Opening Keynote – Overview of Pediatric Cancers and Environmental Exposures

National Cancer Policy Forum Virtual Workshop on the Potential Contribution of Cancer Genomics Information to Community Investigation of Unusual Patterns of Cancer | National Academies of Sciences, Engineering, and Medicine | April 13th, 2023

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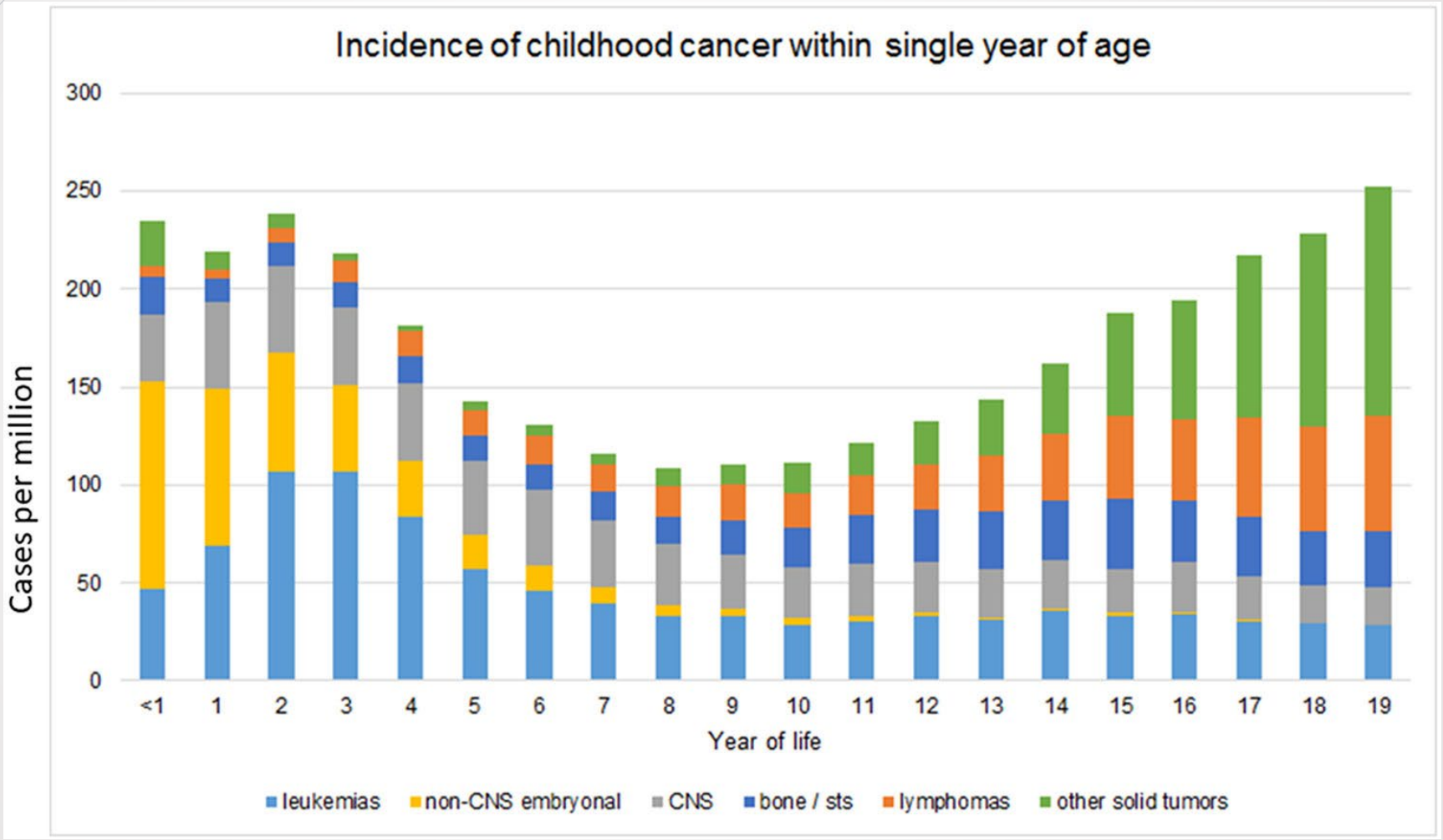
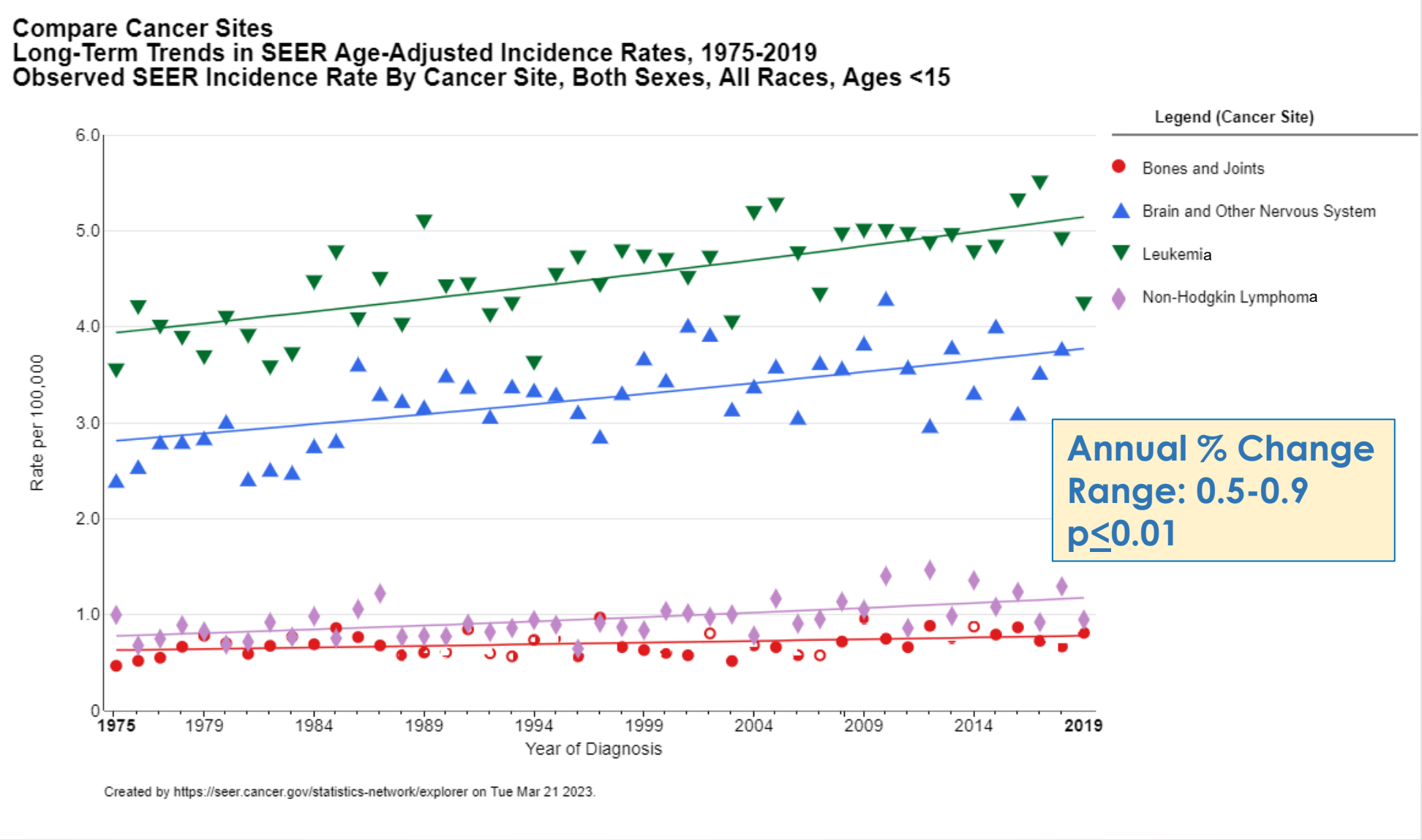
Berkeley
UNIVERSITY OF CALIFORNIA

