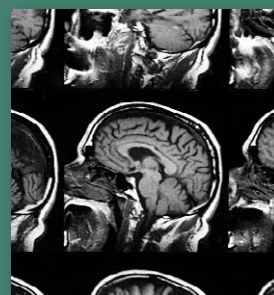
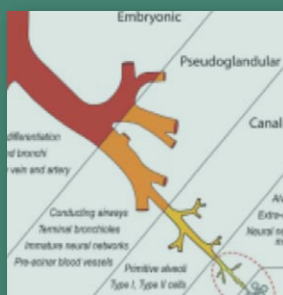
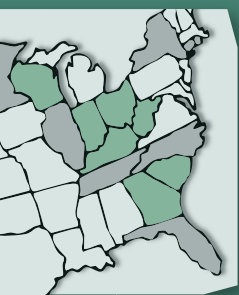


A Story of Health



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University of California, San Francisco: [Program on Reproductive Health and the Environment](#)

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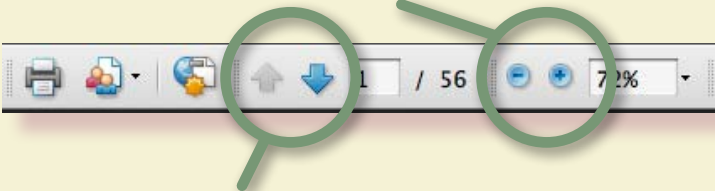
DISCLAIMERS:

1. The Western States Pediatric Environmental Health Specialty Unit (PEHSU) prepared A Story of Health on behalf of the American College of Medical Toxicology (ACMT) and funded as part of the cooperative agreement award number 1U61TS000238-01 from the Agency for Toxic Substances and Disease Registry (ATSDR). CIRCLE is supported with funds from NIEHS grant P50 ES018172 and US EPA grant RD83615901, P.I. Catherine Metayer MD PhD.
2. The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the organizations listed (above) as funders.
3. The ATSDR, US EPA, NIEHS, and Cal EPA/OEHHA do not endorse the purchase of any commercial products or services mentioned in this publication.

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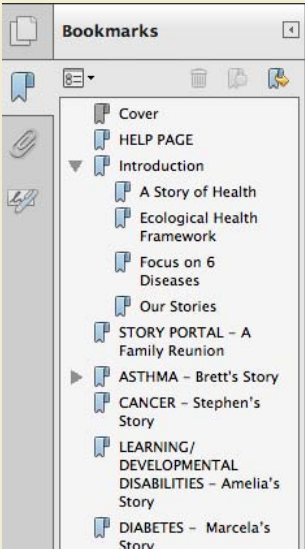


Table of Contents

Use the sidebar **Bookmark Tools** as a table of contents to skip to a section of interest, find your place, or return to this Help page.

THE INDIVIDUAL STORIES OF HEALTH in this eBook are written to address many audiences. For example, some sections are more technical than others – you can skip sections if you wish.

(Note: underlined words or phrases link to online information, prompt down-loads or navigate to a related page.)

EACH OF THE EBOOK STORIES is embedded with a wide range of resources. These help further explain possible environmental and/or genetic “risk factors” – (contributors to the development of a disease, or factors that might make a disease worse) – and how these factors interact. We also provide links for additional resources, including actions you can take to prevent disease, and “tools you can use.”

Our eBook Navigation: Click on selections in the bar at the top of each page to move between stories, navigate back to this ‘Help Page’, and to find out more in the References section.

If you lose your place, use the ‘Go Back’ selection in the navigation bar to return to your previous screen.

Icons

Click on icons that appear throughout the stories for pop-ups, videos, and links to more information as described.



key concept



watch a video



additional resources, tools



technical details for health professionals



skip this section



definition

RESOURCES INCLUDE videos, slides with audio commentary, tables, charts, and graphics. Some ‘pop-up’ in the story, and some connect online. Through these links, you can choose to dig deeper and learn more. Refer to the icons (above) for guidance.

REFERENCES AND CITATIONS: Certain references are cited in the text where we believe they are most warranted. Full references by topic can be found at the end of each story.

You can skip this section and continue to the Story of Health introduction.



INTRODUCTION

This is a story about health.

It is a story of how our own health is intimately connected with the health of our families, friends and communities.

It is a story about how human health is interdependent with our surroundings.

Our overall story is told through the personal stories of a number of fictional people of various ages attending a family reunion.

These individual stories highlight the many ways our health is influenced by the complex environments where we live, eat, work, play, volunteer, gather and socialize.



INTRODUCTION

Our stories explore how many aspects of our lives, and what we are exposed to in our environments, influence health across the lifespan—from the beginning of fetal development to elder years—and how they can promote health and resilience, or disease and disability.

Important determinants of health come from the natural, built, chemical, food, economic, and social environments.

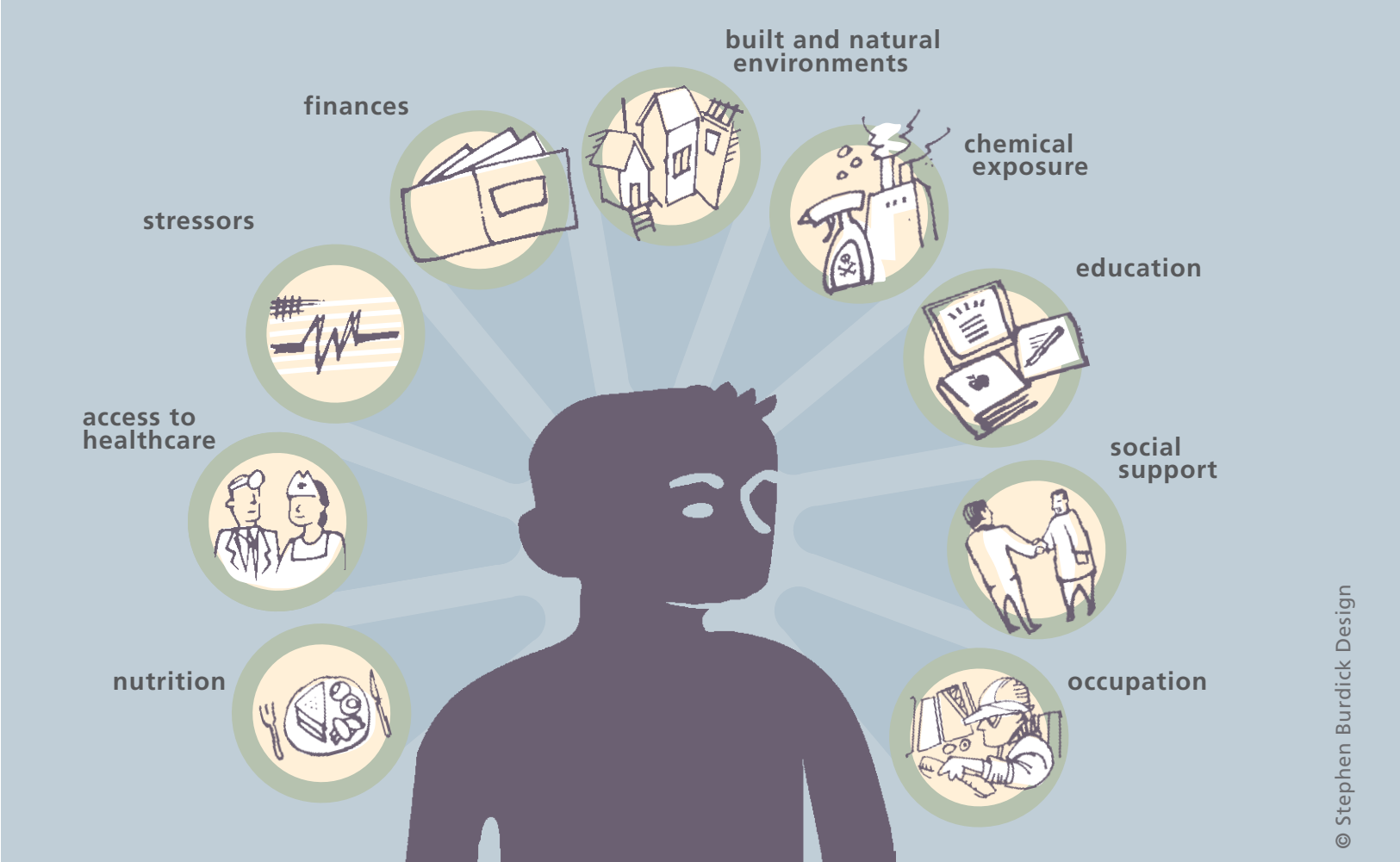
These environments are further expressed through such things as education, housing, nutrition, access to health care, social supports and more.

Many of them interact to create the conditions for health and wellness, or vulnerability to disease.



Watch: Pediatrician Larry Rosen addresses the environment and family health. (2 min.)

Lawrence D. Rosen MD is an integrative pediatrician and founder of the Whole Child Center.



Complex interactions occur among many variables and across individual, community, and societal levels.

Rarely is one particular thing responsible for health or disease, so we refer to this as a multifactorial (or ecological) approach, the best way to promote health and prevent disease.

INTRODUCTION Ecological Health Framework

The ecological framework can include multiple levels from sub-cellular to societal.

It is not hierarchical in the sense that one level is more important than another, but rather in the sense that individual biology is progressively nested within the person, family, community, society and ecosystem.

The interactions and feedback loops within, across, and among these levels are complex and variable. They exert their influences on health across time.



The ecological health framework also extends to the sub-cellular level.

INTRODUCTION

Focus on Six Diseases

Following are stories of people like you and me, our partners, families and friends, our mothers and fathers, sisters and brothers, children, grandparents, cousins, and aunts and uncles.

The personal health stories we will explore include some of the most common and troubling diseases and disorders of our time.

They include:

- Asthma
- Cancer (childhood leukemia)
- Diabetes
- Infertility
- Learning and developmental disabilities
- Cognitive decline



Asthma



Diabetes

Cancer



Cognitive decline



Infertility



Learning and developmental disabilities

INTRODUCTION Our Stories

These stories are not meant to be an exhaustive accounting of every variation of a disease or every possible cause.

Rather, we present current, authoritative scientific evidence to enable you to better understand environmental contributors and make more informed decisions and take action to help improve your health, and the health of your family, friends, community, and patients.



A FAMILY REUNION

Six Stories

This page is your portal to six stories of health.

It is recommended that you read through the [introduction](#) first and then choose stories in the order you wish.



Health professionals can receive Continuing Education (CE) for completing *A Story of Health*. Click [here](#) for more details.



Choose stories in the order you wish. Select a disease term to highlight the affected person. Click the arrow button to read his or her fictional story of health.

INTRODUCTION Free Continuing Education

Information on free Continuing Education offered from the Centers for Disease Control and Prevention/Agency for Toxic Substances and Disease Registry

Each of the fictional stories in *A Story of Health* offers free Continuing Education (CE). On the “Final Thoughts” page of the last story of the entire eBook, or of each story (if you download them separately), you will be prompted to register for CE through a hyperlink.

This hyperlink links to the CDC/ATSDR CE page where you can register and take the test for CE for each story. Before you begin each story, please review the learning objectives at right. These will help you focus as you read each story, and prepare you for each CE test.

Review these learning objectives for each story:



FREE CONTINUING EDUCATION

Continuing education available by specialty

- Continuing Medical Education (CME) for Physicians
- Continuing Nursing Education (CNE) for Nurses
- Continuing Education Units (CEU) for other professionals
- Continuing Education Contact Hours (CECH) for Certified Health Education Specialists (CHES)

ASTHMA: Brett's Story (a fictional case)

Brett is a nine year old boy who lives with his mom, Karen in an urban area in southern California. They live in an apartment near a busy street, and Brett takes the bus to public school. He plays several sports including baseball, soccer, and basketball, and likes to go out with his friends. Unfortunately, today, many kids like Brett also have asthma.



Health professionals:
Click [here](#) to read more about asthma.






Asthma resources and more information from the CDC .



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-  Basic information: Click [here](#) to find our more about asthma.
-  Health professionals: Click [here](#) to read more about asthma.
-  Asthma resources and more information from the CDC .



Asthma Information for Health Professionals

“By definition, all asthmatics share common physiologic abnormalities of airflow limitation such as obstruction on spirometry, airway hyper-responsiveness to methacholine challenge, and symptoms that can include shortness of breath, chest tightness, wheezing, and coughing. Despite these shared features, clinicians have long recognized the great heterogeneity in the severity of airway obstruction and symptoms, degree of reversibility, and the amount of improvement in response to medications.”
(Bhakta, 2011; Holgate, 2010)

From more information check out these online links:

- CDC’s health care [guidelines](#)
- ATSDR’s CASE study, [Environmental Triggers of Asthma](#)
- National Environmental Education Foundation – [Environmental Management of Pediatric Asthma: Guidelines for Health Care Providers.](#)

ASTHMA: A Multifactorial Disease

Brett’s mother sometimes wonders what caused Brett’s asthma, and why so many of his friends have it.

The causes of asthma in Brett may differ considerably from the causes of asthma in another person, or the prevalent causes of asthma in a population.

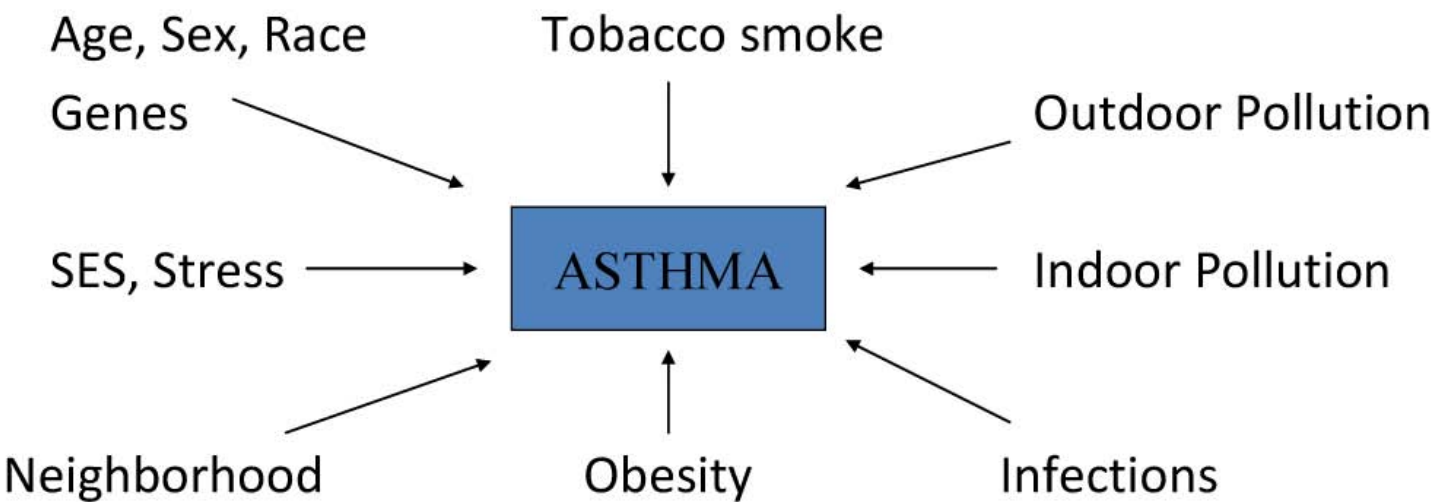
 **Key Concept:** Addressing disease risks in individuals and populations

In general, asthma is a multifactorial disease although in some individuals, a single factor may be predominantly responsible for its onset. For example, an exposure to a chemical airway sensitizer like formaldehyde, or exposure to secondhand smoke.

After asthma develops, various exposures can trigger or exacerbate an asthmatic episode.

 **Key Concept:** Causation and Association

Risk Factors for Asthma



Graphic reproduced with permission.

Watch this short informative video by Dr. John Balmes that explains the many risk factors for developing asthma. (1.5 min.)

John Balmes MD, Professor and Division Chief of Occupational and Environmental Medicine at San Francisco General Hospital, University of California, San Francisco

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KEY CONCEPT:
Addressing Disease Risks in Individuals and Populations

Health care practitioners generally provide advice and care to people and their families, based on individual histories and circumstances. Public health practice widens the lens to include the health of groups or populations of people. Public health practices include advocating for and helping to create and maintain the conditions that promote health for entire communities. Public health practitioners have long recognized the benefits—or risks—associated with small shifts in determinants of health within populations.

In 1985, epidemiologist Geoffrey Rose was interested in strategies for disease prevention. He recognized that small downward population-wide shifts in blood pressure where hypertension was common could have large public health benefits. Community-level interventions differed from what individuals could do to accomplish the same goal.

The North Karelia project in Finland put these ideas to work about 25 years after demographer, Vaino Kannisto, published his doctoral thesis pointing out that eastern Finland had the highest heart disease mortality in the world.^[i] By this time, the Framingham Heart Study, started in 1948, had begun to identify risk factors that contribute to cardiovascular disease by following its development over a long period of time in a large group of participants. Based on its findings, efforts to reduce smoking, cholesterol, and blood pressure, and to increase physical activity, were undertaken in N. Karelia. These efforts did not focus entirely on educating at-risk individuals in order to change their behavior with respect to physical activity, diet, and smoking, but also included community-level interventions that

would help reduce cardiovascular risk factors across the entire population. This involved campaigns and activities in partnerships with the media, supermarkets, food manufacturers, and others, to make healthier choices more readily available to everyone.

The results were dramatic. In 35 years the annual age-adjusted coronary heart disease mortality rate among 35-64 year-old men declined 85 percent. Cancer-related mortality was also reduced, and all-cause mortality reduced for men and women.

One early commentary on the North Karelia project critically called it “shot-gun prevention.”^[ii] But, it worked. It showed the value of multi-level interventions in a population rather than focusing solely on individuals at highest risk. Data from five different surveys showed that an estimated 20 percent of the coronary heart disease mortality could be prevented by reducing cholesterol levels in the entire population by 10 percent, while a 25 percent cholesterol reduction in only those with the highest levels would reduce mortality by only five percent. Lifestyle changes, they concluded, are not just responsibilities of individuals but also of communities.

We often debate which public health interventions should be directed at entire populations or focused more on individuals at risk to address disorders such as cancer, diabetes, cardiovascular disease, obesity, and dementia, among others. But it’s undeniably clear that disease prevention and response after diagnosis is not just an individual responsibility. It belongs to the community as well.

ⁱ Rose G. Sick individuals and sick populations. *Int J Epidemiol.* 1985; 14(1):32-38.

ⁱⁱ Puska P. From Framingham to North Karelia: from descriptive epidemiology to public health action. *Prog Cardiovasc Dis.* 2010; 53(1):15-20.

ⁱⁱⁱ Editorial: Shot-gun prevention? *Int J Epidemiol.* 1973; 2(3):219-220.

Schettler T. The ecology of breast cancer: The promise of prevention, and the hope for healing. *Science and Environmental Health Network and the Collaborative on Health and the Environment.* October, 2013.

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KEY CONCEPT:
Causation and Association

Epidemiologic studies identify associations between an exposure and a health outcome of interest. Identifying the risk factors causally related to a disease is a difficult task for researchers. Origins of individual cases of a disease may result from different combinations of risk factors.

Carefully designed studies can help establish cause and effect relationships, but ultimately causation must be inferred from available epidemiologic and laboratory data. Randomized controlled double blind studies (where neither the subjects of the experiment nor the persons administering the experiment know the critical aspects of the experiment), which are often used for evaluating

intentional medical interventions, are typically not applicable or possible when studying the origins of environmentally-related diseases. A randomized controlled trial that would expose subjects to hazardous chemicals raises ethical concerns. Human studies should be supported by strong biologic explanations and/or animal experiments. Still, it is hard to be certain of the causal relationship and its strength, especially when many complicated factors contribute to a particular disease. Associations between exposures and health outcomes are frequently robust enough to support recommendations. In fact, much preventive medicine depends on making those judgments regularly.

ASTHMAGENS: Risk factors for the development of asthma

There are hundreds of substances known or suspected to cause asthma (“asthmagens”). Some are encountered in the workplace as well as at home, school, and elsewhere – such as formaldehyde (in certain furnishings and building materials like cabinets), vinyl flooring, carpeting, phthalates (in plastic toys and other plastic products), bleach, natural gas combustion products, cleaning solutions and other products. Brett has likely been exposed to many asthmagens in his life.

Our main character Brett is not yet in the workforce but occupational causes of asthma should be considered when treating adults and children.

Though many chemicals shown to cause asthma in workers may not have been studied in children, it is likely that they are capable of causing asthma in the general population including children. And, working parents can bring exposures home to kids on clothing and in other ways, so pediatricians and parents of kids with asthma should also consider occupational exposures of parents.



More details: Asthma in the workplace and elsewhere



Prevention Strategies – Home Checklists:

- [Better Home Visits for Asthma, Lessons Learned from the Seattle–King County Asthma Program \(pdf\)](#)
- [Do-it-yourself Home Environmental Assessment List \(HEAL\)\(pdf\)](#)
- [EPA’s Asthma Home Environment Checklist](#)

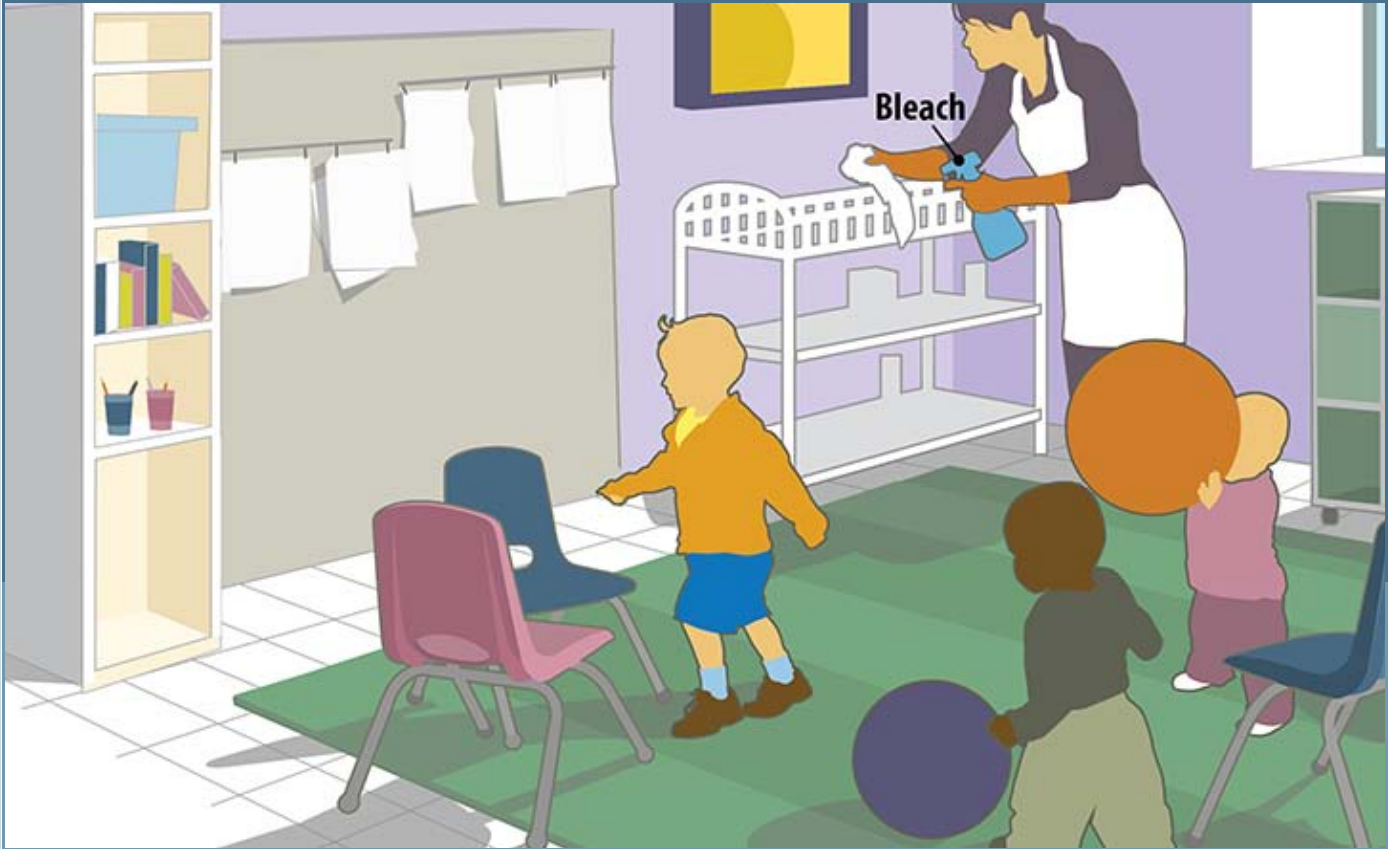
For Clinicians:

- [Pediatric Environmental History Forms, National Environmental Education Foundation](#)



View a database list of asthmagens

- [The Association of Occupational and Environmental Clinics \(AOEC\). Includes those encountered in the workplace, home, school, etc. \(Click ‘display all asthmagens’ on site page.\)](#)



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Asthma in the Workplace and Elsewhere

Epidemiologic studies have found that children face increased risks of developing asthma after early life exposure to chemicals that have also been found to cause asthma in workers like, for example, formaldehyde.

In a study of > 4,000 children in Southern California, exposure during the first year of life to 1) wood or fossil fuel smoke, soot, or exhaust 2) herbicides 3) pesticides or 4) cockroaches was associated with 74%, 450%, 230% and 200% respectively increased risk for being diagnosed with asthma by 5 years of age. Risks noted for asthma after exposure to some pollutants were similar or greater than that of another well established causal risk factor, cockroaches. (Salam et al., 2004)

From the American College of Chest Physicians 2008 consensus statement on the **Diagnosis and Management of Work-Related Asthma:**

Work-related asthma has two categories. They are often clinically indistinguishable, but the distinction can impact treatment strategies and medico-legal decisions.

Occupational asthma. This diagnosis is appropriate when a worker develops new respiratory symptoms and obstructive airway physiology consistent with asthma and an exposure in the workplace is likely to have contributed to its onset. Occupational asthma is often sub-classified as:

- **Sensitizer-induced** (90% of cases)
- **Irritant induced asthma** (10% of cases), including reactive airway dysfunction syndrome (RADS).

Some cases are mixed or unclassifiable.

Work-exacerbated asthma. This occurs when a worker’s previously diagnosed asthma is worsened, but not caused, by agents in the workplace.

At risk occupations include:

- | | |
|---------------------------|---------------------------------------|
| • bakers | • hair stylists |
| • building custodians | • laboratory workers |
| • detergent manufacturers | • nurses |
| • drug manufacturers | • metal workers |
| • farmers | • millers |
| • grain elevator workers | • plastics and other chemical workers |
| | • woodworkers |

ASTHMAGENS: Risk factors for the development of asthma

Some early life environmental risk factors have been identified.

For example, prenatal and early life exposure to social stressors, such as violence, can increase the risk of asthma as well as increase the impacts on respiratory health from allergens, air pollution, and tobacco smoke.

Secondhand smoke alone is a risk factor for new cases of asthma in preschool-aged children.

Karen was surprised to learn that some doctors are even concerned about acetaminophen and its relationship to asthma.

Brett has experienced many of these risk factors in his short life. More details about these can be found as you read his story.



Stress affects our health. Watch this video by Dr. Rosalind Wright to see how social stressors, along with environmental factors, can be linked to asthma. (5 min.)

Rosalind J. Wright, MD MPH, Horace W. Goldsmith Professor of Pediatrics, Vice-chair, Clinical and Translational Research, Department of Pediatrics, Icahn School of Medicine at Mount Sinai



ASTHMA: Prenatal and Early Life Exposures

Karen also thinks about what her doctors told her when she was pregnant about exposure to tobacco smoke, and how she tried to get her husband to quit which was another source of fighting between them.

In her discussions with her OB/GYN she also learned about keeping her weight down and the importance of Vitamin D.

 **Additional Information: About Vitamin D**

Some prenatal variables are well-established as risk factors for asthma, alone or in combination with postnatal exposures. For example, maternal obesity during pregnancy is associated with increased risk of asthma in offspring.



Watch: Dr. John Balmes presents powerful evidence on the detrimental effects of air pollution and smoking on prenatal and early childhood development. (5 min.)



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Vitamin D and Asthma

Higher cord blood levels of vitamin D are associated with decreased risk of transient childhood wheezing. Higher vitamin D intake during pregnancy is associated with decreased risk of wheeze in early childhood. Reduced risk of wheezing may be due to reduced frequency of respiratory infections.

The American Congress of Obstetricians and Gynecologists (ACOG) recommends testing pregnant women who are at increased risk of vitamin D deficiency (e.g., women with limited sun exposure, women with darker skin that limits absorption of vitamin D). If a woman's Vitamin D (25-hydroxy-D) level is 20 ng/mL (50 nmol/L) or less, ACOG recommends vitamin D supplementation in a dosage of 1,000 to 2,000 IU daily.

Reference: ACOG Committee on Obstetric Practice. ACOG Committee Opinion No. 495: Vitamin D: screening and supplementation during pregnancy. *Obstet Gynecol.* 2011;118 (1):197-198.

The Centers for Disease Control and Prevention and the American Academy of Pediatrics (AAP) also find that most US infants and children are not consuming enough vitamin D according to 2008 recommendations. The AAP recommends that all infants, whether being breast fed or formula fed, receive a vitamin D supplement.

Reference: Perrine C, Sharma A, Jeffers M, Serdula M, Scanlon K. Adherence to vitamin D recommendations among US infants. *Pediatrics.* 2010; 125(4):627-632.

Other References:

Carmago CA Jr, et al. References. Carmago CA Jr, et al. Randomized Trial of Vitamin D Supplementation and Risk of Acute Respiratory Tract Infection in Mongolia. *Pediatrics* 2012. doi: 10.1542/peds.2011-3029.

Camargo CA Jr, Ingham T, Wickens K, Thadhani R, et al. Cord-blood 25-hydroxyvitamin D levels and risk of respiratory infection, wheezing, and asthma. *Pediatrics.* 2011 Jan;127(1):e180-7. doi: 10.1542/peds.2010-0442. Epub 2010 Dec 27.

Hollams EM. Vitamin D and atopy and asthma phenotypes in children. *Curr Opin Allergy Clin Immunol.* 2012 Jun;12(3):228-34.

Zosky GR, Berry LJ, Elliot JG, James AL, Gorman S, Hart PH. Vitamin D deficiency causes deficits in lung function and alters lung structure. *Am J Respir Crit Care Med.* 2011 May 15;183(10):1336-43. Epub 2011 Feb 4.

ASTHMA: Triggers

In someone like Brett who already has asthma, an asthma attack can be triggered or set off by a wide range of many of the same environmental agents including exposure to:

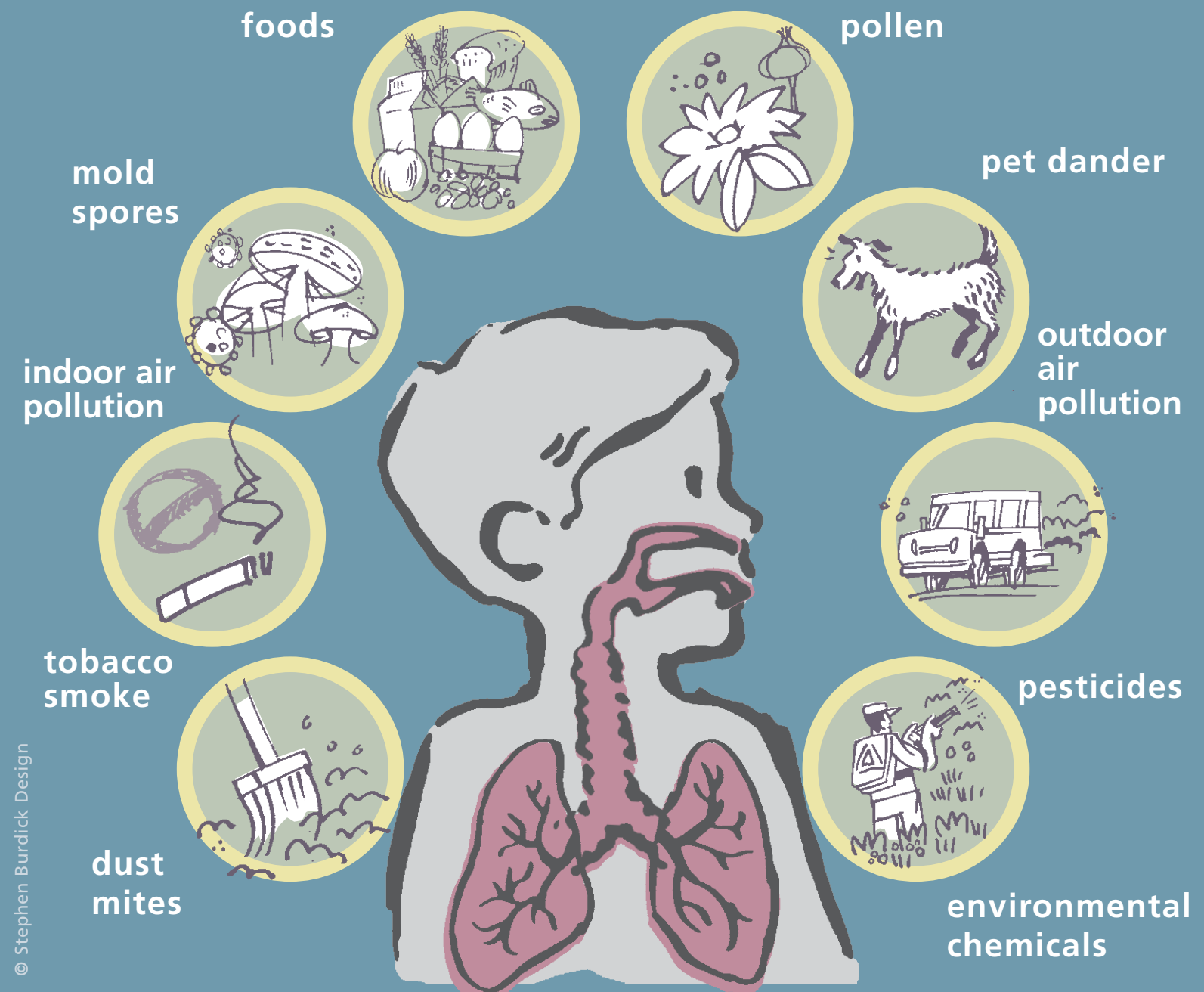
- indoor air pollutants such as tobacco smoke, outdoor air pollution;
- other environmental chemicals including pesticides, and;
- allergens including mold, pollen, cockroach droppings and pet dander.

Exercise and cold weather can also be triggers. These triggers vary from one person to another.

It is sometimes called “allergic asthma” when an individual wheezes in response to exposure to an allergen such as pollen or cat dander.



Potential Asthma Triggers

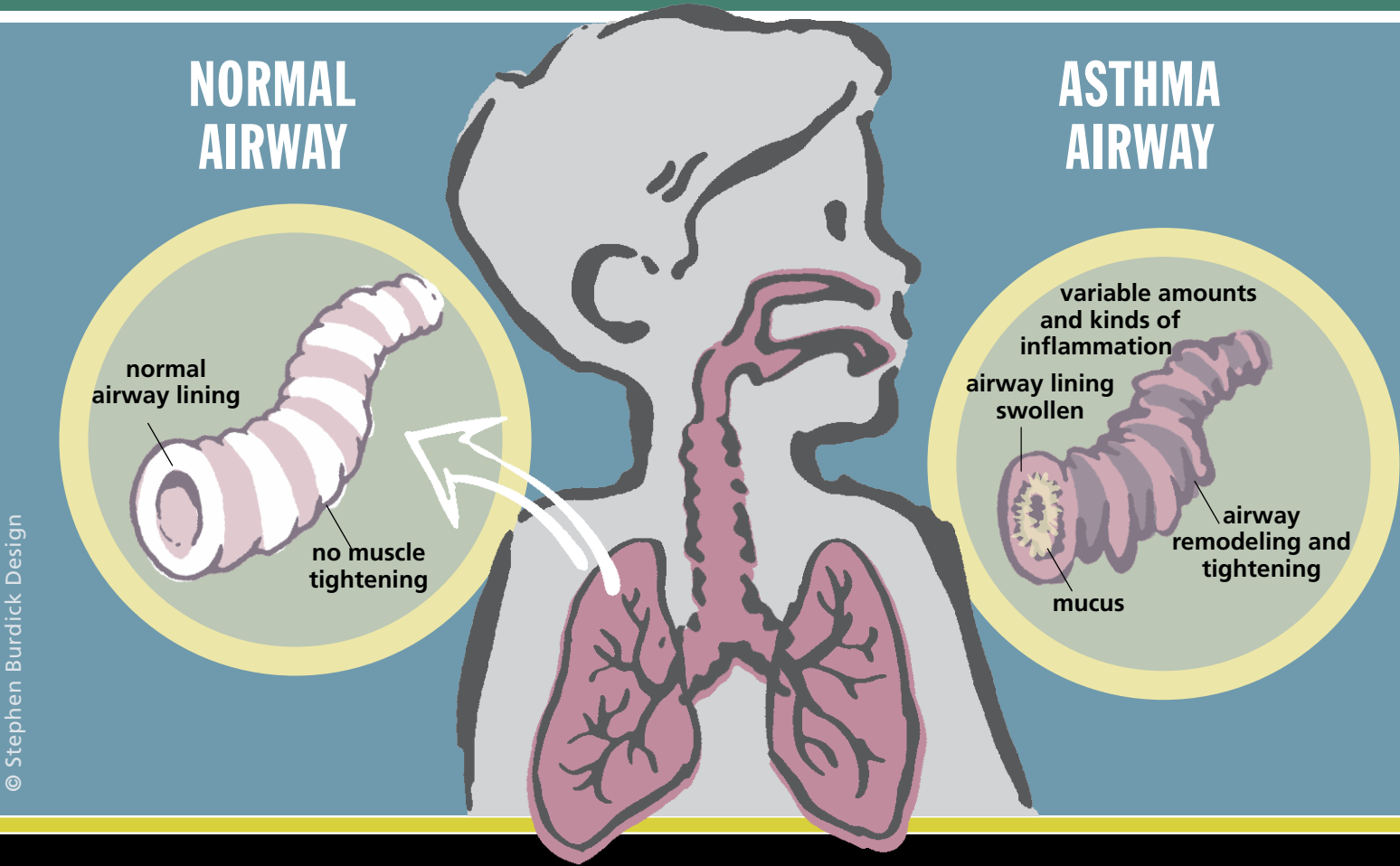
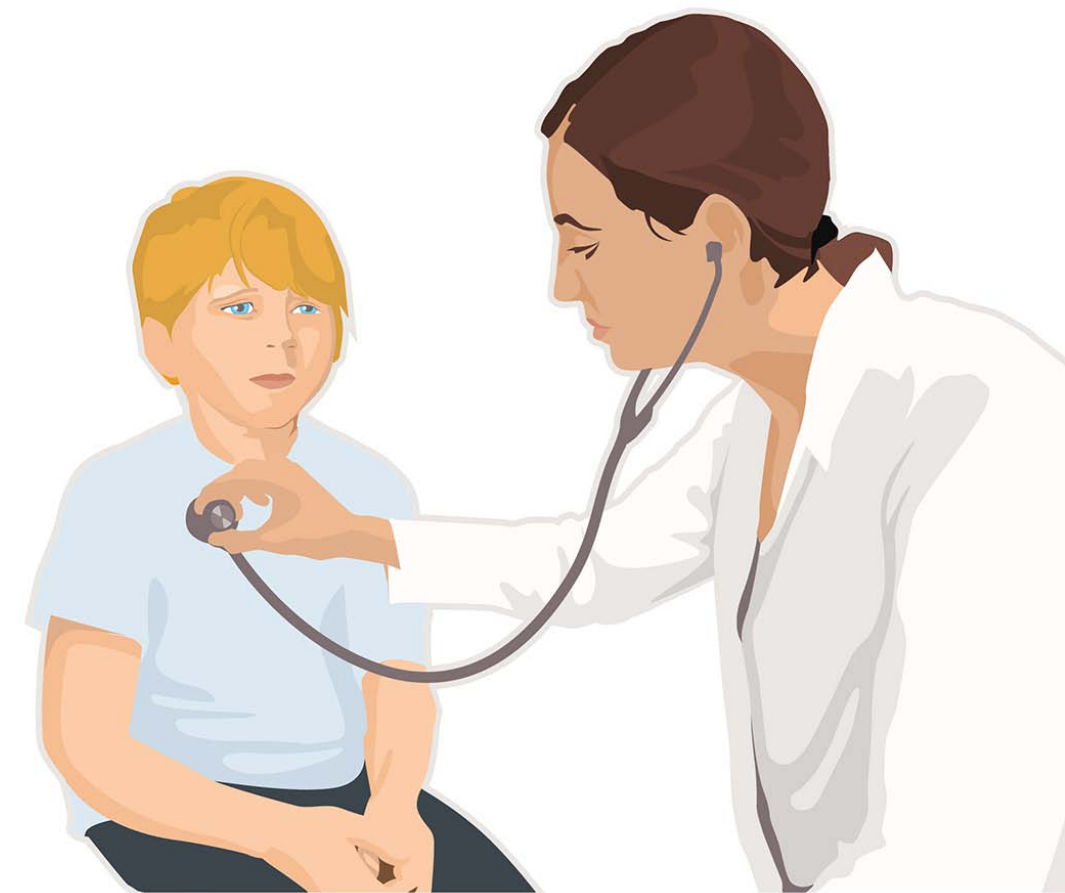


ASTHMA: Effects on the Lungs and Immune System

Brett's doctor told him that the reason he wheezes sometimes is because of inflammation and narrowing of the airways in his lungs.



Watch: Dr. John Balmes discusses the many factors that influence lung development and the severity of asthma. (Technical/academic - 6 min.)




ASTHMA and Lung Development

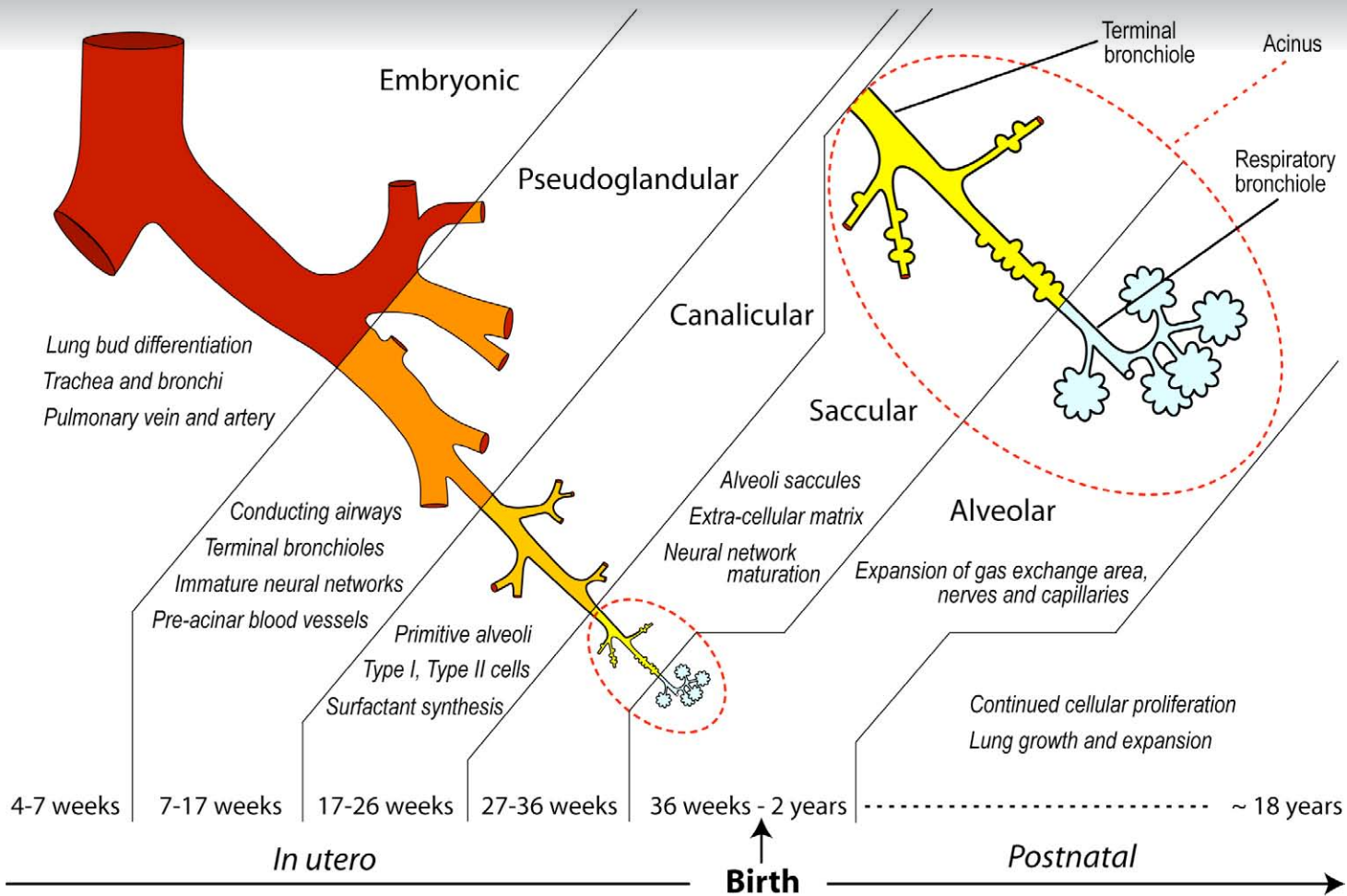
THE LUNG IS SUSCEPTIBLE TO MANY INFLUENCES DURING EARLY DEVELOPMENT.

Though the lung develops into a functioning organ during the fetal period, important stages in lung growth and development continue during early childhood and may be altered by environmental exposures.

 [Click here for more details.](#)

 [You may skip this section and go to "Growing Problem of Asthma"](#)

Stages of Lung Development



Reference: Kajekar R. Environmental factors and developmental outcomes in the lung. *Pharmacol Therap.* 2007;114:129-145. Graphic used with permission.

ASTHMA and Lung Development

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STAGES OF LUNG DEVELOPMENT

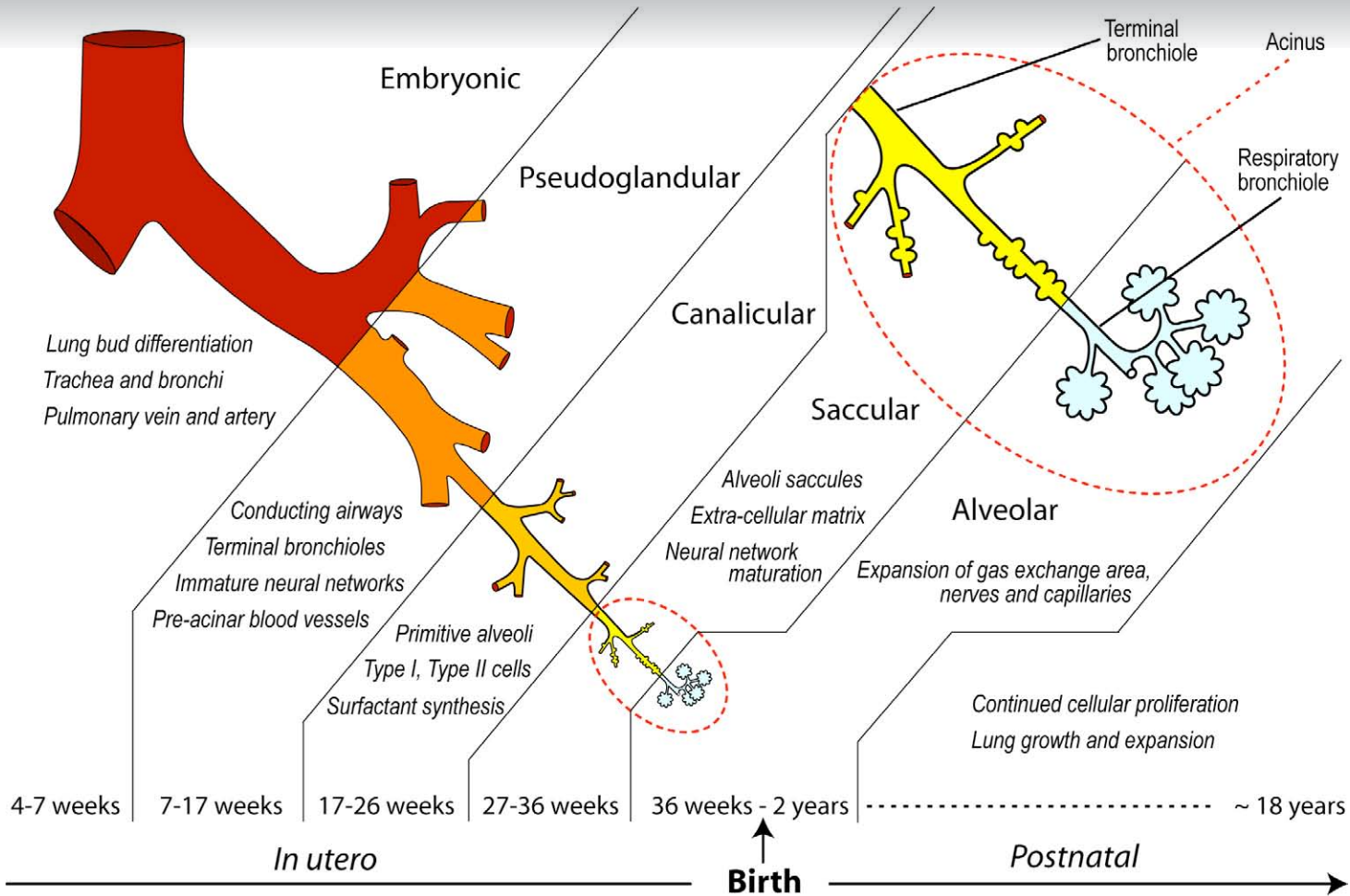
In humans, primary lung buds develop during the fourth week of gestation from the endoderm of the foregut. After early embryonic development, stages in prenatal lung development are pseudoglandular, canalicular, saccular, and alveolar, which are represented in Figure 2, along with associated developmental features (Kajekar, 2007). Only a portion of maturational events are required prenatally for successful survival, with most continuing postnatally during alveolarization (Pinkerton and Joad, 2000).

During the embryonic period primary bronchi develop from the primitive gut, and elongate and divide into two main bronchi. During the pseudoglan-

dular phase (6–16 weeks of gestation in humans), branching continues and mesenchyme differentiates into cartilage, smooth muscle, and connective tissue around the epithelial tubules. By the end of this time, major conducting airways to the terminal bronchioles are developed. Respiratory bronchioles, develop in the canalicular period along with a rich vascular supply. During the saccular phase, first contact between the air space and proliferating pulmonary capillaries takes place. During alveolarization, the primitive alveoli develop secondary septa that form the walls of the true alveoli, resulting in a dramatic increase in surface area.

Chemicals that disrupt the cellular signaling important for these events may alter lung development.

Stages of Lung Development



Reference: Kajekar R. Environmental factors and developmental outcomes in the lung. *Pharmacol Therap.* 2007;114:129-145. Graphic used with permission.



More Information: "Cellular, structural, and functional impacts on lung development of xenobiotics"

ASTHMA and Lung Development

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Chemicals that disrupt the cellular signaling important for these events may alter lung development.

Examples of Chemicals that can Alter Lung Structure and Function During Development

Chemical	Cellular and subcellular level impacts	Structural or functional impacts	Possible clinical impact
Nitrofen 2,4-dichloro- <i>p</i> -nitrophenyl-ether (pesticide)	GATA 6, Wnt7, BMP4, FGF, retinal dehydrogenase2, inhibition T3 receptor binding	Decreased branching, altered smooth muscle, alteration in surfactant and alveolar septation	Pulmonary hypoplasia, immature lung
TCDD (dioxin)	Arylhydrocarbon receptor, thyroid hormone	Delayed lung development, decreased total lung space, increased septal area	Chronic bronchitis, decreased functional capacity, COPD?
Nicotine	Suppression glycolysis and glycogenolysis, reduced synthesis phosphorylase and phosphofructokinase, inhibition Na ⁺ K ⁺ ATPase	Slower septal formation, bleb formation, decrease number alveoli, increase alveolar volume	Emphysema, decreased functional capacity
4-ipomeanol, naphthalene	Bronchiolar cell differentiation and repair inhibited	Injury/loss of Clara cells	Increased susceptibility to inhaled toxicants, alteration in surfactant
Ozone	Depletion proteoglycan and FGF-2, thinned basement membrane zone	Altered bronchiolar growth (longer/decreased diameter), fewer branches, alteration in orientation bronchiolar smooth muscle	Increase airway hyper-reactivity, emphysema?
Arsenic	Increase expression estrogen receptor alpha, alteration gene expression for extracellular matrix (e.g. collagen type III), Sprouty-2, β-catenin, EGFR, L-myc	Alteration branching and cell migration, decreased elasticity and structural support	Cancer, bronchiectasis, airway hyperreactivity
Di(2-ethylhexyl) phthalate	PPARγ, decrease type 2 pneumocyte	Thickened primary septa, fewer/more dilated airspace, increased Type II pneumocytes	Bronchopulmonary dysplasia, altered lung mechanics

Close Window



structural, and functional impacts on lung development of xenobiotics"

on Lung Development - Miller et al., 2010
Online link - Table 1: Cellular, structural, and functional impacts on lung development of xenobiotics

Graphic reproduced with permission.

ASTHMA and Lung Development

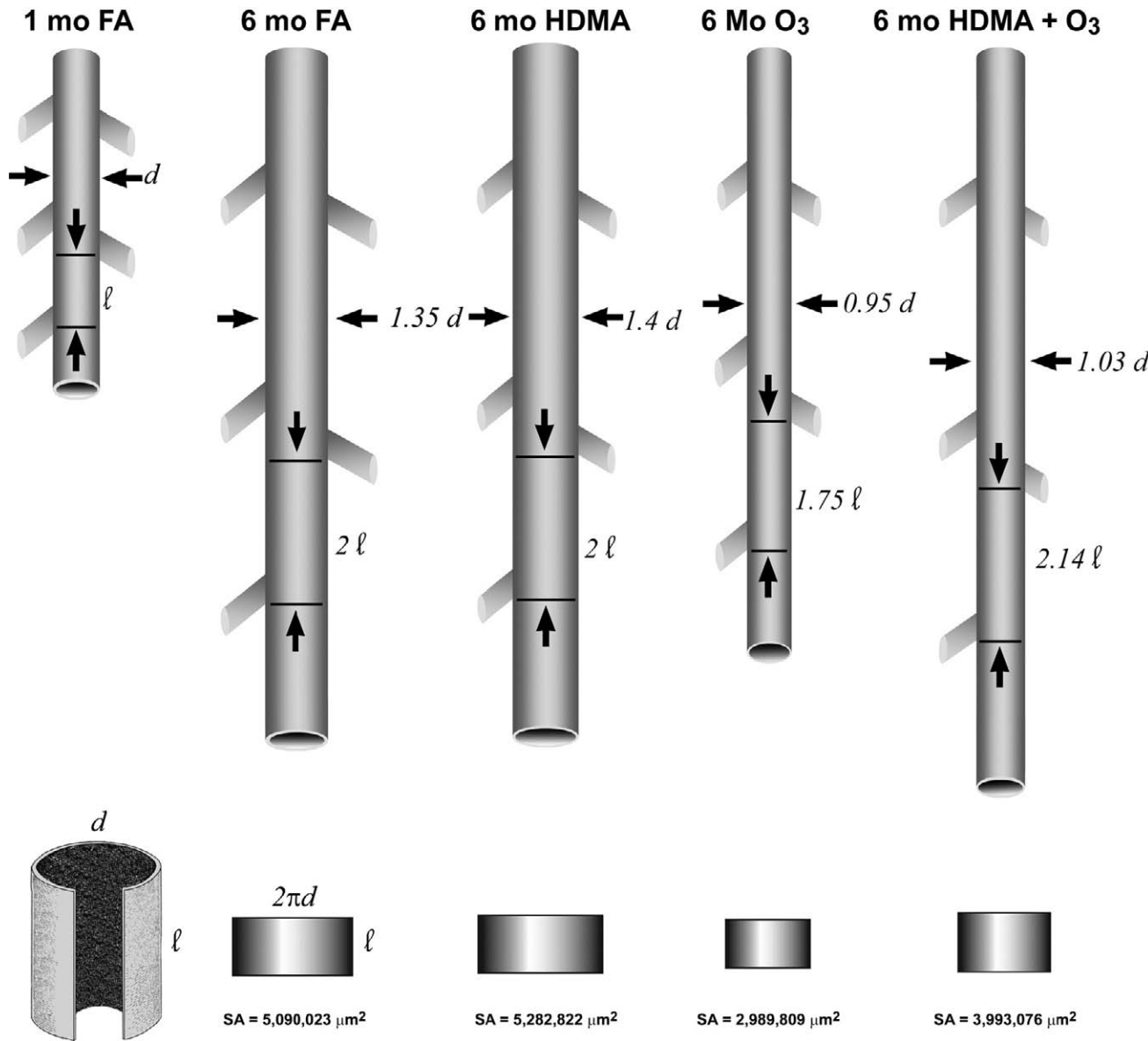
THE LUNG IS SUSCEPTIBLE TO MANY INFLUENCES DURING EARLY DEVELOPMENT.

Environmental exposures during susceptible developmental periods may produce lifelong structural and functional alterations. Monkeys exposed to ozone and house dust mite postnatally develop longer, narrower, and fewer branches of bronchioles along with other changes consistent with increased risk for asthma development.

 [Click here for more details.](#)

 [You may skip this section and go to "Growing Problem of Asthma"](#)

Environmental exposures at critical developmental periods may permanently alter structure of airways



Reference: Plopper CG, Smiley-Jewell SM, Miller LA, Fanucchi MV, Evans MJ, Buckpitt AR, et al., 2007. Asthma/allergic airways disease: does postnatal exposure to environmental toxicants promote airway pathobiology? ([link](#)) Graphic used with permission.

