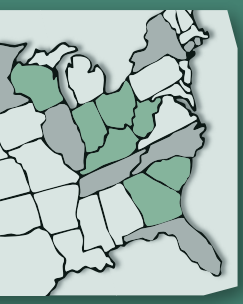
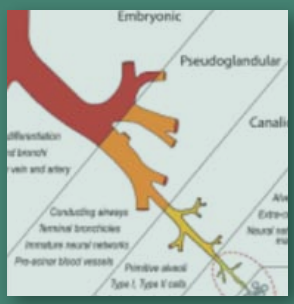
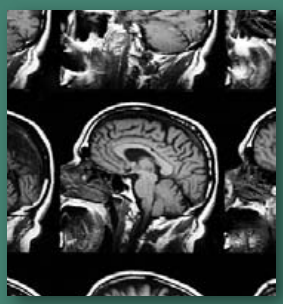
A Story of Health







ACKNOWLEDGEMENTS

Primary Development Organizations

The Agency for Toxic Substances and Disease Registry (ATSDR), the Collaborative on Health and the Environment (CHE), the Office of Environmental Health Hazard Assessment, California Environmental Protection Agency (OEHHA), the Science and Environmental Health Network (SEHN), and the University of California, San Francisco, Pediatric Environmental Health Specialty Unit (UCSF PEHSU) teamed up to leverage our combined resources to develop and produce *A Story of Health*.

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Suggested citation: Miller M, Schettler T, Tencza B, Valenti M. *A Story of Health*. Agency for Toxic Substances and Disease Registry, Collaborative on Health and the Environment, Science and Environmental Health Network, University of California, San Francisco, Pediatric Environmental Health Specialty Unit. PDF file online.

Dedication:

This eBook is dedicated to our designer Stephen Burdick for his extraordinary talent and vision.
- The authors.

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REVIEWERS

We gratefully acknowledge the following people who reviewed draft sections of a Story of Health, noting that their review does not constitute an endorsement of the findings or conclusions. Any errors or misrepresentations that remain are entirely the responsibility of the authors.

Introduction and Asthma (Brett's Story): Polly Hoppin; Catherine Karr; Brian Linde; Maria Mirabelli; Madeleine Scammell; Rebecca Wolf

Developmental Disabilities (Amelia's Story): David Bellinger; Lucy Crain; Katherine Herz; Brian Linde; Elise Miller; Leslie Rubin; Madeleine Scammell; Maureen Swanson

Childhood Cancer (Stephen's Story): Myles Abbott; Gary Dahl; Maida Galvez; Catherine Metayer; Elizabeth Raetz; Joshua Schiffman; Oscar Tarrago; Christopher Vlasses; Joseph Wiemels

FUNDERS

In addition to significant in-kind contributions from all of the primary development organizations, we are grateful to the following funders who have made this project possible:

Agency for Toxic Substances and Disease Registry (ATSDR)

The John Merck Fund

The Jacob & Valeria Langeloth Foundation

The Office of Environmental Health Hazard Assessment, California Environmental Protection Agency (OEHHA)

The UCSF PEHSU

The US Environmental Protection Agency

Disclaimers:

1. The UCSF Regional 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 1U61TS000238-01from the Agency for Toxic Substances and Disease Registry (ATSDR).

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.

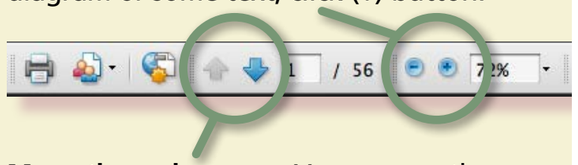
3. The ATSDR, US EPA, and Cal EPA/OEHHA do not endorse the purchase of any commercial products or services mentioned in this publication.

HELP PAGE How to Navigate Our eBook

Adobe Acrobat Tools

This interactive pdf document is best viewed on a laptop or desktop, down-loaded and opened in a current version of Adobe Acrobat Reader. Refer to the top Adobe menu bar for features including:

Magnify - If you want to enlarge a diagram or some text, click (+) button.



Move through pages - You can use the up and down arrows to move through pages.

You can also move through pages using the scroll up and down feature to the right of your screen.

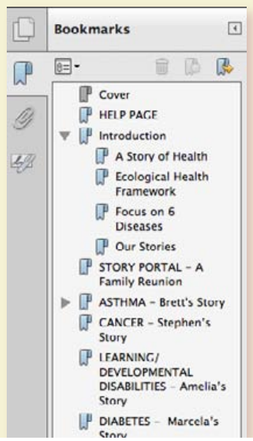


Table of Contents

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.

Skip this section - If you wish to skip a technical section, choose the "Skip this section" arrow and you will jump to the page after the technical sections ends.

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.

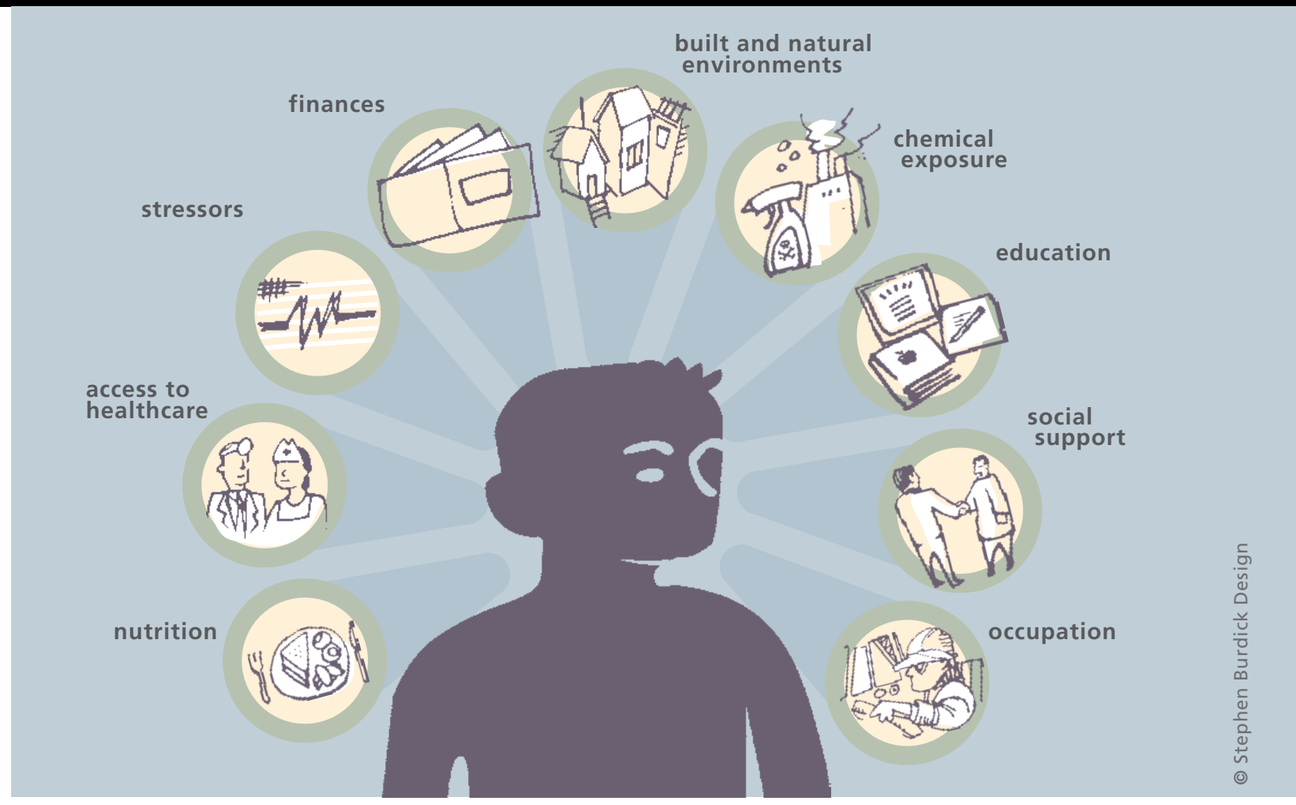
Important determinants of health come from the natural, built, chemical, food, economic, and social environments.

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. These aspects of our lives are not independent of one and other.

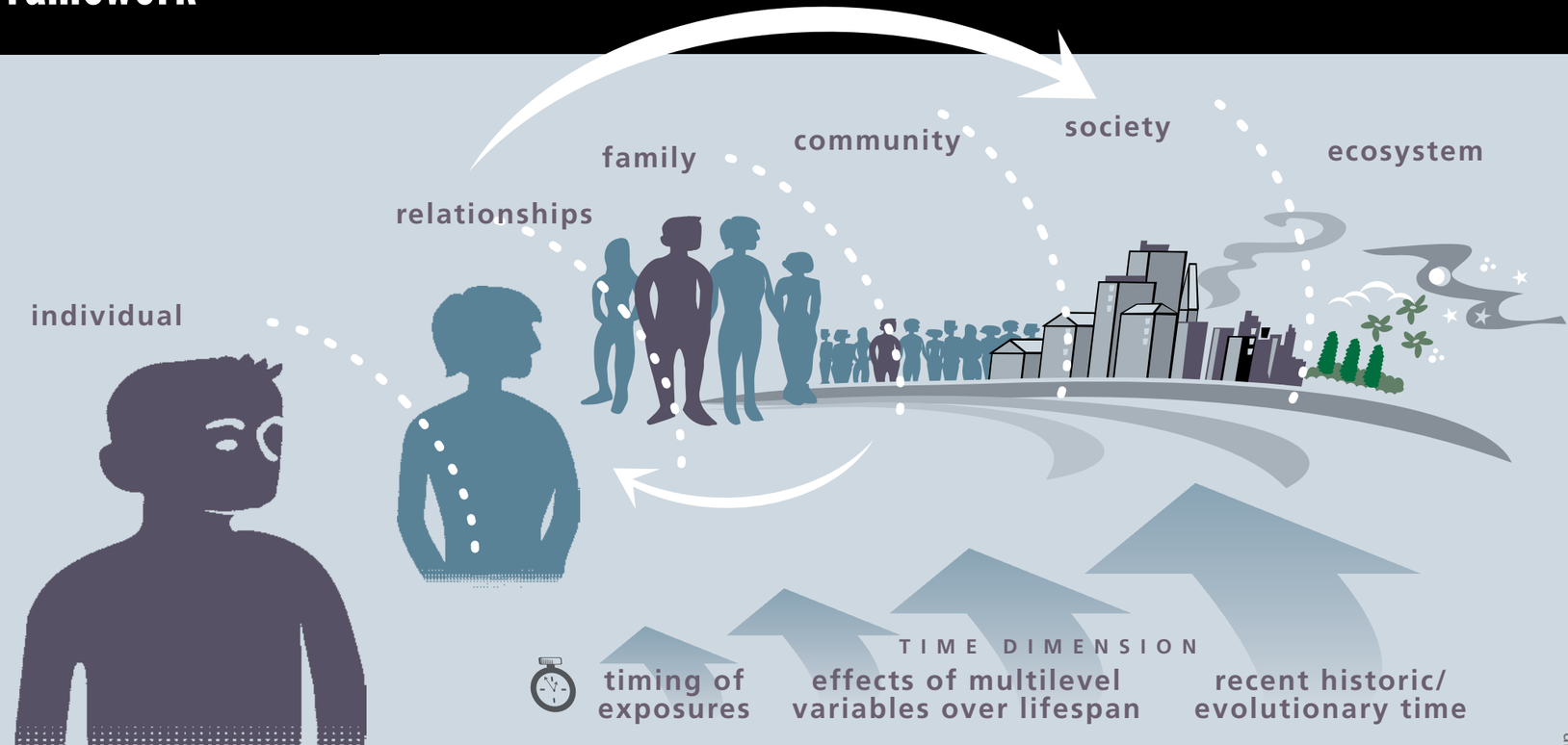
Rarely is one particular thing responsible for health or disease, so we refer to this as a multifactorial (or ecological) approach, the best way to promote health and prevent disease.

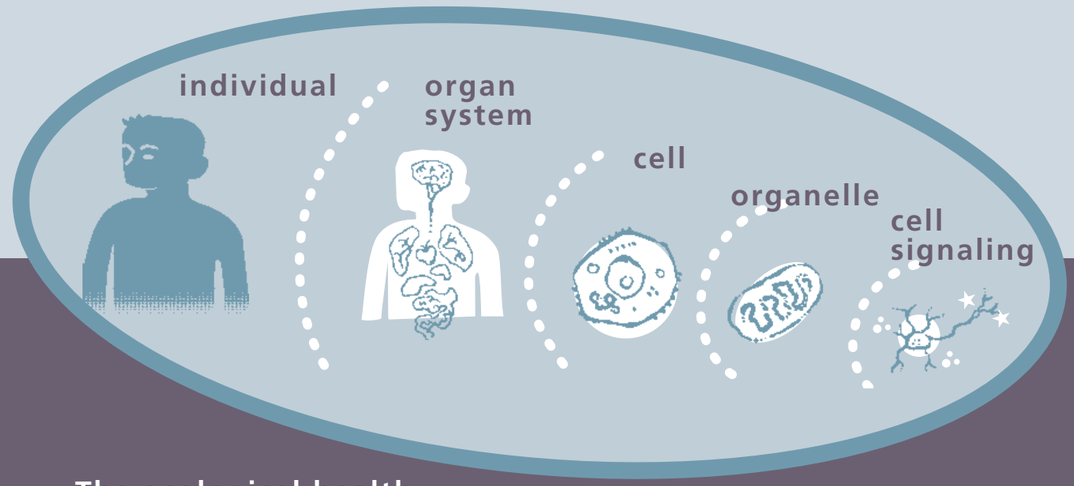
INTRODUCTION Ecological Health Framework

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.

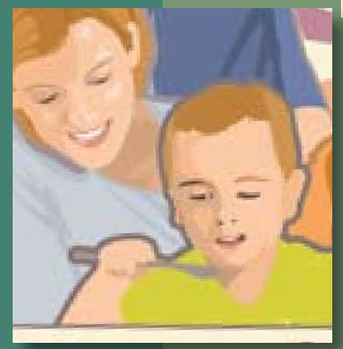
They include:

- 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 CE credits 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.

Asthma | Cancer | Learning/ Developmental Disabilities | Diabetes | Infertility | Cognitive Decline

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 credits for each story (credits are offered by 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:

- Brett's Story (Asthma) >
- Stephen's Story (Cancer/Childhood Leukemia) >
- Amelia's Story (Developmental Disabilities) >

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.

Basic information: Click here to find out more about 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.

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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.

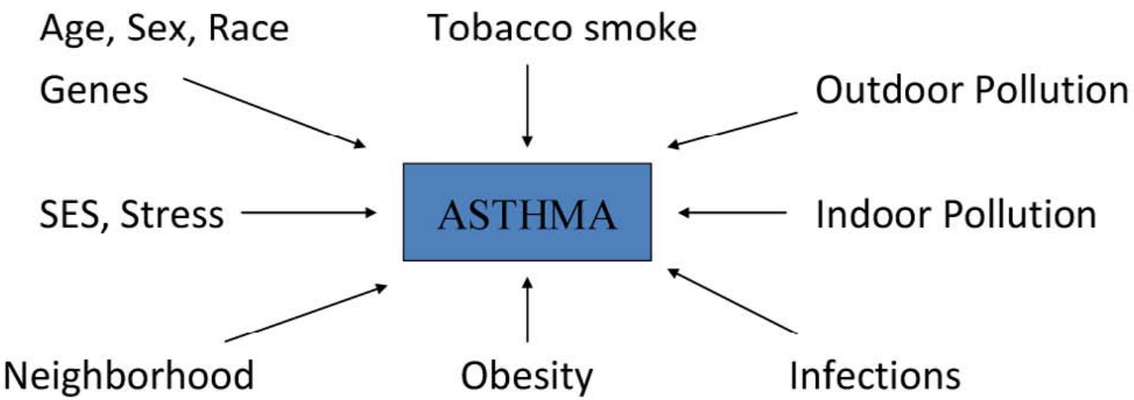
Key Concept: Addressing disease risks in individuals and populations

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 morality 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.

Causes vs. Triggers of Asthma

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)

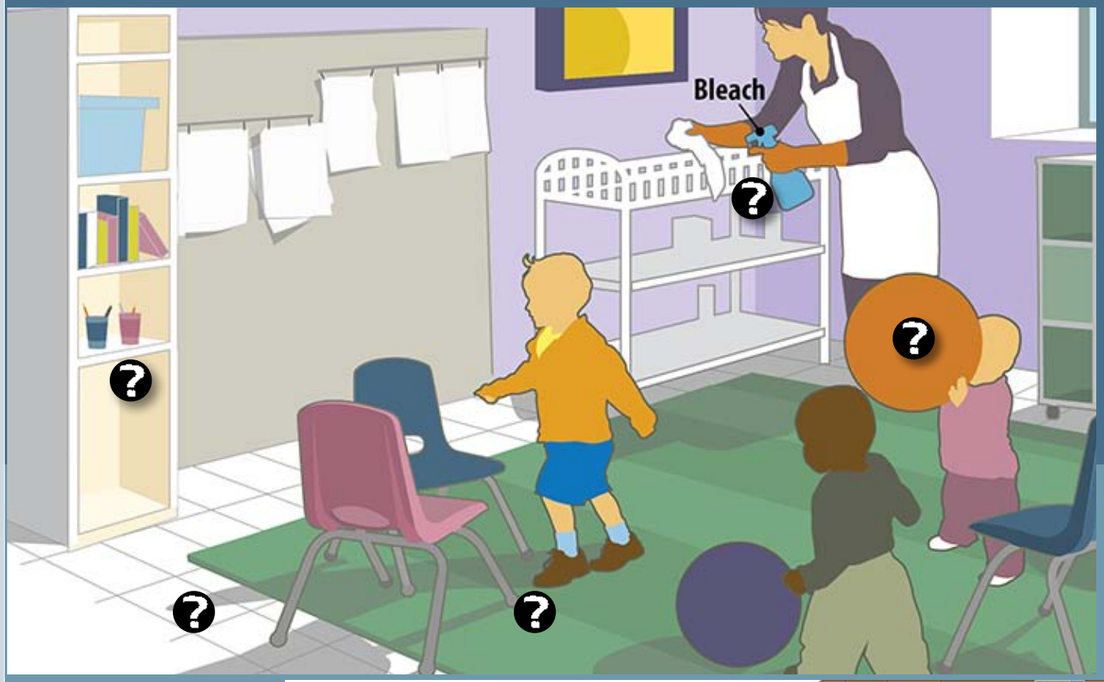
EPA's Asthma Home Environment Checklist

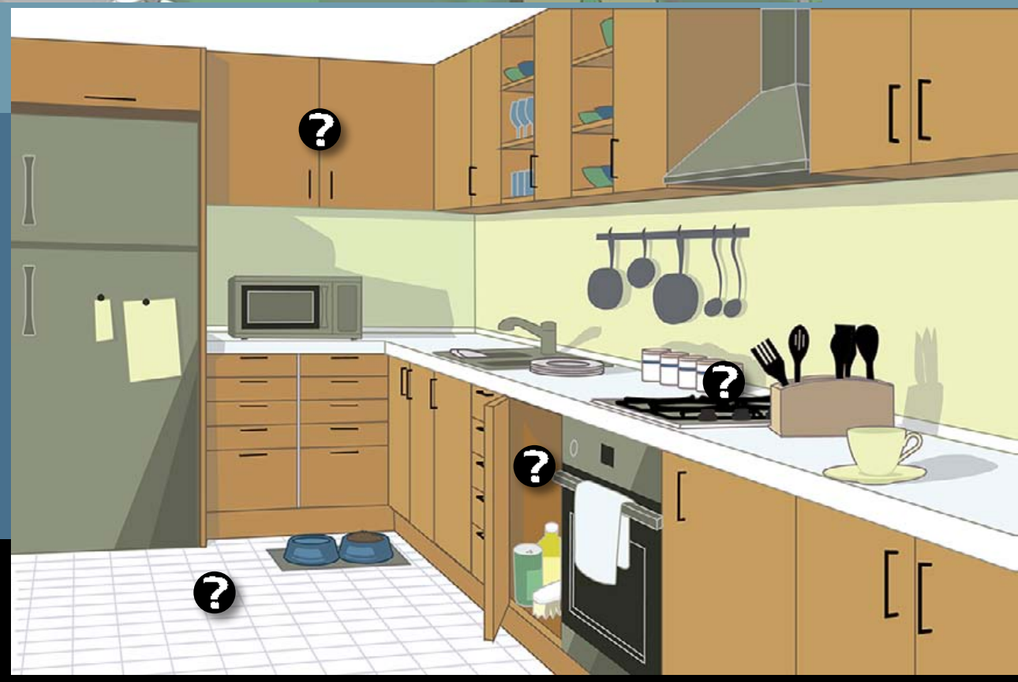
For Clinicians:

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
- building custodians
- detergent manufacturers
- drug manufacturers
- farmers
- grain elevator workers
- hair stylists
- laboratory workers
- nurses
- metal workers
- millers
- 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.

More information on acetaminophen

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.

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

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.

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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. CurrOpin 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 RespirCrit Care Med. 2011 May 15;183(10):1336-43. Epub 2011 Feb 4.

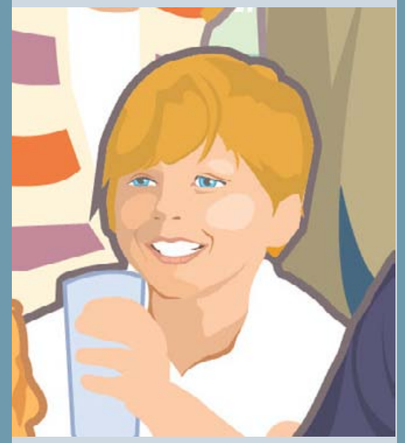
ASTHMA: Triggers

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:

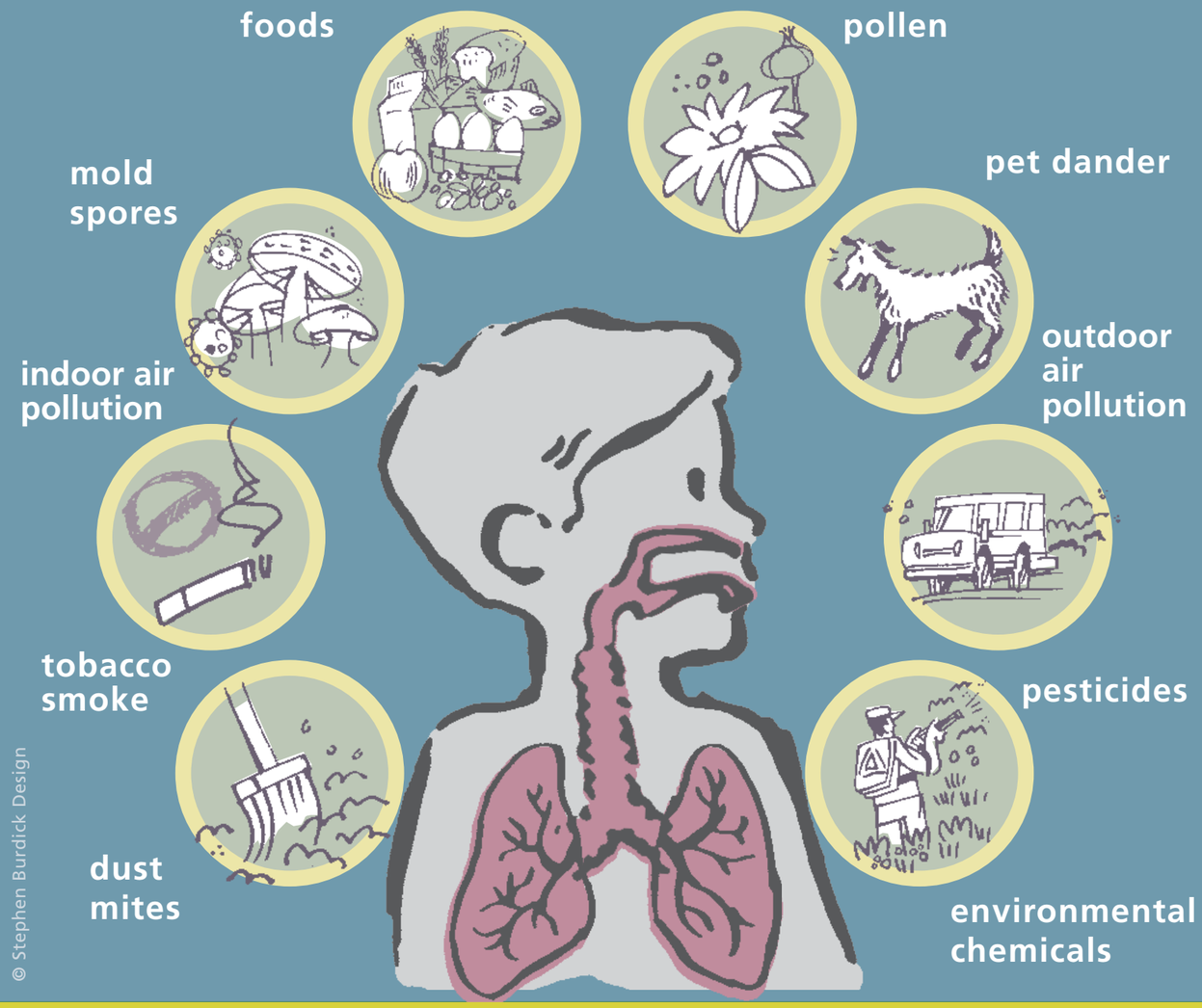
- indoor air pollutants such as tobacco smoke, outdoor air pollution;
- other environmental chemicals including pesticides, and;
- allergens including mold, pollen, cockroach droppings and pet dander.