Childhood cancers in industrialized countries

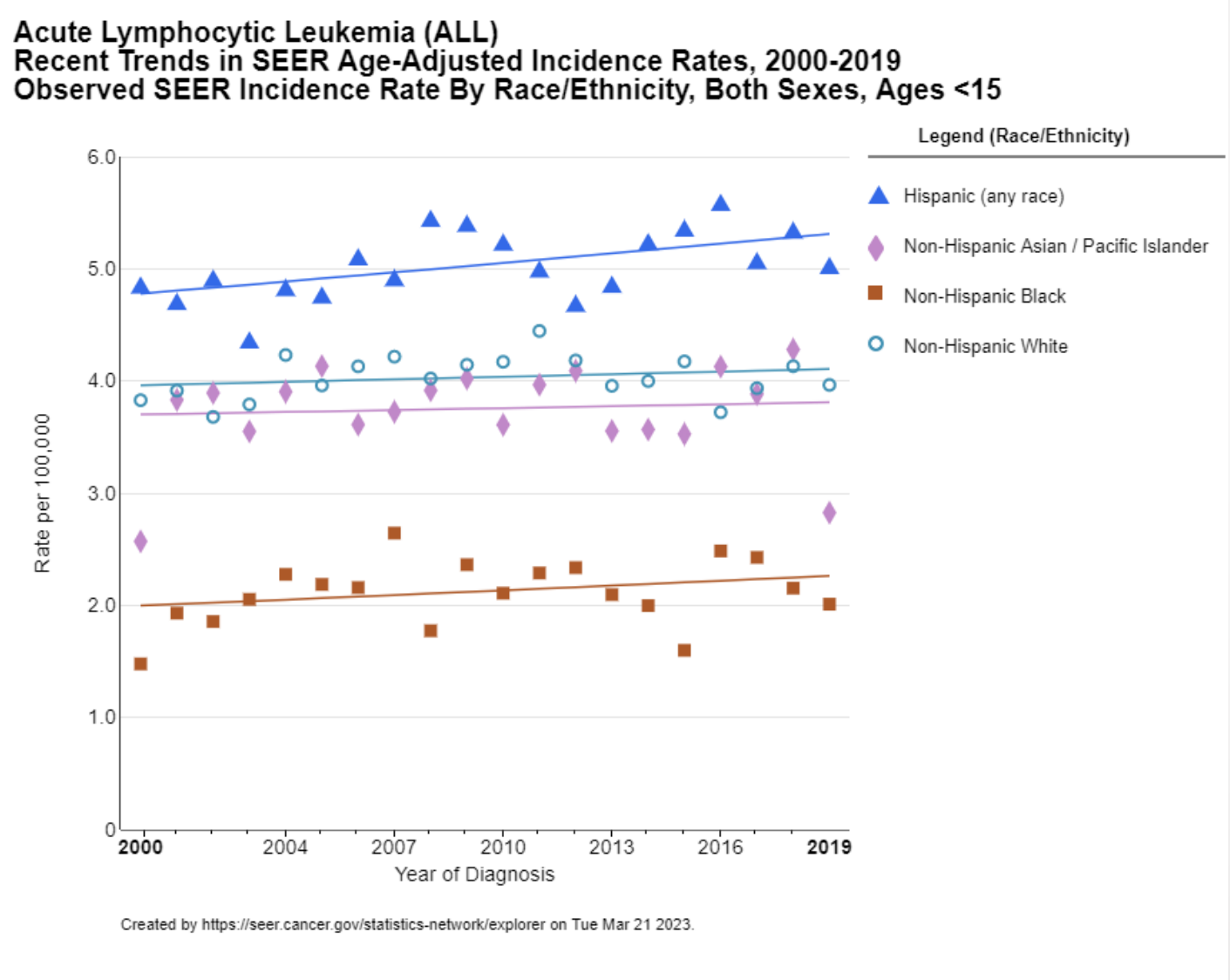


Lupo et al., Cancer Epidemiol Biomarkers Prev. 2020 June ; 29(6): 1081–1094.

Childhood cancers on the rise in the US

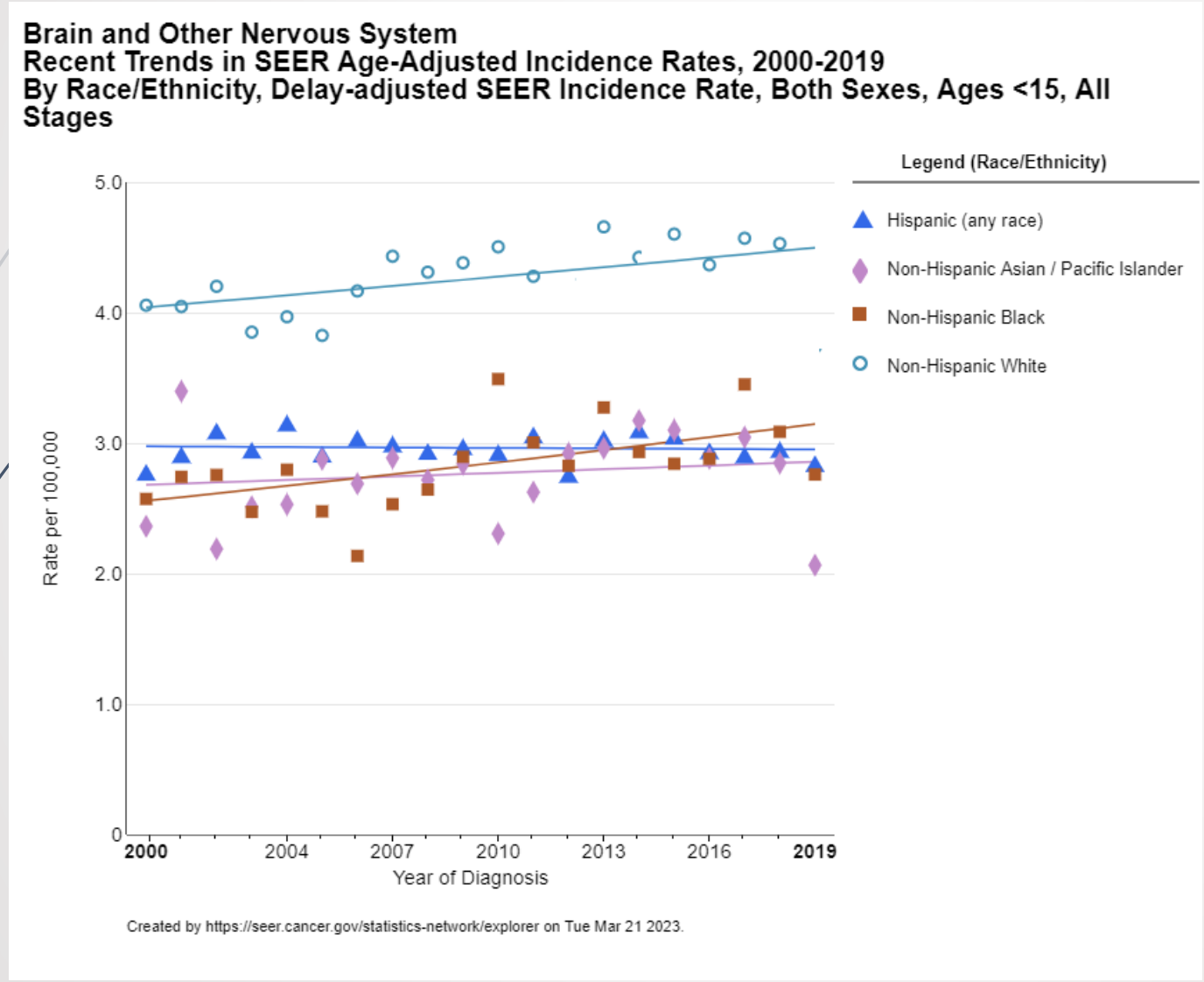


Childhood leukemia & racial/ethnic disparity



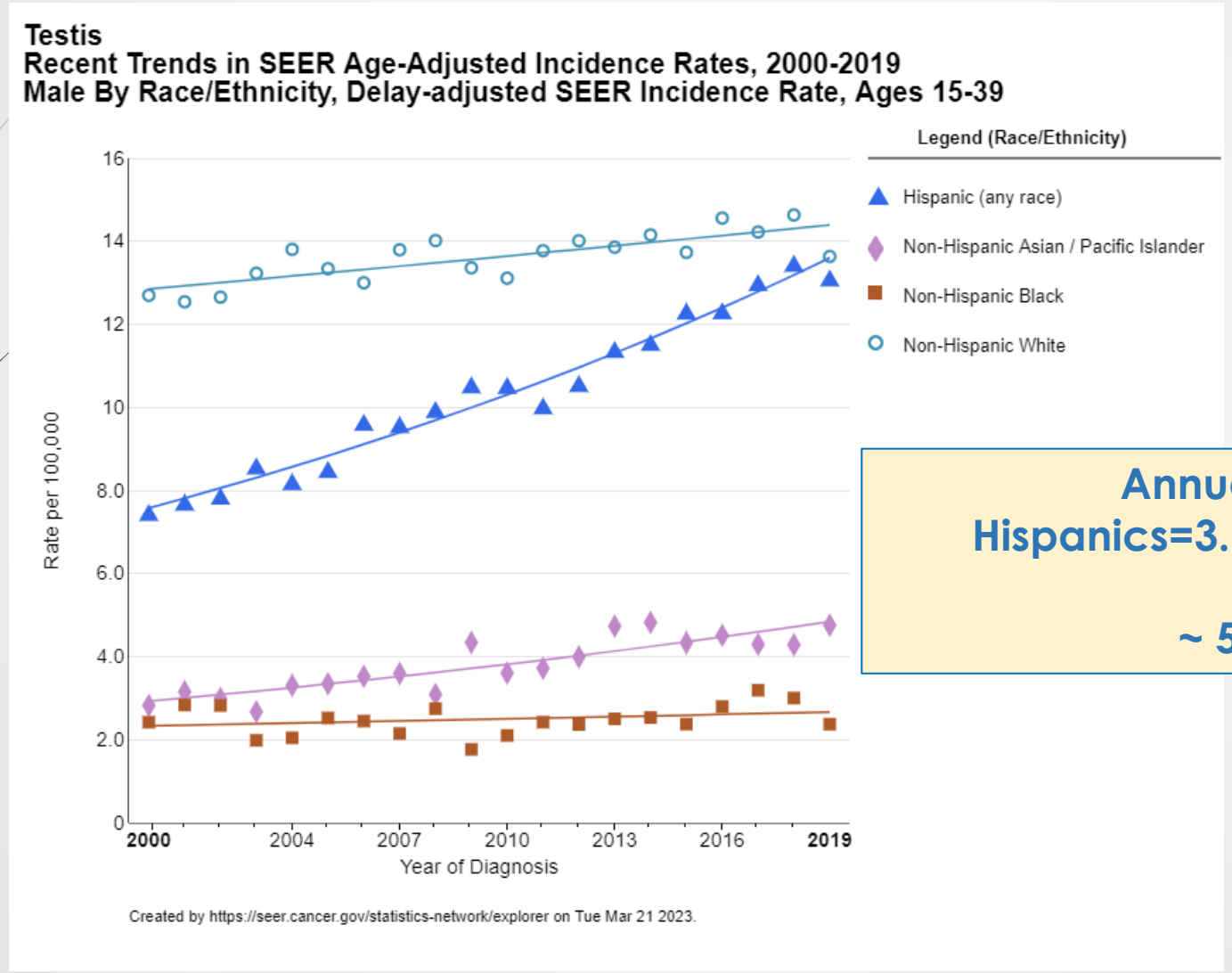
Annual % Change in Hispanic children=0.6
p=0.02

