ECHO
Environmental influences on Child Health Outcomes

NIH Advisory Committee to the Director

Matthew W. Gillman, MD, SM

8 December 2016

NIH National Institutes of Health
Environmental influences on Child Health Outcomes (ECHO)

ECHO Overall Scientific Goal

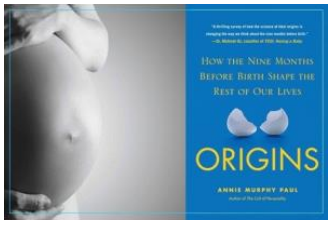
Answer crucial questions about effects
of
broad range of early environmental exposures
on
child health and development

NIH National Institutes of Health
Environmental influences on Child Health Outcomes (ECHO)

Why ECHO?

Why now?

A good start to life…



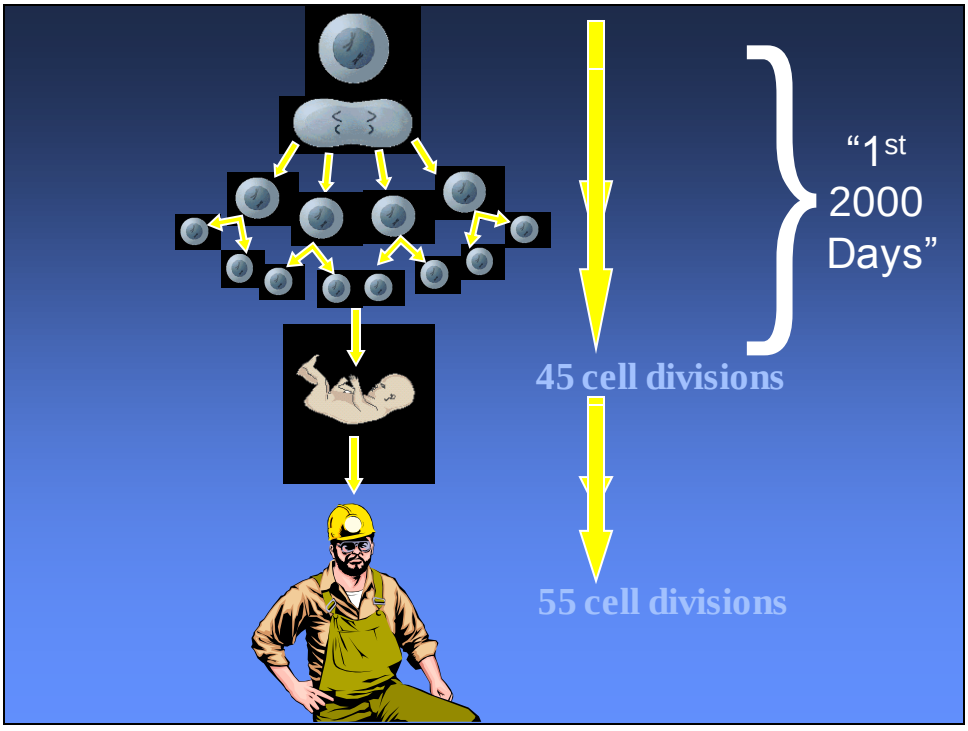
NIH National Institutes of Health
Environmental influences on Child Health Outcomes (ECHO)

…can last a lifetime

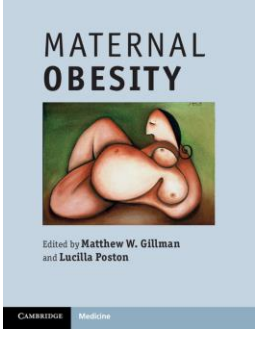
National Institutes of Health
Environmental influences on Child Health Outcomes (ECHO)

…can last a lifetime

National Institutes of Health
Environmental influences on Child Health Outcomes (ECHO)



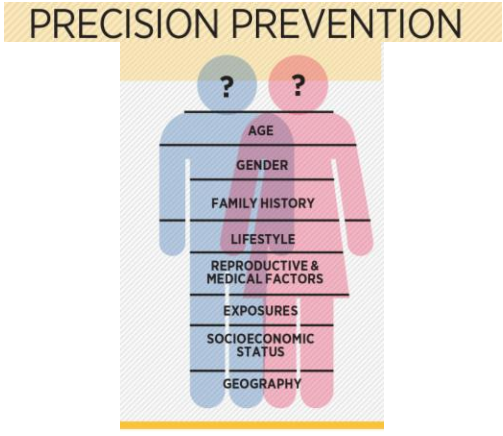
To ensure a good start, need to understand potential risks…



NIH National Institutes of Health
Environmental influences on Child Health Outcomes (ECHO)

To ensure a good start, need to understand potential risks…

…and to whom they apply…



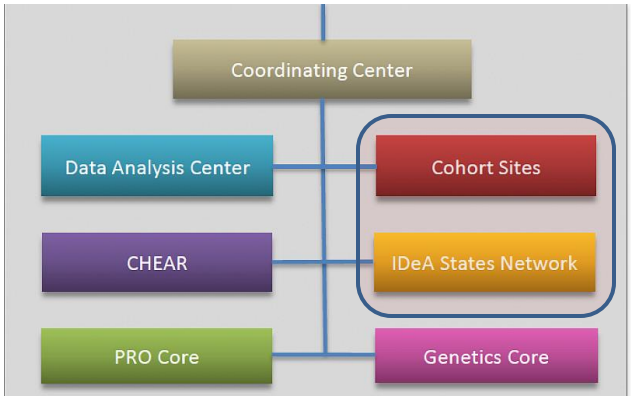
… then take action

ECHO Approach

- Focus on high-impact pediatric conditions
  - Pre/peri/postnatal outcomes
  - Obesity
  - Upper & lower airway
  - Neurodevelopment
  - Child health

NIH National Institutes of Health
Environmental influences on Child Health Outcomes (ECHO)

ECHO Approach



Observational studies

Intervention trials

NIH National Institutes of Health
Environmental influences on Child Health Outcomes (ECHO)