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.



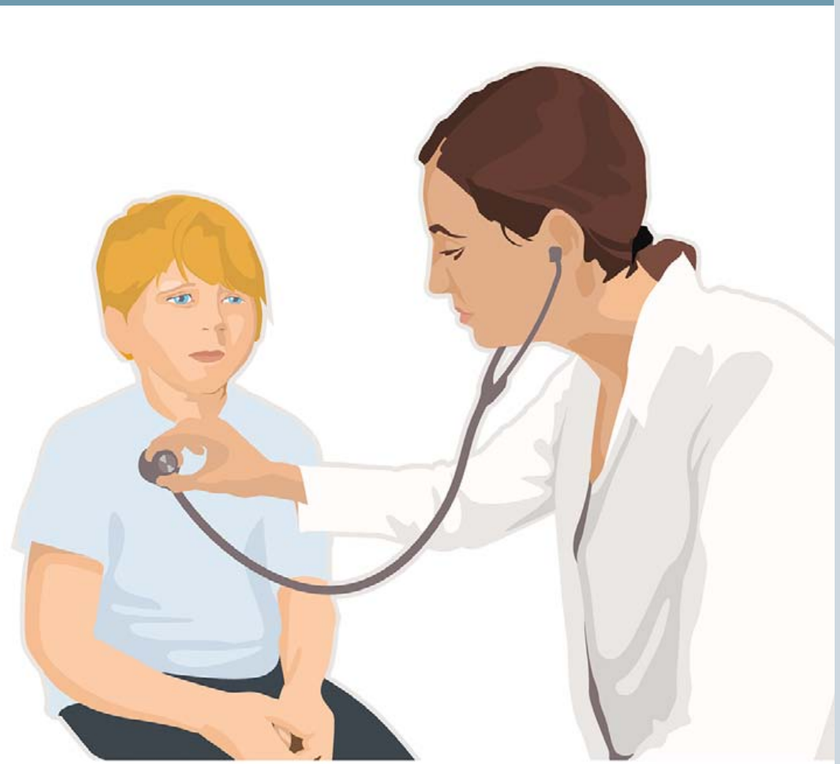
Potential Asthma Triggers

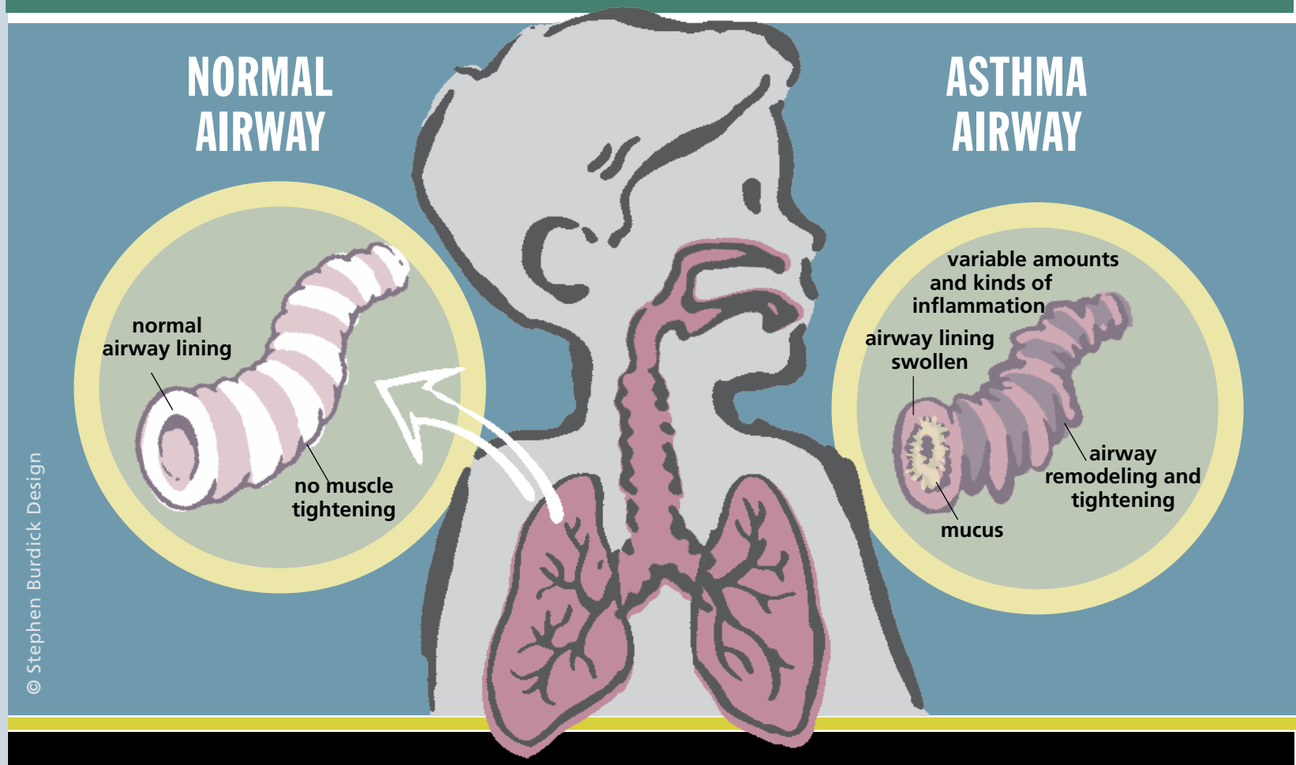


ASTHMA: Effects on the Lungs and Immune System

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.)





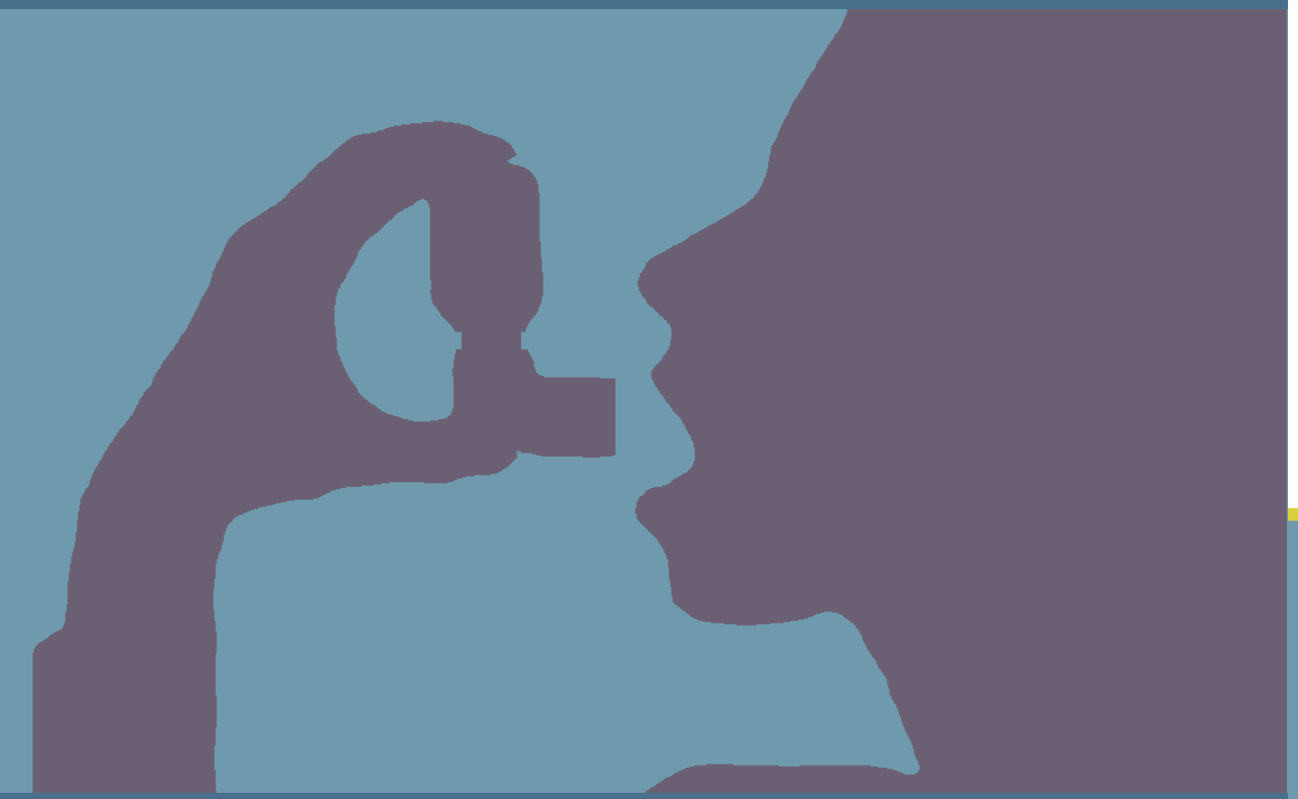
ASTHMA and Lung Development

THE LUNG IS SUSCEPTIBLE TO MANY INFLUENCES DURING EARLY DEVELOPMENT.

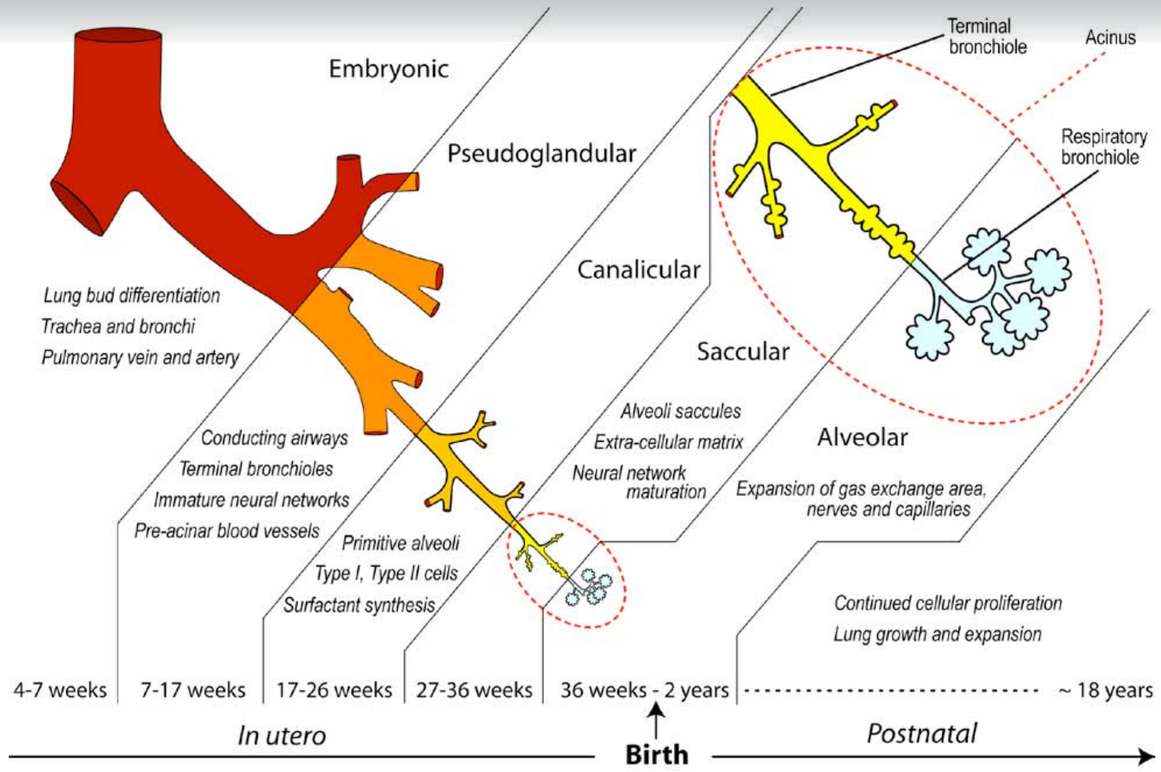
Though the lung develops into a functioning organ during the fetal period, important stages in lung growth and development continue during early childhood and may be altered by environmental exposures.

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.

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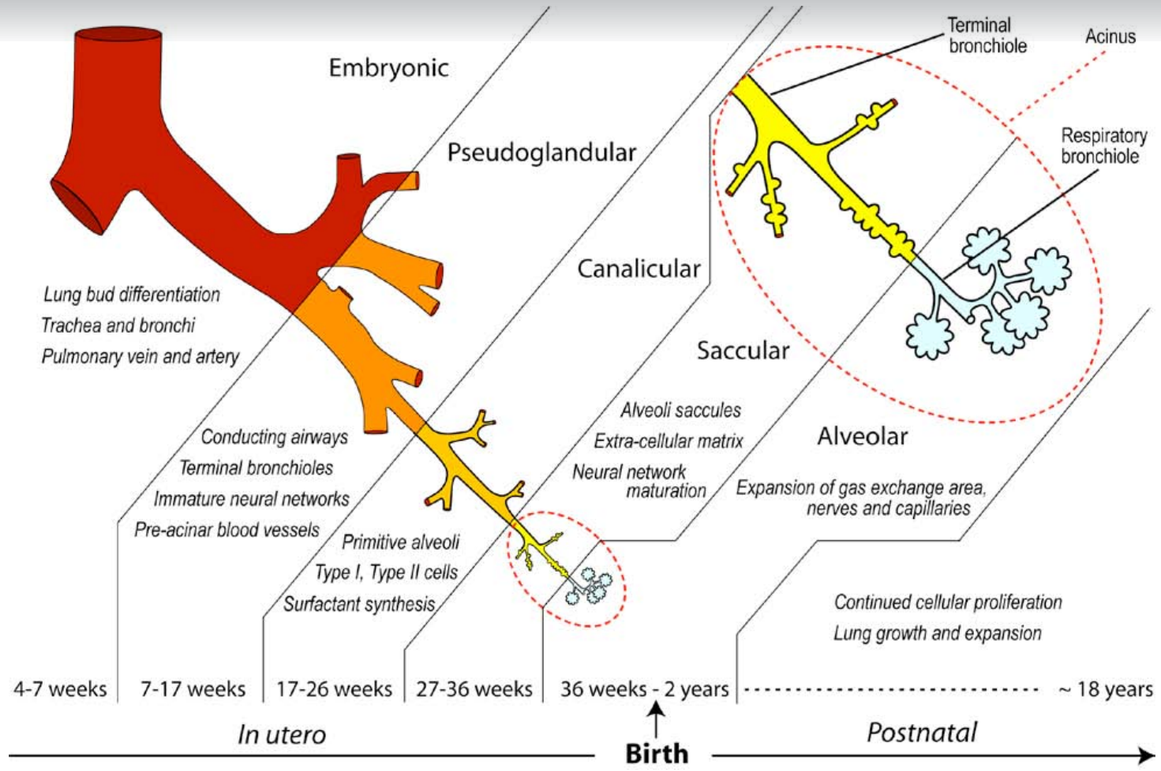
STAGES OF LUNG DEVELOPMENT

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 pseudoglandular 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"

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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-*p*-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 pnuemocyte	Thickened primary septa, fewer/more dilated airspace, increased Type II pneumocytes	Bronchopulmonary dysplasia, altered lung mechanics

Close Window

Stag

Lung bu
Trachea
Pulmona

4-7 weeks

years

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

ASTHMA and Lung Development

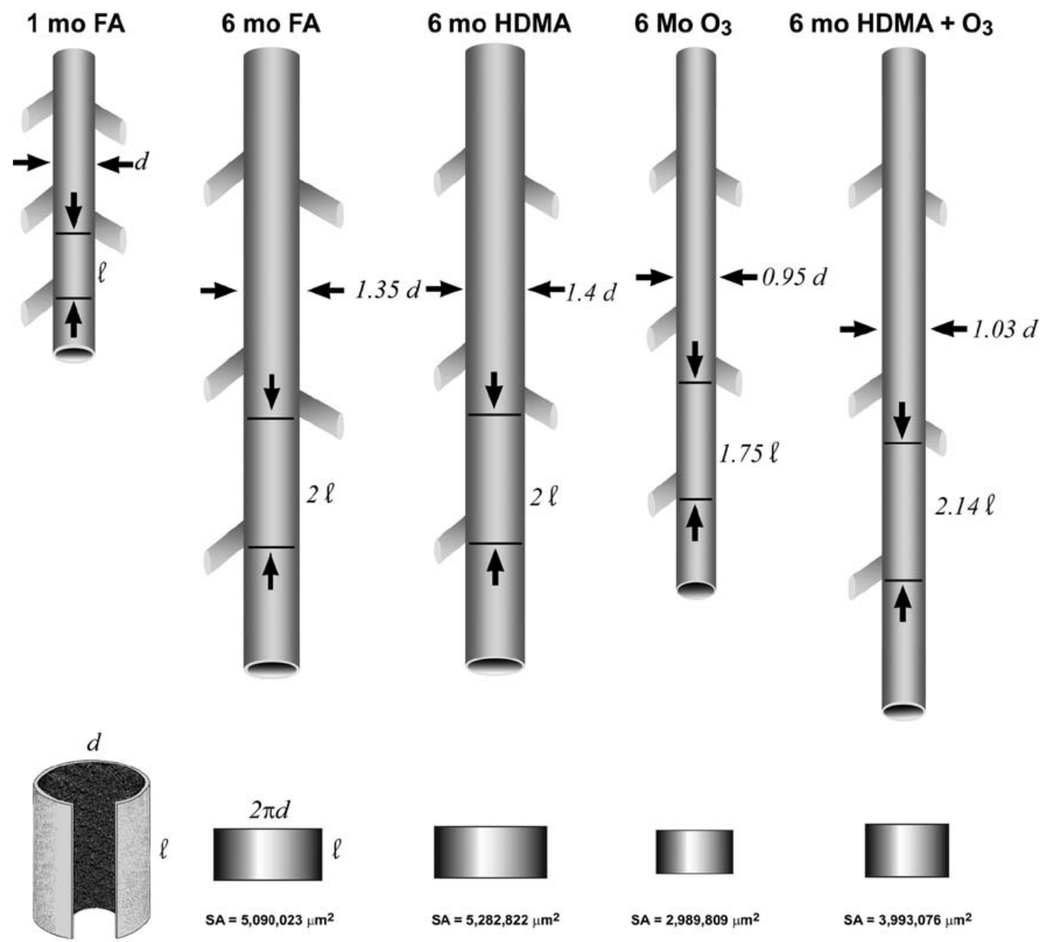
THE LUNG IS SUSCEPTIBLE TO MANY INFLUENCES DURING EARLY DEVELOPMENT.

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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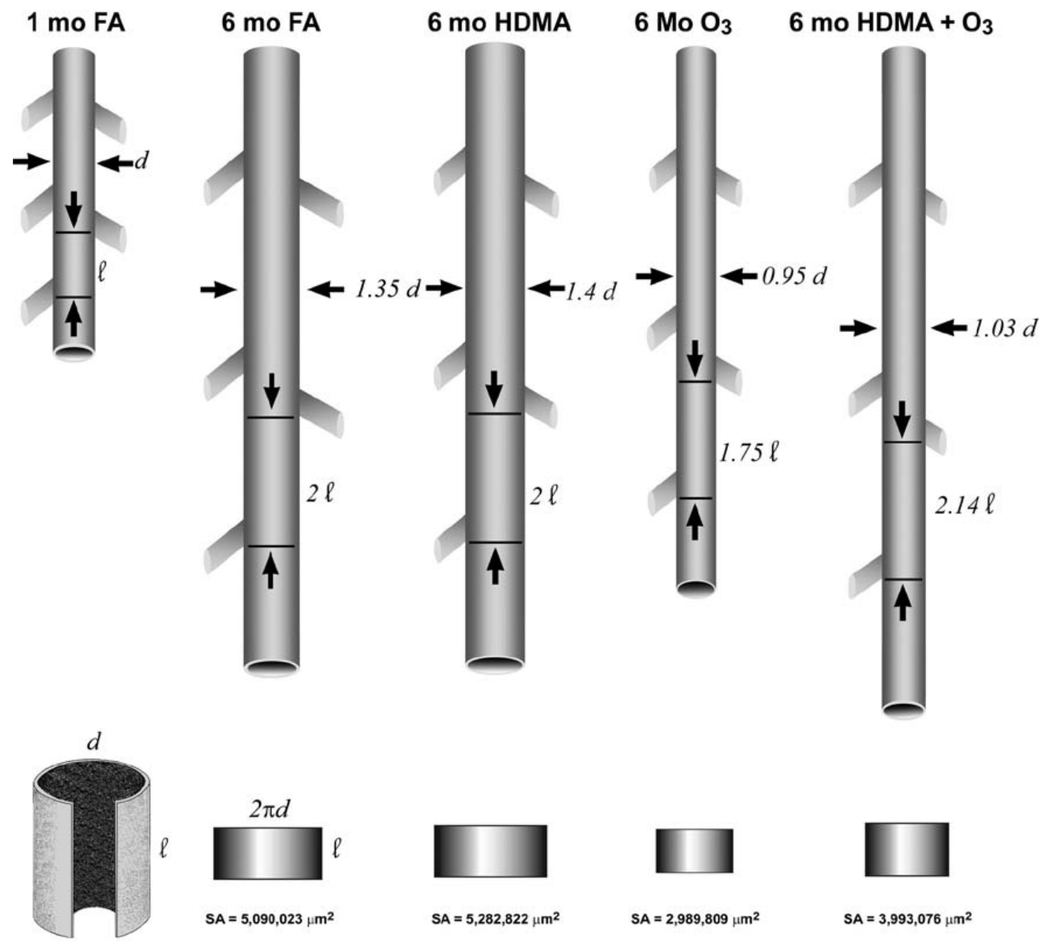
STUDIES CONDUCTED at the University of California–Davis evaluated the impact of ozone (O3) and allergens on lung development in rhesus monkeys. These studies integrated early-life exposures through multiple windows of susceptibility to observe functional and structural changes relevant to human lung 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

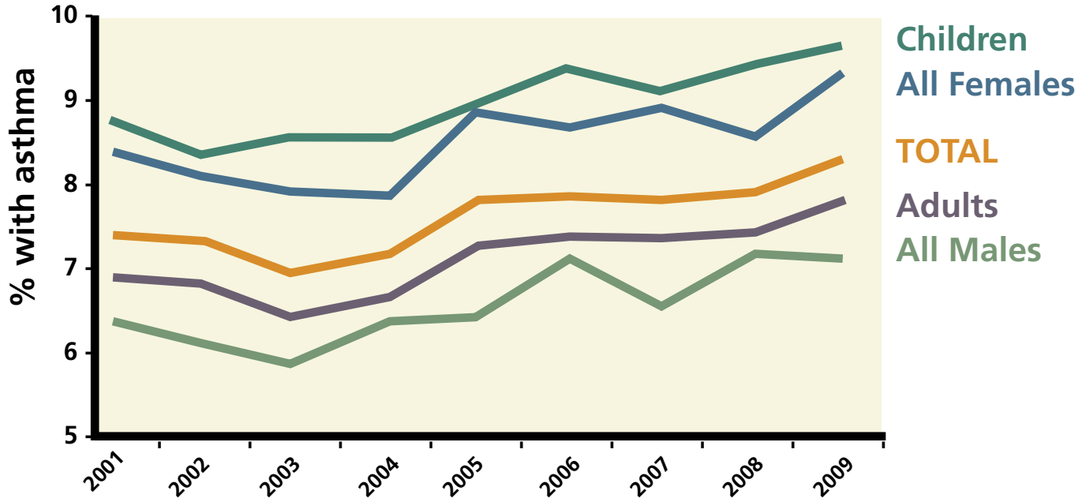
When Brett gets an attack, he has a difficult time breathing and sometimes feels as if he is going to pass out.

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

ASTHMA: Racial and Socioeconomic Disparities

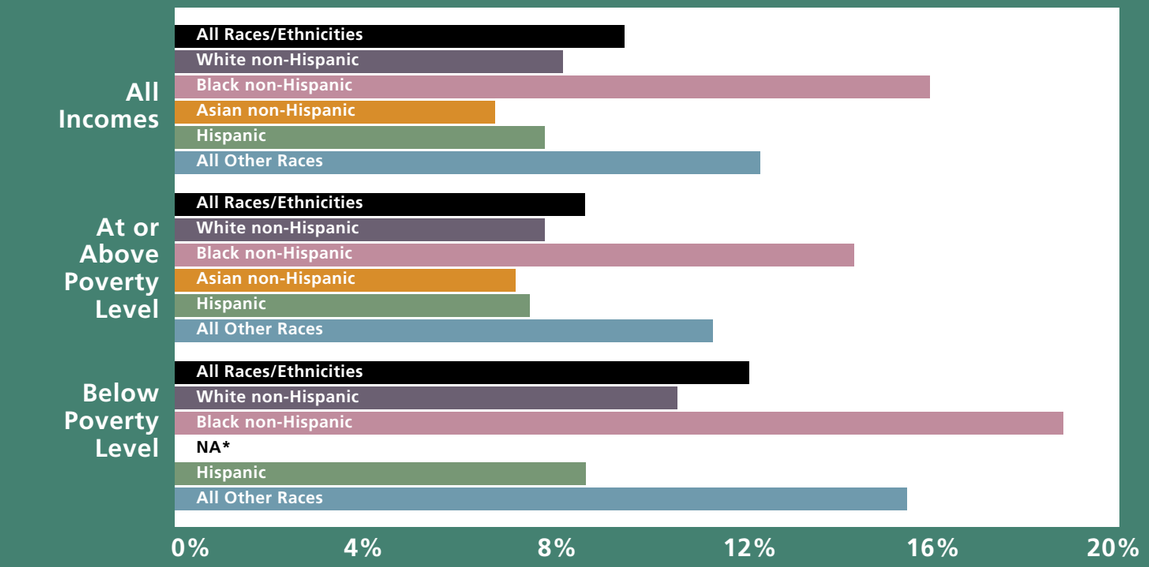
Many of Brett's friends who live in apartments in the city also have asthma.

