



Prenatal Famine & Schizophrenia

Ezra Susser MD DrPH

*Anna Cheskis Gelman and Murray Charles Gelman Professor of Epidemiology
Chairman of the Department of Epidemiology, Mailman School of Public Health
Professor of Psychiatry, College of Physicians and Surgeons
Columbia University
New York State Psychiatric Institute*

The Development of Research In Environmental Exposures



Prenatal Exposure:
Famine

Neurodevelopmental Outcome:
Schizophrenia

Neurodevelopmental Origins Challenges of Developmental Perspective

Conception to Birth ~ Windows on Fetal Life

Morphology * Placenta * Maternal Blood
Maternal Condition * Ultrasound
Cord Blood

Birth To Disease ~ Diagnosing Disease

Large Numbers * Labor intensive assessment * Difficult

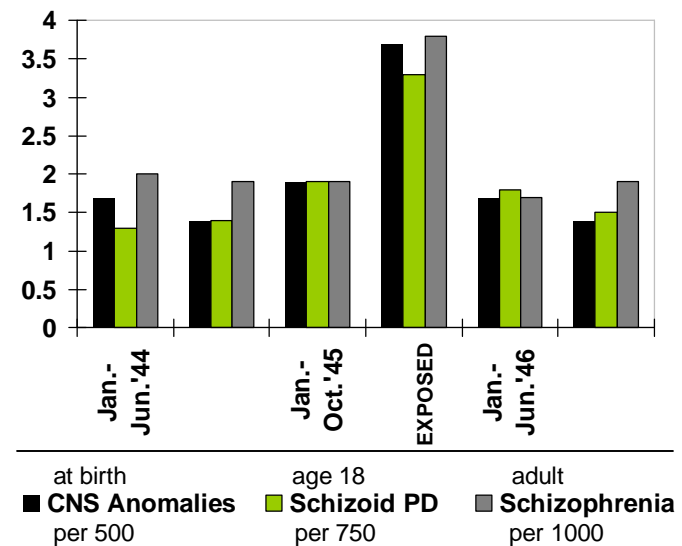
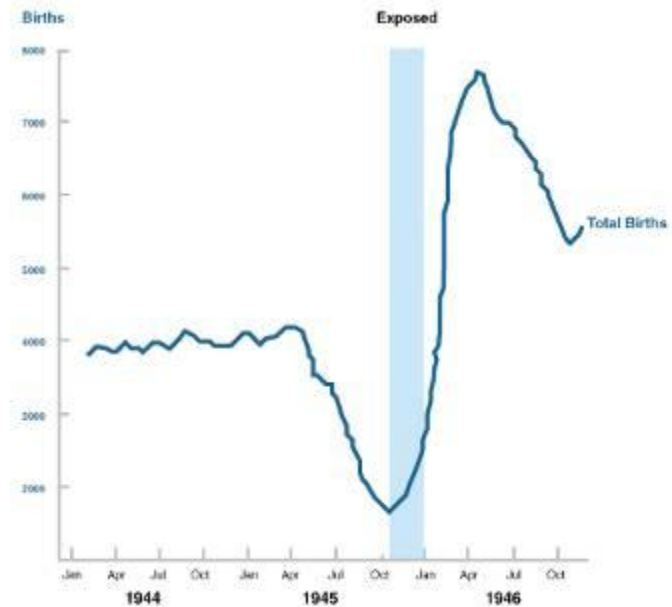


The Dutch Hunger Winter



Conceived at
Height of Famine
Born Oct 15-Dec 31 1945

SUSSER et al. (1998) Am J Epidem 147: 213-6





Standards of Evidence

Design Based on Historical Event

- ◇ Documentation of Dietary Intake
- ◇ Psychiatric Registries
- ◇ Necessary Replication in Different Environment

The Bitter Years The Chinese Famine 1959-1960



The Great Leap Forward

Year	Birth Rate/1000	Risk (%)	RR _{adj} (95%ci)
1956	37.43	1.02	
1957	41.21	0.83	
1958	28.28	0.78	
1959	20.97	0.84	0.89 (0.78-1.03)
1960	8.61	2.15	2.30 (1.99-2.65)
1961	11.06	1.81	1.93 (1.68-2.23)
1962	50.4	0.89	0.95 (0.87-1.04)
1963	52.28	1.00	
1964	49.11	1.02	
1965	50.93	0.88	

Wuhu Region, Anhui Province
St. Clair et al. 2006 JAMA 294:557-62

The Chinese Famine
1959-1960

ANHUI PROVINCE
Wuhu Region

GUANGXI PROVINCE
Liuzhou Region





Summary of Evidence:

Dutch Famine Study
precise exposure timing

Chinese Famine Study
large number of cases

Exploring Latent Effects:

Biological Reasoning

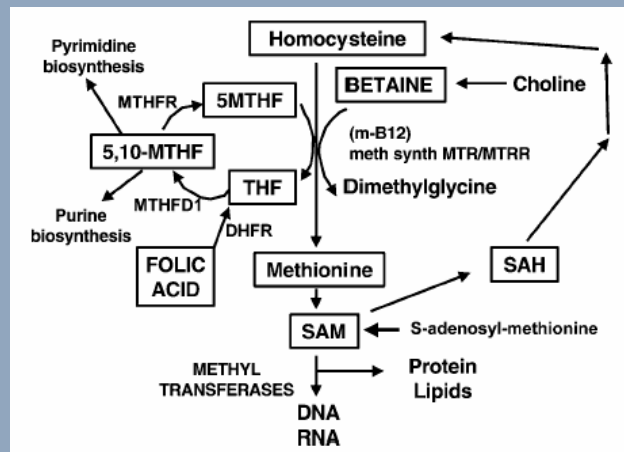
Clues suggesting folate pathway:

- *MTHFR C677T (TT vs. CC)*
- *NTDs & Famine in Holland*

? de Novo Mutations

? Epigenetics

(changes in gene expression that do not entail a change in DNA sequence)



◇ DNA Synthesis/Repair
Misincorporation of uracil

? de Novo Mutations

◇ Methylation

? Epigenetics

Folate Metabolic Pathway



Hypothesis: Disruption of Folate Pathway
If true: Implications for Prevention



The Example of Neural Tube Defects



Preconception Environmental Determinants

◇ *Paternal Age*

Postnatal Environmental Determinants

◇ *Immigration*

◇ *Urban Living*

◇ *Cannabis*

Detecting Environmental Determinants

- ◇ Create & Support Autism Registries
Western Australia Registries
- ◇ Establish Pregnancy Birth Cohorts
Autism Birth Cohort (Norway); National Children's Study (US)
- ◇ Identify the "Natural Experiments"



COLLABORATORS

NEW YORK
Columbia University

EZRA SUSSER

ABERDEEN
University of Aberdeen

DAVID ST CLAIR

SHANGHAI
Jiao Tong University

LIN HE

SEATTLE
University of Washington

MARY-CLAIRE KING

NEW YORK
Cold Spring Harbor

JONATHAN SEBAT