Childhood brain tumors & racial/ethnic disparity



Annual % Change in White children=0.6, p=0.02
Black children=1.1, p=0.01

Testicular cancers in adolescents & young adults



Annual % Change in Hispanics=3.1 vs 0.6 in White males

~ 5 times faster

- **Increasing trends in early-onset cancers are likely due to "environmental" & contextual factors**
  - Chemicals
  - Lifestyle--diet
  - Immune function
  - Social & historical determinants
- **Racial/ethnic differences and/or disparities**
  - Impact of the environment alone or in combination with genetics?
  - Cancer disparity in vulnerable populations => **Where you live matters**

Residential proximity to **pesticide use**

Environment International 143 (2020) 105955

International Journal of Hygiene and Environmental Health 219 (2016) 742–748

Contents lists available at ScienceDirect

Bamouni *et al. Environmental Health* (2022) 21:103
https://doi.org/10.1186/s12940-022-00909-0

Environmental Health

International Journal of Hygiene and Environmental Health 226 (2020) 113486

Contents lists available at ScienceDirect

International Journal of Hygiene and Environmental Health

journal homepage: www.elsevier.com/locate/ijheh

Prenatal pesticide exposure and childhood leukemia – A California statewide case-control study

Andrew S. Park[a], Beate Ritz[a], Fei Yu[b], Myles Cockburn[c], Julia E. Heck[a,d,*]

Occupational & residential exposures to **Pesticides**

Mother Jones and the Foundation for National Progress Photographer Matt Black

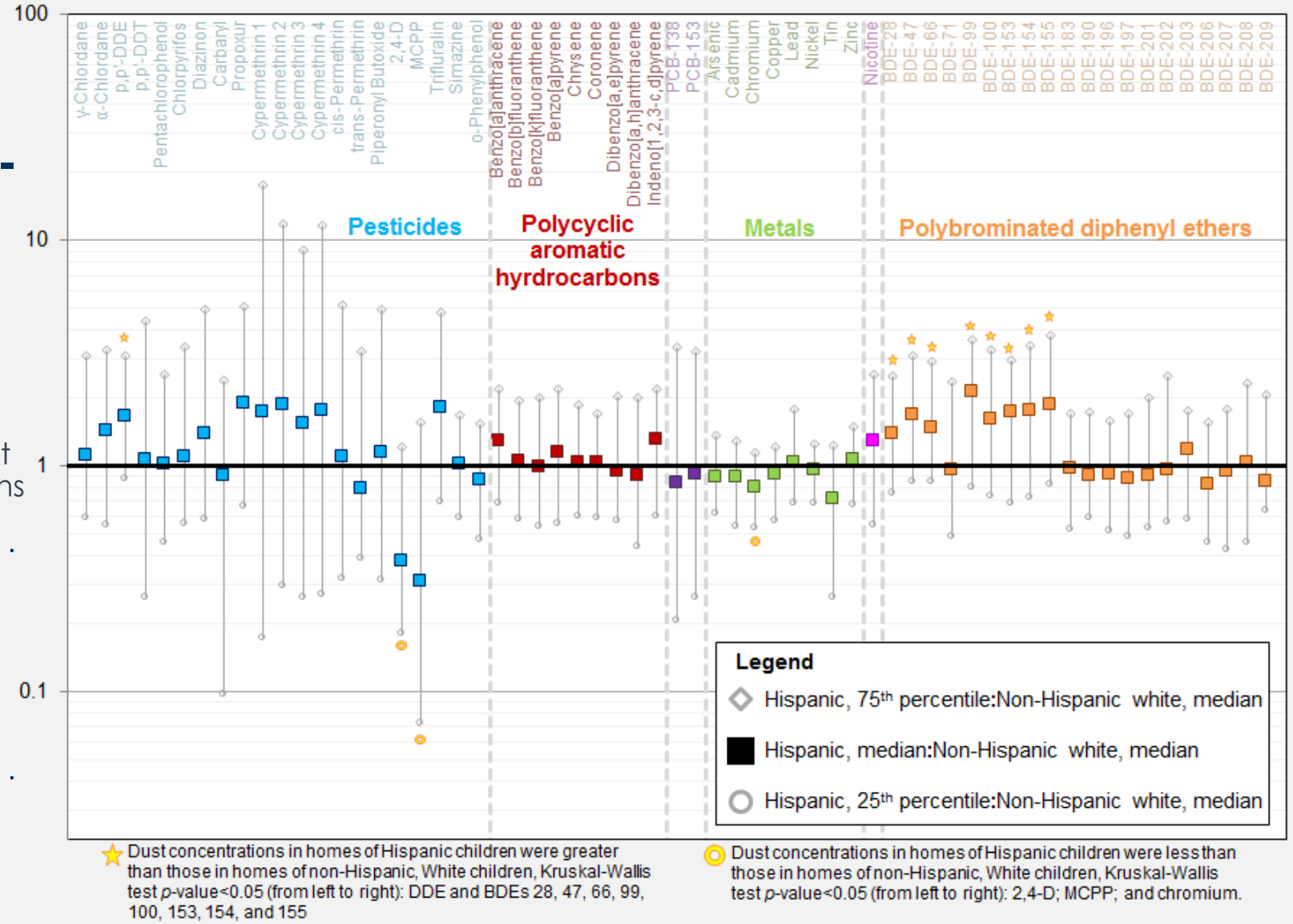
- California produces half of nation's fruits, nuts and vegetables
- California use 22% of the total agricultural pesticides in the US
- California employs 27% of nation's farmworkers
- **The majority of farm workers are Latinos.**

Disparity in home exposure to chemicals

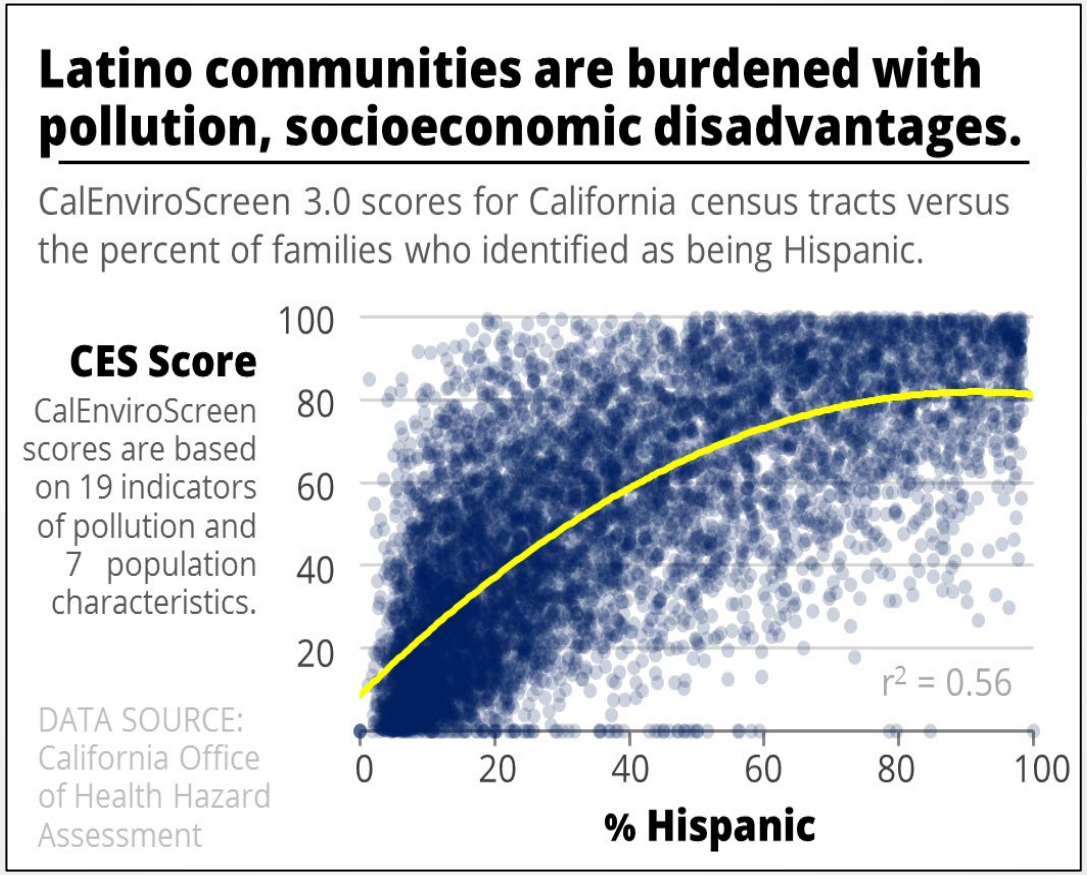
Data from dust samples – California Childhood Leukemia Study