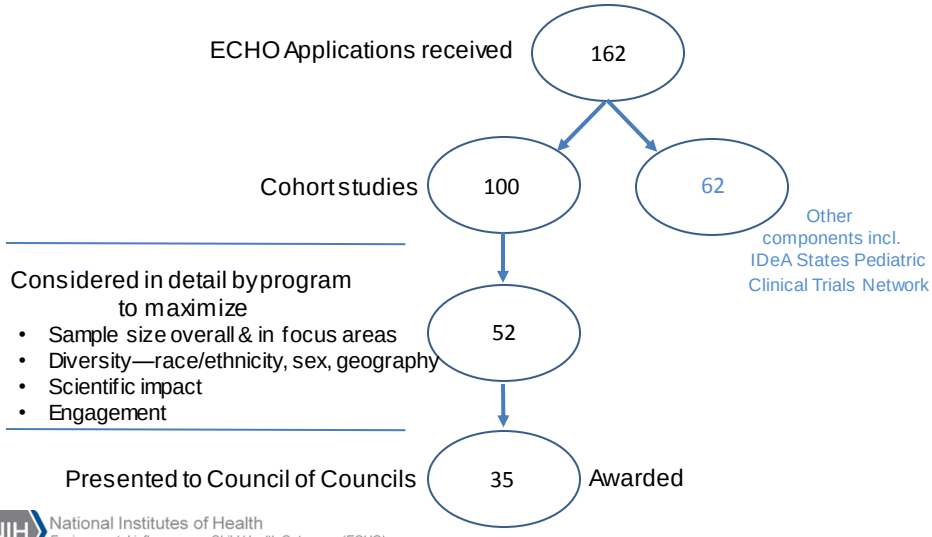
Meet Scientific Needs

- Intervention trials
  - Kids underrepresented in clinical trials
  - Especially hard-to-reach populations
    - Rural, medically underserved
- Observational studies
  - Ask solution-oriented questions
    - Questions that inform practice & policy
    - Inform, and informed by, trials
  - Sufficient number of participants for power, heterogeneity, generalizability
  - Include newer technology, biological pathways
  - Modern concepts of cause-effect relationships

NIH National Institutes of Health
Environmental influences on Child Health Outcomes (ECHO)

Cohort Sites

FY16 Funding



NIH National Institutes of Health
Environmental influences on Child Health Outcomes (ECHO)

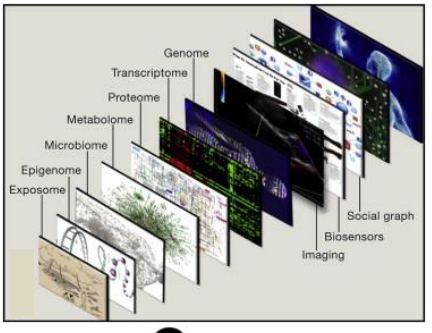
Major Objective: Create ECHO-wide Cohort

- Start with multiple existing cohort studies
  - Increase likelihood of early successes
- Create data platform to conduct solution-oriented observational research
  - Standardized measures
    - Exposures
    - Parent/child-reported outcomes
    - Genes
- Goal >50,000 children
- Use
  - ECHO investigators
  - National research resource

NIH National Institutes of Health
Environmental influences on Child Health Outcomes (ECHO)

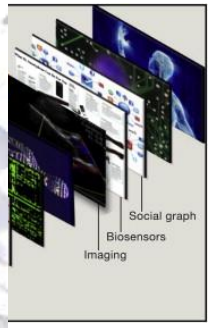
ECHO-wide Cohort

Many people, many layers of data, many stages of life course



NIH National Institutes of Health
Environmental influences on Child Health Outcomes (ECHO)

ECHO-wide Cohort
Integrating into whole



NIH National Institutes of Health
Environmental influences on Child Health Outcomes (ECHO)

35 awards
74 PIs, 78 cohorts

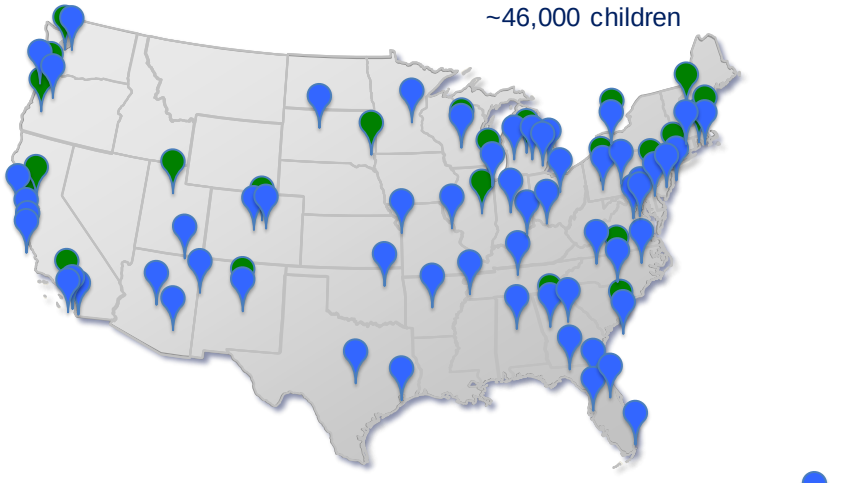
-Majority started prenatally-

Cohort Prime Awardees
Cohort Sub-Awardees

NIH National Institutes of Health
Environmental influences on Child Health Outcomes (ECHO)

On the way to >50,000…

Current:
~33,000 mothers
~46,000 children



Cohort Prime Awardees
Cohort Sub-Awardees

NIH National Institutes of Health
Environmental influences on Child Health Outcomes (ECHO)

Diversity in geography, age, sex, social class, race/ethnicity

~46000 kids, currently

Asian	Black or Af-Am	AI/AN	White	Multi
5%	17%	3%	66%	10%

Hispanic
26%

Preliminary Data

NIH National Institutes of Health
Environmental influences on Child Health Outcomes (ECHO)

ECHO Cohorts
2 Phases

- Phase I: 2 years
  - Pilot/feasibility
  - Engagement

Meet milestones

- Phase II: Additional 5 years
  - Major scientific questions

NIH National Institutes of Health
Environmental influences on Child Health Outcomes (ECHO)

Early Wins
Phase I

- Analyses on existing multiple-cohort data
  - Distributed data analysis approach
    - "Send programs to data"
  - Aggregate results
    - No sharing of individual-level needed yet

NIH National Institutes of Health
Environmental influences on Child Health Outcomes (ECHO)

ECHO-wide Cohort Example
Phase I

- *Factors during pregnancy and infancy that lead to childhood obesity*

ECHO-wide Cohort Example
Phase I

- *Factors during pregnancy and infancy that lead to childhood obesity*
  - *Geographic data*
    - *Air pollution*
    - *Access to food/activity*

ECHO-wide Cohort Example
Phase I

- *Factors during pregnancy and infancy that lead to childhood obesity*
  - *Geographic data*
  - *Biosamples*

National Institutes of Health
Environmental influences on Child Health Outcomes (ECHO)

