Prenatal Exposure to Undernutrition and Obesity Risk in Adulthood

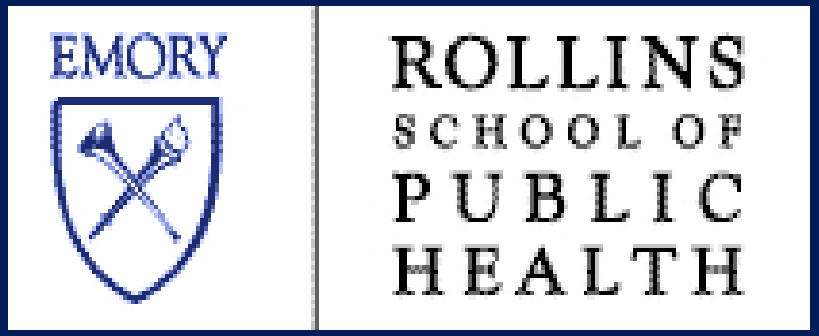
Aryeh D Stein, Ph.D.

Bernice S Edward, M.Sc.

Hubert Department of Global Health

Rollins School of Public Health

Emory University, Atlanta GA 30322, USA



Workshop on Examining a Developmental Approach to Childhood Obesity: The Fetal and Early Childhood Years

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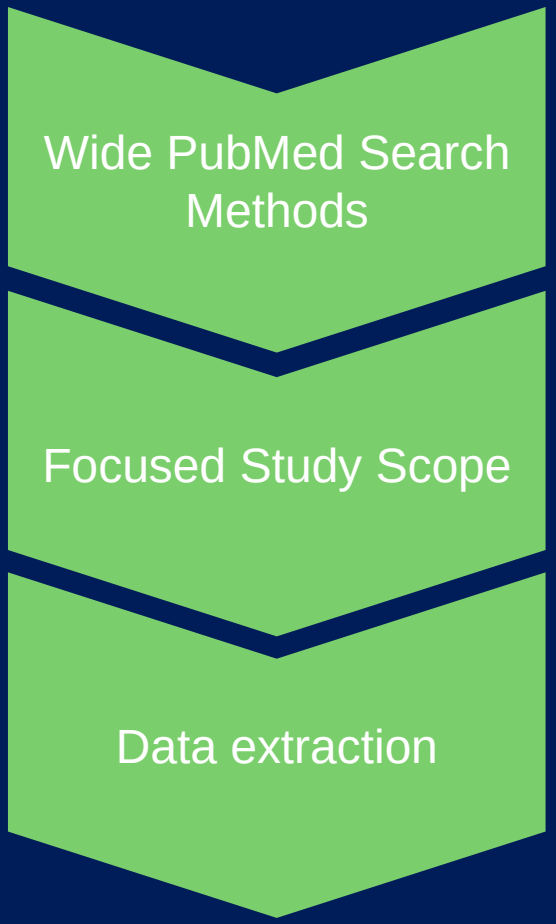
Objective

To review current literature on prenatal exposure to famine/food shortage and its effects on adult body weight and obesity risk in the offspring

Methods

- Started with review by Lumey et al (Ann Rev Publ Health 2011)
- Supplemental search on PubMed using terms [‘famine’ or ‘food-shortage’ or ‘fasting’] and [‘health outcomes’ or ‘obesity’ or ‘anthropometry’ or ‘adiposity’ or ‘body weight’] and ‘pregnancy’ and ‘offspring’
- Screened all identified articles
- Excluded
  - animal studies
  - studies with no measures of anthropometry or obesity risk
- Search yielded 11 independent studies (3 published since 2011 review)

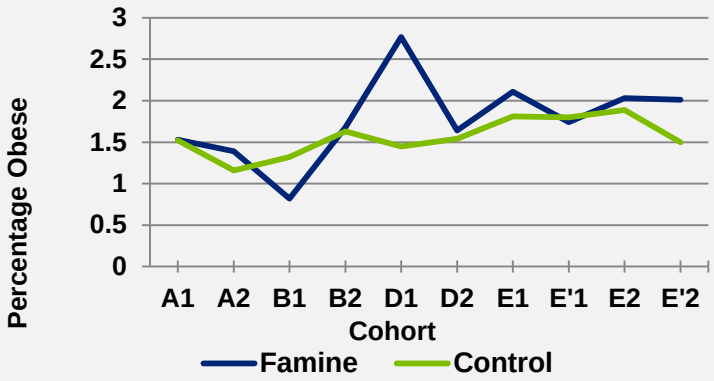


Dutch Hunger Winter, 1944 – 45 (Study 1)