Latino vs. Non-Latino White households

Ratios of dust concentrations



Highly impacted Latinx communities in California



Pediatric Liver Cancer & Hazardous Air Pollutants (HAPs) - Spatial risk analysis in Texas, 1990-2002

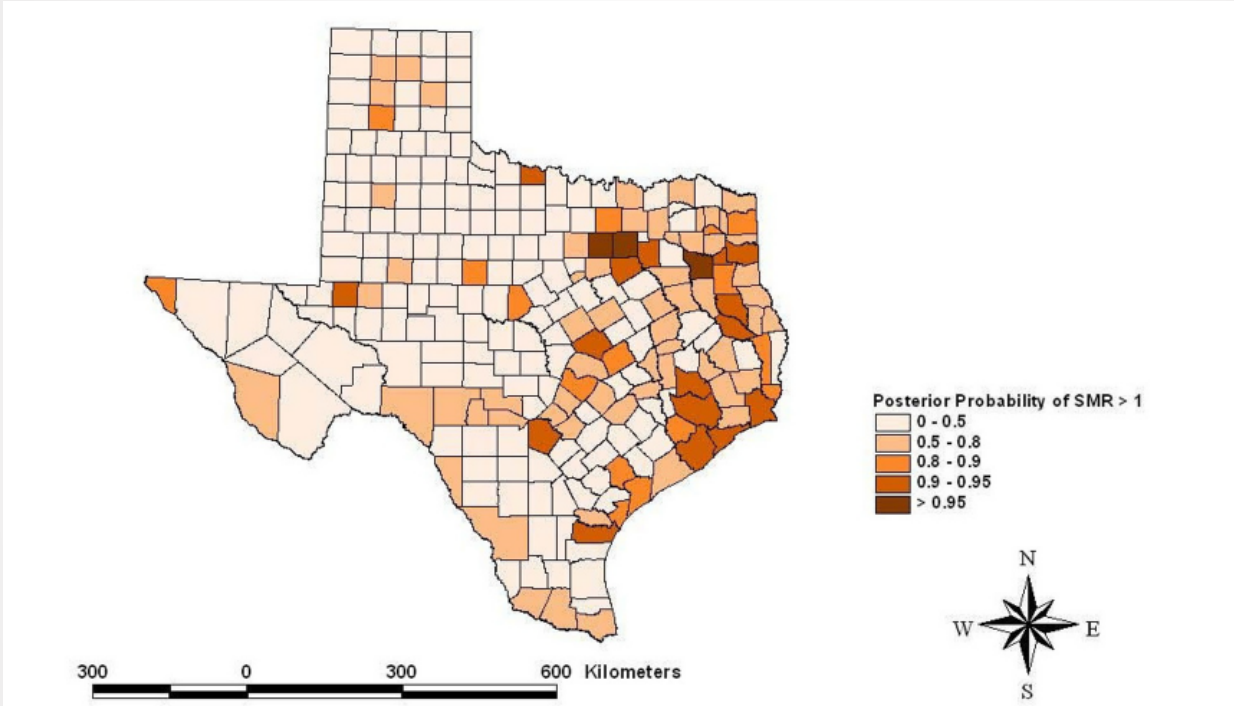


Figure 8
Spatial risks for hepatic tumors by county.

- *"The study supports the increase of childhood hepatic cancer risk [..and not other cancer sites] in areas of intense HAP release.* ***The standard morbidity ratio (SMR) for hepatic tumors was 1.87 (0.95, 3.98)*** *for county-years with greater than 100 tons of HAP releases."* Thompson et al., Env. Health, 2008

Exposure to air pollution in utero activates oxidative stress and inflammation pathways in newborns

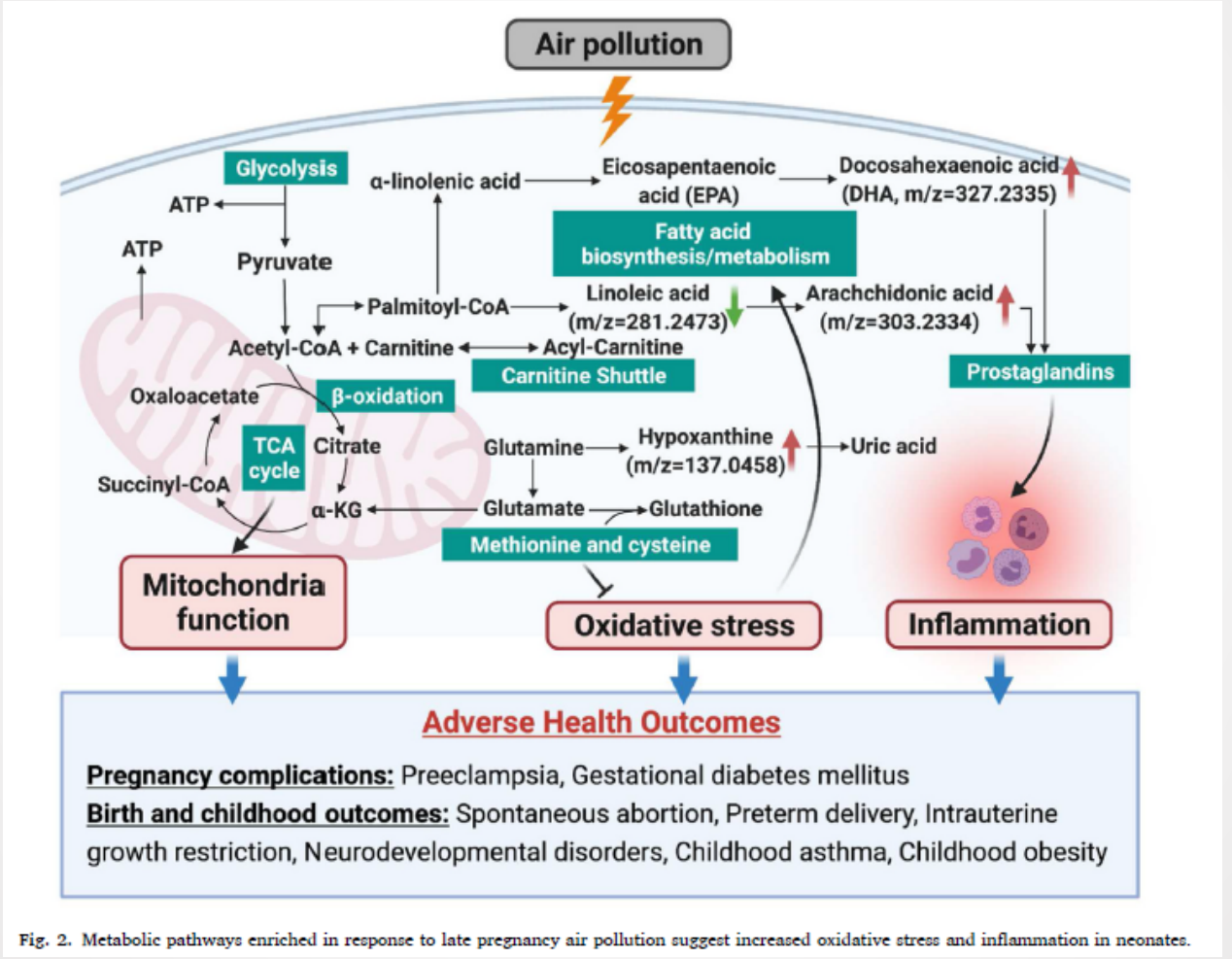
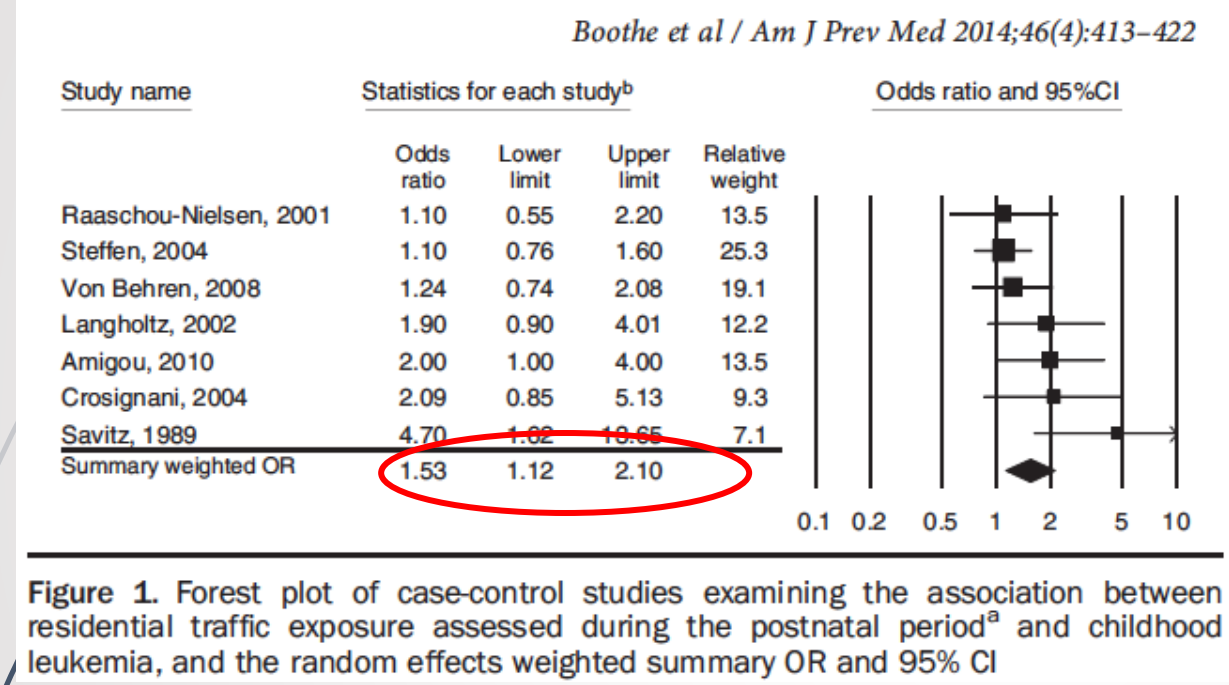