ECHO-wide Cohort Example
Phase I

- *Factors during pregnancy and infancy that lead to childhood obesity*
  - *Geographic data*
  - *Biosamples*
  - *Self-report and sensors*

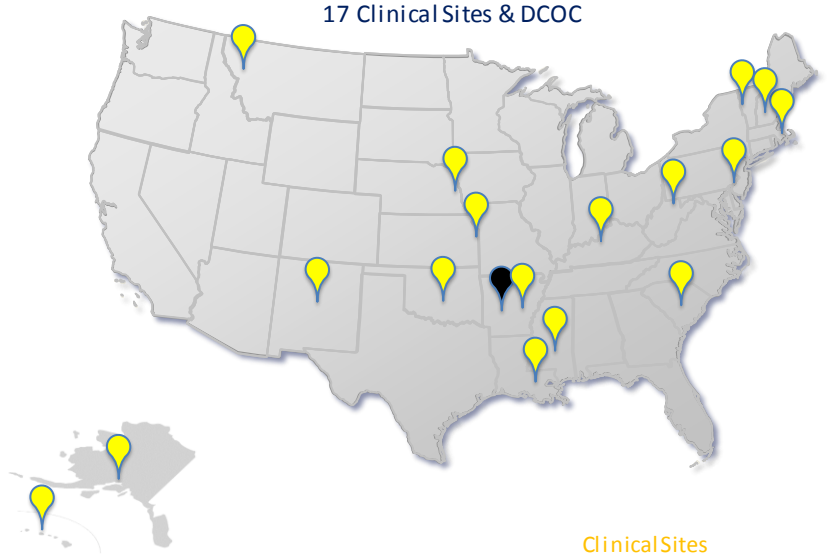
National Institutes of Health
Environmental influences on Child Health Outcomes (ECHO)

Other Major Year 01 Goal

- IDeA States Pediatric Clinical Trials Network
  - Infrastructure and training in place to begin ≥1 clinical trial

NIH National Institutes of Health
Environmental influences on Child Health Outcomes (ECHO)

IDeA States Pediatric Clinical Trials Network
17 Clinical Sites & DCOC



Clinical Sites
Data Coordinating and Operations Center (DCOC)

NIH National Institutes of Health
Environmental influences on Child Health Outcomes (ECHO)

All ECHO Components
Nationwide Program

NIH National Institutes of Health
Environmental influences on Child Health Outcomes (ECHO)

Cohorts Address Wide-Ranging Questions
Phase II

- ECHO-wide cohort
  - Existing *and* new data
  - 2 levels
    - All cohorts: Broad level with common data elements
    - Subset with deeper measures
- Will have in hand
  - Pilot & feasibility results
  - New data collection protocol
    - Informed consent
    - Data & biospecimen sharing policies

NIH National Institutes of Health
Environmental influences on Child Health Outcomes (ECHO)

ECHO-wide Cohort Example
Phase II

- *Pre- and post-natal exposure to smoking, and trajectories of development of childhood wheezing and asthma*
  - *How much associations differ by*
    - *Maternal or child genetics*
    - *Socio-demographic factors*
    - *Sex of child*
  - *Mediated by*
    - *Immune development?*
    - *Functional changes in gut bacteria?*

Getting the Work Done

- Foster culture of collaboration
  - Best practices to conduct team science in 21st c.

Getting the Work Done

- Foster culture of collaboration
- Investigators drive the science
  - Lead working groups

NIH National Institutes of Health
Environmental influences on Child Health Outcomes (ECHO)

Getting the Work Done

- Foster culture of collaboration
- Investigators drive the science
- Active involvement of NIH Institutes, Centers, and Offices
  - Ideas for measures, questions
  - Links with other NIH programs
  - Potential future co-funding
- Guidance by External Scientific Board
  - Reports to NIH Director via Council of Councils

NIH National Institutes of Health
Environmental influences on Child Health Outcomes (ECHO)

Long-term

- Conduct innovative observational and intervention research
  - Answer crucial questions about child health and development
  - Inform programs, policies, and practices that improve health of children and adolescents

Enhance the health of our nation's children for generations to come

NIH National Institutes of Health
Environmental influences on Child Health Outcomes (ECHO)

Extra slides

Capitalizing on ECHO's multiple support components

- Measurement of tobacco-related compounds
  - Children's Health Exposure Analysis Resource (CHEAR)
- Valid covariate and outcome measures
  - Patient-reported Outcomes Core
    - NIH resources, e.g., PROMIS, PhenX, NIH Toolbox
- Genetics Core

Capitalizing on ECHO's multiple support components

- State-of-science analyses involving exposure mixtures, confounding/mediation, combined outcomes
  - Data Analysis Center
- Special features, e.g., microbiome
  - NIH and cohort expertise
- Putting the operational pieces together
  - Coordinating Center

ECHO v. NCS

	NCS	ECHO	Overcomes	Challenge
Cohorts	New	Existing	Recruitment issues	Data harmonization
Mechanism	Contracts	Cooperative agreements	Inflexibility	Engaging PIs in the commons
Lead institute	NICHD	OD	Balkanization	Engaging all ICs
Components	~Single	Multiple, incl. IDeA States Network	No intervention component	Integration into whole
Leadership	Non-scientist	Scientist	Perceived lack of leadership	Following NIH processes
Outcomes	Agnostic	4 initially specified	Lack of focus	Bridging across silos
Phenotyping	More superficial	Deeper	Not enough biology, technology	Biospecimen ownership; measurement
Funding	Not initially appropriated	Line item in OD budget	Year-to-year uncertainty (?)	Still must prove worth

ECHO

Challenges & Responses

	ECHO	Challenge	Response
Cohorts	Existing	Data harmonization	Ontologies, new methods
Mechanism	Cooperative agreements	Engaging PIs in the commons	PI-led working groups, UG3 milestones
Lead institute	OD	Engaging all ICs	Project Scientists (Trans-NIH group)
Components	Multiple, incl. IDeA States Network	Integration into whole	Working group membership, content overlap
Leadership	Scientist	Following NIH processes	Teamwork, incl. trusted deputy
Outcomes	4 initially specified	Bridging across silos	Add Child Health outcome
Phenotyping	Deeper	Biospecimen ownership; measurement	PIs develop policies; CHEAR, PRO & Genetics
Funding	Line item in OD budget	Still must prove worth	Early win analyses

NIH National Institutes of Health
Environmental influences on Child Health Outcomes (ECHO)