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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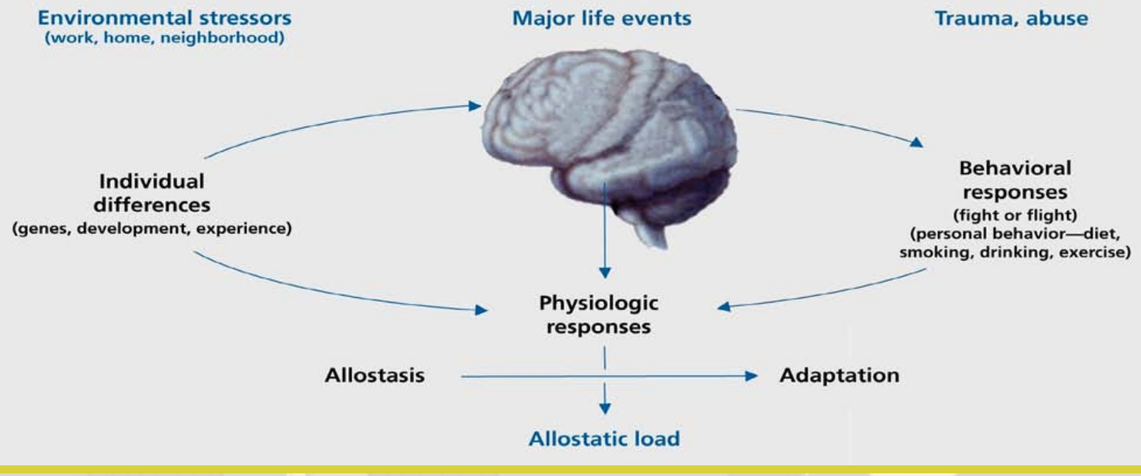

KEY CONCEPT:

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.

Graphic: McEwen B., 2006, with permission

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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 >)

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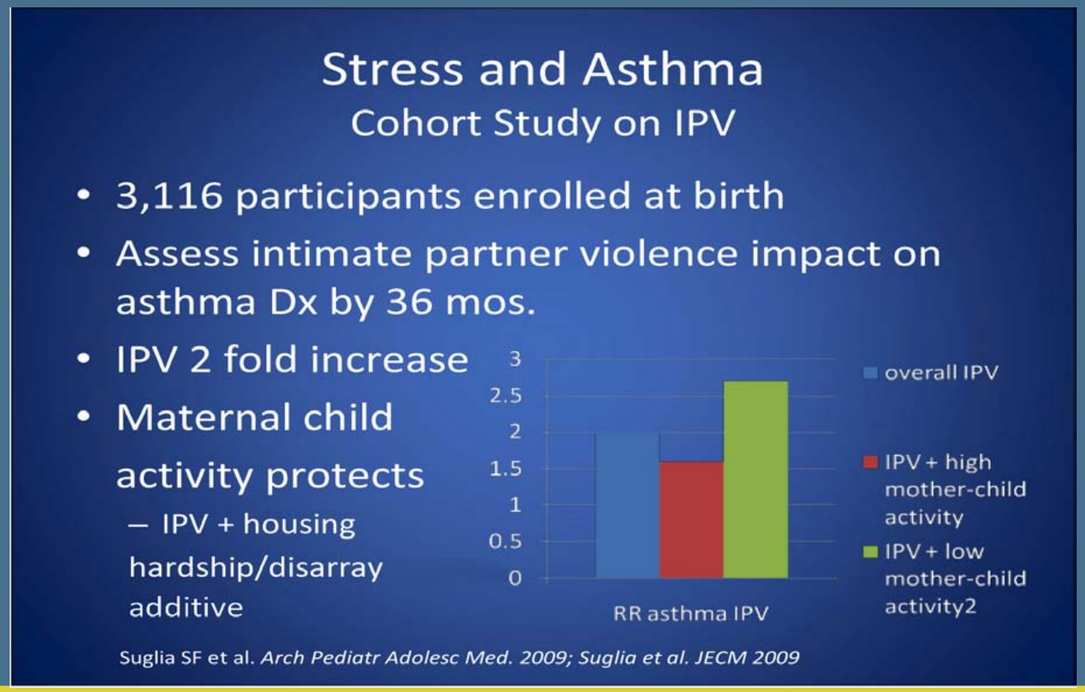
Example: Stress and Asthma Development of Lung Function is Affected by the Home Environment



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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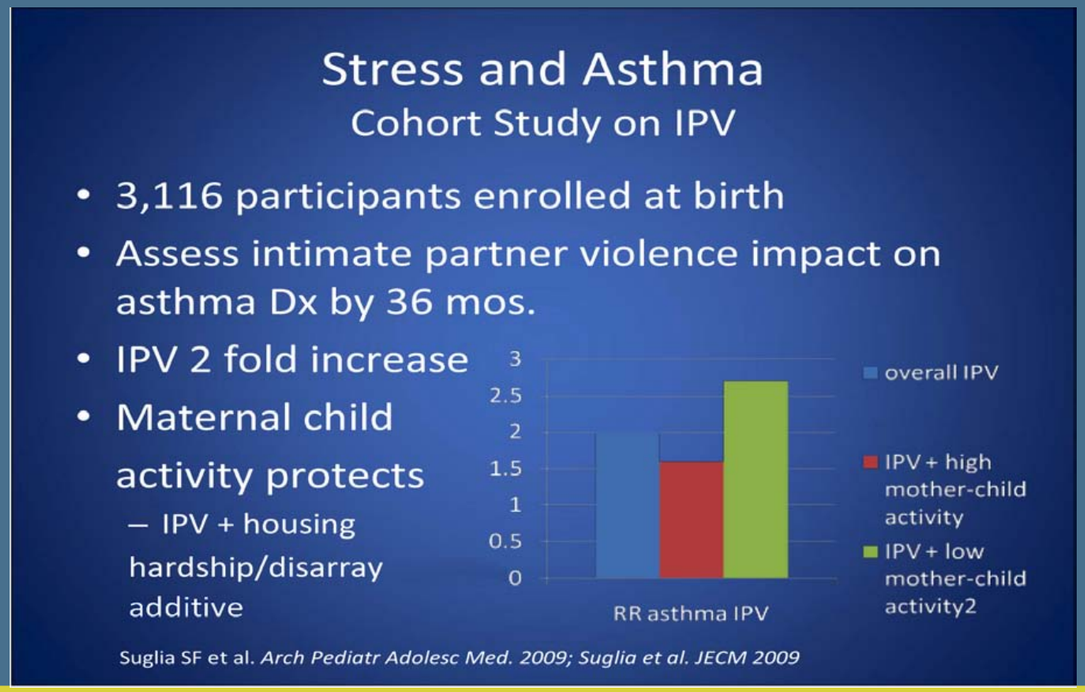

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ASTHMA: Family and Community Stressors

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.

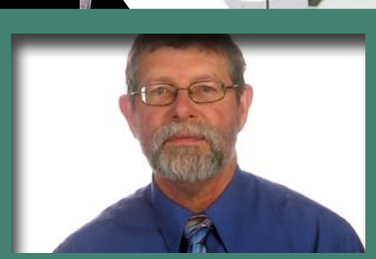
Watch: Dr. Rosalind Wright discusses how caregiver stress, early childhood stress and community violence all have an impact on the development of asthma. (5 min.)

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.

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

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

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

Diesel Emissions and Asthma Demographics in Southern California

Diesel PM

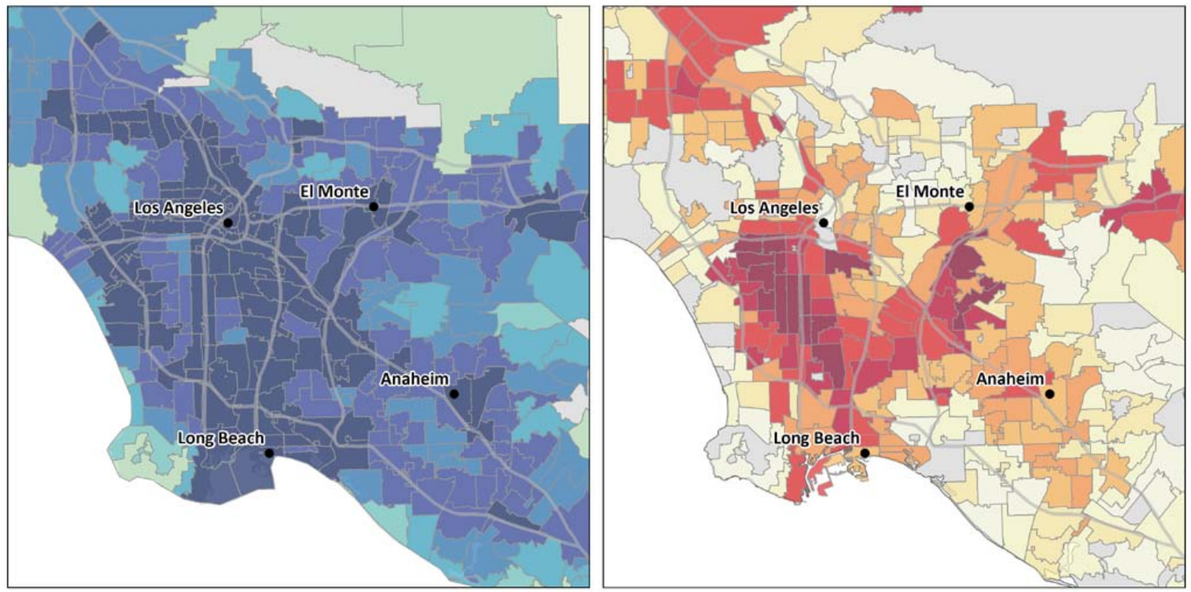
Diesel PM emissions from on-road and non-road sources for a 2010 July day (kg/day)

0.0 - 0.2	4.8 - 8.6
0.3 - 0.7	8.7 - 15.2
0.8 - 2.2	15.3 - 25.7
2.3 - 4.7	25.8 - 163.7

Children's Asthma

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

19.2 - 37.6	67.4 - 79.0
37.7 - 48.2	79.1 - 92.9
48.3 - 57.5	93.0 - 116.0
57.6 - 67.3	116.1 - 408.7



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

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

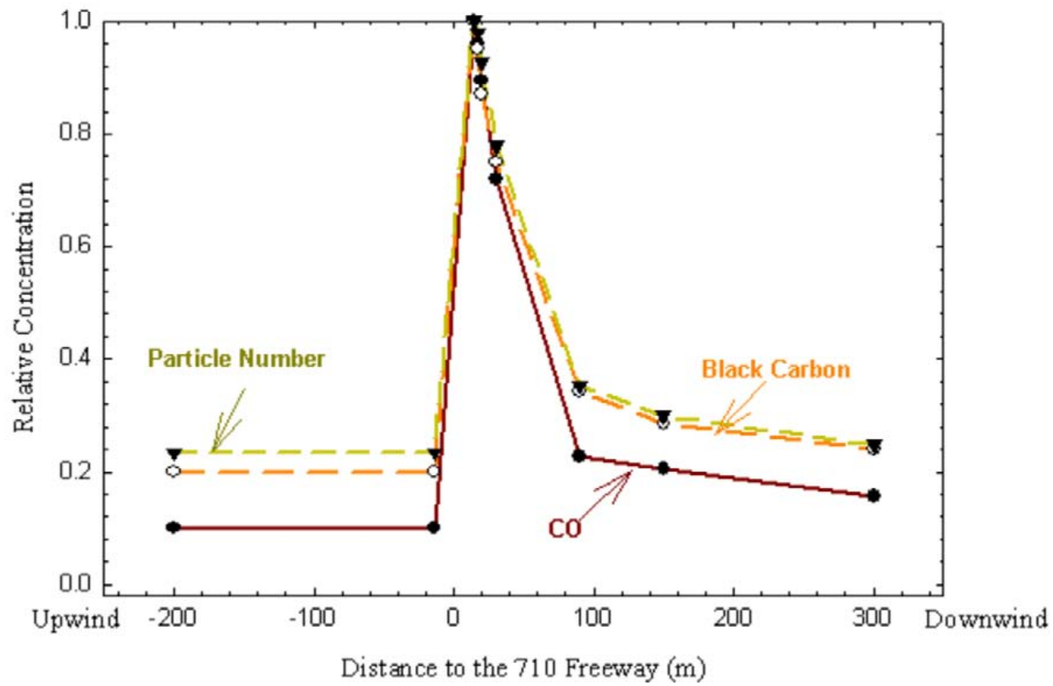
- Respiratory symptoms
- Wheezing (acute)
- Bronchitis (chronic)
- Increased rescue medication use
- Decreased lung function
- Emergency department visits
- Hospitalizations
- School absences

+ Diesel emissions and asthma demographics in southern California

+ Asthma and near roadway exposure to air pollution

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



Slide 1: Air quality is worse close to freeways. Air pollutants are increased closer than 150-300 meters downwind.

Zhu et al., 2002, 2006.

Slide 2: Asthma risk increases for children living closer than 150 meters from a major road.

McConnell et al., 2006

ASTHMA and Air Pollution

EFFECT MODIFIERS – AIR POLLUTION, STRESS AND SOCIOECONOMICS

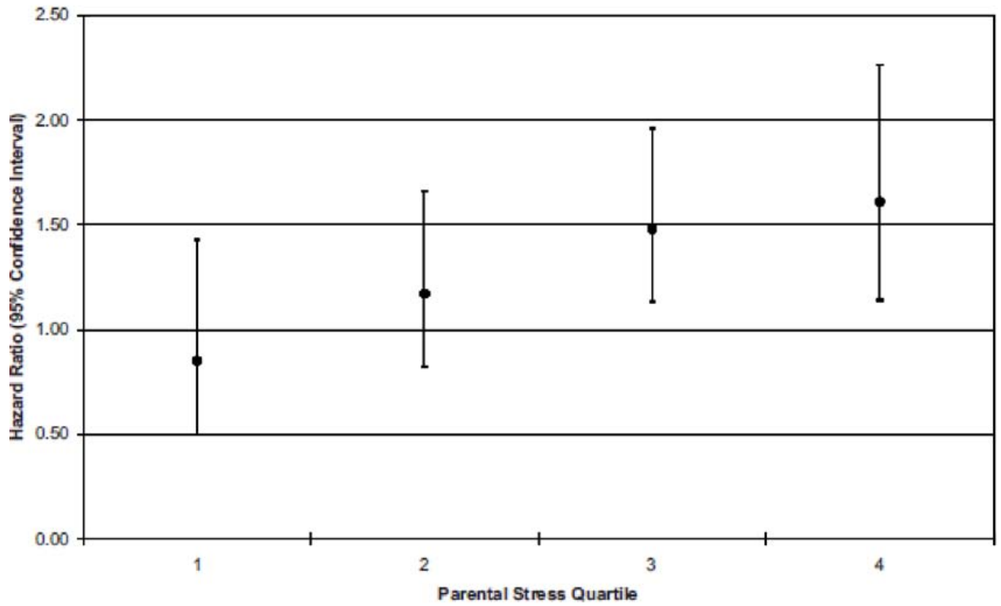
Brett lives in a low-income neighborhood close to Los Angeles and near a major roadway. Children in relatively low-income families and exposed to traffic-related air pollution, such as in Brett's case, are at greater risk of frequent asthma symptoms. Importantly, they are at greater risk than children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

ASTHMA and Air Pollution

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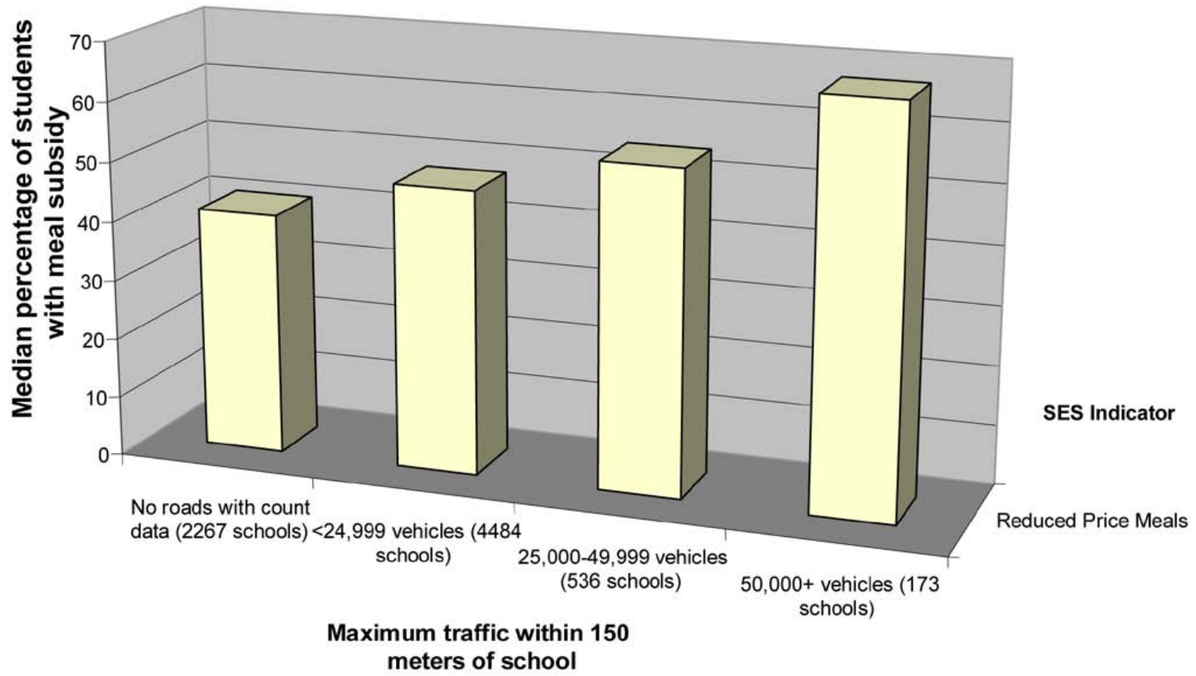
+ Examples: Air pollution and socioeconomics

+ Link: National Environmental Health Tracking Program

+ Asthma in California

Examples: Air pollution and socioeconomics



Slide 1:
Economically disadvantaged students in CA Public Schools have higher traffic exposure.
(Green et al., EHP 2004)

Slide 2 (rollover to view):
Hispanic and non-Hispanic black children are more likely to have high traffic exposure.
(Green et al., EHP 2004)

ASTHMA and Air Pollution

EFFECT MODIFIERS – AIR POLLUTION, STRESS AND SOCIOECONOMICS

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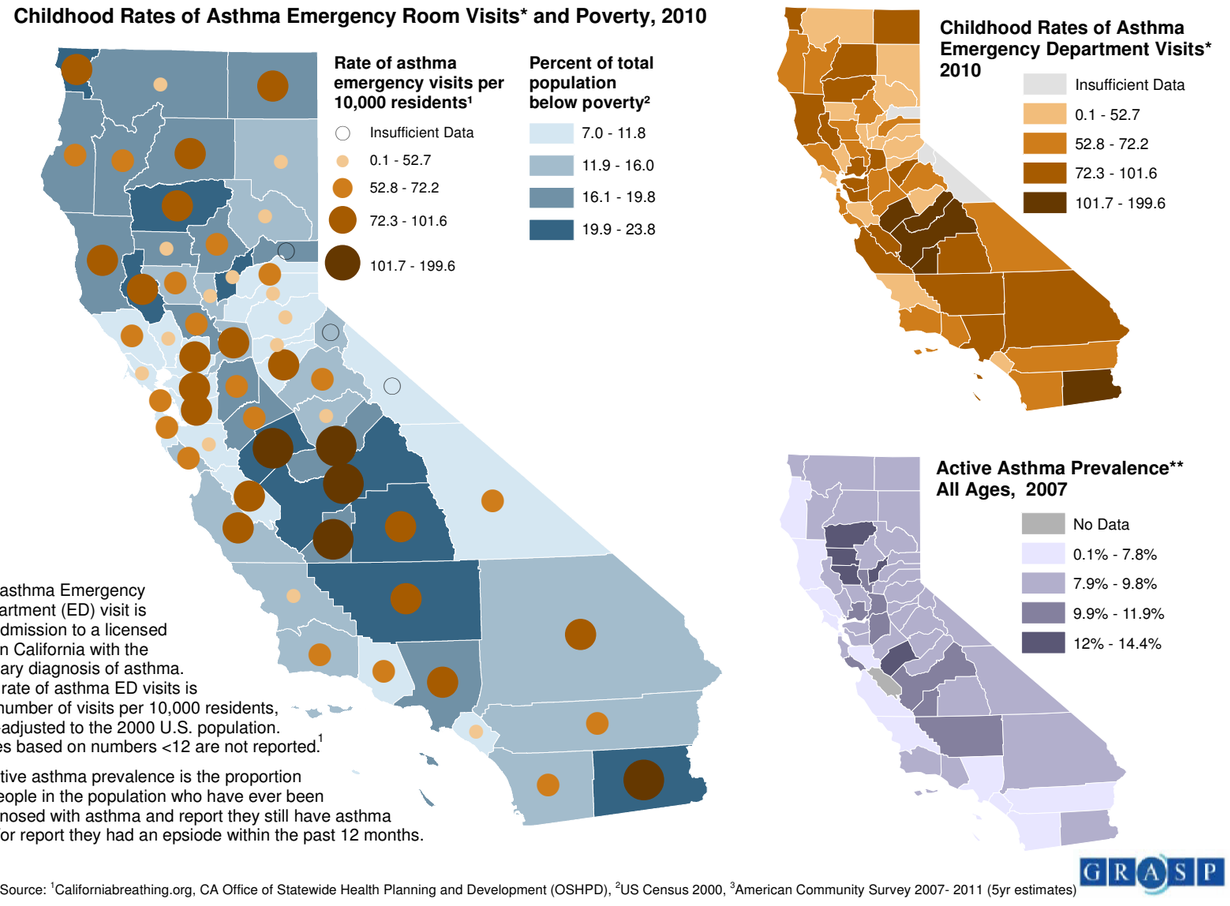
Asthma in California

Asthma in California



*An asthma Emergency Department (ED) visit is an admission to a licensed ED in California with the primary diagnosis of asthma. The rate of asthma ED visits is the number of visits per 10,000 residents, age-adjusted to the 2000 U.S. population. Rates based on numbers <12 are not reported.[1]

**Active asthma prevalence is the proportion of people in the population who have ever been diagnosed with asthma and report they still have asthma and/or report they had an epsiode within the past 12 months.

Data Source: [1]Californiabreathing.org, CA Office of Statewide Health Planning and Development (OSHPD), [2]US Census 2000, [3]American Community Survey 2007- 2011 (5yr estimates)

GRASP

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.

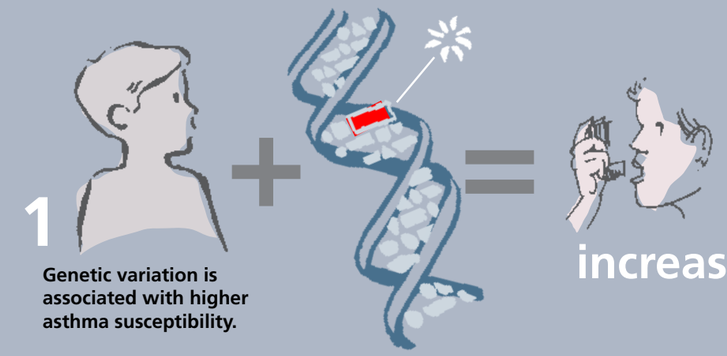
Key Concept: Inflammation and Oxidative Stress

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.

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

Genetics Increase Susceptibility to Air Pollution



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KEY CONCEPT:

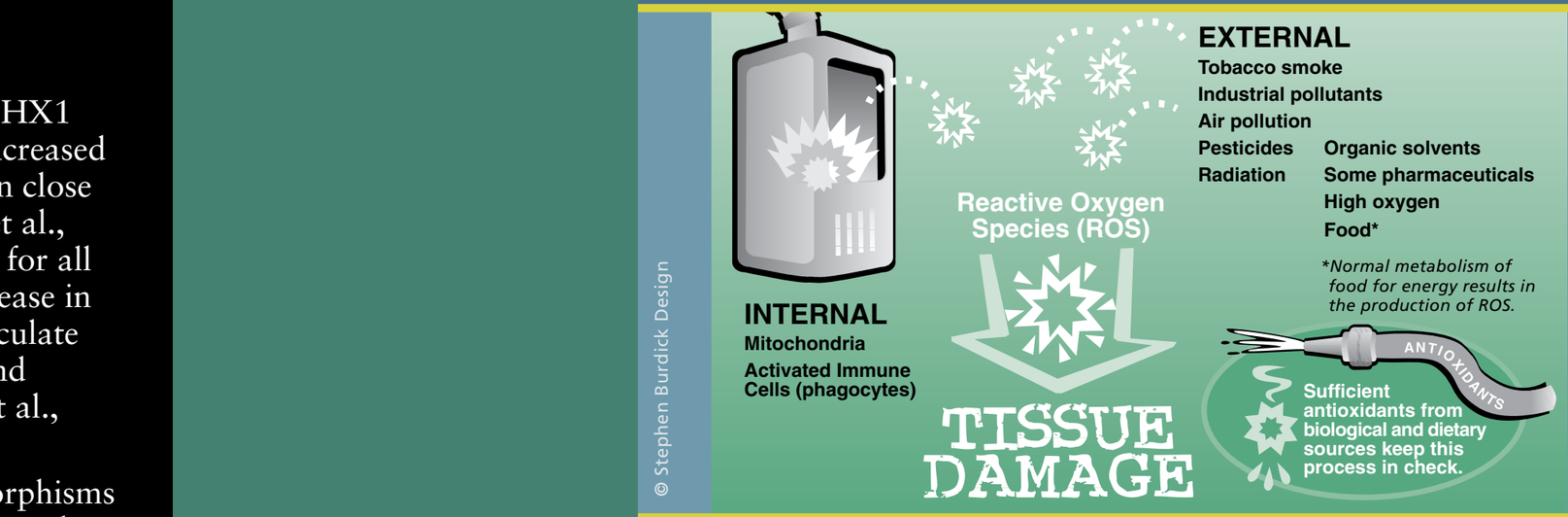
Inflammation and Oxidative Stress

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.