Fig. 2. Metabolic pathways enriched in response to late pregnancy air pollution suggest increased oxidative stress and inflammation in neonates.

Ritz et al., Environmental Research 203 (2022)

Air Pollution and Childhood Leukemia



Boothe et al / Am J Prev Med 2014;46(4):413–422

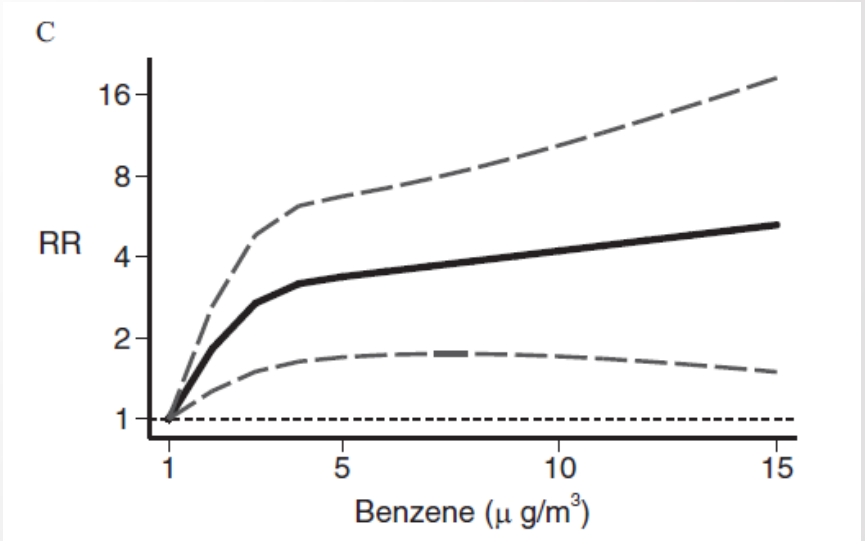
Study name	Odds ratio	Lower limit	Upper limit	Relative weight
Raaschou-Nielsen, 2001	1.10	0.55	2.20	13.5
Steffen, 2004	1.10	0.76	1.60	25.3
Von Behren, 2008	1.24	0.74	2.08	19.1
Langholtz, 2002	1.90	0.90	4.01	12.2
Amigou, 2010	2.00	1.00	4.00	13.5
Crosignani, 2004	2.09	0.85	5.13	9.3
Savitz, 1989	4.70	1.62	13.65	7.1
Summary weighted OR	1.53	1.12	2.10	

Statistics for each study[b] | Odds ratio and 95%CI

Figure 1. Forest plot of case-control studies examining the association between residential traffic exposure assessed during the postnatal period[a] and childhood leukemia, and the random effects weighted summary OR and 95% CI

Childhood acute myeloid leukemia

Fillippini, EHP 2019



Embryonal tumors and maternal residential proximity to major roads - Texas

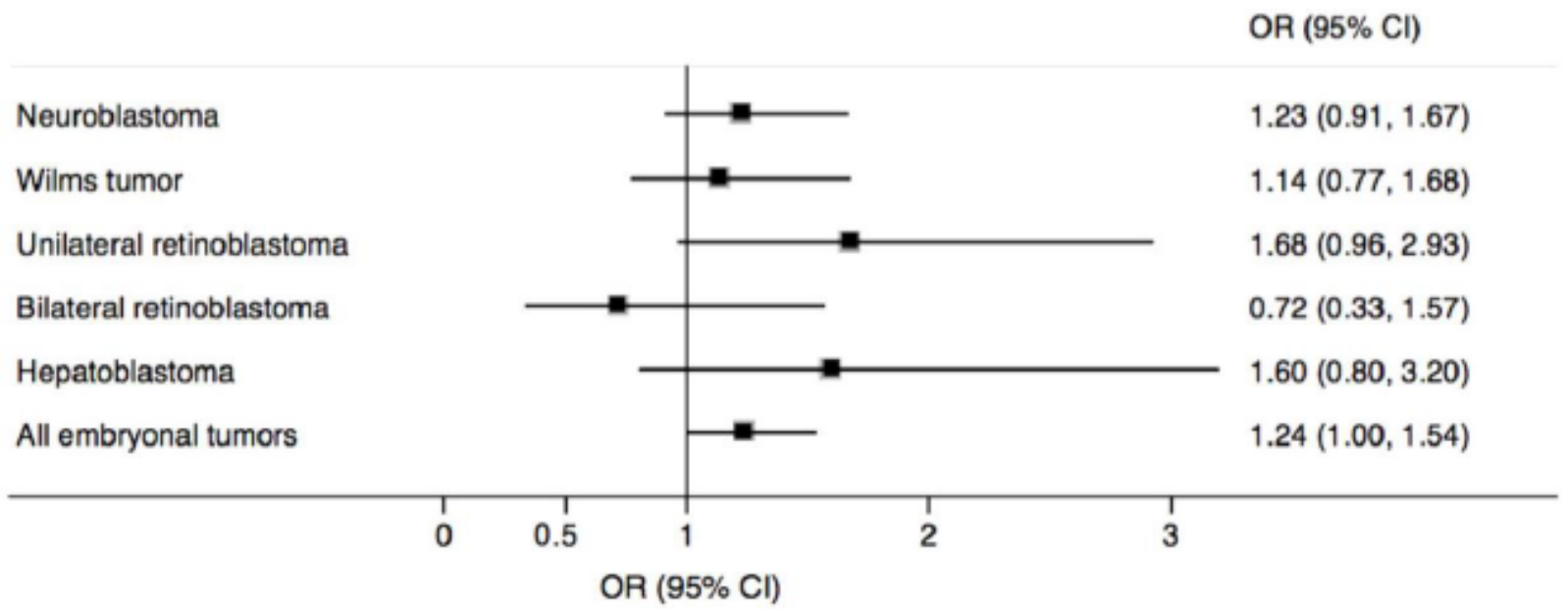


Figure 1. Adjusted odds ratios (OR) and 95% confidence intervals (CI) for maternal residential proximity <500 m from the nearest major roadway and embryonal tumors in offspring. The squares represent the adjusted OR for each tumor type. The horizontal line intersecting each square represents the respective 95% CI.