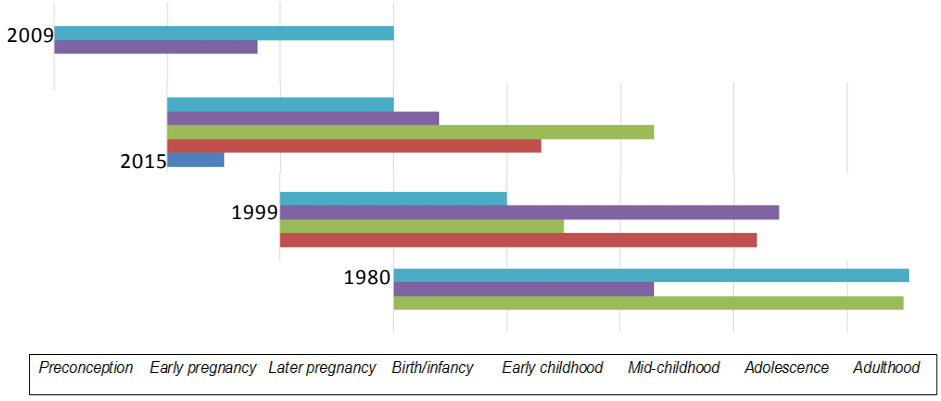
ECHO Cohorts

UG3 Milestones and Performance Metrics

- Cohort-specific
  - Participant retention, accurate data
- Collaborative
  - Showing up, leadership, creating/agreeing to rules of the road, sharing data, participating in multi-cohort-wide analyses
- Stretch Goals and Acceptable Goals
  - Meet 100% Acceptable Goals to go to UH3
    - Achievable

NIH National Institutes of Health
Environmental influences on Child Health Outcomes (ECHO)

ECHO-Wide Cohort
"Dynamic Cohort of Inception Cohorts"



Cohorts recruited at different points in the life course
and
in different eras

National Institutes of Health
Environmental influences on Child Health Outcomes (ECHO)

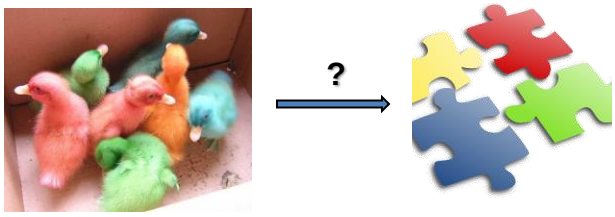
ECHO
"Dynamic Cohort of Inception Cohorts"

Cohorts recruited at different points in the life course
and
in different eras
with
heterogeneity in retention within each
and
different follow-up schedules
and
different measures

National Institutes of Health
Environmental influences on Child Health Outcomes (ECHO)

One Challenge
Phase I

- Harmonizing existing data

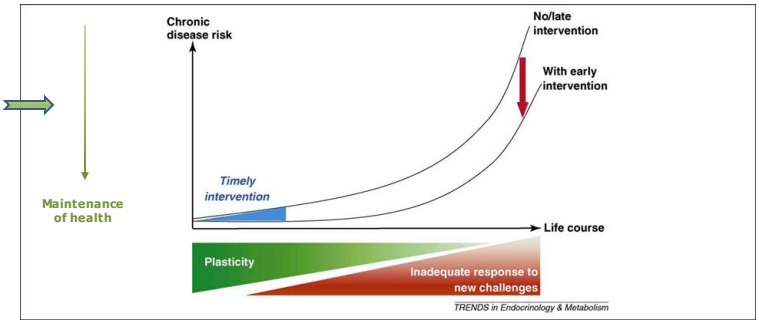


ECHO Funding

- $165m per year for 7 years
  - Annual appropriation
    - CC, DAC, PRO Core, Cohorts
      - NIAID
  - Exceptions
    - CHEAR funded for 4 years
      - NIEHS
    - IDeA States Pediatric Clinical Trials Network
      - Forward funded for 4 years
      - NIGMS, NICHD
    - Genetics Core FY'17
      - NIDCR, NHGRI developing

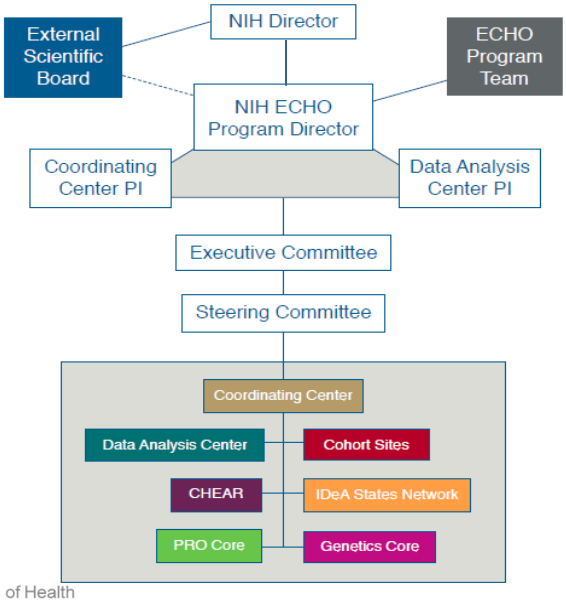
Working Across Disciplines

- What transcends perinatal, airways, neurodevelopment, obesity?
- Child ***health*** rather than disease (EC***H***O)