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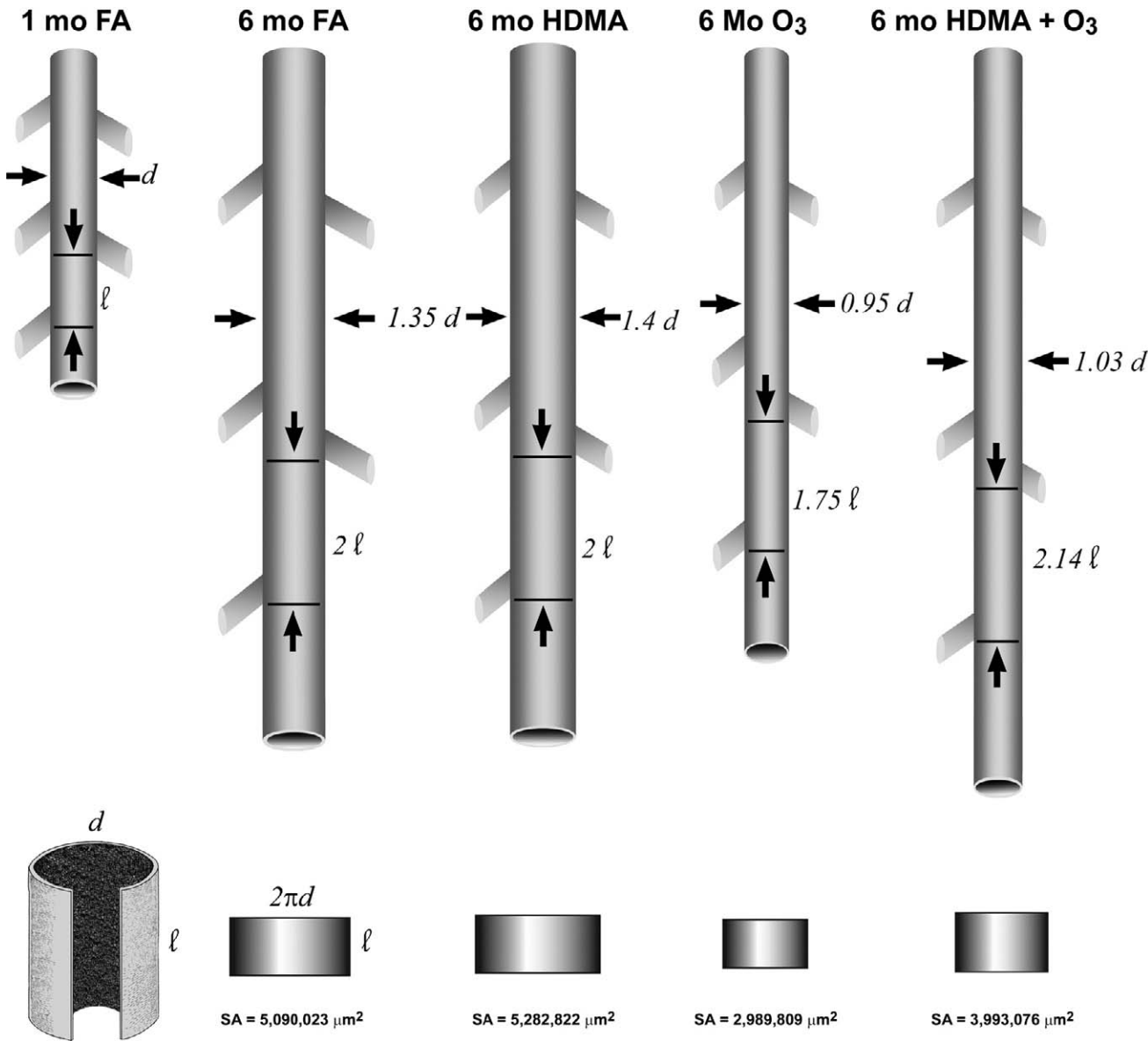
 [Click here for more details.](#)

 [You may skip this section and go to "Growing Problem of Asthma"](#)

STUDIES CONDUCTED at the University of California–Davis evaluated the impact of ozone (O3) and allergens on lung development in rhesus monkeys. These studies integrated early-life exposures through multiple windows of susceptibility to observe functional and structural changes relevant to human lung development and lung disease. In 2004, Tran et al. described conducting airways doubling in length and increasing by 33% in diameter between 1 and 6 months of age.

Postnatal exposure to O3, alone or combined with house dust mite antigen (HDMA), resulted in changes in bronchiolar growth patterns, inhibiting growth in diameter and promoting growth in length as well as reducing the number of conducting airway branches (by as many as six generations) (Fanucchi et al., 2006; Plopper et al., 2007). These changes are consistent with increased propensity to develop asthma and appeared to be permanent because they persisted at least 6 months after exposure ended.

Environmental exposures at critical developmental periods may permanently alter structure of airways



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ASTHMA: The Growing Problem

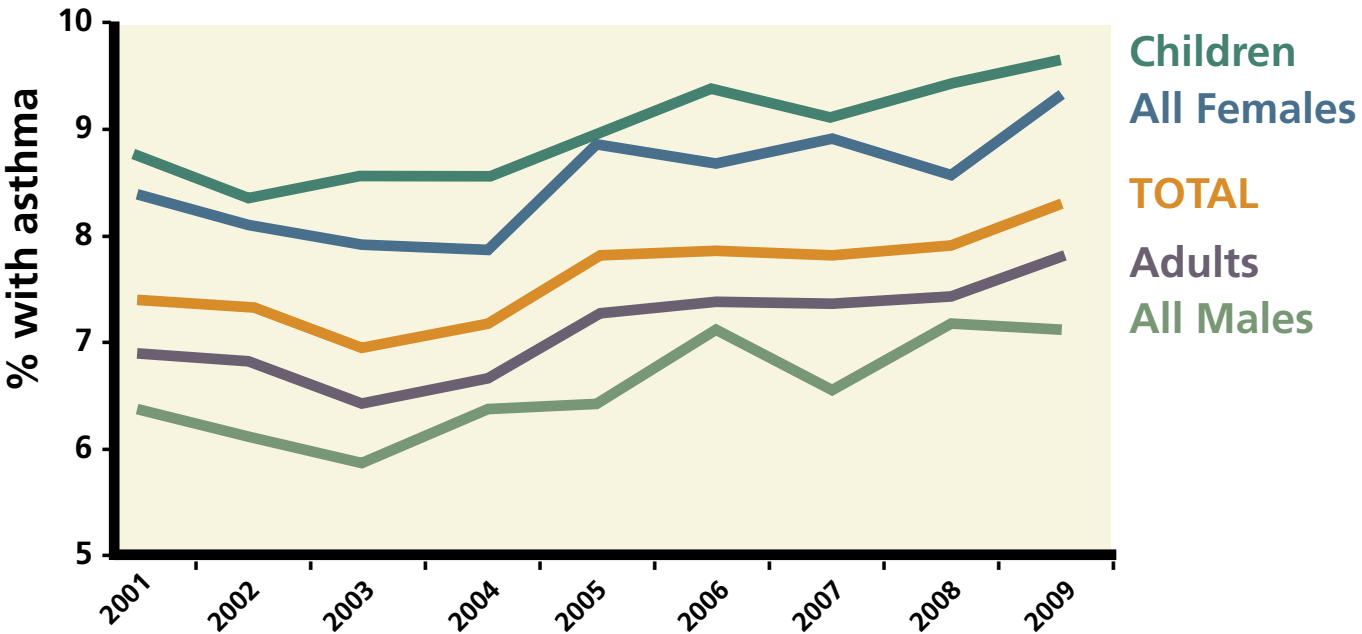
When Brett gets an attack, he has a difficult time breathing and sometimes feels as if he is going to pass out.

He is careful to carry an inhaler with him at all times. Lots of kids have them, so it seems common now even though his doctor says it wasn't like this many years ago. The number of people with asthma, continues to grow.

From 2001 to 2010 overall asthma rates increased 1.5% per year, to about 8.4%.

1 in 10 children, or 10%, now have asthma.

In addition to the human costs, estimated monetary costs measured in 2007 dollars was \$56 billion. (CDC and Amer Children 3rd ed.)



Percentages are age-adjusted

SOURCE: National Center for Health Statistics; 2010
From CDC "[Vital Signs](#)" on asthma

Graphic reproduced with permission.



ASTHMA: Racial and Socioeconomic Disparities

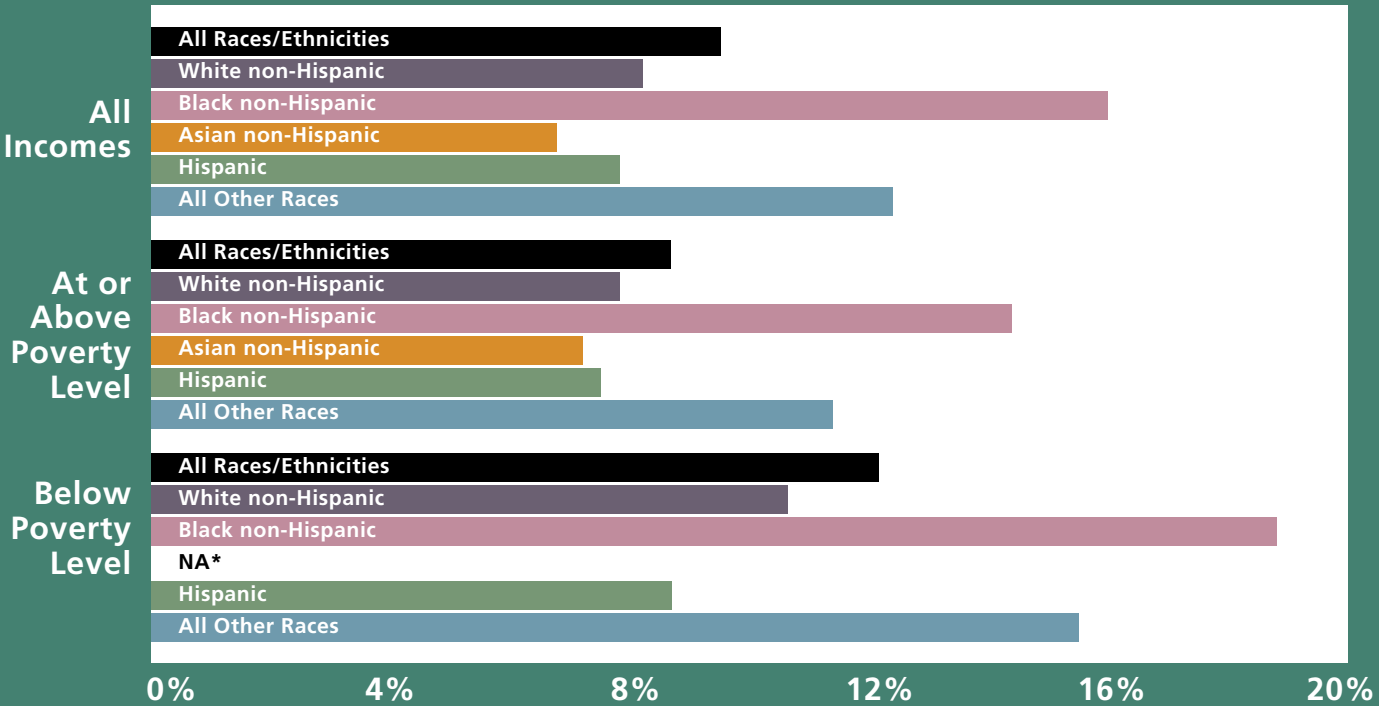
Many of Brett’s friends who live in apartments in the city also have asthma.

Racial and socioeconomic disparities are dramatic (see figure). About 1 in 9 (11%) of non-Hispanic black persons of all ages and about 1 in 6 (17%) of non-Hispanic black children had asthma in 2009, the highest rate among racial/ethnic groups.

The greatest rise in asthma rates was among black children (almost a 50% increase) from 2001 through 2009. Racial disparities (with increased asthma and hospital visits for asthma) are noted with increased risk for blacks compared to whites even after controlling for factors such as economic status. The disparities hold true across economic strata and in urban as well as rural communities. (McDaniel et al., 2006)

Disparities may be explained by higher exposures to risk factors for asthma and lack of comprehensive asthma management, among other things.

Percentage of children ages 0 to 17 years reported to have current asthma, by race/ethnicity and family income, 2007-2010



*Not available. The estimate is not reported because it has large uncertainty: the relative standard error, RSE, is 40% or greater (RSE = standard error divided by the estimate).

Data: Centers for Disease Control and Prevention, National Center for Health Statistics, National Health Interview Survey, *America's Children and the Environment, Third Edition*. Graphic used with permission.



ASTHMA: Family and Community Stressors

“Hi Mom,” says Brett. Brett’s mother, Karen, comes over and gives him a hug. Although Karen doesn’t make a lot of money, they have a stable home life now, but it wasn’t that way when Brett was younger.



ASTHMA: Family and Community Stressors

Karen sometimes wonders whether the constant fights with her ex-husband while she was pregnant and after Brett was born may have had an effect on Brett's asthma.

She may be right.

Family stressors such as money problems, exposure to violence, illnesses and deaths, and divorce can make kids more susceptible to many health problems, including asthma.

Stress can add to and even magnify the impacts of exposure to other environmental conditions that foster the onset or increase the severity of asthma.



 **Key Concept:**
Allostatic Load

 **Key Concept:**
Effect Modifiers



Watch: Dr. John Balmes discusses how multiple factors can interact to increase the risk of developing asthma (effect modification). (3 min.)

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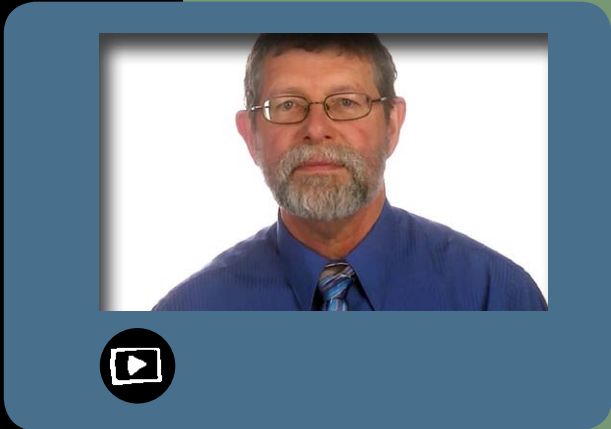
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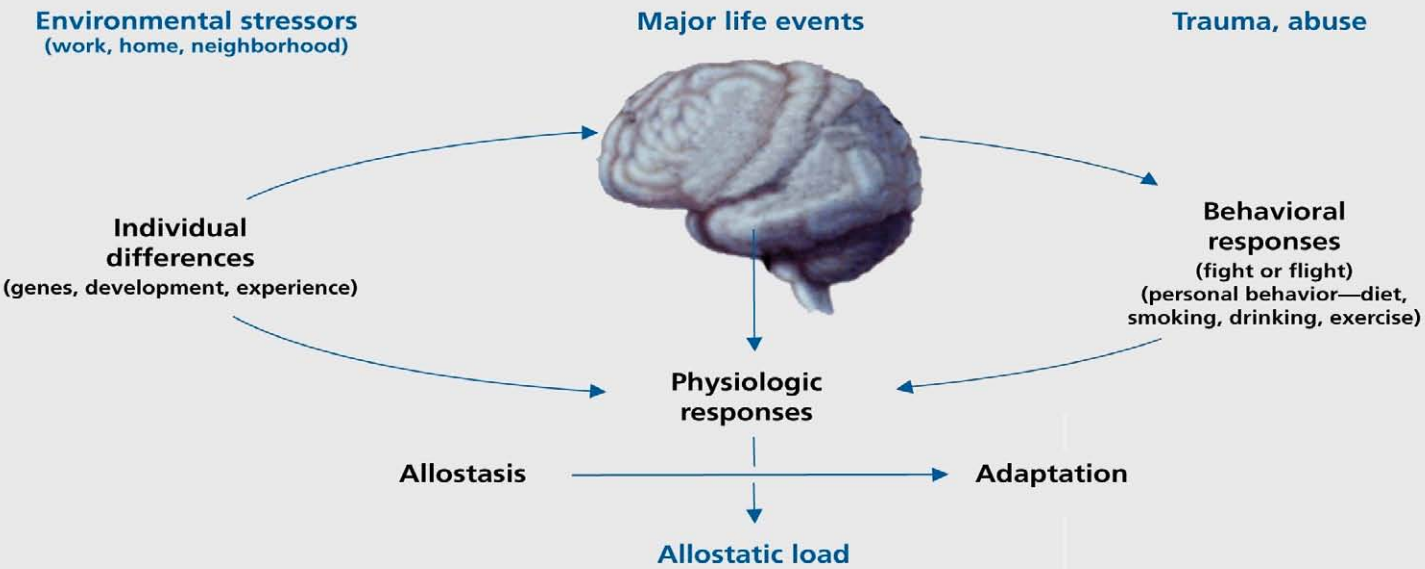


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KEY CONCEPT: Allostatic Load

Homeostasis is the body's ability or tendency to maintain its normal equilibrium by regularly adjusting the processes that influence blood pressure, temperature, blood sugar, and other functions. **Allostasis** is the body's ability to change vital homeostatic functions in response to environmental changes. Like homeostasis, allostasis is complex, and involves responses from the brain and other parts of the nervous system as well as the immune and cardiovascular systems. **Allostatic load** is the cumulative "wear and tear" on the body due to these systems actively maintaining balance in response to stressors.

Real or perceived threats activate stress hormones and can lead to the following:

- Constricted capillaries in the skin
- Dilated bronchial tubes
- A release of sugar and fatty acids (for energy)
- Conversion of muscle protein to fat
- Blocked insulin action
- Release of minerals from bones
- Changes to white blood cells

These actions (and others that are part of the stress response) help the body meet an immediate threat. Long-term functions

such as building muscle, bone, and brain cells are temporarily sacrificed to provide energy to respond to a threat or escape ("fight or flight response").

Because we can experience stress from current events and ideas (remembering past stressful events and anticipating stressful circumstances), our allostatic mechanisms may go into overdrive on a long-term basis. Exposures to various kinds of stress (psychosocial, chemical, nutritional, etc.) during our early life can reprogram the body's mechanisms, resulting in chronic increased responses to stressors that affect our health negatively throughout our life.

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KEY CONCEPT: Effect Modifier

An effect modifier is a variable that differentially modifies the observed effect of a risk factor on disease status. Different groups have different risk estimates when effect modification is present. For example, stress can increase the asthma risk associated with exposure to a given amount of traffic related air pollution addressed later in this story.

An additional reference: Shankardass K, McConnell R, Jerrett M, Milam J, Richardson J, Berhane K. Parental stress increases the effect of traffic-related air pollution on childhood asthma incidence. *Proc Natl Acad Sci USA*. 2009 Jul 28;106(30):12406-11.

ASTHMA: Family and Community Stressors

Because of all the prior family problems, Karen pays a lot of attention to Brett and tries to show him how much she loves him in a lot of ways, including making sure they eat dinner together every night. They have formed a close bond and Karen is happy about that, although like many boys his age Brett usually acts like he doesn't know her when they are in public.

 **Key Concept:**
Windows of Vulnerability and Opportunity

Watch: Dr. Mark Miller discusses early origins of adult disease.



Mark Miller MD MPH, Director, Children's Environmental Health Program, Office of Environmental Health Hazard Assessment, California EPA; Director, UCSF Pediatric Environmental Health Specialty Unit



ASTHMA: Family and Community Stressors

Windows of Vulnerability

A window of vulnerability is a time window (s) during pregnancy or child development when the fetus, infant, or child is especially susceptible to particular environmental exposures, general environmental deprivation, suboptimal nutrition, or psychosocial stress. Exposures during these time windows can disrupt important developmental processes, altering structural or functional development of various organs or physiologic systems, with potential lifelong consequences. Time windows of vulnerability can be relatively long and extend throughout fetal and infant development or they can be relatively short and precise. For example, thalidomide can cause severe limb abnormalities if exposure occurs in the fetus 20-36 days after conception. Alternatively, the manifestations of fetal alcohol exposure can vary considerably depending on the timing and extent of exposure. ([continued](#) >)



Key Concept:
Windows of Vulnerability and Opportunity

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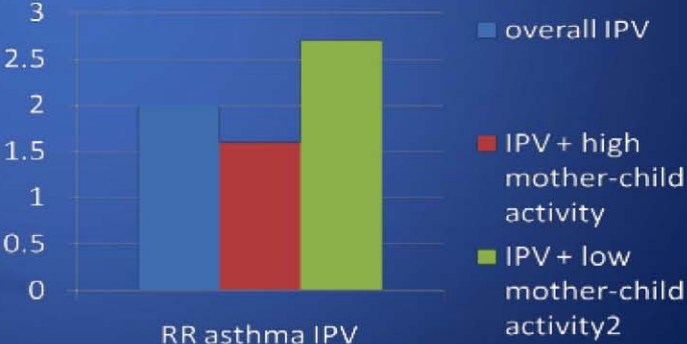


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Example: Stress and Asthma Development of Lung Function is Affected by the Home Environment

Stress and Asthma Cohort Study on IPV

- 3,116 participants enrolled at birth
- Assess intimate partner violence impact on asthma Dx by 36 mos.
- IPV 2 fold increase
- Maternal child activity protects
 - IPV + housing hardship/disarray additive



Suglia SF et al. *Arch Pediatr Adolesc Med.* 2009; Suglia et al. *JECM* 2009

Graphic used with permission.

In a prospective cohort study children were followed from pregnancy through 3 years of age. If there was intimate partner violence (IPV) in the home they had double the risk of developing asthma.


If there was IPV in the home and mother was less interactive with the child/ played less with the child/the child had few educational toys, the risk went up to 2.5 times those without IPV.

If the home had IPV but mother was more interactive, child had more toys etc., the risk was partially ameliorated to about 1.6 times those without IPV.

ASTHMA: Family and Community Stressors

Windows of Opportunity

A window of opportunity is a concept related to *window of vulnerability*. It is a time window when structural or functional developmental processes in the body’s organs or physiologic systems can be positively influenced by a rich, low hazard environment, with healthy nutrition, good education, a positive home environment without unrelenting chronic stress, etc. From conception through the first few years of life, development is rapid, and many key developmental processes (e.g., language acquisition) are programmed during this time. The functional effects of this programming may be apparent immediately or delayed until later in life. Many functions remain plastic (able to be changed) for prolonged periods, providing an opportunity for external influences to partially remediate the potential effects of earlier exposures.

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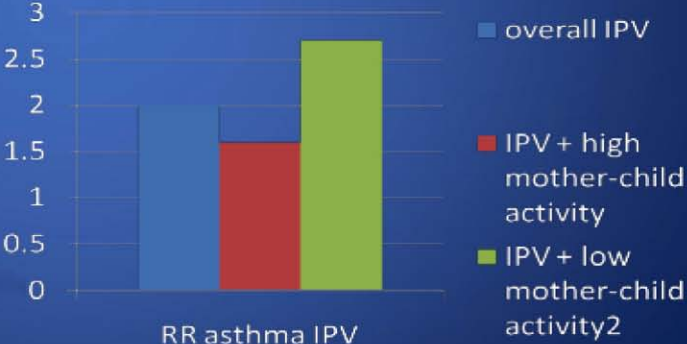


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ASTHMA: Family and Community Stressors

The impact of asthma on the family can be substantial, from emotional to economic.

Children suffer from days lost at school and can be excluded from certain activities.

Parents who need to work must take time off or find adequate care for their children when they need to stay home.

When a child has an acute attack, it can be very stressful and frightening for parents.



Watch: Dr. Rosalind Wright discusses how caregiver stress, early childhood stress and community violence all have an impact on the development of asthma. (5 min.)



More information: Link to resources on comprehensive family asthma management programs – CDC and medical legal



ASTHMA, Exercise and Air Pollution

Brett’s asthma is sometimes triggered by exercising or playing the sports he loves, which is very frustrating for him.

Some research shows that playing multiple sports along with higher exposures to air pollution (ozone) can actually cause the onset of asthma. (McConnell et al., 2002)



Watch: Dr. John Balmes presents compelling scientific evidence that clearly illustrates the relationship between air pollution and incidence of asthma. (6 min.)



For clinicians, link to Dr. Jim Gauderman slide show on Children’s Health and Traffic Exposures.

INDUSTRIAL AND TRAFFIC AIR POLLUTION MAKE ASTHMA WORSE

Adverse Effects of Regional and Traffic-Related Air Pollutants on Children with Asthma

Pollutants

- Ozone
- Nitrogen Oxide
- Respirable particulate matter (PM - <10 and <2.5 µm)
- Vehicle exhaust (trucks, cars, trains, ships, etc.)

Health effects in children with asthma

- Respiratory symptoms
- Wheezing (acute)
- Bronchitis (chronic)
- Increased rescue medication use
- Decreased lung function
- Emergency department visits
- Hospitalizations
- School absences

- + Diesel emissions and asthma demographics in southern California
- + Asthma and near roadway exposure to air pollution



Ozone and Particles Make Asthma Worse:

- More symptoms
- More medications used
- More respiratory illnesses
- More clinic visits
- More emergency room visits
- More hospitalizations

(Sarnat JA, Holquin F. Asthma and air quality
[Curr Opin Pulm Med. 2007; 13: 63-6.](#))

ASTHMA and Air Pollution

INDUSTRIAL AND TRAFFIC AIR POLLUTION MAKE ASTHMA WORSE

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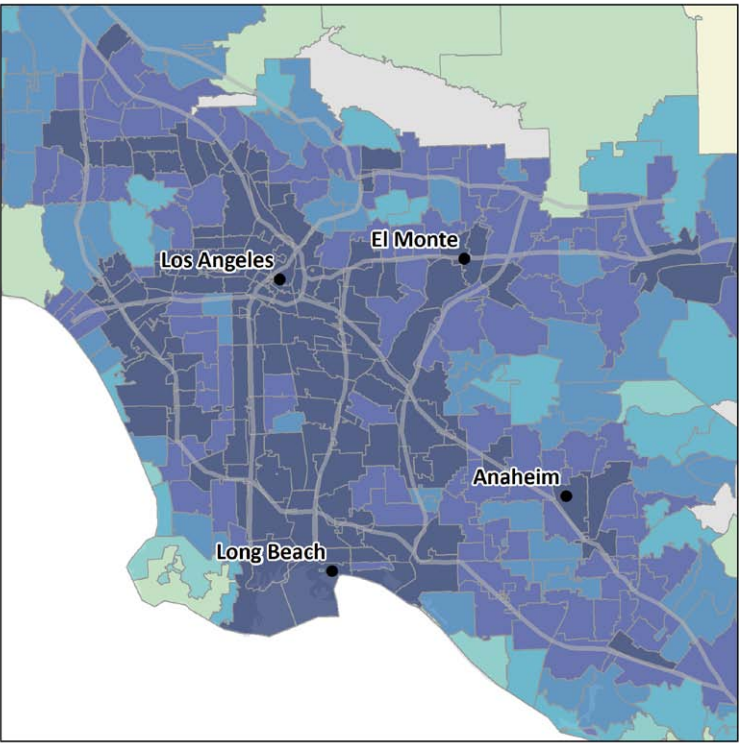
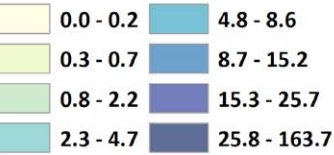
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Diesel Emissions and Asthma Demographics in Southern California

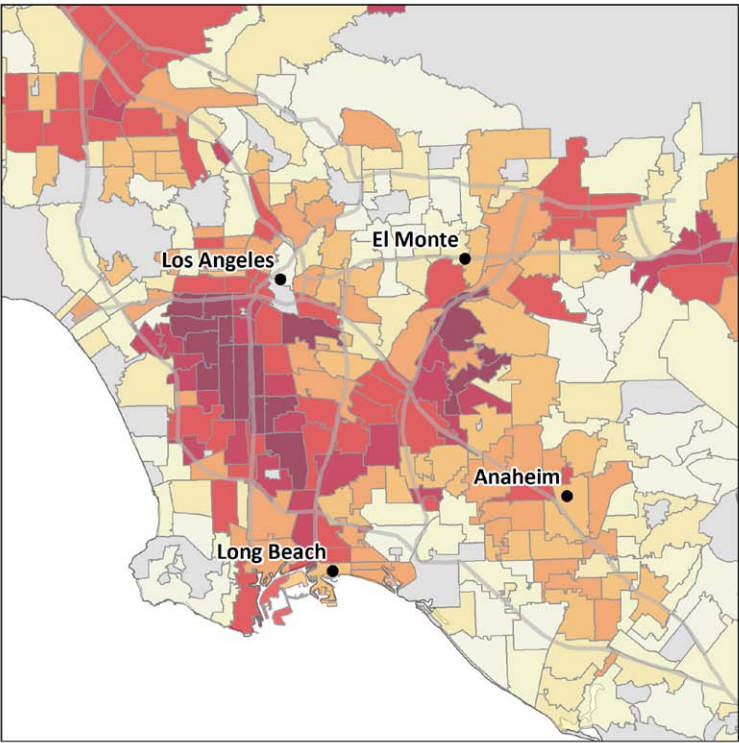
Diesel PM

Diesel PM emissions from on-road and non-road sources for a 2010 July day (kg/day)



Children's Asthma

2009 childhood ED visits for asthma (age-adjusted rate per 10,000 by ZIP code)



- + Credit: CalEnviroScreen, Office of Environmental Health Hazard Assessment, California EPA
- + Link: California Environmental Health Tracking Program Web Portal

Graphic used with permission.

ASTHMA and Air Pollution

INDUSTRIAL AND TRAFFIC AIR POLLUTION MAKE ASTHMA WORSE

Adverse Effects of Regional and Traffic-Related Air Pollutants on Children with Asthma

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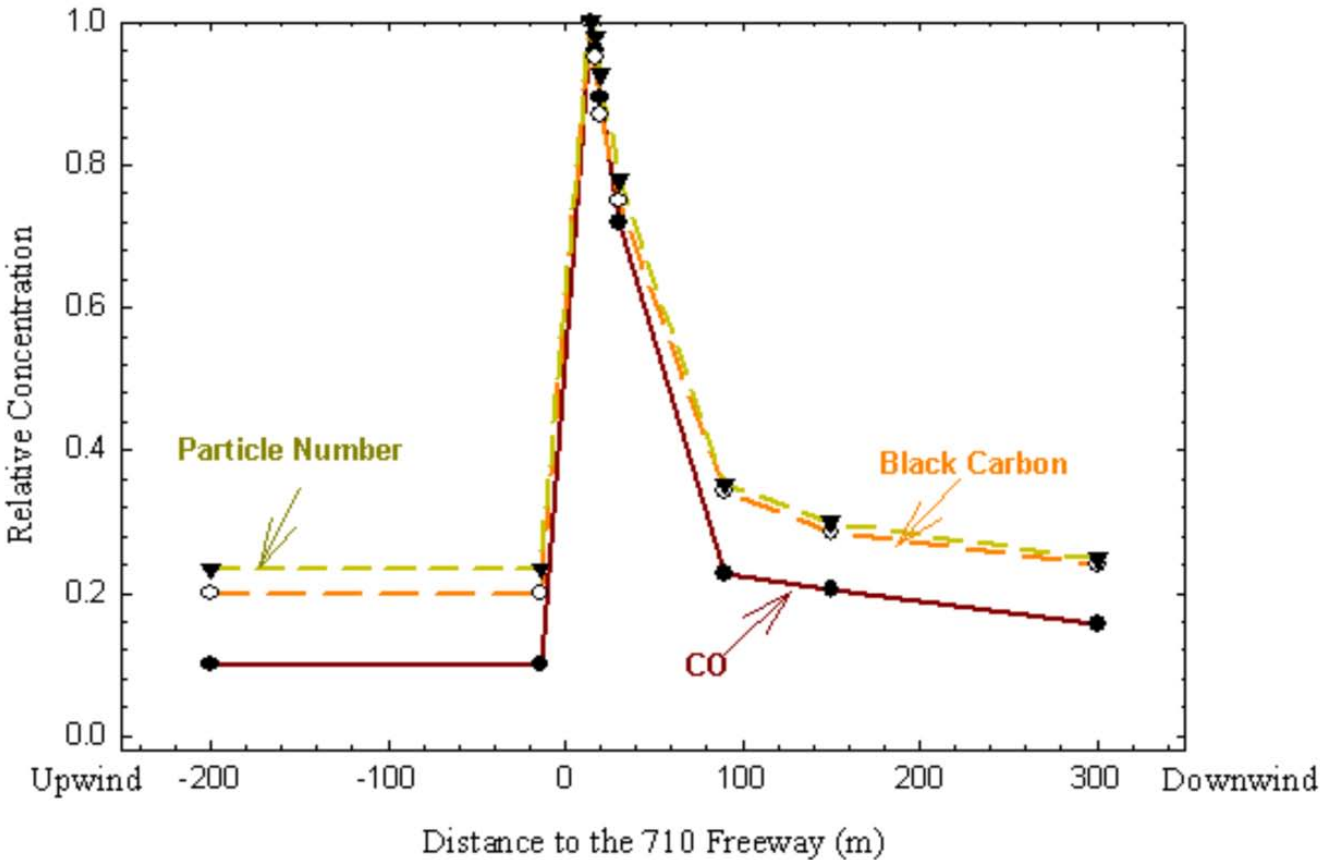
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Asthma and Near Roadway Exposure to Air Pollution

Children in neighborhoods with more traffic-related air pollutants have increased risk of developing asthma and increased risk of bronchitis and asthma episodes



ASTHMA and Air Pollution

EFFECT MODIFIERS — AIR POLLUTION, STRESS AND SOCIOECONOMICS

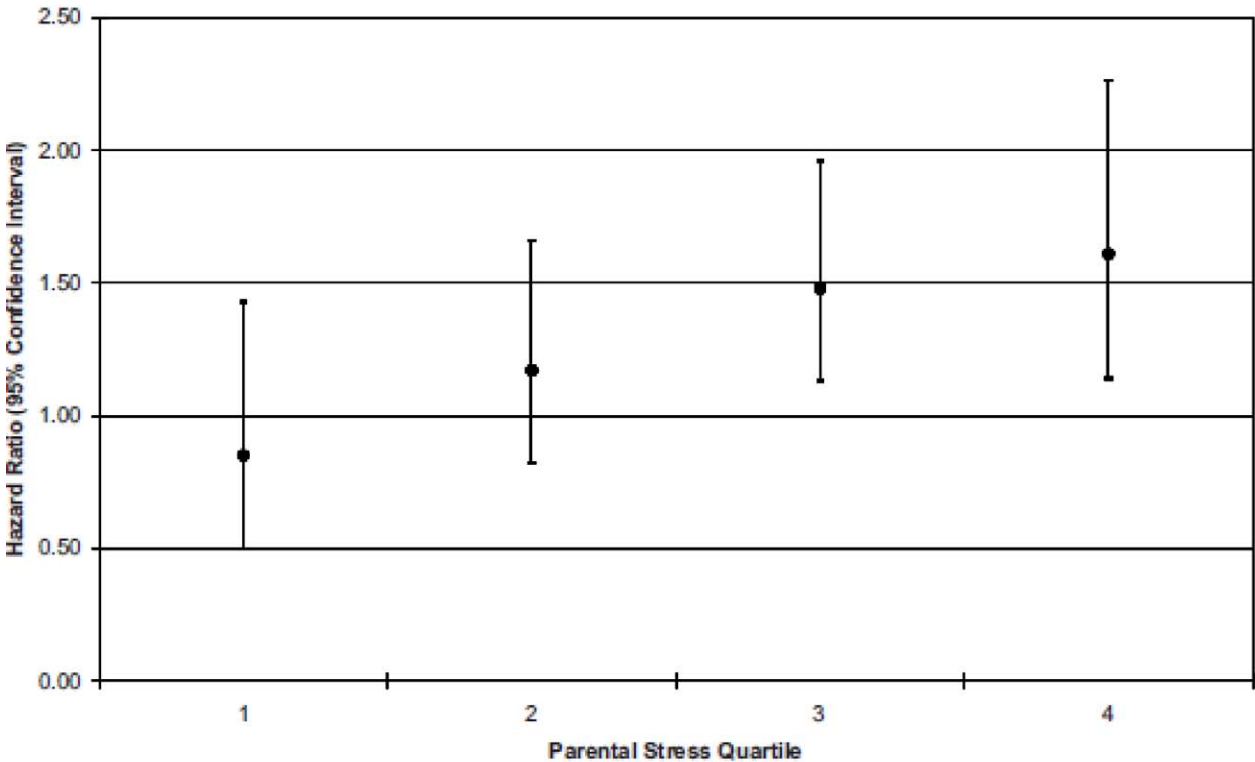
Brett lives in a low-income neighborhood close to Los Angeles and near a major roadway. Children in relatively low-income families and exposed to traffic-related air pollution, such as in Brett’s case, are at greater risk of frequent asthma symptoms. Importantly, they are at greater risk than children in the same neighborhood whose families are financially better off.

(Meng et al., 2008, Shankardass et al., 2009, Clougherty et al., 2007)

And, those with a lower income and people of color are much more likely to go to a school that has a heavily trafficked roadway next to it.

- + [Examples: Air pollution and socioeconomics](#)
- + [Link: National Environmental Health Tracking Program](#)
- + [Asthma in California](#)

Effect of traffic-related pollution on incident asthma across parental stress quartiles



Over a period of 3 years of follow up in a prospective cohort study of 2,497 children aged 5-9 years with no previous history of asthma, the risk of new onset asthma attributable to traffic related air pollution (TRP) was significantly higher for children whose parents were subject to higher amounts of stress.

Stress was estimated using the Perceived Stress Scale (PSS), which is a widely used measure of the degree to which respondents believed their lives were unpredictable, uncontrollable, or overwhelming. Stress was also associated with larger effects of in utero tobacco smoke exposure.

A similar pattern of increased risk of asthma was observed among children from low SES families who also were exposed to either TRP or in utero tobacco smoke. (Shankardass 2009)

Graphic used with permission.

ASTHMA and Air Pollution

EFFECT MODIFIERS — AIR POLLUTION, STRESS AND SOCIOECONOMICS

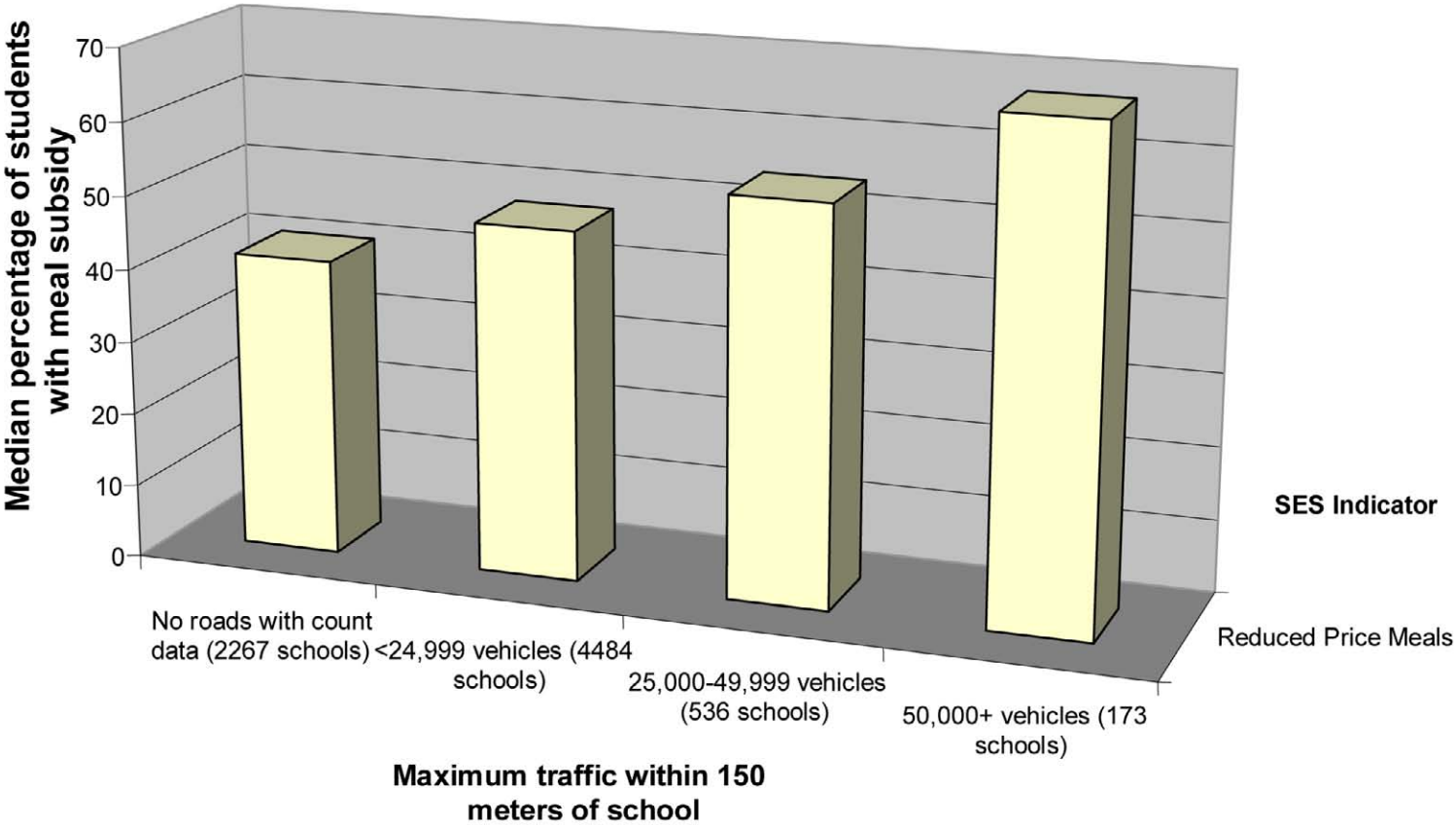
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And, those with a lower income and people of color are much more likely to go to a school that has a heavily trafficked roadway next to it.

- + [Examples: Air pollution and socioeconomics](#)
- + [Link: National Environmental Health Tracking Program](#)
- + [Asthma in California](#)

Examples: Air pollution and socioeconomics



Graphics used with permission.

(Green et al., EHP 2004)

(Green et al., EHP 2004)

ASTHMA and Air Pollution

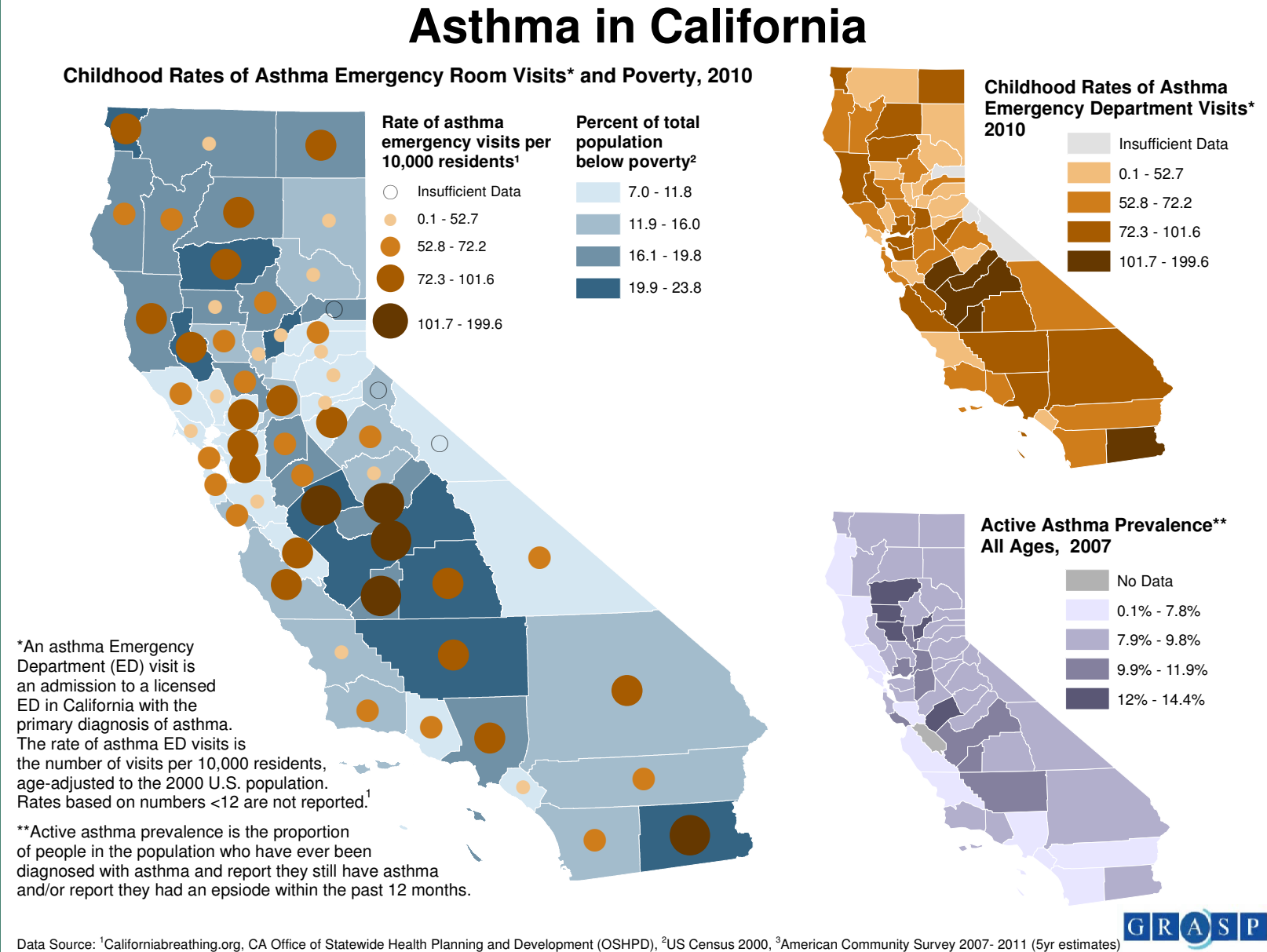
EFFECT MODIFIERS — AIR POLLUTION, STRESS AND SOCIOECONOMICS

Brett lives in a low-income neighborhood close to Los Angeles and near a major roadway. Children in relatively low-income families and exposed to traffic-related air pollution, such as in Brett’s case, are at greater risk of frequent asthma symptoms. Importantly, they are at greater risk than children in the same neighborhood whose families are financially better off.

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- + [Asthma in California](#)



ASTHMA Genetics and Air Pollution

Exposure to oxidants in ambient air contributes to inflammation in the lungs. Oxidants include oxygen, ozone, particulate matter, polycyclic aromatic hydrocarbons (PAHs - a group of chemicals that occur primarily from burning fuel), nitrogen oxides, and cigarette smoke.

The genes glutathione (GST) and epoxide hydrolase (EPHX1) are important for detoxification and elimination of contributors to oxidative stress associated with asthma. Oxidative stress and inflammation are fundamental to the origination and development of asthma.

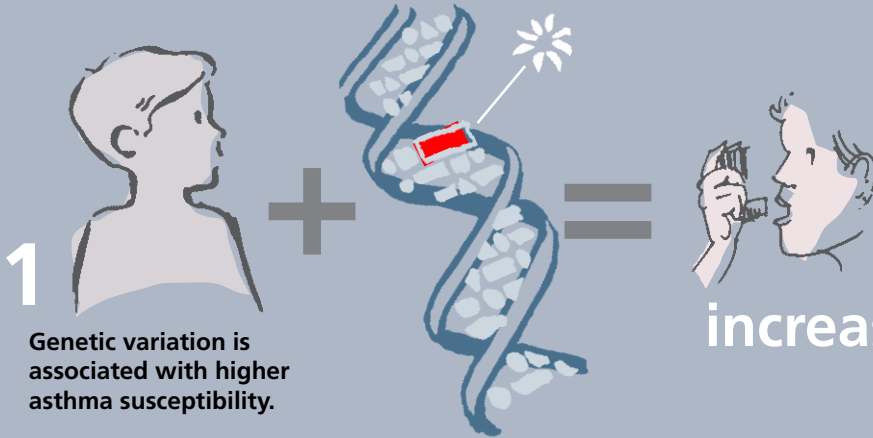
 **Key Concept: Inflammation and Oxidative Stress**

Certain genetic variants in GST and EPHX1 each are individually associated with increased risk of developing asthma, as is living in close proximity to a major roadway. Salam et al., found that being in the high risk group for all three resulted in nearly a nine-fold increase in risk for lifetime asthma. Ultrafine particulate matter has strong oxidant properties and generates inflammatory responses (Li et al., 2003).

Genes metabolizing PAHs have polymorphisms (many forms) that affect how well they mediate tissue damage via development of reactive oxygen species.

Genetics Increase Susceptibility to Air Pollution

1

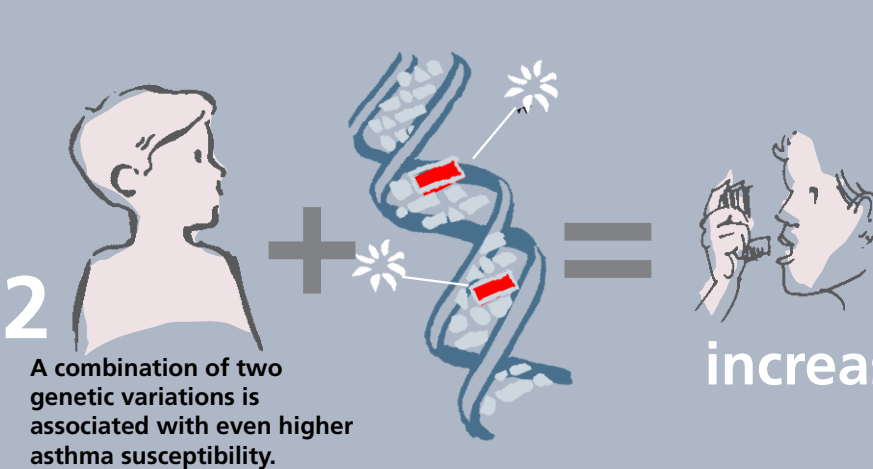


Genetic variation is associated with higher asthma susceptibility.

1) Variation in one gene, epoxide hydrolase (EPHX1) is associated with 50% increase in asthma risk.

increases by half

2

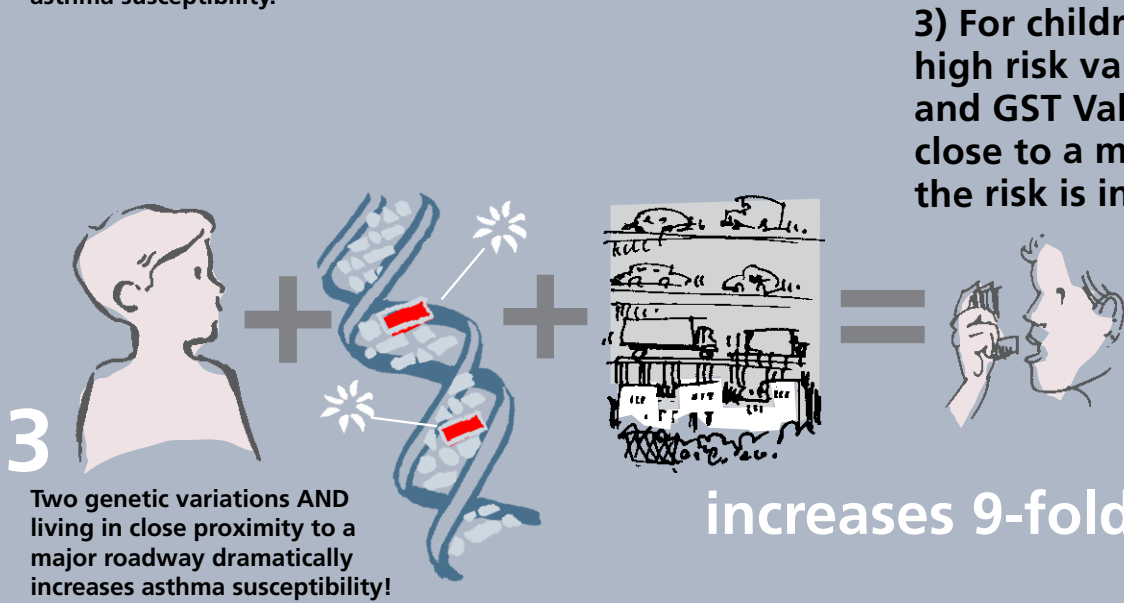


A combination of two genetic variations is associated with even higher asthma susceptibility.

2) The combination of having two high risk variants, EPHX1 and Glutathione S Transferase P1 (GST Val\Val) results in a four-fold increase in risk.

increases 4-fold

3



Two genetic variations AND living in close proximity to a major roadway dramatically increases asthma susceptibility!

3) For children with both high risk variants (EPHX1 and GST Val\Val) who live close to a major roadway, the risk is increased nine-fold.

increases 9-fold

ASTHMA Genetics and Air Pollution

Exposure to oxidants in ambient air contributes to inflammation in the lungs. Oxidants include oxygen, ozone, particulate matter, polycyclic aromatic hydrocarbons (PAHs - a group of chemicals that occur primarily from burning fuel), nitrogen oxides, and cigarette smoke.

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 **Key Concept: Inflammation and Oxidative Stress**

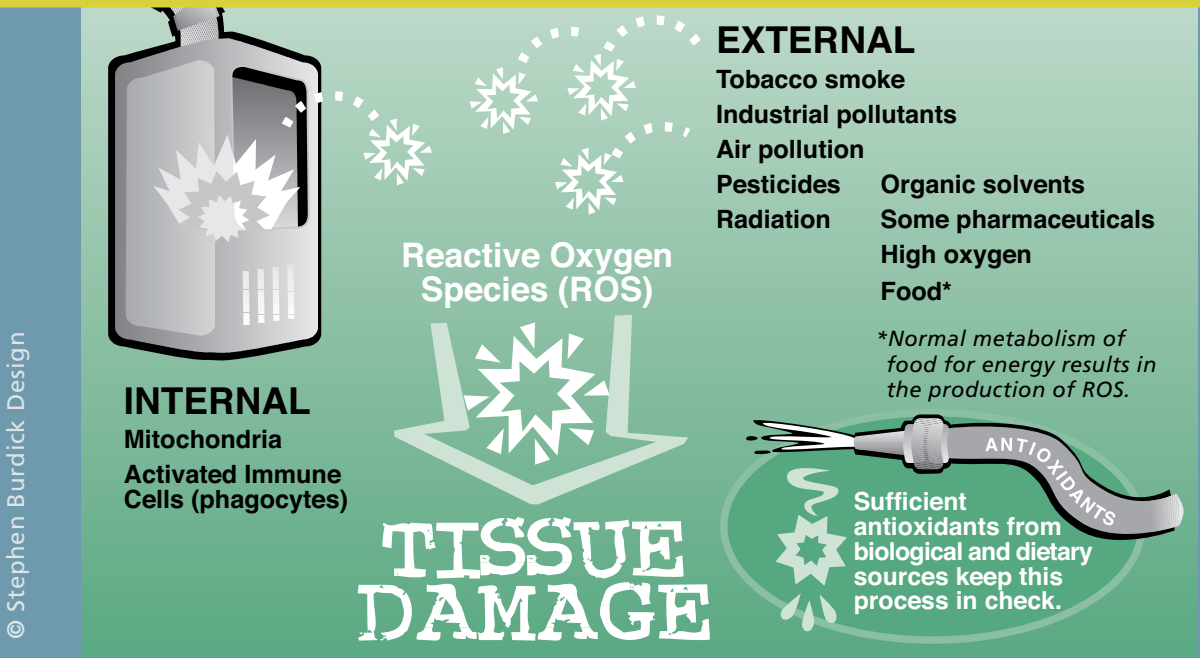
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Salam et al., *Thorax* 2007; 62:1050-1057

KEY CONCEPT:
Inflammation and Oxidative Stress
Chronic inflammation and oxidative stress are two mechanisms that underlie many common chronic diseases, including asthma, diabetes, metabolic syndrome, obesity, cardiovascular disease, some neurodegenerative disorders, cancer, and other chronic illnesses.

Inflammation
Inflammation is the body’s attempt at self-protection in response to injury, infections, and other stresses - the aim being to remove harmful stimuli, including infectious agents, damaged cells, or irritants - and begin the healing process. It can be acute and short-lived or chronic. The inflammatory response can affect blood vessels, the immune system, and cells within involved tissue. Excessive, prolonged, or recurrent inflammation is an aspect of many diseases. Various inflammatory “markers” are involved, some of which can be measured through laboratory testing, for example, various cytokines.
An important contributor to inflammation is oxidative stress.



Oxidative Stress
Excessive oxidative stress (OS) occurs when levels of “reactive oxygen species” (ROS) are chronically elevated, damage tissues, and increase disease risk. ROS are highly reactive oxygen molecules, sometimes called free radicals, normally present in the body as a result of using oxygen to metabolize food and create energy. They play an essential role in some aspects of cell signaling. Antioxidants, including those from dietary sources, keep ROS at healthy levels. Overproduction of ROS and/or insufficient antioxidants leads to excessive OS. Exposure to air pollution, various industrial chemicals, pesticides, heavy metals, and radiation can also cause excessive ROS. Certain people may be genetically predisposed to have a limited capacity to detoxify ROS.

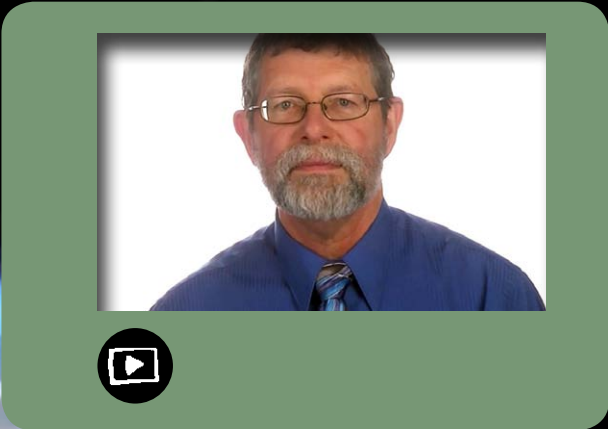
ASTHMA and Climate Change

Brett's generation has heard a lot about climate change. Climate change is expected to increase ground level ozone through increases in temperature and wind patterns. As CO2 levels rise and temperatures increase, airborne pollen levels are also increasing.

The combination of higher levels of asthma-related air pollutants associated with changes in atmospheric conditions are expected to continue to increase the frequency of asthma attacks in people with asthma, and may also increase the prevalence of asthma in populations.



Watch: In this short video Dr. John Balmes clearly outlines how climate changes will increase the incidence of asthma. (2 min.)



It is easy to check the air quality in your area on the weather channel on television, in the newspaper, on the internet, or via your smartphone. The EPA's Air Quality Index is a good resource.

POLLEN COUNT	
WEATHERWATCH	TODAY
Oak, Mulberry	X-High
Maple, Ash	X-High
Sycamore	X-High
Cedar, Birch	High
Willow	Mod
Grass, Mold	Low

Courtesy: Intermountain Allergy

AQI AIR QUALITY INDEX		
Air Quality Index Levels of Health Concern	Numerical Value	Meaning
Good	0 to 50	Air quality is considered satisfactory, and air pollution poses little or no risk.
Moderate	51 to 100	Air quality is acceptable; however, for some pollutants there may be a moderate health concern for a very small number of people who are unusually sensitive to air pollution.
Unhealthy for Sensitive Groups	101 to 150	Members of sensitive groups may experience health effects. The general public is not likely to be affected.
Unhealthy	151 to 200	Everyone may begin to experience health effects; members of sensitive groups may experience more serious health effects.
Very Unhealthy	201 to 300	Health warnings of emergency conditions. The entire population is more likely to be affected.
Hazardous	301 to 500	Health alert: everyone may experience more serious health effects.