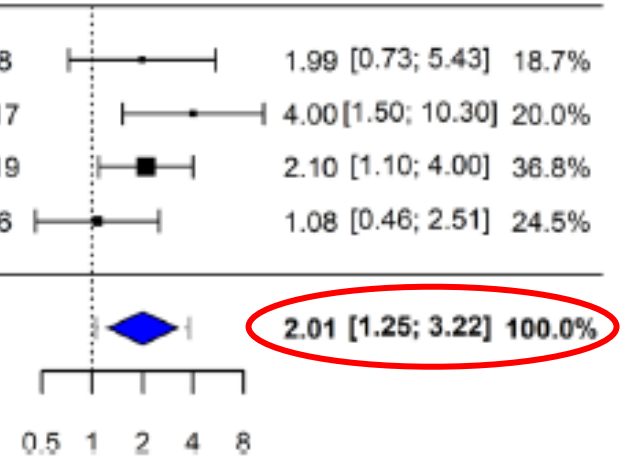
Shwetha V. Kumar

Int. J. Environ. Res. Public Health **2018**, *15*, 505

Residential Proximity to **Gas Stations** & Childhood Leukemia Risk

Authors, Year	Country	Years	Outcome	Age	Exposure: Source	Exposure: Contrast	Exposure: Time	Cases	Odds Ratio [95% CI]	Weight
Harrison et al, 1999	UK	1990–1994	Leukemia	0-15	Petrol stations	<100m v. >100m	At diagnosis	8	1.99 [0.73; 5.43]	18.7%
Steffen et al, 2004	France	1995–1999	ALL+ANLL	0-14	Repair garages or petrol stations	adjacent yes/no	Childhood	17	4.00 [1.50; 10.30]	20.0%
Brosselin et al, 2009	France	2003–2004	ALL+AML	0-18	Petrol stations	adjacent yes/no	Conception to diagnosis	19	2.10 [1.10; 4.00]	36.8%
Mazzei-Abba et al, 2021	CH	1985-2015	Leukemia	0-15	Petrol stations	<50m v. ≥500m	At diagnosis	6	1.08 [0.46; 2.51]	24.5%
Random Effect Model									**2.01 [1.25; 3.22]**	**100.0%**

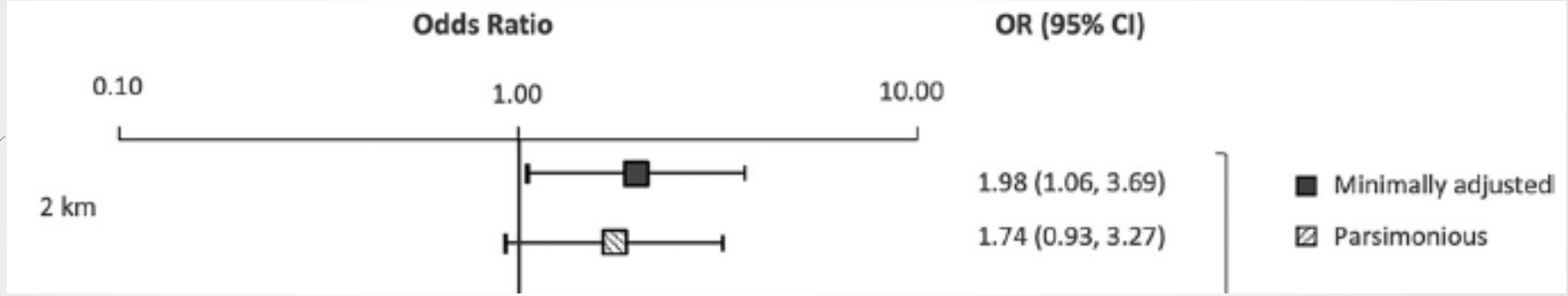
Q = 4.04, df = 3, p = 0.26; I^2 = 21% [0; 95]



Mazzei International Archives of Occupational and Environmental Health (2022) 95:927–938

Proximity to "**Fracking**" wells => Chemical and Radiological Contamination of Air and Water

- **Well count matrix within 2km buffer** – any time from preconception to 1 year prior diagnosis



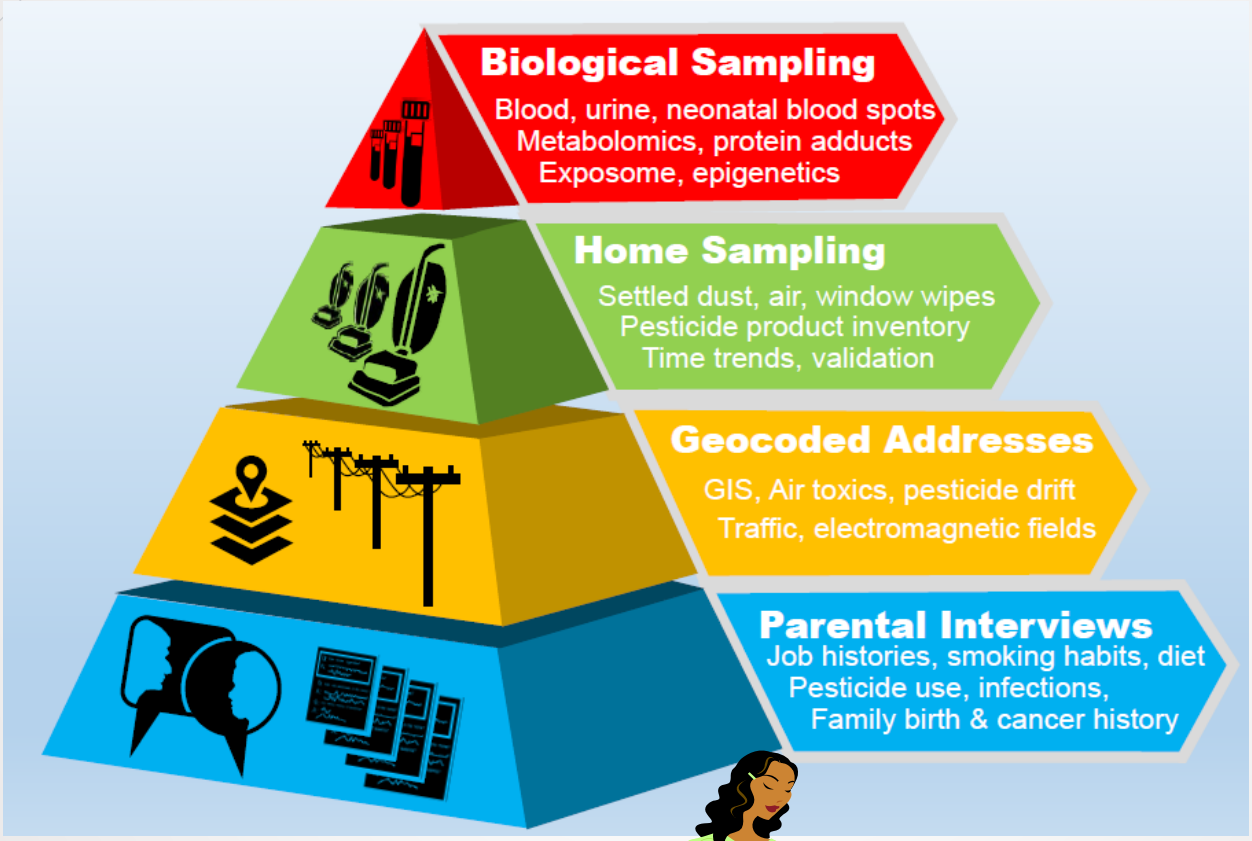
- **Well count matrix within 2km buffer** – any time from preconception to birth

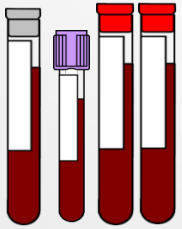
Deziel, EHP 2022

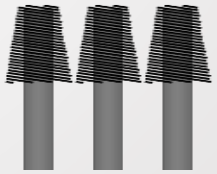
Challenges in studying pediatric & AYA cancers

- **Childhood cancers are rare ~ 25 times less frequent than in adults**
  - Registry-based studies and international collaborations
- **Cancers are heterogeneous**
  - Molecular characterization
- **Case-control design is most efficient**
  - Retrospective assessment of exposure
- **Biospecimens for biomarkers studies are sparse**
  - Exposure assessment and tumor biology studies
- **Most childhood (and AYA) cancers have a fetal origin**
  - Need for prenatal/neonatal specimens

Multidisciplinary approach







Biomarkers of maternal smoking during pregnancy

Yano, Anal Bioanal Chem. 2019; 411(11):2351-62

- Protein adducts

  - The Cys34 adduct of cyanide measured in neonatal blood spots was found to consistently discriminate between newborns of self-reported smoking and nonsmoking mothers with a mean fold change (smoking/nonsmoking) of 1.31

  - The elevated levels of the cyanide adduct among newborns of smoking mothers are consistent with inhalation of hydrogen cyanide from tobacco smoke

Gonseth, Epigenetics, 2016; 11(2):664-673

- Validated epigenetic markers

  - DNA methylation in aryl-hydrocarbon receptor repressor (*AHRR*- CpG cg05575921), a sentinel epigenetic biomarker of exposure to maternal smoking during pregnancy was correlated with self-reported smoking.