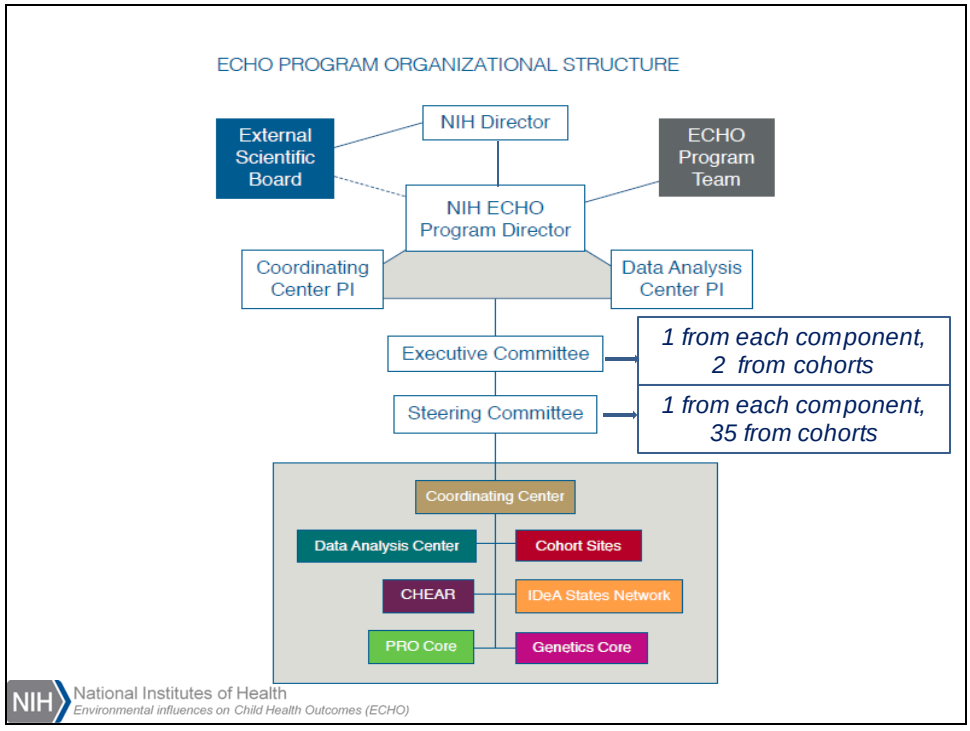


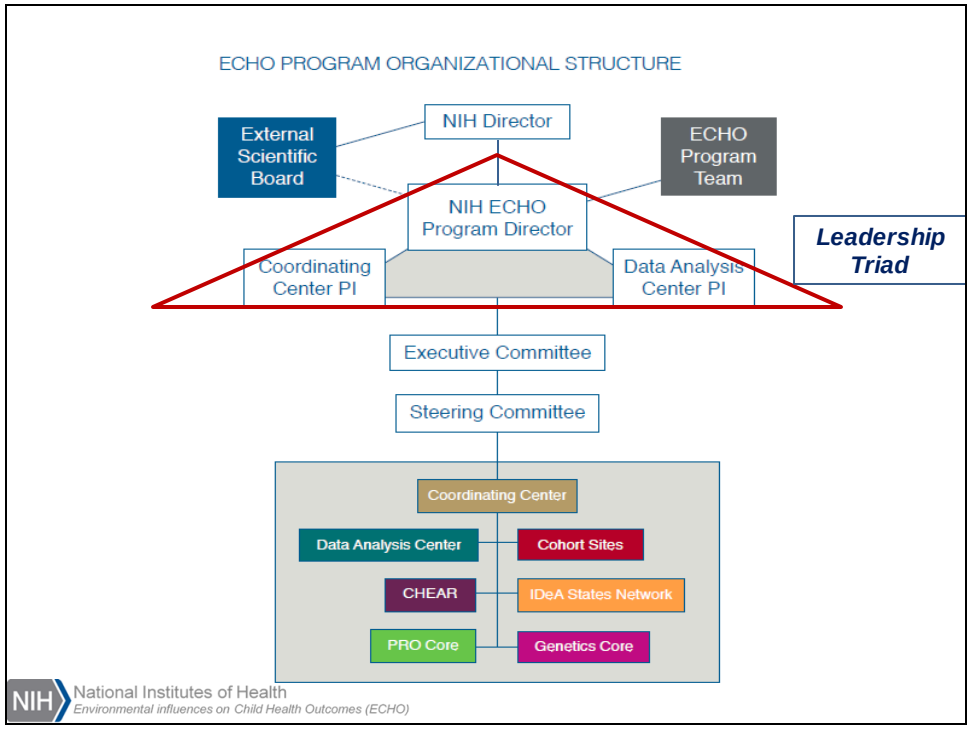
NIH National Institutes of Health
Environmental influences on Child Health Outcomes (ECHO)