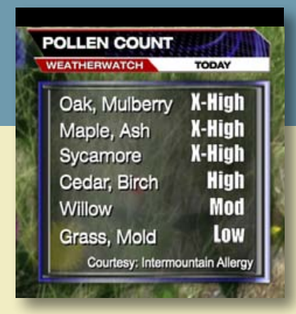
ASTHMA and Climate Change

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.



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.

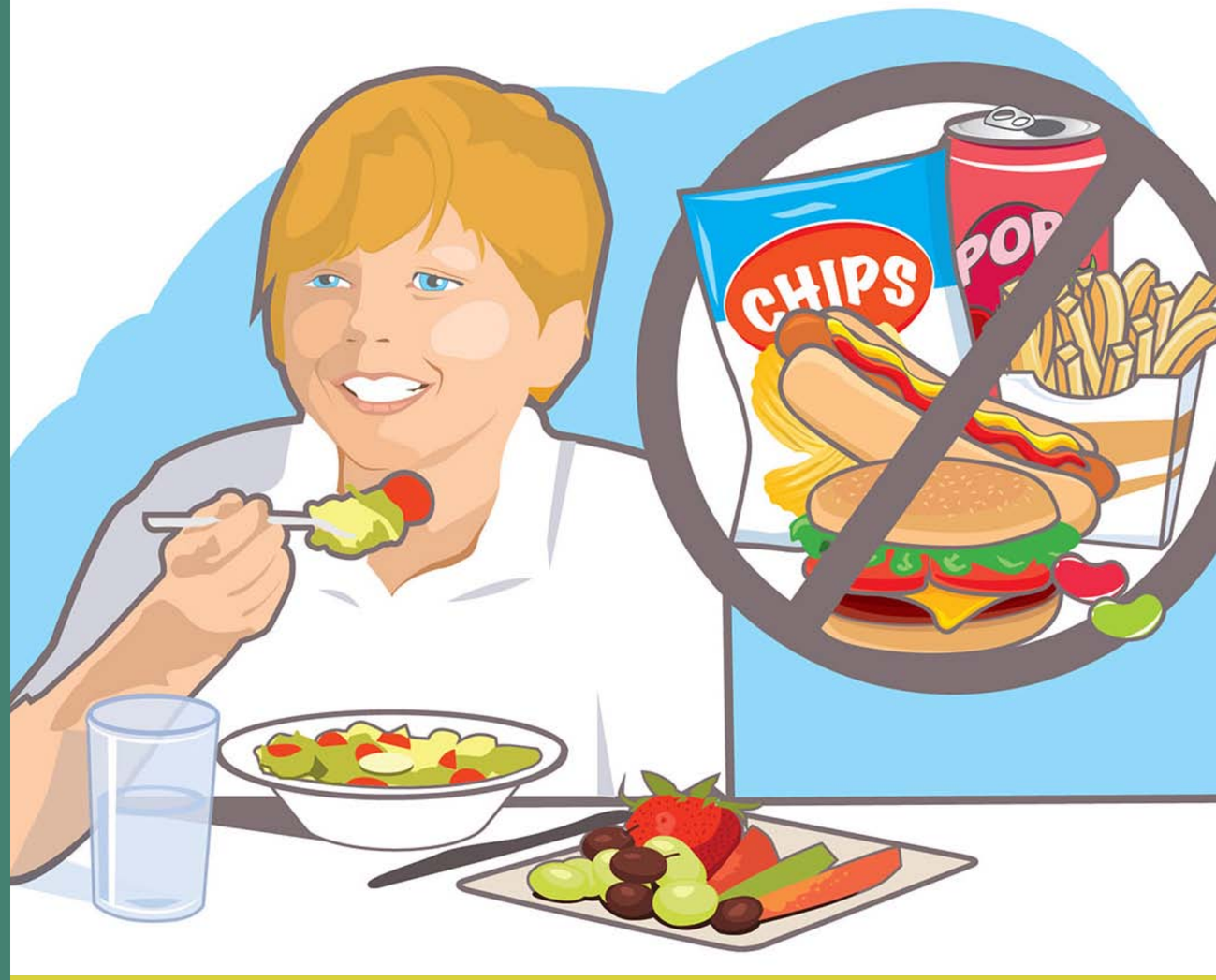
*pollutants measured: PM 2.5, ozone

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

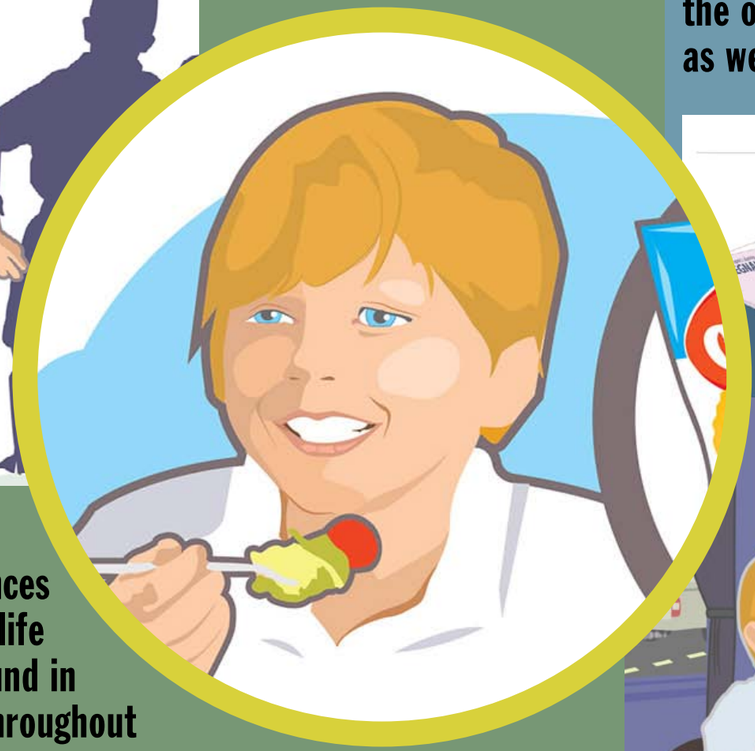
We have seen throughout the pages of Brett's story that a wide range of factors, and their interactions across his lifespan, are risk factors for both the onset of asthma, as well as triggering it. These include environmental chemicals and other contaminants, family and community social stressors, diet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

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.



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

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

A Story of Health

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.

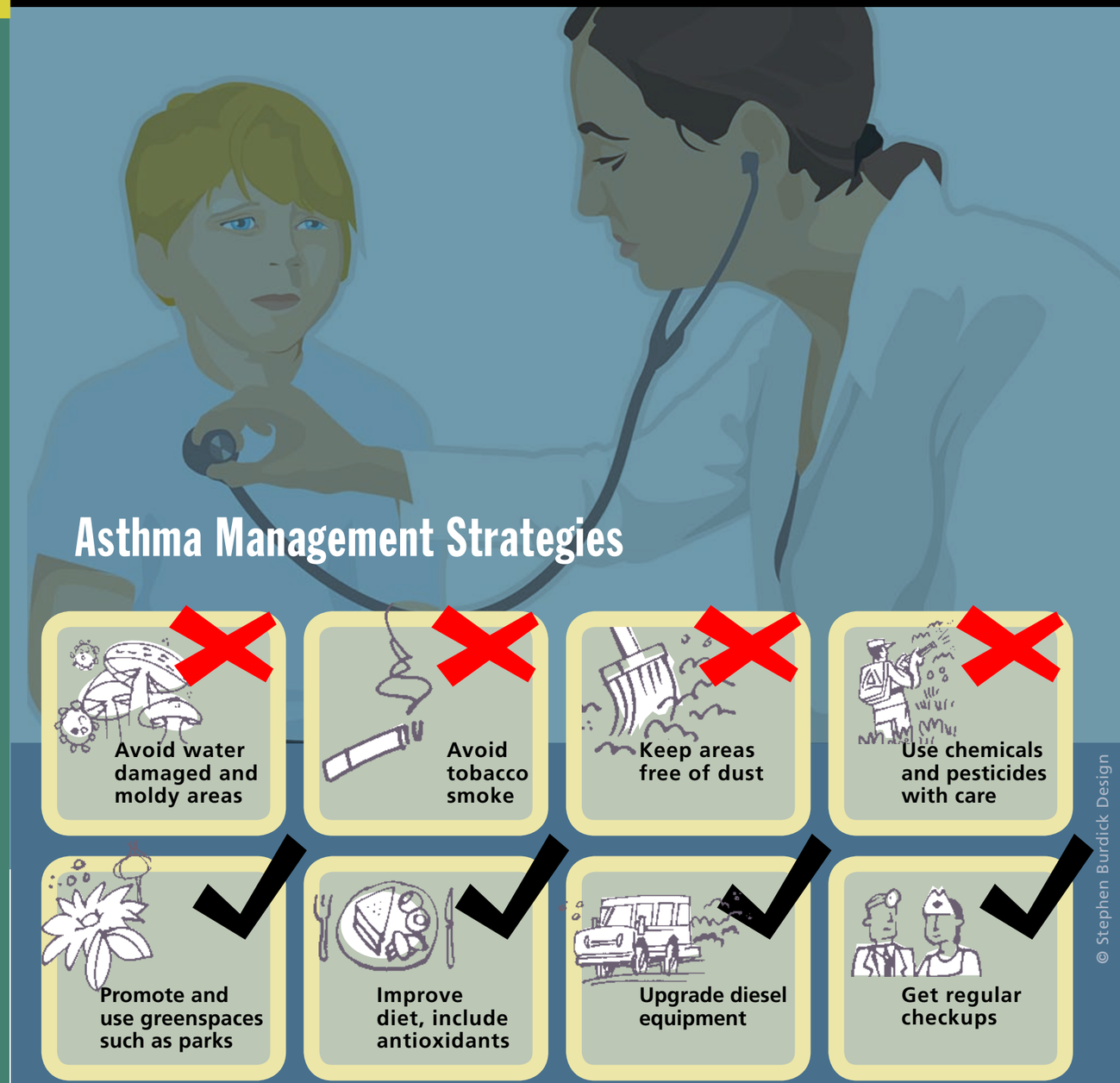
Other protective factors include the following, if possible:

- 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: 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 Pollustion

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.

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Childhood Leukemia

Learning/ Developmental Disabilities

Diabetes

Infertility

Cognitive Decline

Asthma Case References and Resources by Topic

Note: there are many topic overlaps

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National Environmental Health Tracking Network

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continued >

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Asthma

Childhood Leukemia

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Diabetes

Infertility

Cognitive Decline

Occupational Asthma

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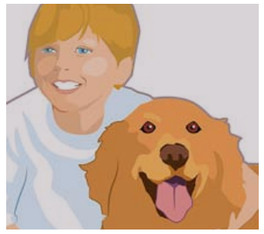

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Mold video on EPA Asthma science notebook

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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

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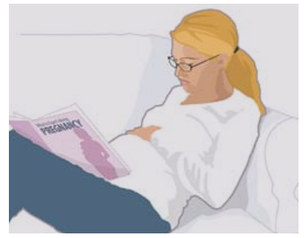

Asthma Management, Treatment

National Medical-legal Partnership

CDC: Health Care Guidelines

National Environmental Education Foundation: Pediatric Environmental History forms

Intervention Guidance

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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.

"Diagnosing the Leukaemic Cells"
by Susan Macfarlane,
reproduced with permission.

About this painting, with words of the artist in *italics* >

See this page for more information on the artist.

CHILDHOOD LEUKEMIA Stephen's Story

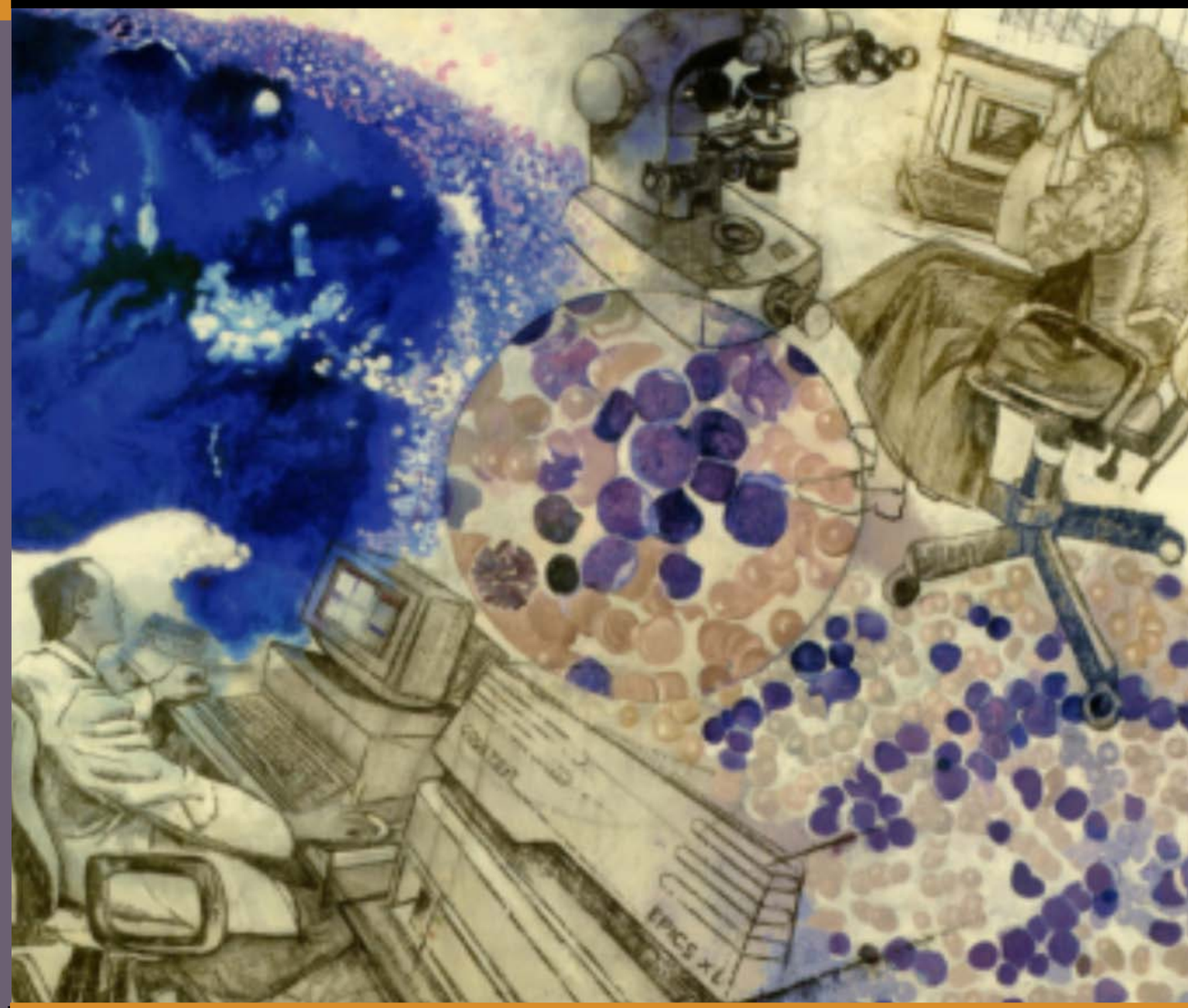
The pediatric oncologist, Dr. Baker, looked at Stephen's blood tests to confirm the findings from the laboratory.

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.

? Bone marrow aspiration >



"Typing the Leukaemic Cells"
by Susan Macfarlane,
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About this painting, with words of the artist in *italics* >

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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.

? What is Leukemia?

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.

? Leukemia Survival Statistics

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

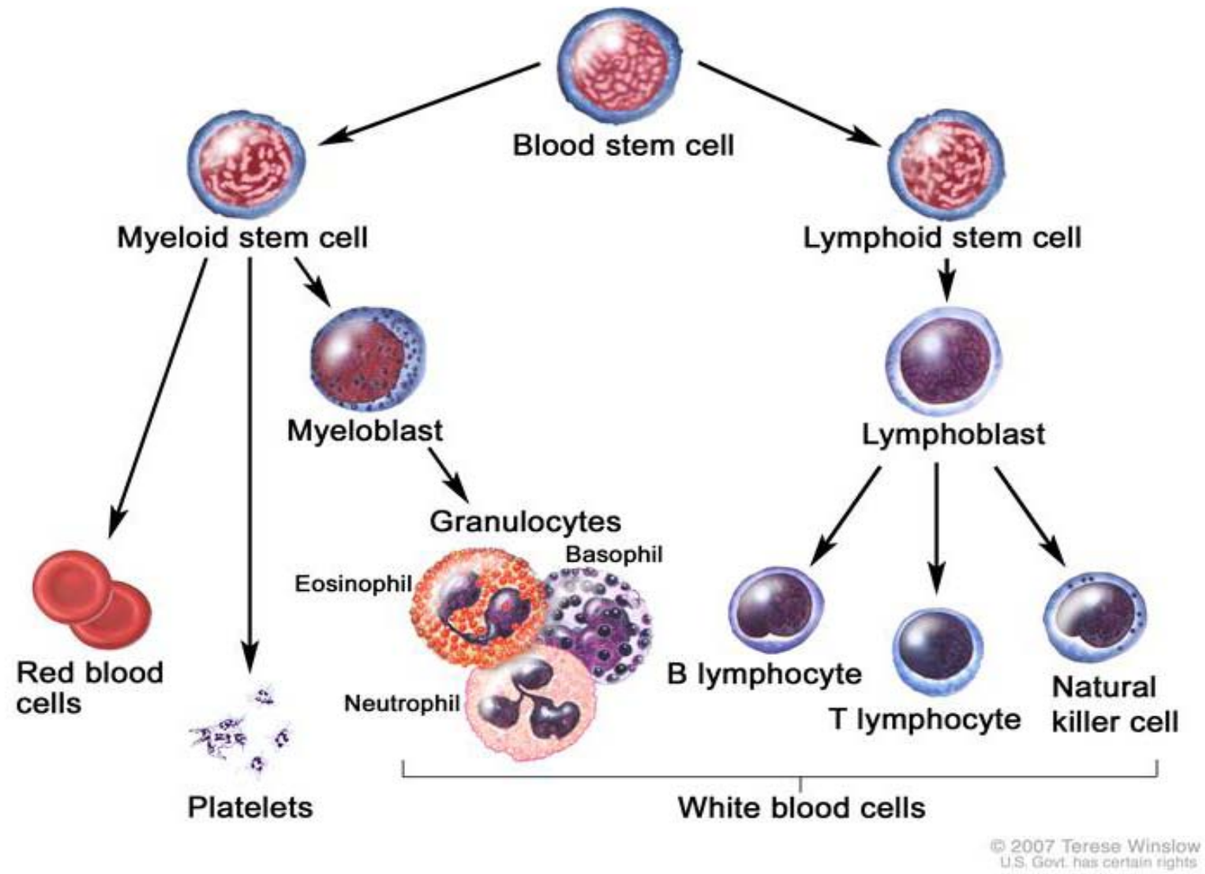
Early life exposures are important: age-specific incidence chart

More Detail on ALL Subtypes

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.



Graphic: Terese Winslow 2007.
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Types of leukemia vary by age

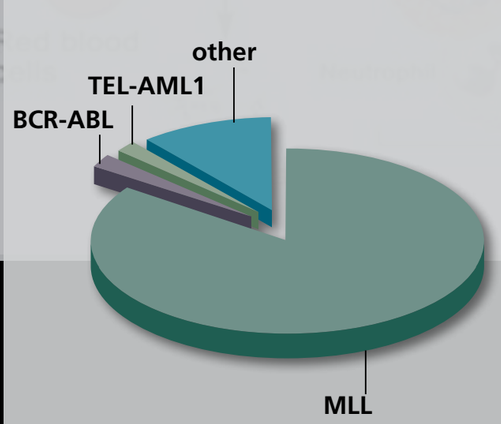
The two main types of leukemia based on cell histology are ALL and AML, but even within these groups, there are many different characteristics based on the presence of abnormalities of the chromosomes, whether the number of chromosomes is higher than expected (hyperdiploidy), or whether or not we see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

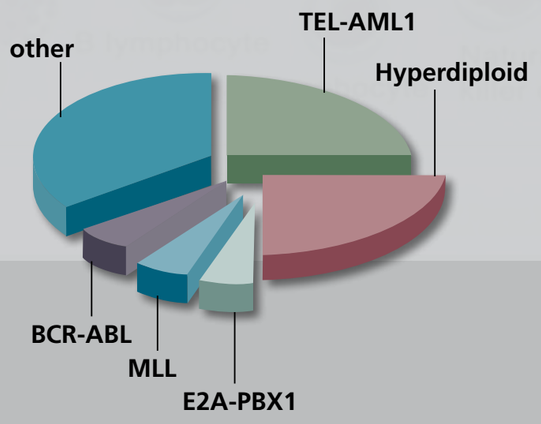
When grouped by underlying molecular markers, certain leukemias occur more frequently at different ages. MLL (mixed leukemia or Myeloid/ lymphoid leukemia) is the predominant form in infants but relatively rare in older children. MLL is a particularly aggressive form of leukemia.

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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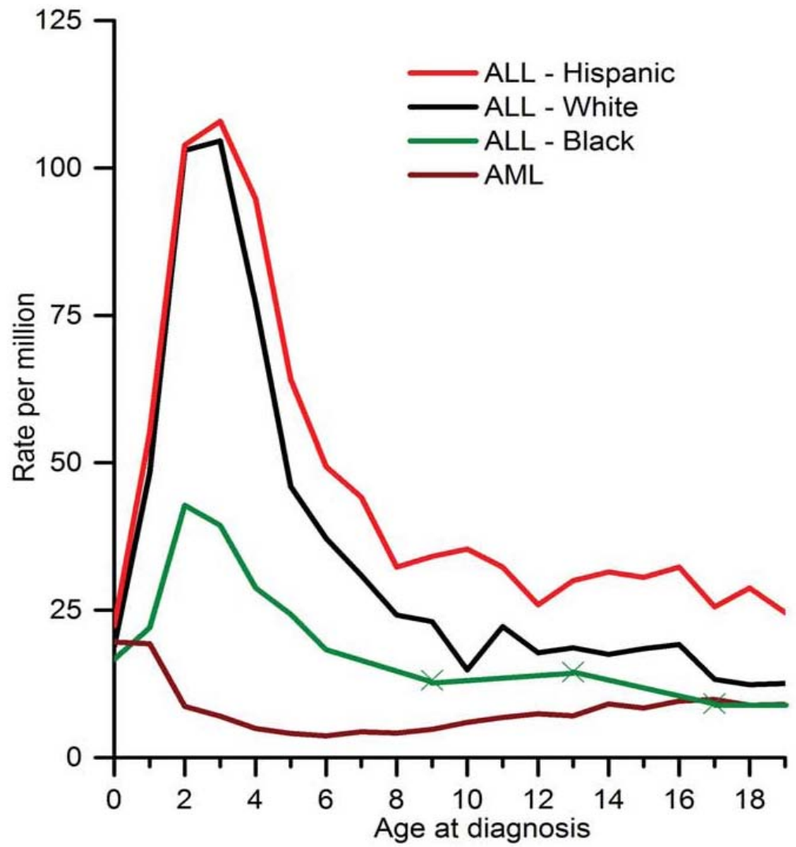
Early Life Exposures are Important

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.

Ward, et al., 2014. Used with permission.

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

+ About the artist

"Initial Blood Test"

About this painting, with the words of artist Susan Macfarlane in *italics* >

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.