Maternal smoking and tumor genetics of childhood ALL

de Smith, Cancer Res, 2017
Kaur, Arc Med Res, 2016
Metayer, CEBP, 2013

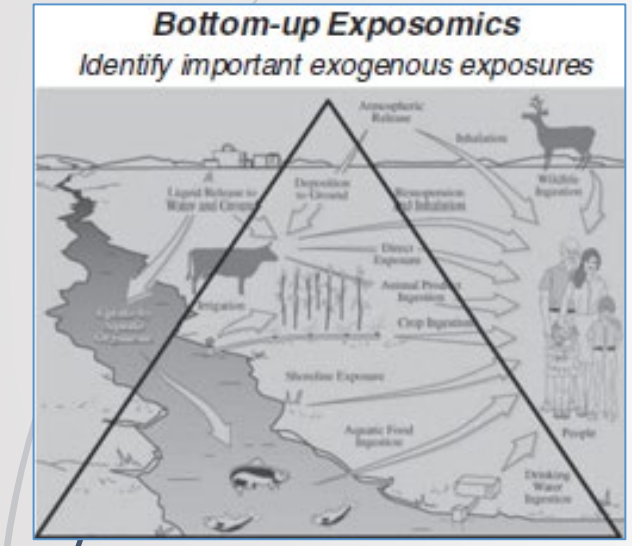
Molecular subtypes assessed in pretreatment tumor samples

- RAS mutations, TEL-AML translocation, high-hyperdiploidy
- Somatic copy number of 8 genes frequently deleted in ALL: *CDKN2A*, *ETV6*, *IKZF1*, *PAX5*, *RB1*, *BTG1*, PAR1 region, and *EBF1*

Leukemia Subtypes	Exposure	OR/RM*	95% CI
All combined (n=767)	- Pregnancy	0.83	(0.56-1.24)
With RAS mutations (n=122)	- Pregnancy	0.72	(0.33-1.57)
With deletions (n=353)	- Anytime	1.31	(1.08-1.59)
	- Pregnancy	1.48	(1.12-1.94)
	AHRR CpG site	***1.32***	***(1.02-1.69)***
	- Breastfeeding	2.11	(1.48-3.02)

- OR (odds ratio) or RM (ratio of mean) adjusted for child's age, sex, maternal race, household annual income, and paternal smoking; **Estimate was calculated for a 0.1 beta-value decrease at cg05575921, to reflect a biologically relevant difference.

Exposome



TARGETED SEARCH

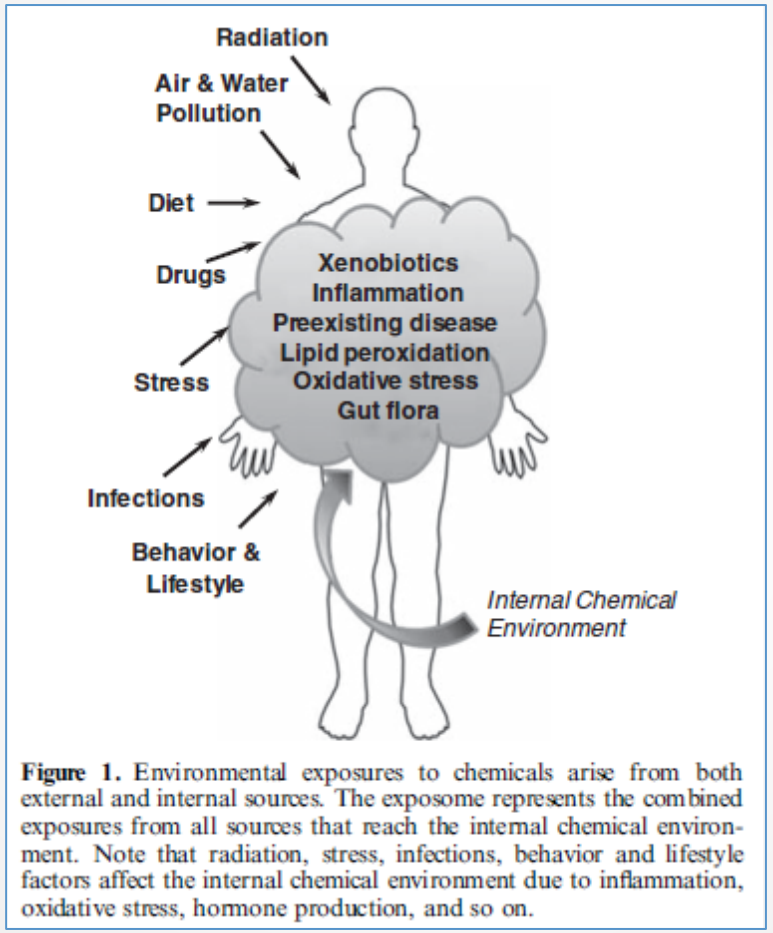
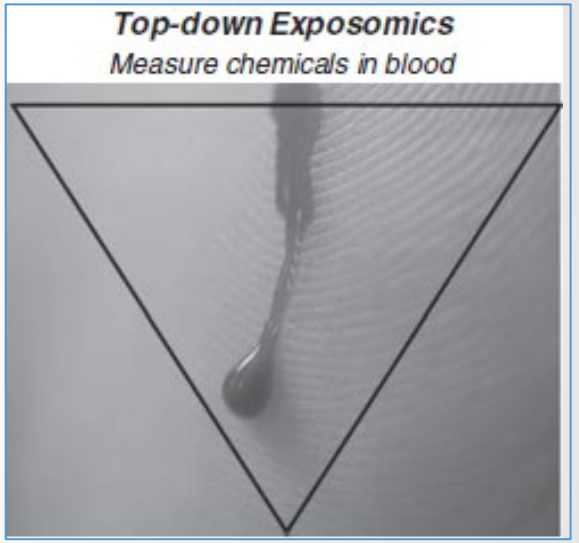


Figure 1. Environmental exposures to chemicals arise from both external and internal sources. The exposome represents the combined exposures from all sources that reach the internal chemical environment. Note that radiation, stress, infections, behavior and lifestyle factors affect the internal chemical environment due to inflammation, oxidative stress, hormone production, and so on.