Study Design

- **Study Design:** Historical cohort study
- **Sample:**
  - 307,700 males examined at military induction (94,800 exposed to famine, 212,900 unexposed)
  - Grouped into birth-month cohorts according to timing of exposure during gestation in both famine-exposed areas as well as control (unexposed to famine) areas
- **Age at assessment:** 19 y
- **Outcome measured:** Obesity, defined as weight for height ≥ 120% of the standard

Key Results



- In D1 cohort (exposed to famine during first two trimesters of pregnancy), obesity prevalence was higher in famine area than in unaffected area ($P<0.005$)
- In B1 cohort (exposed to famine late in pregnancy), obesity prevalence was lower in famine areas than in unaffected areas ($P<0.005$)

Reference

Ravelli GP, Stein ZA, Susser MW. Obesity in young men after famine exposure in utero and early infancy. N Engl J Med 1976;295:349–53.

Dutch Hunger Winter, 1944 – 45 (Study 2)

Study Design

- **Study Design:**
  - Follow-up of hospital birth cohort.
  - Compared people exposed to famine in late, mid, or early gestation (exposed) and those born before or conceived after the famine period (non-exposed)
- **Sample size:** 741 men and women (298 exposed)
- **Age at assessment:** 50 y
- **Outcome measured:** Body size

Key Results

Sex and body measure	Time of gestational exposure to famine		
	Late	Mid	Early
Men			
Weight (kg)	0.8	-2.3	1.5
Height (cm)	0.5	-1.5	0.9
BMI (%)	0.4	-1.2	0.5
Women			
Weight (kg)	-1.8	-1.5	7.9
Height (cm)	0.1	-0.6	0.9
BMI (%)	-2.1	-1.3	7.4

Weight, height and BMI differences were more significant for early gestational exposure and were more pronounced in women than in men

Reference Ravelli AC, van Der Meulen JH, Osmond C, et al. Obesity at the age of 50 y in men and women exposed to famine prenatally. Am J Clin Nutr 1999;70:811–6.

Dutch Hunger Winter, 1944 – 45 (Study 3)

Study Design

- **Study Design:**
  - Follow-up of hospital birth cohort
    - Exposed: persons born to mothers who experienced the Dutch famine
    - Categorized exposure to famine into 4 windows:
      - Gestational weeks 1–10, 11–20, 21–30, and 31 through delivery, on the basis of exposure to a ration of <900 kcal/d
    - Unexposed:
      - Persons born to mothers who did not experience famine during this pregnancy
      - Same-sex siblings
- **Sample size:** 956: 427 males and 529 females (350 exposed)
- **Age at assessment:** 59 y
- **Outcome:** Anthropometric measures

Key Results

Sex and body measure	Period of gestational exposure to famine (weeks)			
	1 - 10	11 – 20	21 – 30	31+
Men				
Weight (kg)	3.37	-1.63	2.08	-1.17
Waist (cm) circumference	1.82	-1.28	1.88	-0.37
BMI (kg/m^2)	1.06	-0.49	0.66	-0.35
Women				
Weight (kg)	3.98	3.71	3.53	2.75
Waist (cm) circumference	1.96	2.83	3.88	2.50
BMI (kg/m^2)	1.44	1.45	1.34	1.08

- Exposure to famine associated with increased weight and greater indexes of fat deposition in women but not in men (*P* for interaction <0.01)
- No specific timing within gestation was identified as critical for affecting these changes
- Suggestion of association for men exposed in weeks 1-10

Reference Stein A.D., Kahn H. S., Rundle A., et al. Anthropometric measures in middle age after exposure to famine during gestation: evidence from the Dutch famine. Am J Clin Nutr 2007;85:869–76.