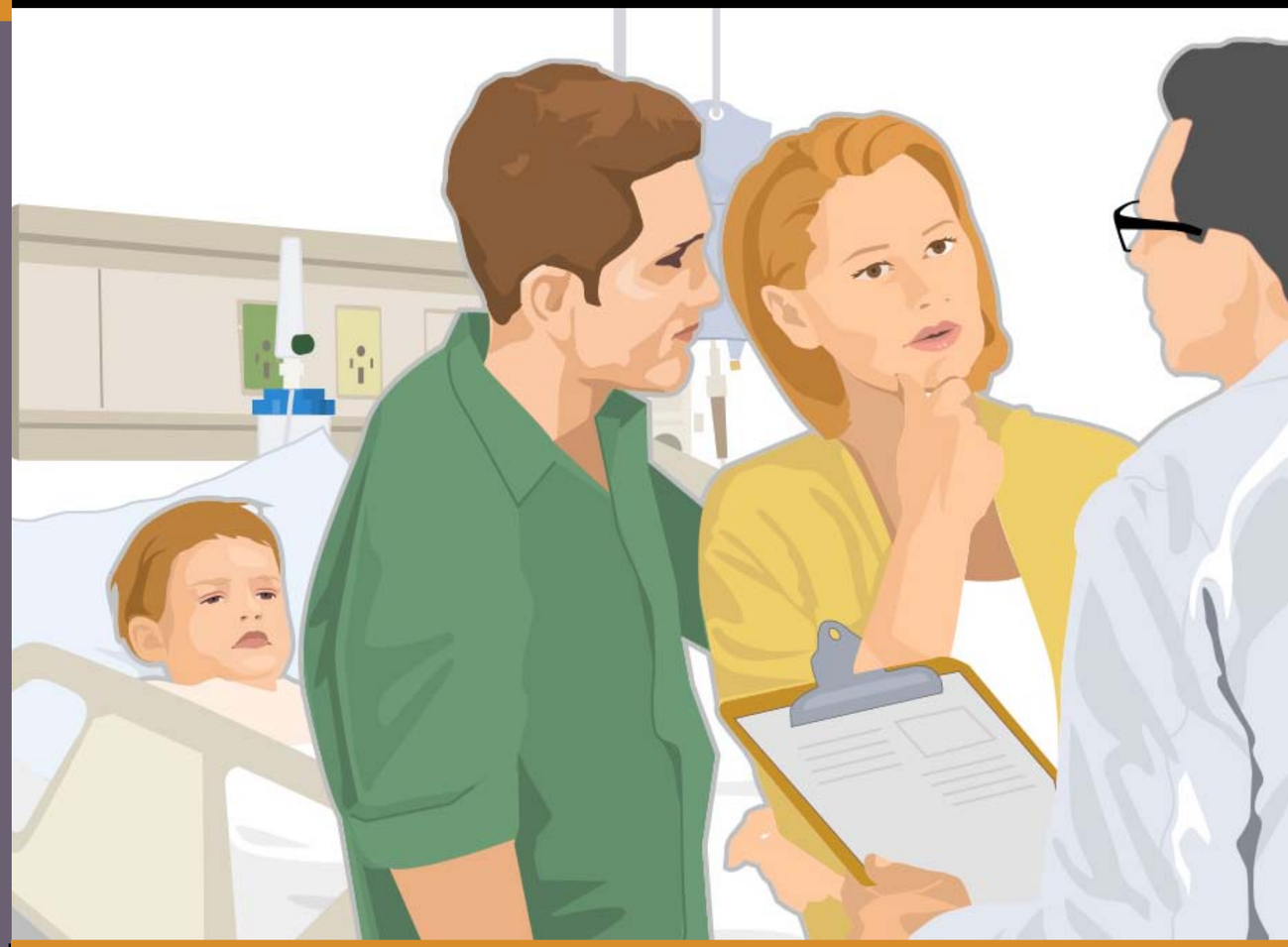
Childhood leukemia is difficult to study because it is relatively rare, which limits the design of studies intended to help clarify its etiology (cause). Nevertheless, substantial evidence identifying a number of risk factors has emerged over the past two decades. The etiology is likely to be attributable 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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Two-Hit Model Hypothesis

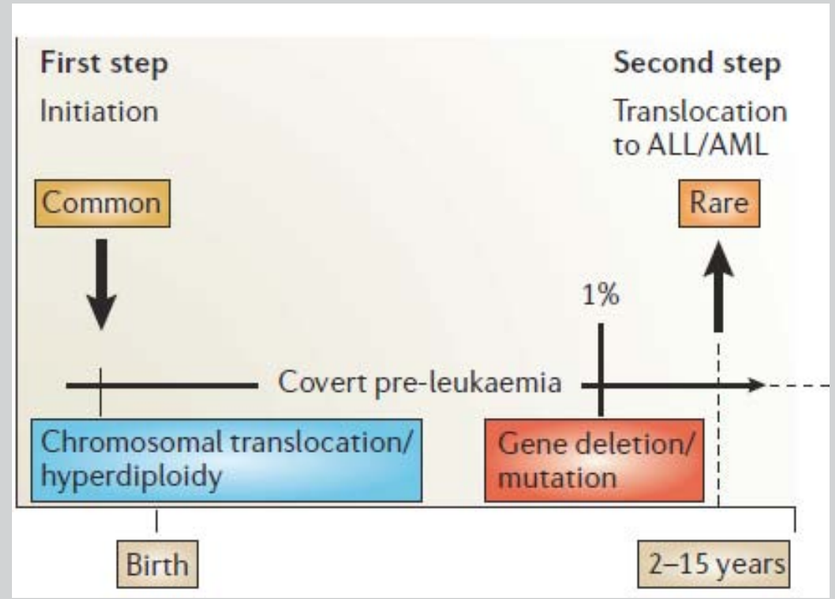
TEL-AML1 Gene Fusion

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.

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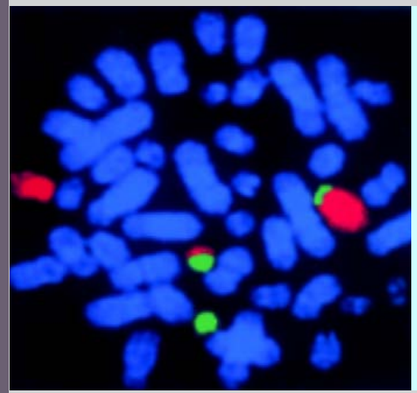
Changes to DNA that cause leukemia:

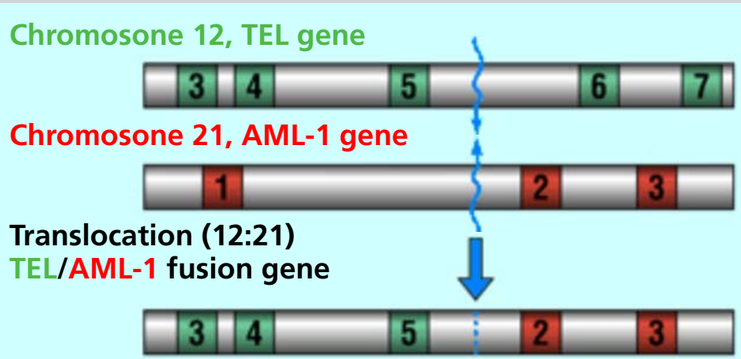
Two-Hit Model Hypothesis

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.

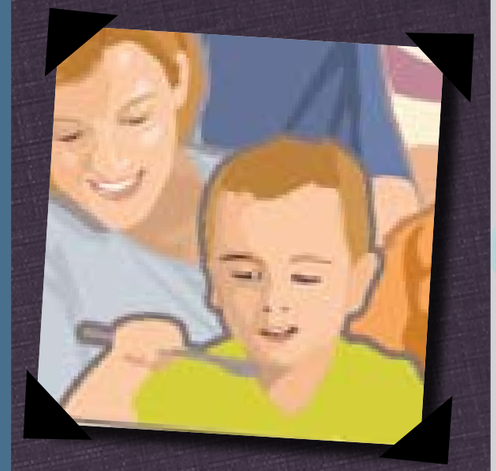
This translocation has been identified in blood specimens that are collected at birth. It indicates that there is an already ongoing process of DNA insult; however we know that not all of the children with this translocation at birth develop childhood leukemia.

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.

Graphics source: Greaves, 2000, used with permission.

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.

"Weekly Co-Ordinating Meeting" by Susan Macfarlane, reproduced with permission.

About this painting, with words of the artist in *italics* >

CHILDHOOD LEUKEMIA Stephen's Story

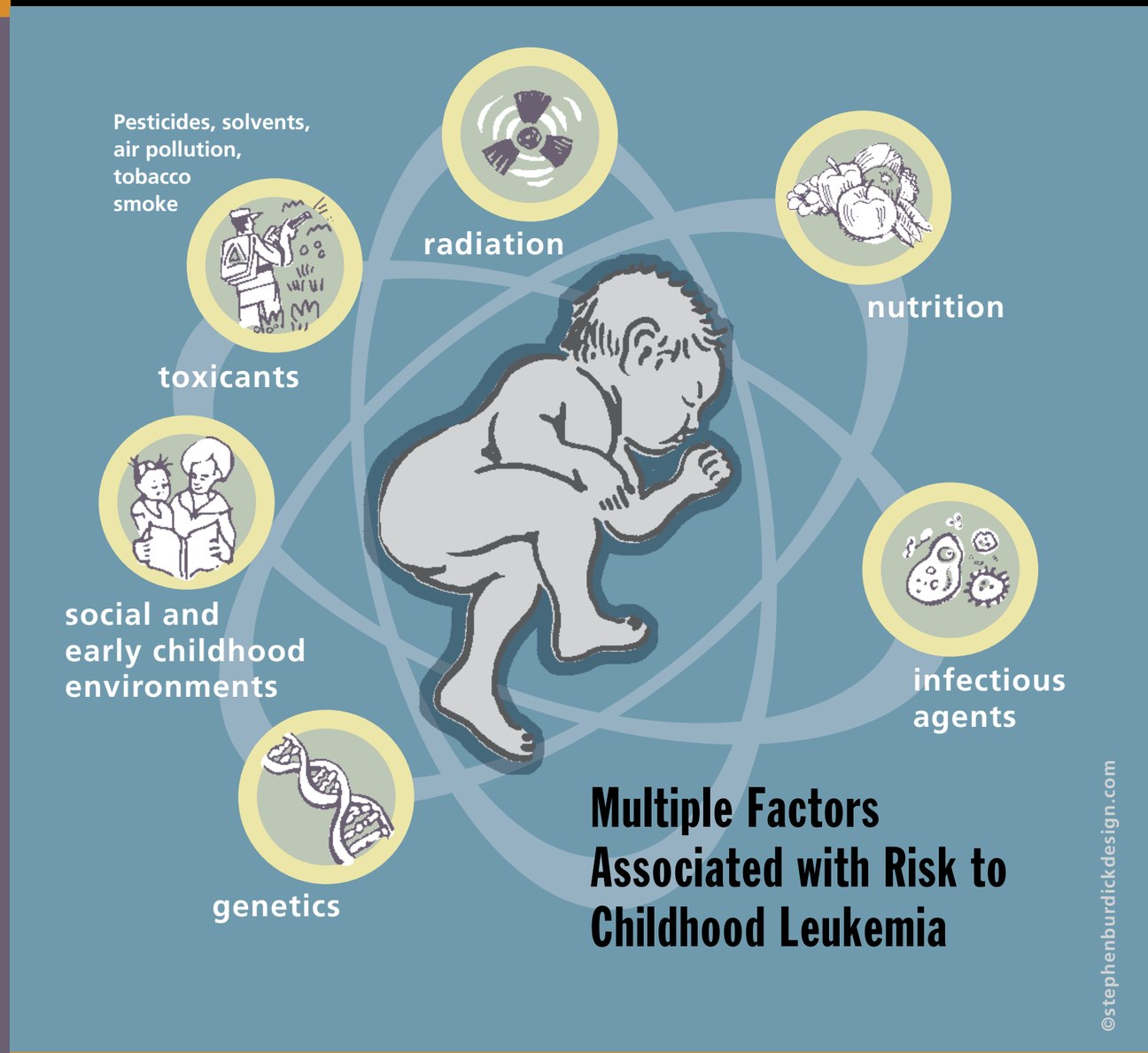
FACTORS ASSOCIATED WITH RISK FOR CHILDHOOD LEUKEMIA

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.

Key Concept: Causation vs. Association



CHILDHOOD LEUKEMIA Stephen's Story

CHILDHOOD LEUKEMIA: US TRENDS

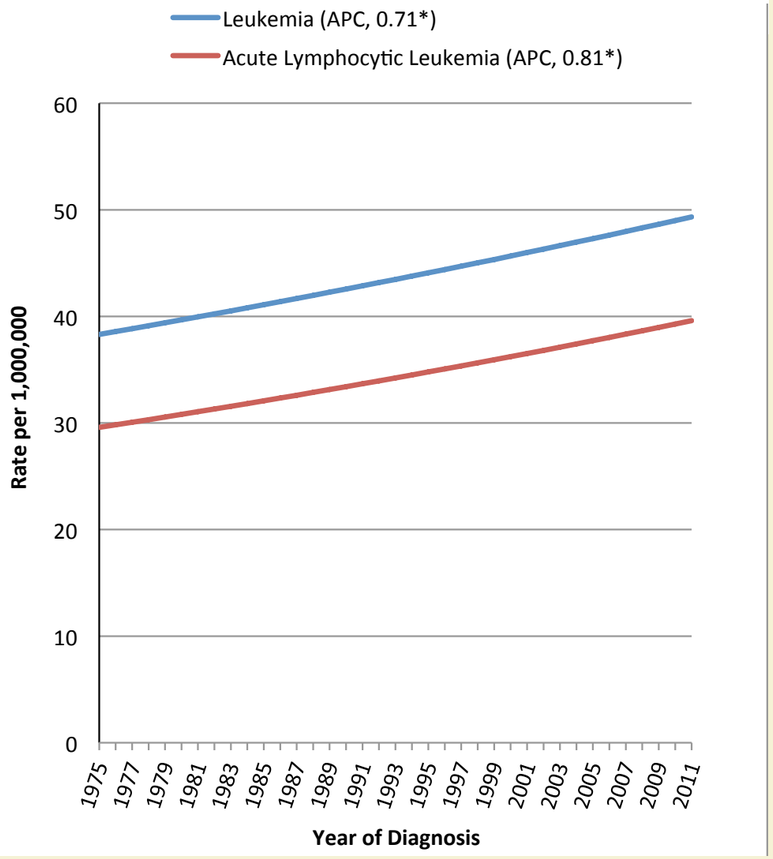
Although childhood leukemia is still rare, Stephen is one of a growing number of children with this cancer.

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**

Trends in the Age-Adjusted Incidence Rate of Childhood Leukemia and Acute Lymphocytic Leukemia, Ages 0-14, SEER 9, 1975-2011



***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>

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ETHNIC TRENDS:

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

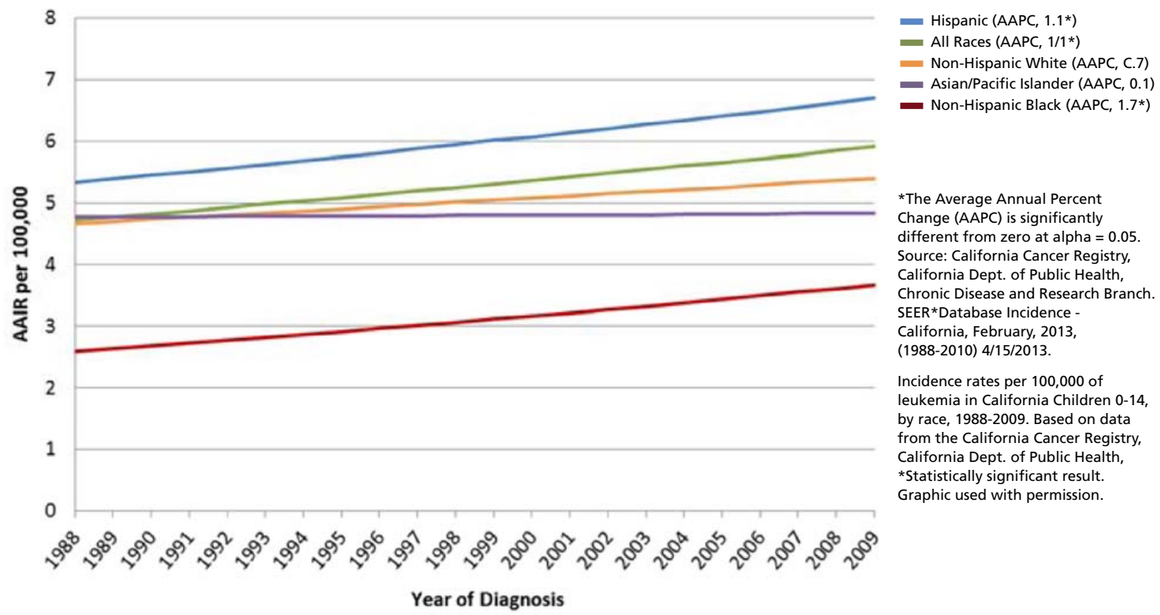
California with its large population and excellent data collection on cancer is the location of one of the largest studies designed to look at causes of childhood leukemia. Hispanic babies account for about half of all births in CA, making it a good place to examine possible genetic and environmental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



*The Average Annual Percent Change (AAPC) is significantly different from zero at alpha = 0.05. Source: California Cancer Registry, California Dept. of Public Health, Chronic Disease and Research Branch. SEER*Database Incidence - California, February, 2013, (1988-2010) 4/15/2013.

Incidence rates per 100,000 of leukemia in California Children 0-14, by race, 1988-2009. Based on data from the California Cancer Registry, California Dept. of Public Health, *Statistically significant result. Graphic used with permission.

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Ethnic Trends

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

CHILDHOOD LEUKEMIA Stephen's Story

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.

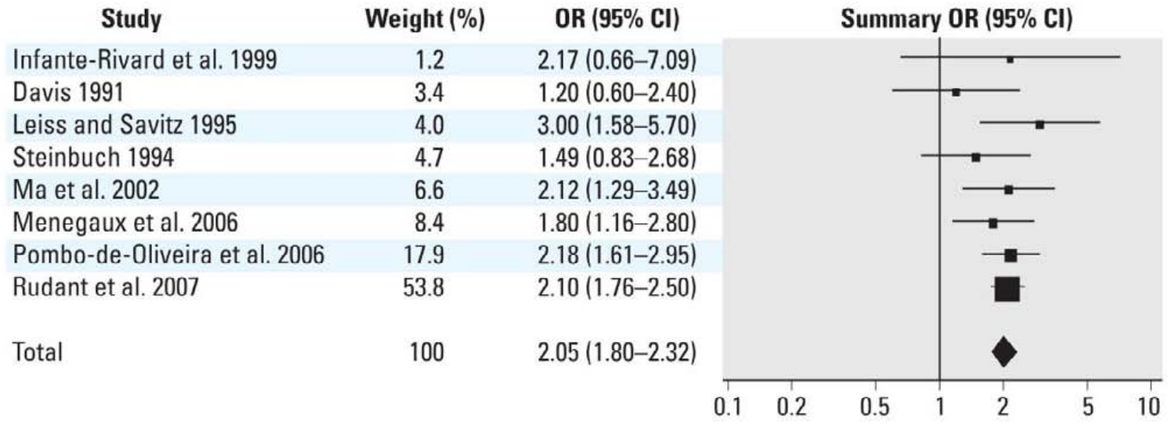
Tricia thought that Stephen's daycare might occasionally use pesticides to spray for ants and flying insects. Dr. Baker consulted the pediatrician at his regional Pediatric Environmental Health Specialty Unit, who confirmed that many studies from around the world have found statistically significant 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.

CHILDHOOD LEUKEMIA Stephen's Story

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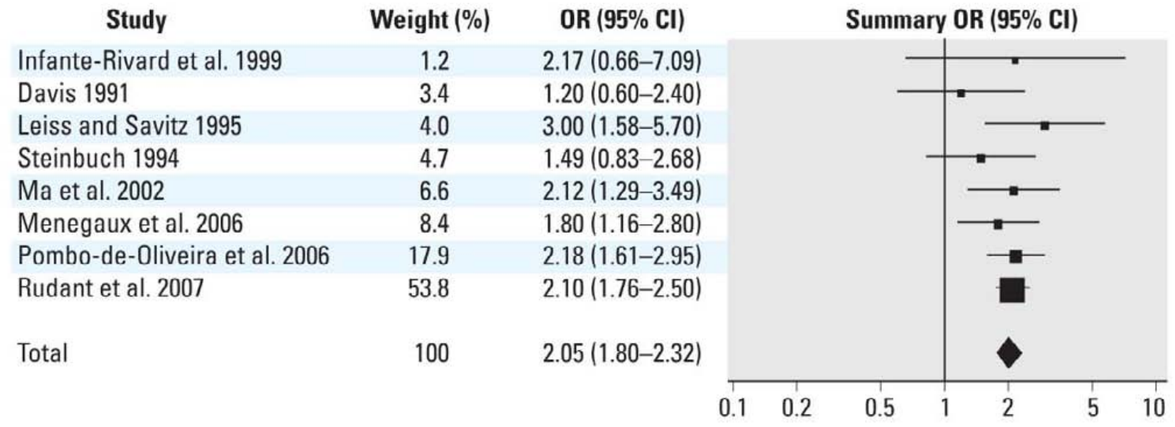

What is a meta-analysis?

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

CHILDHOOD LEUKEMIA Stephen's Story

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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

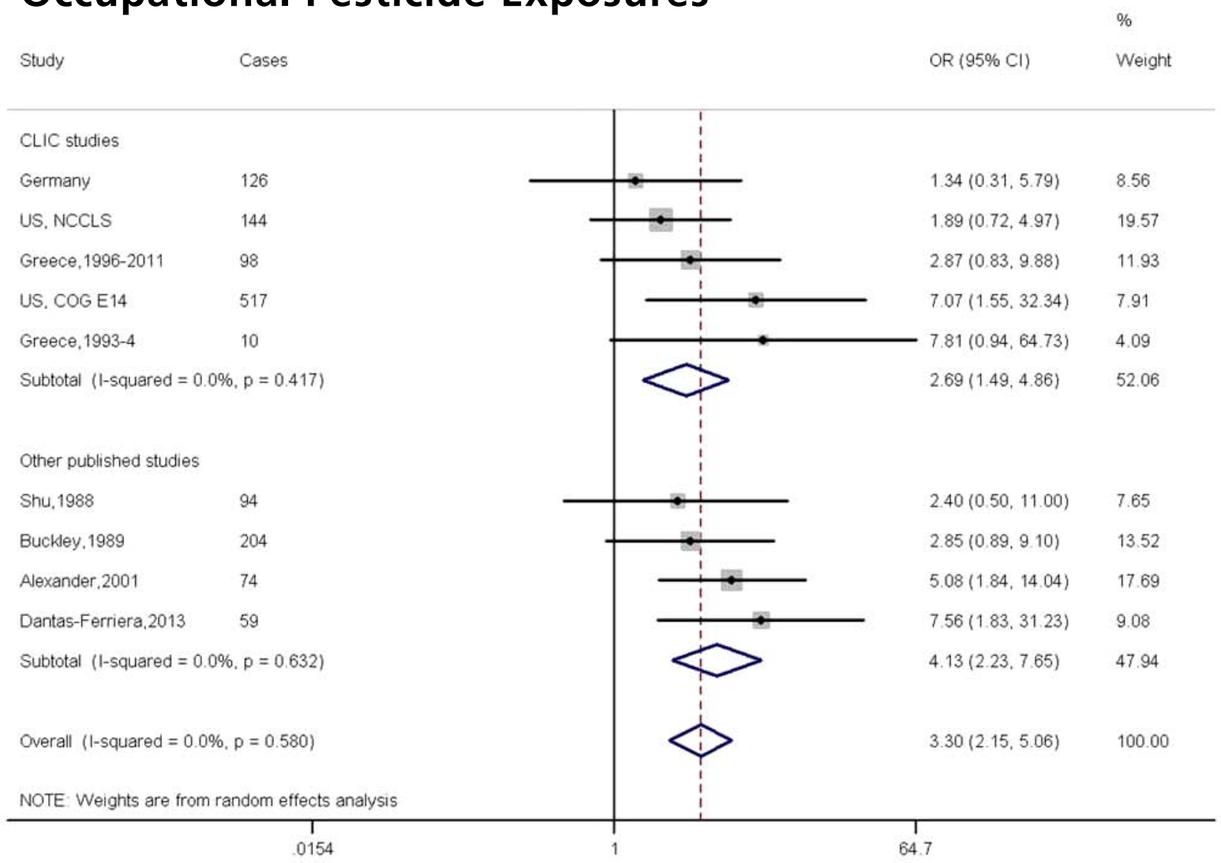
Dr. Baker asked a few more details about the garden center. Tricia said she worked in the back office while she was pregnant, up until a few months before Stephen was born.

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.