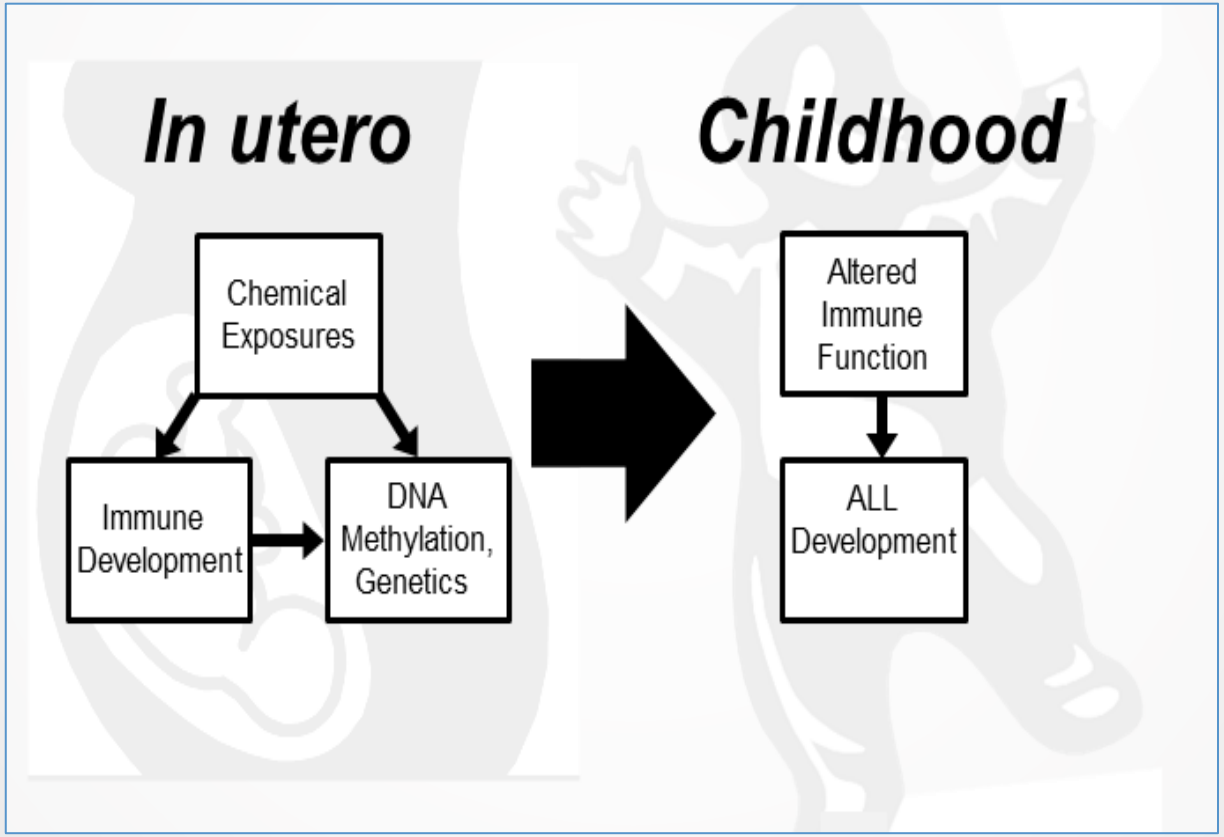


UNTARGETED & SEMI-TARGETED SEARCH

Rappaport, JESEE, 2012

Developmental Origins of Health and Diseases (DOHaD) Theory

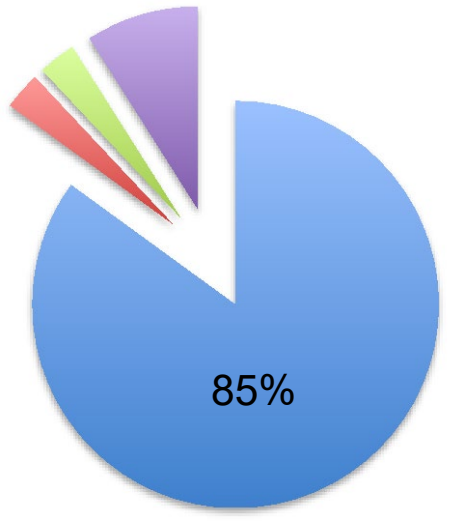
Preconception



Subtypes of childhood ALL

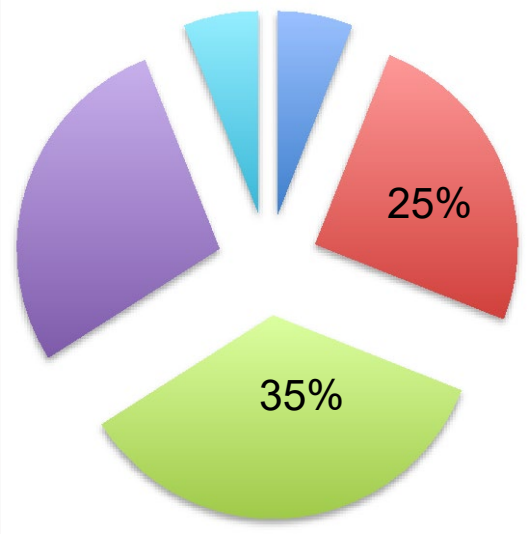
INFANTS

< 1 YR



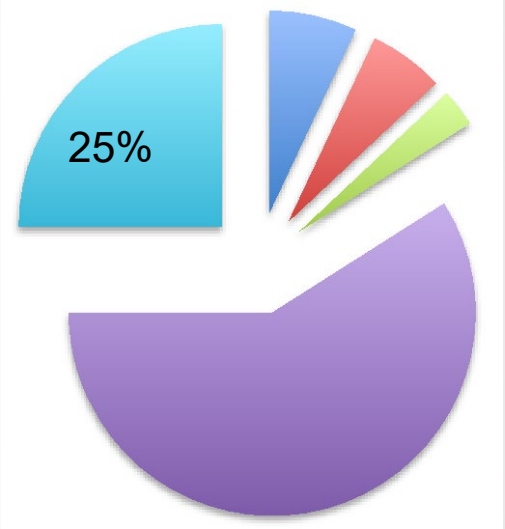
CHILDREN

1 – 15 YRS



ADULTS

16+ YRS

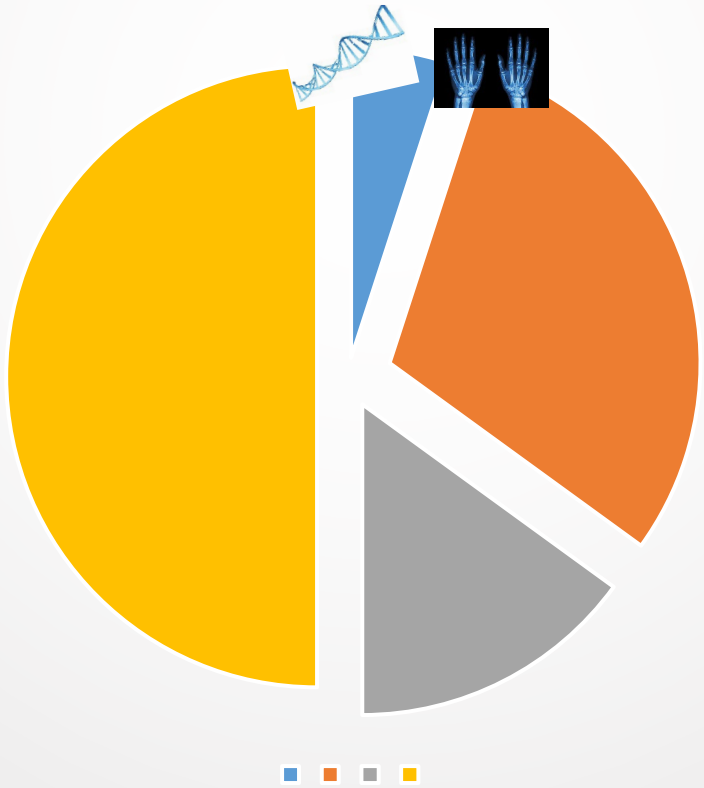


- Hyperdiploidy
- t(12;21) *TEL-AML1*
- 11q23 *MLL*
- Others
- t(9;22) *BCR-ABL1*

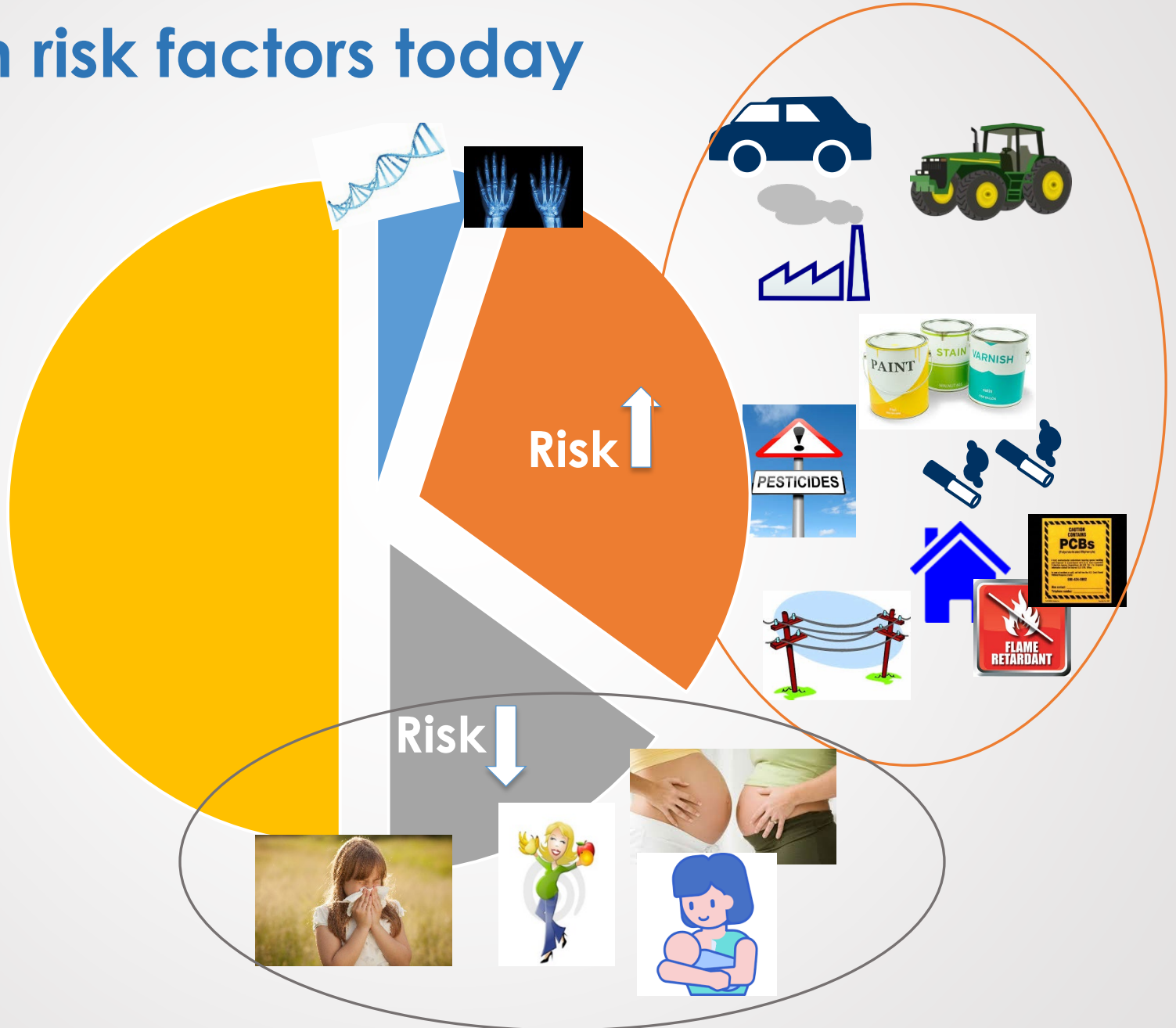
25 years ago

Known risk factors accounted for <10% of all childhood leukemia

genetic syndromes & x-rays



Known risk factors today



Whitehead, Curr Probl Pediatr Adolesc Health Care 2016; 46(10)):317-352

Metayer, pediatrics. 2016; 138(Suppl 1): S45-S55

Silos vs. Bridges

Cancer cluster investigations

- **Woburn, MA– Cluster of childhood leukemia**
  - Established link to water contamination with trichloroethylene (TCE) and perchloroethylene (PCE)
  - Known human carcinogens in adults
  - Positive associations also reported in population-based childhood leukemia studies looking at parental exposures
- **"Unsolved" pediatric cancer clusters:** Seacoast, NH; Fallon NV; Fayetteville NC (PFAS?), more??

Population-based studies

- **Proactive cancer registry monitoring** at small spatial/temporal resolution
- **Incorporating molecular tools**
  - Germline genetics
  - Tumor genetics
  - Epigenetics
  - Exposome

Thank you