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AQI AIR QUALITY INDEX		
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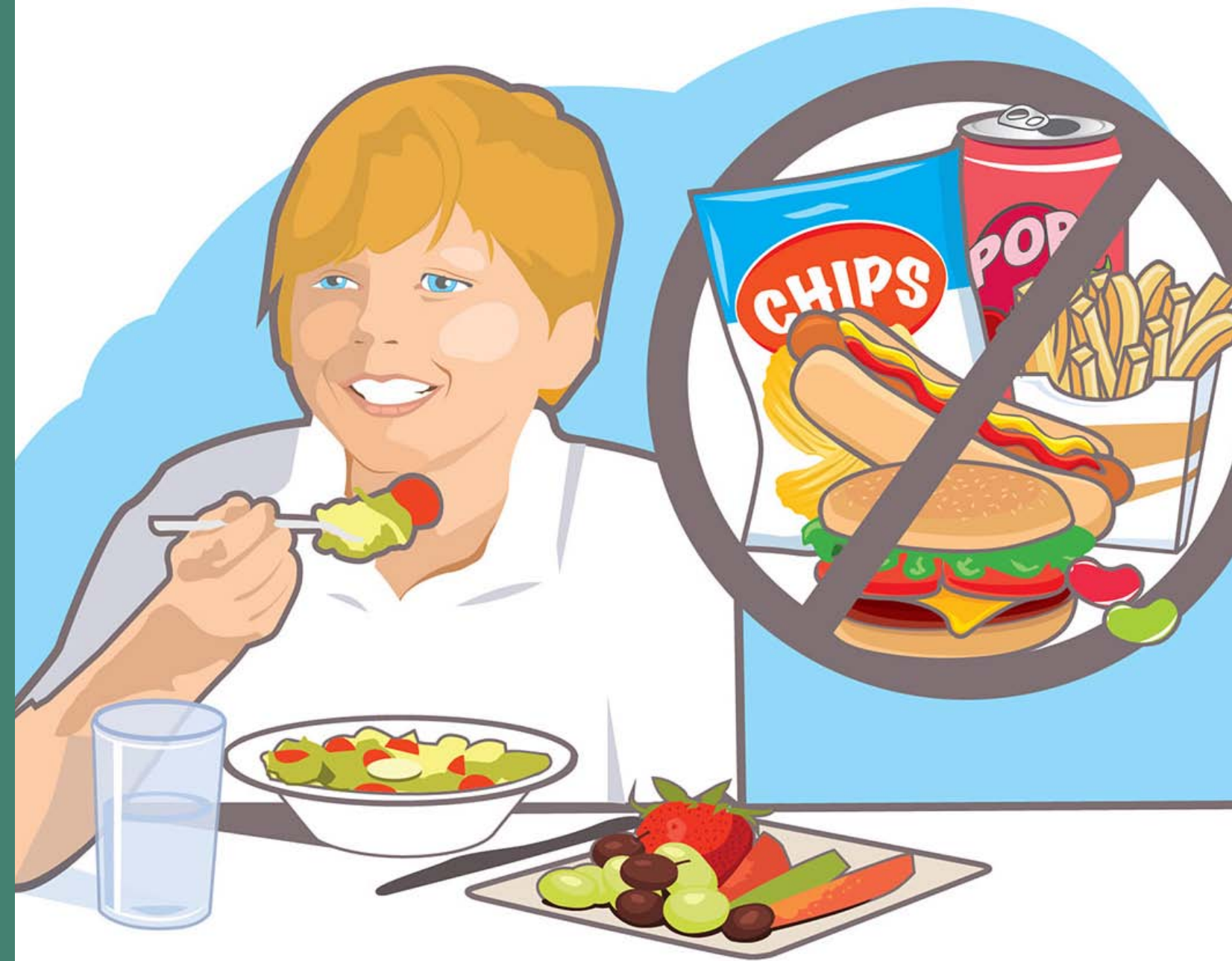
*pollutants measured: PM 2.5, ozone

ASTHMA: Healthy Eating Habits

At the family reunion it is time to eat. Brett grabs a sandwich off the buffet table. Karen is glad that Brett has chosen a sandwich on healthier whole wheat bread, rather than processed white bread.

Because of his asthma, Karen wants Brett to stay as healthy as possible, and also not to become overweight as it could worsen his asthma. (Obesity can also increase risk of developing asthma.)

His pediatrician regularly emphasizes the importance of eating nutritious foods high in antioxidants such as colorful fruits and vegetables, and other healthy foods including fish that have omega-3 fatty acids.



ASTHMA

Hey, there comes Max, his cousin’s dog, running right at him!

“Hey Max,” Brett says as he pets him and holds him close, forgetting for a minute that dogs can also cause him to have an asthma attack, something about their hair. (Hastert et al., 2007, Popplewell et al., 2000)

Brett doesn’t care, Max is so friendly.



ASTHMA: Brett's Story

We have seen throughout the pages of Brett's story that a wide range of factors, and their interactions across his lifespan, are risk factors for both the onset of asthma, as well as triggering it. These include environmental chemicals and other contaminants, family and community social stressors, diet and nutrition, economics, and how these might interact with each other and with genetics.

Although Brett's story is fictional, and it is difficult to determine what risk factors might be most important to him, the circumstances of his life can be found in children throughout our country.

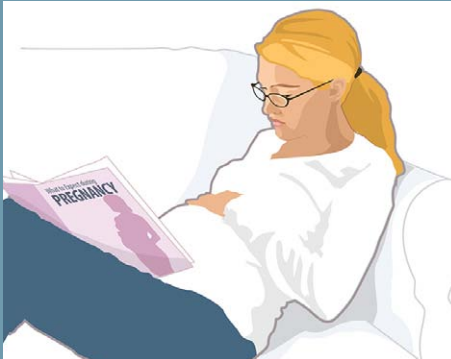
It is therefore critical that we consider multiple environmental influences on asthma when we design prevention strategies and treatment.

Continue on to the [next page](#) to learn more about preventive strategies.



The circumstances of Brett's life can be found in children throughout our country

A wide range of factors, and their interactions across Brett's lifespan, are risk factors for both the onset of asthma, as well as triggering it.



It is critical that we consider multiple environmental influences on asthma when we design prevention strategies and treatment.

ASTHMA: Management and Prevention Strategies

Children with asthma should:

- Not be exposed to secondhand smoke (SHS) and other types of combustion smoke,
- Not exercise outdoors on bad air quality days, but outdoor exercise should otherwise be encouraged, and,
- Avoid allergens to which they are sensitized.

Other protective factors include the following, if possible:

- Choosing homes and walking routes away from major roadways with heavy traffic,
- Improved access to health care, healthy foods, and green space for disadvantaged children with asthma,
- Dietary antioxidants, including vegetables,
- Avoidance of water-damaged environments,
- Improved ventilation in buildings to discourage mold growth,
- Using household chemicals and pesticides sparingly if at all, and with care, and,
- Replacing or retrofitting older diesel vehicles.



For clinicians - more information on asthma management:

Guidelines from the National Environmental Education Foundation

Guidelines from the National Heart, Lung and Blood Institute

Asthma Management Strategies



Avoid water damaged and moldy areas



Avoid tobacco smoke



Keep areas free of dust



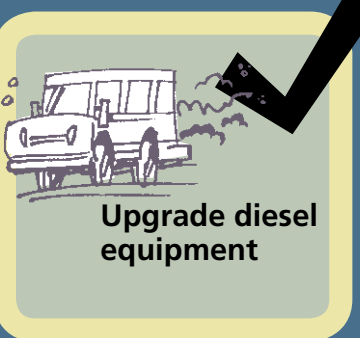
Use chemicals and pesticides with care



Promote and use greenspaces such as parks



Improve diet, include antioxidants



Upgrade diesel equipment



Get regular checkups

ASTHMA: Policy Initiatives to Protect Health

Policy initiatives to protect health include:

- Improved city and highway planning,
- Improved public transportation, bicycle friendly streets, accessible sidewalks,
- Changes in zoning laws, where appropriate, to allow mixed use neighborhoods resulting in less driving,
- Healthy building practices for schools and public buildings, including improved ventilation, reducing use of toxic chemicals in building materials and maintenance, incentives for green buildings,
- Increased use of renewable and less polluting energy, e.g. solar,
- Chemical policy reform,
- Smoking ordinances,
- Asthma home visiting programs for asthma education on trigger control and disease management,
- School sitings should be >500 meters from highways, and,
- Regulations to limit wood burning and outdoor wood boilers.

Continue to [Final Thoughts](#) >



Watch: Public polices can help improve health. Dr. John Balmes offers specific recommendations to reduce air pollution. (7 min.)



More on policies to prevent asthma:
[CDC Asthma](#)
[EPA Indoor Air Pollution](#)
[Asthma Community Network](#)

Policy Initiatives for Cleaner Air in California

California has instituted a number of policy initiatives to improve air quality which other states and communities could replicate.

- Reduction of diesel emissions
- On-road bus and truck rule
- Off-road construction vehicles
- Other surface goods movement efforts (ports and rail yards)
- Financial incentives for cleaner trucks and school buses
- Advanced Clean Cars rule - Smart growth = decreased VMTs
- No-burn rules to limit wood smoke emissions



Graphic used with permission.

Asthma

Childhood Leukemia

Learning/ Developmental Disabilities

Diabetes

Infertility

Cognitive Decline

Asthma Case References and Resources by Topic

Note: there are many topic overlaps

Acetaminophen

McBride JT. The association of acetaminophen and asthma prevalence and severity. [Pediatrics](#); doi: 10.1542/peds.2011-1106

Martinez-Gimeno A, García-Marcos L. The association between acetaminophen and asthma: should its pediatric use be banned? [Expert Rev Respir Med](#). 2013 Apr;7(2):113-22. doi: 10.1586/ers.13.8

Air Pollution

Galizia A, Kinney PL. Long-term residence in areas of high ozone: as-sociations with respiratory health in a nationwide sample of nonsmoking young adults. [Environ Health Perspect](#) 1999;107(8):675-9

Gauderman WJ et al. Association between air pollution and lung function growth in Southern California children. [Am. J. Respir. Crit. Care Med](#); July 1, 2002 vol. 166 no. 1 76-842002

Li N, et al. Ultrafine particulate pollutants induce oxidative stress and mitochondrial damage. [Environ Health Perspect](#) Vol 11: 4, 2003

Li N, Hao M, Phalen RF, Hinds WC, Nel AE. Particulate air pollutants and asthma. A paradigm for the role of oxidative stress in PM-induced adverse health effects. [Clin Immunol](#). 2003 Dec;109(3):250-65

Nadeau K, McDonald-Hyman C, Noth, EM, Pratt B, Hammond, K, Balmes, J and Tager I. Ambient air pollution impairs regulatory T-cell function in asthma. [J Allergy Clin Immunol](#) Volume 126, Number 4

Tager IB, Balmes J, Lurmann F, et al. Chronic exposure to ambient air pollution and lung function in young adults. [Epidemiology](#). 2005;16(6):751-9

Air Pollution - Exercise

McConnell R, Berhane K, Gilliland F, London SJ, Islam T, Gauderman WJ, Avol E, Margolis HG, Peters JM.. Asthma in exercising children exposed to ozone: a cohort study. [Lancet](#). 2002 Feb 2;359(9304):386-91



Gene-environment – Air Pollution

Salam MT, Lin PC, Avol EL, Gauderman WJ, Gilliland FD. Microsomal epoxide hydrolase, glutathione S-transferase P1, traffic and childhood asthma [Thorax](#). 2007 Dec;62(12):1050-7

Air Pollution - Traffic specific

Balmes J. Can traffic-related air pollution cause asthma? [Thorax](#) 2009;64:646-647 doi:10.1136/thx.2009.116418

Gauderman WJ. Children’s health and traffic exposures [Powerpoint](#)

Gauderman WJ, Vora H, Mc-Connell R, Berhane K, Gilliland F, Thomas D, Lurmann F, Avol E, Kunzli N, Jerrett M, Peters J. Effect of exposure to traffic on lung development from 10 to 18 years of age: a cohort study. [Lancet](#). 2007 Feb 17;369(9561):571-7

Green R, Smorodinsky S, Kim JJ, McLaughlin R, Ostro1 B. Proximity of California public schools to busy roads. [Environ Health Perspect](#) 2004;Vol 112:1

Jerrett M, Shankardass K, Berhane K, Gauderman WJ, Künzli N, Avol E, Gilliland F, Lurmann F, Molitor JN, Molitor JT, Thomas DC, Peters J, McConnell R. Traffic-related air pollution and asthma onset in children: a prospective cohort study with individual exposure measurement. [Environ Health Perspect](#) 2008 Oct;116(10):1433-8. doi: 10.1289/ehp.10968. Epub 2008 Jun 18

Kim JJ, Smorodinsky S, Lipsett M, Singer BC, Hodgson AT, Ostro B. Traffic-related air pollution near busy roads: the East Bay Children’s Respiratory Health Study. [Am J Respir Crit Care Med](#). 2004 Sep 1;170(5):520-6. Epub 2004 Jun 7

Kim JJ, Huen K, Adams S, Smorodinsky S, Hoats A, Malig B, Lipsett M, Ostro B. Residential traffic and children’s respiratory health. [Environ Health Perspect](#). 2008 Sep;116(9):1274-9. doi: 10.1289/ehp.10735

Meng Y, Wilhelm M, Rull R, PEnglish P, Nathan S, and Ritz B. Are frequent asthma symptoms among low-income individuals related to heavy traffic near homes, vulnerabilities, or both? [AEP Vol. 18, No. 5 May 2008: 343-350](#)

McCormack MC, Breyse PN, Eggleston PA, Matsui EC, Hansel NN, Brosnan JC, Eggleston PA, Diette GB. In-home particle concentrations and childhood asthma morbidity. [Environ Health Perspect](#) 2009 Feb; 117(2):294-8.

Sarnat JA. Asthma and air quality. [Curr Opin Pulm Med](#). 2007; Jan; 13(1): 63-6

Zhu Y, Hinds WC, Shen S, Kim S, Sioutas C. Study of ultrafine particles near a major highway with heavy-duty diesel traffic. 2002 [Atmospheric Environment](#). 36: 4323-4335

Zhu Y, Kuhn T, Mayo P, Hinds WC. Comparison of daytime and nighttime concentration profiles and size distributions of ultrafine particles near a major highway. 2006 [Environmental Science and Technology](#) 40: 2531-2536

Air pollution - Weight gain

Bolton S, Smith S, Huff N, Gilmour MI, Foster WM, Auten R, Bilbo S. et al. Prenatal air pollution exposure induces neuroinflammation and predisposes offspring to weight gain in adulthood in a sex-specific manner. [FASEB Journal](#) article fj.12-210989. Published online July 19, 2012

Allostatic Load

McEwen B. Protective and damaging effects of stress mediators: central role of the brain.Dialogues. [Clin Neurosci](#). 2006 December; 8(4): 367–381

McEwen BS. Central effects of stress hormones in health and disease: understanding the protective and damaging effects of stress and stress mediators. [Eur J Pharma-col](#).2008 April 7; 583(2-3): 174–185



Classifications

Koterba A, Saltoun C. Chapter 9: asthma classification. [Allergy Asthma Proc](#). 2012; 33 (suppl 1) : S28-31

Climate change and respiratory health

D Amato G, Cagnani CE, Cecchi L, Annesi-Maesano I, Nunes C, Ansotegui I, D Amato M, Liccardi G, Sofia M, Canonica WG. Climate change, air pollution and extreme events leading to increasing prevalence of allergic respiratory diseases. [Multidiscip Respir Med](#). 2013 Feb 11;8(1):12

Kinney PL. Climate change, air quality, and human health. [Am J Prev Med](#). 2008; 35(5):459-67

Knowlton K, Rosenthal JE, Hogrefe C, Lynn B, Stuart Gaffin, Richard Goldberg, Cynthia Rosenzweig, Kevin Civerolo, Jia-Yeong Ku, Patrick L. Kinney. Assessing Ozone-Related Health Impacts under a Changing Climate. [Environ Health Perspect](#). 2004 November; 112(15): 1557-1563

Demographics

CDC:

[National Surveillance of Asthma: US, 2001–2010](#)

[Asthma in the US](#)

[CDC Vital Signs: Asthma in the US](#)

National Environmental Health Tracking [Network](#)

Diet and Asthma

Dotterud CK, Storror O, Simpson MR, Johnsen R, Oien T. The impact of pre- and postnatal exposures on allergy related diseases in childhood: a controlled multicentre intervention study in primary health care. [BMC Public Health](#). 2013 Feb 8;13:123

Garcia-Marcos L, Castro-Rodriguez JA, Weinmayr G, Panagiotakos DB, Priftis KN, Nagel G. Influence of

Mediterranean diet on asthma in children: A systematic review and meta-analysis. [Pediatr Allergy Immunol](#). 2013 Apr 11. doi: 10.1111/pai.12071

Gilliland. Outdoor Air Pollution, Genetic Susceptibility, and Asthma Management. [Pediatrics](#). Vol 123. No. Supplement 3 March 1, 2009. “Emerging research indicates that dietary supplementation for individuals with low antioxidant levels is one promising approach to reducing susceptibility to air pollution.”

Nakamura K, Wada K, Sahashi Y, Tamai Y, Tsuji M, Watanabe K, Ohtsuchi S, Ando K, Nagata C. Associations of intake of antioxidant vitamins and fatty acids with asthma in pre-school children. [Public Health Nutr](#). 2012 Oct 1:1-6. pubmed/23021626

Exercise Induced

Spector S, Tan R.Exercise-induced bronchoconstriction update: therapeutic management. [Allergy Asthma Proc](#). 2012 Jan-Feb;33(1):7-12

Health Disparities

Roberts EM, English PB, Wong M, Wolff C, Valdez S, Van den Eeden SK, et al. Progress in pediatric asthma surveillance II: geospatial patterns of asthma in Alameda County, California. [Prev Chronic Dis](#) 2006 Jul

Heterogeneity of Asthma Phenotypes

Bhakta NR, Woodruff PG. Human asthma phenotypes: from the clinic, to cytokines, and back again. [Immunol Rev](#).2011 Jul;242(1): 220-32

Holgate ST. A look at the pathogenesis of asthma: the need for a change in direction. [Discov Med](#).2010 May;9(48):439-47

Lung Development, Fetal and Early life programming, Early life risk factors

Duijts L. Fetal and infant origins of asthma. [Eur J Epidemiol](#). 2012 Jan;27(1):5-14. doi: 10.1007/s10654-012-9657-y. Epub 2012 Feb 1

Fanucchi MV, Plopper CG, Evans MJ, Hyde DM, Van Winkle LS, Gershwin LJ, et al. Cyclic exposure to ozone alters distal airway development in infant rhesus monkeys. [Am J Physiol Lung Cell Mol Physiol](#). 2006;291(4):L644–L650

Kajekar R. Environmental factors and developmental outcomes in the lung. [Pharmacol Therap](#). 2007;114:129–145

Miller M, Marty M. Impact of environmental chemicals on lung development. [Environ Health Perspect](#)Vol 118: 8. August 2010

Pinkerton KE, Joad JP. The mammalian respiratory system and critical windows of exposure for children’s health. [Environ Health Perspect](#) 2000;108(suppl 3):457–462

Plopper CG, Smiley-Jewell SM, Miller LA, Fanucchi MV, Evans MJ, Buckpitt AR, et al. 2007. Asthma/allergic airways disease: does post-natal exposure to environmental toxicants promote airway pathobiology? [ToxicolPathol](#) 35:97–110.

Salam MT et al. Early-Life Environmental Risk Factors for Asthma: Findings from the Children’s Health Study [Environ Health Perspect](#) 112:760–765 (2004)

Stern DA, Morgan WJ, Wright AL, et al. Poor airway function in early infancy and lung function by 22 years: a non-selective longitudinal cohort study. [Lancet](#) 2007;370(9589):758–764

Tran MT, Weir AJ, Fanucchi MV, Rodriguez AE, Pantle LM, Smiley-Jewell SM, et al. Smooth muscle hypertrophy in distal airways of sensitized infant rhesus monkeys exposed to house dust mite allergen. [Clin Exp Allergy](#).2004b;34:1627–1633

Wright R. Perinatal stress and early life programming of lung structure and function.[Biol Psychol](#). 2010 April; 84(1): 46–56

Obesity and Asthma

Maternal obesity before and during pregnancy and childhood asthma:

Guerra S, Sartini C, Mendez M, Morales E, et al. Maternal prepregnancy obesity is an independent risk factor for frequent wheezing in infants by age 14 months. [Paediatr Perinat Epidemiol](#).2013 Jan;27(1):100-8

Lowe A, Bråbäck L, Ekeus C, Hjern A, Forsberg B. Maternal obesity during pregnancy as a risk for early-life asthma. [J Allergy Clin Immunol](#).2011 Nov;128(5):1107-9

Scholtens S, Wijga AH, Brunekreef B, Kerkhof M, et al. Maternal overweight before pregnancy and asthma in offspring followed for 8 years. [Int J Obes \(Lond\)](#).2010 Apr;34 (4):606-13.

Childhood obesity:

Papoutsakis C, Priftis KN, Drakouli M, Prifti S, Konstantaki E, Chondronikola M, Antonogeorgos G, Matziou V. Childhood overweight/obesity and asthma: is there a link? A systematic review of recent epidemiologic evidence. [J Acad Nutr Diet](#). 2013 Jan;113(1):77-105. doi: 10.1016/j.jand.2012.08.025

continued >

Asthma

Childhood Leukemia

Learning/ Developmental Disabilities

Diabetes

Infertility

Cognitive Decline

Occupational Asthma

Baur X, Aasen T, Burge P, Heederik D, et al. The management of work-related asthma guidelines: a broader perspective. [Eur Respir Rev.](#) 2012; 21(124):125-139

Burge P, Moore V, Robertson A. Sensitization and irritant-induced occupational asthma with latency are clinically indistinguishable. [Occup Med \(Lond\).](#) 2012; 62(2):129-133

Tarlo SM, Balmes J, Balkissoon R, Beach J, et al. Diagnosis and management of work-related asthma: American College Of Chest Physicians Consensus Statement. [Chest.](#) 2008 Sep;134(3 Suppl):1S-41S

Zock J, Vizcaya D, Le Moual N. Update on asthma and cleaners. [Curr Opin Allergy Clin Immunol.](#) 2010; 10(2):114-120



Pet Allergies

Hastert TA, Babey SH, Brown ER, Meng YY. Pets and smoking in the home associated with asthma symptoms and asthma-like breathing problems. [Policy Brief UCLA Cent Health Policy Res.](#) 2007 Feb;(PB2007-2):1-7

Popplewell EJ, Innes VA, Lloyd-Hughes S, Jenkins EL, Khdir K, Bryant TN, Warner JO, Warner JA. The effect of high-efficiency and standard vacuum-cleaners on mite, cat and dog allergen levels and clinical progress. [Pediatr Allergy Immunol.](#) 2000 Aug;11(3):142-8

Population Health

Puska P. From Framingham to North Karelia: from descriptive epidemiology to public health action. [Prog Cardiovasc Dis.](#) 2010; 53(1):15-20

Rose G. Sick individuals and sick populations. [Int J Epidemiol.](#) 1985; 14(1):32-38

Schettler T. The ecology of breast cancer: The promise of prevention, and the hope for healing. [Science and Environmental Health Network and the Collaborative on Health and the Environment.](#) October, 2013

Protective Measures

Champagne Frances A.; Meaney, Michael J. Transgenerational effects of social environment on variations in maternal care and behavioral response to novelty. [Behavioral Neuroscience, Vol 121\(6\), Dec 2007, 1353-1363.](#)doi: 10.1037/0735-7044.121.6.1353

Suglia FS, Enlow MC, Kullowatz A, Wright RJ. Maternal intimate partner violence and increased asthma incidence in children: buffering effects of supportive caregiving. [Arch Pediatr Adolesc Med.](#) 2009 Mar;163(3):244-50

Racial Disparities

McDaniel M, Paxson C, Waldfoegel J. Racial disparities in childhood asthma in the United States: Evidence from the national health interview survey, 1997 to 2003. [PEDIATRICS Vol. 117 No. 5 May 1, 2006 pp. e868 -e877](#)

Smoking

Neuman A, Hohmann C, Orsini N, Pershagen4 G, Eller E, Fomsgaard Kjaer6 H, Gehring, U, Granell R, et al . Maternal smoking in pregnancy and asthma in preschool children: a pooled analysis of 8 birth cohorts [Am J Respir Crit Care Med.](#) 2012 Nov 15;186(10):1037-43

Burke H, Leonardi-Bee J, Hashim A, Pine-Abata H, Chen Y, Cook DG, Britton JR, McKeever TM. Prenatal and passive smoke exposure and incidence of asthma and wheeze: systematic review and meta-analysis. [Pediatrics.](#) 2012 Apr;129(4):735-44. doi: 10.1542/peds.2011-2196. Epub 2012 Mar 19

Stress

Chiu et al. Prenatal and Postnatal Maternal Stress and Wheeze in Urban Children. [Am J Respir Crit Care Med Vol 186, Iss. 2, pp 147-154, Jul 15, 2012](#)

Stress, Socioeconomics, Air pollution

Bryant-Stephens T. Asthma disparities in urban environments. [J Allergy Clin Immunol](#) June 2009

Charafeddine R, Boden LI. Does income inequality modify the association between air pollution and health? [Environmental Research](#) 106 (2008) 81-88

Chen E, Hanson M, Paterson L, Griffin MJ, Walker HA, and Miller GE. Socioeconomic status and inflammatory processes in childhood asthma: The role of psychological stress. [J Allergy Clin Immunol. Vol-ume 117, Number 5. March 2006](#)

Clougherty JE, Levy JJ, Kubzansky LD, et al. Synergistic effects of traffic-related air pollution and exposure to violence on urban asthma etiology. [Environ Health Perspect](#) 2007;115(8):1140-1146

Islam T, Urman, Gauderman WJ, Milam J, Lurmann F, Shankardass K, Avol E, Gilliland F and McConnell R. Parental Stress Increases the Detrimental Effect of Traffic Exposure on Children's Lung Function. [Am. J. Respir. Crit. Care Med.](#) October 1, 2011 vol. 184 no. 7 822-827

Reyes et al. Relationship between maternal demoralization, wheeze, and immunoglobulin E among inner-city children [Ann Allergy Asthma Immunol.](#) 2011;107:42-49

Shankardass K, McConnell R, Jerrett M, Milam J, Richardson J, and Berhane K. Parental stress increases the effect of traffic-related air pollution on childhood asthma incidence. [PNAS July 28, 2009 vol. 106 no. 30](#)

Shonkoff JP, Garner AS, and the Committee on Psychosocial Aspects of Child and Family Health, Committee on Early Childhood, Adoption, and Dependent Care, and Section on Developmental and Behavioral Pediatrics. The lifelong effects of early childhood adversity and toxic stress. [AAP Technical Report. Pediatrics.](#) 2012 Jan;129(1):e232-46

Suglia FS, Duarte CS, Sandel MT, et al. Social and environmental stressors in the home and childhood asthma. [J Epidemiol Community Health](#) 2010;64(7):636-642

Williams DR, Sternthal M, Wright RJ. Social determinants: Taking the social context of asthma seriously. [PEDIATRICS Volume 123, Supplement 3, March 2009](#)

Wright RJ. Epidemiology of stress and asthma: from constricting communities and fragile families to epigenetics. [Immunol Allergy Clin N Am](#) 31 (2011) 19-39. doi:10.1016/j.iac.2010.09.011

Violence, Lung function, Asthma

Suglia FS, Ryan L, Laden F, Dockery DW and Wright RJ. Violence exposure, a chronic psychosocial stressor, and childhood lung function [Psychosomatic Medicine](#) 70:160-169 (2008)

Suglia FS, Enlow MB, Kullowatz A, et al. Maternal intimate partner violence and increased asthma incidence in children. [Arch Pediatr Adolesc Med](#) 2009;163(3):244-250

Vitamin D and Lung Development, Wheezing, Asthma

Carmago et al. Randomized trial of vitamin d supplementation and risk of acute respiratory tract infection in Mongolia. [Pediatrics](#) 2012. doi: 10.1542/peds.2011-3029

Camargo CA Jr, Ingham T, Wickens K, Thadhani R, et al. Cord-blood 25-hydroxyvitamin D levels and risk of respiratory infection, wheezing, and asthma. [Pediatrics.](#) 2011 Jan;127(1):e180-7. doi: 10.1542/peds.2010-0442. Epub 2010 Dec 27

Hollams EM. Vitamin D and atopy and asthma phenotypes in children. [Curr Opin Allergy Clin Immunol.](#) 2012 Jun;12(3):228-34

Zosky GR, Berry LJ, Elliot JG, James AL, Gorman S, Hart PH. Vitamin D deficiency causes deficits in lung function and alters lung structure. [Am J Respir Crit Care Med.](#) 2011 May 15;183(10):1336-43. Epub 2011 Feb 4

Recommendations for Vit D supplementation: American Academy of Pediatrics (AAP) Perrine C, Sharma A, Jeffers M, Serdula M, Scanlon K. Adherence to vitamin D recommendations among US infants. [Pediatrics.](#) 2010; 125(4):627-632

The American College of Obstetricians and Gynecologists: Committee Opinion 495. Vitamin D: Screening and Supplementation During Pregnancy. 2011 [Obstet Gynecol.](#) 2011;118 (1):197-198



Toxic Chemicals and Other Indoor Exposures

Heinrich J. Influence of indoor factors in dwellings on the development of childhood asthma. [Int J Hyg Environ Health.](#) 2011; 214(1):1-25

Mendell M. Indoor residential chemical emissions as risk factors for respiratory and allergic effects in children: a review [Indoor Air](#) 2007; 17: 259-277

Mold

Facts about mold and dampness. [CDC.](#)

Mold video on EPA Asthma science notebook

Phthalates

Bornehag CG, NanbergE .Phthalate exposure and asthma in children. [Int J Androl.](#) 2010 Apr;33(2):333-45. Epub 2010 Jan 4. Review

Hsu NY, Lee CC, Wang JY, Li YC, Chang HW, Chen CY, Bornehag CG, Wu PC, Sundell J, Su HJ. Predicted risk of childhood allergy, asthma, and reported symptoms using measured phthalate exposure in dust and urine [Indoor Air.](#) 2012 Jun;22(3):186-99. doi: 10.1111/j.1600-0668.2011.00753.x. Epub 2011 Nov 16



PVC

Larsson M, Hägerhed-Engman L, Kolarik B, James P, Lundin F, Janson S, Sundell J, Bornehag CG. Indoor. PVC—as flooring material—and its association with incident asthma in a Swedish child cohort study. [Air.](#) 2010 Dec;20(6):494-501. doi: 10.1111/j.1600-0668.2010.00671.x

General Resources

EPA: Science Notebook on Asthma

CDC: [Asthma](#)

CDC: [Triggers](#)

CDC: [Workplace Asthma](#)

ATSDR's CASE study “[Environmental Triggers of Asthma](#)”

[List of asthmagens](#) from Association of Occupational and Environmental Clinics

Association of Occupational and Environmental Clinics [Exposure Code Lookup](#)

Collaborative on Health and the Environment (CHE): [Toxicant Database](#)

ALA's “State of the Air” [search page](#)

(most relevant for CE course):

EPA/NIEHS Children's Centers 2012 Webinar Series

- In particular:
- Embracing Complexity: Animal Models of Environmental Exposure Health Effects - *Richard Auten, Duke University*
 - Effects of Prenatal Environmental Exposures on Child Health and Development -*Frederica Perera, Columbia University*

[CalEnviroScreen](#), Office of Environmental Health Hazard Assessment, California EPA

Ekanayake R, Miller M, Marty, M.

Office of Environmental Health Hazard Assessment, California Environmental Protection Agency. [Report to the Legislature, Children's Environmental Health Program.](#) February 2014

U.S. EPA. America's children and the environment [Third Edition](#)



Asthma Management, Treatment

[National Medical-legal Partnership](#)

CDC: [Health Care Guidelines](#)

National Environmental Education Foundation: [Pediatric Environmental History forms](#)

Intervention Guidance

Krieger JW, Philby Miriam L, Brooks Marissa Z. Better Home Visits for Asthma Lessons Learned from the Seattle-King County Asthma Program. [Am J Prev Med](#) 2011;41(2S1):S48-S51

Master Home Environmentalist: [Do-it-yourself Home Environmental Assessment List \(HEAL\)](#)

EPA's Asthma Home Environment Checklist

EPA [Air Quality Index](#)

CHILDHOOD LEUKEMIA

Stephen's Story*

Stephen is a 3-year-old boy who lives with his parents David and Tricia in a suburb in Connecticut.

He is an only child, and his parents spend as much time as they can with him even though they manage a successful plant nursery and garden center.

He spends four days a week at child care and is with his parents the other three days, sometimes at their house and sometimes at the garden center.

Stephen had been an active toddler, but during the past month, Tricia noticed that Stephen was not as lively and energetic as usual. His child care providers also mentioned this.

When he became listless and started to run a fever, Tricia became concerned. She took Stephen to see his pediatrician, Dr. Jones.

(*a fictional case)



CHILDHOOD LEUKEMIA

Stephen's Story

After talking with Tricia and examining Stephen, Dr. Jones was also concerned. She confirmed that Stephen appeared ill and that the cause could be a number of things. She said she needed laboratory tests to make an accurate diagnosis.

Dr. Jones ordered blood tests that could be done at the local hospital and called to make an appointment for Stephen to get his blood drawn that same day.

Tricia was upset and called her husband David with the news. She started to ask a lot of questions. Dr. Jones tried to calm her and said she would call her as soon as she had the results.

Tricia brought Stephen to the hospital laboratory for the tests and went home very worried.



CHILDHOOD LEUKEMIA

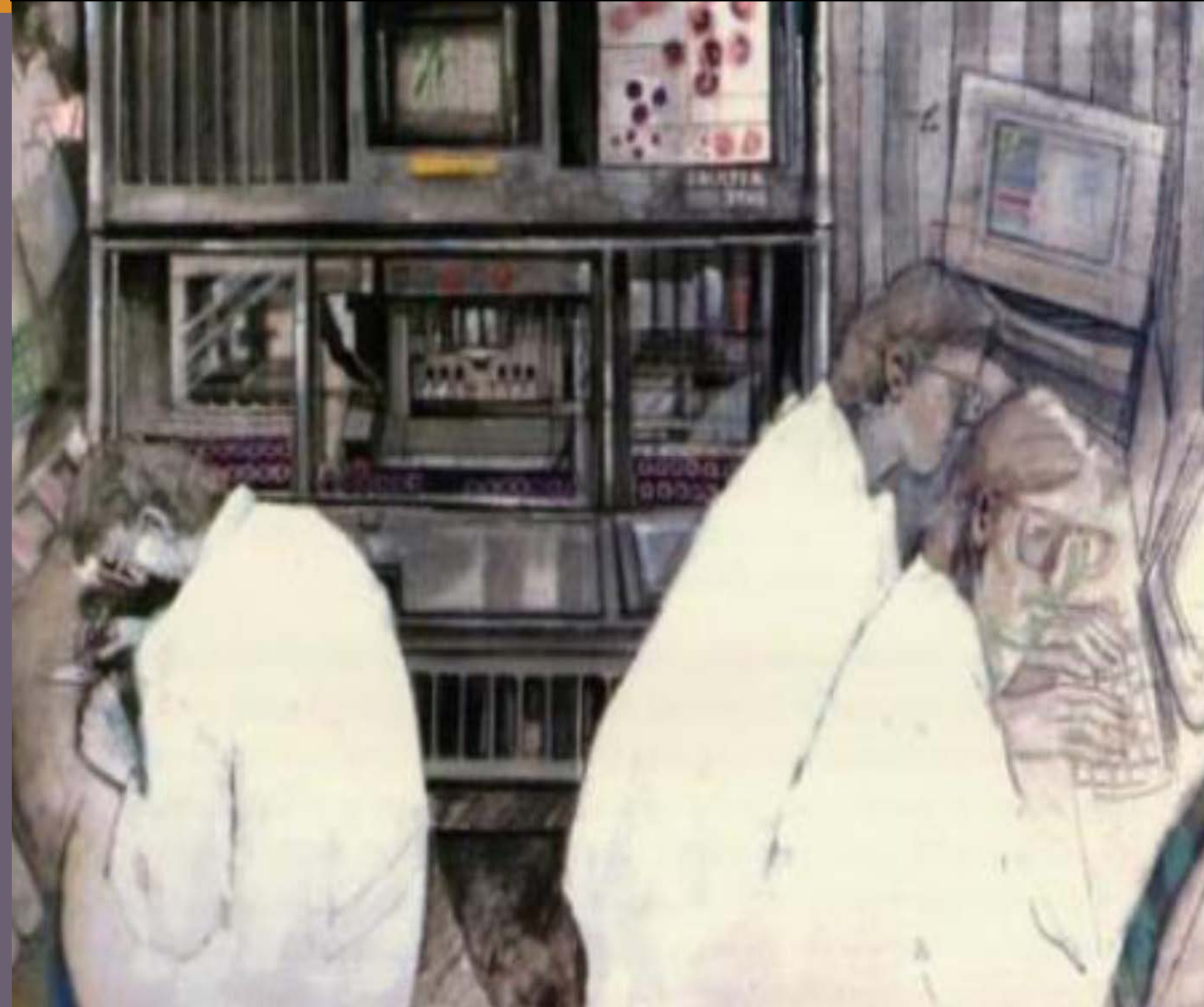
Stephen's Story

When Dr. Jones received the test results she called Tricia and David back into her office. She told them that the test results showed a very high white blood count and very low platelet count.

Dr. Jones said that Stephen would need to see a pediatric oncologist, Dr. Baker. She said she would arrange the appointment for Stephen at Dr. Baker's office next to the hospital and that he should go right over.

Tricia and David were shocked. They knew that oncologists dealt with cancer. Dr. Jones tried to reassure them and said they should wait to speak with Dr. Baker before drawing any conclusions.

They left Dr. Jones office still very worried.



See [this page](#) for more information on the artist.

CHILDHOOD LEUKEMIA

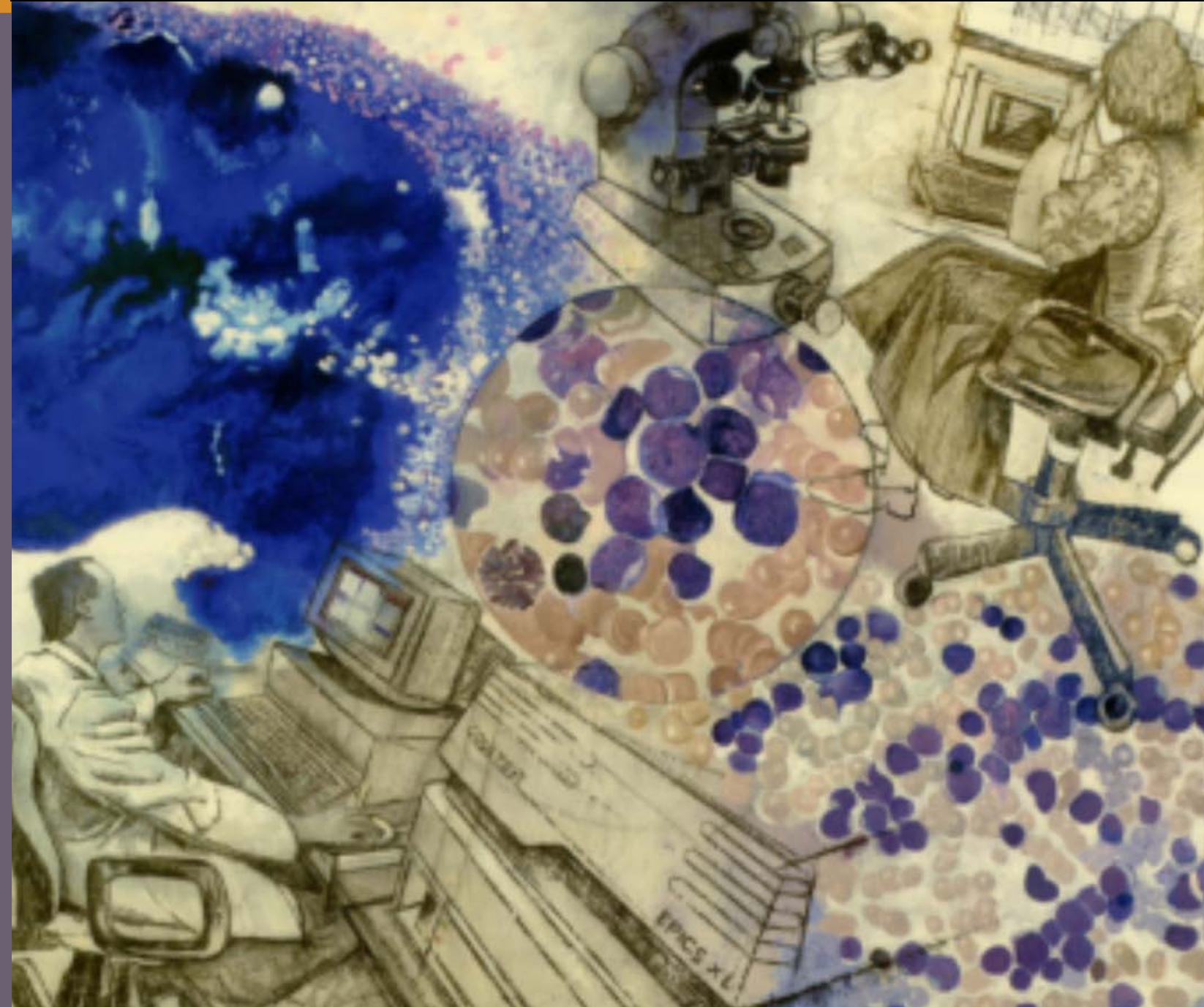
Stephen's Story

The pediatric oncologist, Dr. Baker, looked at Stephen's blood tests to confirm the findings from the laboratory.

Dr. Baker told Tricia and David that he was concerned that Stephen may have leukemia and needed to run more tests to confirm the diagnosis.

Since Stephen had a fever and suppressed immune system, Dr. Baker admitted Stephen to the hospital to start antibiotics and hydration therapy immediately.

Dr. Baker explained to Tricia and David that he would return in the morning to perform a bone marrow aspirate.



See [this page](#) for more information on the artist.

CHILDHOOD LEUKEMIA

Stephen's Story

The next day when Dr. Baker came to visit, Stephen looked well. He no longer had a fever and was playing. Dr. Baker explained the bone marrow procedure to Tricia and David and then performed the aspirate in a special room for procedures.

When he returned to discuss the bone marrow test results, Dr. Baker tried to calm Tricia and David, but they were upset and imagined the worst.

Unfortunately, their fears were realized when Dr. Baker told them that Stephen's test results confirmed that he had leukemia. He said that further tests were being done to find out more about what type of leukemia he had. He said they should know the type of leukemia the following day, and then they can begin treatment. They were devastated.



CHILDHOOD LEUKEMIA

Stephen's Story

Dr. Baker discussed with them what the course of treatment should be, including intravenous (IV) hydration (liquids), and initiating a course of chemotherapy.

Stephen would need to be in the hospital for this, since the initial treatment is the riskiest time period.

Dr. Baker arranged for Stephen to continue his hospital stay and begin treatment immediately.



CHILDHOOD LEUKEMIA

Stephen's Story

Later Dr. Baker explained that the type of leukemia Stephen had was called acute lymphoblastic leukemia (ALL). Dr. Baker told Stephen that he was sick, and that he would have to be in the hospital for a while so that the doctors can give him medicines to make him better.

Dr. Baker also explained to Tricia and David how the cure rate for children has improved dramatically over the past few decades.

Watch: Dr. Gary Dahl discusses types of leukemia (4:13 mins.)



Gary Dahl MD, Professor of Pediatrics (Hematology/ Oncology) at the Lucile Salter Packard Children's Hospital, Stanford School of Medicine



CHILDHOOD LEUKEMIA

Stephen's Story

CHILDHOOD LEUKEMIA IS NOT A SINGLE DISEASE

Acute leukemias in childhood comprise a group of related but different diseases. In the United States they represent 31% of malignancies occurring among children under the age of 15.

Eighty percent of acute childhood leukemias, including Stephen's, are acute lymphoblastic leukemia (ALL). Approximately 17% are acute myeloblastic leukemia (AML).

It is important to identify characteristics of the leukemia at its presentation since this information helps to determine the course of treatment as well as prognosis. The types of cells involved in the leukemia (immunophenotype) are used to determine whether a person has ALL or AML.

Factors such as age, initial white blood count at diagnosis, and cytogenetics (the specific differences or changes in DNA) of the leukemic cells at diagnosis are utilized to identify the most appropriate course of treatment.



Types of leukemia vary by age



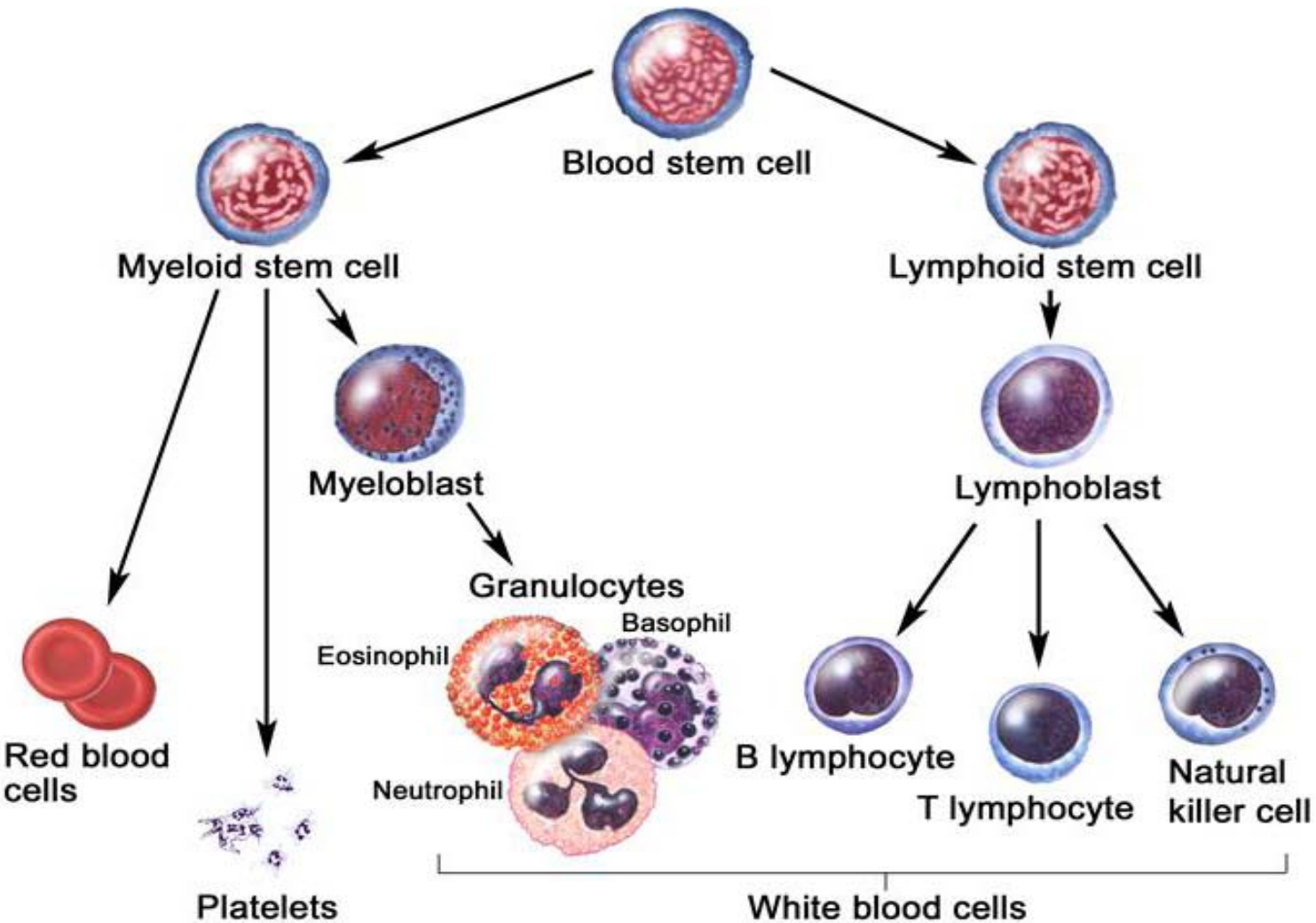
Early life exposures are important: age-specific incidence chart

Watch: Dr. Patricia Buffler discusses leukemia classification (1:59 mins.)



Patricia Buffler PhD MPH, Professor of Epidemiology and Dean Emerita (deceased) of the School of Public Health, University of California-Berkeley

Leukemias originate in B and T cells, which have important immune system functions.



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Graphic: Terese Winslow 2007.
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CHILDHOOD LEUKEMIA

Stephen's Story

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Types of leukemia vary by age



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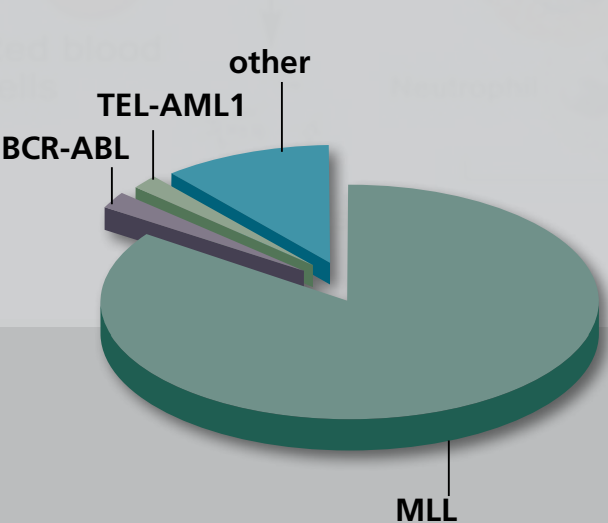
The two main types of leukemia based on cell histology are ALL and AML, but even within these groups, there are many different characteristics based on the presence of abnormalities of the chromosomes, whether the number of chromosomes is higher than expected (hyperdiploidy), or whether or not we see translocation or deletion in a specific chromosome.

These differences have practical implications: subgroups may have very specific risk factors. The leukemia subgroup also impacts treatment decisions.

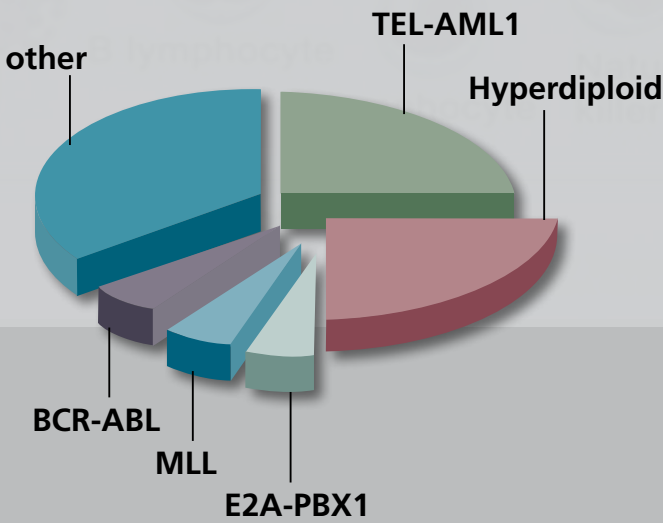
When grouped by underlying molecular markers, certain leukemias occur more frequently at different ages. MLL (mixed leukemia or Myeloid/lymphoid leukemia) is the predominant form in infants but relatively rare in older children. MLL is a particularly aggressive form of leukemia.

More details on translocations, hyperdiploidy, and other genetic changes in childhood leukemia are discussed later in this module.

INFANTS



CHILDREN



Types other than MLL are identified by various acronyms that refer to other subtypes of leukemia.

CHILDHOOD LEUKEMIA

Stephen's Story

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Early life exposures are important: age-specific incidence chart

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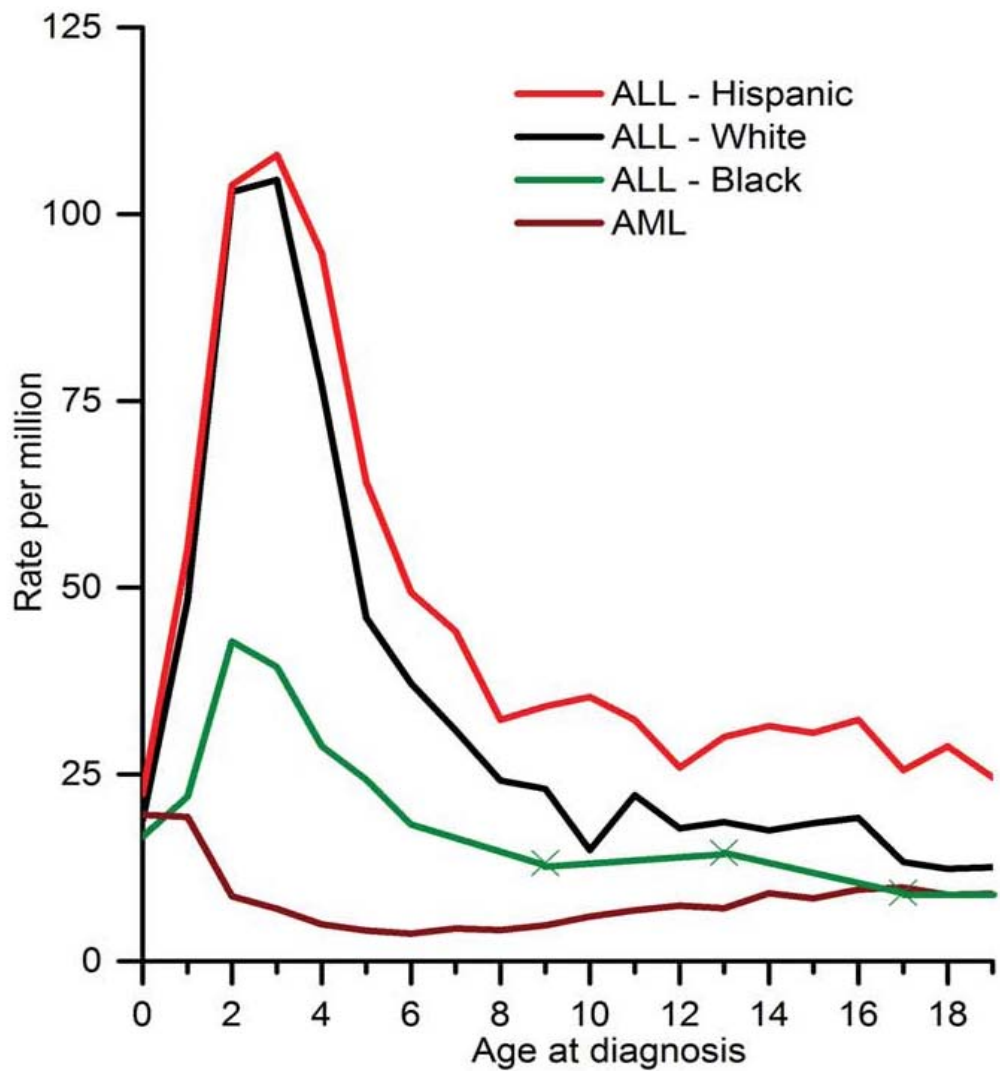
Patricia Buffler PhD MPH, Professor of Epidemiology and Dean Emerita (deceased) of the School of Public Health, University of California-Berkeley

Early Life Exposures are Important

There is a peak of incidence of childhood ALL between the ages of two and five. This has led researchers to think that critical windows of vulnerability to environmental exposures are very important before conception, during pregnancy, and in the early years of life.

In contrast to ALL, the childhood AML rate seems to be more stable across ages, which implies different risk factors, windows of vulnerability, or mechanisms that may lead to AML in contrast to ALL.

Age-Specific Incidence Rates of Acute Lymphocytic Leukemia (ALL) by Race/Ethnicity and Acute Myeloid Leukemia (AML) for All Races Combined



Rates are not shown when based on fewer than 25 cases. Data for whites and blacks exclude Hispanic ethnicity. Due to sparse data for ALL in blacks for some ages, data are shown for combined age groups: 7 to 10 years, 11 to 14 years, and 15 to 19 years as marked by asterisks. Source: Surveillance, Epidemiology, and End Results (SEER) program, 18 SEER Registries, National Cancer Institute.

CHILDHOOD LEUKEMIA

Stephen's Story

Stephen spent the first two weeks of his treatment in the hospital, then his protocol was continued on outpatient status. The treatment course would be up to three years with induction, consolidation, and maintenance therapy stages.

Dr. Baker warned Tricia and David that any time Stephen had a fever he would need to be evaluated, and if his white blood count was low he would need to be hospitalized.

Dr. Baker, along with the rest of the hospital team, carefully explained how the chemotherapy medications work and what side effects they might expect. Stephen's hospital stay was difficult for his parents. Stephen hated being away from home and the nausea and vomiting made him uncomfortable.



Treatment information
for the general public



For clinicians



click a preview image to view above

CHILDHOOD LEUKEMIA

Stephen's Story

After the initial shock of the diagnosis and while dealing with Stephen's first chemotherapy course, Tricia and David began to ask Dr. Baker and others more questions about what might have been the cause of Stephen's disease.

Childhood leukemia is difficult to study because it is relatively rare, which limits the design of studies intended to help clarify its etiology (cause). Nevertheless, substantial evidence identifying a number of risk factors has emerged over the past two decades. The etiology is likely to be attributable to a mixture of genetic and environmental factors and may vary by subtype or for ALL, immunophenotype.

As with some cancers, it is thought that childhood leukemia is a result of distinct exposures during two time periods.

Changes to DNA that cause leukemia:



Two-Hit Model Hypothesis



TEL-AML1 Gene Fusion



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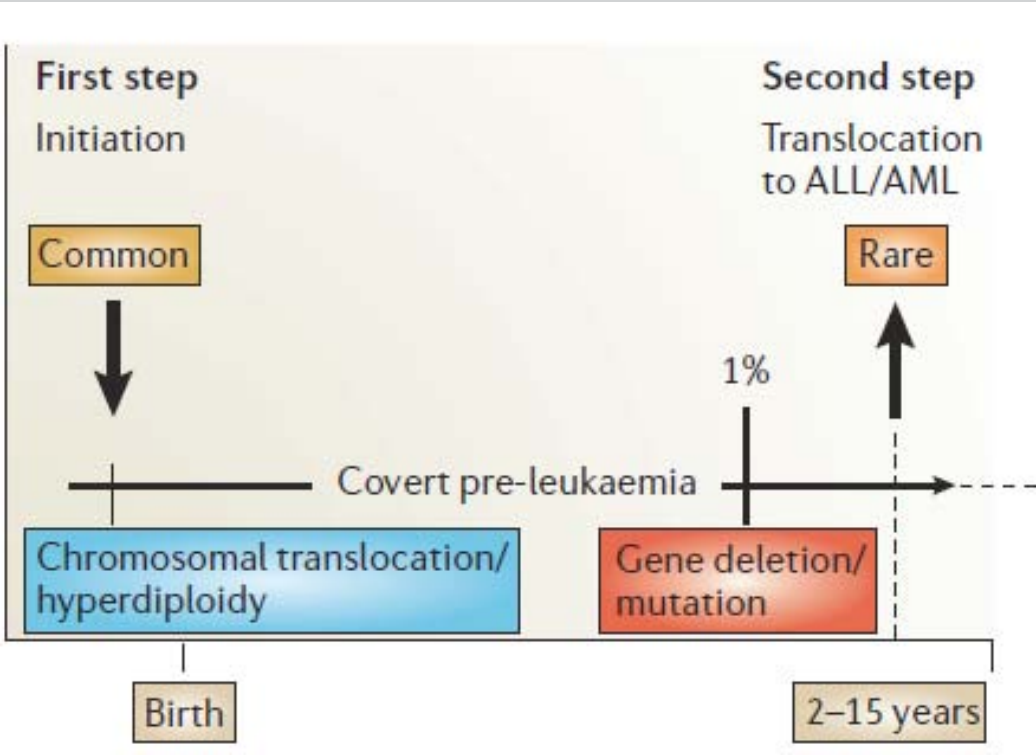
TEL-AML1 Gene Fusion

Changes to DNA that cause leukemia:

Two-Hit Model Hypothesis

Childhood leukemia results from more than one insult to DNA

Researchers consider cancer to often be a result of more than one temporal event. For childhood ALL and AML, there are two exposure windows: one prenatal (before conception or in utero), when leukemia is commonly initiated through chromosomal rearrangements, and a second, postnatal window that is linked to the emergence of overt disease through secondary genetic changes.



This model is supported by evidence that the genetic changes are far more frequent than the actual disease. This suggests that initiation of leukemia may be a common event, but the second "hit" that transitions to ALL or AML is rare (Greaves, 2006).

Note: 1% refers to an estimated frequency of transition between covert pre-leukemia and overt clinical leukemia. Infant ALL and AML (<1 year of age) has a much-abbreviated natural history in which all the necessary genetic events are thought to occur prenatally. Greaves, 2006, graphic used with permission.