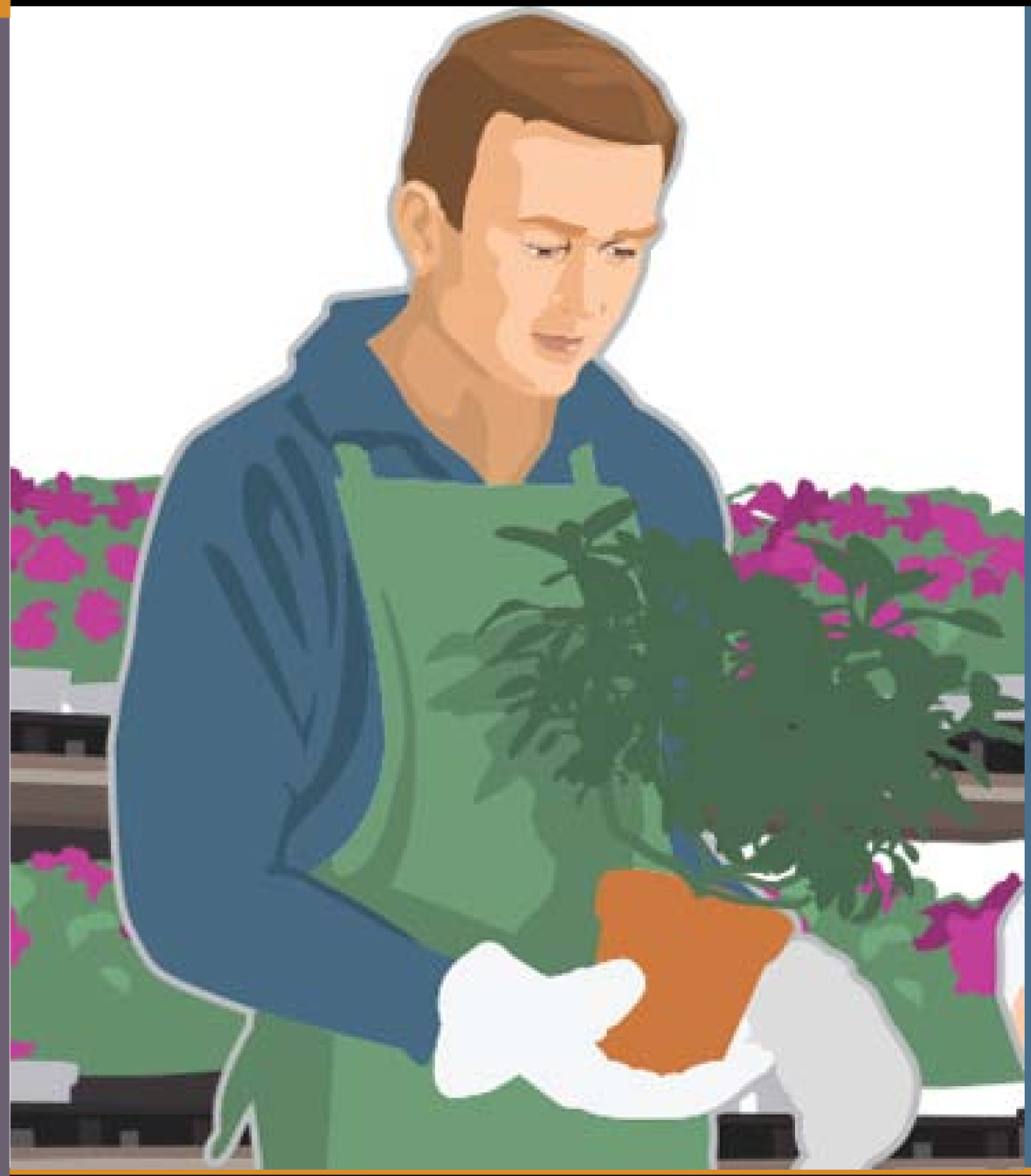
PATERNAL OCCUPATIONAL EXPOSURES AROUND TIME OF CONCEPTION MAY CONTRIBUTE TO CHILDHOOD LEUKEMIA RISK

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

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

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

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

? Folate supplementation recommendations for women

? Studies on Folate and Leukemia

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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.

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**

Image source: Centers for Disease Control and Prevention, used with permission

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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

Image source: Centers for Disease Control and Prevention, used with permission

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.

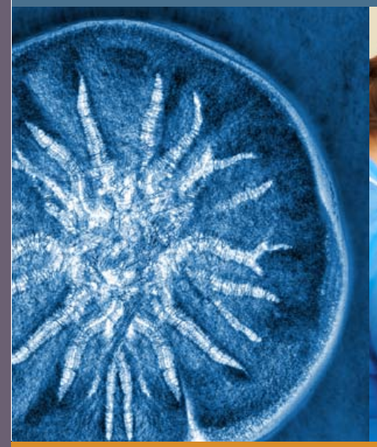
We know that tobacco smoke could be affecting the development of the fetus and the child during pregnancy and during the early years of life. We also know that tobacco smoke can affect the germ cells.

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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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.)

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 Stephen's Story

CRITICAL WINDOWS OF EXPOSURE TO TOBACCO SMOKE

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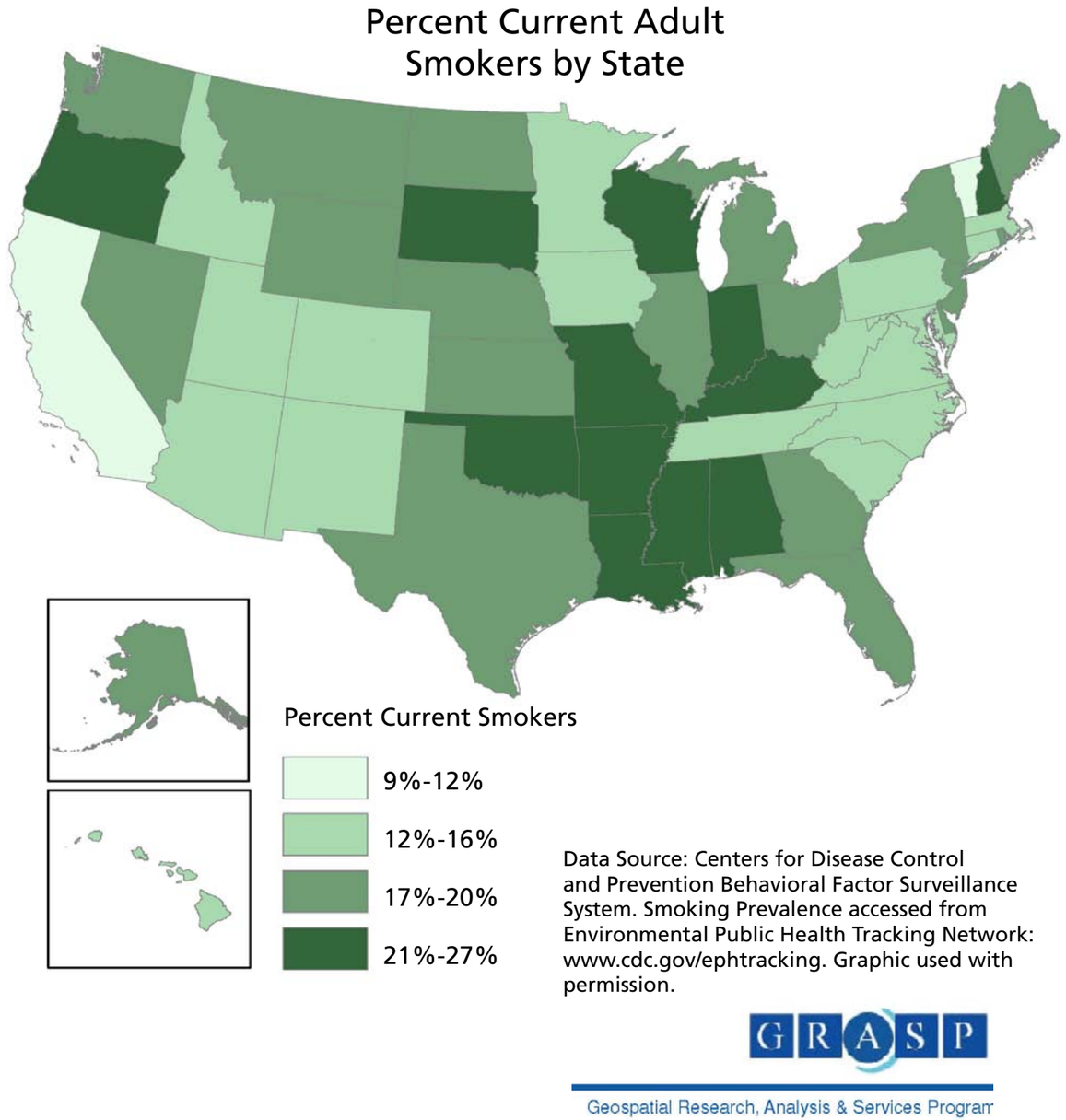

CHILDHOOD LEUKEMIA Stephen's Story

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
- Germ Cell Formation

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 Stephen's Story

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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 Stephen's Story

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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?

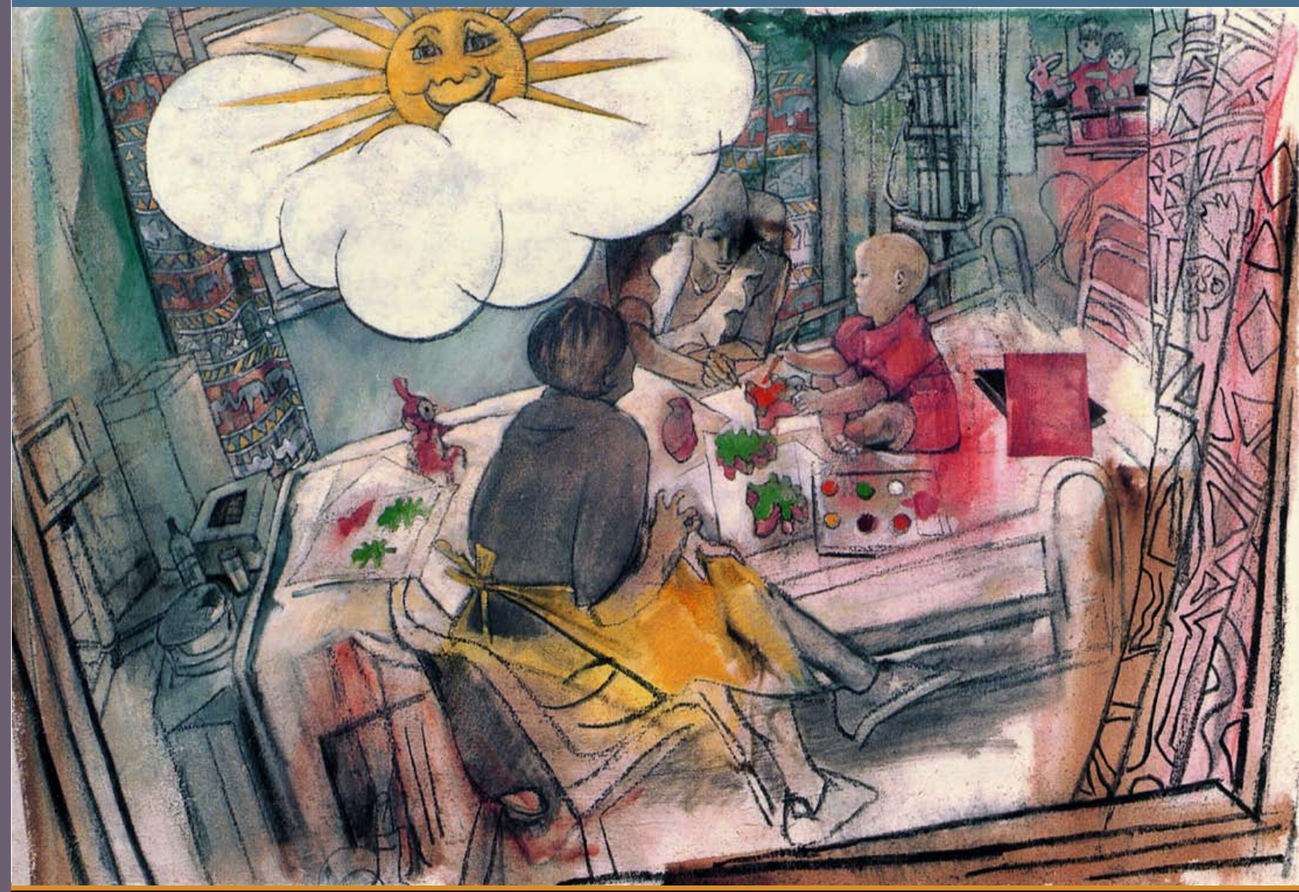
Toward the end of their clinic visit, Tricia and David were visibly distressed about all of the potential factors that could have contributed to their son's leukemia.

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.

Ecological Approach to Disease

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



**"Playschool."
by Susan Macfarlane,
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About this painting, with words of the artist in *italics* >

CHILDHOOD LEUKEMIA Stephen's Story

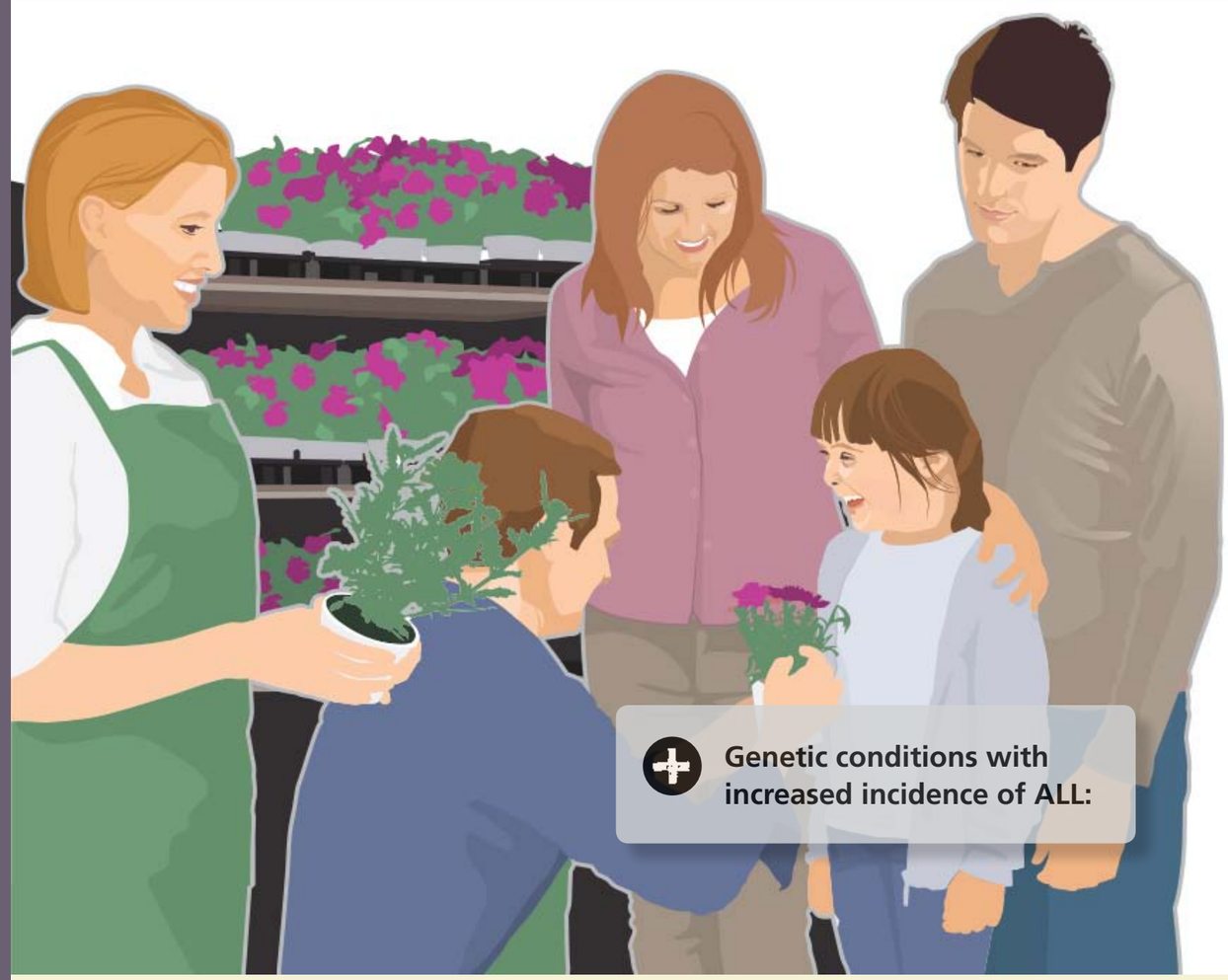
SOME CHILDREN ARE AT HIGHER RISK

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

? Family History and Childhood Leukemia



Genetic conditions with increased incidence of ALL:

CHILDHOOD LEUKEMIA Stephen's Story

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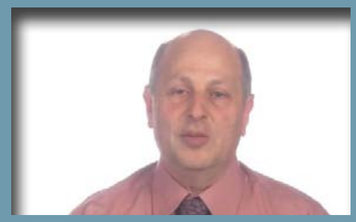
KEY CONCEPT:

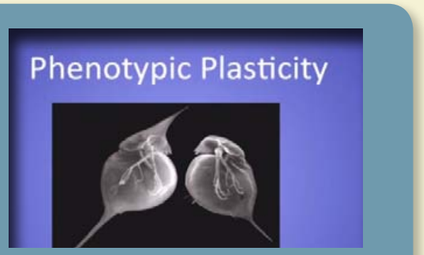
Epigenetics

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.



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.

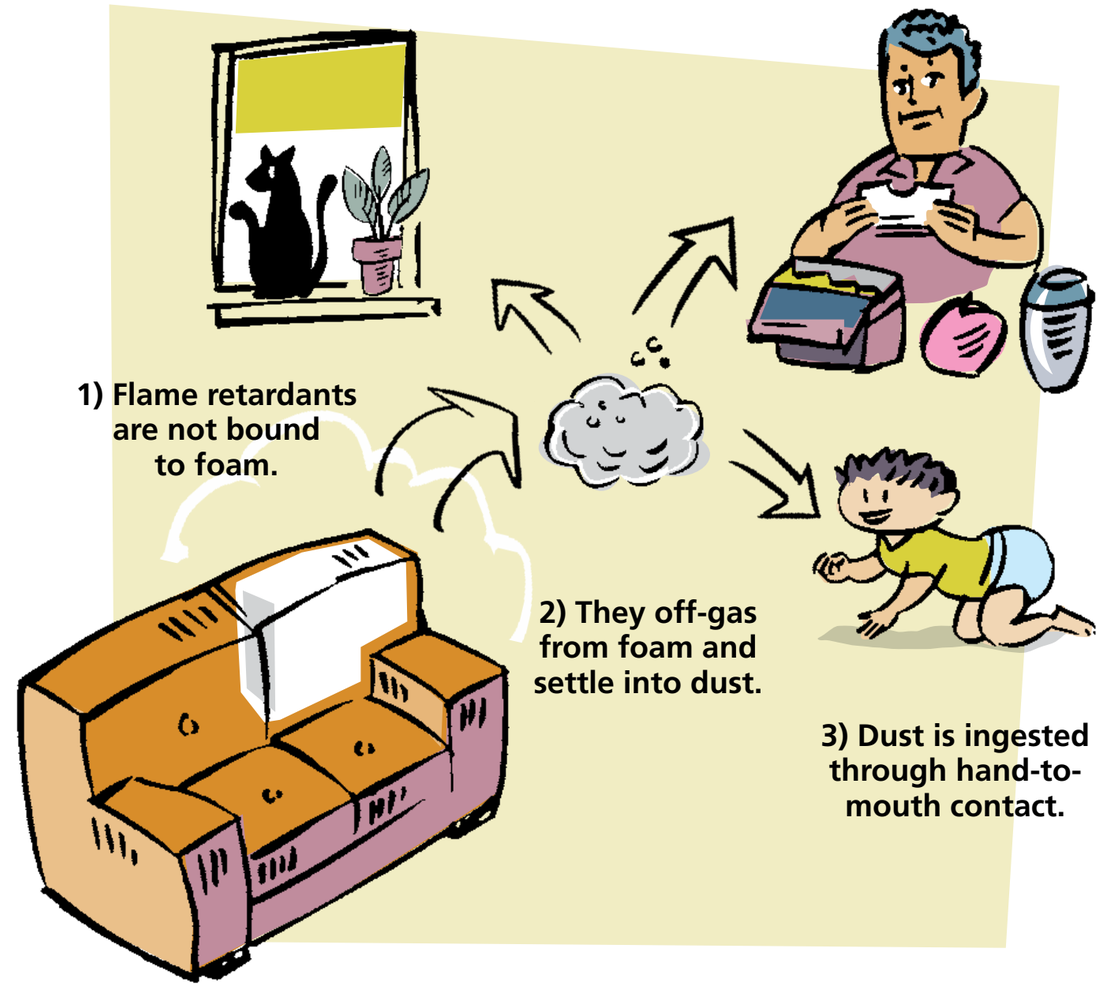
These chemicals can migrate from consumer products and collect in house dust. Because children crawl on the floor and put their hands in their mouth, they may be exposed to higher amounts of chemicals commonly found in house dust than adults.

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

- **PCBs in house dust.**
- **PBDEs in house dust.**
- **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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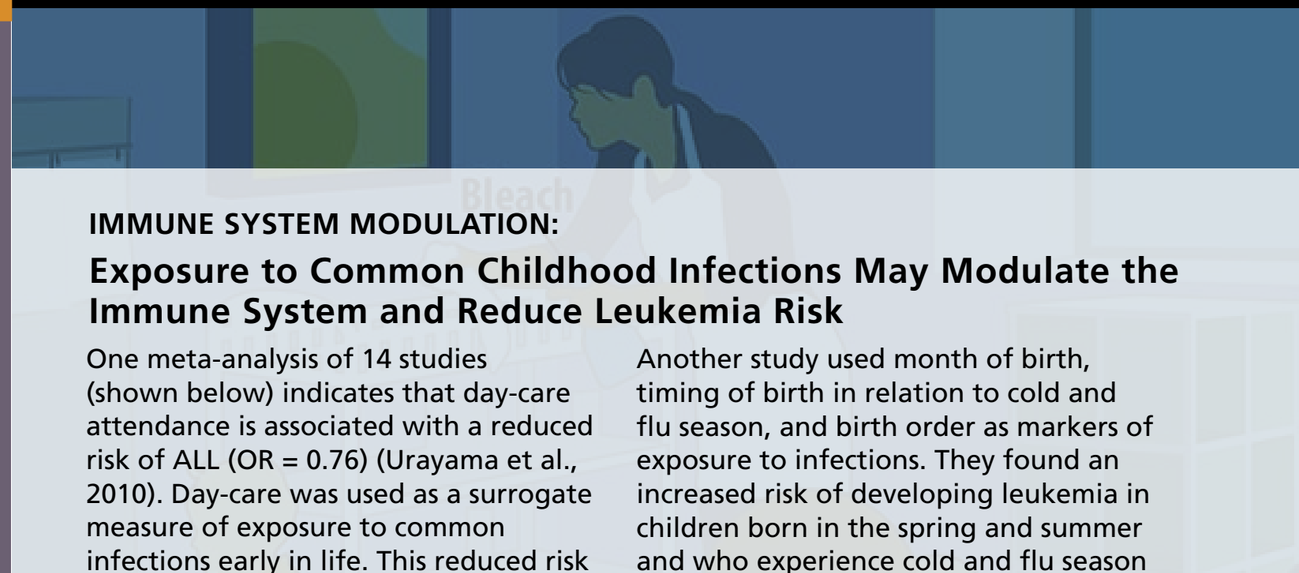
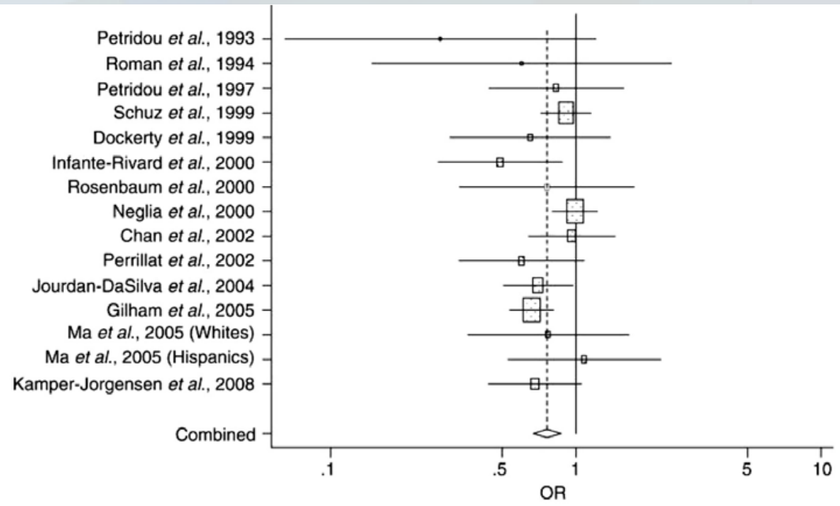


IMMUNE SYSTEM MODULATION:

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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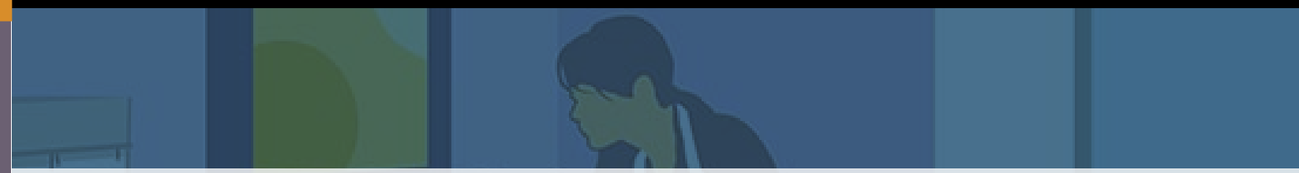

Infection-related damage leading to leukemia

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)

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CHILDHOOD LEUKEMIA Stephen's Story