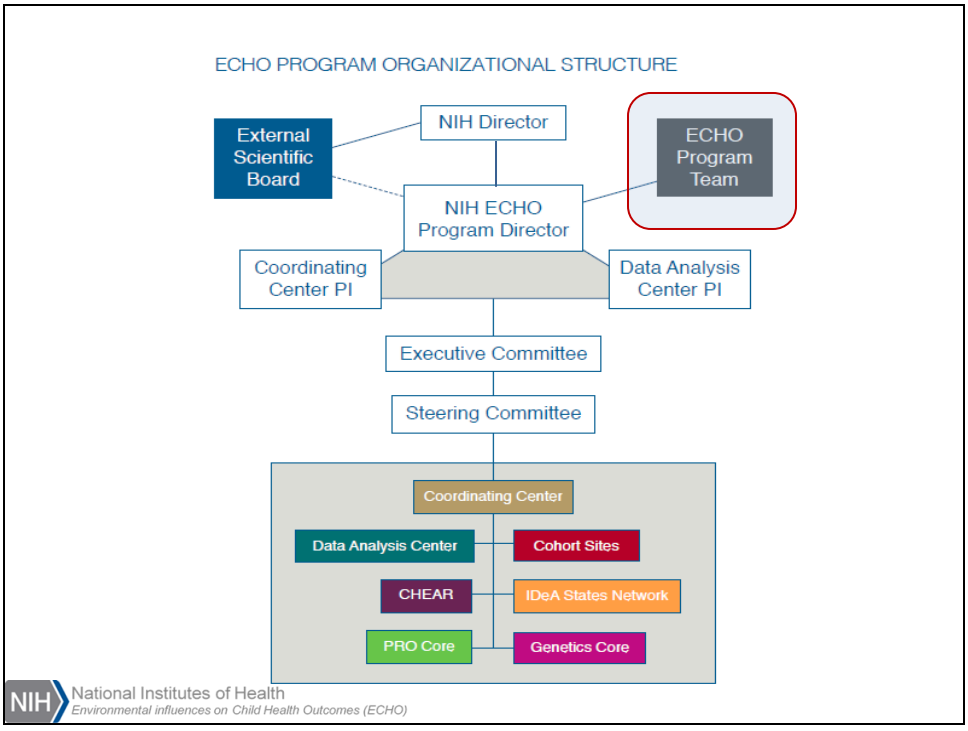
ECHO PROGRAM ORGANIZATIONAL STRUCTURE

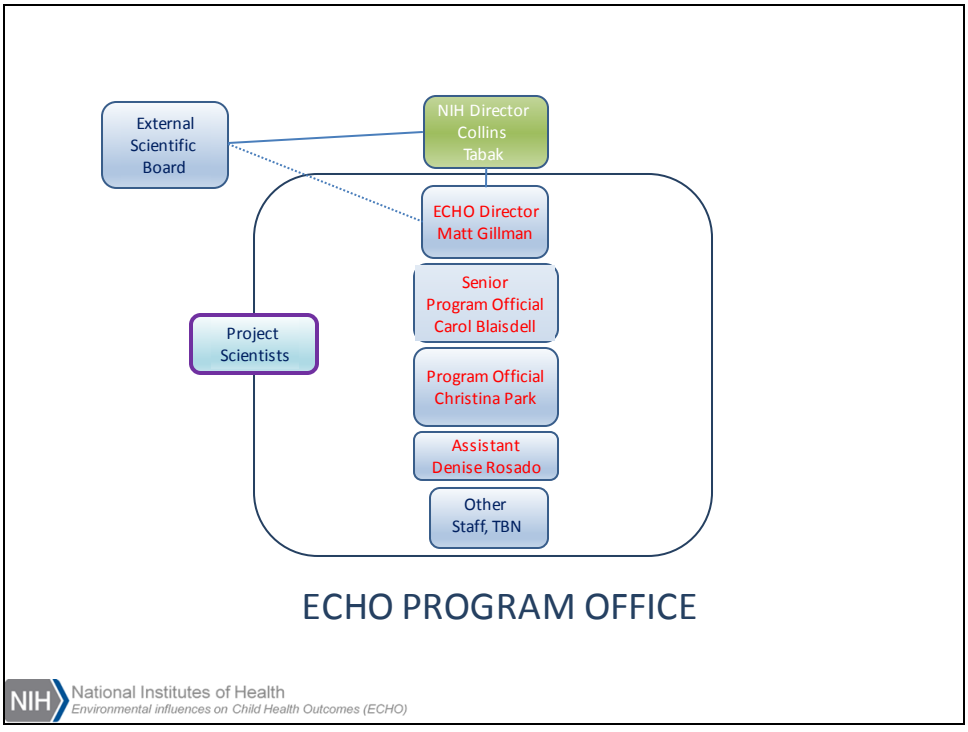


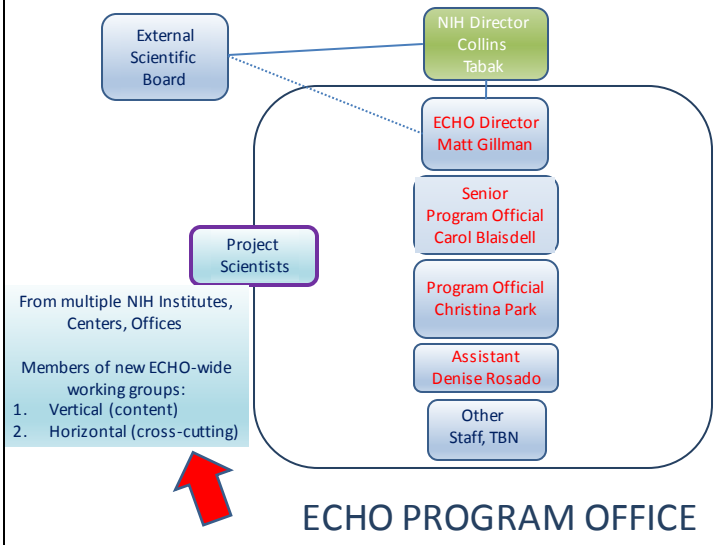
NIH National Institutes of Health
Environmental influences on Child Health Outcomes (ECHO)


ECHO PROGRAM ORGANIZATIONAL STRUCTURE
External Scientific Board
NIH Director
ECHO Program Team
NIH ECHO Program Director
Coordinating Center PI
Data Analysis Center PI
Executive Committee
1 from each component, 2 from cohorts
Steering Committee
1 from each component, 35 from cohorts
Coordinating Center
Data Analysis Center
Cohort Sites
CHEAR
IDeA States Network
PRO Core
Genetics Core
NIH National Institutes of Health
Environmental influences on Child Health Outcomes (ECHO)


ECHO PROGRAM ORGANIZATIONAL STRUCTURE
External Scientific Board
NIH Director
ECHO Program Team
NIH ECHO Program Director
Coordinating Center PI
Data Analysis Center PI
Leadership Triad
Executive Committee
Steering Committee
Coordinating Center
Data Analysis Center
Cohort Sites
CHEAR
IDeA States Network
PRO Core
Genetics Core
NIH National Institutes of Health
Environmental influences on Child Health Outcomes (ECHO)


ECHO PROGRAM ORGANIZATIONAL STRUCTURE
External Scientific Board
NIH Director
ECHO Program Team
NIH ECHO Program Director
Coordinating Center PI
Data Analysis Center PI
Executive Committee
Steering Committee
Coordinating Center
Data Analysis Center
Cohort Sites
CHEAR
IDeA States Network
PRO Core
Genetics Core
NIH National Institutes of Health
Environmental influences on Child Health Outcomes (ECHO)


External Scientific Board
NIH Director Collins Tabak
ECHO Director Matt Gillman
Senior Program Official Carol Blaisdell
Project Scientists
Program Official Christina Park
Assistant Denise Rosado
Other Staff, TBN
ECHO PROGRAM OFFICE
NIH National Institutes of Health
Environmental influences on Child Health Outcomes (ECHO)



ECHO Themes

Strategy

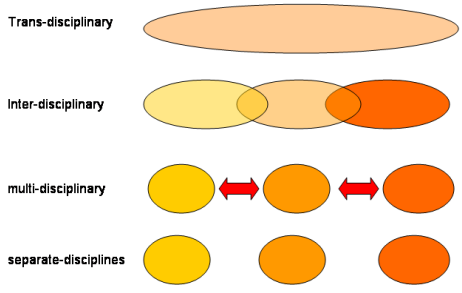
- Provide best practices for how to do team science in 21st century
  - ECHO as Learning System
    - Promote transdisciplinary collaboration among many layers of stakeholders
    - Team science evaluation to improve our program processes and outcomes in real time

ECHO Themes
Strategy

- Provide best practices for how to do team science in 21st century
  - ECHO as Learning System
    - Promote transdisciplinary collaboration among many layers of stakeholders
    - Team science evaluation to improve our program processes and outcomes in real time
  - Innovations and consensus-building in data sharing, data harmonization, use of biospecimens, publication policies
    - Intellectual enterprises, potential publications
    - Needed to achieve our scientific aims
    - Our Cross-cutting working groups

The science of team science

Transdisciplinary approach



--K. Hall, NCI, and others

NIH National Institutes of Health
Environmental influences on Child Health Outcomes (ECHO)

Move the Needle on Data Sharing

- Among investigators
- For public use
- With individual participants

Move the Needle on Data Sharing

- "It's just for genetics"
- "I've got 10 million variables in raw form and another 10,000 derived variables, and I've spent years cleaning them. No one else will understand how to use them, especially longitudinally."
- "I don't want my data out there before my team—esp. my junior investigators—and I have a chance to analyze them."
- "NIH says I have to do it, so I will—but just the minimum necessary."