CHILDHOOD LEUKEMIA

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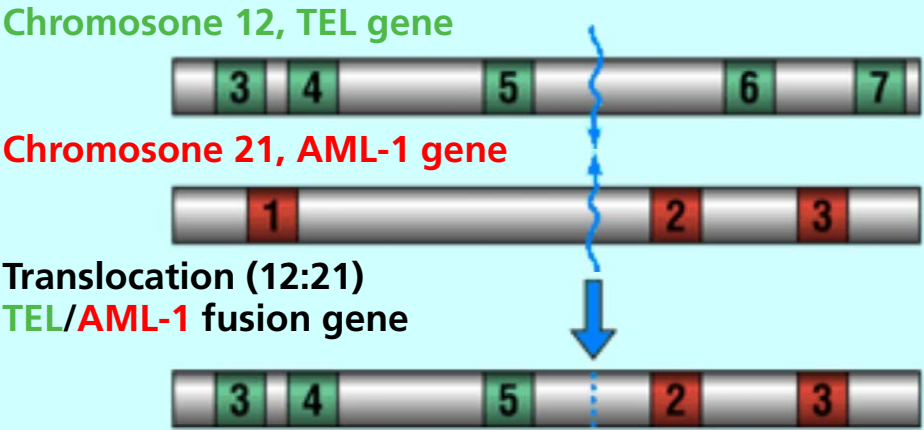
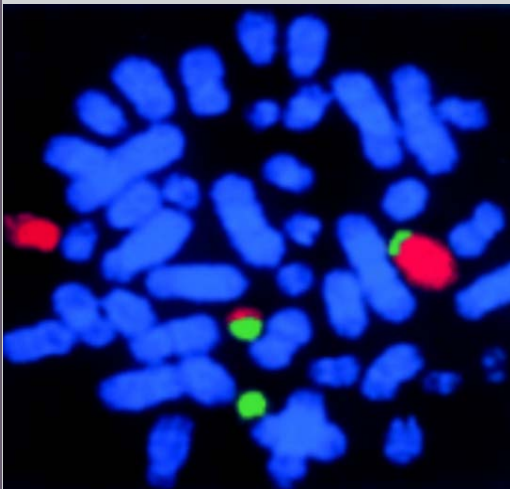
Two-Hit Model Hypothesis



TEL-AML1 Gene Fusion

Changes to DNA that cause leukemia:

Translocations Associated with ALL Occur In Utero: TEL-AML1 Gene Fusion



Results from FISH (fluorescent in-situ hybridization) study – Shows chromosomal fragments from 12 (green) and 21 (red) switched.

One of the common chromosomal abnormalities that has been identified is called the translocation TEL-AML, where there is a shift of genes between chromosome 12 and 21.

This translocation has been identified in blood specimens that are collected at birth. It indicates that there is an already ongoing process of DNA insult; however we know that not all of the children with this translocation at birth develop childhood leukemia.

Therefore, there may be another process after birth that is necessary to lead to a full-blown childhood leukemia disease.

- Occurs in approximately 20-25% of patients with pre B-cell ALL (the most common type of childhood ALL) with peak incidence between ages 2 – 5 years.
- Strong evidence that this occurs in utero.
- Frequency of this translocation at birth is 100-fold greater than the risk of developing the corresponding leukemia.

CHILDHOOD LEUKEMIA

Stephen's Story

Since childhood leukemia is a rare disease and it takes many cases to identify environmental risk factors, the Childhood Leukemia International Consortium (CLIC) was established in 2007 (locations represented by the white dots on the map at right). CLIC develops and supports collaborations among member groups to identify factors that influence the risk of childhood leukemia through epidemiological studies and related research.

This consortium serves to strengthen the available data set regarding the role of environmental and genetic risk factors and critical windows of exposure, as well as to provide a more robust translation to clinical audiences worldwide.



CHILDHOOD LEUKEMIA

Stephen's Story

FACTORS ASSOCIATED WITH RISK FOR CHILDHOOD LEUKEMIA

One of the hospital's pediatric residents asks Dr. Baker about the risk factors for childhood leukemia.* Dr. Baker mentions that this would be a great topic for everyone to hear at rounds and asked the resident to review the literature and develop a presentation.

The resident reported that there are many epidemiologic (human) studies that find exposures to certain groups of chemicals, air pollution, tobacco smoke, and radiation to be consistently associated with increased risk for a child developing leukemia. Additionally, some factors are associated with a protective effect such as early supplementation with folate.

*In the following pages of Stephen's story we describe environmental and genetic factors significantly associated with increased leukemia risk. Keep in mind, however, that childhood leukemia is a relatively uncommon disease. Thus, even if a person were exposed to something that doubled the risk of developing leukemia, the risk for that person would remain quite low.



CHILDHOOD LEUKEMIA

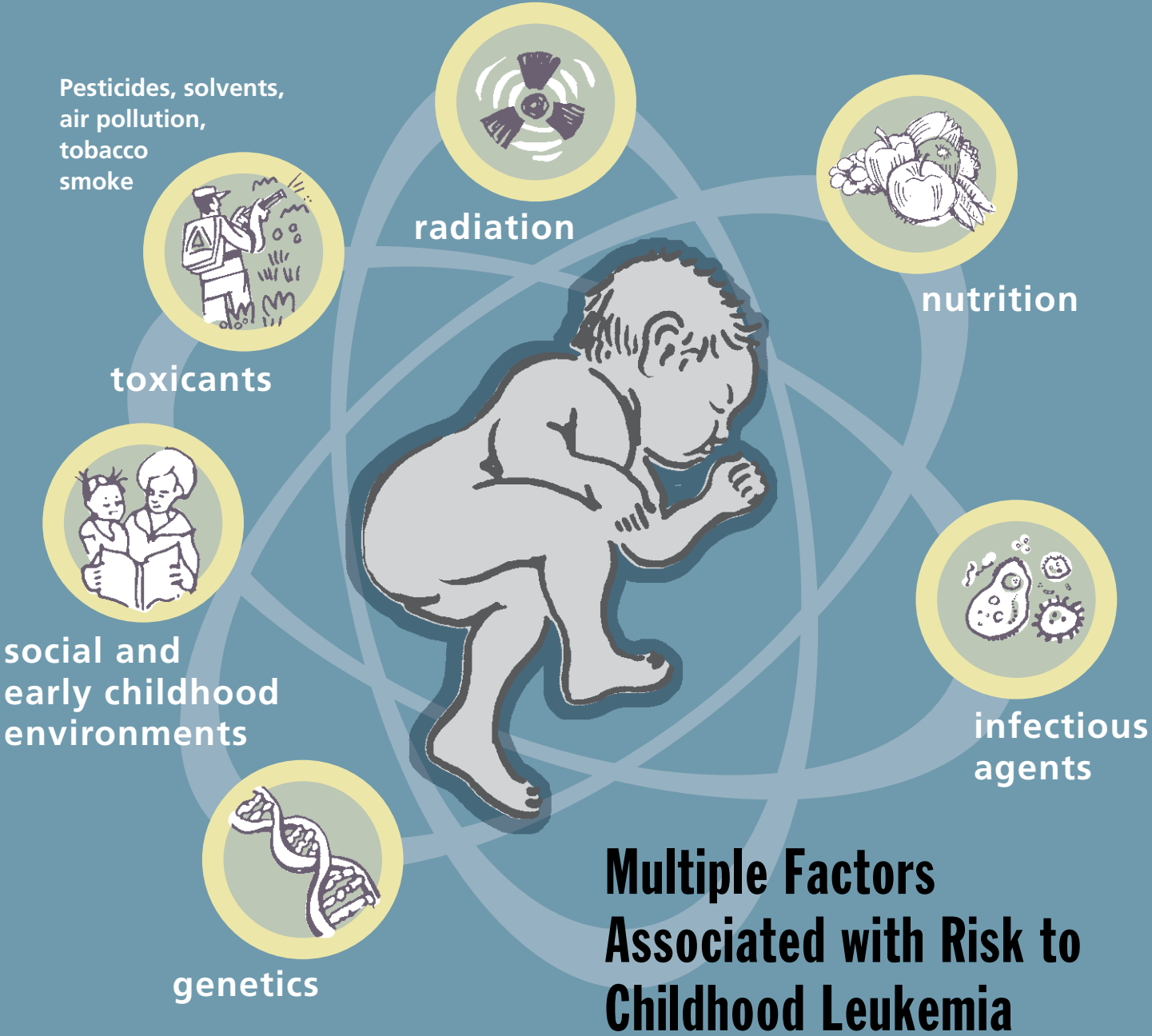
Stephen's Story

FACTORS ASSOCIATED WITH RISK FOR CHILDHOOD LEUKEMIA

Dr. Baker is careful to note that, “Scientists and policy makers will continue to study and debate for years to come whether these associations are truly causal. And, there are also ethnic and demographic factors associated with leukemia risk. Interactions among risk factors and their common co-occurrence make it even more difficult to establish the cause of leukemia in a particular person or to identify the most important determinants of leukemia in a population. But, many environmental exposures associated with leukemia are also associated with other health problems, such as neurodevelopmental disabilities, asthma and other respiratory diseases, and reproductive disorders. For all these reasons, most people would want to avoid exposure as much as possible. The association with cancer is an additional reason.”

He adds, “Some of these exposures simply cannot be reduced by individual action alone. Rather, in some instances, policy interventions that reduce exposures across the entire population will be necessary and more effective.”

Childhood cancer risk also generally shares a number of common themes that we have seen in other disorders highlighted in *A Story of Health*, such as greater susceptibility during certain periods of development, underlying genetic risk factors, and gene-environment interactions.



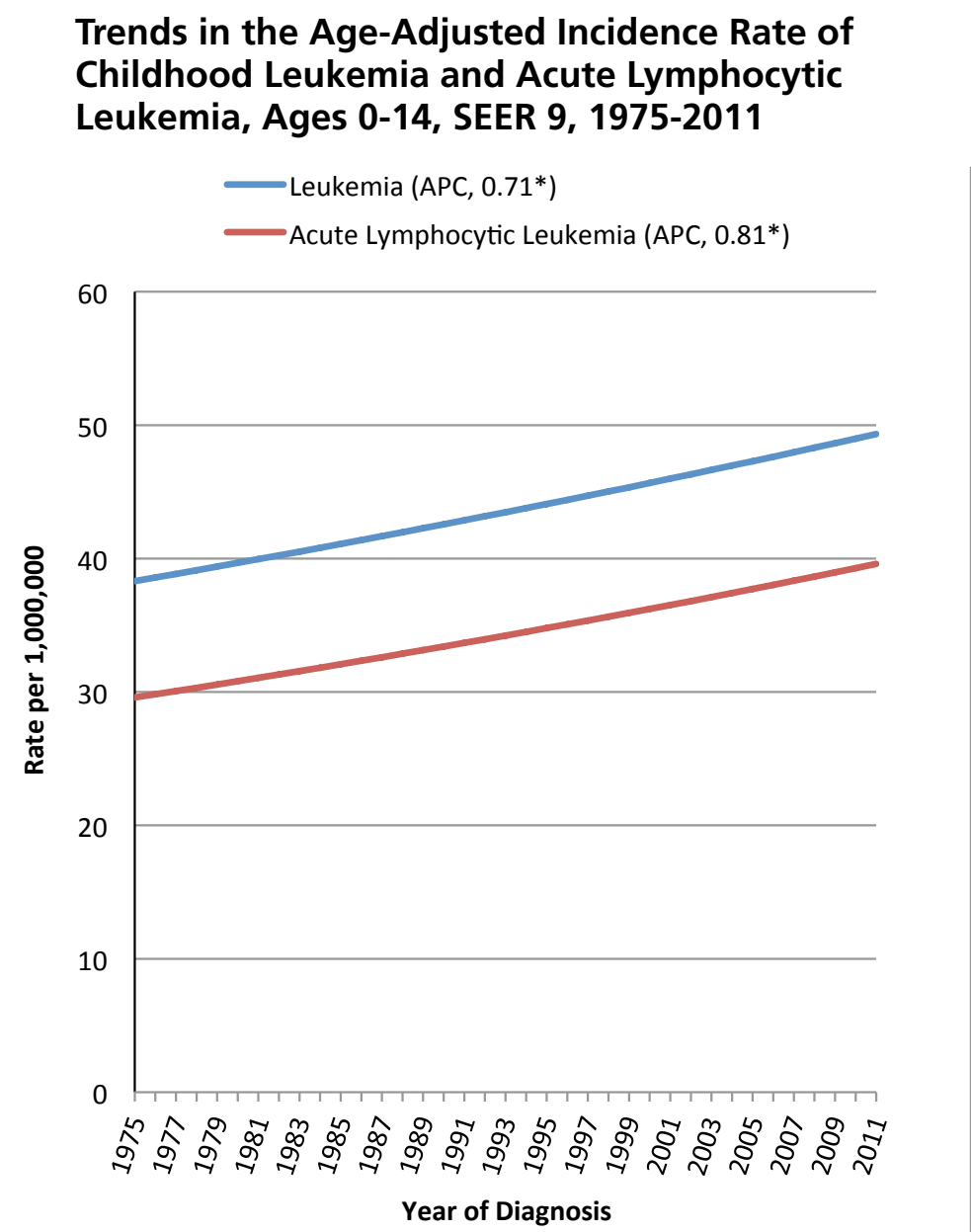
CHILDHOOD LEUKEMIA

Stephen's Story

CHILDHOOD LEUKEMIA: US TRENDS

Although childhood leukemia is still rare, Stephen is one of a growing number of children with this cancer. Childhood leukemia incidence has been increasing in the US (0.8% per year) during the last two decades. In the US, between 1975 and 2010, the rate of leukemia among children 0-14 years increased 0.7% per year. This adds up to a 55% increase over 35 years.

- + Ethnic Trends
- + Genetic susceptibility to leukemia in Hispanics



*The Annual Percent Change (APC) is significantly different from zero at $\alpha=0.5$


Source: Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 9 Regs Research Data, Nov 2013 Sub (1973-2011) <Katrina/Rita Population Adjustment>

Graphic used with permission.

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 Ethnic Trends

 Genetic susceptibility to leukemia in Hispanics

ETHNIC TRENDS:

Childhood leukemia is increasing more amongst certain ethnic groups such as Hispanics

California with its large population and excellent data collection on cancer is the location of one of the largest studies designed to look at causes of childhood leukemia. Hispanic babies account for about half of all births in CA, making it a good place to examine possible genetic and environmental interactions that may underlie the recognized higher incidence of leukemia in children of Hispanic origin.

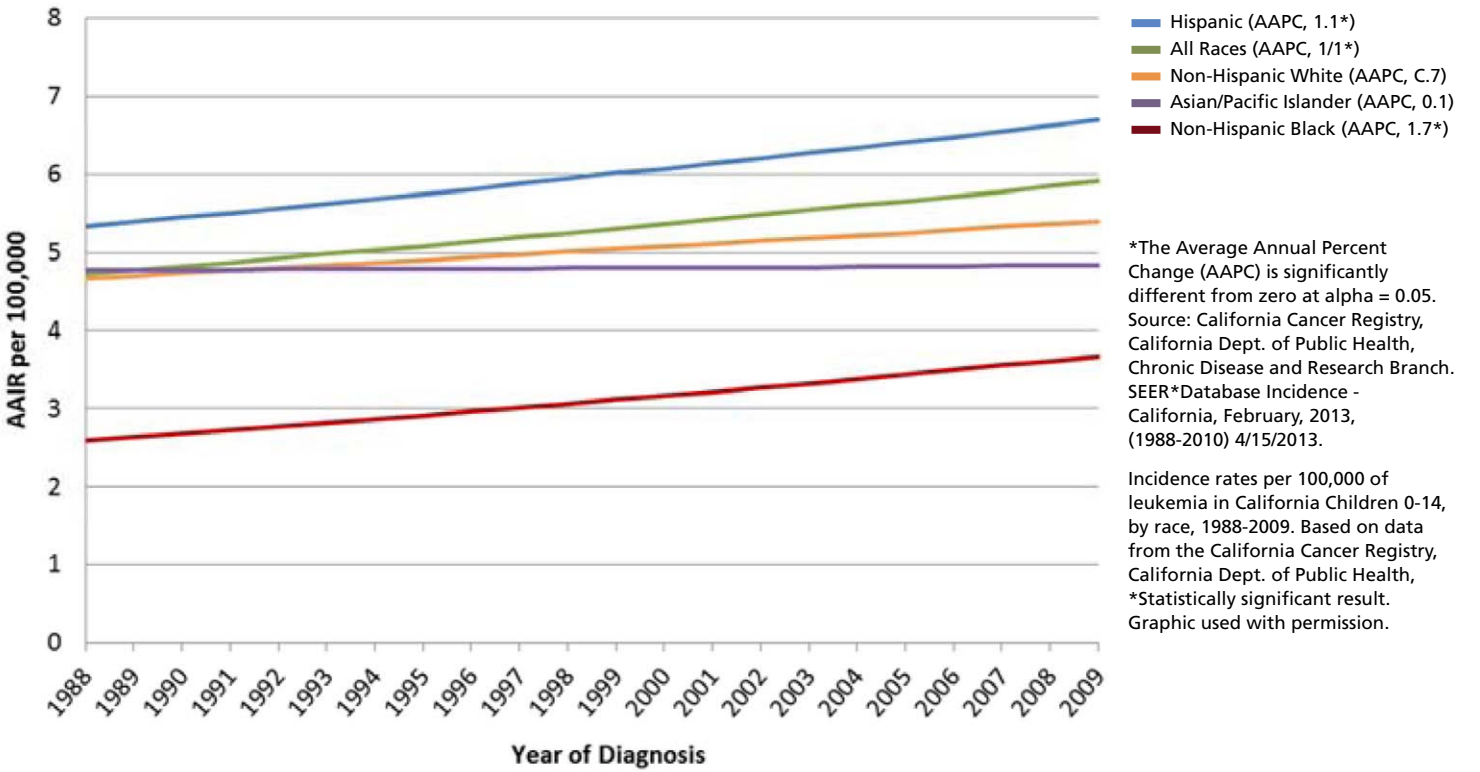
On average, childhood leukemia has been increasing 1.1% per year in Hispanics since 1988. Though much more rare in non-

Hispanic Black children, it is increasing at 1.7% per year amongst them. This is compared with an increase of 0.7% in non-Hispanic White children. The rate seems to be stable among Asian/Pacific Islanders.

These trends may represent an interaction between predisposing genetics and environmental exposures.

Not only do Hispanic children have the highest incidence of leukemia but it is growing faster than in the non-Hispanic White population.

Trend in the Age-Adjusted Incidence Rate of Leukemia Among Children Aged 0-14 Years by Race/Ethnicity, CA, 1988-2009




CHILDHOOD LEUKEMIA

Stephen's Story

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 Genetic susceptibility to leukemia in Hispanics

Genetic susceptibility to leukemia in Hispanics

Leukemia is more common among Hispanic Americans compared to other ethnicities. While the causes of this are still uncertain, what is now clear is that part of the answer is genetics. There are several rare genetic syndromes that predispose strongly for childhood leukemia, but account for only a few cases among any ethnic group. There are much more common genetic factors which contribute weakly to leukemia risk, but due to their high frequency they are responsible for a larger proportion of leukemia incidence. Interestingly, the proportion of these common genetic factors varies by ethnicity: the frequency of many genetic factors is higher in Native Americans and Hispanics than in whites and blacks. These genetic polymorphisms in the genes, ARID5B, GATA3, PIP4K2A, and CEBPE, collectively account for a large proportion of the increased risk of leukemia in Hispanics. There are also likely to be environmental risk factors that also contribute to the increased risk in Hispanics including lifestyle and exposures from occupation, which are known to vary in frequency between ethnicities.

CHILDHOOD LEUKEMIA

Stephen's Story

PESTICIDES AND LEUKEMIA

At their next visit to Dr. Baker, Tricia mentions that she heard from a friend that pesticides might cause leukemia. This reminds Dr. Baker of the information on environmental exposures and childhood leukemia that the pediatric resident presented during rounds. Dr. Baker asks if Stephen could have come into contact with any pesticides and specifically asks about pesticide use in the home and garden. Tricia says that they own a plant nursery and garden center, and they use some pesticides. Stephen sometimes visits the nursery after preschool and on weekends.






Pesticide Exposure in Children: Policy Statement from the American Academy of Pediatrics



PESTICIDES

Tricia mentions to Dr. Baker that other families in the neighborhood have regular pesticide applications to the perimeter of their house and some have lawn service, but they do not. Tricia thought that Stephen's daycare might occasionally use pesticides to spray for ants and flying insects. Dr. Baker consulted the pediatrician at his regional Pediatric Environmental Health Specialty Unit, who confirmed that many studies from around the world have found statistically significant associations between pesticide exposure and childhood leukemia.

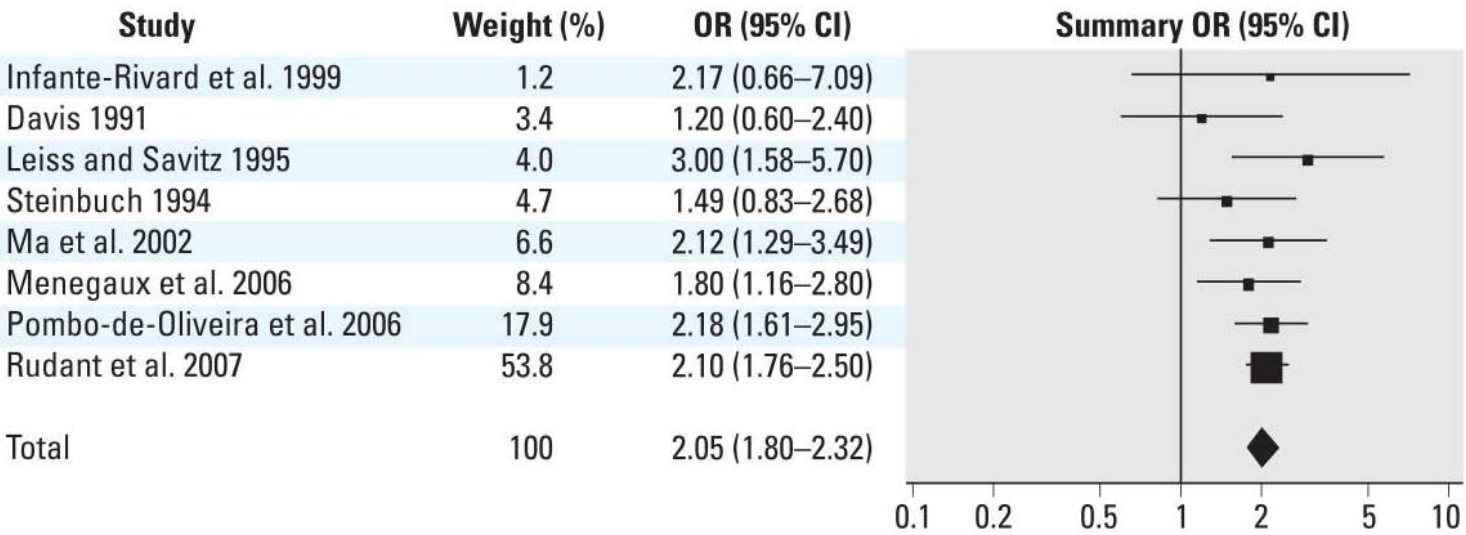
-  How to read and interpret the figure at right. What is a meta-analysis?
-  Pesticide Regulation
-  Find a local Pediatric Environmental Health Specialty Unit (PEHSU): A respected network of experts in children's environmental health.

Watch: Dr. Catherine Metayer discusses insecticides and herbicides (4:15 mins.)



Catherine Metayer MD PhD, Associate Adjunct Professor, Epidemiology/Biostatistics and Epidemiology, University of California-Berkeley, Principal Investigator, Center for Integrative Research on Childhood Leukemia and the Environment

Residential Pesticide Exposures



In a meta-analysis by Turner et al. (2010), residential insecticide use during pregnancy was associated with a doubling of risk for childhood leukemia (OR*=2.05). The association was somewhat stronger for ALL than AML, and was found to be consistent over a variety of study designs. Differences in leukemia risk associated with residential and occupational pesticide exposures may be due to differences in chemical doses and co-exposures.

*OR= Odds ratio

Turner, 2010. Graphic used with permission.

PESTICIDES

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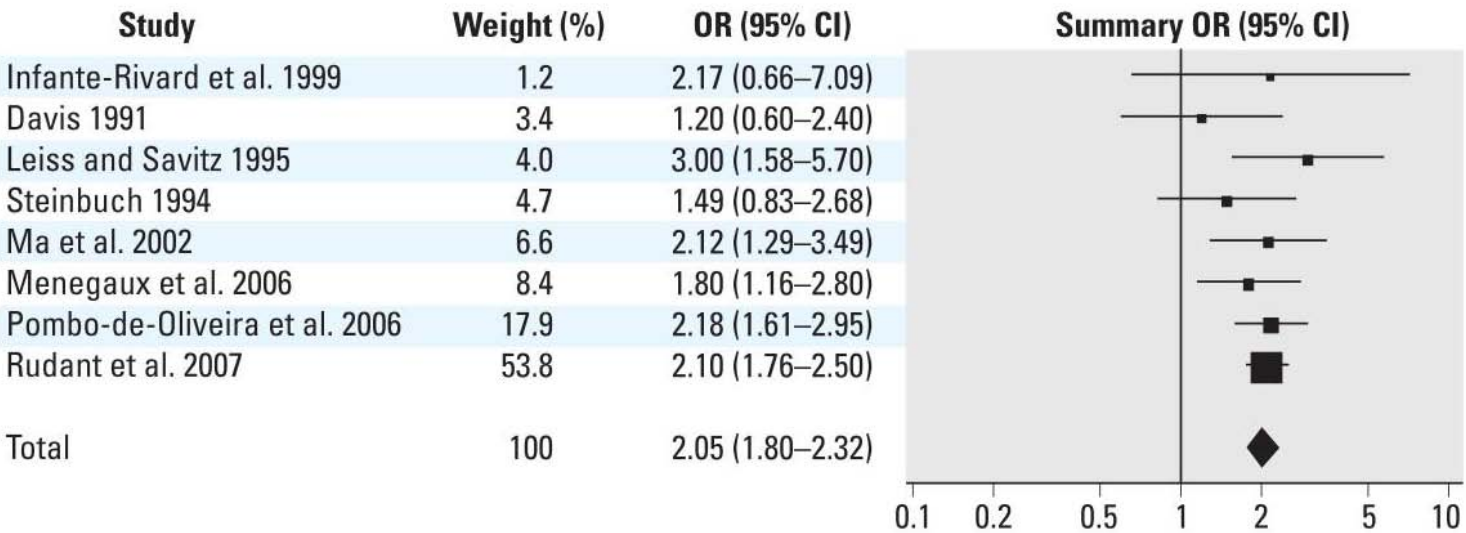
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What is a meta-analysis?

A meta-analysis uses statistical methods to combine the results of different studies in order to identify an overall trend in the data. Generally, studies are grouped by a common measurement, and some studies are excluded on the basis of quality or study design. Certain studies are given more weight in the meta-analysis. Weighting is usually related to the sample size in the individual studies. This method can have some limitations. It usually relies on published studies, which may exclude studies that show negative or insufficient results that are less likely to be published. Additional bias can also skew the results if studies are cherry-picked using unsound methodology for selecting studies.

A graphic known as a Forest Plot (shown above) is often used to display the results of a meta-analysis. The size of the square is proportional to the weight assigned to the study. The horizontal line is the study's confidence interval (a measure of how the results might vary due to chance). The vertical line at 1 represents "no effect." If the confidence intervals for individual studies overlap with this line, it demonstrates that there is no statistically significant effect observed. The diamond represents the summary measure of all studies combined.

- + More information: "5 Key Things to Know about a Meta-Analysis" Scientific American blog post

PESTICIDES

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Pesticide Regulation

EPA and each of the fifty states register or license pesticides for use in the US. EPA receives its authority to register pesticides under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). States are authorized to regulate pesticides under FIFRA and under state pesticide laws. States may place more restrictive requirements on pesticides than EPA. Pesticides must be registered both by EPA and the state before distribution.

Before registering a new pesticide or new use for a registered pesticide, EPA is supposed to ensure that the pesticide, when used according to label directions, can be used with a reasonable certainty of no harm to human health and without posing unreasonable risks to the environment. To do that, EPA is authorized to require various scientific studies and tests from

applicants. Where pesticides may be used on food or feed crops, EPA also sets tolerances (maximum pesticide residue levels) for the amount of the pesticide that can legally remain in or on foods. Already-registered pesticides are supposed to undergo periodic tolerance reassessment and registration review.

A recent analysis of EPA practices, however, concluded that the government has allowed the majority of pesticides onto the market without a public and transparent process and in some cases, without a full set of toxicity tests, using a loophole called a conditional registration. In fact, as many as 65 percent of more than 16,000 pesticides were first approved for the market using this loophole (NRDC, 2013).

- + Link to EPA website for more information on FIFRA

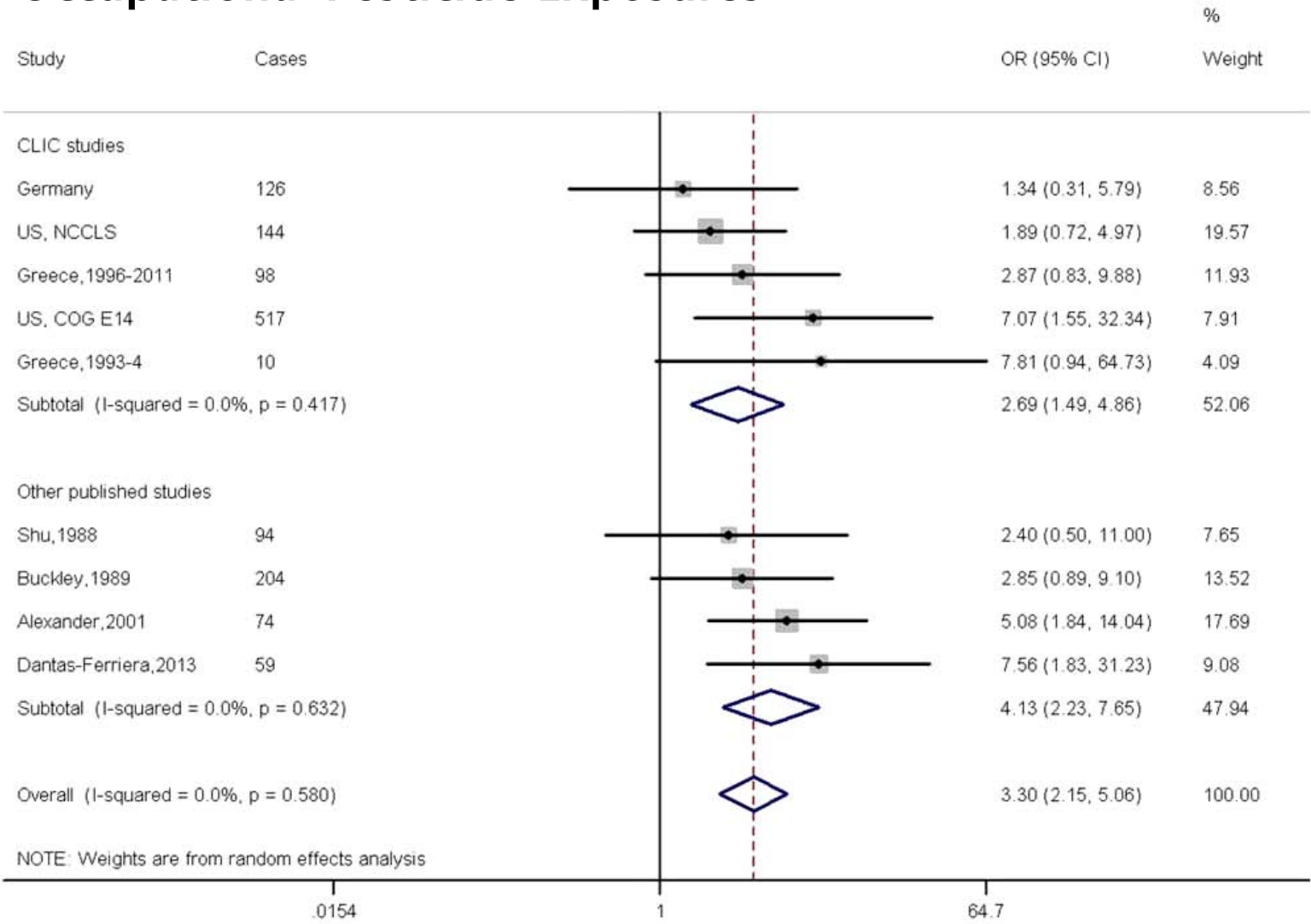
OCCUPATIONAL EXPOSURES DURING PREGNANCY MAY CONTRIBUTE TO CHILDHOOD LEUKEMIA RISK

Dr. Baker asked a few more details about the garden center. Tricia said she worked in the back office while she was pregnant, up until a few months before Stephen was born. Pesticides, solvents, and other chemicals may cause chromosomal alterations in parents' eggs and sperm cells that increase the risk of their children developing certain cancers, or maternal exposure may affect the child directly while in utero. Studies have demonstrated a link between maternal occupational exposures to pesticides and childhood leukemia. Maternal use of pesticides at home has also been associated with AML risk. In case studies, maternal exposure to certain insecticides has been associated with translocations seen in children with AML.



Sample prenatal environmental health history form for clinicians from the Consortium for Reproductive Environmental health in Minority Communities

Occupational Pesticide Exposures



The largest analysis combining original data from studies (1,329 cases) around the world found a near doubling of risk for AML if mothers were exposed occupationally to pesticides during pregnancy OR 1.94 (CI 1.19, 3.18). No associations

were found for childhood ALL. This forest plot of pooled data shows individual and summary odds ratios for maternal occupational pesticide exposure during pregnancy and the risk of AML in the offspring, using random effects model.

Source: Bailey, et al., 2014. Reproduced with permission.

CHILDHOOD LEUKEMIA

Stephen's Story

PATERNAL OCCUPATIONAL EXPOSURES AROUND TIME OF CONCEPTION MAY CONTRIBUTE TO CHILDHOOD LEUKEMIA RISK

Analysis of data (pooled) from studies around the world, including over 8,000 cases of childhood leukemia showed a 20% increased risk of ALL associated with paternal occupational exposure to pesticides around the time of conception. The risk was about 40% increased in children whose diagnosis was at age 5 years or greater and in those with T cell ALL. This highlights the importance of considering both critical windows of exposure as well as the different sub-types of leukemia when possible.

Though “pesticides” includes a wide variety of different chemicals and these findings do not implicate specific agents, more than 20 pesticides have been classified as “possible” or “probable” human carcinogens by the International Agency for Research on Cancer (IARC).

Paternal exposures to solvents, paints, and employment in motor vehicle-related occupations have also been shown to be associated with childhood leukemia. Paternal exposures before conception could result in germ cell damage or changes in gene expression. Parental exposures after the child is born may result in exposure to the family by materials from work being brought home on clothing.



Key Concept:
Take-Home
Exposures



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Key Concept:
Take-Home Exposures

KEY CONCEPT: Take-Home Exposures

A “take-home” exposure refers to exposure of a child (or other household member) to chemicals, fibers, metals, or dusts brought home from a work site by a parent or from someone else. Examples of take home exposures have included solvents, heavy metals, and pesticides. These can be brought into the home on family members’ or visitors’ clothing or shoes. Workers might also bring home chemicals from work and use them around the house.

Take home exposures can be prevented by actions such as:

- Changing clothes at work
- Showering before leaving work
- Laundering work clothes separately
- Removing shoes before entering the home
- Not using chemicals at home that are meant to be used in the workplace



If hazardous substances are used by individuals working at home, care should be taken to keep the work and living areas separate – and hazardous materials should be stored and disposed of properly.

Similarly, hobbies such as painting, model building, furniture refinishing, and auto repair often involve using solvents. Children and pregnant or breastfeeding women and children should avoid these exposures.



More information: Pesticide Safety Information from the California EPA

CHILDHOOD LEUKEMIA

Stephen's Story

EXPOSURES TO PAINTS AND SOLVENTS MAY INCREASE RISKS

David thought back to painting the nursery while Tricia was pregnant and wondered if using paint or paint thinners had exposed Stephen to substances linked to the development of leukemia.

In one study of household use of paints and solvents, paint was associated with a 65% increase in ALL risk, and risk was higher with postnatal or frequent use.* When the analysis was restricted to the translocation (12;21) the risk increased four-fold.* Solvents were associated with a two-fold increased AML risk* (Scelo et al., 2009).

While some previous studies do not identify increased risks, other studies support these findings (Freedman et al., 2001; Bailey et al., 2010). In addition, a number of studies of exposure to gasoline and traffic exhaust find elevated risks. These complex exposures include a variety of solvents (see next section on traffic exposure). Many solvents are recognized carcinogens. While studies of the relationship between solvent exposure and childhood leukemia risk are not as extensive as those examining tobacco or pesticides, parents may wish to avoid paint and solvent exposures (when feasible) during the immediate pre-conception period and pregnancy. This will also help lower the risk of other adverse health outcomes associated with the same agents.

*Statistically significant



CHILDHOOD LEUKEMIA

Stephen's Story

TRAFFIC-RELATED AIR POLLUTION MAY INCREASE CHILDHOOD LEUKEMIA RISK

Living near major roadways results in exposure to many potential carcinogenic substances. Estimates place as much as 10% of the U.S. population and as many as 30-45% of urban residents living near major roadways.

Studies have suggested that chemicals and other components of air pollution may contribute to childhood leukemia. A recent meta-analysis of seven studies from Europe and the United States conducted by the CDC suggests that living near highly trafficked roadways after birth increases children's risk for leukemia by over 50% (OR 1.53; 95% CI 1.12, 2.10) (Boothe et al., 2014).

Studies examining exposure to benzene, one component of air pollution (for example, living near a gas station), have suggested an increase in risk for childhood leukemia. Benzene is recognized as a cause of leukemia in adults.



CHILDHOOD LEUKEMIA

Stephen's Story

EARLY PRECONCEPTION AND PRENATAL INTRODUCTION OF VITAMINS AND FOLATE REDUCES RISK OF CHILDHOOD LEUKEMIA

At their next visit, Dr. Baker asks Tricia about her pregnancy with Stephen. Like many other women, she didn't think about taking vitamins before or during the first two months of the pregnancy, especially because she ate a nutritious diet. Otherwise she was very careful to live a healthy lifestyle while pregnant and did not smoke or drink. She started on prenatal vitamins with folate at her first prenatal visit at eight weeks gestation.

Folate supplementation has been associated with reductions in risk for childhood leukemia, at least for those at risk for lower folate consumption. Folate supplementation before conception and early in pregnancy not only appears to be protective in the case of leukemia risk, but also reduces neural tube and other birth defects, and may reduce the risk of developing autism. (Schmidt et al., 2012; Suren et al., 2012)



Preconception and Healthy Child Development



Prenatal Care and Healthy Child Development



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Preconception and Healthy Child Development



Prenatal Care and Healthy Child Development

PRECONCEPTION AND HEALTHY CHILD DEVELOPMENT

Preconception care for women and men is important for lifetime health as well as healthy child development.



All women and men can benefit from healthy habits throughout life, whether or not they plan to have a baby one day. These include eating healthy food, getting regular exercise, avoiding toxic substances, and reducing excessive stress. Even prior to conception some specific actions are important for prospective parents to take because they can influence birth outcomes. Maternal exposures to toxic chemicals before or around the time of conception can adversely affect the quality of eggs (ova) and newly-conceived embryos. But these exposures can be harmful to men's reproductive health as well. For example, a father's occupational exposure to pesticides has been associated with increased risk of some childhood cancers and birth defects in his offspring. (Roberts et al., 2012). Parents can also take home from the

workplace toxicants like lead and pesticides on their clothing, resulting in direct exposures to other family members. (Gerson et al., 1996; Fenske et al., 2013) Nutritionally, a prospective father's diet that is deficient in folate (a "B" vitamin) increases the risk of birth defects in his offspring. (Lambrot et al., 2013). Similarly, maternal folate supplements in the periconceptual period (~ 6 weeks before and after conception) are associated with decreased risk of having a child with an autism spectrum disorder. (Lyall, 2014) Of course optimal nutrition and appropriate vitamin and mineral supplements throughout pregnancy are also important to help promote optimal fetal development.



More information: CDC's Preconception care for women and men

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Preconception and Healthy Child Development



Prenatal Care and Healthy Child Development

PRENATAL CARE FOR HEALTHY DEVELOPMENT



The fetus can be harmed by environmental exposures including:

- Mom's smoking and second hand smoke,
- Mom's drinking alcohol and her exposure to other solvents like those in certain paints, and in products used in nail salons,
- Mom's exposure to lead, mercury (from some fish and other sources), pesticides, PCBs (banned in the US but still found in the environment) and certain polybrominated diphenyl ethers (PBDEs – a family of chemicals long-used as flame retardants in foam and furniture), among others.

Positive actions to protect the fetus:

- Avoid smoking or drinking,
- Maintain a healthy diet,
- Supplement with prenatal vitamins, including folic acid, iodine, and vitamin D if maternal serum levels are inadequate,
- Avoid toxicants.

More information:

- CDC on [pregnancy](#)
- American Congress of Obstetrics and Gynecology (ACOG):
 - [Good Health Before Pregnancy](#) (pdf)
 - [Prenatal Nutrition](#)
 - [Environmental Chemicals](#)
- Royal Congress of OB/GYN:
 - [Chemical Exposures During Pregnancy](#)
- UCSF: [Program on Reproductive Health and the Environment](#)

CHILDHOOD LEUKEMIA

Stephen's Story

CRITICAL WINDOWS OF EXPOSURE TO TOBACCO SMOKE

David smoked before Stephen was born but quit when his wife found out she was pregnant.

We know that tobacco smoke could be affecting the development of the fetus and the child during pregnancy and during the early years of life. We also know that tobacco smoke can affect the germ cells.

That means at the time of conception, or even before conception, tobacco smoke may have an effect. Exposures during multiple time periods may add additional risk.

Key Concept: Windows of Vulnerability

Map: Percent Current Adult Smokers by State

- Smoking Cessation Resources:
- Free Help to Quit Smoking (Nat'l Cancer Institute)
 - Getting Help to Quit Smoking (American Lung Assoc.)



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KEY CONCEPT: Windows of Vulnerability

A window of vulnerability is a time window(s) during pregnancy or child development when the fetus, infant, or child is especially susceptible to particular environmental exposures, general environmental deprivation, suboptimal nutrition, or psychosocial stress. Exposures during these time windows can disrupt important developmental processes, altering structural or functional development of various organs or physiologic systems, with potential lifelong consequences.

Time windows of vulnerability can be relatively long and extend throughout fetal and infant development, or they can be relatively short and precise. For example, thalidomide can cause severe limb abnormalities if exposure occurs in the fetus 20-36 days after conception. Alternatively, the manifestations of fetal alcohol exposure can vary considerably depending on the timing and extent of exposure throughout pregnancy.

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CHILDHOOD LEUKEMIA

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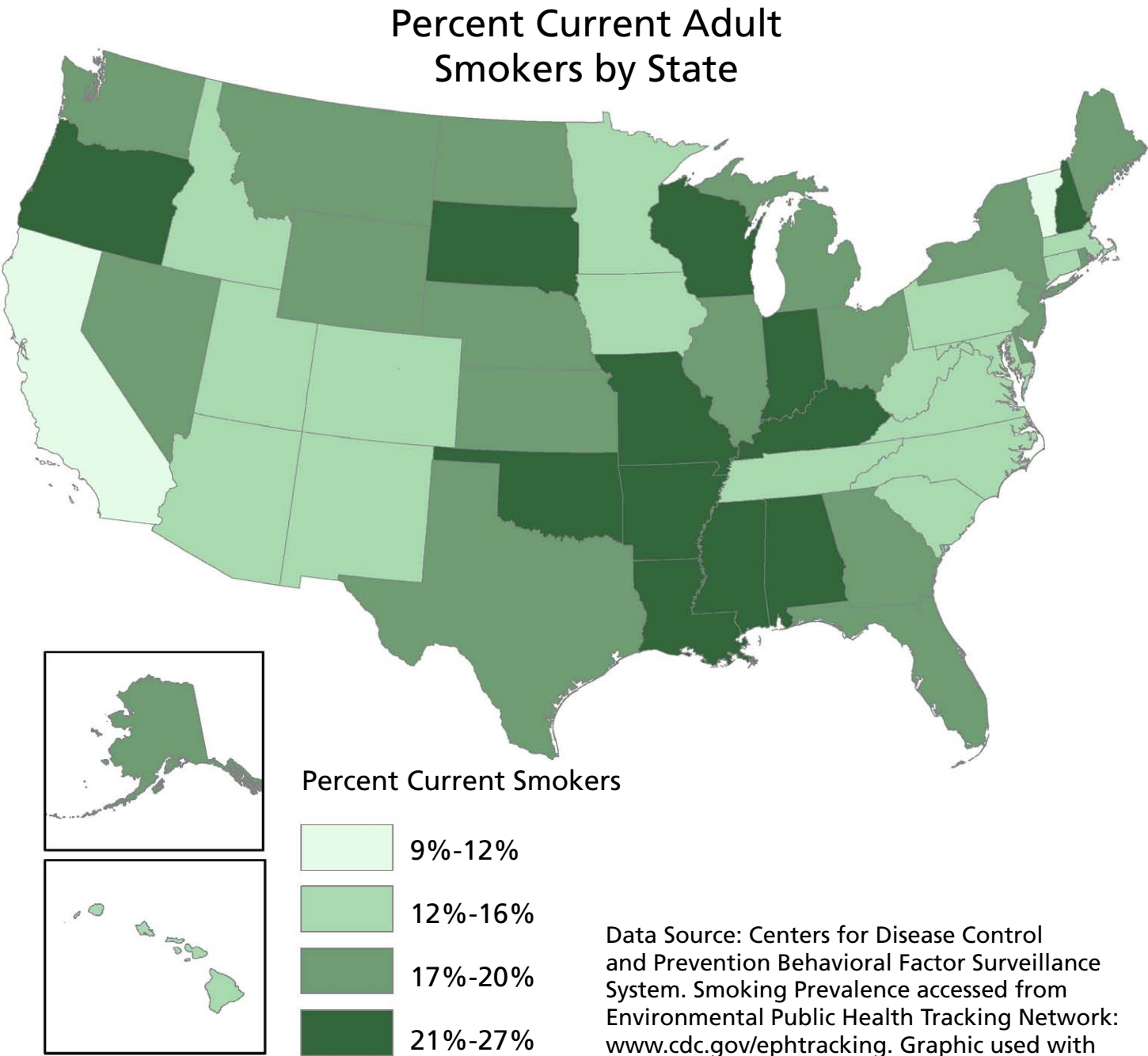
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CHILDHOOD LEUKEMIA

Stephen's Story

EXPOSURE TO FATHER SMOKING BEFORE BIRTH COMBINED WITH POSTNATAL EXPOSURE TO SECOND- HAND SMOKE RESULT IN INCREASED RISK FOR CHILDHOOD B-CELL ALL

Prenatal and postnatal exposures to environmental tobacco smoke are associated with increased childhood leukemia risk. Paternal smoking, in particular, prior to conception has also been linked to increased risk of childhood acute lymphoblastic leukemia (ALL). Father's smoking before birth combined with second-hand smoke, from any source, after birth increases risk for childhood leukemia. This seems to support the two-hit model previously discussed.

Studies of maternal smoking are inconsistent. There could be several reasons for negative findings including maternal under-reporting or fetal loss. Differences in how eggs and sperm are formed may also account for these differences.

-  Paternal smoking associated with increased risk of specific leukemia subtype
-  Tobacco Smoke and Childhood AML

Watch: For clinicians: Dr. Joe Wiemels discusses timing of environmental exposures (2:23 mins.)



Joseph L. Wiemels PhD,
Professor, Division of
Cancer Epidemiology
Leukemia & Lymphoma
Society Scholar in Clinical
Research, University of
California-San Francisco
School of Medicine

Exposure to father smoking before birth combined with postnatal exposure to SHS result in increased risk for childhood B-cell ALL

FATHER smoked before birth	CHILD exposed to passive smoking	Number of cases (n=689)	Number of controls (n=975)	OR (95% CI)
No	No	444	670	Reference
No	Yes	90	127	0.94 (0.69-1.27)
Yes	No	44	74	0.90 (0.57-1.41)
Yes	Yes	104	88	1.60 (1.07-2.38)*

The odds ratios are derived from logistic regression, adjusted for age, sex, race/ethnicity, household income, and maternal smoking.
*p-value for interaction <0.05

Graphic: Based on Metayer et al., 2013, used with permission

CHILDHOOD LEUKEMIA

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Joseph L. Wiemels PhD, Professor, Division of Cancer Epidemiology Leukemia & Lymphoma Society Scholar in Clinical Research, University of California-San Francisco School of Medicine

Joint Effect of Paternal Smoking and Early Childhood Exposure to Passive Smoking on Risk of Childhood B-cell ALL with Translocation

FATHER smoked before birth	CHILD exposed to passive smoking	Number of cases (n=130)	Number of controls (n=975)	OR (95% CI)
No	No	82	670	Reference
No	Yes	12	127	0.69 (0.36-1.32)
Yes	No	8	74	0.85 (0.35-2.03)
Yes	Yes	26	88	2.08 (1.04-4.16)*

The odds ratios are derived from logistic regression, adjusted for age, sex, race/ethnicity, and household income.
*p-value for interaction =0.01

Graphic: Based on Metayer et al., 2013, used with permission

Paternal smoking associated with increased risk of specific leukemia subtype

This analysis separates the different time windows before and after birth. Exposure to tobacco smoke was associated with an increased risk only of the translocation (12;21) but not the hyperdiploid subtype.

Excess risk of childhood B-cell ALL, with the specific translocation (12;21), is prominently identified when the father was smoking before

birth (including preconception and prenatal exposure) and when the child was also exposed after birth. The identified risk is higher when restricted to this specific molecular subtype of leukemia.

Fathers who smoked pre-conceptionally can still impact their child's risk by not exposing them to passive smoke.

CHILDHOOD LEUKEMIA

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Society Scholar in Clinical
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School of Medicine

Exposure to Tobacco Smoke Increases Risk of Childhood AML

Childhood AML is very difficult to study because it only makes up a fraction of all childhood leukemias. Tobacco smoke contains known carcinogens, and smoking is recognized to cause adult AML (IARC, 2002).

One recent study found that a child's passive exposure to tobacco smoke in the home is associated with a 40% higher risk of AML (OR = 1.41).

Although the numbers in this analysis are relatively small, this shows a similar pattern as ALL in that exposure in the home to tobacco smoke doubled the risk of getting AML for those subtypes that have structural abnormalities like translocation, deletion, or inversion (OR = 2.76;95% CI 1.01-7.58) (Metayer et al. 2013).

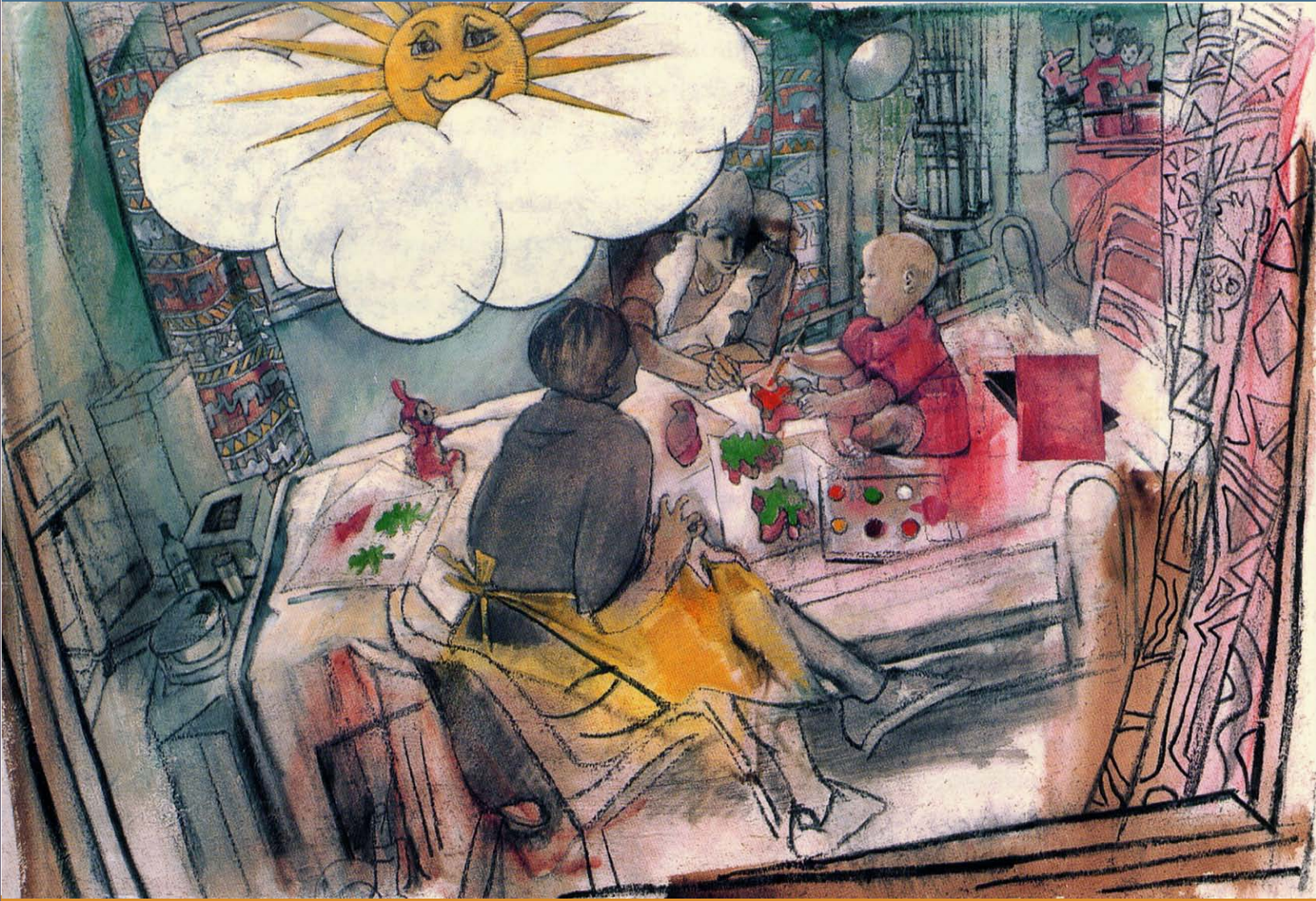
CHILDHOOD LEUKEMIA

Stephen's Story

DOCTOR — IS ANY ONE RISK FACTOR THE IDENTIFIABLE CAUSE OF STEPHEN'S LEUKEMIA?

Toward the end of their clinic visit, Tricia and David were visibly distressed about all of the potential factors that could have contributed to their son's leukemia. Dr. Baker told Tricia and David that they cannot blame themselves for their son's disease. He explained, for example, that studies examining the link between pesticide exposures and leukemia involve fairly large groups of people and cannot be used to establish the cause of disease in an individual. He pointed out that most children exposed to pesticides do not get leukemia and in most cases there is no clear explanation for the cause of a specific child's leukemia. He added, that due to health concerns about exposures to environmental toxicants, it would be a good idea for everyone to minimize their exposures to them.

Watch: Dr. Gary Dahl discusses the clinic visit (3:08 mins.)



CHILDHOOD LEUKEMIA

Stephen's Story

SOME CHILDREN ARE AT HIGHER RISK

A few months after Stephen began treatment, Tricia and David start chatting with a customer, Lynn, while she is purchasing plants at their garden center. Tricia recognizes Lynn's daughter Ava in the shopping cart because she used to be in Stephen's child care.

Ava has Down syndrome. Lynn asks about Stephen, who is napping nearby. Tricia explains about Stephen's illness. Lynn mentions that their pediatrician told her that kids with Down syndrome are at higher risk for leukemia (10-20-fold higher risk). Fortunately, fewer than one percent of children with Down syndrome get childhood leukemia.



Key Concept:
Epigenetics



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Key Concept: Epigenetics

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Cancer is an epigenetic disease as much as it is a genetic disease; fully 10% of the leukemia genome is epigenetically altered compared to normal blood cells. Some of these alterations may be a result of adaptations to our environment very early in our development. Such adaptations may be appropriate at the time, but have consequences later for disease risk. Such an idea was well explained in the Barker Hypothesis (developmental origins of health and disease), now known to have epigenetic mechanisms.



Watch: Dr. Mark Miller discusses the Barker hypothesis (1:40 min.)

As the extent to which epigenetic mechanisms play a role in cancer become better understood, we will also better understand the influence of environmental variables on these mechanisms. This remains a highly active research field.

Phenotypic Plasticity



Watch: Dr. Mark Miller discusses epigenetics (1:45 mins)

WHAT IS EPIGENETICS?

The genetic code, or DNA sequence, is exactly the same in each body cell. We need some way, however, to express our genes in a correct manner for each cell type, be it blood, bone, muscle, brain, etc. Early in development, our genes are encoded with a set of distinguishing marks on top of genes, or epigenetic marks, that influence gene expression. Epigenetic marks are important to all stages of all cell types, to keep each cell organized within our whole human organism.

Exposures to environmental chemicals, infections, and diet can result in the turning of genes on or off. For instance, in a high pollution environment, our bodies can turn on detoxification enzymes. In a low folic acid environment, the body can adjust to retain more folate within our cells.

Mark Miller MD MPH, Director, Children's Environmental Health Program, Office of Environmental Health Hazard Assessment, California EPA; Director, UCSF Pediatric Environmental Health Specialty Unit

CHILDHOOD LEUKEMIA

Stephen's Story

HOME EXPOSURES VIA DUST

After Stephen's diagnosis, his parents were approached by researchers and asked to participate in a study to analyze their household's dust. Stephen's parents wondered what could possibly be in the house dust that would give researchers clues as to what may cause childhood leukemia. The researchers were very clear that the study is designed to learn about the possible causes of leukemia and would not be able to pinpoint a specific cause of Stephen's leukemia.

The researchers explained that they were going to analyze the dust for polychlorinated biphenyls (PCBs) and structurally-similar polybrominated diphenyl ethers (PBDEs), classes of chemicals that can remain in the environment for long periods of time. PCBs had many industrial and commercial applications, including electrical equipment and building materials. PBDEs are used as flame retardants in plastics, textiles, and furniture.

These chemicals can migrate from consumer products and collect in house dust. Because children crawl on the floor and put their hands in their mouth, they may be exposed to higher amounts of chemicals commonly found in house dust than adults.

Watch: Dr. Todd Whitehead on chemical exposures from house dust (1:56 mins.)