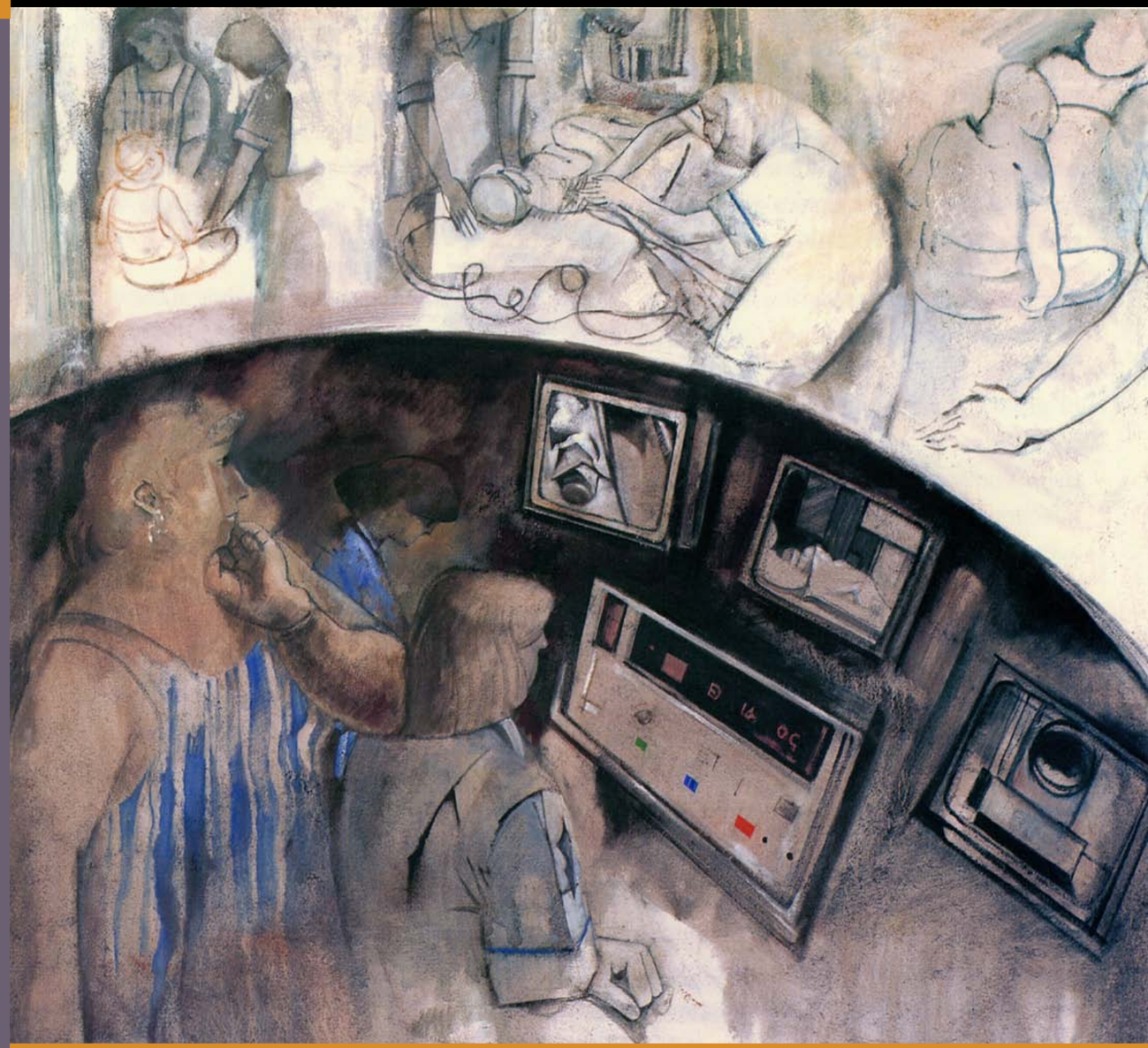
IONIZING RADIATION (INCLUDING X-RAY AND CT SCAN) EXPOSURE AND CHILDHOOD LEUKEMIA

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 (Linet et al., 2009). **More >**

- The Electromagnetic Spectrum
- Non-ionizing Radiation
- National Cancer Institute - Radiation Risks and Pediatric Computed Tomography (CT)



"Radiotherapy"
by Susan Macfarlane,
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About the painting with the words of the artist in *italics* >

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

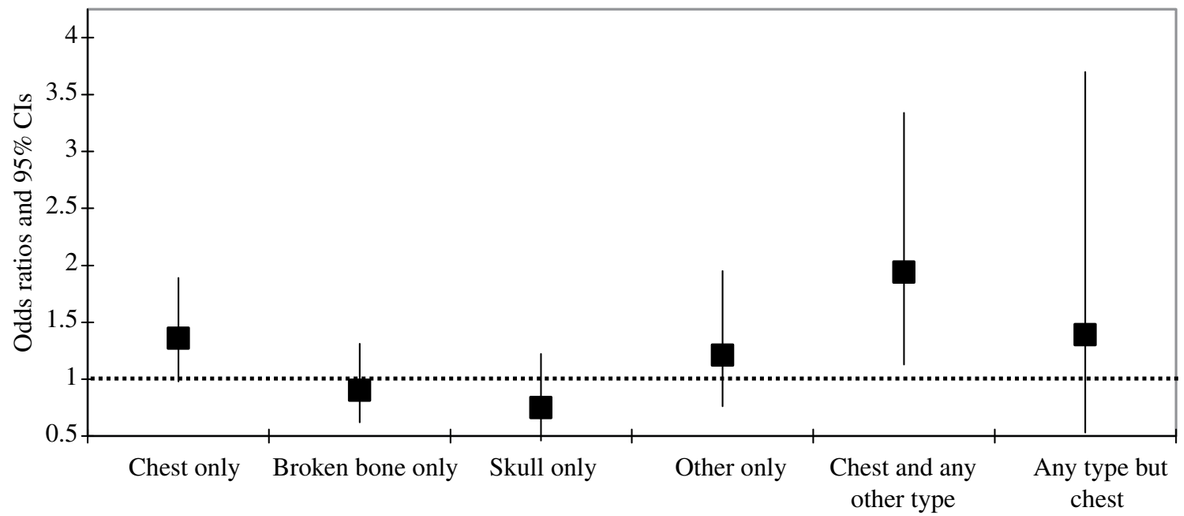
(continued)

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.

The Electromagnetic Spectrum

Non-ionizing Radiation

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



One study's results suggest elevated risks of ALL associated with chest X-rays only (OR=1.36, 95% CI 0.99–1.89) and chest X-rays combined with other regions exposed (OR=1.94, 95% CI 1.13–3.34), indicating that risk of exposure may differ by region of body exposed.

Bartley et al, 2010. Graphic used with permission.

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"Radiotherapy"
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About the painting with the words of the artist in *italics* >

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.

Integrated Pest Management

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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

Drawing courtesy of the Bio-Integral Resource Center. Artist Diane Kuhn.

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?"

REFERENCES: Childhood Leukemia

Asthma

Childhood Leukemia

Learning/ Developmental Disabilities

Diabetes

Infertility

Cognitive Decline

Childhood Leukemia Case References and Resources by Topic

Note: there are many topic overlaps

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continued >

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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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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

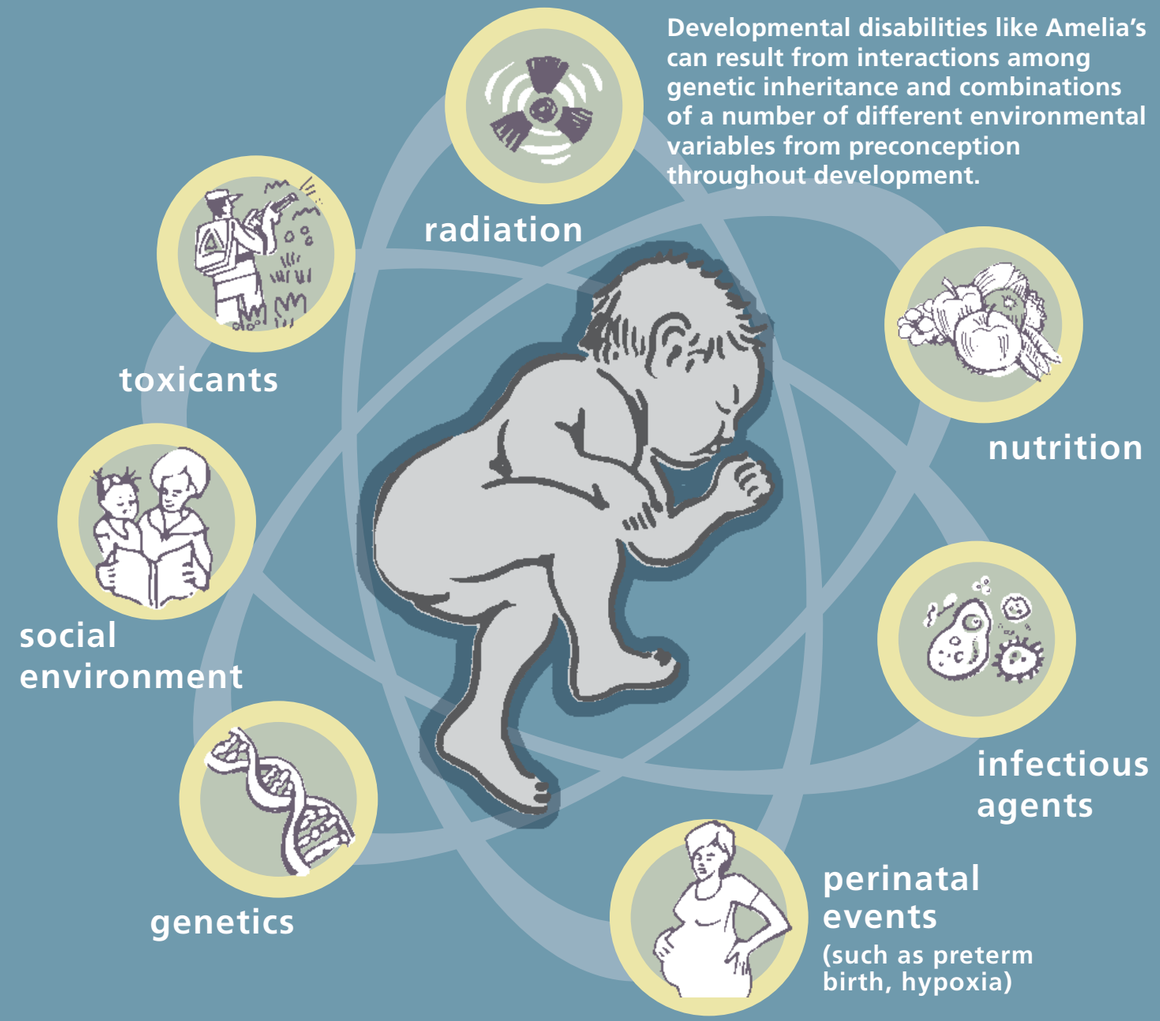
A single variable, such as birth trauma or prenatal exposure to alcohol, may sometimes be the cause of a developmental disability.

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.

Environmental factors reported to be associated with ADHD*

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.

? **More information on Developmental Milestones >**

Checklists for Parents:

CDC's Developmental Milestones by specific age

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

Learning and math disabilities and IQ

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.

The beneficial effects of an enriched social environment

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.

? Evaluation – What does it mean?

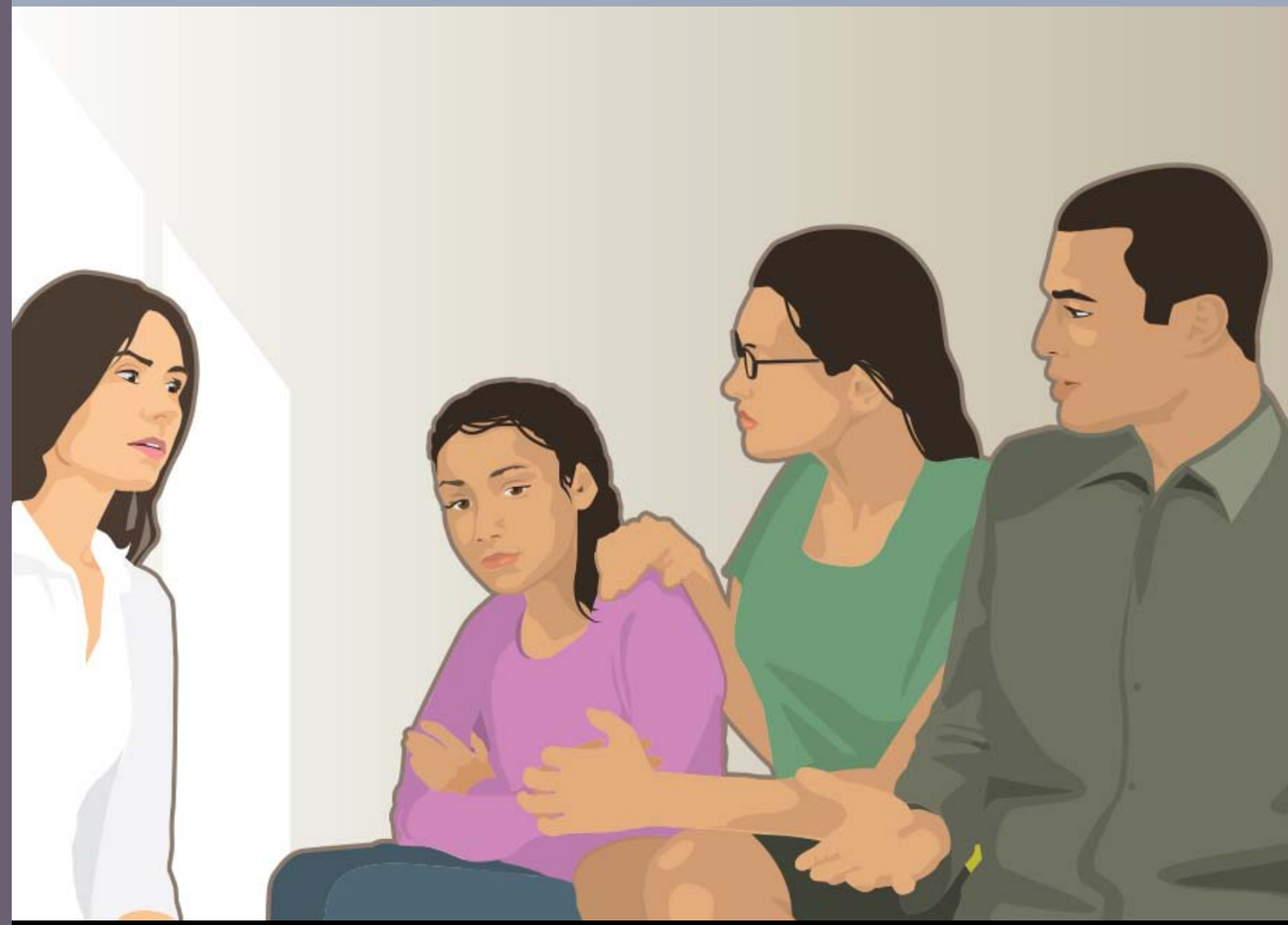
The medical setting was somewhat intimidating at first, but the people at the center made them feel at ease. They were introduced to Dr. Bradley, a developmental pediatrician, who said she would be conducting a number of screening procedures with Amelia.

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

LDA Learning Disabilities Association of America



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.

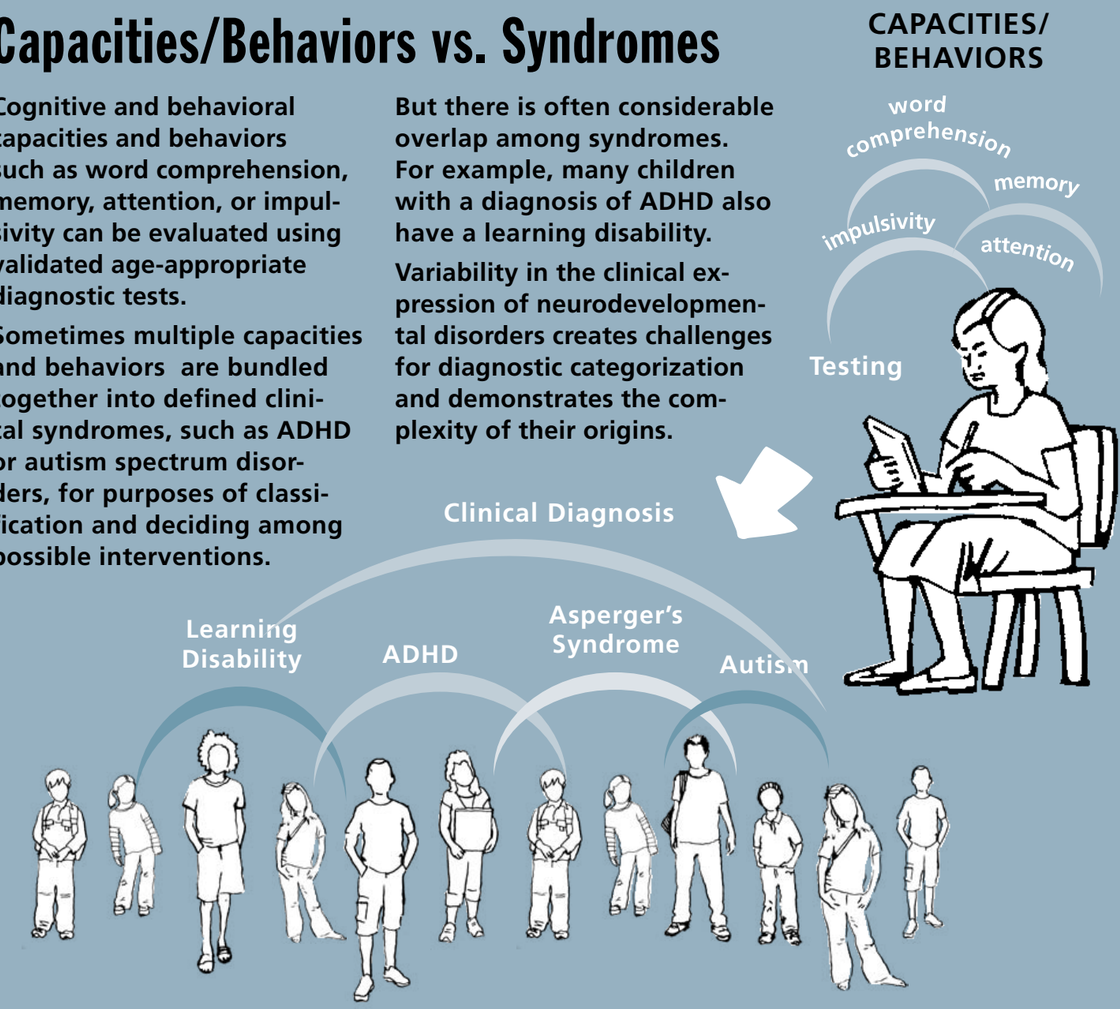
Capacities/Behaviors vs. Syndromes

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.

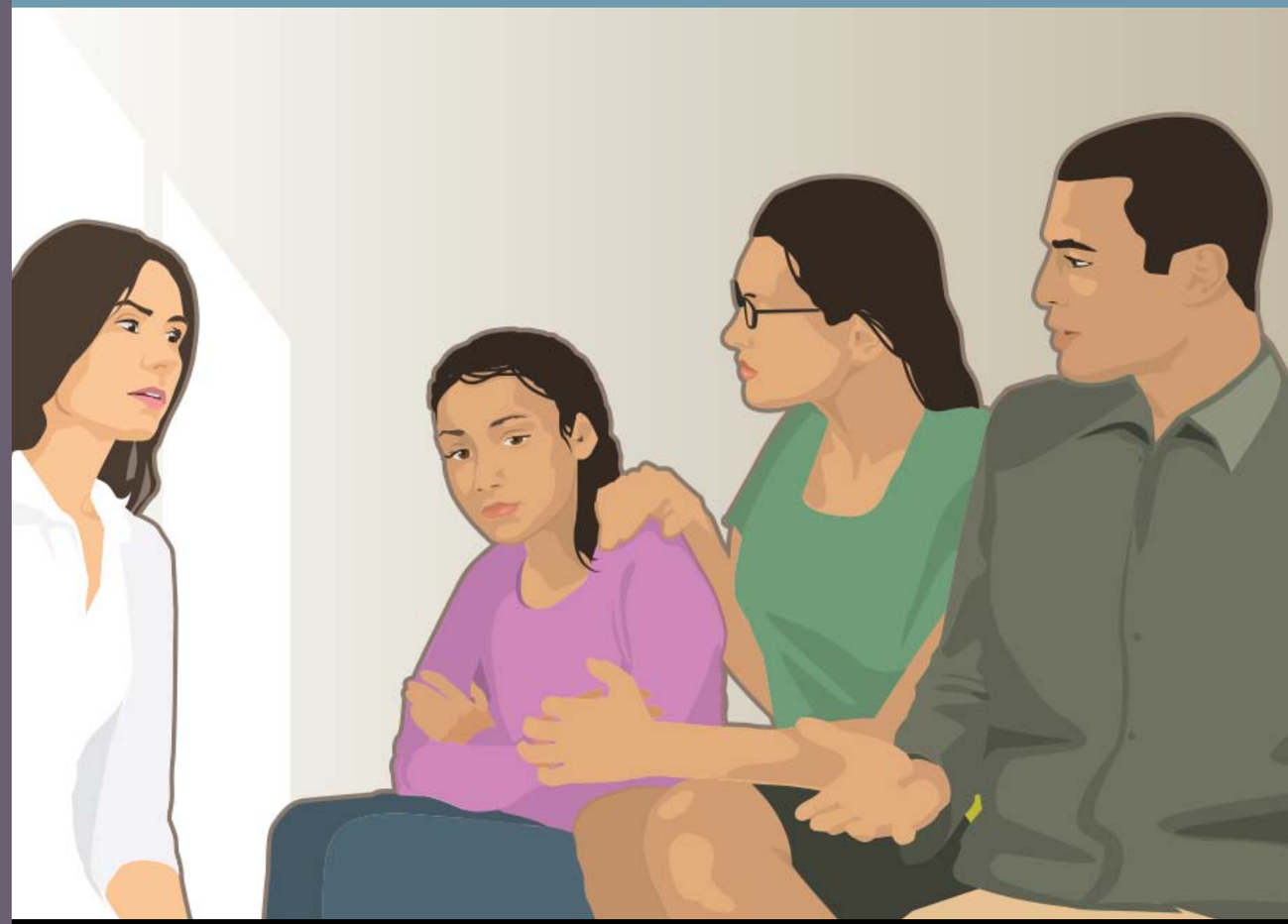
Preconception and Healthy Child Development

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



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

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 specturm 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.

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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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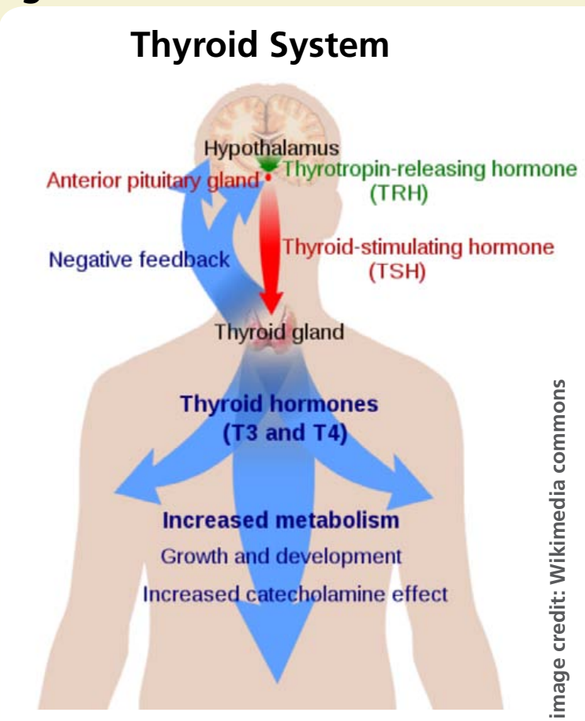
PRENATAL HEALTHY CARE

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.



Thyroid disruption technical diagram

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.

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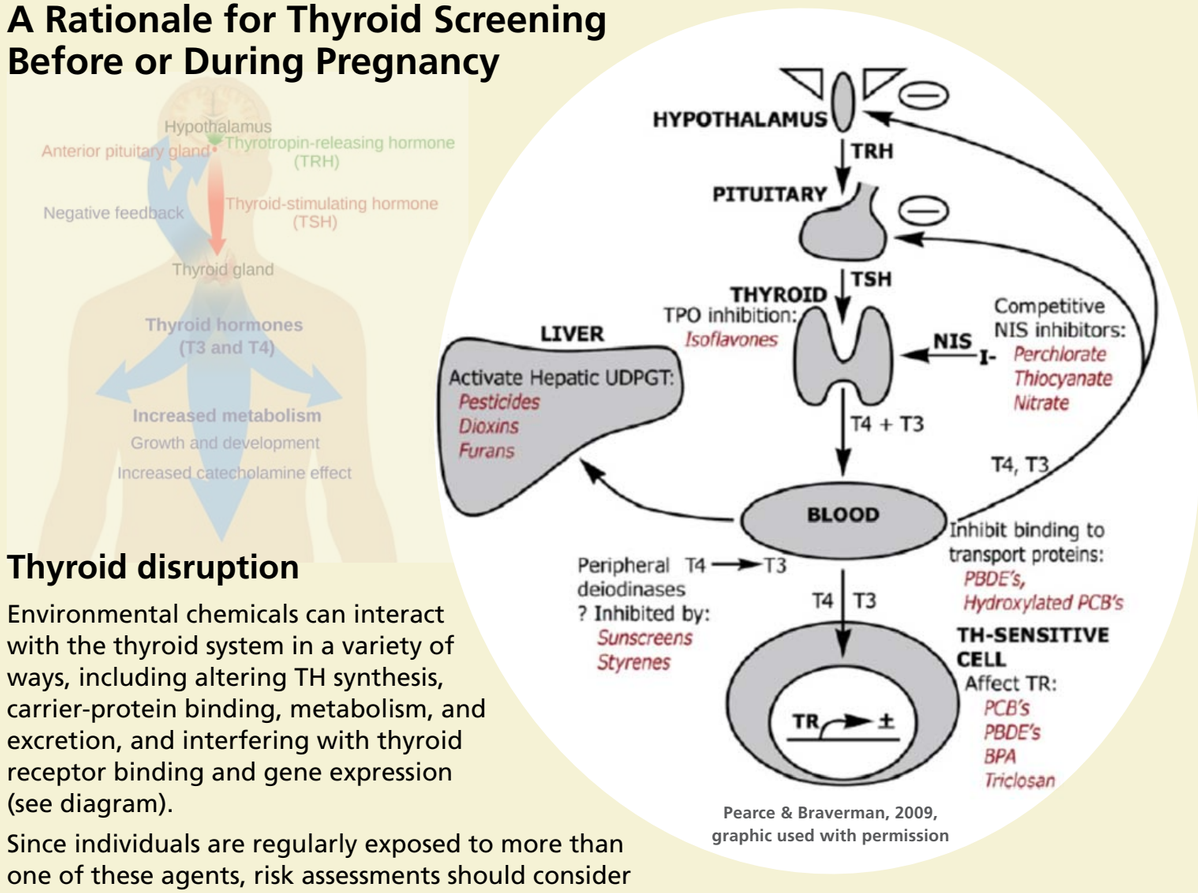


Pearce & Braverman, 2009, graphic used with permission

Thyroid disruption

Environmental chemicals can interact with the thyroid system in a variety of ways, including altering TH synthesis, carrier-protein binding, metabolism, and excretion, and interfering with thyroid receptor binding and gene expression (see diagram).