Move the Needle on Data Sharing

- Need for nuanced approach
  - Adheres to the principles
    - We win when we all win
    - Big data are better than small
    - Publicly funded data are, in the end, public
  - Takes into account investigators' fears
  - Plays by the rules
- Lessons learned from IC consortia

NIH National Institutes of Health
Environmental influences on Child Health Outcomes (ECHO)

Preliminary Data

Preliminary Data

Cohorts "Demographic" Data (N = 84)

Life course stage at enrollment of participants	N (%) cohorts
Preconception	3 (4%)
Prenatal	48 (57%)
Infancy	27 (32%)
Toddler/early childhood	6 (7%)

Characteristic of participants	
Mothers enrolled, N	~33000
Children enrolled, N	~46000
Age of children, y	
Range	0 – 36
Minimum age, median	1.5
Maximum age, median	7.0

NIH National Institutes of Health
Environmental influences on Child Health Outcomes (ECHO)

Solution-oriented Questions

- "So-what" questions in observational studies that lead to impactful interventions, policies, programs, practices
- Prevention
  - Primordial prevention?
  - Risk stratification, "Precision prevention?"

Analytic Methods to Mirror Solution-Oriented Questions

- Conceptual causal models
  - Intergenerational transmission
    - Biological ("fetal programming")?
    - Socio-cultural, e.g., shared family factors?

Analytic Methods to Mirror Solution-Oriented Questions

- Exposure mixtures
- Conceptual causal models
  - Intergenerational transmission
    - Biological ("fetal programming")?
    - Socio-cultural, e.g., shared family factors?
- Trajectories of child health
  - Critical periods
  - Reversibility

Analytic Methods to Mirror Solution-Oriented Questions

- Exposure mixtures
- Conceptual causal models
  - Intergenerational transmission
    - Biological ("fetal programming")?
    - Socio-cultural, e.g., shared family factors?
- Trajectories of child health
- Shared vulnerability for > 1 outcome
  - Obesity & asthma
    - Each one causes the other, and
    - They have common underpinnings

NIH National Institutes of Health
Environmental influences on Child Health Outcomes (ECHO)

Analytic Methods to Mirror Solution-Oriented Questions

- Exposure mixtures
- Conceptual causal models
  - Intergenerational transmission
    - Biological ("fetal programming")?
    - Socio-cultural, e.g., shared family factors?
- Trajectories of child health
- Shared vulnerability for > 1 outcome
- Unpacking complexity
  - Sophisticated approaches to mediation and time-varying confounding
  - Computational systems science simulation modeling

Cross-cutting issues

- Heterogeneity
  - Geographic, social, demographic (incl. sex)
- Explaining disparities
  - Racial/ethnic, socio-economic
- Replication

Solution-oriented Questions

From Kickoff Meeting—Use extant data

- To what extent do the following modifiable exposures in the pre- and peri-natal periods, individually and in combination, affect trajectories of linear growth during infancy (which predicts better later health)?
  - Hypertensive disorder of pregnancy
  - Gestational weight gain
  - Smoking
  - Infection of mom or baby
  - Pre- or postnatal steroids
  - Feeding type
- How do these associations differ according to genetic predisposition, preterm v. term, geography, sex, race/ethnicity?

All Components Under 1 Umbrella

- Ideas for integrating Cohorts and IDeA States Network
  - Test observations in intervention trials
    - And vice versa
  - Trials favor prevention or treatment of ECHO focus area conditions
  - IDeA States Network investigators members of cross-cutting working groups
    - Develop principles and policies for 21st c. team science

External Scientific Board

Requested Counsel

- Incorporating all ECHO components under one umbrella
- Attending to numerous strata of stakeholders
- Building a culture of collaboration and synergy
- Harmonizing data across disparate cohorts
- Capitalizing on expertise within as well as outside NIH
- Ensuring early and sustained successes
- Using funds wisely
- …Others?

NIH National Institutes of Health
Environmental influences on Child Health Outcomes (ECHO)

External Scientific Board

Membership

- Working group of Council of Councils
  - 1 Council member
    - Children's Environmental Health Network
  - 1 IDeA States Network Steering Comm. Chair
  - 3 Academic leaders
    - Genetics, toxic environment, neighborhood and social factors
    - NIH, NCS, FDA, CDC, IOM, Gates, etc.
  - 1 Parent, nominated by March of Dimes
  - 1 AI/AN representative, nominated by TCAC
  - 1 Big data maven?

NIH National Institutes of Health
Environmental influences on Child Health Outcomes (ECHO)

"ECHO is like herding…lions"

NIH National Institutes of Health
Environmental influences on Child Health Outcomes (ECHO)

ECHO

- Engender culture of collaboration
- Hit the scientific ground running

↓

- Show early successes

↓

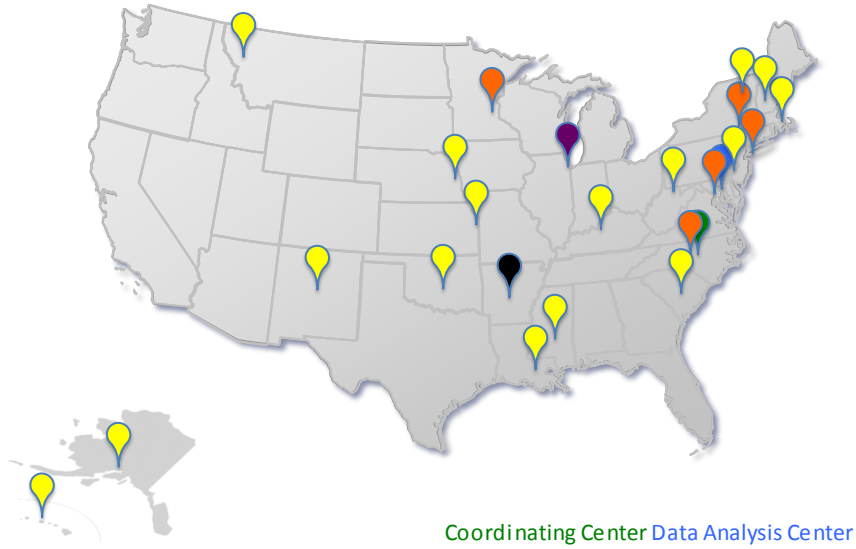
- Become one of the nation's pre-eminent research program in child health

NIH National Institutes of Health
Environmental influences on Child Health Outcomes (ECHO)