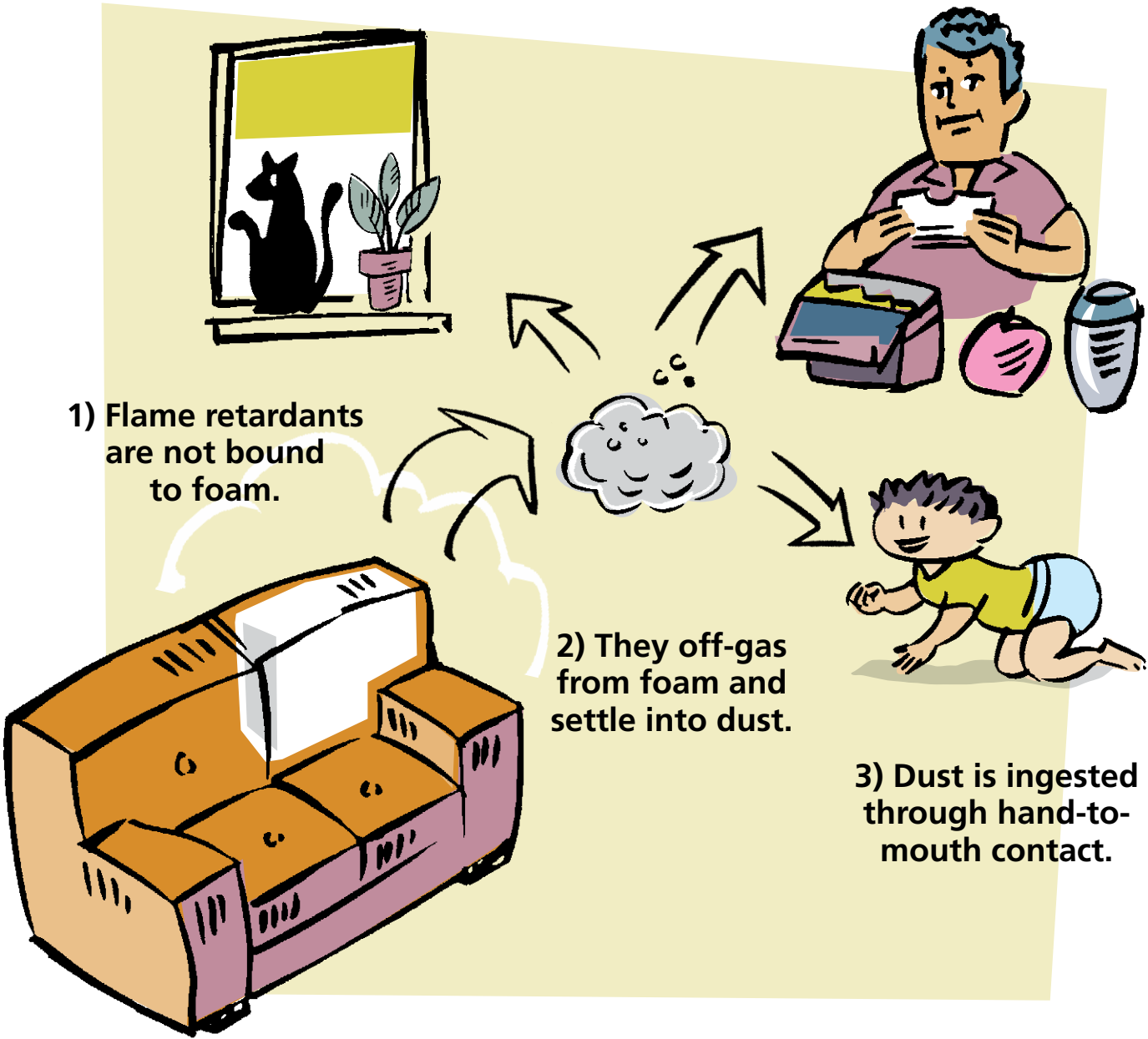


Todd Whitehead PhD, post-doctoral fellow, School of Public Health, University of California-Berkeley



Find out more: Green Science Policy Institute - California's policy and consumer resources

How do we come in contact with flame-retardant chemicals?



CHILDHOOD LEUKEMIA

Stephen's Story

INFECTIONS AS A PROTECTIVE FACTOR

Stephen attended preschool before he started chemotherapy.

One day, Tricia and David ran into parents at the grocery store whose children also attended Stephen's preschool. They mentioned that their daughter had just gotten over a cold. Tricia thought it seemed like she was always hearing about someone getting sick in that school, but it was one of the larger preschools. She started to worry about whether something was going around at school that could have made Stephen sick.

Stephen got several serious infections as a young child and they emailed Dr. Baker about whether this could be related to their son's leukemia.

Dr. Baker responded that going to a large pre-school could actually be protective against childhood cancer, but that children with leukemia report more frequent severe infections throughout their childhood before diagnosis, perhaps indicating an altered or more severe immune system response to common infections.

Watch: Dr. Joe Wiemels discusses theories about infection and leukemia rates (3:55 mins.)



Infection and leukemia risk



Infection-related damage leading to leukemia



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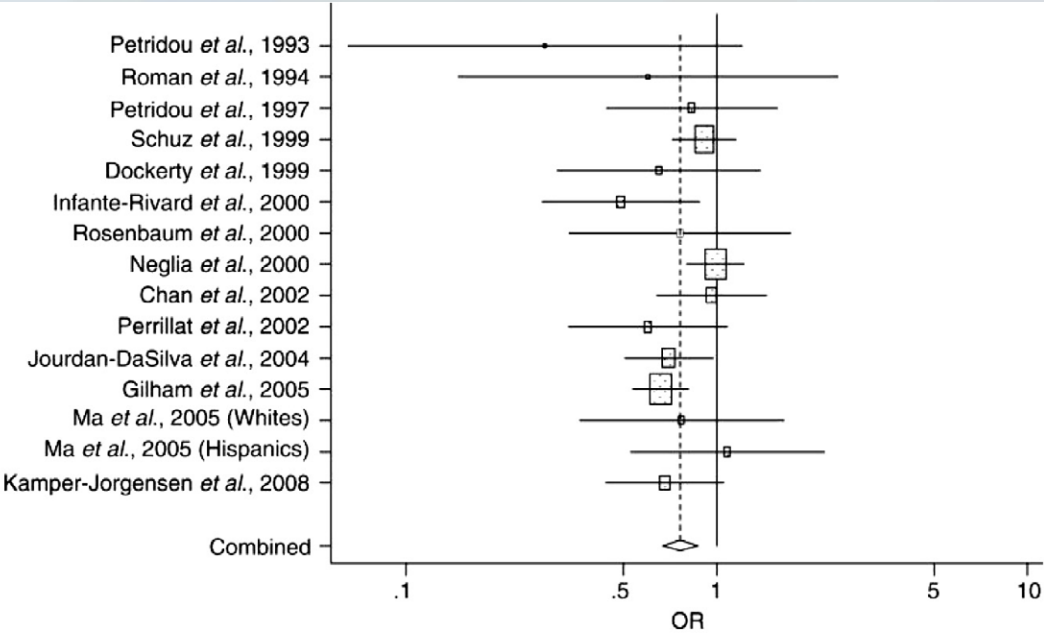
+ Infection and leukemia risk

+ Infection-related damage leading to leukemia

IMMUNE SYSTEM MODULATION: Exposure to Common Childhood Infections May Modulate the Immune System and Reduce Leukemia Risk

One meta-analysis of 14 studies (shown below) indicates that day-care attendance is associated with a reduced risk of ALL (OR = 0.76) (Urayama et al., 2010). Day-care was used as a surrogate measure of exposure to common infections early in life. This reduced risk supports the hypothesis that common infections can be protective against exaggerated responses by the immune system that may be implicated in childhood leukemia.

Another study used month of birth, timing of birth in relation to cold and flu season, and birth order as markers of exposure to infections. They found an increased risk of developing leukemia in children born in the spring and summer and who experience cold and flu season at 9-12 months old (OR = 1.44) (Marcotte et al., 2014). This may indicate that early mild infections could be protective against leukemia.



Urayama et al, 2010.
Graphic used with permission.

CHILDHOOD LEUKEMIA

Stephen's Story

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Infection and leukemia risk



Infection-related damage leading to leukemia

Infection-related damage leading to leukemia

Exposure to a variety of infections followed by an appropriate immune response is a healthy part of growing up, and seems to decrease leukemia risk. However, recent advances in DNA sequencing technology have revealed a mechanism by which strong immune response to infections may induce specific damage leading to leukemia. Researchers have now determined the detailed genetic code of the entire genome of cancer cells from many patients. Childhood leukemia cells have among the lowest level of mutations compared to all other cancer types, which is not surprising since there is very little time in a child's brief life prior to diagnosis to accumulate mutations. Interestingly, point mutations in leukemia cells appear to be predominantly produced by a

specific enzyme, APOBEC, which has a role in protecting our cells from viruses. APOBEC enzyme can attack and mutate invading viruses causing clusters of specific mutations in the viruses, but this activity can result in collateral damage to our own genetic code. Finding these mutation "signatures" in leukemia reveals a link between epidemiologic evidence that strong infections can trigger leukemia, and the mutations within leukemia cells themselves. We know that leukemia results from both prenatal and postnatal genetic events (the "two hit" hypothesis), and infection in this regard represents a cause for the second, postnatal hit. Prevention of this second "hit" by modifying our responses to infections may lead to prevention strategies for leukemia.

CHILDHOOD LEUKEMIA

Stephen's Story

CANCER CLUSTERS

One day while waiting in the hospital for Stephen's treatment, Tricia and David meet a military family who recently moved to the area. The family tells them about a study they learned of that showed possible clusters of leukemia near a military base in Fallon, Nevada. A cancer cluster occurs when a greater than expected number of cancer cases arise among people in a defined geographic area over some time. Due to the nature of the disease and the time it takes for cancers to develop, investigations to determine if a cancer cluster exists and what might be the potential cause are very challenging. Most investigations of a suspected possible cluster are not fruitful, meaning no cause is identified and the clustering of cases turns out to be random.



[Find out more:](#)
[Community Health Studies and Environmental Contamination](#)



[Read the Cancer Clusters Fact Sheet from the National Cancer Institute](#)



[Watch:](#) View video of Steve Francis' presentation, "Could infection contribute to a possible leukemia cluster in Fallon?" (Long - 23:07 mins)



A cancer cluster occurs when a greater than expected number of cancer cases arise among people in a defined geographic area over time.

CHILDHOOD LEUKEMIA

Stephen's Story

IONIZING RADIATION (INCLUDING X-RAY AND CT SCAN) EXPOSURE AND CHILDHOOD LEUKEMIA

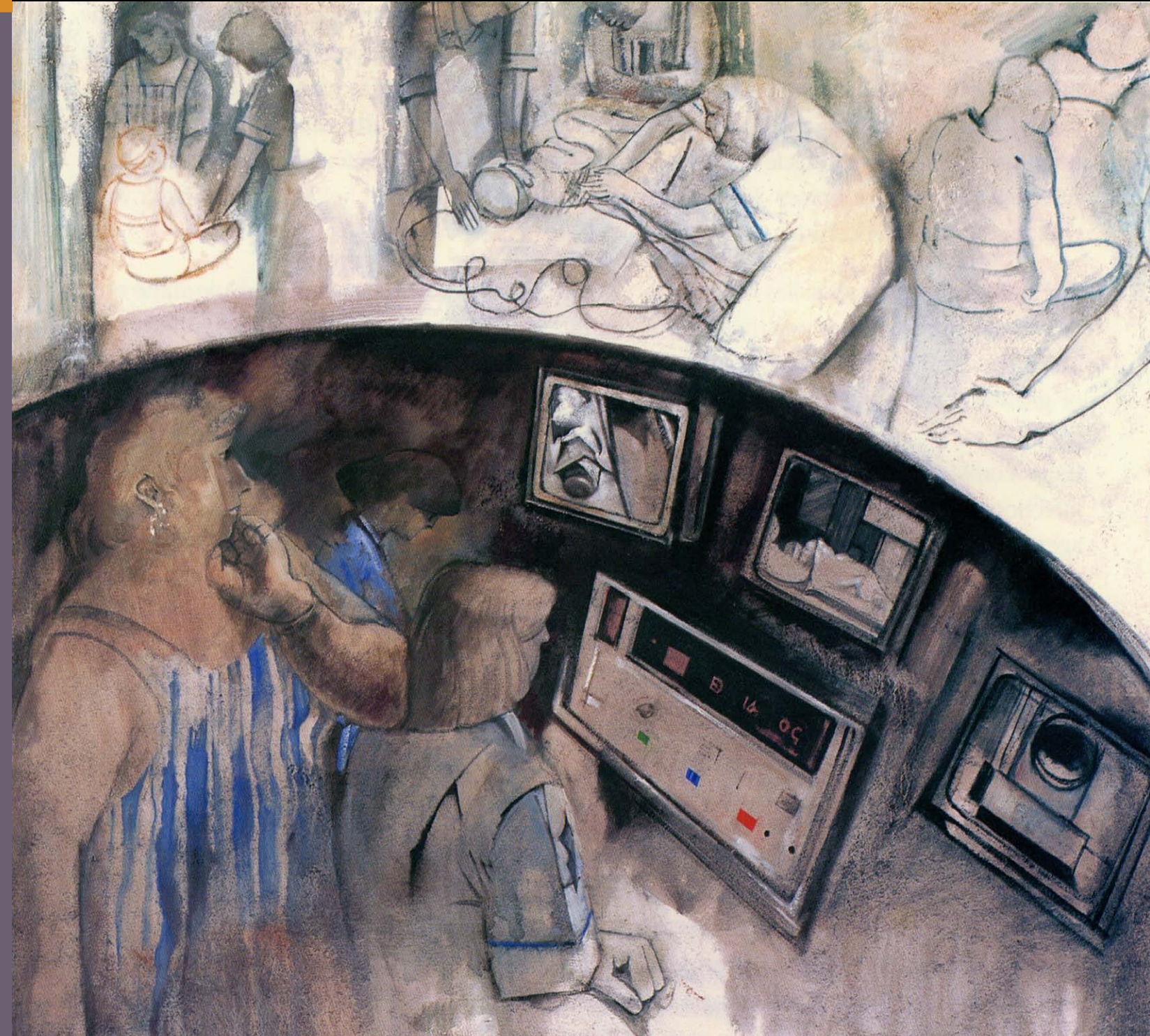
Along with the few infections that Stephen had as a baby, he caught pneumonia when he was six months old. This required a trip to the doctor and a few chest x-rays.

Exposure to ionizing radiation from nuclear accidents, x-rays, or radiation therapy has been associated with increased risk of childhood leukemia. Multiple studies have consistently shown in utero exposures to ionizing radiation increase the risk of leukemia by approximately 40% (Buffler et al., 2005).

CT-scans are of particular concern for children because children are considerably more sensitive to radiation than adults, they have a longer life expectancy resulting in a larger window of opportunity for expressing radiation damage, and doses are cumulative over a lifetime. CT-scans have not been extensively studied for links to leukemia, but their use has substantially increased in recent years and they often result in higher radiation exposures than X-rays (Linnet et al., 2009). [More >](#)



[National Cancer Institute - Radiation Risks and Pediatric Computed Tomography \(CT\)](#)



CHILDHOOD LEUKEMIA

Stephen's Story

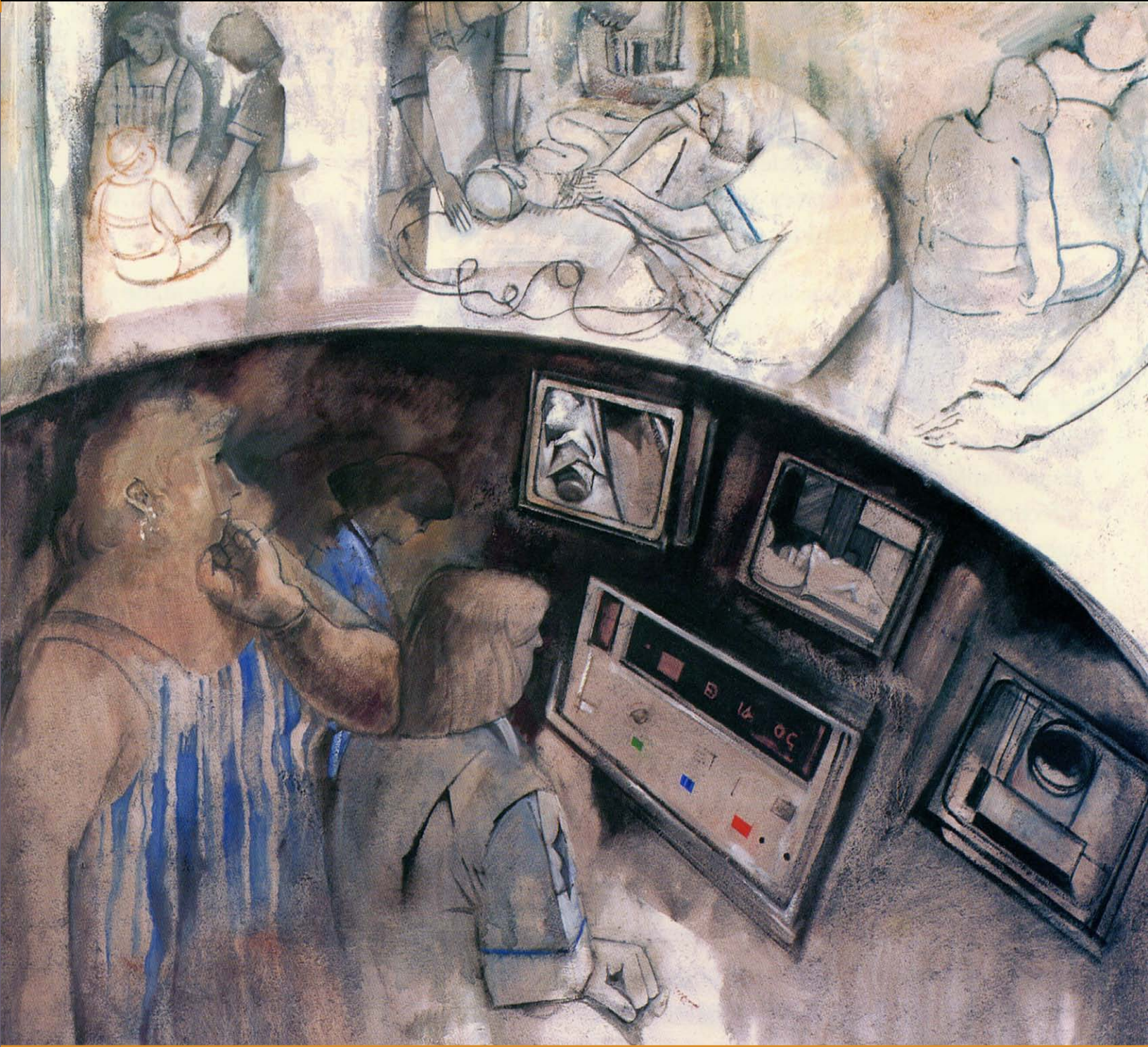
IONIZING RADIATION (INCLUDING X-RAY AND CT SCAN) EXPOSURE AND CHILDHOOD LEUKEMIA

(continued)

However, if the imaging test is necessary and clinically justified, then the parents can be reassured that the benefits will outweigh the long-term cancer risks. In recent years, radiologists and technicians in many hospitals have undertaken steps to reduce the exposure from x-rays and CT scans while maintaining the necessary quality of the image (Lambert et al., 2014). Many clinicians are considering whether a patient evaluation involving radiation exposure is truly necessary, or if the information of interest can be acquired in some other way.



[National Cancer Institute](#) - Radiation Risks and Pediatric Computed Tomography (CT)



CHILDHOOD LEUKEMIA

Stephen's Story

SOCIAL SUPPORT

Dr. Baker emphasizes to Tricia and David the importance of Stephen continuing his chemotherapy medications throughout the duration of recommended treatment. Stephen will undergo an intensive therapy period that ranges from 6-9 months, requiring frequent visits to Dr. Baker's office or the hospital. After this time, Stephen will receive maintenance chemotherapy where he visits the oncologist approximately once a month, but the frequency of these visits will depend on how well Stephen tolerates his medications.

A month into Stephen's therapy his parents joined a support group for parents of kids with leukemia and learned about different resources. Studies indicate that social support can improve the quality of life in pediatric cancer patients. These benefits can include reduced anxiety and post-traumatic stress among childhood cancer survivors. More adaptive coping strategies were also observed with family and social support.

- + [Hope Labs](#)
- + [Commonweal Cancer Help Program](#)
- + Find out more about support groups, community links: [CureSearch for Children's Cancer](#)
[Cancer.Net](#)
[The Leukemia & Lymphoma Society \(LLS\)](#)



Watch: Dr. Gary Dahl on chemotherapy compliance (1:30 mins.)



CHILDHOOD LEUKEMIA

Stephen's Story

After learning about the risks of chemical substances in the environment, Stephen's parents are taking steps to reduce exposures to their family and their community.

The nursery that they own will be transitioning to an all organic business model, and they are working with other local businesses like the town's golf course to partner together and use Integrated Pest Management (IPM). They have also become active in the local school board to help Stephen's preschool switch to IPM.

Tricia and David are considering having another child after Stephen completes chemotherapy and is in full remission. They are relieved that the risk of leukemia for siblings remains low.

After researching the possible causes of Stephen's disease and becoming more knowledgeable about how many environmental factors impact health, they will take extra precautions to promote a healthy pregnancy. Tricia will be taking folate supplements before conception and during the pregnancy. She also plans to avoid the various environmental exposures that she has learned about to the extent possible.



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Integrated Pest Management

Integrated Pest Management: Reducing Use of Pesticides in Homes, Schools and Other Buildings

Integrated pest management (IPM) is an approach to pest control that begins with avoiding the use of pesticides at all unless absolutely necessary. Many non- pesticide techniques can help to keep unwanted pests, like insects and rodents, from your home, lawn and garden, as well as public buildings and spaces.

If pesticides must be employed, preference is given to the least toxic alternatives. According to the EPA, IPM is "an effective and environmentally sensitive approach to pest management that relies on a combination of common-sense practices. IPM programs use current, comprehensive information on the life cycles of pests and their interaction with the environment. This information, in combination with available pest control methods, is used to manage pest damage by the most economical means, and with the least possible hazard to people, property, and the environment. The IPM approach can be applied to both agricultural and non- agricultural settings, such as the home, garden, and workplace."



More Resources:

- Pesticides: [EPA - Integrated Pest Management](#)
- Bio-Integral Resource Center ([BIRC](#))
- Pesticide Action Network ([PANNA](#))
- University of California – [Pesticide Application Equipment](#)
- [IPM in Early Care and Education](#)

CHILDHOOD LEUKEMIA

Stephen's Story

When Tricia, David, and Stephen joined the rest of the family at this year's reunion, they were cautiously optimistic about the future.

Stephen was responding well to chemotherapy and the family had found comfort in their local cancer support group and advocacy efforts to bring about change in their Connecticut town.

David tells the family about how far cancer treatments have progressed in recent years and that Stephen has approximately a 90% chance of being free of cancer in 5 years. They were all still concerned about the possibility of a relapse but have grown stronger as a family and as a community.



CHILDHOOD LEUKEMIA

Stephen's Story

SUMMING UP

Several common themes arise in Stephen's story that are similar to others in *A Story of Health*. These include the importance of critical windows of susceptibility, the consideration of sub-groups within a disease, the multiple risk factors, and the interaction of underlying genetics with the chemical, social and other environments. We are also reminded that population studies can illuminate underlying risk factors of disease (and therefore possible preventive actions), but generally cannot answer the specific question, "what caused this illness in this child?"

Like other chronic diseases that have been increasing in recent years, childhood leukemia is complex. Although there is no consensus amongst experts about its causes, except in a small percentage of cases, evidence implicating a variety of risk factors continues to accumulate. For example, considerable evidence from multiple studies around the world implicates exposures to tobacco smoke, pesticides, radiation, and traffic-related air pollution. The evidence of protective effects of peri-conception folate supplementation and early exposures in daycare also has substantial support.

Other associations that we have discussed in Stephen's story (e.g., PCBs and PBDEs) have been examined in only one or two studies and highlight the need for further investigation.

Though it may seem daunting, viewing health and disease as a result of the complex ecology of modern life reveals many key leverage points in which preventive actions may reduce disease incidence and improve health. Several of these are merely reinforcing current recommendations from medical societies and other expert practice guidance.

Many of the risk factors associated with childhood leukemia are also risk factors for other diseases discussed in *A Story of Health*. People will benefit in a variety of ways from avoiding unnecessary exposures to tobacco smoke, pesticides, and other environmental concerns.

Continue to [Final Thoughts](#) >

Viewing health and disease as a result of the complex ecology of modern life reveals many key leverage points in which preventive actions may reduce disease incidence and improve health



Population studies can illuminate underlying risk factors of disease (and therefore possible preventive actions), but generally cannot answer the specific question, "what caused this illness in this child?"

Childhood Leukemia Case References and Resources by Topic

Note: there are many topic overlaps

Cancer Clusters

Abrams B, Anderson H, Blackmore C, et al. Investigating suspected cancer clusters and responding to community concerns: Guidelines from CDC and the Council of State and Territorial Epidemiologists. September 27, 2013 / 62(RR08):1-14

Francis SS, Selvin S, Yang W, Buffler PA, Wiemels JL. Unusual space-time patterning of the Fallon, Nevada leukemia cluster: Evidence of an infectious etiology. Chem. Biol. Interact. 2012;196(3).

National Cancer Institute; National Institutes of Health. Cancer Clusters. March 18, 2014

Chemical Exposures and Leukemia - Specific Pollutants:

Air Pollution

Boothe VL, Boehmer TK, Wendel AM, Yip FY. Residential traffic exposure and childhood leukemia a systematic review and meta-analysis. Am J Prev Med 2014;46(4):413-422.

Heck JE, Wu J, Lombardi C, et al. Childhood cancer and traffic-related air pollution exposure in pregnancy and early life. Environ Health Perspect 2013;121(11-12):1385-1391).

Reynolds P, Von Behren J, Gunier RB, et al. Childhood cancer incidence rates and hazardous air pollutants in California: An exploratory analysis. Environ Health Perspect 2003;111(4):663-8.

Steffen C, Auclerc MF, Auvrignon A, et al. Acute childhood leukaemia and environmental exposure to potential sources of benzene and other hydrocarbons; a case-control study. Occup Environ Med 2004;61:773-778.

Vinceti M, Rothman KJ, Crespi CM, et al. Leukemia risk in children exposed to benzene and PM10 from vehicular traffic: A case-control study in an Italian population. Eur J Epidemiol 2012;27(10):781-90

House Dust

Flame retardants: Green Science Policy Institute

U.S. EPA. Polychlorinated biphenyls (PCBs): Basic Information

U.S. EPA Polybrominated Diphenyl Ethers (PBDEs) Action Plan Summary



Ward MH, Colt JS, Metayer C, et al. Residential exposure to polychlorinated biphenyls and organochlorine pesticides and risk of childhood leukemia. Environ Health Perspect 2009;117(6):1007-1013.

Ward MH, Colt JS, Deziel NC, et al. Residential Levels of Polybrominated Diphenyl Ethers and Risk of Childhood Acute Lymphoblastic Leukemia in California. Environ Health Perspect; DOI:10.1289/ehp.1307602

Pesticides

American Academy of Pediatrics. Policy Statement: Pesticide Exposure in Children. November 2012

Infante-Rivard C, Weichenthal S. Pesticides and childhood cancer: An update of Zahm and Ward's 1998 review. J Toxicol Environ Health B Crit Rev 2007;10(1-2): 81-99.

Ma X, Buffler PA, Gunier RB, et al. Critical windows of exposure to household pesticides and risk of childhood leukemia. Environ Health Perspect 2002;110(9):955-60.

Metayer C, Buffler PA. Residential exposures to pesticides and childhood leukaemia. Radiation Protection Dosimetry 2008;132(2):212-9.

Metayer C, Colt JS, Buffler PA, et al. Exposure to herbicides in house dust and risk of childhood acute lymphoblastic leukemia. Journal of Exposure Science and Environmental Epidemiology 2013; 23:363-370. Natural Resources Defense Council. Superficial safeguards: Most pesticides are approved by flawed EPA process. March 2013

Rull RP, Gunier R, Von Behren J, et al. Residential proximity to agricultural pesticide applications and childhood acute lymphoblastic leukemia. Environ Res 2009;109(7):891-899.

Turner MC, Wigle DT, Krewski D. Residential pesticides and childhood leukemia: A systematic review and meta-analysis. Environ Health Perspect 2010;118(1):33-41.



Solvents

Bailey HD, Milne E, de Klerk NH, Fritschi L, Attia J, Cole C, Armstrong BK; Aus-ALL Consortium. Exposure to house painting and the use of floor treatments and the risk of childhood acute lymphoblastic leukemia. Int J Cancer. 2011 May 15;128(10):2405-14.

Freedman DM, Stewart P, Kleinerman RA, Wacholder S, Hatch EE, Tarone RE, Robison LL, Linet MS. Household solvent exposures and childhood acute lymphoblastic leukemia. Am J Public Health. 2001 Apr;91(4):564-7.

Scelo G, Metayer C, Zhang L, et al. Household exposure to paint and petroleum solvents, chromosomal translocations, and the risk of childhood leukemia. Environ Health Perspect 2009;117(1):133-139.

Take Home Exposures to Chemicals

Gerson M, Van den Eeden SK, Gahagan P. Take-home lead poisoning in a child from his father's occupational exposure. Am J Ind Med. 1996 May;29(5):507-8.

Fenske RA, Lu C, Negrete M, Galvin K. Breaking the take home pesticide exposure pathway for agricultural families: workplace predictors of residential contamination. Am J Ind Med. 2013 Sep;56(9):1063-71.

Tobacco Smoke

Cogliano VJ, Baan R, Straif K, et al. Preventable exposures associated with human cancers. J Natl Cancer Inst 2011;103(24):1827-39.

IARC. Tobacco smoke and involuntary smoking. monographs on the evaluation of carcinogenic risks to humans. Volume 83. July 2002

Liu R, Zhang L, McHale CM, Hammond SK. Paternal smoking and risk of childhood acute lymphoblastic leukemia: systematic review and meta-analysis. J Oncol. 2011. Epub 2011 May 29.

Metayer C, Zhang L, Wiemels JL, et al. Tobacco smoke exposure and the risk of childhood acute lymphoblastic and myeloid leukemias by cytogenetic subtype. Cancer Epidemiol Biomarkers Prev 2013; 22(9):1600-11.

Milne E, Greenop KR, Scott RJ, Bailey HD, Attia J, Dalla-Pozza L, de Klerk NH, Armstrong BK. Parental prenatal smoking and risk of childhood acute lymphoblastic leukemia. Am J Epidemiol. 2012 Jan 1;175(1):43-53.

Office of Environmental Health Hazard Assessment. Proposed identification of environmental tobacco smoke as a toxic air contaminant. Part B: Health effects. California Environmental Protection Agency.

U.S. Department of Health and Human Services. Chapter Five: Reproductive and developmental effects from exposure to second-hand smoke. In: The health consequences of involuntary exposure to tobacco smoke: A report of the surgeon general. Atlanta, GA: Centers for Disease Control and Prevention, Coordinating Center for Health Promotion, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2006: p. 165-256.

Genetics

Knappe S, Zelley K, Nichols KE, et al. American Society of Clinical Oncology. 2012. Identification, management, and evaluation of children with cancer-predisposition syndromes. 2012

Curtin K, Smith KR, Fraser A, Pimentel R, Kohlmann W, Schiffman JD Familial risk of childhood cancer and tumors in the Li-Fraumeni spectrum in the Utah Population Database: implications for genetic evaluation in pediatric practice. Int J Cancer. 2013 Nov 15;133(10):2444-53

Infections

Greaves MF. Infection, immune responses and the aetiology of childhood leukaemia. Nat Rev Cancer. 2006;6:193-203

Marcotte EL, Ritz B, Cockburn M, et al. Exposure to infections and risk of leukemia in young children. Cancer epidemiol biomarkers Prev 2014. DOI: 10.1158/1055-9965.EPI-13-1330

Urayama KY, Buffler PA, Gallagher ER, et al. A meta-analysis of the association between day-care attendance and childhood acute lymphoblastic leukaemia. Int J Epidemiol 2010;39(3):718-732.

Leukemia Definition, Statistics

Cancer Research UK. Statistics and outlook for acute lymphoblastic leukaemia. August 2013

Cancer Research UK. Childhood cancer incidence statistics. May 6, 2014

Greaves MF. Childhood leukaemia. BMJ. 2002;324:283

Metayer C, Milne E, Clavel J, et al. The Childhood Leukemia International Consortium. Cancer Epidemiol 2013;37(3):336-47.

National Cancer Institute. General information about childhood acute lymphoblastic leukemia (ALL) – Health Professional Version. May 2014

U.S. National Library of Medicine. MedlinePlus: Bone marrow aspiration

Ward E, DeSantis C, Robbins A, Betsy Kohler, et al. Childhood and Adolescent Cancer Statistics, 2014. CA Cancer J Clin 2014;64:83-103

Wiemels J. Perspectives on the causes of childhood leukemia. Chem Biol Interact. 2012 Apr 5; 196(3):59-67

Occupational Exposures

Bailey HD, Fritschi L, Infante-Rivard C, et al. Parental occupational pesticide exposure and the risk of childhood leukemia in the offspring: Findings from the childhood leukemia international consortium. Int J Cancer 2014; DOI: 10.1002/ijc.28854.

Borkhardt A, Wilda M, Fuchs U, et al. Congenital leukaemia after heavy abuse of permethrin during pregnancy 3. Arch Dis Child Fetal Neonatal Ed 2003;88:F436-7.

Colt JS, Blair A. 1998. Parental occupational exposures and risk of childhood cancer. Environmental Health Perspectives 106 (Suppl. 3):909-925. 42 4314

Etzel RA, Balk SJ (eds.). Pediatric Environmental Health. American Academy of Pediatrics Council on Environmental Health. 3rd Ed. 2012

Feychting, M., N. Plato, G. Nise, and A. Ahlbom. 2001. Paternal occupational exposures and childhood cancer. Environ Health Perspect 109 (2):193-6

Infante-Rivard C, Siemiatycki J, Lakhani R, Nadon L. Maternal exposure to occupational solvents and childhood leukemia. Environ Health Perspect 2005;113 (6):787-92.

LaFiura KM, Bielawski DM, Posecion NC, et al. Association between prenatal pesticide exposures and the generation of leukemia-associated t(8;21). Pediatr Blood Cancer 2007;49:624-8.

Pediatric Environmental Health Toolkit. Physicians for Social Responsibility and UCSF Pediatric Environmental Health Specialty Unit

continued >

Asthma

Childhood Leukemia

Learning/ Developmental Disabilities

Diabetes

Infertility

Cognitive Decline

Childhood Leukemia Case References and Resources by Topic (continued)

Wigle DT, Arbuckle TE, Turner MC, et al. Epidemiologic evidence of relationships between reproductive and child health outcomes and environmental chemical contaminants. *J Toxicol Environ Health B Crit Rev* 2008;11(5-6):373-517.

Wigle DT, Turner MC, Krewski D. A systematic review and meta-analysis of childhood leukemia and parental occupational pesticide exposure. *Environ Health Perspect* 2009;117:1505-1513.

Prenatal/Preconception Care, Nutrition, Folic Acid

ACOG Practice Bulletin No. 44 Neural Tube Defects. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2003;102 (1):203-213.

ACOG FAQ: *Nutrition During Pregnancy*. 2013

Bailey HD, Miller M, Langridge A, de Klerk NH, van Bockxmeer FM, Attia J, Scott RJ, Armstrong BK, Milne E. Maternal dietary intake of folate and vitamins B6 and B12 during pregnancy and the risk of childhood acute lymphoblastic leukemia. *Nutr Cancer*. 2012;64(7):1122-30

Lambrot R, Xu C, Saint-Phar S, Chountalos G, Cohen T, Paquet M. Suderman M, Hallett M, and Kimmins S. Low paternal dietary folate alters the mouse sperm epigenome and is associated with negative pregnancy outcomes. *Nature Communications* 4. 2013; Article number:2889

Lyall K, Schmidt R, Hertz-Picciotto I. Maternal lifestyle and environmental risk factors for autism spectrum disorders. *Int J Epidemiol* 2014;43(2):443-464.

Metayer C, Milne E, Dockerty JD, et al. Maternal supplementation with folic acid and other vitamins and risk of leukemia in the offspring: a childhood leukemia international consortium study *Epidemiology*. 2014 Nov;25(6):811-22



Schmidt RJ, Tancredi DJ, Ozonoff S, et al. Maternal periconceptional folic acid intake and risk of autism spectrum disorders and developmental delay in the CHARGE (Childhood Autism Risks from Genetics and Environment) case-control study. *Am J Clin Nutr* 2012;96:80–9.

Surén P, Roth C, Bresnahan M, Haugen M, Hornig M, Hirtz D, Lie KK, Lipkin WI, Magnus P, Reichborn-Kjennerud T, Schjølberg S, Davey Smith G, Øyen AS, Susser E, Stoltenberg C. Association between maternal use of folic acid supplements and risk of autism spectrum disorders in children. *JAMA*. 2013 Feb 13;309(6):570-7.

U.S. Preventive Services Task Force. Folic acid for the prevention of neural tube defects: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2009; 150:626-631.

Radiation

Ionizing Radiation

Arthurs O, Bjorkum A. Safety in pediatric imaging: an update. *Acta Radiol*. 2013; 54(9):983-990.

Bartley K, Metayer C, Selvin S, Ducore J, Buffler P. Diagnostic X-rays and risk of childhood leukemia. *Int J Epidemiol*. Dec 2010; 39(6): 1628–1637. doi: 10.1093/ije/dyq162.

Boice JD Jr, Miller RW. Childhood and adult cancer after intrauterine exposure to ionizing radiation. *Teratology* 1999;59(4):227-33.

Buffler, P.A., M.L. Kwan, P. Reynolds, and K.Y. Urayama. 2005. Environmental and genetic risk factors for childhood leukemia: appraising the evidence. *Cancer Investigation* 23 (1):60-75.

Chokkalingam AP, Bartley K, Wiemels JL, et al. Haplotypes of DNA repair and cell cycle control genes, X-ray exposure, and risk of childhood acute lymphoblastic leukemia. *Cancer Causes Control* 2011;22(12):1721-1730

Doll R, Wakeford R. Risk of childhood cancer from fetal irradiation. *Br J Radiol* 1997;70:130-139.

Infante-Rivard C, Mathonnet G, Sinnett D. Risk of childhood leukemia associated with diagnostic irradiation and polymorphisms in DNA repair genes. *Environ Health Perspect* 2000;108(6):495-8.

Linét M, Kim K, Rajaraman P. Children's exposure to diagnostic medical radiation and cancer risk: epidemiologic and dosimetric considerations. *Pediatr Radiol* 2009; 39 Suppl 1:S4-26.

Lambert J, MacKenzie J, Cody D, Gould R. Techniques and tactics for optimizing CT dose in adults and children: state of the art and future advances. *J Am Coll Radiol*. 2014; 11(3):262-266.

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Asthma

Cancer (Childhood Leukemia)

Learning/ Developmental Disabilities

Diabetes

Infertility

Cognitive Decline

References



Non-ionizing Radiation

Ahlbom A, Day N, Feychting M, et al. A pooled analysis of magnetic fields and childhood leukaemia. *Br J Cancer*, 83 (2000), pp. 692–698.

Chen G, Xu Z. Global protein expression in response to extremely low frequency magnetic fields. *Adv Exp Med Biol*. 2013; 990: 107-110.

Greenland S, Sheppard AR, Kaune WT, Poole C, Kelsh MA. A pooled analysis of magnetic fields, wire codes, and childhood leukemia Childhood Leukemia-EMF Study Group. *Epidemiology*, 11 (2000), pp. 624–634

IARC. Non-Ionizing Radiation, Part 1: Static and Extremely Low-Frequency (ELF) Electric and Magnetic Fields. Monographs on the Evaluation of Carcinogenic Risks to Humans. *Volume 80*. March 2002

Kheifets L, Ahlbom A, Crespi CM, et al. Pooled analysis of recent studies on magnetic fields and childhood leukaemia. *Br J Cancer*. 103 (2010), pp. 1128–1135

Simko M. Cell type specific redox status is responsible for diverse electromagnetic field effects. *Curr Med Chem*. 2007; 14(10):1141-1152.

Trends

Ekanayake R, Miller M, Marty, M. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency. *Report to the Legislature, Children's Environmental Health Program*. February 2014.

Howlader N, Noone AM, Krapcho M, Garshell J, Miller D, Altekruse SF, Kosary CL, et al., (eds). *SEER Cancer Statistics Review, 1975-2011*, National Cancer Institute. Bethesda, MD, July 2014.

Ward E, DeSantis C, Robbins A, Kohler B, Jemal A. Childhood and Adolescent Cancer Statistics, 2014. *CA Cancer J Clin*. 2014 Mar-Apr;64(2):83-103

LEARNING/DEVELOPMENTAL DISABILITIES Amelia's Story*

Amelia is a 13-year-old who lives with her parents Darrell and Gloria in a small town in Louisiana.

She enjoys being with her friends, riding her bike, playing soccer, listening to music, and helping out at the restaurant where her mother is the bookkeeper.

Amelia likes school, although she has difficulty learning and is occasionally socially awkward.

Like one in six young people in America, Amelia has a developmental disability.



More information
on learning and
developmental
disabilities
definitions
and US trends



(*a fictional case)

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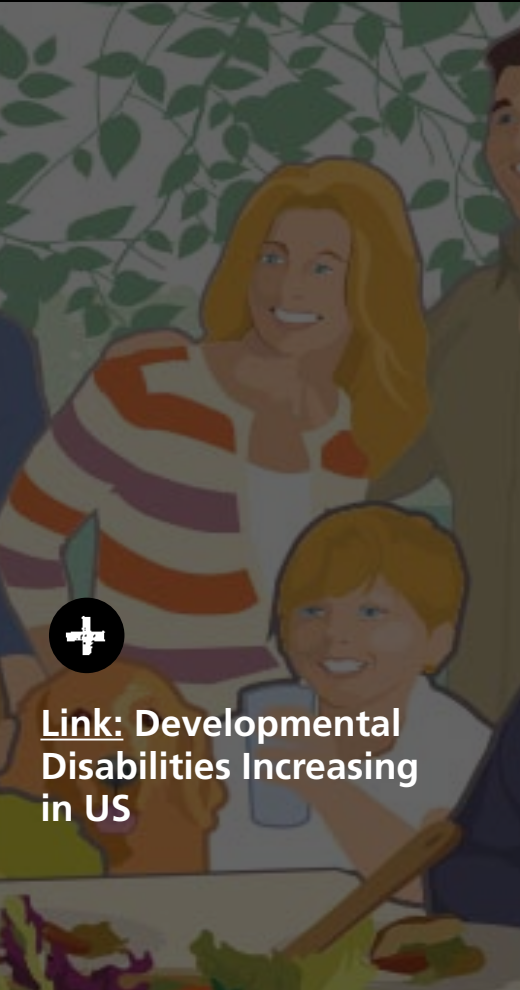
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[+ More information on learning and developmental disabilities definitions and US trends](#)

Specific Developmental Disabilities in U.S. Childrens Aged -17 Years*

Disability	Percent Change between 1997-1999 and 2006-2008
Any developmental disability	17.1%^
ADHD	33.0%^
Autism	289.5%^
Blind/unable to see at all	18.2%
Cerebral palsy	-
Moderate to profound hearing loss	-30.9%
Learning disability	5.5%
Intellectual disability	-1.5%
Seizures, past 12 months	9.1%
Stuttered or stammered, past 12 months	3.1%
Other developmental delay	24.7%^



[+ Link: Developmental Disabilities Increasing in US](#)

Developmental Disabilities Definitions and US Trends


Developmental disabilities (DD) are a diverse group of conditions that are neurologically based and result in physical and/or mental impairments that affect function and performance in many ways. People with DD may have difficulty with physical activities such as walking or manipulating objects, difficulties with speech, language, communication, interaction, and socialization, as well as difficulties with learning and cognitive skills that may affect their ability to live and work independently. Developmental disabilities begin anytime during development up to 22 years of age and usually last throughout a person's lifetime. It is very important that any disabilities are

identified as early as possible in order to provide the necessary therapies, interventions, and education that will help the child reach his or her full potential. As can be seen from the table above, there has been an alarming increase in the rate of most DD conditions that indicate a serious public health challenge requiring urgent attention. Not all children are affected equally, for example, boys are more likely than girls to have autism and ADHD (Ekanayake et al., 2014), and poor children who are insured with Medicaid are also more likely to have ADHD, learning disabilities and intellectual disabilities than their more affluent peers who have private insurance. (Rubin et al., 2012)

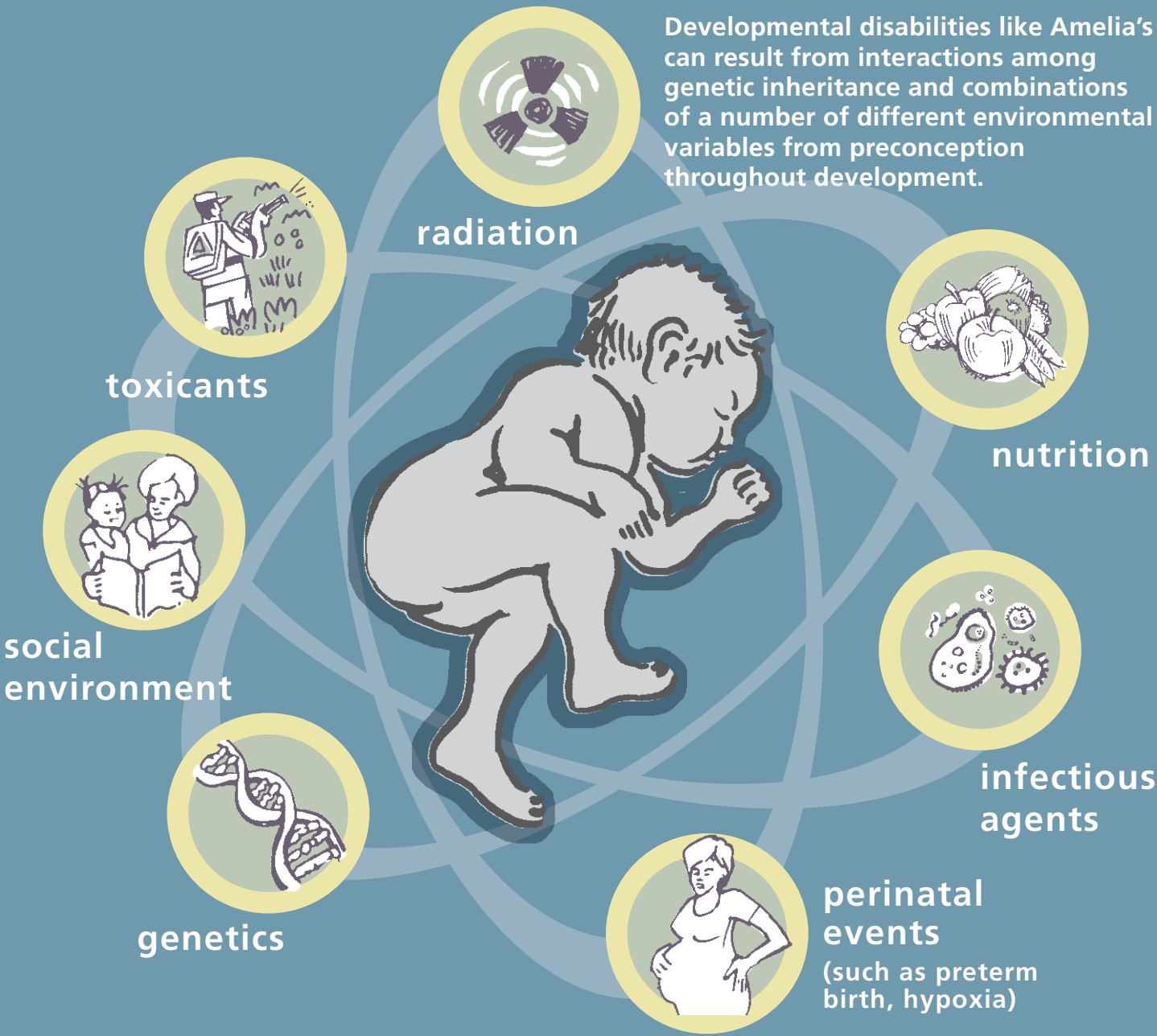
*Centers for Disease Control and Prevention, National Center for Health Statistics, NHS, 1997-2008.
^Statistically significant trend over four time periods (1997-1999, 2000-2002, 2003-2005, 2006-2008).
Graphic used with permission.

LEARNING/DEVELOPMENTAL DISABILITIES Amelia's Story

A single variable, such as birth trauma or prenatal exposure to alcohol, may sometimes be the cause of a developmental disability. More commonly, however, multiple risk factors combine to alter brain development and/or function in a variety of ways, resulting in a developmental disability. Developmental disorders are generally better conceptualized as heterogeneous (different) conditions arising from interactions among genetic and environmental factors. (See “More” below for in-depth information.)


 **More on environmental and genetic contributors to developmental disabilities**

Multiple Contributors to Developmental Disabilities



LEARNING/DEVELOPMENTAL DISABILITIES Amelia's Story

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More on environmental and genetic contributors to developmental disabilities

Environmental and Genetic Contributors to Developmental Disabilities

While environmental chemicals like lead or organophosphate pesticides are toxic to everyone, certain inherited genes can influence the response of particular individuals and increase their susceptibility to cognitive and behavioral problems after exposures.

For example, some genes affect the metabolism of organophosphate pesticides (such as the paraoxonase gene) while others may have modest effects on lead absorption and metabolism (such as the vitamin D receptor and delta-aminolevulinic acid dehydratase genes).

Twin Studies

Family and twin studies help in estimating the extent to which the origins of various developmental disabilities can be attributed to genetic inheritance or the shared and unshared environments. Twins share the same uterine environment and usually, but not always, share the same home environment after birth. Shared environmental influences are those that are more common among individuals within a family than in unrelated individuals in the

general population. They may include environmental influences within the home or other shared experiences such as having mutual friends or teachers. Non-shared environmental influences for twins who live in the same home could be a head injury, another kind of unique traumatic event, exposure to a physical or toxic chemical substance, or some kind of abuse to which the other twin was not similarly exposed. Twin studies of children with ADHD generally find a relatively high genetic correlation with symptoms of inattention, hyperactivity, and impulsivity in children with ADHD. (Thapar, 2012) But even in identical twins who are more likely to have similar symptoms than fraternal twins, the concordance is not 100%, suggesting that non-inherited factors also contribute. In comparison, inherited genetic predisposition to reading and math problems in children with learning disabilities appears to be considerably less. (Willcutt et al., 2010) Autism spectrum disorder has historically been thought to result primarily from genetic susceptibility, but recent twin studies show that shared environmental factors contribute at least 50% of autism risk. (Hallmayer, 2011; Sandin, 2014) These observations are reminders of the importance of gene-environment interactions in individuals with and without particular genetic susceptibility.

*Thapar A, Cooper M, Jeffries R, Stergiakouli E. What causes attention deficit hyperactivity disorder? Arch Dis Child. 2012;97:260–265

LEARNING/DEVELOPMENTAL DISABILITIES Amelia's Story

DEVELOPMENTAL MILESTONES

Amelia's developmental disability was not particularly noticeable at a young age. Her developmental milestones had been only slightly delayed compared to her peers, and she also seemed to be somewhat inattentive, but otherwise progressed reasonably well. In addition, the subtle expression of her delays and difficulties was missed by her parents, who were distracted after her baby brother David was born.

Checklists for Parents:
[CDC's Developmental Milestones](#) by specific age

Watch: How early recognition of developmental disabilities can assist parents and providers.



LEARNING/DEVELOPMENTAL DISABILITIES Amelia's Story

Amelia's parents, Darrell and Gloria, first became somewhat concerned that she might be having difficulty with school work when she was in the second grade. She seemed to be having trouble paying attention and finishing tasks like her homework.

They decided, though, that she was just going through some normal adjustments at school and at home. Because they were both working long hours at their jobs, taking care of a new baby, and struggling with finances, they did not seek help for Amelia at that time as her difficulties did not seem to be very serious.

Both parents did make sure they spent time with her to help her read and comfort her when she seemed frustrated.

For these and other reasons, her parents put off addressing Amelia's problem until a parent-teacher meeting in the third grade, where they learned more about the difficulty Amelia was having in school. They realized they needed to take action.

Watch: Dr. Mark Miller describes the benefits of an enriched social environment and the way it influences brain structure and function.



Mark Miller MD MPH, Director, Children's Environmental Health Program, Office of Environmental Health Hazard Assessment, California EPA; Director, UCSF Pediatric Environmental Health Specialty Unit



LEARNING/DEVELOPMENTAL DISABILITIES Amelia's Story

EVALUATION OF LEARNING DISABILITIES

Amelia's parents met with the school psychologist, Mr. Richards, who did an evaluation to determine Amelia's education needs. He also offered to refer them to a medical setting to see if the family wanted to pursue further diagnosis. When they asked, he referred them to a center in a large city where she could be further evaluated.

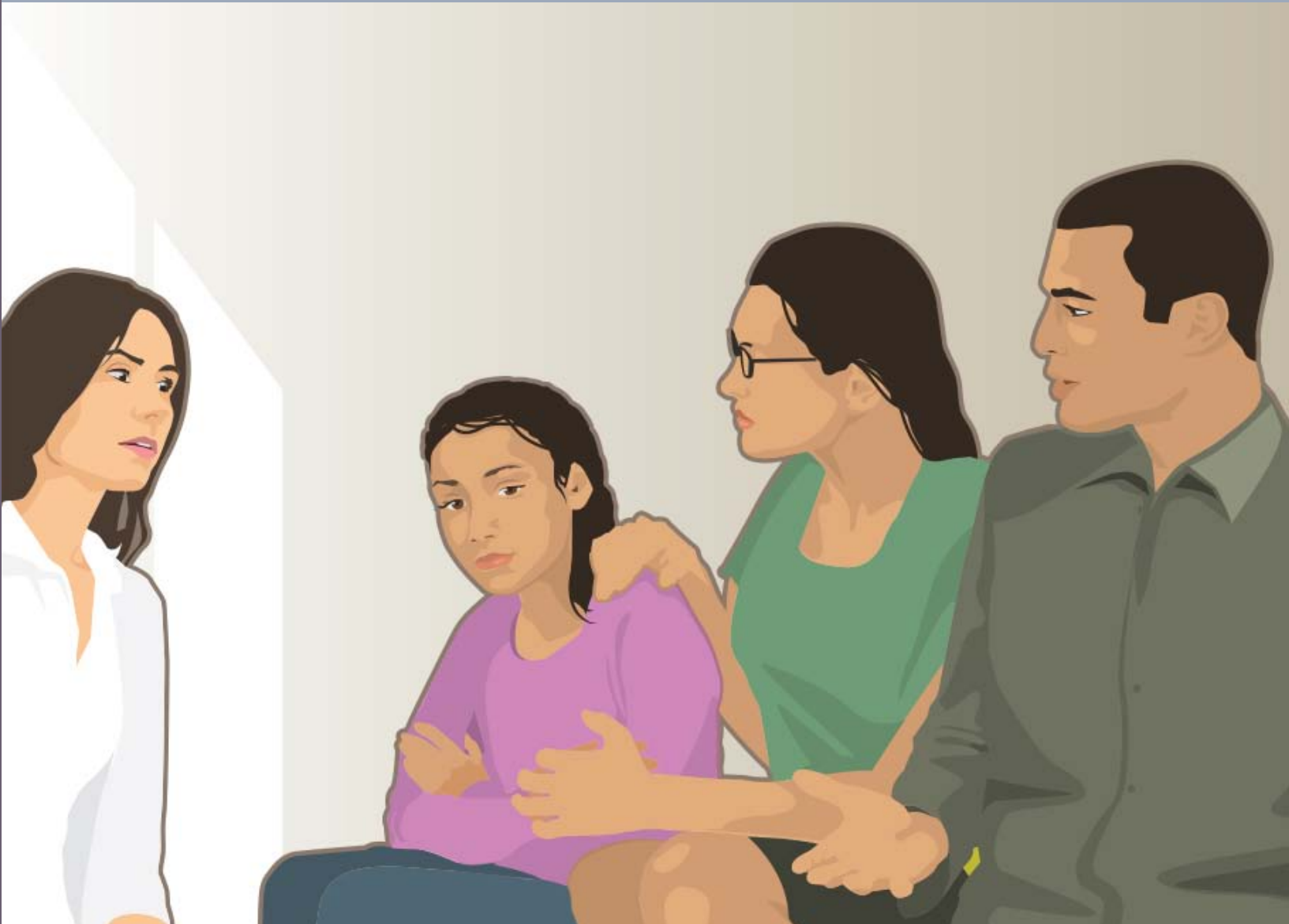
The medical setting was somewhat intimidating at first, but the people at the center made them feel at ease. They were introduced to Dr. Bradley, a developmental pediatrician, who said she would be conducting a number of screening procedures with Amelia.

After the screening, Dr. Bradley met with Amelia and her parents. She explained that Amelia's challenges were somewhat difficult to categorize as she had several that cut across syndromes they might have heard of, such as ADHD.

She explained that Amelia's reading and comprehension difficulties qualified as a learning disability. However, Amelia also exhibited inattention during the testing but not sufficiently for a diagnosis of ADHD.



Find out more about Evaluations



LEARNING/DEVELOPMENTAL DISABILITIES Amelia's Story



Dr. Bradley said she thought Amelia would do well with some extra help at school along with making other healthy living choices.

-
- Developmental Screening Tools for Clinicians:

Developmental Screening in Early Childhood Systems, American Academy of Pediatrics (AAP)

Developmental and Behavioral Screening Initiative, Administration for Children & Families (ACF)

OVERLAPPING SYNDROMES

Learning and behavioral disorders often overlap with other categories. For example:

Among children with ADHD:

- 10-30% also have learning disabilities;
- 30-50% also have language disability;
- 30-80% have other behavior disorders.

ADHD is also frequently associated with autism spectrum disorder, obsessive compulsive disorder, tic disorders, and intellectual disabilities.

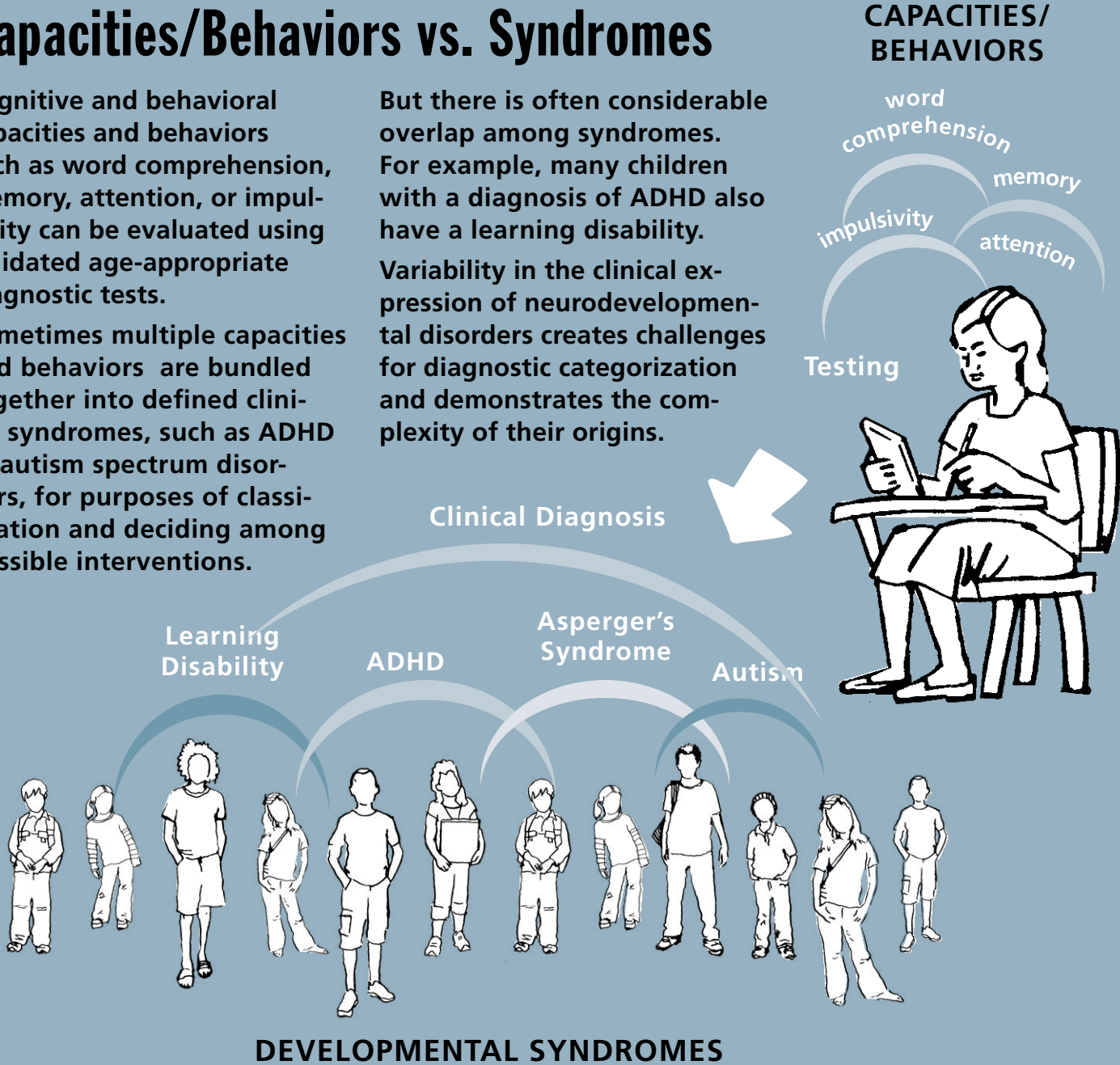
Capacities/Behaviors vs. Syndromes

Cognitive and behavioral capacities and behaviors such as word comprehension, memory, attention, or impulsivity can be evaluated using validated age-appropriate diagnostic tests.