Since individuals are regularly exposed to more than one of these agents, risk assessments should consider cumulative exposures when assessing the safety of a single chemical. (Science and Decisions: Advancing Risk Assessment. Natl. Research Council.) Unfortunately this is not yet routine practice.

Clinicians should be aware of the many variables that can influence the thyroid hormone status of patients, and strongly consider assessing thyroid hormone status in women of reproductive age and women who are pregnant.

LEARNING/DEVELOPMENTAL DISABILITIES Amelia's Story

BRAIN DEVELOPMENT

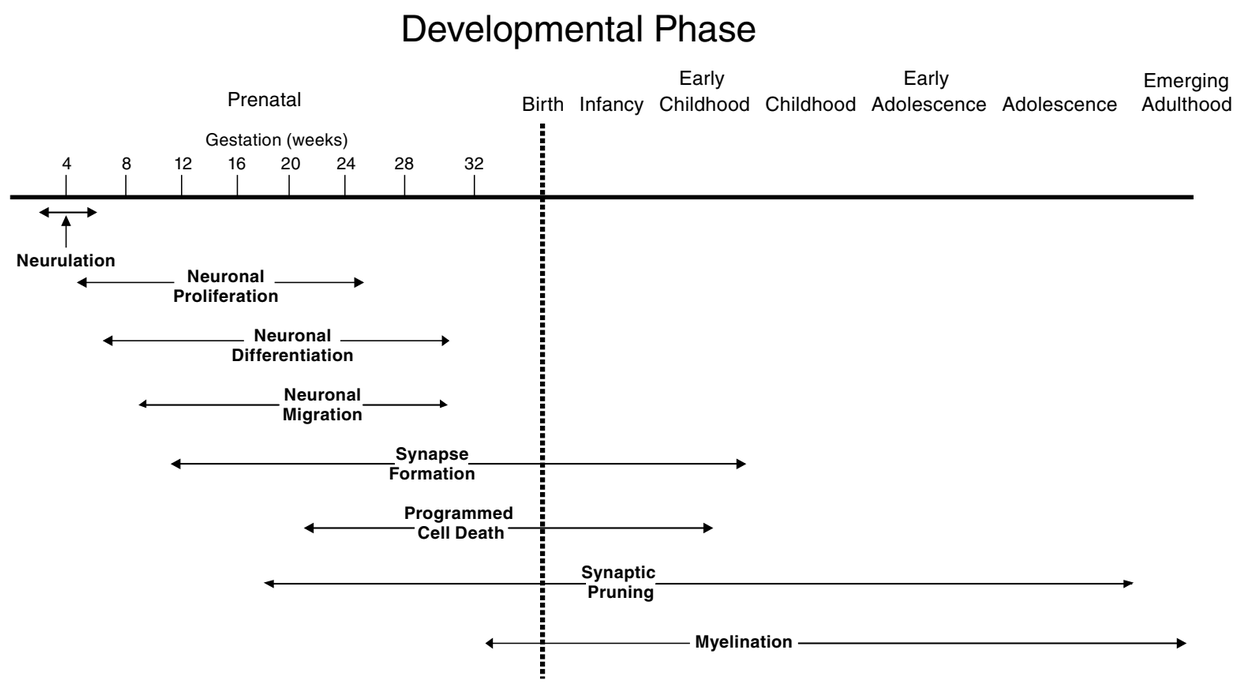
Brain development begins soon after conception and continues throughout adolescence into adulthood. It is characterized by a critical sequence of events that helps to determine brain structure and function. Each of these processes is subject to disruption by exposure to various environmental agents.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

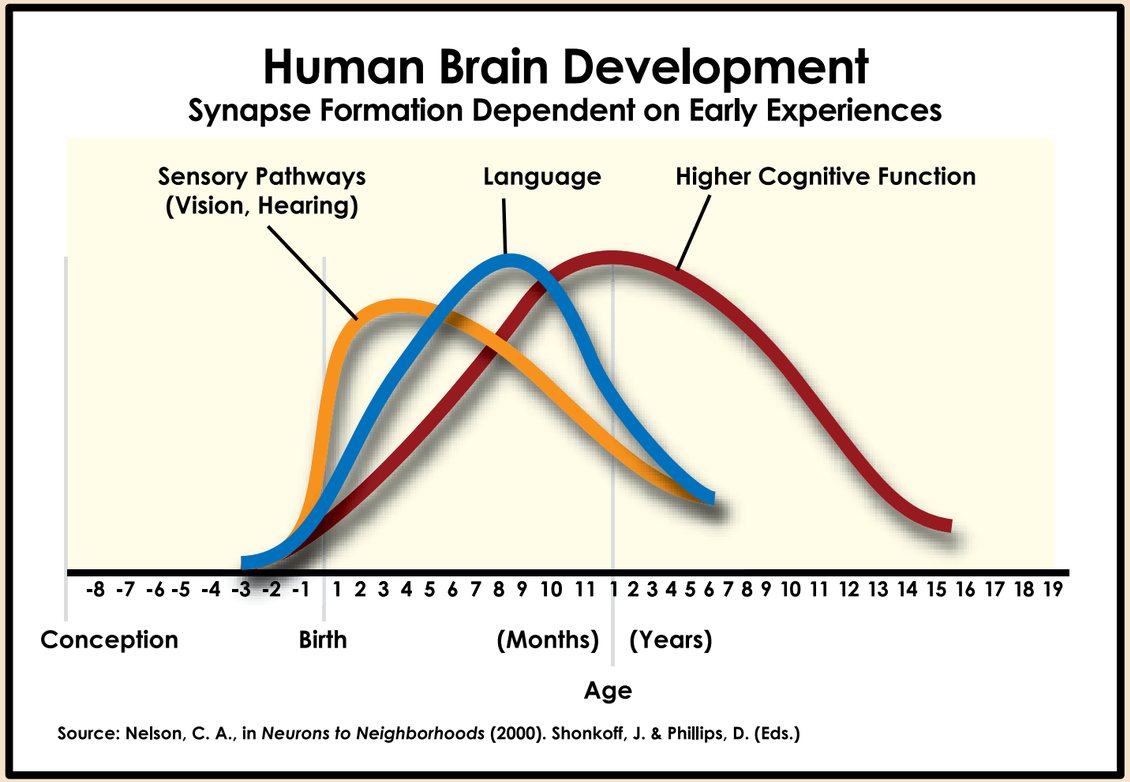
BRAIN DEVELOPMENT

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.

+ 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.)

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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.

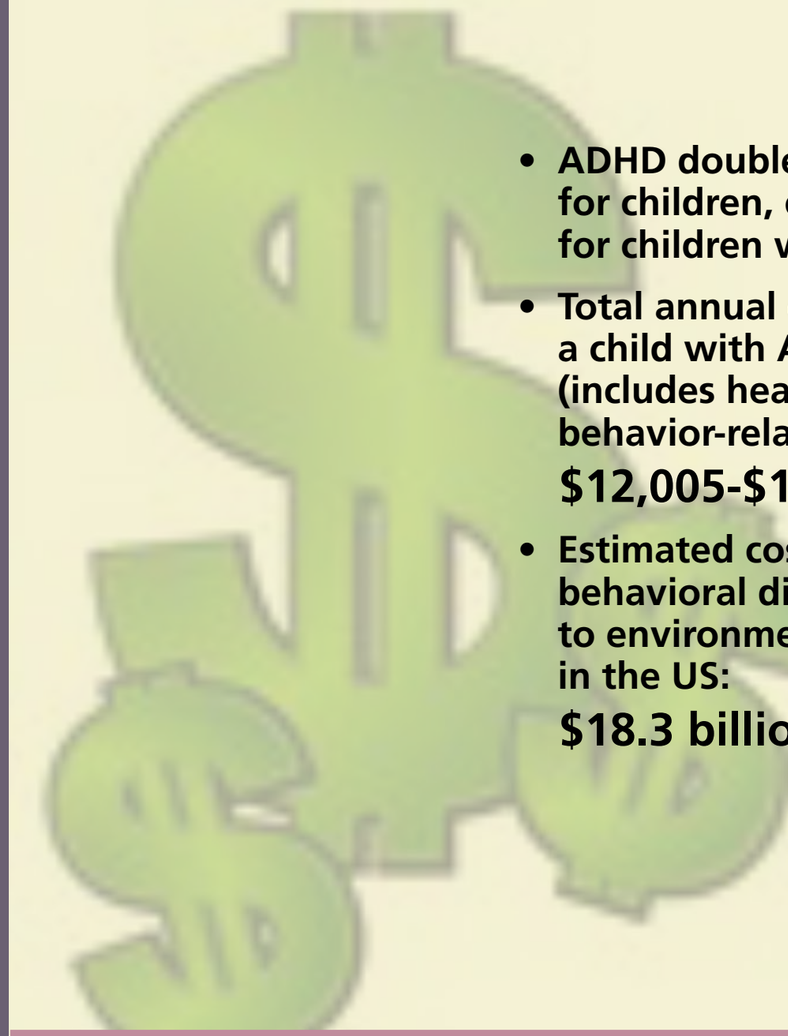
LEARNING/DEVELOPMENTAL DISABILITIES Amelia's Story

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.

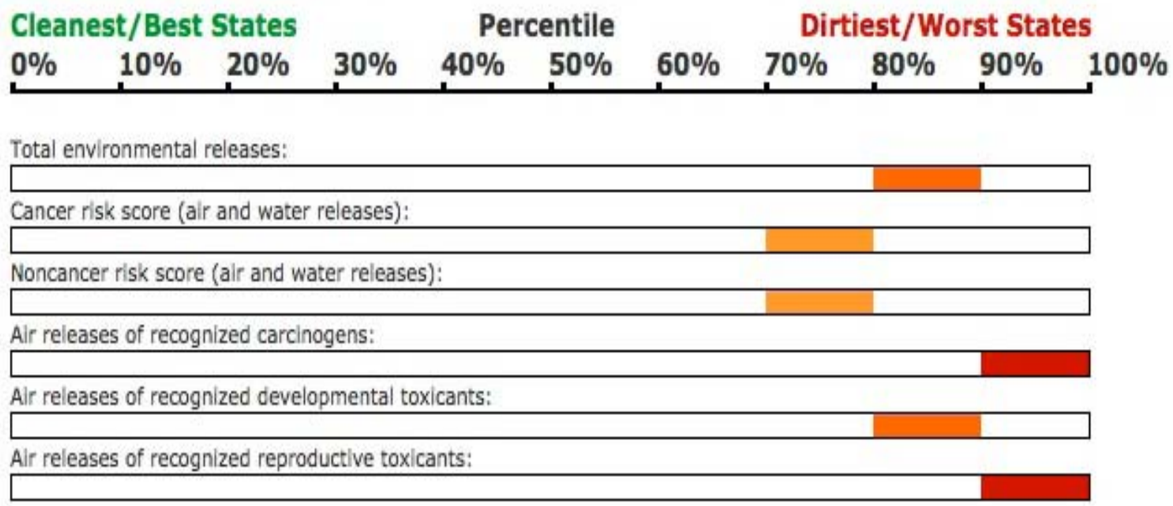
Gloria and Darrell moved to their current home just as Gloria was beginning her second trimester of pregnancy.

Scorecard
THE POLLUTION INFORMATION SITE

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.

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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.

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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 off-spring 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."

Graphic: Bio-integral Resource Center, reproduced with permission.

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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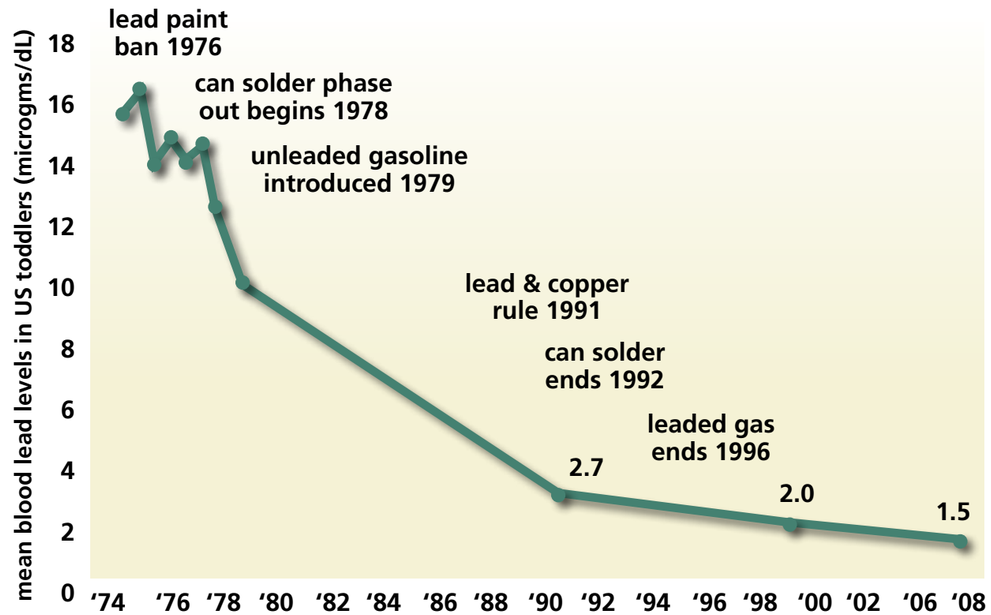
Lead removal – a public health success story

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

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.

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 of15dB 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:

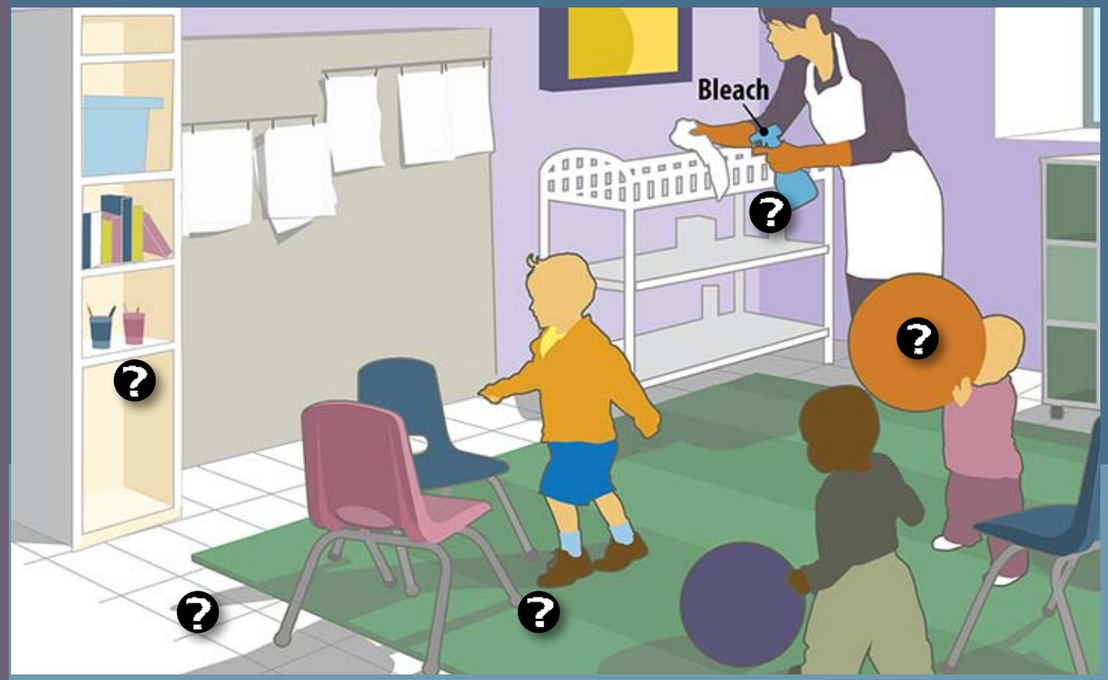
Benefits of early childhood education and policies:

- 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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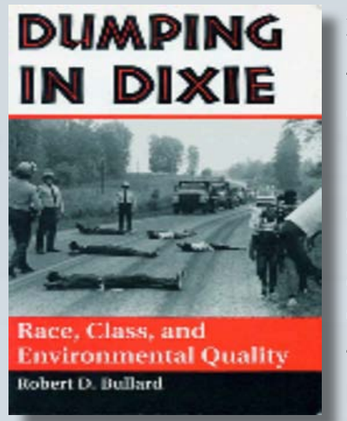
KEY CONCEPT:

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.



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

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

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

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

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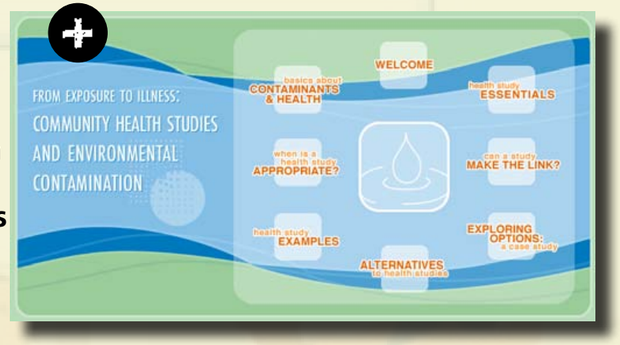
Chemical regulations

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.

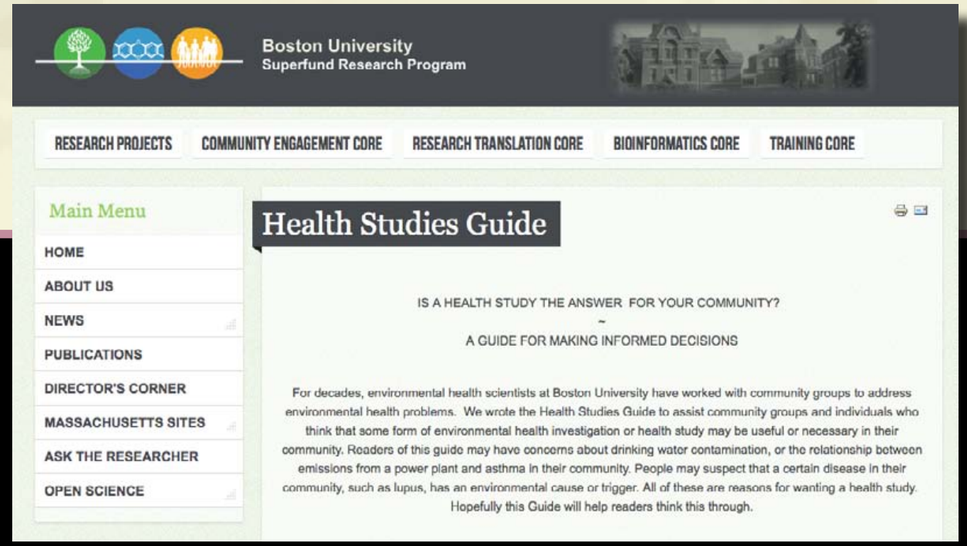
HEALTH STUDIES GUIDE: Boston University Superfund Research Project

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.



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.

Benefits of spending time in green space or natural surroundings on cognition and general health.

Link: Animation on "Healthy Food and Exercise" – UCSF Pediatric Environmental Health Specialty Unit.

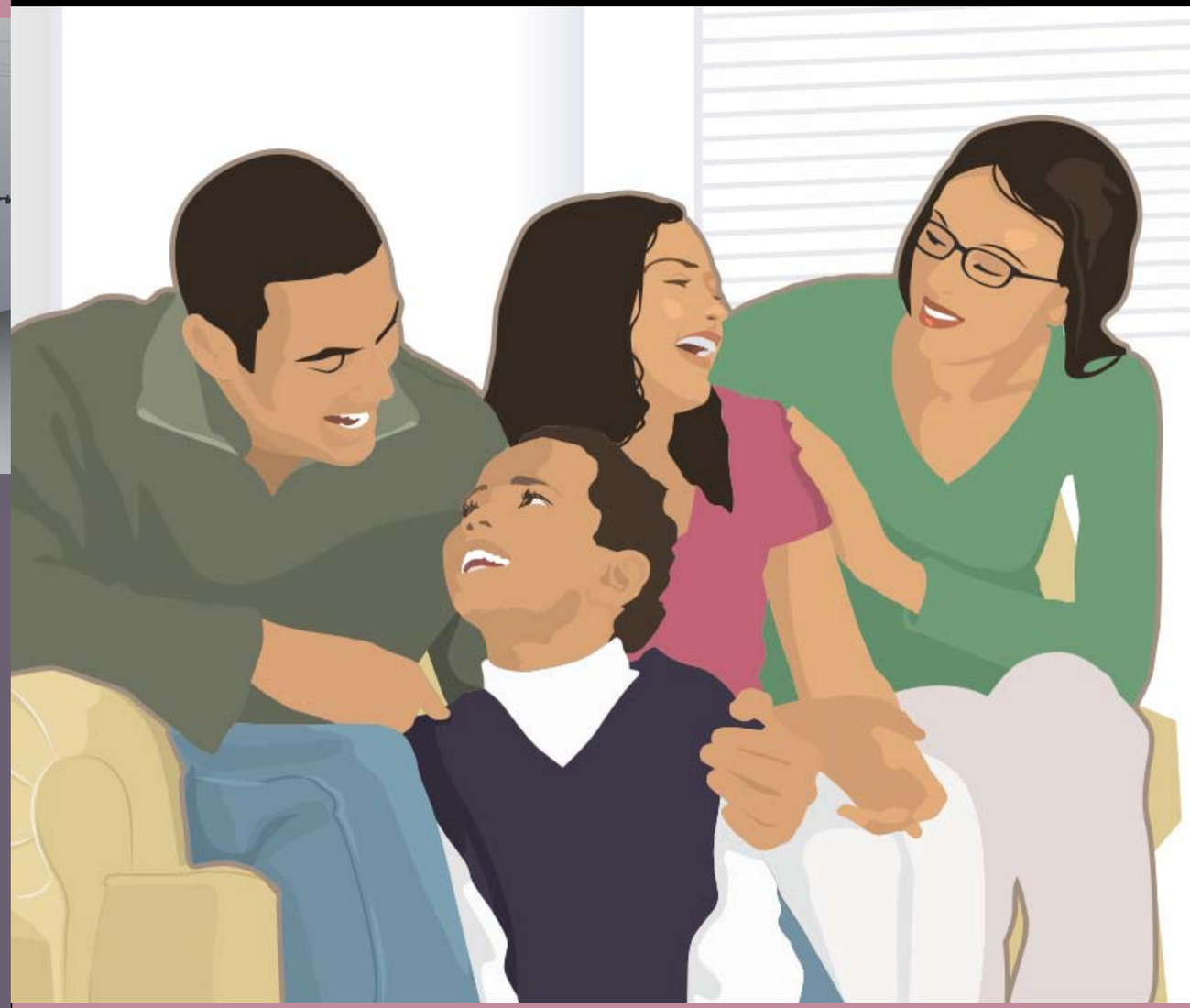
LEARNING/DEVELOPMENTAL DISABILITIES Amelia's Story

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 >

A wide range of interacting factors across Amelia's lifespan may increase the risk for developmental disabilities

Children throughout our country face a similar range of exposures and consequences.

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.

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:

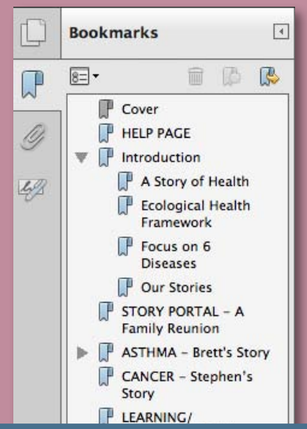
- Important environmental influences come from the natural, chemical, food, built, and social environments.
- Although there are exceptions, most diseases as well as good health are the result of complex interactions among multiple environmental influences and genetics.
- Early-life experiences, particularly 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

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Childhood Leukemia

Learning/ Developmental Disabilities

Diabetes

Infertility

Cognitive Decline

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