ECHO Foci

- Outcome focus areas
  - Pre-, peri-, postnatal
  - Upper and lower airway
  - Obesity
  - Neurodevelopment
- Core elements for cohorts
  - Demographics
  - Typical early health and development
  - Genetic influences on early childhood health and development
  - Environmental factors
  - Patient/Person (parent and child) Reported Outcomes (PROs)

ECHO—The Other Five FY'16 Components



Coordinating Center Data Analysis Center
Health Measurement Core
CHEAR ISPCTN DCOC

NIH National Institutes of Health
Environmental influences on Child Health Outcomes (ECHO)

Strategic

- Harmonization
  - Squared-off pegs in rounded-off holes
  - Core data elements for cohorts
    - Demographics
    - Typical early health and development
    - Genetic influences on early childhood health and development
    - Environmental factors
    - Patient/Person (parent and child) Reported Outcomes (PROs)
  - Bioinformatics is another area of harmonization

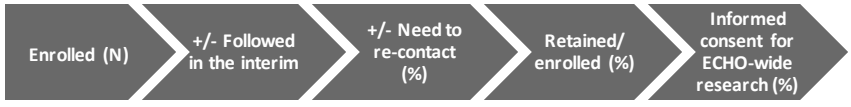
NIH National Institutes of Health
Environmental influences on Child Health Outcomes (ECHO)

ECHO Cohorts

UG3 Milestones and Performance Metrics

Cohort-specific

	Individual cohort-specific—NIH negotiates with each cohort		
	Item	***Metric***	***Due***
	Enrollment (for some)	N	June 2018
Retention	Re-contacted Retained Informed consent	%	June 2018
Accurate data	Analyzable data including exposures of interest	Cohort-specific	June 2018
	Publications	1+	June 2018



NIH National Institutes of Health
Environmental influences on Child Health Outcomes (ECHO)

ECHO Cohorts

UG3 Milestones and Performance Metrics

Collaborative

Collaborative—Standard across all cohorts		
Item	***Metric***	***Due***
Policies: publication, data sharing, biospecimen	Agreed (~signed)	September 2017
New ECHO multi-cohort data collection protocol	Submitted to IRB	September 2017
Participation in "early-win" collective analyses	1+	September 2017
Attendance	Steering Committee meetings (>90%)	June 2018
Leadership	Leader of working group or its subcommittee	June 2018
Submission of participant-level data to Data Analysis Center	Enough for 1+ multi-cohort analyses	June 2018
ECHO multi-cohort publications	1+	June 2018

NIH National Institutes of Health
Environmental influences on Child Health Outcomes (ECHO)

DOHaD Interdisciplinary Approach

Population-based Studies

- Cohort studies
- Randomized trials
- Biomarkers

Animal Models

- Physiology
- Metabolism
- Genetic Susceptibility
- Epigenetic mechanisms

Clinical Studies

- Tissue biopsies
- Molecular markers
- Small trials

In Vitro Studies

- Isolated tissue studies
- Molecular markers
- Epigenetic mechanisms

Thanks to Sue Ozanne

For maximal impact…

Need the right evidence…

Guiding Principles

- Teamwork
  - Working well together
- Impact
  - Research that has an impact on health
- Responsibility
  - Scientifically & ethically sound research
- Value
  - Return on investment in the eyes of Congress, NIH, investigators, and public

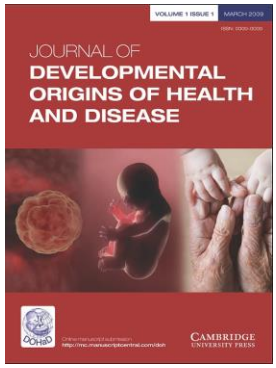
Developmental Origins of Health and Disease

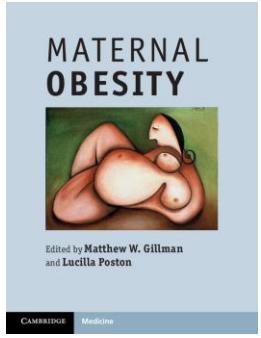
- DOHaD emphasizes prenatal period and early childhood as important periods for development of chronic disease throughout life

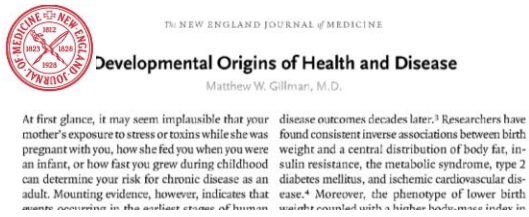
Ann Nutr Metab 2013;63:291–292

Appreciating David Barker (1938–2013)

Matthew W. Gillman[a, b] Vincent W.V. Jaddoe[c]







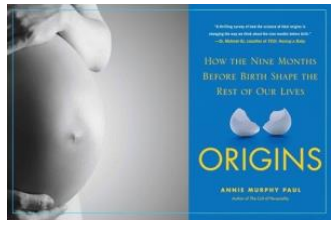
The NEW ENGLAND JOURNAL of MEDICINE

Developmental Origins of Health and Disease

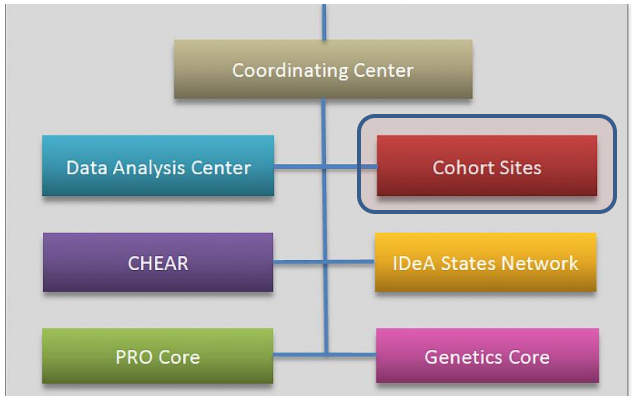
Matthew W. Gillman, M.D.

At first glance, it may seem implausible that your mother's exposure to stress or toxins while she was pregnant with you, how she fed you when you were an infant, or how fast you grew during childhood can determine your risk for chronic disease as an adult. Mounting evidence, however, indicates that

disease outcomes decades later.[3] Researchers have found consistent inverse associations between birth weight and a central distribution of body fat, insulin resistance, the metabolic syndrome, type 2 diabetes mellitus, and ischemic cardiovascular disease.[4] Moreover, the phenotype of lower birth



Today



Cohort = group of participants followed over time

NIH National Institutes of Health
Environmental influences on Child Health Outcomes (ECHO)