Sometimes multiple capacities and behaviors are bundled together into defined clinical syndromes, such as ADHD or autism spectrum disorders, for purposes of classification and deciding among possible interventions.

But there is often considerable overlap among syndromes. For example, many children with a diagnosis of ADHD also have a learning disability.

Variability in the clinical expression of neurodevelopmental disorders creates challenges for diagnostic categorization and demonstrates the complexity of their origins.



Learning Disability



ADHD



Autism spectrum disorder



LEARNING/DEVELOPMENTAL DISABILITIES Amelia's Story

Amelia's parents, Darrell and Gloria, asked Dr. Bradley what could have caused Amelia's learning disability, and Dr. Bradley was interested in exploring that as well.

Dr. Bradley suggested that there is often a genetic predisposition and added that if Amelia had been born prematurely, or had a low birth weight, either could be a risk factor for her developmental disability.

Gloria told her that Amelia was a little underweight when she was born, but no one seemed very concerned about it at the time. Dr. Bradley also mentioned that smoking or drinking during pregnancy could increase the risk. Gloria told her that her husband had smoked during her pregnancy, although when Amelia was born he had quit with help from their local medical clinic.


Finally, Dr. Bradley told them about the risk to brain development from exposures early in life to other toxic chemicals and substances, such as lead, mercury, and diesel fumes from trucks and cars.

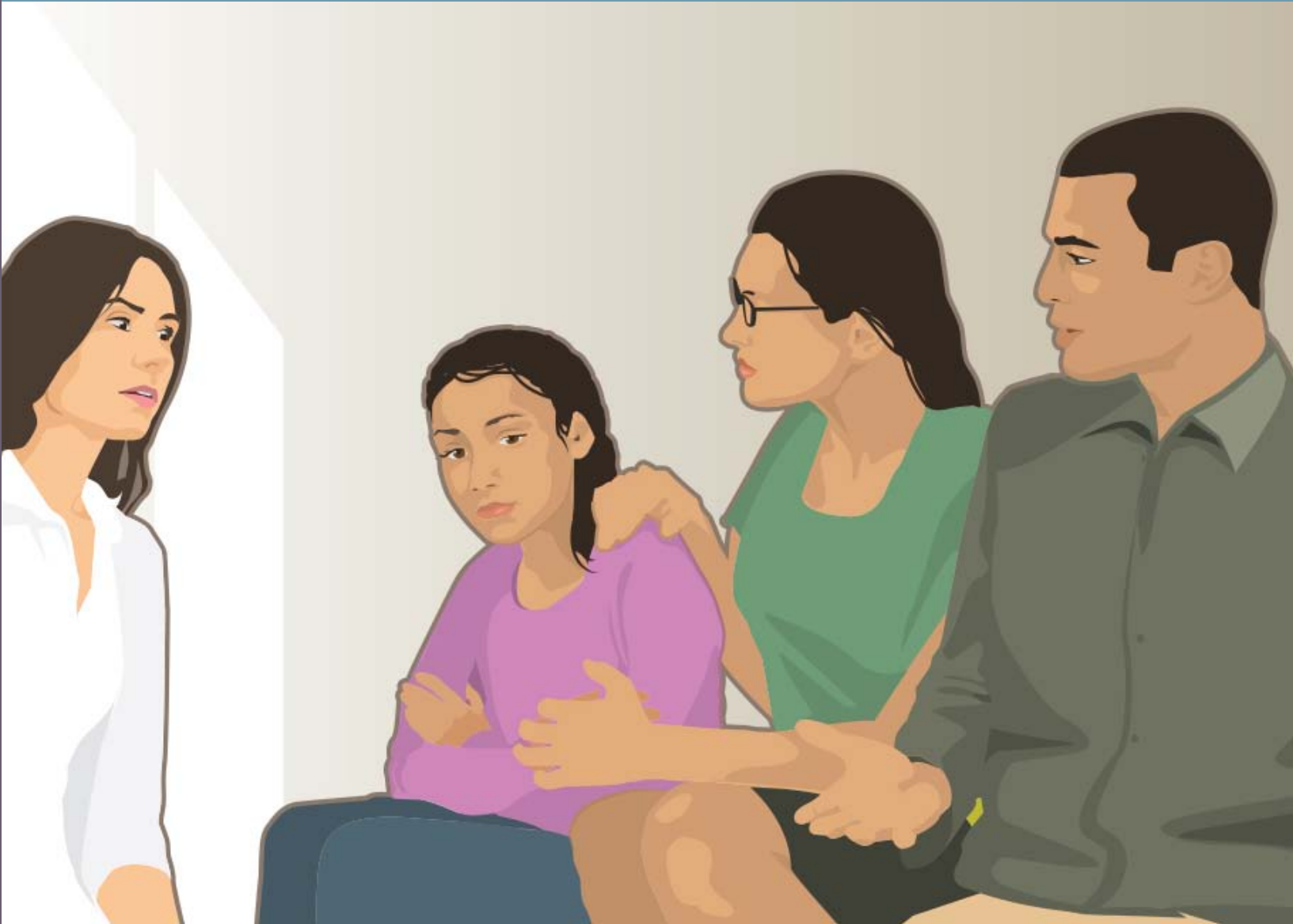
 **Preconception and Healthy Child Development**

 **Prenatal Care and Healthy Child Development**

Folate supplementation recommendations for women

 **A Rationale for Thyroid Screening**

 **For Clinicians: Prenatal environmental health history form, [PEHSU Region 5](#)**



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Preconception and Healthy Child Development



Prenatal Care and Healthy Child Development

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PRECONCEPTION AND HEALTHY CHILD DEVELOPMENT

Preconception care for women and men is important for lifetime health as well as healthy child development.



Images: Centers for Disease Control and Prevention

All women and men can benefit from healthy habits throughout life, whether or not they plan to have a baby one day. These include eating healthy food, getting regular exercise, avoiding toxic substances, and reducing excessive stress.

Some specific actions are also important for prospective parents to take even prior to conception because they can influence birth outcomes.

Maternal exposures to toxic chemicals before or around the time of conception can adversely affect the quality of eggs (ova) and newly-conceived embryos. But these exposures can be harmful to men's reproductive health as well. For example, a father's occupational exposure to pesticides has been associated with increased risk of some childhood cancers and birth defects in his offspring. (Roberts et al., 2012).

Parents can also take home from the workplace toxicants like lead and pesticides on their clothing, resulting in direct exposures to other family members. (Gerson et al., 1996; Fenske et al., 2013)

Nutritionally, a prospective father's diet that is deficient in folate (a "B" vitamin) increases the risk of birth defects in his offspring. (Lambrot et al., 2013). Similarly, maternal folate supplements in the periconceptual period (the time period around conception) help reduce the risk of birth defects

Recent studies also show periconceptual folate supplements associated with a significantly decreased risk of having a child with an autism spectrum disorder. (Schmidt et al, 2012; Suren et al, 2013; Lyall, 2104)

Schmidt et al. also found greater risk reduction with daily folate > 0.6 mg when either the mother or child had specific higher risk polymorphisms in MTHFR genes. The MTHFR gene provides instructions for making methylenetetrahydrofolate reductase, a

More information: CDC's Preconception care for women and men

rate limiting enzyme in the methyl cycle. Some genetic variants of the enzyme result in altered or inactivated enzyme function. Altered enzyme activity can interfere with its ability to help process folate, a key nutrient for neurodevelopment. Some variants have been associated with increased risk for developing neural tube defects and other neurologic disorders. About 60% of the US population have at least one risk-conferring MTHFR gene.

Of course optimal nutrition and appropriate vitamin and mineral supplements throughout pregnancy are also important to help promote optimal fetal development.

LEARNING/DEVELOPMENTAL DISABILITIES Amelia's Story

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PRENATAL CARE FOR HEALTHY DEVELOPMENT



Images: Centers for Disease Control and Prevention

The fetus can be harmed by environmental exposures including:

- Mom's smoking and second hand smoke,
- Mom's drinking alcohol, and her exposure to other solvents like those in certain paints and in products used in nail salons,
- Mom's exposure to lead, mercury (from some fish and other sources), pesticides, PCBs (banned in the US but still found in the environment), and certain polybrominated diphenyl ethers (PBDEs – a family of chemicals long-used as flame retardants in foam and furniture), among others.

Actions to help protect the fetus:

- Avoid smoking or drinking,
- Maintain a healthy diet,
- Supplement with prenatal vitamins, including folic acid, iodine, and vitamin D if maternal serum levels are inadequate,
- Avoid toxicants.

More information:

- CDC on [pregnancy](#)
- American Congress of Obstetrics and Gynecology (ACOG):
 - [Good Health Before Pregnancy](#) (pdf)
 - [Prenatal Nutrition](#)
 - [Environmental Chemicals](#)
- Royal College of OB/GYN:
 - [Chemical Exposures During Pregnancy](#)
- UCSF: [Program on Reproductive Health and the Environment](#)

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PRENATAL HEALTHY CARE

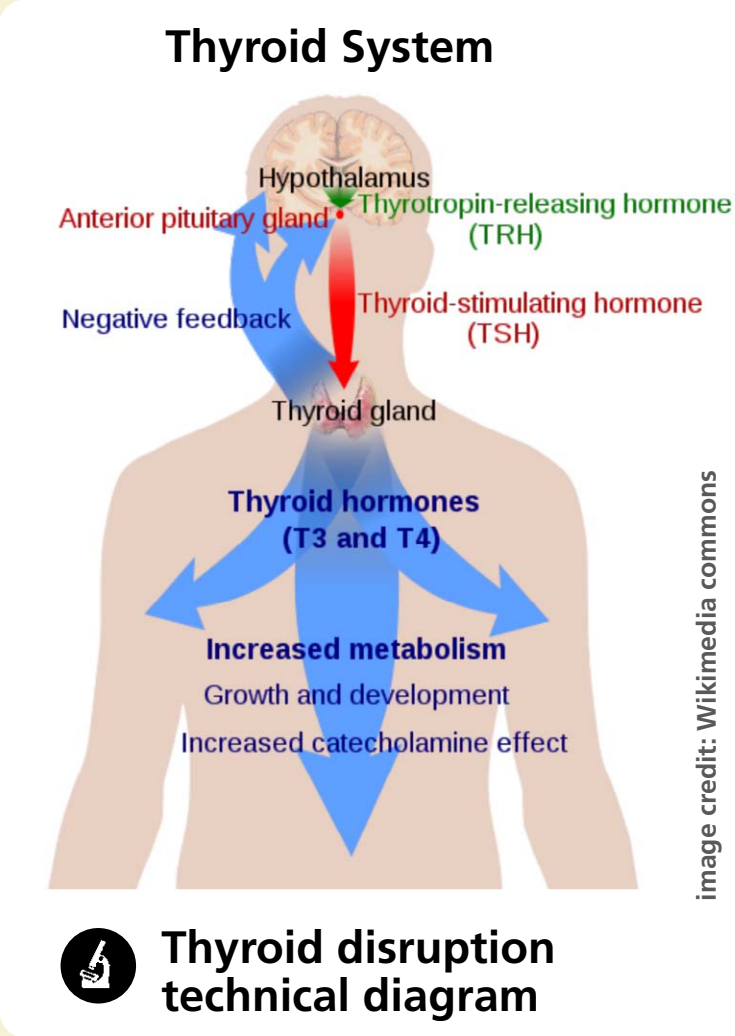
A Rationale for Thyroid Screening Before or During Pregnancy

Adequate levels of thyroid hormone are necessary for normal brain development. During the first trimester of pregnancy, before onset of fetal thyroid hormone production, an adequate supply of maternal thyroid hormone is essential. Recent studies show that even modest reduction in maternal TH, as in subclinical hypothyroidism (moderately elevated TSH and normal or low-normal T4 levels) or low-normal free T4 levels (below the 5th or 10th percentiles) with or without elevated TSH, is associated with suboptimal neurodevelopment (Haddow, 1999; Pop et al., 1999; LaFranchi, 2005)

According to the CDC, about 30% of women of reproductive age in the US have insufficient iodine intake. Iodine is an essential element in the production of thyroid hormones. The American Congress of Obstetricians and Gynecologists (ACOG) recommends that all prenatal vitamins contain at least 150 micrograms iodine, but many vitamins do not contain this amount.

A number of environmental chemicals can disrupt thyroid hormone levels and function through a variety of mechanisms. (Pearce & Braverman, 2009)

Opinions about the value of universal screening for maternal thyroid status during pregnancy differ between the Endocrine Society and American Thyroid Association. Nevertheless, experts generally agree that clinicians should attempt to identify women at risk for inadequate thyroid hormone and undertake corrective measures.



LEARNING/DEVELOPMENTAL DISABILITIES Amelia's Story

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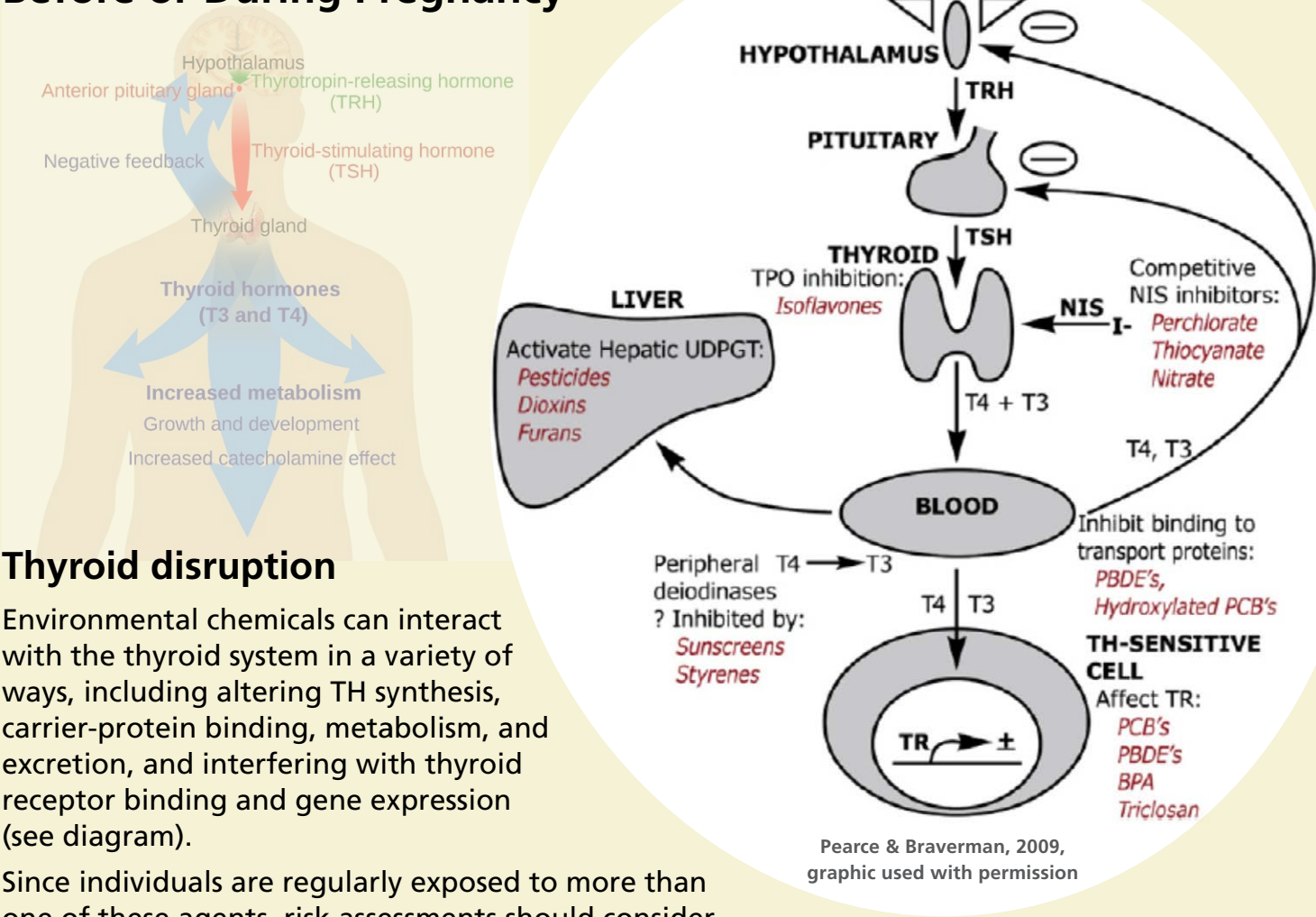
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A Rationale for Thyroid Screening

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PRENATAL HEALTHY CARE

A Rationale for Thyroid Screening Before or During Pregnancy



LEARNING/DEVELOPMENTAL DISABILITIES Amelia's Story

BRAIN DEVELOPMENT

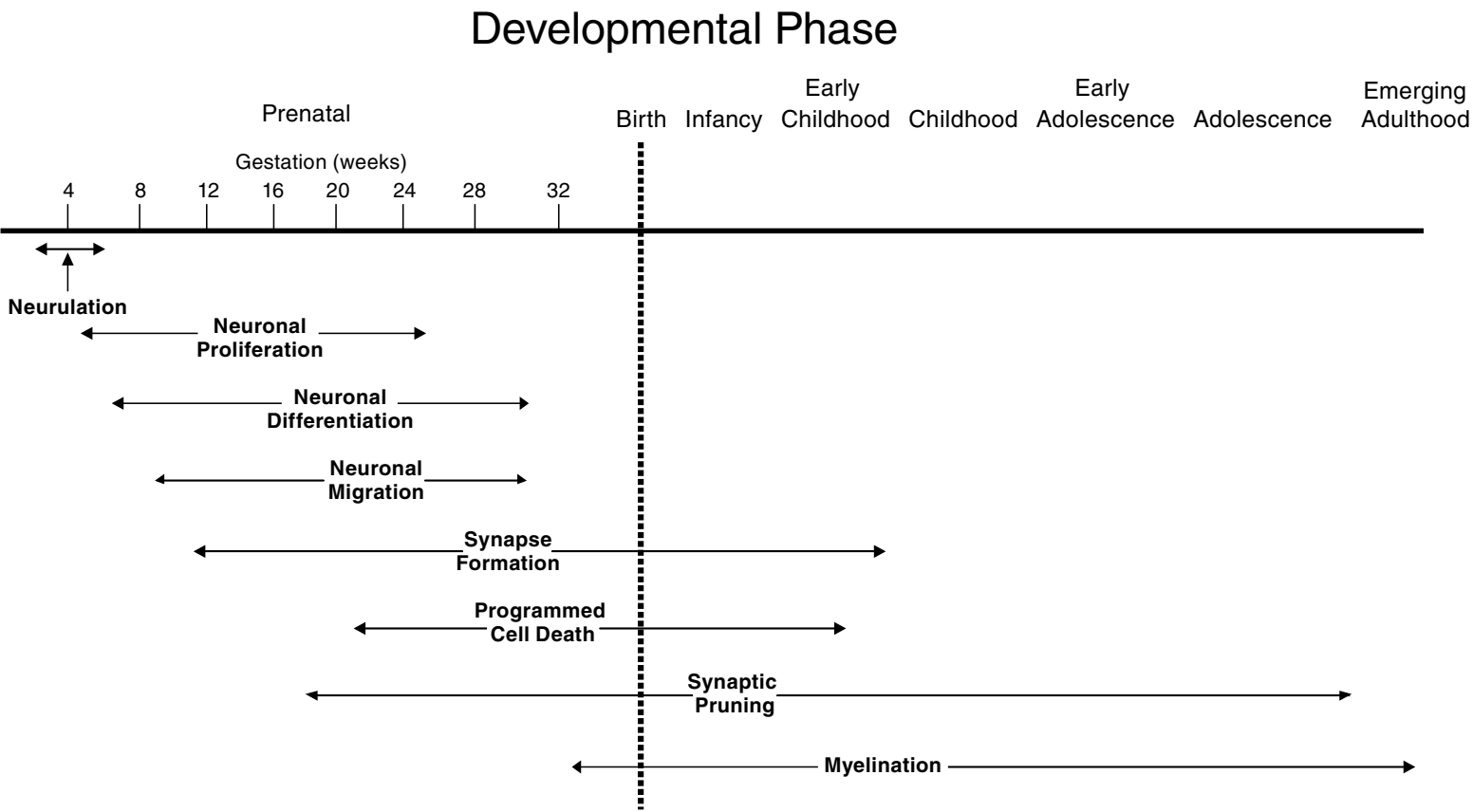
Brain development begins soon after conception and continues throughout adolescence into adulthood. It is characterized by a critical sequence of events that helps to determine brain structure and function. Each of these processes is subject to disruption by exposure to various environmental agents. Inadequate nutrition and adverse social circumstances can also impair these developmental processes.

Even brief disruptions during critical periods of early brain development can have significant downstream effects with long-lasting consequences.

The clinical manifestation of disruption from neurodevelopmental toxicants or other stressors depends on the nature of the agent as well as the size, timing, and duration of exposure.

Find out more:
Cellular events in neurodevelopment

Timeline of major events in brain development



Source: [Preventing Mental, Emotional and Behavioral Disorders Among Young People: Progress and Possibilities](#). Mary Ellen O'Connell, Thomas Boat, and Kenneth E. Warner, Eds. Natl Academies Press, Washington, DC. 2009. Graphic used with permission.

LEARNING/DEVELOPMENTAL DISABILITIES Amelia's Story

BRAIN DEVELOPMENT

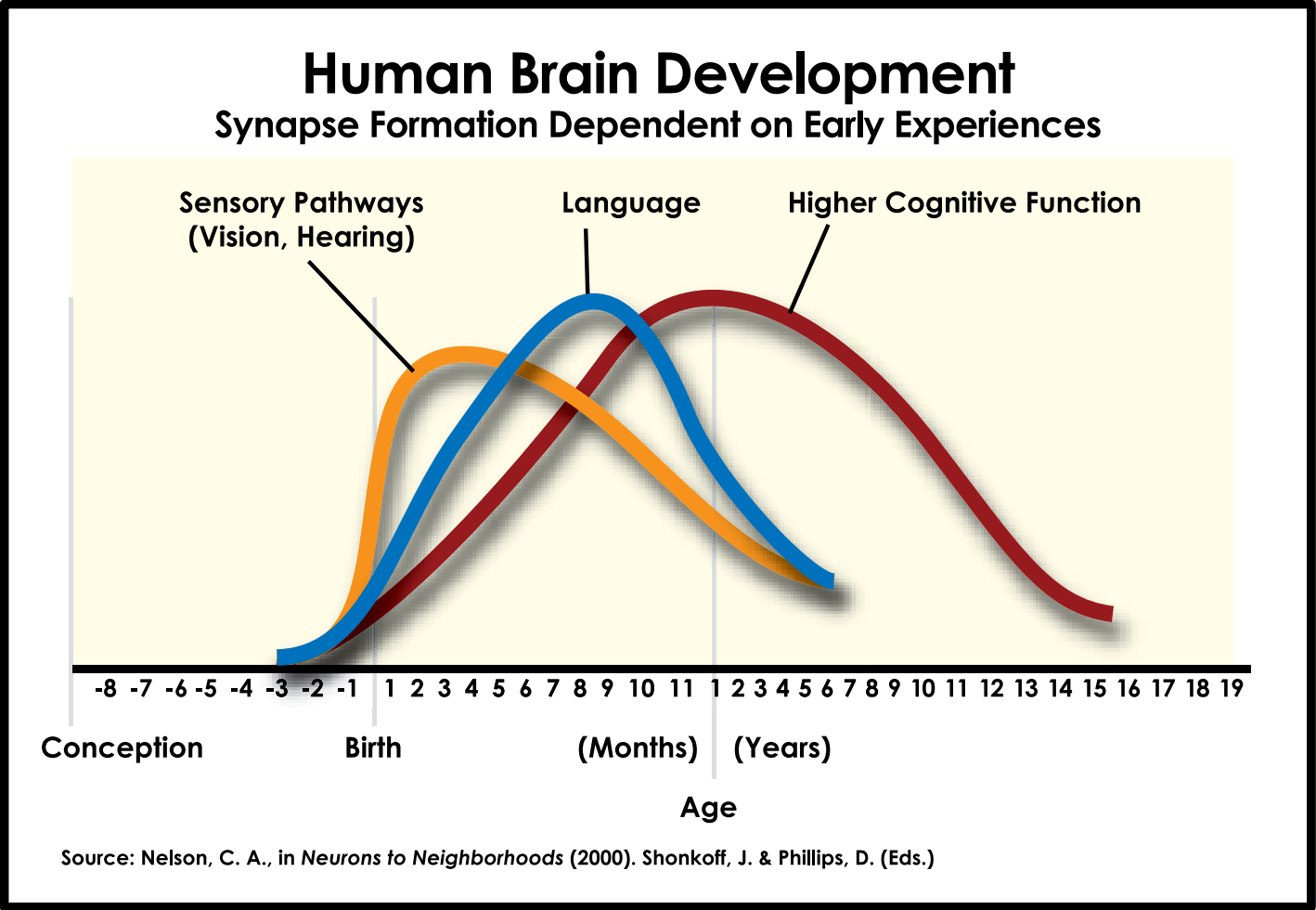
The pattern of formation of nerve connections (synapses) in the cerebral cortex is characterized by rapid proliferation and over-production of synapses, followed by a phase of synapse elimination (pruning) that reduces the number of synapses to more adult-like levels.

This process is prominent in the first years of life, although it extends to some degree into adolescence. However, different brain regions with different functions develop on different time courses.



“Core Concepts in the Science of Early Childhood Development” Harvard Univ. Center for the Developing Child

Experience-dependent synapse formation



Graphic: “A Science-Based Framework for Early Childhood Policy” Center on the Developing Child, Harvard University
Reproduced with permission.

LEARNING/DEVELOPMENTAL DISABILITIES Amelia's Story

Dr. Bradley discussed some of the ways that Gloria and Darrell could help Amelia with her learning problems and discussed eligibility that would allow support for Amelia to attend special programs.

She encouraged them by saying that it was never too late to focus on habits to promote health for the whole family, like healthy eating, exercise, avoiding toxic chemicals, and trying to deal positively with stress.

She referred them back to Mr. Richards at the school to discuss developing a school program tailored to Amelia's needs.

She gave them some booklets and brochures. Amelia's parents thought Dr. Bradley was helpful but left feeling a little overwhelmed.

Amelia was worried because she figured there was extra school work in her future.



Effect modifiers:
iron deficiency, poverty,
lead exposure.



Resources to help parents:
Learning Disabilities Association

Watch: Dr. Mark Miller describes how lead and stress affect brain functioning, and the benefits of an enriched environment. (4 min.)



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Healthy eating habits



Effect modifiers:
iron deficiency, poverty,
lead exposure.



Resources to help parents:
[Learning Disabilities Association](#)

Watch: Dr. Mark Miller describes how lead and stress affect brain functioning, and the benefits of an enriched environment. (4 min.)

Effect modifiers – Iron deficiency, poverty, lead exposure

Although Amelia has generally had good nutrition throughout her life, many children and families are not able to access nutritious food for many reasons.

For example, nutritious food may not be available or affordable, resulting in "food insecurity." According to the USDA, about 20% of US households with children suffer from food-insecurity. In half of those, only adults were food-insecure (perhaps because the adults go hungry while giving food to their children), while in half both children and adults were food-insecure.

Nutritional deficiencies can have significant adverse impacts on child development, including neurodevelopment. All nutrients are necessary for optimal brain development and growth, but some are more important than others. They include protein, iron, zinc, iodine, selenium, folate, vitamin A, choline, and polyunsaturated fatty acids.

Dietary iron deficiency with or without associated anemia is quite

common and is a risk factor for impaired cognitive development. Iron-supplemented formula, however, can adversely impact brain development in infants whose iron stores are already adequate as evidenced by high hemoglobin levels (Lozoff et al., 2012). Poverty also adversely impacts brain growth and development. The neurotoxicant lead is also a well-recognized cause of impaired neurodevelopment with adverse impacts on cognition, behavior, and attention. Lead exposure, dietary iron deficiency, and lower socioeconomic status often co-occur, and their impacts may be more than additive.

For example, the consequences of lead exposure can be accentuated by iron deficiency because lead uptake from the intestine and lead deposition in the brain increase. (Hubbs-Tait et al., 2005, Weiss et al., 2006) Similarly, while stressful life events can worsen negative impacts of poverty, nurturing caregiving can help to mitigate them.

These are examples of effect modification.

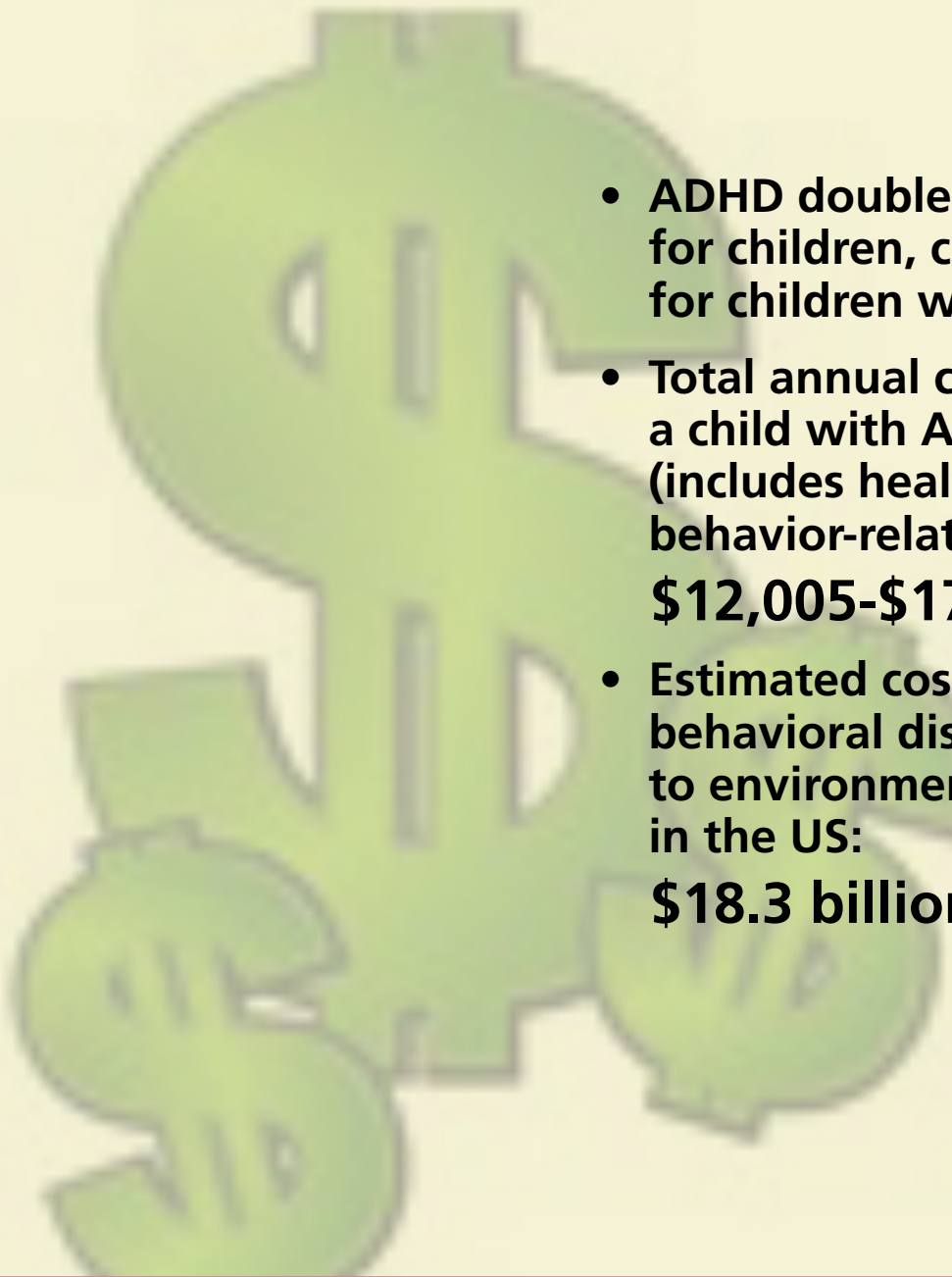
LEARNING/DEVELOPMENTAL DISABILITIES Amelia's Story

ECONOMIC COSTS

Developmental disabilities affect individuals, families, and communities and have staggering economic costs.

Effects can include:

- academic difficulties,
- employment problems,
- financial stress,
- emotional stress,
- substance abuse,
- lawbreaking , *and even*
- suicide.



- ADHD doubles health care costs for children, comparable to costs for children with asthma.
- Total annual cost-of-illness for a child with ADHD in the US (includes health-, education-, behavior-related costs):
\$12,005-\$17,458/yr.
- Estimated costs of neuro-behavioral disorders attributable to environmental pollutants in the US:
\$18.3 billion/yr.

(CDC, National Center on Birth Defects and Developmental Disabilities – ADHD Data and Statistics; Trasande & Liu, 2011)

LEARNING/DEVELOPMENTAL DISABILITIES Amelia's Story

TOXICANTS AND HEALTH

Gloria decided to look online to learn more about environmental chemicals that can contribute to learning and developmental disabilities.

She began to think of the many ways that her family might have been exposed to lead, mercury, pesticides, endocrine disruptors, solvents, air pollution and other substances that she read about.

+ Chemicals and neurodevelopmental health effects – an overview.

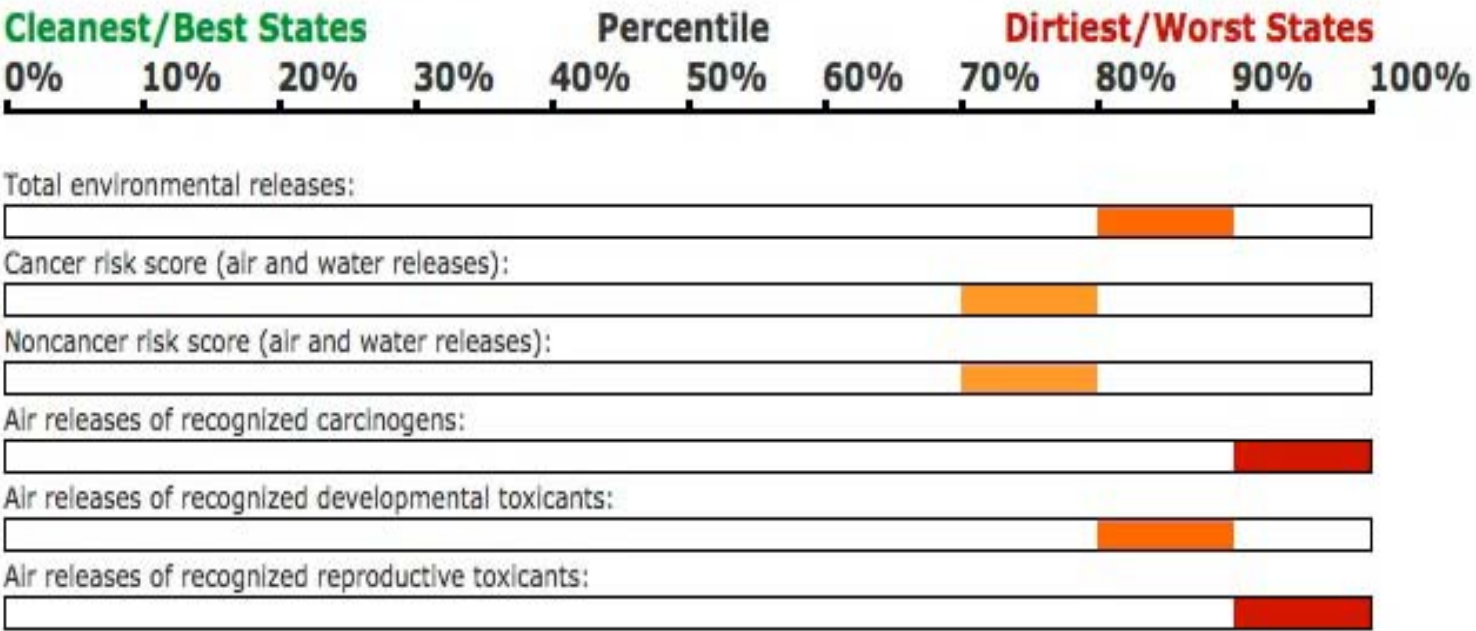
It was not difficult. Before Amelia was born her parents lived in Baton Rouge, Louisiana where Gloria worked at a petrochemical factory. At the factory she had noticed the smell of solvents nearly every day. The smells from the factory were more bothersome when Gloria was dealing with morning sickness.

Gloria and Darrell moved to their current home just as Gloria was beginning her second trimester of pregnancy.

+ [Link: Scorecard: Get an in-depth pollution report for your county, covering air, water, chemicals, and more.](#)

+ [Link: California Proposition 65 - chemicals known to cause cancer or reproductive toxicity](#)

2002 Rankings: Major Chemical Releases or Waste Generation in LOUISIANA*



See how this state ranks on other chemical release and waste management attributes tracked by Scorecard
Graphic used with permission.

LEARNING/DEVELOPMENTAL DISABILITIES Amelia's Story

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Chemicals and neurodevelopmental effects: an overview

Long-lasting, adverse neurodevelopmental (brain and central nervous sysytem) impacts of prenatal, infant, and/or childhood exposures to lead, alcohol, and methylmercury are well known. They demonstrate the vulnerability of the developing brain to neurotoxicant exposures at levels that have fewer and less severe effects in adults. In recent years, the list of environmental chemicals that can adversely impact brain development at environmentally relevant levels of exposure has grown rapidly. It includes additional metals (e.g., arsenic, manganese), various solvents, some pesticides, and a range of persistent, organic compounds that contaminate the general food supply, among others.

In a recent book, *Only One Chance: How Environmental Pollution Impairs Brain Development—and How to Protect the Brains of the Next Generation*, Dr. Philippe

Grandjean provides an updated list of 213 industrial chemicals known to be toxic to the nervous system in adults. Many of these chemicals are present not only in the workplace but also in consumer products and the general environment, resulting in exposure to the general population.

Unfortunately, most of these chemicals have not undergone developmental neurotoxicity testing in laboratory animals, nor have their impacts been examined in epidemiologic studies of developing children. As a result, our ability to estimate the contribution of environmental chemicals to adverse brain development and function is limited. Nonetheless, enough is known from studies of limited numbers of chemicals to justify more routine neurodevelopmental testing of chemicals to which the general population is likely to be exposed.

Grandjean P, Landrigan P. Neurobehavioural effects of developmental toxicity [Lancet Neurol.](#) 2014 March;(13):330-338.

LEARNING/DEVELOPMENTAL DISABILITIES Amelia’s Story

TOXICANTS AND HEALTH - AIR POLLUTION

When Darrell and Gloria moved from Baton Rouge to a smaller town in Louisiana, they chose their new home because of its affordability. The house was a nice size for the growing family, but it was on a busy street, where many trucks passed on their way to factories in surrounding towns.

Soon after the family moved to their new home, Gloria and Darrell undertook some remodeling. Darrell was very busy with his new job, and Gloria (who was pregnant with Amelia) did most of the painting and had new carpet installed.

It was not until many years after moving that Gloria learned that air pollution from traffic emissions can have adverse effects on child development. She also learned that remodeling projects can involve exposures to chemicals that can harm a developing child’s brain.



Air pollution, family stress and nutrition - synergistic effects on brain development.



LEARNING/DEVELOPMENTAL DISABILITIES Amelia's Story

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Air pollution, family stress and nutrition - synergistic effects on brain development.

Air pollution and neurodevelopment – additional impacts of family stress and sub-optimal nutrition

Exposure to higher levels of indoor and outdoor air pollution during pregnancy has an adverse impact on infant mental development (Bayley Scales of Infant Development) (Guxens et al., 2012; Friere et al., 2010; Perera et al., 2006). In one study, the effect was greater among children whose mothers reported low intakes of fruits and vegetables during pregnancy, suggesting a role for oxidative stress and beneficial effects of antioxidants. (Guxens et al., 2012)

Studies have also identified a significantly increased risk of autism spectrum disorder in children exposed to higher levels of air pollution, mostly from traffic-related sources, during gestation and early life. (Becerra, 2013; Volk, 2013; Roberts, 2013; Volk, 2014)

Except for tobacco smoke, the interactive effects of other kinds of air pollution and maternal stress on

human infant neurodevelopment have not been studied. However, a study in mice (Maternal Stress and Effects of Prenatal Air Pollution on Offspring Mental Health Outcomes in Mice; Bolton, et al.) "hypothesized that the addition of maternal stress to the impact of prenatal air pollution exposure would act synergistically in offspring to impair mental health outcomes, compared with the effects of either exposure alone."

It concluded "that maternal stress during late gestation increases the susceptibility of offspring—particularly males—to the deleterious [negative] effects of prenatal air pollutant exposure, which may be due to a synergism of these factors acting on innate immune recognition genes and downstream neuroinflammatory cascades within the developing brain."

LEARNING/DEVELOPMENTAL DISABILITIES Amelia's Story

TOXICANTS AND HEALTH - PESTICIDES

Gloria recalled that they had the new house sprayed for pests after receiving promotional materials in the mail soon after Amelia was born. Although they do not use pesticides in their home or outside any longer, their neighbors regularly spray their lawns with pesticides. She later learned that pesticides, some of which are neurotoxic and can impair brain development, are widely used.

Gloria also thought about Darrell's job as a carpenter and how he works with a lot of chemicals.

She was amazed at how many exposures to toxic chemicals her family had experienced that she had never thought about before!



Prevention Strategies:
Integrated Pest Management



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Prevention Strategies: Integrated Pest Management

Integrated Pest Management: Reducing Use of Pesticides in Homes, Schools and Other Buildings

Integrated pest management (IPM) is an approach to pest control that begins with avoiding the use of pesticides at all unless absolutely necessary. Many non-pesticide techniques can help to keep unwanted pests, like insects and rodents, from your home, lawn and garden, as well as public buildings and spaces.

If pesticides must be employed, preference is given to the least toxic alternatives. According to the EPA, IPM is "an effective and environmentally sensitive approach to pest management that relies on a combination of common-sense practices. IPM programs use current, comprehensive information on the life cycles of pests and their interaction with the environment. This information, in combination with available pest control methods, is used to manage pest damage by the most economical means, and with the least possible hazard to



people, property, and the environment. The IPM approach can be applied to both agricultural and non-agricultural settings, such as the home, garden, and workplace."



More Resources:

- Pesticides: [EPA - Integrated Pest Management](#)
- Bio-Integral Resource Center ([BIRC](#))
- Pesticide Action Network ([PANNA](#))

Drawing courtesy of the Bio-Integral Resource Center, artist Diane Kuhn

LEARNING/DEVELOPMENTAL DISABILITIES Amelia's Story

TOXICANTS AND HEALTH - MERCURY

Amelia liked to go fishing with her father, who was an avid fisherman. For several years they had enjoyed catching and eating a variety of fish from the local lake.

Gloria remembered Darrell coming home from fishing one day and telling her about a posted fish advisory, warning fisherman not to eat the fish due to contamination from mercury.

The advisory included a state web site where Gloria was able to learn more. She read that mercury, like lead, is a heavy metal that disrupts brain development. She also read about the health benefits of eating uncontaminated fish and about nutritious fish with low contaminant levels available in local supermarkets.

Gloria searched for an alternative place where Darrell and Amelia could continue to enjoy fishing and from which the family could also eat the fish they caught. She found a nearby river where the fish were not contaminated. Amelia was happy that she and her dad could still fish together.



Link: EPA fish advisories



Link: Pediatric Environmental Health Toolkit animation on mercury in fish and children's health



Illustration © Stephen Burdick Design



Photos from EPA: <http://water.epa.gov/scitech/swguidance/fishshellfish/fishadvisories/index.cfm>, used with permission.

LEARNING/DEVELOPMENTAL DISABILITIES Amelia’s Story

TOXICANTS AND HEALTH - LEAD

Finally, Gloria thought about the older houses they had lived in and the lead paint problems. They had been careful to remove the paint properly, but maybe they had not removed it all.

+ Lead removal from gasoline and other products – a public health success story

Luckily, she didn’t have to worry about lead in gasoline anymore. She read about how that was a public health success story and how it had reduced blood lead levels in children.

+ Lead - developmental effects

+ Pediatric Environmental Health Toolkit animation on lead exposure and children’s health



Link: CDC: Primary prevention of lead exposure

Where is the Lead?

- Formerly used in house paint, gasoline, water pipes, solder in food cans.
- Currently found in imported pottery, some cosmetics, some traditional (indigenous or folk) medicine, older water pipes, older house paint, some types of industrial paint, aviation fuel, car batteries, and bullets.
- Most common sources of exposures: older paint, dust, and water pipes.



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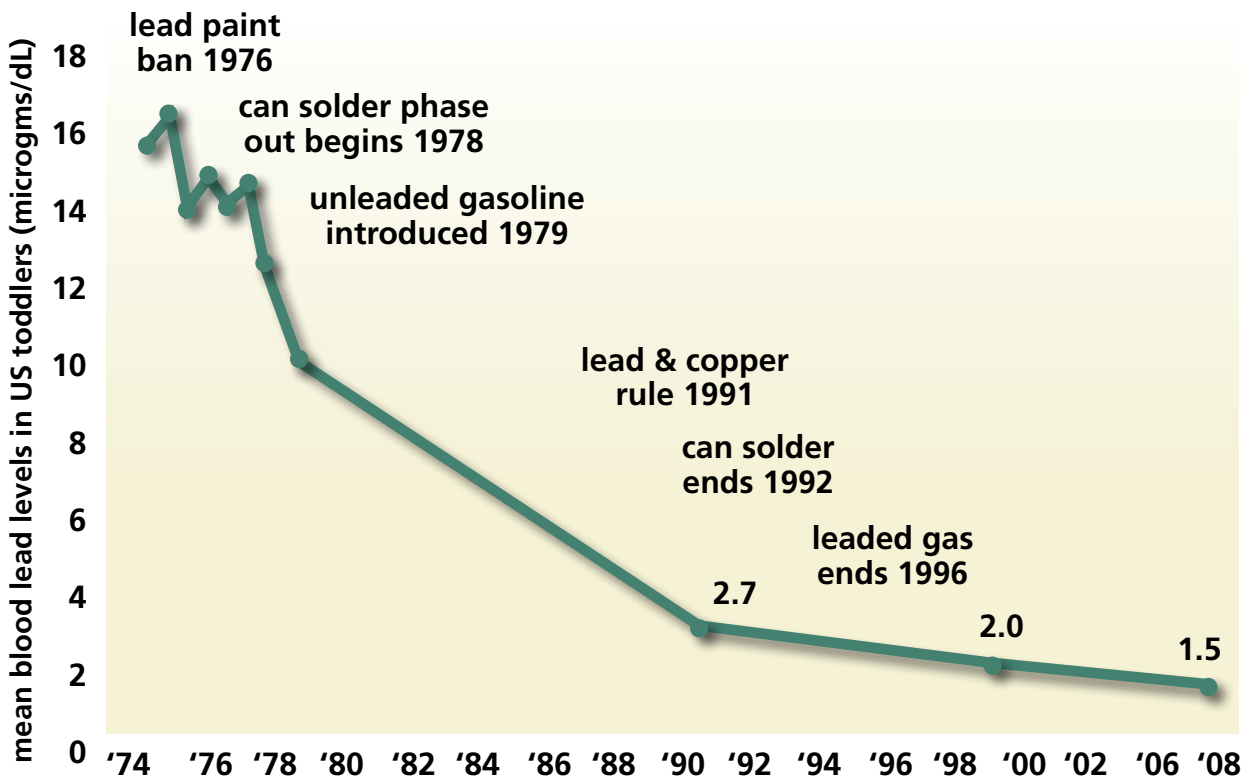
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Lead removal – a public health success story

This graph shows declining mean blood lead levels in US toddlers from 16 to 1.5 microgms/dL since the 1970s, corresponding to public health interventions removing lead from various products, including paint and gasoline. This is an important public health success story. It is an example of what we can do

when we prioritize a problem, and address it upstream with policy actions, rather than expecting to solve the problem through individual behavior changes. In this case, some products were reformulated and lead was completely eliminated rather than relying exclusively on attempts to control exposures from lead-containing materials.

Mean blood lead levels in toddlers in the US population 1976-2008



Today elevated blood lead levels remain a problem for a significant number of children, particularly in older housing and urban environments, but the population-wide exposures resulting from air releases have been substantially reduced by removal of lead from gasoline and other products.

LEARNING/DEVELOPMENTAL DISABILITIES

Amelia's Story

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Cognitive and Behavioral Traits Associated with Lead

Traits that Tend to Increase

- Hyperactivity
- Impulsivity
- Distractibility
- Conduct problems
- Difficulty with instructions
- Aggressiveness
- Antisocial behaviors
- Getting off-task

Traits that Tend to Decrease

- Executive function
- Attention/vigilance
- Social skills
- Fine motor skills
- Visual motor coordination
- Academic skills (reading, math, spelling, pattern recognition, and word recognition)

Hearing may be impacted even at very low levels. In adolescents, >2mcg/dl compared to <1mcg/dl lead levels are associated with twice the rate of 15dB high frequency hearing loss. High frequency hearing loss may reduce the ability to understand speech and thus may impact many of the traits noted above.

LEARNING/DEVELOPMENTAL DISABILITIES Amelia's Story

TOXICANTS AND HEALTH

Gloria also wondered about other chemicals that she was exposed to when she was pregnant with Amelia, including second-hand tobacco smoke and solvents at the factory where she worked before they moved.

Amelia had thrived in her daycare. She seemed happy there and learned some of the basic skills she needed for kindergarten. Amelia's daycare was a good choice, but Gloria thought about hazardous chemicals Amelia might have been exposed to when she was there.

These include formaldehyde emitted from certain furnishings and building materials like cabinets, hazardous chemicals in carpeting, phthalates in flexible plastic toys and vinyl flooring, bleach and other cleaning solutions, and air pollutants from indoor natural gas combustion.



More information:

Benefits of early childhood education and policies:

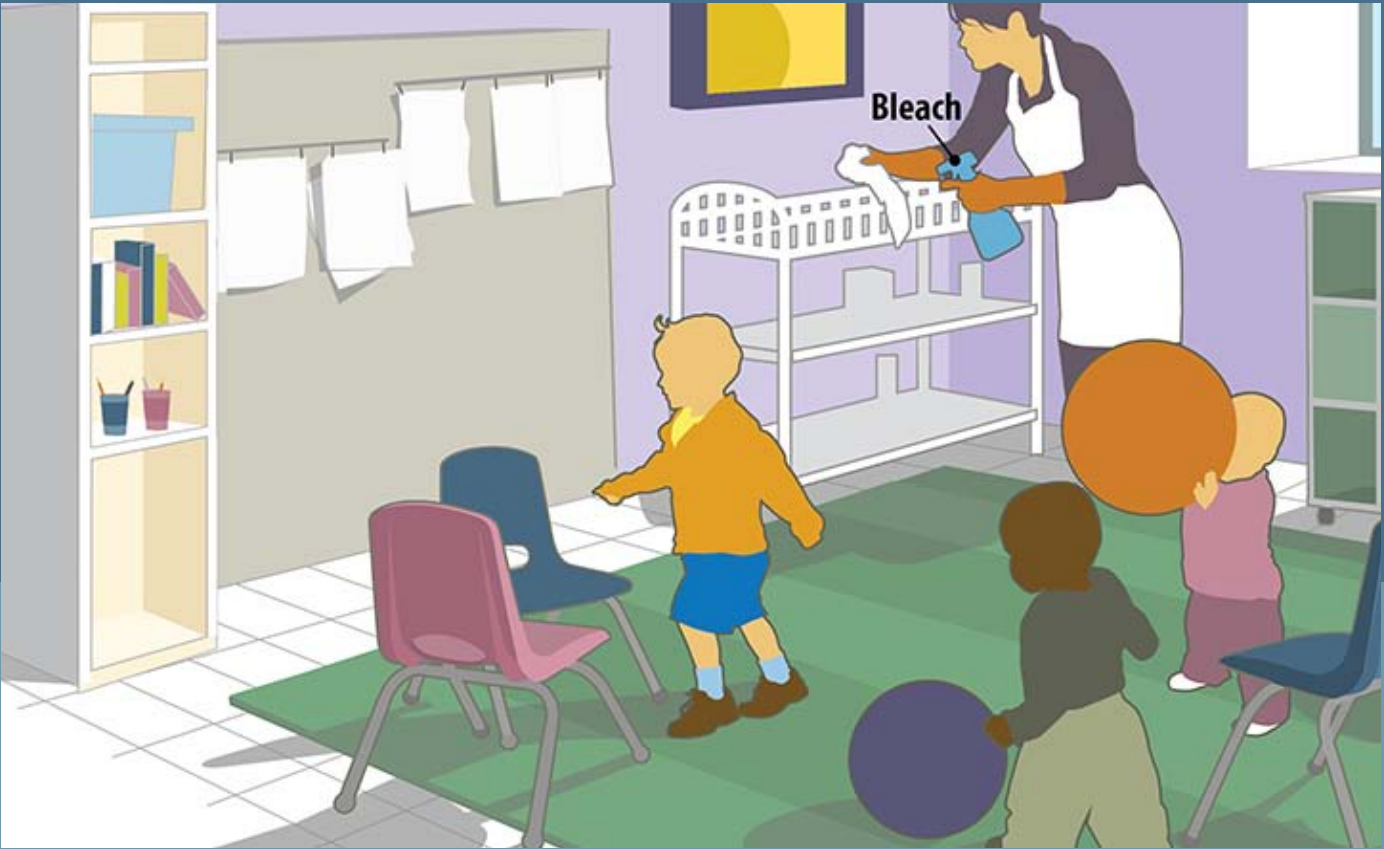
- [Benefits of early childhood education](#)
- [Early childhood policy](#)

Preventing/reducing toxic chemical exposures in child care settings:

- [Eco-Healthy Child Care](#)
- [Integrated pest management curriculum and Green cleaning toolkit](#)



Watch: Watch Dr. Mark Miller describes the benefits of early childhood education (1.42 min.)



LEARNING/DEVELOPMENTAL DISABILITIES Amelia's Story

TOXICANTS AND COMMUNITY HEALTH

Gloria and Darrell became worried that there might not be much they could do about reducing the family's ongoing exposures to hazardous chemicals.

Gloria decided to call up a friend who was involved in the community to see if she knew more about community exposures to toxic chemicals.

Her friend told her there was a local group called "Clean and Green" that was working on reducing the use of chemicals in their town and other issues relating to the environment. She said they had received information from other communities facing similar issues.

Gloria heard the term "environmental justice" for the first time.



Key Concept:
Environmental Justice



Watch: Representative Donna Christensen from the U.S. Virgin islands speak about EJ from a physician's perspective. (2.47 min.)



Watch: Peggy Shepard of WE ACT for Environmental Justice addresses "sacrifice zones" at TEDxHarlem (8 min.)



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Watch: Representative Donna Christensen from the U.S. Virgin islands speak about EJ from a physician's perspective. (2.47 min.)



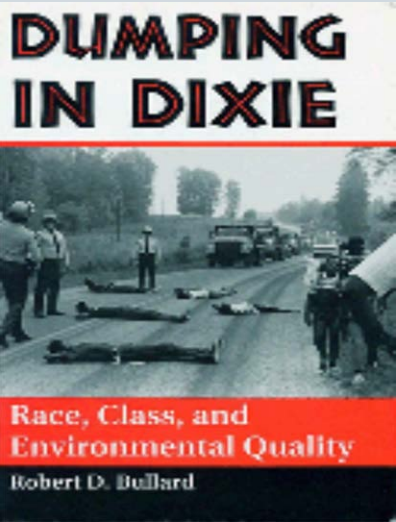
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KEY CONCEPT: Environmental Justice

The modern "environmental justice" or "EJ" movement emerged in 1982 as a result of demonstrations by the residents of Warren County, North Carolina against the dumping of contaminated wastes in their community. Hundreds in this predominantly black, lower income community lay their bodies across the road and were arrested in protest of the trucks' delivery of PCB (polychlorinated biphenyls) contaminated waste to a new dump. Their actions sparked national attention to the issue of race, class, and toxic exposures and a movement of solidarity among civil rights and environmental activists.

The United Church of Christ's Commission for Racial Justice landmark 1987 publication, *Toxic Wastes and Race in the United States: A National Report on the Racial and Social Economic Characteristics of Communities of Hazardous Waste Sites*, identified a national pattern of hazardous waste landfills disproportionately located in

low income and communities of color in the United States, further catalyzing the national movement for environmental justice. Robert D. Bullard, author of *Dumping in Dixie*, was a leader in this movement.



According to African American Voices in Congress, the origins of the EJ movement may be traced even further back to the Civil Rights Movement of the 1960s. "Low income communities of color emerged as strong activists against what they viewed as environmental attacks on their civil rights."

The U.S. Environmental Protection Agency defines Environmental Justice as "the fair treatment and meaningful involvement of all people regardless of race, color, national origin, or income with respect to the development, implementation, and enforcement of environmental laws, regulations, and policies."



Find out more: Toxic Wastes and Race at Twenty: 1987-2007 (pdf)

Read the latest goals for the EPA's national EJ program, "Plan EJ 2014"

Browse maps: Interactive Global Atlas of Environmental Justice

"Dumping in Dixie"
photo by Jenny Labalme,
used with permission.

LEARNING/DEVELOPMENTAL DISABILITIES Amelia's Story

TOXICANTS AND COMMUNITY HEALTH

Gloria started attending meetings of Clean and Green. She learned a lot about the many sources of pollution in the community, in the air, in the water, and on land. The group had information about environmental contamination and community health studies. They were working with scientists from a nearby university who were considering doing a health study, as there seemed to be higher than expected levels locally of several diseases, including cancer, and concerns that there were excessive numbers of children being born with birth defects.



Chemical regulations



Community Health Studies



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Chemical regulations



Community Health Studies

Chemical Regulations

Federal regulatory laws addressing chemicals have evolved over decades, although some have been more effective than others. The Environmental Protection Agency (EPA) is authorized to regulate pesticides under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA); other industrial chemicals under the Toxic Substances Control Act (TSCA); air pollutants under the Clean Air Act; and water pollutants under the Safe Drinking Water and the Clean Water Acts. Pharmaceuticals, chemicals in food, and cosmetics are under the regulatory authority of the Food and Drug Administration (FDA).

Over 80,000 chemicals are currently in the TSCA inventory. Among its many weaknesses, when TSCA was first passed in 1976, tens of thousands of chemicals on the market were grandfathered and remain in use today with very limited safety data. Moreover, chemical manufacturers are not required to evaluate the safety of new chemicals before notifying the US EPA of their intent to manufacture and market them. And the EPA has very limited authority to require pre-market safety testing. As a result, thousands of chemicals known to be harmful or for which safety data are largely missing are present in



consumer products and the general environment. Studies of human blood, urine, hair, or other tissues show that exposures to hundreds of these chemicals are widespread in the general population. Several versions of legislation to reform TSCA have been introduced in Congress in the past several years, but none has been adopted. Some states have enacted laws intended to restrict, phase out, or label certain hazardous chemicals. They include California's Proposition 65, which requires warning labels on products containing chemicals known to cause cancer or reproductive disorders, and also prohibits discharge of these chemicals into drinking water sources. Washington state has adopted a plan to phase out of commerce certain persistent, bioaccumulative, toxic chemicals. California has also enacted a green chemistry law that will slowly require safer alternatives for a few chemicals in consumer products.

