FA p<0.1

Future Directions

- Expand research into broader, more diverse and representative populations – National ECHO Program (Environmental influences on Child Health Outcomes)
- As we learn more about the biological responses and pathways involved, we can understand how to better mitigate adverse health consequences
- Might also be able to understand which components are driving associations to ensure masks and filters eliminate those components for better interventions

UCDAVIS HEALTH SYSTEM

Collaborating Investigators

- **Deborah Bennett** – Exposure Measurement
- **Daniel Tancredi** – Biostatistician
- **Miriam Nuno** – Biostatistician
- **Katie Conlon** – Exposure Assessment; Geo Indexes
- **Sean Raffuse** – Exposure Assessment, Modeling
- **Mike Kleeman** – Exposure Assessment, Modeling
- **Ameer Taha** – Blood Exposure Measurements
- **Hong Ji** – Nasal Respiratory Epigenetics / Cytokines
- **Lisa Miller** – Primates Respiratory Immune Profiles
- **Anh P Nguyen** – Pediatric Allergist and Immunologist
- **Irva Hertz-Picciotto** – Environmental Epidemiologist
- **Tanya Khemet** – Community Engagement/Outreach
- **Erin Kinnally** – NHP Behavior, Epigenetics, **CNPRC**
- **Beate Ritz** – AP Exposure Modeling, **UCLA**
- **Manish Arora** – Hair Metals Measurement, **Mt. Sinai**
- **Susan O'Neille** – Exposure Assessment, **HAQAST**

Team

- **McKenzie Oliver** – Study Manager
- **Cheryl Walker** – Ob/Gyn, Placenta Expertise
- **Maria Mora** – Phlebotomist, Field, Lab
- **Elizabeth Angel** – Data Manager/Analyst
- **Amanda Goodrich** – Research Analyst
- **Logan Williams** – GRA, WGBS Analyst
- **Cole Torevick** – Laboratory
- **Luis Perucho Jaimes** – Laboratory
- **Gertrud Schuster** – Laboratory Manager

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UCD Environmental Health Sciences Center; MIND Institute IDDRC; Cancer Center

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