Links for more info:



[Safer Chemicals Healthy Families](#)



EPA: [Laws and Executive Orders](#)

LEARNING/DEVELOPMENTAL DISABILITIES Amelia's Story

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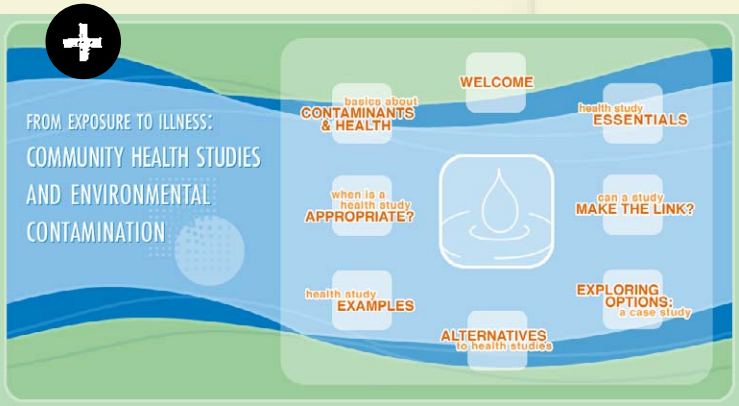
Chemical regulations



Community Health Studies

Community Health Studies and the Environment

Citizens concerned about pollution in their community, or about apparent high levels of diseases like cancer, sometimes turn to scientists and health experts to ask them to study their town to see if there are connections between pollution and their health. These studies are difficult and expensive, and citizens are often disappointed in the results.



Find out why with these two resources.

HEALTH STUDIES GUIDE: Boston University Superfund Research Project

A guide for making informed decisions, written to assist community groups and individuals who think that some form of environmental health investigation or health study may be useful or necessary in their community.

FROM EXPOSURE TO ILLNESS: Community Health Studies and Environmental Contamination

The Environmental Health Investigations Branch, California Department of Public Health

Created as a means to share the experience and perspective of public health staff dedicated to studying links between environmental exposure to chemicals and health effects in California communities.



RESEARCH PROJECTS

COMMUNITY ENGAGEMENT CORE

RESEARCH TRANSLATION CORE

BIOINFORMATICS CORE

TRAINING CORE

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- ASK THE RESEARCHER
- OPEN SCIENCE

Health Studies Guide

IS A HEALTH STUDY THE ANSWER FOR YOUR COMMUNITY?

A GUIDE FOR MAKING INFORMED DECISIONS

For decades, environmental health scientists at Boston University have worked with community groups to address environmental health problems. We wrote the Health Studies Guide to assist community groups and individuals who think that some form of environmental health investigation or health study may be useful or necessary in their community. Readers of this guide may have concerns about drinking water contamination, or the relationship between emissions from a power plant and asthma in their community. People may suspect that a certain disease in their community, such as lupus, has an environmental cause or trigger. All of these are reasons for wanting a health study. Hopefully this Guide will help readers think this through.

LEARNING/DEVELOPMENTAL DISABILITIES Amelia's Story

The next time Amelia went to her new family practice for a checkup, Gloria told them about Amelia's diagnosis of a learning disability.

Her nurse practitioner, Robert, suggested some things to do that could help Amelia. They included making sure she got enough exercise, adequate sleep, healthy and nutritious foods, and encouragement to spend time outdoors in green space or natural surroundings, such as in the park, because that could help her with her attention and focus.



[Link](#): Animation on "Healthy Food and Exercise" – UCSF Pediatric Environmental Health Specialty Unit.



LEARNING/DEVELOPMENTAL DISABILITIES Amelia's Story

Amelia's parents both became involved in the community group. Over the years they had some major successes, including getting the truck route that used to go by their house changed to a less residential area. They knew that would promote the health of their entire family and community.

The education plan that the school, the developmental pediatrician, and Amelia's parents put together included learning strategies for reading and math that Amelia found helpful.

Amelia still struggles to some extent with particular tasks in school and can sometimes become frustrated in social situations, but she knows she has the support of her family and friends and that means a lot.

Her parents know they are doing everything they can to improve the health of their family.



LEARNING/DEVELOPMENTAL DISABILITIES Amelia's Story

Throughout the pages of Amelia's story we've seen a wide range of interacting factors across her lifespan that may have increased her risk for developmental disabilities.

These include exposure to toxic chemicals and community stressors, diet, socioeconomics, genetics, and gene-environment interactions.

We have also seen factors that can increase resilience and enhance healthy development, such as parental love and attention, childhood enrichment activities, and early childhood education.

Although Amelia's story is fictional, children throughout our country face a similar range of issues and circumstances. Developmental disabilities are widespread. It is critical that we consider the multiple environmental influences associated with increased risks of developmental disabilities, and their long term consequences for children like Amelia, when we design prevention strategies and treatments to address them.

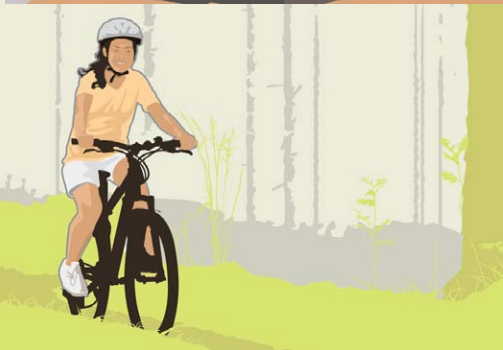
Continue to [Final Thoughts](#) >



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A wide range of interacting factors across Amelia's lifespan may increase the risk for developmental disabilities



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SOME FINAL THOUGHTS

COMMON THEMES

Although the fictional narratives in *A Story of Health* describe the lives of people with different diseases, common themes resonate. They include:

- Important environmental influences come from the natural, chemical, food, built, and social environments.
- Although there are exceptions, most diseases as well as good health are the result of complex interactions among multiple environmental influences and genetics.
- Early-life experiences, particularly during critical windows of development, can have profound beneficial or detrimental lifelong effects, even into elder years.
- Preventing disease and promoting health require actions and commitments from the individual, family, community and society, as they are all interconnected.



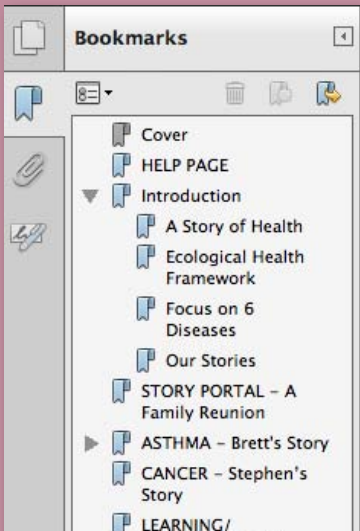
- Common themes in stories
- Additional Resources
- Register for Continuing Education Credits



We'd love to hear from you. Give us your feedback on *A Story of Health*. [Click here!](#)

Resources

We have linked to many useful resources in each story relevant to a wide range of audiences, including clinicians. To quickly access resources on specific topics in each story, use the **Bookmarks** toolbar on the left (which you can open or close), or return to the [Help page](#) for more details on other eBook features.



Additional resources to help prevent disease and promote health:

Portal to Science Resources: Hundreds of additional resources on environmental health including organizations, publications, videos and more.

Pediatric Environmental Health Toolkit: Materials for health care providers and patients in English and Spanish.

Out of Harm's Way: Preventing Toxic Threats to Child Development: Fact Sheets in English and Spanish.

Approaches to Healthy Living: A 4-page guide on how to avoid toxicants, eat healthier, reduce stress.

Healthy Aging: The Way Forward: An ecological approach to policy level interventions for healthy aging across the lifespan.

Continuing Education

Register for Continuing Education (CE) credits for *A Story of Health* for a variety of health professions. Free credits are offered by the Centers for Disease Control and Prevention/Agency for Toxic Substances and Disease Registry [at this link](#).



Another free CE course on environmental health offered by the CDC/ATSDR is the **Pediatric Environmental Health Toolkit** online course.

REFERENCES: Learning/Developmental Disabilities

Asthma

Childhood
Leukemia

Learning/
Developmental
Disabilities

Diabetes

Infertility

Cognitive Decline

Developmental and Learning Disabilities Case References and Resources by Topic

Note: there are many topic overlaps

ADHD

Nussbaum N. ADHD and female-specific concerns: a review of the literature and clinical implications. Journal of Attention Disorders. 2012 Feb; vol. 16 no. 2 87-100

Pastor PN, Reuben CA. Diagnosed attention deficit hyperactivity disorder and learning disability: United States, 2004-2006. Vital Health Stat 2008. 10(237)

Semrud-Clikeman M, Bledsoe J.Updates on attention-deficit/hyperactivity disorder and learning disorders. Curr Psychiatry Rep. 2011 Oct;13(5):364-73. doi: 10.1007/s11920-011-0211-5. Review

Sexton CC, Gelhorn HL, Bell JA, Classi PM. The co-occurrence of reading disorder and ADHD: epidemiology, treatment, psychosocial impact, and economic burden. J Learn Disabil. 2012 Nov-Dec;45(6):538-64. doi: 10.1177/0022219411407772. Epub 2011 Jul 14

Skogli EW, Teicher MH, Andersen PN, Hovik KT, Oie M. ADHD in girls and boys - gender differences in co-existing symptoms and executive function measures. BMC Psychiatry. 2013 Nov 9;13:298

Thapar A, Langley K, Muñoz-Solomando A. The ADHD debate: being mindful of complexity and wary of reductionist explanations and polarization: Commentary on ‘A social relational critique of the biomedical definition and treatment of ADHD; ethical, practical and political implications’. J Fam Ther. 2013 May;35(2):219-223

Thapar A, Cooper M, Jeffries R, Stergiakouli E. What causes attention deficit hyperactivity disorder? Arch Dis Child. 2012;97:260–265

United States Environmental Protection Agency. America’s children and the environment – third edition. Report number EPA 240 R-13-001, 2013



Autism

Hallmayer J, Cleveland S, Torres A, Phillips J, et al. Genetic heritability and shared environmental factors among twin pairs with autism. Arch Gen Psychiatry. 2011;68(11):1095-1102

Sandin S, Lichtenstein P, Kuja-Halkola R, Larsson H, et al. The familial risk of autism. JAMA. 2014;311(17):177-1777

Schmidt RJ, Tancredi DJ, Ozonoff S, et al. Maternal periconceptional folic acid intake and risk of autism spectrum disorders and developmental delay in the CHARGE (Childhood Autism Risks from Genetics and Environment) case-control study. Am J Clin Nutr 2012;96:80–9.

Surén P, Roth C, Bresnahan M, et al. Association between maternal use of folic acid supplements and risk of autism spectrum disorders in children. JAMA. 2013 Feb 13;309(6):570-7.

Chemical exposures and neurodevelopment – general

Braun JM, Kahn RS, Froehlich T, Auinger P, Lanphear BP. Exposures to environmental toxicants and attention deficit hyperactivity disorder in U.S. children. Environ Health Perspect. 2006 Dec;114(12):1904-9

Ekanayake R, Miller M, Marty, M. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency. Report to the Legislature, Children’s Environmental Health Program. February 2014

Grandjean P. Only one chance: How environmental pollution impairs brain development—and how to protect the brains of the next generation. Oxford Univ Press; New York, 2013

Grandjean P, Landrigan P. Neurobehavioural effects of developmental toxicity Lancet Neurol. 2014 March;(13):330-338

Hubbs-Tait L, Nation J, Krebs, N, Bellinger D. Neurotoxicants, micronutrients, and social environments: Individual and combined effects on children’s development. Psychological Sci in the Public Interest. 2005; 6(3): 57-121

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References

Julvez J, Grandjean P. Neurodevelopmental toxicity risks due to occupational exposure to industrial chemicals during pregnancy. Ind Health. 2009 Oct;47(5):459-68

Koger SM, Schettler T, Weiss B. Environmental toxicants and developmental disabilities: a challenge for psychologists. Amer Psychol. 2005 April; 60 (3), 243-255

Schettler T. Toxic threats to neurologic development of children. Environ Health Perspect. Dec 2001; 109(Suppl 6): 813–816

Schettler T, Stein J, Valenti M, Wallinga D. In Harm’s Way: Toxic Threats to Child Development. January 2001. Greater Boston Physicians for Social Responsibility and Clean Water Fund

Stein J, Schettler T, Wallinga D. Valenti M. In harm’s way: toxic threats to child development. J Dev Behav Pediatr. 2002 Feb;23(1 Suppl):S13-22



Chemical exposures and neurodevelopment – Specific Pollutants

Air pollution, air pollution and stress

Anthopolos R, Edwards S, Mikranda M. Effects of maternal prenatal smoking and birth outcomes extending into the normal range on academic performance in fourth grade in North Carolina, USA. Paediatr Perinat Epidemiol. 2013 Nov;27(6):564-74. doi: 10.1111/ppe.12081. Epub 2013 Aug 25

Becerra T, Wilhelm M, Olsen J, Cockburn M, Ritz B. Ambient air pollution and autism in Los Angeles county, California. Environ Health Perspect. 2013; 121(3):380-386

Bolton JL, Huff NC, Smith SH, Mason SN, Foster WM, Auten RL, Bilbo SD. Maternal stress and effects of prenatal air pollution on offspring mental health outcomes in mice. Environmental Health Perspectives. 2103 Sept; Volume 121:9

Bradman A. Air pollution and contaminants at child-care and preschool facilities in California. California Environmental Protection Agency Air Resources Board. Fact Sheet. April 2012

Chen R, Clifford A, Lang L, Anstey KJ. Is exposure to secondhand smoke associated with cognitive parameters of children and adolescents?-a systematic literature review. Ann Epidemiol. 2013 Oct;23(10):652-61

Freire C, Ramos R, Puertas R, Lopez-Espinosa MJ, Julvez J, Aguilera I, Cruz F, Fernandez MF, Sunyer J, Olea N. Association of traffic-related air pollution with cognitive development in children. J Epidemiol Community Health. 2010 Mar;64(3):223-8

Guxens M, Aguilera I, Ballester F, Estarlich M, Fernández-Somoano A, Lertxundi A, Lertxundi N, Mendez MA, Tardón A, Vrijheid M, Sunyer J, INMA (Infancia y Medio Ambiente) Project. Prenatal exposure to residential air pollution and infant mental development: modulation by antioxidants and detoxification factors. Environ Health Perspect. 2012 Jan;120(1):144-9

Herrmann M, King K, Weitzman M. Prenatal tobacco smoke and postnatal secondhand smoke exposure and child neurodevelopment. Curr Opin Pediatr. 2008 Apr;20(2):184-90

Perera FP, Rauh V, Whyatt RM, Tsai WY, Tang D, Diaz D, Hoepner L, Barr D, Tu YH, Camann D, Kinney P. Effect of prenatal exposure to airborne polycyclic aromatic hydrocarbons on neurodevelopment in the first 3 years of life among inner-city children. Environ Health Perspect. 2006 Aug;114(8):1287-92

Rauh VA, Whyatt RM, Garfinkel R, Andrews H, Hoepner L, Reyes A, Diaz D, Camann D, Perera FP. Developmental effects of exposure to environmental tobacco smoke and material hardship among inner-city children. Neurotoxicol Teratol. 2004 May-June;26(3):373-85

Roberts A, Lyall K, Hart J, Laden F, et al. Perinatal air pollutant exposures and autism spectrum disorder in the children of Nurses’ Health Study II participants. Environ Health Perspect. 2013; 121(8): 978-984

Volk H, Kerin T, Lurmann F, Hertz-Picciotto I, McConnell R, Campbell D. Autism spectrum disorder: interaction of air pollution with the MET receptor tyrosine kinase gene. Epidemiology. 2014; 25(1):44-47

Volk H, Lurmann F, Penfold B, Hertz-Picciotto I, McConnell R. Traffic-related air pollution, particulate matter, and autism. JAMA Psychiatry. 2013; 70(1):71-77

Alcohol

O’Leary C, Taylor C, Zubrick S, et al. Prenatal alcohol exposure and educational achievement in children aged 8-9 years. Pediatrics. 2013 Aug;132(2):e468-75

Lead

Fergusson DM and Horwood. The effects of lead levels on the growth of word recognition in middle childhood. Intern J Epidemiol. 1993 Oct;22:891-897

Munoz H, Romiew I, Palazuelos E, et al. Blood lead levels and neurobehavioral development among children living in Mexico City. Arch Environ Health. 1993 May-June;48(3):132-139.

Needleman HL, Reiss JA, Tobin MJ, et al. Bone lead levels and delinquent behavior. JAMA. 1996 Feb 7; 275:363-369



Rice DC. Developmental lead exposure: neurobehavioral consequences. In Slikker W. and Chang LW (ed): Handbook of developmental neurotoxicology. San Diego, CA: Academic Press, 1998, p 544

Silva PA, Hughes P, Williams S, et al. Blood lead, intelligence, reading attainment and behaviour in eleven year old children in Dunedin, New Zealand. J Child Psychol Psychiatry. 1988 Jan;29(1):43-52

Thomson GO, Raab GM, Hepburn WS, et al. Blood-lead levels and children’s behaviour – results from the Edinburgh lead study. J Child Psychol Psychiatry. 1989 July;30(4):515-528, 1989

Tuthill RW. Hair lead levels related to children’s classroom attention-deficit disorder. Arch Environ Health. 1996 May-June;51:214-220

Winneke G, Kramer U, Brockhaus A, et al. Neuropsychological studies in children with elevated tooth-lead concentrations. II. Extended study. Int Arch Occup Environ Health. 1983; 51(3):231-252

Winneke G, Kramer U. Neuropsychological effects of lead in children: interactions with social background variables. Neuropsychobiology 1984; 11(3):195-202

Yule W, Urbanowicz MA, et al. Teachers’ ratings of children’s behavior in relation to blood lead levels. Br J Dev Psych. 1984;2(295)

Yule W. The relationship between blood lead concentration, intelligence, and attainment. Dev Med Child Neurol. 1981; 23:567-576

continued >

REFERENCES: Learning/Developmental Disabilities, continued

Asthma

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Mercury

National Research Council. [Toxicological effects of methylmercury](#). Washington, DC: The National Academies Press, 2000

Pesticides

Eskenazi B, Huen K, Marks A, et al. PON1 and neurodevelopment in children from the CHAMACOS study exposed to organophosphate pesticides in utero. [Environ Health Perspect](#). 2011;118(12):1775-1781

Horton MK, Rundle A, Camann DE, Boyd Barr D, Rauh VA, Whyatt RM. Impact of prenatal exposure to piperonyl butoxide and permethrin on 36-month neurodevelopment. [Pediatrics](#). 2011 Mar;127(3):e699-706

Levin E, Slotkin T. Research brief 230: [Combined exposure to glucocorticoids and chlorpyrifos influences neurobehavioral development](#), NIEHS Superfund Research Program. Jan 2014

Muñoz-Quezada MT, Lucero BA, Barr DB, Steenland K, et al. Neurodevelopmental effects in children associated with exposure to organophosphate pesticides: A systematic review. [Neurotoxicology](#). 2013 Dec;39:158-68

Potera C. Newly discovered mechanism for chlorpyrifos effects on neurodevelopment. [Environ Health Perspect](#). 2012 Jul;120(7):a270-1

Rauh V, Perera F, Horton M, et al. Brain abnormalities in children exposed prenatally to a common organophosphate pesticide. [Proc Natl Acad Sci USA](#). 2102; 109(20):7871-7876

Rauh V, Arunajadai S, Horton M, et al. Seven-year neurodevelopmental scores and prenatal exposure to chlorpyrifos, a common agricultural pesticide. [Environ Health Perspect](#). 2011;119(8):1196-1201

Roberts JR, Karr CJ; Council On Environmental Health. Pesticide exposure in children. [Pediatrics](#). 2012 Dec;130(6):e1765-88



Solvents

Eskenazi B, Gaylord L, Bracken MB, Brown D. In utero exposure to organic solvents and human neurodevelopment. [Dev Med Child Neurol](#). 1988 Aug;30(4):492-501

Laslo-Baker D, Barrera M, Knittel-Keren D, Kozar E, et al. Child neurodevelopmental outcome and maternal occupational exposure to solvents. [Arch Pediatr Adolesc Med](#). 2004 Oct;158(10):956-61

Effects of enriched social environment and early childhood education on neurodevelopment

Arling GL, Harlow HF. Effects of social deprivation on maternal behavior of rhesus monkeys. [J Comp Physiol Psychol](#). 1967 Dec;64(3):371-7

Carlson M, Earls F. Psychological and neuroendocrinological sequelae of early social deprivation in institutionalized children in Romania. 1997. [Annals of the New York Academy of Sciences](#), 807: 419–428

Caldji C, Tannenbaum B, Sharma S, Francis D, Plotsky PM, Meaney MJ. Maternal care during infancy regulates the development of neural systems mediating the expression of fearfulness in the rat. [Proc Natl Acad Sci USA](#). 1998 Apr 28;95(9):5335-40

Harlow HF, Dodsworth RO, Harlow MK. Total social isolation in monkeys. [Proc Natl Acad Sci U S A](#). Jul 1965; 54(1): 90–97

High PC; American Academy of Pediatrics Committee on Early Childhood, Adoption, and Dependent Care and Council on School Health. School readiness. [Pediatrics](#). 2008 Apr;121(4):e1008-15

Hubbs-Tait L, Nation JR, Krebs NF, and Bellinger DC. Neurotoxins, micronutrients, and social environments individual and combined effects on children's development. [Psychological Science in the Public Interest](#). 2005 Dec;vol. 6 no. 357-121

Liu D, Caldji C, Sharma S, Plotsky PM, Meaney MJ. Influence of neonatal rearing conditions on stress-induced adrenocorticotropin responses and norepinephrine release in the hypothalamic paraventricular nucleus. [J Neuroendocrinol](#). 2000 Jan;12(1):5-12

Liu D, Diorio J, Tannenbaum B, Caldji C, Francis D, Freedman A, Sharma S, Pearson D, Plotsky PM, Meaney MJ. Maternal care, hippocampal glucocorticoid receptors, and hypothalamic-pituitary-adrenal responses to stress. [Science](#). 1997 Sep 12;277(5332):1659-62

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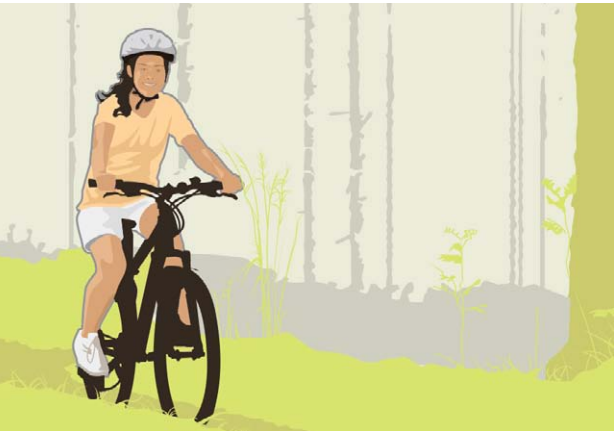
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References

Financial Costs of Developmental Disabilities

Centers for Disease Control and Prevention, National Center on Birth Defects and Developmental Disabilities– [ADHD Data and Statistics – Accessed Jan 16, 2014](#)

Trasnade L, Liu Y. Reducing the staggering costs of environmental disease in children, estimated at \$76.6 billion in 2008. [Health Aff \(Millwood\)](#). 2011 May;30(5):863-70. doi: 10.1377/hlthaff.2010.1239



Walker SP, Chang SM, Powell CA, Grantham-McGregor SM. Effects of early childhood psychosocial stimulation and nutritional supplementation on cognition and education in growth-stunted Jamaican children: prospective cohort study. [Lancet](#). 2005 Nov 19;366(9499):1804-7

Weiss B, Bellinger DC. Social Ecology of Children's Vulnerability to Environmental Pollutants. [Environ Health Perspect](#). 2006 October; 114(10):1479–1485

Zuckerman B, Halfon N. School readiness: an idea whose time has arrived. [Pediatrics](#). 2003 Jun;111(6 Pt 1):1433-6

Gene-environment interactions

Bergdahl IA, Grubb A, Schutz A, et al. Lead binding to delta-aminolevulinic acid dehydratase in human erythrocytes. [Pharmacology and Toxicology](#). 1997 Oct;81(4):153-158

Claudio L, Lee T, Wolff MS, et al. A murine model of genetic susceptibility to lead bioaccumulation. [Fundam Appl Toxicol](#). 1997 Jan;35(1):84-90

Costa LG, Li WF, Richter RJ, et al. The role of paraoxonase (PON1) in the detoxification of organophosphates and its human polymorphism. [Chemico-Biological Interactions](#). May 141999;119-120:429-38

Genc S, Gurdol F, Guvene S, et al. Variations in serum cholinesterase activity in different age and sex groups. [European Journal of Clinical Chemistry and Clinical Biochemistry](#). 1997;35(3):239-240

Mutch E, Blain PG, Williams FM. Interindividual variations in enzymes controlling organophosphate toxicity in man. [Human and Experimental Toxicology](#). 1992 March;11(2):109-116

Pilkington A, Buchanan D, Jamal GA, Gillham R, Hansen S, Kidd M, Hurley JF, Soutar CA. An epidemiological study of the relations between exposure to organophosphate pesticides and indices of chronic peripheral neuropathy and neuropsychological abnormalities in sheep farmers and dippers. [Occup Environ Med](#). 2001 Nov;58(11):702-10

Schwartz BS, Lee BK, Stewart W, et al. Delta-aminolevulinic acid dehydratase genotype modifiers four hour urinary lead excretion after oral administration of dimercaptosuccinic acid. [Occupational and Environmental Medicine](#). 1997;54(4):241-246

Sithisarankul P, Cadorette M, Davoli CT, et al. Plasma 5- aminolevulinic acid concentration and lead exposed children. [Environmental Research](#). 1999 Jan;80(1):41-49

Sithisarankul P, Schwartz BS, Lee BK, et al. Aminolevulinic acid dehydratase genotype mediates plasma levels of the neurotoxin, 5-aminolevulinic acid, in lead-exposed workers. [Amer J Industrial Med](#). 1997 July;32(1):15-20

Smith CM, Wang X, Hu H, et al. A polymorphism in the delta-aminolevulinic acid dehydratase gene may modify the pharmacokinetics and toxicity of lead. [Environ Health Perspect](#). 1995 Mar;103(3):248-253

Tomokuni K, Ichiba M, Fujisiro K. Interrelation between urinary delta-aminolevulinic acid, serum ALA, and blood lead in workers exposed to lead. [Industrial Health](#). 1993; 31(2):51-57

Wetmur JG. Influence of the common human delta-aminolevulinic acid dehydratase polymorphism on lead body burden. [Environ Health Perspect](#). 1994 Sept;102 suppl 3:215-219

Wetmur JG, Lehnert G, Desnick RJ. The delta-aminolevulinic acid dehydratase polymorphism higher blood lead levels in lead workers and environmentally exposed children with the 1-2 and 2-2 isozymes. [Environmental Research](#). 1991;56(2):109-119

Willcutt E, Pennington B, Duncan L, Smith S, et al. Understanding the complex etiologies of developmental disorders: behavioral and molecular genetic approaches. [J Dev Behav Pediatr](#). 2010 Sept; 31(7):533-544

Health Disparities

Rubin LI, et al. Break the cycle of environmental health disparities in vulnerable children. [Int Journal of Disability and Human Develop](#). 2012;11:301-305

Learning Disabilities

Alexander D. Learning disabilities as a public health concern. In Cramer SC, Ellis E (eds). Learning disabilities: Lifelong issues. Paul H. Brookes Publishing Company, Inc., Baltimore, MD 1996, pp 249-253

American Psychiatric Association. Diagnostic and statistical manual of mental disorders, Fourth edition. Washington, DC 1994

Butterworth B, Kovas Y. Understanding neurocognitive developmental disorders can improve education for all. [Science](#). 2013; 340: 300-305

Cramer SC, Ellis E. Learning disabilities: Lifelong issues. Paul H. Brookes Publishing Company, Inc., Baltimore, MD 1996

Dickman GE. The link between learning disabilities and behavior. In Cramer SC, Ellis E.(eds). Learning disabilities: Lifelong issues. Paul H. Brookes Publishing Company, Inc., Baltimore, MD 1996, pp 215-228

continued >

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Dyson LL. The experience of families of children with learning disabilities: Parental stress, family functioning and sibling concept. [Journal of Learning Disabilities](#) 1996;29(3):280-286

McBride HEA, Siegel LS. Learning disabilities and adolescent suicide. [Journal of Learning Disabilities](#). 1997 Nov-Dec;30(6):652-659

Wagner M, Newman L, et al. In Cramer SC, Ellis E (eds). Learning disabilities: Lifelong issues. Paul H. Brookes Publishing Company, Inc., Baltimore, MD 1996 (introduction)

Nature – Health Benefits

Frumkin H, Louv R. The powerful link between conserving land and preserving health. [Land Trust Alliance Special Anniversary Report 2007](#)

Grassman V, et al. Possible Cognitive Benefits of Acute Physical Exercise in Children With ADHD: A Systematic Review. [J Atten Disord](#). 2014 Mar (epub)

Maller C, Townsend M, Pryor A, St. Leger L. Healthy nature, healthy people: contact with nature as an upstream health promotion intervention for populations. [Health Promotion International](#) 2006; 21(1):45-54

Mitchell R, & Popham F. Effect of exposure to natural environment on health inequalities: an observational population study. [Lancet](#). 2008;372(9650):1655-60

St. Leger L. Health and nature – new challenges for health promotion. [Health Promotion International](#). 2003;18:173-175

Taylor, AF & Kuo, FE Children with attention deficits concentrate better after walk in the park. [J. of Att. Dis](#). 2009; 20(10) 1-20

Ulrich RS. Effects of health care environmental design on medical outcomes. In: Dilani A, editor. Design and health: Proceedings of the 2nd international conference on health and design. Stockholm, Sweden: Svensj Byggtjanst; 2001:49-59

Neurodevelopment

Gerson M, Van den Eeden SK, Gahagan P. Take-home lead poisoning in a child from his father’s occupational exposure. [Am J Ind Med](#). 1996 May;29(5):507-8

Fenske RA, Lu C, Negrete M, Galvin K. Breaking the take home pesticide exposure pathway for agricultural families: workplace predictors of residential contamination. [Am J Ind Med](#). 2013 Sep;56(9):1063-71

Lambrot R, Xu C, Saint-Phar S, Chountalos G, Cohen T, Paquet M. Suderman M, Hallett M, and Kimmins S. Low paternal dietary folate alters the mouse sperm epigenome and is associated with negative pregnancy outcomes. [Nature Communications](#) 4. 2013;Article number:2889

Rice D, Barone S. Critical periods of vulnerability for the developing nervous system: evidence from human and animal models. [Environ Health Perspect](#). 108 (Suppl 3):511-533. 2000

Shonkoff P Phillips D. Eds. [From neurons to neighborhoods: the science of early childhood development](#). National Academy Press, Washington DC. 2000

Nutrition and Neurodevelopment

Carter et al. Iron deficiency anemia and cognitive function in infancy. [Pediatrics](#). 2010 Aug;126(2):e427-34

Jacka FN1, Ystrom E, Brantsaeter AL, Karevold E, Roth C, Haugen M, Meltzer HM, Schjolberg S, Berk M. Maternal and early postnatal nutrition and mental health of offspring by age 5 years: a prospective cohort study. [J Am Acad Child Adolesc Psychiatry](#). 2013 Oct;52(10):1038-47

Lyall K, Schmidt R, Hertz-Picciotto I. Maternal lifestyle and environmental risk factors for autism spectrum disorders. [Int J Epidemiol](#) 2014;43(2):443-464

Lozoff B, Castillo M, Clark K, Smith J. Iron-fortified vs low-iron infant formula: developmental outcome at 10 years. [Arch Pediatr Adolesc Med](#). 2012 Mar;166(3):208-215



Miilichap JG, Yee MM. The diet factor in attention-deficit/hyperactivity disorder. [Pediatrics](#). Published online January 9, 2012 .doi: 10.1542/peds.2011-2199

Suglia SF, Solnick S, PhD, Hemenway D. Soft drinks consumption is associated with behavior problems in 5-year-olds. [J Pediatr](#) 2013 Nov;163(5):1323-8

Poverty - brain development

Hanson JL, Hair N, Shen DG, Shi F et al. Family poverty affects the rate of human infant brain growth. [PLoS One](#). 2013 Dec 11;8(12):e80954

Hubbs-Tait L, Nation J, Krebs N, Bellingier D. Neurotoxics, micronutrients. and social environments. Individual and combined effects on children’s development. [Psychological Science in the Public Interest](#); 2005;6(3):57-121

Luby J, Belden A, Botteron K, Marrus N, et al. The effects of poverty on childhood brain development: the mediating effect of caregiving and stressful life events. [JAMA Pediatr](#). 2013 Dec 1;167(12):1135-42

Weiss B, Bellingier D. Social ecology of children’s vulnerability to environmental pollutants. [Environ Health Perspect](#) 2006;114(10):1479-1485

Preterm birth, low birth weight and mental health

Singh G, Kenney M, Ghandour R, et al. Mental health outcomes in US children and adolescents born prematurely or with low birth weight. [Depress Res Treat](#). 2013; 2013:570743

Thyroid

Cooper DC, Biondi B. Subclinical thyroid disease. [Lancet](#). 2012 Mar 24;379(9821):1142-54

Garber JR, Cobin RH, Gharib H, Hennessey JV, Klein I, Mechanick JJ, Pessah-Pollack R, Singer PA, Woeber KA; American Association of Clinical Endocrinologists and American Thyroid Association Taskforce on Hypothyroidism in Adults. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. [Endocr Pract](#). 2012 Nov-Dec;18(6):988-1028

Haddow JE, Palomaki GE, Allan WC, Williams JR, et al. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. [N Engl J Med](#). 1999 Aug 19;341(8):549-55

Hynes KL, Otahal P, Hay I, Burgess JR. Mild iodine deficiency during pregnancy is associated with reduced educational outcomes in the offspring: 9-year follow-up of the gestational iodine cohort. [J Clin Endocrinol Metab](#). 2013 98(5):1954-62

LaFranchi SH, Haddow JE, Hollowell JG. Is thyroid inadequacy during gestation a risk factor for adverse pregnancy and developmental outcomes? [Thyroid](#). 2005 Jan;15(1):60-71

Mitka M. Even mild iodine deficiency during gestation may impair brain function in children. [JAMA](#) 2013 Jun 19;309(23):2428

Pearce EN, Braverman LE. Environmental pollutants and the thyroid. [Best Pract Res Clin Endocrinol Metab](#). 2009 Dec;23(6):801-13

Pop VJ, Brouwers EP, Vader HL, Vulsma T, van Baar AL, de Vijlder JJ. 2003. Maternal hypothyroxinaemia during early pregnancy and subsequent child development: a 3-year follow-up study. [Clin Endocrinol \(Oxf\)](#) 59(3):282–288

Pop VJ, Kuijpers JL, van Baar AL, Verkerk G, van Son MM, de Vijlder JJ, et al. 1999. Low maternal free thyroxine concentrations during early pregnancy are associated with impaired psychomotor development in infancy. [Clin Endocrinol \(Oxf\)](#) 50(2):149–155

Pop VJ, Vulsma T. 2005. Maternal hypothyroxinaemia during (early) gestation. [Lancet](#) 365(9471):1604–1606

Stagnaro-Green A, Pearce E. Thyroid disorders in pregnancy. [Nat Rev Endocrinol](#). 2012 Nov;8(11):650-8

Trends

Boyle, C, Boulet S, Schieve LA, Cohen RA, Blumberg SJ, Yeargin-Allsop M, Visser S, Kogan MD. Trends in the prevalence of developmental disabilities in US children, 1997–2008 [Pediatrics Volume 127, Number 6, June 2011](#)

Centers for Disease Control: [Developmental disabilities increasing in US](#)

INFERTILITY

Reiko & Toshio's Story

Reiko and Toshio are a Japanese-American couple in their early 30's who met in college and married five years ago. They have been trying to have a child for about a year and feel frustrated that Reiko is not yet pregnant. They are not alone – infertility is not uncommon.

US infertility statistics

Enlarge Table 1

Global and US infertility trends



INFERTILITY

Reiko & Toshio's Story

At her annual exam, Reiko speaks with her gynecologist, Dr. Lopez, about the couple's frustration at not being able to conceive. Reiko says that they are now more than ready to start a family.

At an earlier appointment Dr. Lopez had explained that Reiko may have some degree of endometriosis due to her history of unusually painful menses. This could play a role in her difficulty conceiving. She tells Reiko that about 10% of women of reproductive age have endometriosis.

She also tells her that 30-50% of women with endometriosis are infertile and that about the same percentage who are infertile have endometriosis. Reiko is surprised at these percentages. Dr. Lopez tells Reiko she will discuss treatment options with her.

Definition:
endometriosis
and infertility

Endometriosis,
infertility and the
environment



Watch: Endometriosis and the Environment
Linda C. Giudice, MD, PhD, MSc, Distinguished Professor and Chair
The Robert B. Jaffe, MD Endowed Professor in the Reproductive Sciences, University of California San Francisco.



INFERTILITY

Reiko & Toshio's Story

Dr. Lopez also notes that Reiko is quite thin at 5' 5" inches tall and 110 pounds, considered underweight based on her Body Mass Index or "BMI." She asks about Reiko's eating and exercise habits as she had lost weight since her last annual checkup.

Reiko says she has become an avid athlete and has started to compete in sprint triathlons. Her training routine before a race includes swimming a mile at least 2-3 times/week, biking around 50-75 miles/week, and running about 20-25 miles/week.

Dr. Lopez is impressed but explains that intense exercise combined with Reiko's thinness is likely causing her irregular menstrual cycles, which decrease the chance of pregnancy.

Intense exercise and infertility



INFERTILITY

Reiko & Toshio's Story

Dr. Lopez and Reiko discuss some of the ways that Reiko's reproductive system may be malfunctioning, including issues related to ovulation, egg fertilization, or implantation of the fertilized egg (blastocyst). Dr. Lopez says that there may be more than one thing contributing to her inability to conceive, including issues related to her husband, Toshio, or a combination of factors from them both. Let's leave our story for a moment to look at normal reproductive system development.

Classifications of infertility



INFERTILITY

Reiko & Toshio's Story

NORMAL REPRODUCTIVE SYSTEM DEVELOPMENT

During embryonic life, the reproductive structures undergo remarkable transitions. Early on, (prior to six weeks of pregnancy), male and female reproductive structure of the fetus are identical.

The gonads are the reproductive glands (ovary or testis) that produce gametes/germ cells (i.e., sperm or egg). Initially, the gonads form near the kidney. During weeks seven and eight, the primitive gonads differentiate into ovary or testis based on whether or not a Y chromosome is present.

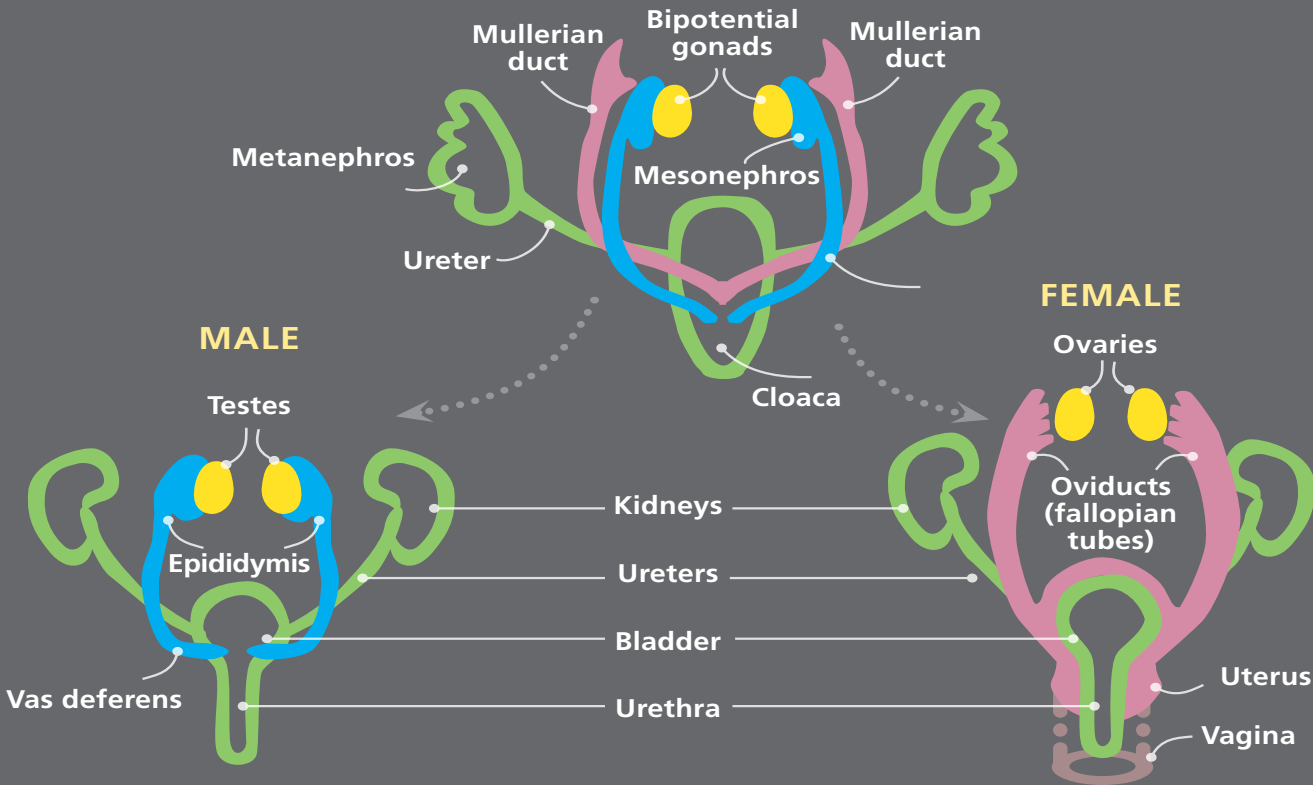
The Wolffian and Mullerian ducts develop into the internal genitalia. Prior to six weeks, the embryo has both types of ducts. After six weeks, in the male embryo, the Wolffian ducts develop into the ductus deferens, epididymis, and spermatic cords, while there is atrophy of Mullerian ducts caused by anti-Mullerian hormone (AMH) made in the gonads.



Hypothalamic-pituitary-gonadal (HPG) axis

Graphic used with permission from: [Sex development: Genetics and biology](#) by Peter Koopman, PhD, FAA

Normal Reproductive System Development



INFERTILITY

Reiko & Toshio's Story

NORMAL REPRODUCTIVE SYSTEM DEVELOPMENT

In the female embryo, Mullerian ducts arise beside the Wolffian ducts and develop into the fallopian tubes, uterus, cervix and upper vagina, and the Wolffian ducts atrophy.

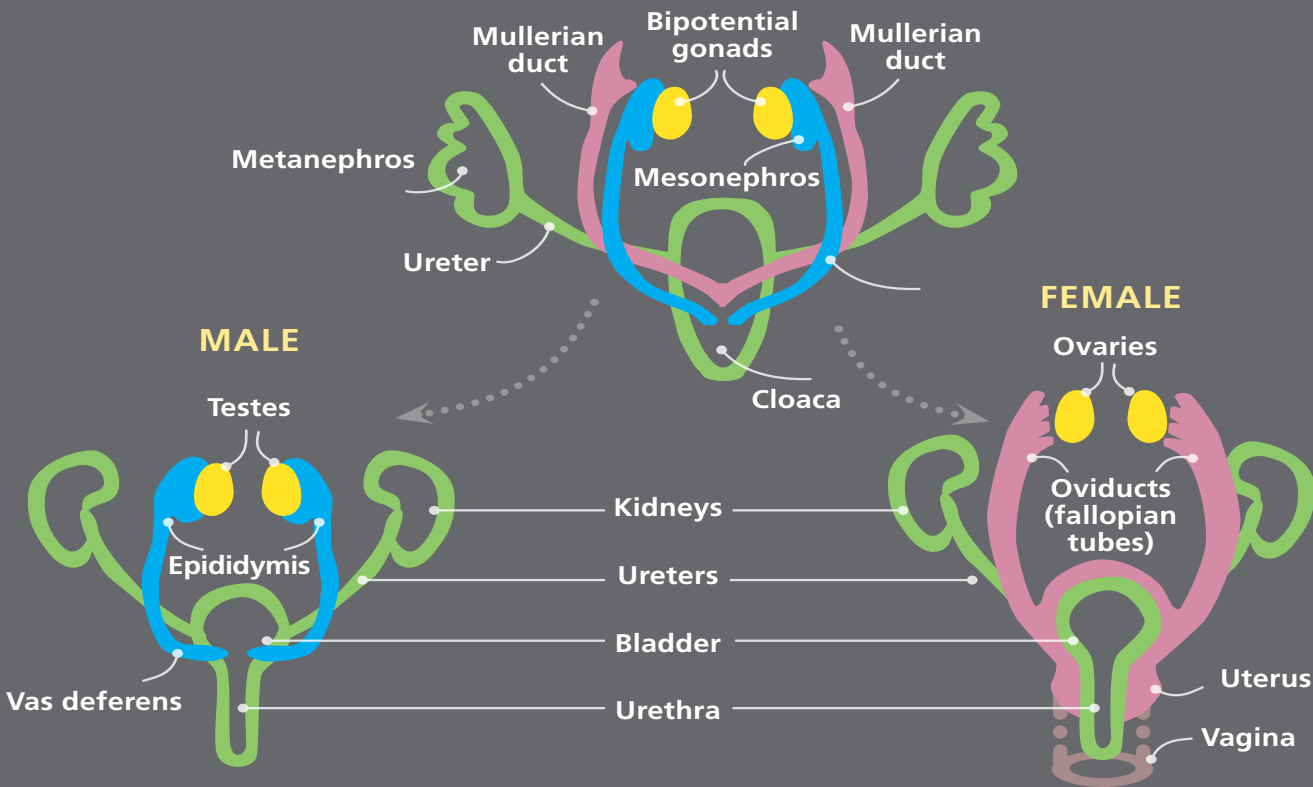
The external genitalia are also identical (or “ambiguous”) until six weeks, consisting of a genital tubercle, genital swelling, and cloaca. In males, when the testes begin to secrete testosterone, the formation of male external genitalia is signaled. In females, the lack of hormone secretion results in female genitalia.

During embryonic development, not only do the male and female reproductive structures differentiate, there is sexual differentiation of the developing brain. The hormones produced by the developing male testis impact the fetal brain in sex-specific ways.



Life cycle of an ovarian follicle

Normal Reproductive System Development



Watch: Environmental Influences on the Developing Follicles
Ulrike Luderer, MD, PhD, MPH discusses environmental influences on the developing ovaries.
Ulrike Luderer, MD, PhD, MPH, Consultant, Western States PEHSU, Professor, School of Medicine, Director, Environmental Health Sciences Graduate Program, University of California, Irvine

INFERTILITY

Reiko & Toshio's Story

Reiko and Dr. Lopez then discuss some general healthy habits for couples planning to have children.

They discuss briefly that a healthy diet in general will also be beneficial for fertility. This includes eating lots of fruits and vegetables, whole grains, and healthy fats, as illustrated in the graphic at the right from the Harvard School of Public Health.

Some studies suggest that specific nutrients may increase fertility, including a daily multivitamin that contains folate and iron, and substituting high-fat for low-fat dairy.

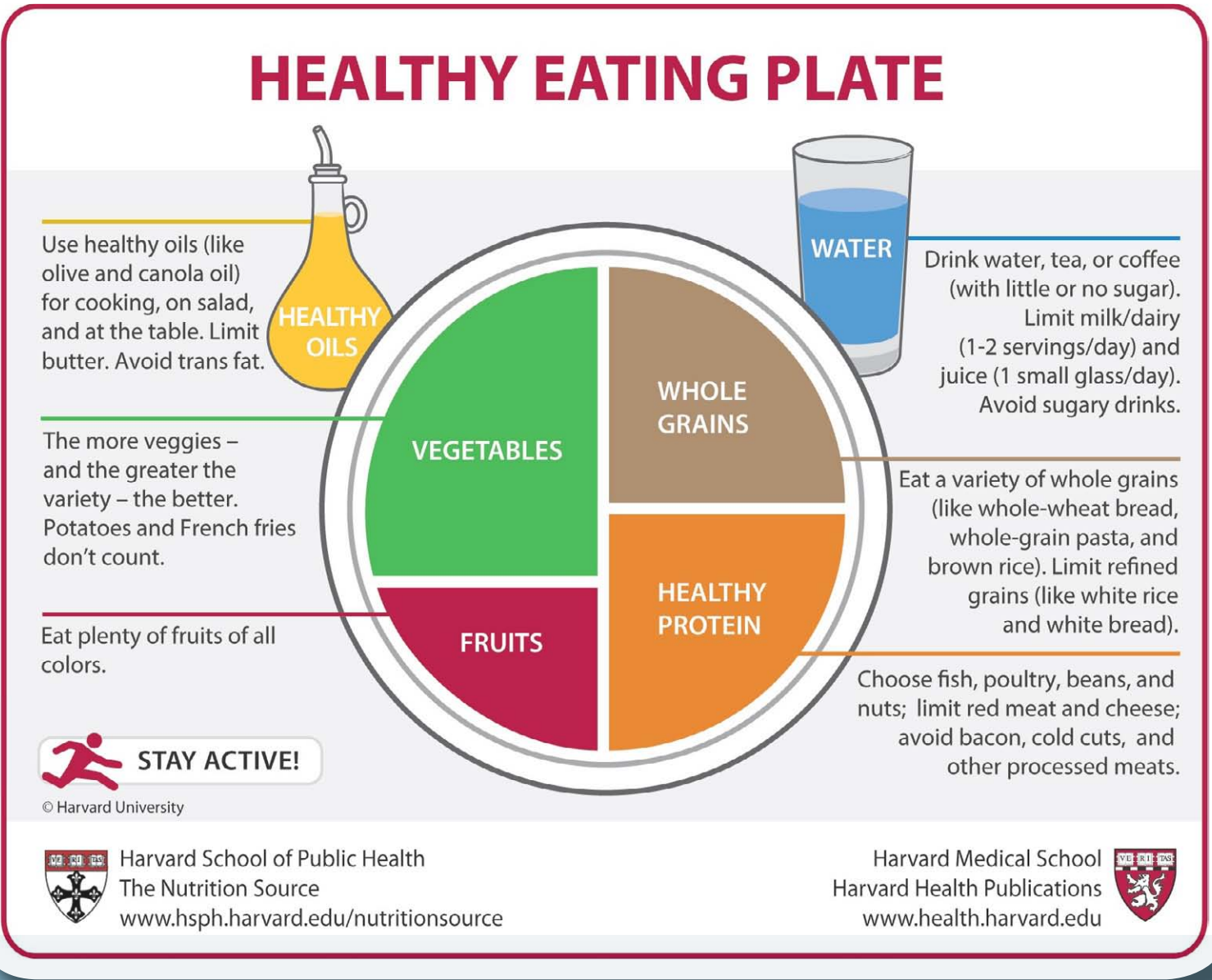
Preconception health

Key concept: Multigenerational nutrition

[Link to graphic credit](#)



Watch: Preconception Counseling and Environment, Marya Zlatnik MD, Professor, UCSF School of Medicine



Link:
[More information: CDC's Preconception care for women and men](#)

Healthy Eating Plate graphic copyright © 2011 Harvard University www.hsph.harvard.edu/nutritionsource/healthy-eating-plate. Used with permission. For more information about The Healthy Eating Plate, please see The Nutrition Source, Department of Nutrition, Harvard School of Public Health, www.thenutritionsource.org and Harvard Health Publications, www.health.harvard.edu.

INFERTILITY

Reiko & Toshio's Story

Dr. Lopez also gives Reiko some information on prenatal care for healthy child development, which she recommends Reiko incorporate into her life now that she is trying to become pregnant.

Prenatal Care
for Healthy
Development

Folate
supplementation
recommendations
for women



MORE INFORMATION:

- CDC on [pregnancy](#)
 - American Congress of Obstetrics and Gynecology (ACOG):
 - [Good Health Before Pregnancy](#) (pdf)
 - [Prenatal Nutrition](#)
 - [Environmental Chemicals](#)
- Royal College of OB/GYN:
 - [Chemical Exposures During Pregnancy](#)
 - UCSF: [Program on Reproductive Health and the Environment](#)

INFERTILITY

Reiko & Toshio's Story

Dr. Lopez includes information on the influence of toxic chemicals such as lead and the solvents in paints and other materials.

She again mentions the important nutrition issues they had discussed earlier.



Reproductive health effects of solvents

Reproductive health effects of lead

Key concept: Unintended adverse consequences of improvements to the environment

- Links:
- [TedX The Endocrine Disruption Exchange](#)
 - [Generations at Risk Reproduction Health and the Environment](#)
 - [CDC's Lead and Pregnancy](#)



Tracey Woodruff, PhD, MPH
Director of the Program on Reproductive Health and the Environment
Professor in the Department of Obstetrics, Gynecology & Reproductive Sciences
UC San Francisco



Watch: Chemicals and Infertility

Tracey J. Woodruff, PhD, MPH

Director, Program on Reproductive Health and the Environment; Professor in the Department of Obstetrics, Gynecology, and Reproductive Sciences at the University of California, San Francisco

KEY CONCEPT:

Multiple environmental factors can influence reproductive health.

Environmental factors, alone or in combination with other variables, can have adverse impacts on reproductive health, increasing the risk of infertility, miscarriage, abnormal fetal growth, fetal death, preterm birth, birth defects or other developmental abnormalities.

In many cases, a specific cause of an adverse outcome cannot be

identified. With the exception of birth defect registries in some states, lack of comprehensive data collection pertaining to most abnormal outcomes makes epidemiologic studies intended to identify causal factors difficult to conduct.



TOXICANTS
including: pesticides, endocrine disruptors, metals, air pollution, solvents

RADIATION

STRESS

NUTRITION

CLIMATE CHANGE

INFECTIOUS AGENTS such as:
Viruses: CMV, varicella, herpes
Bacteria: syphilis, listeria
Parasites: toxoplasmosis, Zika, rubella

 **KEY CONCEPT:**

CHALLENGES OF CONNECTING ENVIRONMENTAL EXPOSURES TO OUTCOMES



How can we measure exposure levels in the body or environment?

- By testing chemical concentrations in people’s blood serum or urine.
- By testing chemicals in the environment of the home, workplace, or other place, for example, in the dust or air.

The higher the chemical levels in the environment, generally the higher the levels in the serum and/ or urine.

We know that exposure to environmental chemicals is widespread. For example, the National Health and Nutrition Examination Survey (NHANES) reported that BPA by-products were detected in over 90% of their urine samples from a representative population of the US (Calafat et al., 2008).

Knowing that exposures have occurred does not necessarily mean that they have caused a harmful effect.

People can be exposed to toxicants through air, water, soil, food and consumer and industrial products

RESOURCE LINKS:

- [CDC–Reproductive and birth outcomes](#)
- [CDC–Tracking birth defects](#)
- [National environmental health tracking program](#)
- [Pesticide Action Network Database](#)

Examples of issues that can complicate assessments of links between an exposure and health effects:

- An exposure pathway must be completed. Exposure pathways are means by which hazardous substances move through the environment from a source to contact with people. A complete exposure pathway must have four parts: (1) a source of contamination; (2) a mechanism for transport of a substance from the source to a person through the air, water, food, or via direct contact; (3) a way by which people come in contact with contaminated air, water, food, or other products, and; (4) a route of entry into the body. Routes of entry can be eating or drinking contaminated materials, breathing contaminated air, or absorbing contaminants through the skin. If any part of an exposure pathway is absent, the pathway is incomplete and no exposure or risk is possible.
- We should know the dose, duration, and pattern of exposure necessary to cause a harmful effect but sometimes do not.
- Randomized controlled trials to conclusively establish the dose necessary to cause harms are unethical. So, we must use animal or basic science models in addition to observational data from exposed people.
- In observational studies, exact exposure levels over time are typically unknown and can only be estimated.
- The timing of exposure may be unclear or have occurred in the distant past.

- Different people can have different levels of sensitivity (stemming from nutritional status, life stage, metabolism, or genetics).

Evidence of Health Effects

Evidence comes from demonstrating health effects in experimental animal models and from human epidemiologic data. But epidemiologic studies require reliable collection of health outcome data. Unfortunately, except for fairly high-quality birth defect registries in a few states, and routine collection of birth weight data, ongoing tracking of reproductive and developmental abnormalities is generally lacking in the US. Periodically, an agency attempts to estimate the prevalence of various developmental disabilities in order to identify trends, but attempts to link cases with environmental exposures are usually not possible with these data. Improved tracking of reproductive health outcomes would help to link them to environmental exposures.

Tracking some adverse outcomes can be done through state vital records that include information on all births including the use of fertility drugs and assisted reproductive technology. These data can also be linked to a fertility database managed by the [Society for Assisted Reproductive Technology](#) to collect even more data about the patients and their individual treatment. With these types of data, the birth address could be used in statistical models to produce maps of areas where infertility may be higher. These maps could then be overlaid with environmental data to generate new hypotheses.

INFERTILITY

Reiko & Toshio’s Story

Dr. Lopez asks more about Reiko and Toshio’s backgrounds and lifestyles to try to find some clues pointing to other possible reasons for the couple’s infertility.



Taking environmental and psychosocial histories

Environmental history

Download a sample pdf

Link: Antenatal psychosocial health assessment

Multiple stressors and health risks

Link: Centering Healthcare Institute Improving maternal child health by transforming care

Taking Environmental and Psychosocial Histories

Taking environmental and psychosocial histories can be routinely incorporated into clinical practice not only for couples with infertility but with all people of reproductive age. This will help identify opportunities for primary prevention of adverse reproductive outcomes prior to pregnancy.

Environmental History

Environmental History Form	
What do you do for work?	Always wear proper personal protective equipment. Contact an Occupational and Environmental physician with questions about workplace exposures. www.aeec.org
Are you exposed to any of the following at work:	
Metals	
Solvents	
Chemicals (including those for cleaning)	
Radiation	
Fumes	
Lead can cause brain damage, especially in babies and children	Eat foods enriched with iron (lean red meats, chicken), calcium (dairy, green leafy vegetables), and vitamin C (oranges, grapefruits, tomatoes, green peppers).
Have you or anyone living in your house ever been treated for lead poisoning?	
Do you live in a house built before 1978?	Have your home tested for lead if it was built before 1978. Chipping paint may release lead into the house.
Are there any plans to remodel your home?	Avoid remodeling or hire a certified contractor. Call 1-800-424-LEAD for more information.
Have you ever lived outside the United States?	
Does your family use imported pottery or ceramics for cooking, eating, or drinking?	Imported pottery or ceramics may contain lead, which can leach into food.
Have you used any home remedies such as azarcon, greta, pay-loo-ah?	Do not use lead-containing home remedies.
Have you ever eaten any of the following:	Do not eat clay, soil, dirt, pottery, or paint chips because they may contain high levels of lead.
Clay	
Soil or dirt	
Pottery	
Paint chips	
Mercury is another metal that can damage the developing fetal brain. Small children are also sensitive.	It’s important to clean up mercury spills in a special way. https://www.atsdr.cdc.gov/mercury/docs/residential_hg_spill_cleanup.pdf
Is there a mercury thermometer in your home?	Use a digital or mercury-free thermometer.
In general, do you eat fish more than twice a week?	Eat a variety of fish low in mercury twice a week. Contact local health dept. about local fish advisories.
Do you eat any of the following types of fish:	Do not eat shark, swordfish, king mackerel or tilefish because they contain high levels of mercury.
Shark	
King Mackerel	
Swordfish	
Tilefish	
Orange Roughy	
Big eye tuna	
Marline	
Albacore tuna (“white” tuna)	Albacore tuna contains more mercury than canned light tuna; do not eat more than 6 oz. per week of albacore tuna.
Air pollution is harmful to pregnant women who are “breathing for two” and also for fetuses, babies, and children.	

INFERTILITY

Reiko & Toshio's Story

Reiko tells Dr. Lopez she was born and raised in the agricultural region of Okayama, Japan. She met Toshio when they were both attending college in California.

She says that Toshio has always been quite healthy. He grew up on his family's farm in the Central Valley of California during the 1980's, then moved to Los Angeles to attend college.



INFERTILITY

Reiko & Toshio's Story

Soon after graduating college the couple got married and settled in a suburb of Los Angeles. Toshio worked for a software development company for a few years. Reiko worked in a private nonprofit company designing their web products.

When Toshio's parents got older and needed help on the family farm, the couple decided to move there and help them. That was three years ago.

Toshio has been working on the farm to supplement their income while he launches a small business in web design. Reiko is able to continue her job remotely, driving into Los Angeles for monthly meetings.

Reiko knew that pesticides were used on the farm and asks whether that might be a problem. Dr. Lopez said yes and offered to send her information on this.

Pesticides and fertility



Photo: Copyright © 2000 The Regents of the University of California. Used by permission.
Source: California Agriculture 54(6):14-19. DOI: 10.3733/ca.v054n06p14. November-December 2000.

INFERTILITY

Reiko & Toshio's Story

Dr. Lopez mentioned other environmental exposures that might affect fertility, such as air pollution, and says there are some good resources that she can also send to Reiko.

Reiko thinks about her training runs around some of the major roads, and remembers the emissions from the trucks and cars. She wonders how that might have affected her.

Dr. Lopez suggests that a fertility specialist may be able to provide even more information.



Vulnerable populations and environmental disparities

Air pollution and fertility, reproductive health



[Link: ACOG Evaluating Infertility](#)

Links:

[ACOG American Congress of Ob/Gyn: Vulnerable populations and environmental disparities](#)
[FIGO Opinion International Federal of Gyn/Ob: Reproductive health impacts of exposure to toxic environmental chemicals](#)



INFERTILITY

Reiko & Toshio's Story

Meanwhile, Dr. Lopez suggests that Reiko consider cutting down on intense exercise, but when she is training include a higher caloric intake of healthy food. She stressed that Reiko should return to her regular healthy diet when not in training.

Dr. Lopez recommends a diagnostic laparoscopy to determine if Reiko has endometriosis. If she does, Dr. Lopez says that Reiko could consider treating her endometriosis and describes what that might entail.

The usual next step would be for Reiko and her husband to see a reproductive endocrinologist/fertility specialist.

Dr. Lopez said she could recommend someone as Reiko got up to leave.

Endometriosis treatment



INFERTILITY

Reiko & Toshio's Story

When Reiko went home, her head was spinning. She thought that she was doing everything she could to get pregnant, so hearing Dr. Lopez's suggestions and concerns was a bit overwhelming. She couldn't wait to talk with Toshio.

Reiko and Toshio spent a long while discussing the appointment with Dr. Lopez.

They then had a nice relaxing dinner with Toshio's parents.

Reiko was missing her family back in Japan but was going to call her sister that evening to tell her all about what was happening and ask her advice.



INFERTILITY

Reiko & Toshio's Story

In the next few days, after Reiko speaks more to Toshio and to her sister, she decides to have the laparoscopy. She calls Dr. Lopez and schedules it for a month later after she participates in her next mini-triathlon.

A month later...

When Reiko goes to Dr. Lopez for the laparoscopy she tells her that she placed second in her age group in the triathlon, the best she had ever done. Dr. Lopez congratulates her but reminds her about considering changes to her activity routine. Reiko says she had been thinking about that and had decided to get back to yoga on a regular basis, which she had practiced before.

Dr. Lopez performs the laparoscopy and informs Reiko that she does not have endometriosis. Reiko is happy to hear the news as is Toshio who is waiting for her in the reception area.

On the drive home they decide to make an appointment with Dr. Patel, the fertility specialist recommended by Dr. Lopez.



INFERTILITY

Reiko & Toshio's Story

Reiko and Toshio are able to get an appointment three weeks later with the fertility specialist Dr. Patel. The first thing Dr. Patel does is take a thorough medical history from Reiko and Toshio, including questions about occupations now and in the past. She orders lab tests as part of their initial visit.

Dr. Patel was recommended by Dr. Lopez because of her training in environmental influences on health, and because she regularly consulted with the regional Pediatric Environmental Health Specialty Unit (PEHSU) that also offered OB/GYN expertise.

Occupational influences on female reproductive health

Occupational exposures and male reproductive health

[Link](#) to credit

For clinicians: Safety Data Sheets

More information about the [PEHSU network](#)

Link: the [PEHSU network](#)



Additional Resources:

SDS sheets are notoriously incomplete, use these additional resources to further understand the health effects of toxicants:

- [Proposition 65](#)
- [New Jersey Hazardous Substance Fact Sheets](#)
- [CHE Toxicant and Disease Database](#)
- [Toxics Release Inventory](#)

INFERTILITY

Reiko & Toshio's Story

During the course of the history Toshio tells Dr. Patel that he spends a good deal of his time on the laptop each day.

Dr. Patel informs them, though controversial, there are some potential concerns related to low-frequency electromagnetic radiation.

Electromagnetic exposure and male fertility





They discuss a range of other possible environmental exposures including endocrine disruptors. Dr. Patel says she will have the test results in about a week, so they set up another appointment.

Watch: Little Things Matter: The Impact of Toxins on the Developing Brain
Dr. Bruce P. Lanphear, MD MPH
Professor, Simon Fraser University



Bisphenol A (BPA) and how it can mimic estrogen

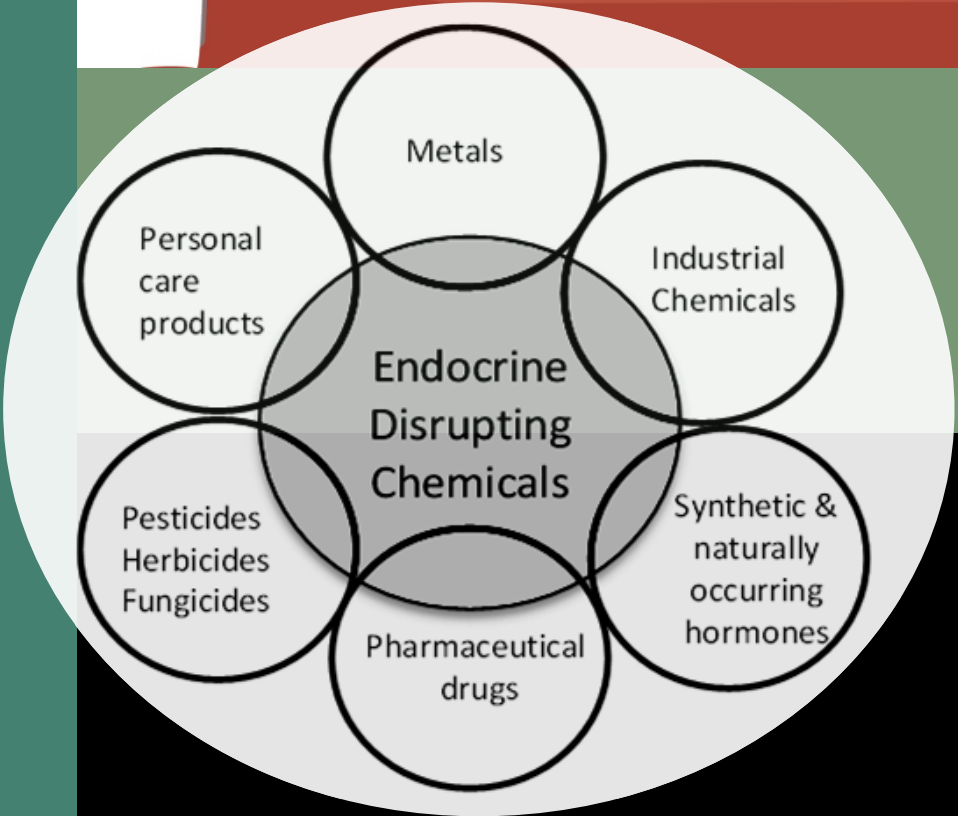
Bone disrupting chemicals: Fatty bones and osteoporosis

Parabens and reproductive health

Endocrine disruptors and infertility/ reproductive health

Endocrine disruptors are chemicals that impact endocrine functions by interfering with the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body that are responsible for development, behavior, fertility, and maintenance of homeostasis (normal cell metabolism).

These disruptions can cause cancerous tumors, birth defects, and other developmental disorders. As the cells begin to grow and differentiate, there are critical balances of hormones and protein changes that must occur. The Endocrine Society released a statement on Endocrine-Disrupting Chemicals (EDCs) specifically listing obesity, diabetes, female reproduction, male reproduction, hormone-sensitive cancers in females, prostate cancer in males, thyroid, and neurodevelopment and neuroendocrine systems as possible effects of being exposed to EDCs.



INFERTILITY

Reiko & Toshio's Story

TESTICULAR DYSGENESIS SYNDROME

Although Toshio is not affected by this, a number of studies in the US and some countries in Europe have shown increasing trends in testicular cancer; declining semen quality, including lower sperm counts; and increases in hypospadias (an abnormality of the penis with the urethral opening along the underside of the shaft instead of at the tip) and cryptorchidism (undescended testes).

Testicular germ cell cancer arises from primordial germ cells that escaped fetal differentiation. Hypospadias and cryptorchidism result from incomplete masculinization of the reproductive tract during fetal development. It has been proposed that each of these represent different manifestations of the same underlying condition called testicular dysgenesis syndrome (TDS).

Clinical evidence of this syndrome comes from the observation that males with rare genetic abnormalities that cause testicular dysgenesis are at higher risk of testicular cancer, often combined with cryptorchidism and hypospadias.

But the majority of cases of these abnormalities occur in individuals without known underlying genetic abnormalities and the cause remains unclear. Moreover, countries with higher incidence of testicular cancer, such as Denmark, tend to have higher prevalence of cryptorchidism, hypospadias, and poor semen quality.

Thus, scientists have looked for environmental factors that may help explain the observations.



Prenatal Phthalate Exposure: Effect on AGI (anogenital distance) in boys

Endocrine disrupting chemicals (EDCs) that interfere with normal testosterone production or androgen action are prime candidates. In laboratory animal studies, fetal exposures to various phthalates, the insecticide DDT, and the fungicide vinclozolin cause a TDS-like phenotype in rats although an equivalent to human male germ cell cancer does not exist in rodents.

Many of these same chemicals also cause a decrease in anogenital distance, a marker of anti-androgenic activity that can be measured in laboratory animals and people. Humans are regularly exposed to a cocktail of endocrine disrupting chemicals including phthalates, bisphenol A, polybrominated diphenyls, polyfluorinated compounds, alkylphenol, and many others.

The shortened anogenital distance associated with prenatal exposure to phthalates previously described in humans, as well as with the endocrine disruptor bisphenol A, is consistent with an anti-androgenic effect and has been associated with lower sperm count and quality (Mendiola et al).

The animal and human studies, combined with trends in male reproductive health described above, support the hypothesis that exposure to EDCs may play a significant role in these findings.

Epidemiologic studies continue to identify environmental chemicals linked to adverse male reproductive tract development with the aim of identifying those that pose risk, including male infertility, in populations, helping to make the case for removing them from commerce.

Humans are regularly exposed to a cocktail of endocrine disrupting chemicals.

INFERTILITY

Reiko & Toshio's Story

Even though Dr. Patel had done her best to reassure them, Reiko and Toshio were nervous as they drove to their next appointment. What if there was nothing Dr. Patel could recommend to help them? When they get to her office she tried to put them at ease and told them about some key test results.

Key test results



INFERTILITY

Reiko & Toshio's Story

They discuss the meaning of the test results.

Dr. Patel makes some initial recommendations to Reiko and Toshio:

For Reiko:

- Decrease the amount of weekly exercise.
- Increase calorie intake with healthy foods, to achieve a weight of 120 pounds.

For Toshio:

- Be sure to use safe application practices when working with pesticides.
- Take an omega 3 fatty acid supplement such as fish oil and a multivitamin. Look for supplements that have been tested for contaminants and say “mercury free.” Note: there is no regulation of these supplements.



Link: Pesticide Safety Rules for Farmworkers – Cal. EPA:

<http://www.cdpr.ca.gov/docs/whs/pdf/hs1587.pdf>

Fertility diet

[Link to reference](#)

Enlarge Table 2



INFERTILITY

Reiko & Toshio's Story

Dr. Patel also suggests Reiko needs therapy to begin ovulation.

The first step would be for her to change her exercise regimen, gain weight, and even see a therapist to deal with stress if that is an issue. If her weight increases she'll likely start ovulating.

For many women, including those with polycystic ovarian syndrome (PCOS), the next step would be to take the oral medication Clomiphene, or Clomid, a selective estrogen receptor modulator (or SERM) which increases the release of GnRH (Gonadotropin-releasing hormone) which stimulates ovulation.

Reiko, and other women with functional hypothalamic amenorrhea who have low estrogen levels, will likely need injectable gonadotropins (FSH injections) to produce ovulation, as their brain may not respond to GnRH.

She also suggests she undergo intrauterine insemination (IUI) and explains the procedure and also the costs, which she says may not be covered by their insurance.

In addition, she also suggests that Toshio see another clinician in the practice who is a urologist specializing in male infertility. She says he could probably see him within the next week.



INFERTILITY

Reiko & Toshio's Story

They ask Dr. Patel to set up an appointment with the urologist and explain that they'd like to discuss next steps and investigate insurance coverage before they make any decisions on how to proceed.

Toshio is indeed able to see the urologist Dr. Richardson within the week and undergoes a thorough history, physical exam and blood work to look for endocrine (hormonal) causes of a low sperm count.

The urologist offered a test to look for DNA damage in Toshio's sperm, but this test was not covered by his insurance.



INFERTILITY

Reiko & Toshio's Story

The next week after more discussion and research, they decide to go ahead with the injections. and to proceed with the intrauterine insemination.

Reiko calls Dr. Patel and asks when this might occur.

Dr. Lopez explains that in order to assess the response to therapy Reiko will need to undergo a series of ultrasounds to gauge follicular growth. Once follicles are mature, ovulation is triggered to time the intrauterine insemination. (Women on Clomid will use OTC ovulation prediction kits to time intercourse or IUI.)



INFERTILITY

Reiko & Toshio's Story

Meanwhile the couple does more research about infertility and afterward decide to take some additional steps.

Toshio talks with his parents and tells them his concerns about using pesticides on the peach farm, especially since they are trying to have a child. He shows them some studies about pesticides and health.

Toshio says that if he is going to be taking over the farm full time he wants to try to convert to organic production. He has been following trends showing that organic produce and fruit are popular with consumers and highly marketable, even though organic production presents new challenges.

His parents agree to introduce Integrated Pest Management (IPM) at the peach farm as a first step, and to work with him for a full transition.

Integrated pest management (IPM)

Links:

Source: [What is Integrated Pest Management?](#)
University of California, Davis
Image source: [Wikipedia](#)

More Resources:

Pesticides: EPA – [Integrated Pest Management](#)
[Bio-integral Resource Center \(BIRC\)](#)
[Pesticide Action Network \(PANNA\)](#)
University of California – [Pesticide Application Equipment](#)



Watch: Epitaph for a Peach

From Huell Howser California's Gold Archive, presented by Chapman University (long – 28 min.)



INFERTILITY

Reiko & Toshio's Story

Toshio also starts using his laptop computer on a table, not on his lap, and starts to take fish oil supplements and a multivitamin.

Reiko commits to her yoga routine and also to practicing meditation, and decides to decrease her intense exercising.



INFERTILITY

Reiko & Toshio's Story

When the ultrasound indicates that the follicles have matured and Reiko is ovulating, Dr. Patel is able to proceed with the IUI.

Toshio's sperm is prepared and sterilely placed in Reiko's uterus with a syringe.

Dr. Patel assures Reiko she can resume her normal activities after the IUI.



INFERTILITY

Reiko & Toshio's Story

After two more cycles of IUI, and no pregnancy, they start to feel discouraged. Toshio and her family urge her to continue.

After the fourth cycle she has a positive pregnancy test!

When they hear the good news, they rush to tell Toshio's parents, and Reiko is already texting her sister with the good news that she will be an aunt in the next year. They ask them to keep the news confidential until they are ready to tell others.

Over the next few weeks they spend time learning about the stages of growth of the fetus and review all the prenatal health recommendations that they can incorporate into both of their daily activities.

Watch: The Epigenome at a Glance

University of Utah, Genetic Science Learning Center
(2 min.)

Embryo development

The placenta – vital to human survival

Link: [NICHD/NIH Human Placenta Project](#)

Links:

[ARHP Environmental Impacts on Reproductive Health](#)

[CHAMACOS Environmental Health Kiosk](#)

An interactive, touch-screen, audio-visual tutorial to learn about environmental hazards in English and Spanish.

Watch: Epigenetics

Mark Miller MD, MPH
(2 min.)



INFERTILITY

Reiko & Toshio's Story

KEY POINTS

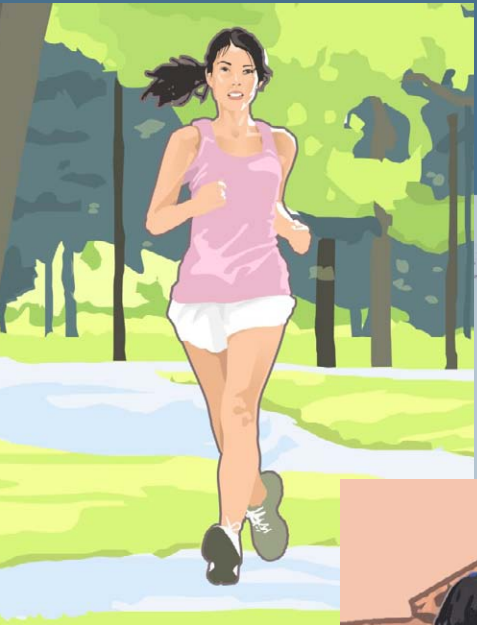
Throughout the pages of Reiko and Toshio's story we've seen a wide range of interacting variables that may contribute to infertility or reproductive health problems.

These include exposure to toxic chemicals, diet, body weight/excessive exercise, socioeconomics, genetics, and gene-environment interactions.

We have also seen actions that can increase resilience and enhance healthy reproduction and development, such as avoiding toxic exposures and eating a healthy diet throughout life.

Although Reiko and Toshio's story is fictional, women, men and couples throughout the world may face a similar range of issues depending on their circumstances.

It is critical that we consider the multiple environmental influences associated with increased risks for infertility, reproductive harm, and impaired development, and their long term consequences when we design prevention strategies and treatments to address them.



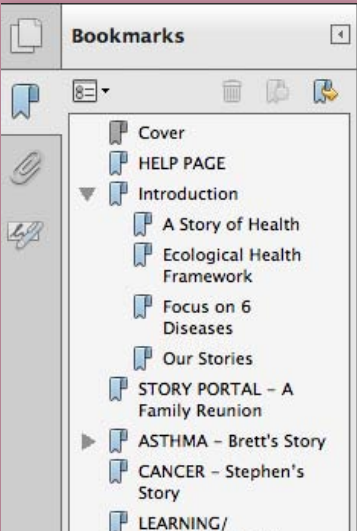
COMMON THEMES

Although the fictional narratives in *A Story of Health* describe the lives of children and adults with different conditions and diseases – infertility, asthma, developmental disabilities and childhood leukemia - common themes resonate. They include:

- Important environmental influences come from the natural, chemical, food, built, and social environments.
- Although there are exceptions, most diseases as well as good health are the result of complex interactions among multiple environmental influences and genetics.
- Early-life experiences, particularly during critical windows of development, can have profound beneficial or detrimental lifelong effects, even into elder years.
- Healthy people and healthy communities are interdependent. All people do not have equal access to nutritious food, clean air and water, safe workplaces, healthy housing, green spaces, peaceful neighborhoods or quality health care.
- Preventing disease and promoting health require actions and commitments from the individual, family, community and society. Health promoting public policies are necessary to make healthy living available to all people.

Resources

We have linked to many useful resources in each story relevant to a wide range of audiences, including clinicians. To quickly access resources on specific topics in each story, use the **Bookmarks** toolbar on the left (which you can open or close), or return to the [Help page](#) for more details on other eBook features.



Additional resources to help prevent disease and promote health:

Portal to Science Resources: Hundreds of additional resources on environmental health including organizations, publications, videos and more.

Pediatric Environmental Health Toolkit application for mobile devices

Out of Harm’s Way: Preventing Toxic Threats to Child Development: Fact Sheets in English and Spanish.

Approaches to Healthy Living: A 4-page guide on how to avoid toxicants, eat healthier, reduce stress.

Healthy Aging: The Way Forward: An ecological approach to policy level interventions for healthy aging across the lifespan.

Continuing Education

Register for Continuing Education (CE) for *A Story of Health* for a variety of health professions. Free credits are offered by the Centers for Disease Control and Prevention/Agency for Toxic Substances and Disease Registry [at this link](#).



Another free CE course on environmental health offered by the CDC/ATSDR is the **Pediatric Environmental Health Toolkit** online course.

INFERTILITY

Reiko & Toshio's Story

Clinical and personal opportunities to support a healthy life and reproductive health

THINGS TO CONSIDER:

Learn to cook and eat a healthy diet

- Take recommended amounts of folic acid supplement (helps to prevent birth defects).
- Eat fresh fruits and vegetables, organic if possible.
- Never microwave your food in plastic (endocrine disruptors can leach from plastic).
- Avoid trans fats (in processed foods).
- Limit alcohol intake and avoid alcohol during pregnancy.
- Limit or eliminate sugary beverages.
- Eat more:
 - monounsaturated fats (such as in olive oil, avocados, nuts);
 - vegetable protein (such as in beans, peas, nuts, and soybeans or tofu);
 - high-fiber, low glycemic carbohydrates (whole grains, vegetables, whole fruits, and beans);

- plant sources of iron such as leafy green vegetables;
- fish high in omega 3 fatty acids (but avoid eating fish high in mercury – see fish guide resources.)

Reduce exposure to toxic substances

- Reduce exposure to indoor and outdoor air pollution including cigarette smoke.
- Reduce exposure to toxic chemicals in products including those used for household cleaning and personal care. Replace with less toxic alternatives.
- Reduce exposure to lead in paints and water.
- Eliminate or reduce pesticide use in home and lawn/garden.

For clinicians: Proposition 65

Links:

[Proposition 65](#)

[Fact sheets](#) for the public on Prop 65 chemicals

Additional Resources:

Reproductive health/infertility and the environment:

- [CHE](#) series of calls on infertility
- [PePH](#) – The environment’s role in infertility
- [TEDX](#) – The Endocrine Disruption Exchange

Personal actions to protect your health:

- [UCSF](#) Program on Reproductive Health and the Environment “Toxic Matters”

Fish consumption guidelines including those based on health, sustainability:

- [EPA/FDA](#) fish consumption guidelines
- [Physicians for Social Responsibility’s](#) “Healthy Fish, Healthy Families”
- [Monterey Bay Aquarium](#) “Seafood Watch”

Consumer product guides and apps including food, personal care, cleaning products:

- [Environmental Working Group’s](#) consumer guides
- [EPA’s](#) Safer Choice
- [Good Guide](#)
- [Silent Spring’s](#) “Detox Me”

In the workplace:

- [Occupational Safety and Health Administration: Reproductive Hazards/Possible Solutions](#)
- [A Guide for Nail Salon Workers](#)



INFERTILITY

Reiko & Toshio's Story

POLICY RECOMMENDATIONS

In Reiko and Toshio's story we have discussed a range of risk factors that may affect fertility and reproductive health. Reducing those risk factors may involve personal choices, but many require public policy actions.

Policies include legislative and institutional actions to reduce exposure to toxic chemicals, improve access to healthy food, and encourage community solutions to reduce social stressors, among others. At right are a few policy actions recommended to reduce reproductive health risk factors.

These include exposure to toxic chemicals, diet, body weight/excessive exercise, socioeconomics, genetics, and gene-environment interactions.

Regrettable substitutions

LINK: [The Commons Principles for Alternatives Assessment](#)



POLICY RECOMMENDATIONS

- Reduce exposure to reproductive and developmental toxicants through federal, state and local policies.**
 - ▶ Legislate policies that keep air, water, food, and other sources of exposure free of pollutants.
 - ▶ Ensure that consumer products, from household cleaning supplies to cosmetics, are free of harmful substances.
 - ▶ Promote public transportation to reduce air pollution sources.
 - ▶ Ensure that workers are not exposed to harmful substances on the job.
 - ▶ Reduce the use of pesticides in public spaces, schools, homes, workplaces and promote Integrated Pest Management (IPM).
- Increase access to healthy foods.**
 - ▶ Cities and towns can change zoning and tax laws to make it easier to create new grocery stores, farmers' markets, and community gardens.
 - ▶ Regulations and incentives can help existing stores increase the number and variety of healthy products they sell.
 - ▶ Maternal and child health programs, and food programs for low income families , young children, and elders, should prioritize optimum nutrition and include incentives and opportunities to purchase fresh, healthy foods.
 - ▶ Local governments can create food policy councils to give residents a voice on how best to improve access to healthy food.
 - ▶ Encourage breastfeeding through health care and workplace policies.
- Support services and increase communication and education on preconception health and prenatal health.**

All women and men can benefit from education on preconception health, whether or not they plan to have children as preconception health includes staying healthy throughout life. In addition, nearly half of all pregnancies in the United States are not planned.

 - ▶ Provide support for pregnant women through innovative programs such as group prenatal care.
 - ▶ Healthcare providers should include counseling on environmental influences on health and interventions to reduce risk in all specialties, from maternal and child health to elder care.

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Chemical Hazards

Air pollution

Checa Vizcaino, M.A., M. Gonzalez-Comadran, and B. Jacquemin. Outdoor air pollution and human infertility: a systematic review. *Fertil Steril*. 2016.

Currie, J. and R. Walker. Traffic Congestion and Infant Health: Evidence from E-ZPass. *American Economic Journal: Applied Economics*. 2011. 3(1): p. 65-90.

Dadvand, P., et al. Maternal exposure to particulate air pollution and term birth weight: a multi-country evaluation of effect and heterogeneity. *Environ Health Perspect*. 2013. 121(3): p. 267-373.

Devine, P.J., S.D. Perreault, and U. Luderer. Roles of Reactive Oxygen Species and Antioxidants in Ovarian Toxicity. *Biology of Reproduction*. 2012. 86(2): p. 27.

Gray, S.C., et al. Assessing the impact of race, social factors and air pollution on birth outcomes: a population-based study. *Environmental Health*. 2014. 13(1): p. 1-8.

Liu, S., et al. Association between gaseous ambient air pollutants and adverse pregnancy outcomes in Vancouver, Canada. *Environ Health Perspect*. 2003 Nov;111(14):1773-8.

Mahalingaiah, S., et al. Adult air pollution exposure and risk of infertility in the Nurses' Health Study II. *Hum Reprod*. 2016. 31(3): p. 638-47.

Mohallem, S.V., et al. Decreased fertility in mice exposed to environmental air pollution in the city of Sao Paulo. *Environ Res*. 2005. 98(2): p. 196-202.

Nieuwenhuijsen, M.J., et al. Air pollution and human fertility rates. *Environ Int*. 2014. 70: p. 9-14.

Perin, P.M., et al. Impact of short-term preconceptional exposure to particulate air pollution on treatment outcome in couples undergoing in vitro fertilization and embryo transfer (IVF/ET). *J Assist Reprod Genet*. 2010. 27(7): p. 371-82.



Perin, P.M., et al. Effects of exposure to high levels of particulate air pollution during the follicular phase of the conception cycle on pregnancy outcome in couples undergoing in vitro fertilization and embryo transfer. *Fertil Steril*. 2010. 93(1): p. 301-3.

Reproductive and Cancer Hazard Assessment Branch Office of Environmental Health Hazard Assessment California Environmental Protection Agency. Evidence on the developmental and reproductive toxicity of sulfur dioxide Feb 2011. oehha.ca.gov/media/downloads/proposition-65//so2hid022511.pdf

Slama, R., et al. Short-term impact of atmospheric pollution on fecundability. *Epidemiology*. 2013. 24(6): p. 871-9.

Veras, M.M., et al. Chronic exposure to fine particulate matter emitted by traffic affects reproductive and fetal outcomes in mice. *Environ Res*. 2009. 109(5): p. 536-43.

Chemical Hazards

Endocrine Disruptors

Bromer JG, Zhou Y, Taylor MB, Doherty L, Taylor HS. Bisphenol-A exposure in utero leads to epigenetic alterations in the developmental programming of uterine estrogen response. *FASEB journal: official publication of the Federation of American Societies for Experimental Biology*. 2010;24(7):2273-2280.

Calafat AM, Ye X, Wong LY, Reidy JA, Needham LL. Exposure of the U.S. population to bisphenol A and 4-tertiary-octylphenol: 2003-2004. *Environ Health Perspect*. 2008;116(1):39-44.

Diamanti-Kandarakis E, Bourguignon JP, Giudice LC, et al. Endocrine-disrupting chemicals: an Endocrine Society scientific statement. *Endocr Rev*. 2009;30(4):293-342.

Ehrlich S, Williams PL, Missmer SA, et al. Urinary bisphenol A concentrations and early reproductive health outcomes among women undergoing IVF. *Human reproduction (Oxford, England)*. 2012;27(12):3583-3592.

FitzGerald RE, Wilks MF. Bisphenol A--Why an adverse outcome pathway framework needs to be applied. *Toxicology letters*. 2014;230(2):368-374.

Furst P. Dioxins, polychlorinated biphenyls and other organohalogen compounds in human milk. Levels, correlations, trends and exposure through breastfeeding. *Mol Nutr Food Res*. 2006;50(10):922-933.

Gore AC, Chappell VA, Fenton SE, et al. EDC-2: The Endocrine Society's Second Scientific Statement on Endocrine-Disrupting Chemicals. *Endocr Rev*. 2015;36(6):E1-E150.

Grun F, Blumberg B. Environmental obesogens: organotins and endocrine disruption via nuclear receptor signaling. *Endocrinology*. 2006;147(6 Suppl):S50-55.

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References

Herbst AL, Ulfelder H, Poskanzer DC. Adenocarcinoma of the vagina. Association of maternal stilbestrol therapy with tumor appearance in young women. *N Engl J Med*. 1971;284(15):878-881.

Hernandez CJ, Beaupre GS, Carter DR. A theoretical analysis of the relative influences of peak BMD, age-related bone loss and menopause on the development of osteoporosis. *Osteoporos Int*. 2003;14(10):843-847.

Hoover RN, Hyer M, Pfeiffer RM, et al. Adverse health outcomes in women exposed in utero to diethylstilbestrol. *N Engl J Med*. 2011;365(14):1304-1314.

Kabir ER, Rahman MS, Rahman I. A review on endocrine disruptors and their possible impacts on human health. *Environ Toxicol Pharmacol*. 2015;40(1):241-258.

Kannus P, Niemi S, Parkkari J, et al. Why is the age-standardized incidence of low-trauma fractures rising in many elderly populations? *J Bone Miner Res*. 2002;17(8):1363-1367.

Kirchner S, Kieu T, Chow C, Casey S, Blumberg B. Prenatal exposure to the environmental obesogen tributyltin predisposes multipotent stem cells to become adipocytes. *Mol Endocrinol*. 2010;24(3):526-539.

Lees B, Molleson T, Arnett TR, Stevenson JC. Differences in proximal femur bone density over two centuries. *Lancet*. 1993;341(8846):673-675.

Min KB, Min JY. Urinary phthalate metabolites and the risk of low bone mineral density and osteoporosis in older women. *The Journal of clinical endocrinology and metabolism*. 2014;99(10):E1997-2003.

National Institute of Environmental Health Sciences. *Endocrine Disruptors*. 2010.

Palmer JR, Herbst AL, Noller KL, et al. Urogenital abnormalities in men exposed to diethylstilbestrol in utero: a cohort study. *Environmental health : a global access science source*. 2009;8:37.

Pillai HK, Fang M, Beglov D, et al. Ligand binding and activation of PPARgamma by Firemaster(R) 550: effects on adipogenesis and osteogenesis in vitro. *Environ Health Perspect*. 2014;122(11):1225-1232.

Rizzoli R, Bianchi ML, Garabedian M, McKay HA, Moreno LA. Maximizing bone mineral mass gain during growth for the prevention of fractures in the adolescents and the elderly. *Bone*. 2010;46(2):294-305.

Rubin BS. Bisphenol A: an endocrine disruptor with widespread exposure and multiple effects. *The Journal of steroid biochemistry and molecular biology*. 2011;127(1-2):27-34.

Swan SH, Main KM, Liu F, et al. Decrease in anogenital distance among male infants with prenatal phthalate exposure. *Environ Health Perspect*. 2005;113(8):1056-1061.

Watt J, Schlezinger JJ. Structurally-diverse, PPARgamma-activating environmental toxicants induce adipogenesis and suppress osteogenesis in bone marrow mesenchymal stromal cells. *Toxicology*. 2015;331:66-77.



Chemical Hazards

Lead and other metals

Grandjean P, Landrigan PJ. Neurobehavioural effects of developmental toxicity. *The Lancet Neurology*. 2014;13(3):330-338.

Rabito FA, Kocak M, Werthmann DW, Tylavsky FA, Palmer CD, Parsons PJ. Changes in low levels of lead over the course of pregnancy and the association with birth outcomes. *Reproductive toxicology (Elmsford, N.Y.)*. 2014;50:138-144.

Sallmen M. Exposure to lead and male fertility. *Int J Occup Med Environ Health*. 2001;14(3):219-222.

National Institute for Occupational Safety and Health. Workplace Safety & Health Topics: [Lead: Information for Workers](#). 2013.

Chemical Hazards

Pesticides

Abell A, Juul S, Bonde JP. Time to pregnancy among female greenhouse workers. *Scandinavian journal of work, environment & health*. 2000;26(2):131-136.

Harley KG, Marks AR, Bradman A, Barr DB, Eskenazi B. DDT exposure, work in agriculture, and time to pregnancy among farmworkers in California. *Journal of occupational and environmental medicine/American College of Occupational and Environmental Medicine*. 2008;50(12):1335-1342.

Lam T, Williams PL, Lee MM, et al. Prepubertal Serum Concentrations of Organochlorine Pesticides and Age at Sexual Maturity in Russian Boys. *Environ Health Perspect*. 2015;123(11):1216-1221.

Roeleveld N, Bretveld R. The impact of pesticides on male fertility. *Curr Opin Obstet Gynecol*. 2008;20(3):229-233.

Sanborn M, Kerr KJ, Sanin LH, Cole DC, Bassil KL, Vakil C. Non-cancer health effects of pesticides: systematic review and implications for family doctors. *Canadian family physician Medecin de famille canadien*. 2007;53(10):1712-1720.

Sharpe RM, Fisher JS, Millar MM, Jobling S, Sumpter JP. Gestational and lactational exposure of rats to xenoestrogens results in reduced testicular size and sperm production. *Environ Health Perspect*. 1995;103(12):1136-1143.

Chemical Hazards

Phthalates

Marsee K, Woodruff TJ, Axelrad DA, Calafat AM, Swan SH. Estimated daily phthalate exposures in a population of mothers of male infants exhibiting reduced anogenital distance. *Environ Health Perspect*. 2006;114(6):805-809.

Swan SH, Main KM, Liu F, et al. Decrease in anogenital distance among male infants with prenatal phthalate exposure. *Environ Health Perspect*. 2005;113(8):1056-1061.

Chemical Hazards

Polybrominated Diethyl
Ethers (PBDEs)

Johnson PI, Stapleton HM, Mukherjee B, Hauser R, Meeker JD. Associations between brominated flame retardants in house dust and hormone levels in men. *The Science of the Total Environment*. 2013;445-446:177-184.

Chemical Hazards

Safety Data Sheets

Nicol AM, Hurrell AC, Wahyuni D, McDowall W, Chu W. Accuracy, comprehensibility, and use of material safety data sheets: a review. *Am J Ind Med*. 2008;51(11):861-876.

Chemical Hazards

Solvents

Aschengrau A, Weinberg JM, Janulewicz PA, et al. Prenatal exposure to tetrachloroethylene-contaminated drinking water and the risk of congenital anomalies: a retrospective cohort study. *Environmental health : a global access science source*. 2009;8:44.

Aschengrau A, Weinberg JM, Janulewicz PA, et al. Affinity for risky behaviors following prenatal and early childhood exposure to tetrachloroethylene (PCE)-contaminated drinking water: a retrospective cohort study. *Environmental health : a global access science source*. 2011;10:102.

Chiu WA, Jinot J, Scott CS, et al. Human health effects of trichloroethylene: key findings and scientific issues. *Environ Health Perspect*. 2013;121(3):303-311.

Elliott RC, Jones JR, McElvenny DM, et al. Spontaneous abortion in the British semiconductor industry: An HSE investigation. Health and Safety Executive. *Am J Ind Med*. 1999;36(5):557-572.

Kumar S. Occupational, environmental and lifestyle factors associated with spontaneous abortion. *Reprod Sci*. 2011;18(10):915-930.

Logman JF, de Vries LE, Hemels ME, Khattak S, Einarson TR. Paternal organic solvent exposure and adverse pregnancy outcomes: a meta-analysis. *Am J Ind Med*. 2005;47(1):37-44.

McMartin KI, Chu M, Kopecky E, Einarson TR, Koren G. Pregnancy outcome following maternal organic solvent exposure: a meta-analysis of epidemiologic studies. *Am J Ind Med*. 1998;34(3):288-292.

Schettler T, Solomon G, Valenti M, A. H. Generations at Risk: Reproductive Health and the Environment. *Boston, MA: MIT Press*; 1999.

Snijder CA, te Velde E, Roeleveld N, Burdorf A. Occupational exposure to chemical substances and time to pregnancy: a systematic review. *Hum Reprod Update*. 2012;18(3):284-300.

Stillerman KP, Mattison DR, Giudice LC, Woodruff TJ. Environmental exposures and adverse pregnancy outcomes: a review of the science. *Reprod Sci*. 2008;15(7):631-650.

Climate change

Basu R, Malig B, Ostro B. High ambient temperature and the risk of preterm delivery. *American journal of epidemiology*. 2010;172(10):1108-1117.

Dadvand P, Basagana X, Sartini C, et al. Climate extremes and the length of gestation. *Environ Health Perspect*. 2011;119(10):1449-1453.

Khan AE, Scheelbeek PF, Shilpi AB, et al. Salinity in drinking water and the risk of (pre)eclampsia and gestational hypertension in coastal Bangladesh: a case-control study. *PloS One*. 2014;9(9):e108715.

Rylander C, Odland JO, Sandanger TM. Climate change and the potential effects on maternal and pregnancy outcomes: an assessment of the most vulnerable--the mother, fetus, and newborn child. *Glob Health Action*. 2013;6:19538.



Electromagnetic radiation

Adams JA, Galloway TS, Mondal D, Esteves SC, Mathews F. Effect of mobile telephones on sperm quality: a systematic review and meta-analysis. *Environment international*. 2014;70:106-112.

Avendano C, Mata A, Sanchez Sarmiento CA, Doncel GF. Use of laptop computers connected to internet through Wi-Fi decreases human sperm motility and increases sperm DNA fragmentation. *Fertility and sterility*. 2012;97(1):39-45.e32.

Gorpinchenko I, Nikitin O, Banyra O, Shulyak A. The influence of direct mobile phone radiation on sperm quality. *Central European journal of urology*. 2014;67(1):65-71.

Li DK, Yan B, Li Z, et al. Exposure to magnetic fields and the risk of poor sperm quality. *Reproductive toxicology (Elmsford, N.Y.)*. 2010;29(1):86-92.

Liu K, Li Y, Zhang G, et al. Association between mobile phone use and semen quality: a systemic review and meta-analysis. *Androl-ogy*. 2014;2(4):491-501.

Wang C, Cui YG, Wang XH, et al. transient scrotal hyperthermia and levonorgestrel enhance testosterone-induced spermatogenesis suppression in men through increased germ cell apoptosis. *The Journal of clinical endocrinology and metabolism*. 2007;92(8):3292-3304.

Zilberlicht A, Wiener-Megnazi Z, Sheinfeld Y, Grach B, Lahav-Baratz S, Dirnfeld M. Habits of cell phone usage and sperm quality - does it warrant attention? *Reprod Biomed Online*. 2015;31(3):421-426.

Endometriosis

Ahn SH, Monsanto SP, Miller C, Singh SS, Thomas R, Tayade C. Pathophysiology and Immune Dysfunction in Endometriosis. *BioMed research international*. 2015;2015:795976.

American College of Obstetrics and Gynecology Endometriosis. 2012.

American Society for Reproductive Medicine. *Fact sheet - Endometriosis: Does It Cause Infertility?*

Bruner-Tran KL, Osteen KG. Dioxin-like PCBs and endometriosis. *Syst Biol Reprod Med*. 2010;56(2):132-146.

Centers for Disease Control (CDC). Common Reproductive Health Concerns for Women: Endometriosis. 2015.

Crain DA, Janssen SJ, Edwards TM, et al. Female reproductive disorders: the roles of endocrine-disrupting compounds and developmental timing. *Fertility and sterility*. 2008;90(4):911-940.

de Ziegler D, Borghese B, Chapron C. Endometriosis and infertility: pathophysiology and management. *Lancet*. 2010;376(9742):730-738.

Hufnagel D, Li F, Cosar E, Krikun G, Taylor HS. The Role of Stem Cells in the Etiology and Pathophysiology of Endometriosis. *Seminars in reproductive medicine*. 2015;33(5):333-340.

Macer ML, Taylor HS. Endometriosis and infertility: a review of the pathogenesis and treatment of endometriosis-associated infertility. *Obstet Gynecol Clin North Am*. 2012;39(4):535-549.

Naqvi H, Ilagan Y, Krikun G, Taylor HS. Altered genome-wide methylation in endometriosis. *Reprod Sci*. 2014;21(10):1237-1243.

Upton K, De Roos AJ, Thompson ML, et al. Organochlorine pesticides and risk of endometriosis: findings from a population-based case-control study. *Environ Health Perspect*. 2013;121(11-12):1319-1324.

Upton K, Sathyanarayana S, Scholes D, Holt VL. Early-life factors and endometriosis risk. *Fertility and sterility*. 2015;104(4):964-971.e965.

Wolff EF, Sun L, Hediger ML, et al. In utero exposures and endometriosis: the Endometriosis, Natural History, Disease, Outcome (ENDO) Study. *Fertility and sterility*. 2013;99(3):790-795.

Endometriosis

Endometriosis Treatment

Brown J, Farquhar C. Endometriosis: an overview of Cochrane Reviews. *The Cochrane database of systematic reviews*. 2014(3):CD009590.

Lee HJ, Lee JE, Ku S-Y, et al. Natural conception rate following laparoscopic surgery in infertile women with endometriosis. *Clinical and Experimental Reproductive Medicine*. 2013;40(1):29-32.

Marcoux S, Maheux R, Berube S. Laparoscopic surgery in infertile women with minimal or mild endometriosis. *Canadian Collaborative Group on Endometriosis*. *N Engl J Med*. 1997;337(4):217-222.



Environmental disparities

ACOG. ACOG Committee Opinion No 575: Exposure to toxic environmental agents. *Obstet Gynecol*. 2013;122(4):931-935.

Di Renzo GC, Conry JA, Blake J, et al. International Federation of Gynecology and Obstetrics opinion on reproductive health impacts of exposure to toxic environmental chemicals. *Int J Gynaecol Obstet*. 2015;131(3):219-225.

Environmental history taking

ATSDR. ATSDR Case Studies in Environmental Medicine: *Taking an Exposure History*. 2015.

Chicago Consortium for Reproductive Environmental Health in Minority Communities (CREHM). *Prenatal Environmental Exposure History*.

National Environmental Education Foundation. *Taking a Pediatric Environmental Health History*.

Infertility

Causes – General

Aiken CE, Tarry-Adkins JL, Ozanne SE. Transgenerational Developmental Programming of Ovarian Reserve. *Sci Rep*. 2015;5:16175.

de Kretser DM. Male infertility. *The Lancet*. 349(9054):787-790.

Reiss HE. Population study of causes, treatment and outcome of infertility. *Br Med J (Clin Res Ed)*. 1986;292(6522):761.

Richardson MC, Guo M, Fauser BC, Macklon NS. Environmental and developmental origins of ovarian reserve. *Hum Reprod Update*. 2014;20(3):353-369.

Evaluation

ACOG *Infertility evaluation*.

Trends

CDC/National Center for Health Statistics. *National Survey of Family Growth*. 2012.

CDC/National Center for Health Statistics. *FastStats: Infertility*. 2015.

Chandra A, Copen CE, Stephen EH. Infertility and impaired fecundity in the United States, 1982-2010: data from the National Survey of Family Growth. *Natl Health Stat Report*. 2013(67):1-18, 11 p following 19.

Levine H, Jorgensen N, Andrade AM, Mendiola J, et al. Temporal trends in sperm count: a systematic review and meta-regression analysis. *Human Reprod Update*. 2017; 1-14.

Mascarenhas MN, Flaxman SR, Boerma T, Vanderpoel S, Stevens GA. National, regional, and global trends in infertility prevalence since 1990: a systematic analysis of 277 health surveys. *PLoS Med*. 2012;9(12):e1001356.

Speroff L, Glass R, N K. Clinical gynecologic endocrinology and infertility. Baltimore: Williams and Wilkins; 1994.

Nutrition

American College of Obstetricians and Gynecologists. *ACOG statement on prenatal nutrition*. 2015.

Buck Louis GM, Sapra KJ, Schisterman EF, et al. Lifestyle and pregnancy loss in a contemporary cohort of women recruited before conception: The LIFE Study. *Fertility and sterility*. 2016;106(1):180-188.

Chan KA, Tsoulis MW, Sloboda DM. Early-life nutritional effects on the female reproductive system. *The Journal of endocrinology*. 2015;224(2):R45-62.

Chavarro JE, Rich-Edwards JW, Rosner B, Willett WC. A prospective study of dairy foods intake and anovulatory infertility. *Human reproduction (Oxford, England)*. 2007;22(5):1340-1347.

Chavarro JE, Rich-Edwards JW, Rosner BA, Willett WC. Diet and lifestyle in the prevention of ovulatory disorder infertility. *Obstet Gynecol*. 2007;110(5):1050-1058.

Jacka FN, Ystrom E, Brantsaeter AL, et al. Maternal and early postnatal nutrition and mental health of offspring by age 5 years: a prospective cohort study. *J Am Acad Child Adolesc Psychiatry*. 2013;52(10):1038-1047.

U.S. Preventive Services Task Force. Folic acid for the prevention of neural tube defects: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2009; 150:626-631.

Occupational health

Cloeren M, Gean C, Kesler D, et al. American College of Occupational and Environmental Medicine's Occupational and Environmental Medicine Competencies-2014: ACOEM OEM Competencies Task Force*. *Journal of occupational and environmental medicine / American College of Occupational and Environmental Medicine*. 2014;56(5):e21-40.

Luderer U, Hieb M, Diaz J, Baker B, American College of Occupational and Environmental Med. Reproductive and developmental hazard management guidance: ACOEM Task Force on Reproductive Toxicology. *Journal of Occupational and Environmental Medicine*. 2011;53(8):941-949.

Schrader SM, Marlow KL. Assessing the reproductive health of men with occupational exposures. *Asian Journal of Andrology* 2014 16, (23–30).

Snijder CA, te Velde E, Roeleveld N, Burdorf A. Occupational exposure to chemical substances and time to pregnancy: a systematic review. *Hum Reprod Update*. 2012;18(3):284-300.

U.S. Equal Employment Opportunities Commission. EEOC Enforcement Guidance on Pregnancy Discrimination and Related Issues. In: *U.S. Equal Employment Opportunities Commission*, ed. 2015.

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Parabens

Ahn HJ, An BS, Jung EM, Yang H, Choi KC, Jeung EB. Parabens inhibit the early phase of folliculogenesis and steroidogenesis in the ovaries of neonatal rats. *Mol Reprod Dev.* 2012 Sep;79(9):626-36.

Chen J, Ahn KC, Gee NA, Gee SJ, Hammock BD, Lasley BL. 2007. Antiandrogenic properties of parabens and other phenolic containing small molecules in personal care products. *Toxicol Appl Pharmacol* 221(3):278-284.

Fisher M, MacPherson S, Braun JM, Hauser R, Walker M, Feeley M, et. al. Paraben concentrations in maternal urine and breast milk and its association with personal care product use. *Environ Sci Technol.* 2017 Mar 20.

Lee JH, Lee M, Ahn C, Kang HY, Tran DN, Jeung EB. Parabens accelerate ovarian dysfunction in a 4-vinylcyclohexene diepoxide-induced ovarian failure model. *Int J Environ Res Public Health.* 2017 Feb 8;14(2).

Mínguez-Alarcón L, Chiu YH, Messerlian C, Williams PL, Sabatini ME, Toth TL, et. al. Urinary paraben concentrations and in vitro fertilization outcomes among women from a fertility clinic. *Fertil Steril.* 2016 Mar;105(3):714-2.

National Toxicology Program. 2005. Butylparaben [CAS No. 94-26- 8]: *Review of Toxicological Literature.*

Smarr MM, Sundaram R, Honda M, Kannan K, Buck Louis GM. Urinary concentrations of parabens and other antimicrobial chemicals and their association with couples' fecundity. *Environ Health Perspect.* 2016 Jun 10.

Smith KW, Souter I, Dimitriadis I, Ehrlich S, Williams PL, Calafat AM, Hauser R. Urinary paraben concentrations and ovarian aging among women from a fertility center. *Environ Health Perspect.* 2013 Nov-Dec;121(11-12):1299-305.

Vo TT, Yoo YM, Choi KC, Jeung EB. 2010. Potential estrogenic effect(s) of parabens at the prepubertal stage of a postnatal female rat model. *Reprod Toxicol* 29(3):306-316.



Placenta

Barker DJ, Thornburg KL. Placental programming of chronic diseases, cancer and lifespan: a review. *Placenta.* 2013;34(10):841-845.

Barker DJP. Developmental origins of chronic disease. *Public Health.* 2012;126(3):185-189.

Barker DJP, Lampl M, Roseboom T, Winder N. Resource allocation in utero and health in later life. *Placenta.* 2012;33, Supplement 2:e30-e34.

Gundacker C, Hengstschlager M. The role of the placenta in fetal exposure to heavy metals. *Wiener medizinische Wochenschrift* (1946). 2012;162(9-10):201-206.

Januar V, Desoye G, Novakovic B, Cvitic S, Saffery R. Epigenetic regulation of human placental function and pregnancy outcome: considerations for causal inference. *American Journal of Obstetrics and Gynecology.* 2015;213(4, Supplement):S182-S196.

Maccani JZ, Koestler DC, Houseman EA, Marsit CJ, Kelsey KT. Placental DNA methylation alterations associated with maternal tobacco smoking at the RUNX3 gene are also associated with gestational age. *Epigenomics.* 2013;5(6):619-630.

Nelson DM. How the placenta affects your life, from womb to tomb. *Am J Obstet Gynecol.* 2015;213(4, Supplement):S12-S13.

Thornburg KL, Marshall N. The placenta is the center of the chronic disease universe. *Am J Obstet Gynecol.* 2015;213(4 Suppl):S14-20.

Polycystic ovary syndrome

Barrett ES, Sobolewski M. Polycystic ovary syndrome: do endocrine-disrupting chemicals play a role? *Seminars in Reproductive Medicine.* 2014;32(3):166-176.

Nilsson E, Larsen G, Manikkam M, Guerrero-Bosagna C, Savenkova MI, Skinner MK. Environmentally induced epigenetic transgenerational inheritance of ovarian disease. *PloS One.* 2012;7(5):e36129.

Preconception health

Centers for Disease Control (CDC). *Preconception Health and Health Care.* 2015.

Gerson M, Van den Eeden SK, Gahagan P. Take-home lead poisoning in a child from his father's occupational exposure. *Am J Ind Med.* 1996 May;29(5):507-8.

Fenske RA, Lu C, Negrete M, Galvin K. Breaking the take home pesticide exposure pathway for agricultural families: workplace predictors of residential contamination. *Am J Ind Med.* 2013 Sep;56(9):1063-71.

Lambrot R, Xu C, Saint-Phar S, Chountalos G, Cohen T, Paquet M. Suderman M, Hallett M, and Kimmins S. Low paternal dietary folate alters the mouse sperm epigenome and is associated with negative pregnancy outcomes. *Nature Communications* 4. 2013; Article number:2889.

Lyall K, Schmidt R, Hertz-Picciotto I. Maternal lifestyle and environmental risk factors for autism spectrum disorders. *Int J Epidemiol* 2014;43(2):443-464.

McDiarmid MA, Gehle K. Pre-conception brief: occupational/ environmental exposures. *Maternal and Child Health Journal.* 2006;10(5 Suppl):S123-128.

Metayer C, Milne E, Dockerty JD, et al. Maternal Supplementation with Folic Acid and Other Vitamins and Risk of Leukemia in the Offspring: a Childhood Leukemia International Consortium Study. *Epidemiology.* 2014 Nov;25(6):811-22.

Roberts JR, Karr CJ. Council on Environmental Health. Pesticide exposure in children. *Pediatrics.* 2012 Dec;130(6):e1765-88.

Schmidt RJ, Tancredi DJ, Ozonoff S, et al. Maternal periconceptional folic acid intake and risk of autism spectrum disorders and developmental delay in the CHARGE (CHildhood Autism Risks from Genetics and Environment) case-control study. *Am J Clin Nutr* 2012;96:80-9.

Surén P, Roth C, Bresnahan M, Haugen M, Hornig M, Hirtz D, Lie KK, Lipkin WI, Magnus P, Reichborn-Kjennerud T, Schjølberg S, Davey Smith G, Øyen AS, Susser E, Stoltenberg C. Association between maternal use of folic acid supplements and risk of autism spectrum disorders in children. *JAMA.* 2013 Feb 13;309(6):570-7.

Prenatal health

American College of Obstetricians and Gynecologists. *Good Health Before Pregnancy: Preconception Care.* 2015.

American Congress of Obstetricians and Gynecologists. *Toxic Environmental Agents.*

Centers for Disease Control (CDC). *Pregnancy: During Pregnancy.* 2016.

Program on Reproductive Health and the Environment, Univ of Cal. San Francisco. *Toxic Matters.* 2015.

Royal College of Obstetrics and Gynecology. Chemical Exposures During Pregnancy: *Dealing with Potential, but Unproven, Risks to Child Health.* 2013.

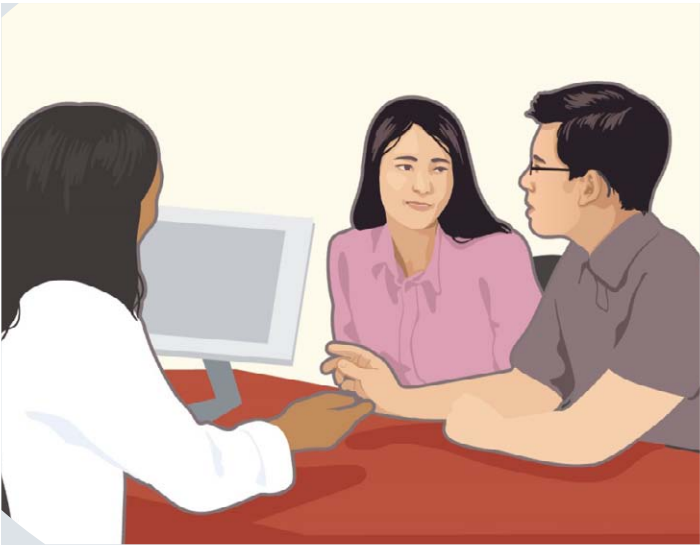
Program on Reproductive Health and the Environment. *Resources for health care professionals to promote environmental health.* 2015.

Group Prenatal Care

Ickovics JR, Earnshaw V, Lewis JB, et al. Cluster Randomized Controlled Trial of Group Prenatal Care: Perinatal Outcomes Among Adolescents in New York City Health Centers. *Am Journal Public Health.* 2016;106(2):359-365.

Ickovics JR, Kershaw TS, Westdahl C, et al. Group prenatal care and perinatal outcomes: a randomized controlled trial. *Obstet Gynecol.* 2007;110(2 Pt 1):330-339.

Ickovics JR, Reed E, Magriples U, Westdahl C, Schindler Rising S, Kershaw TS. Effects of group prenatal care on psychosocial risk in pregnancy: results from a randomised controlled trial. *Psychol Health.* 2011;26(2):235-250.



Testicular dysgenesis syndrome

Mendiola J, Stahlhut RW, Jørgensen N, Liu F, Swan SH. Shorter anogenital distance predicts poorer semen quality in young men in Rochester, New York. *Environ Health Perspect.* 2011. 119:958-963.

Skakkebaek N. A brief review of the link between environment and male reproductive health: lessons from studies of testicular germ cell cancer. *Horm Res Paediatr.* 2016. Feb 13. [Epub ahead of print]

Virtanen H, Rajpert-De Meyts E, Main K, Skakkebaek N, Toppari J. Testicular dysgenesis syndrome and the development and occurrence of male reproductive disorders. *Toxicol Appl Pharmacol.* 2005. 207(2 suppl):501-505.

Tracking of reproductive disorders

Centers for Disease Control & Prevention. *Reproductive and Birth Outcomes.* 2012.

Centers for Disease Control & Prevention. *Tracking Birth Defects.* 2012.

Centers for Disease Control and Prevention. *National Environmental Public Health Tracking Program.*

Unintended adverse consequences of environmental improvements

Flint water crisis: Bellinger DC. Lead Contamination in Flint--An Abject Failure to Protect Public Health. *N Engl J Med.* 2016;374(12):1101-1103.

Vinyl-lined pipes and their installation: Larson CD, Love OT, Reynolds G, McCallie SW, Moser RH, Calabrese EJ. Tetrachloroethylene leached from lined asbestos-cement pipe into drinking water [with Discussion]. *Journal American Water Works Association.* 1983;75(4):184-190.

Massachusetts Department of Environmental Quality Engineering. Status report on tetrachloroethylene contamination of public drinking water supplies caused by vinyl-lined asbestos cement pipe. Boston 1982.

EPANET modeling software: Rossman L. EPANET users manual. Cincinnati, OH: Environmental Protection Agency, *Risk Reduction Engineering Laboratory*;1994.

Birth defects: Aschengrau A, Weinberg JM, Janulewicz PA, et al. Prenatal exposure to tetrachloroethylene-contaminated drinking water and the risk of congenital anomalies: a retrospective cohort study. *Environmental health: a global access science source.* 2009;8:44.

Stillbirths: Carwile JL, Mahalingaiah S, Winter MR, Aschengrau A. Prenatal drinking-water exposure to tetrachloroethylene and ischemic placental disease: a retrospective cohort study. *Environmental health: a global access science source.* 2014;13:72.

Risky behaviors: Aschengrau A, Weinberg JM, Janulewicz PA, et al. Affinity for risky behaviors following prenatal and early childhood exposure to tetrachloroethylene (PCE)-contaminated drinking water: a retrospective cohort study. *Environmental health : a global access science source.* 2011;10:102.

Weight and Body Mass Index Centers for Disease Control & Prevention. *Body Mass Index (BMI) calculator* 2015.

Jacobsen BK, Knutsen SF, Oda K, Fraser GE. Body mass index at age 20 and subsequent childbearing: the Adventist Health Study-2. *J Womens Health (Larchmt).* 2013;22(5):460-466.

DIABETES

Marcela's Story

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