Siege of Leningrad, 1941 – 44

Study Design

- **Study Design:** Cross-sectional study
- **Sample:** 549 men and women (169 exposed in utero)

  Categorized as:

  – Born during the siege (intrauterine group)

  – Born just before rationing began (infant group)

  – Born concurrently with the first two groups but outside the area of the siege (unexposed group)
- **Age at assessment:** 52-53 y
- **Outcome measured:** Body mass index, skinfolds ratio

Key Results

	Exposed groups			
	Intrauterine (n=169)	**Infant (n=192)**	**Unexposed (n=188)**	**P**
Body mass index (kg/m^2)				
Male	24.6	25.4	25.2	0.4
Female	26.9	27.0	26.7	0.9
Subscapular: triceps skinfold ratio				
Male	1.26	1.32	1.41	0.5
Female	1.01	0.93	0.88*	0.2

*P<0.05

Subjects in the unexposed group had gender-specific differences in subscapular to triceps skinfold ratio compared with the exposed groups.

Reference Stanner SA, Bulmer K, Andres C, et al. Does malnutrition in utero determine diabetes and coronary heart disease in adulthood? Results from the Leningrad Siege Study, a cross sectional study. BMJ 1997;315:1342–8.

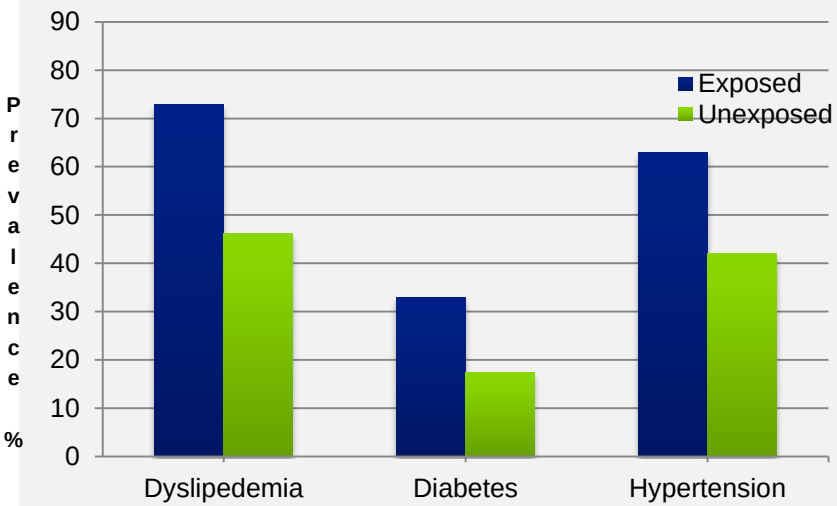
Holocaust, 1940 – 45

Study Design

- **Study Design:** Cross-sectional study
- **Sample size:** 300
  - Exposed group were convenience sample (n=70)
  - Controls: data from the Israel National Health Interview Survey-2 (n=230)

  Categorized as:
  - Exposed - European Jews born in countries under Nazi rule (exposed to the starvation and stress in the Holocaust) during the period 1940-1945
  - Control - Israeli-born individuals of the same descent, age, and gender distribution
- **Age at assessment:** 69 y
- **Outcomes measured:** Cardiovascular risk factors - body mass index (BMI), hypertension, dyslipidemia, diabetes, angina pectoris and congestive heart failure
  - Did not explore gestation-timing specific effects

Key Results



Males: BMI 29.1 in exposed vs 27.0 in unexposed ($p<0.02$); no differences in females

Reference Bercovich E., Keinan-Boker L., Shasha S.M. Long-term Health effects in adults born during the Holocaust. IMAJ 2014; 16: 203–207.

China Famine, 1959 – 61 (Study 1)

Study Design

- **Study Design:** Secondary analysis of data from the China-U.S. Collaborative Project for Neural Tube Defect Prevention
- **Sample:** 35,025 women (6934 exposed)

Categorized as born before (1957, 1958), during (1959–1961), and after (1962, 1963) the famine

- **Age at assessment:** 29-34 y (Mean 31.7 y)
- **Outcomes measured:** Adult height, BMI, and hypertension
  - Did not explore gestation-timing specific effects

Key Results

	Rural sample	Urban sample
Birth cohort	**Average effect on BMI (kg/m^2)**	
1957	0.92**	0.03
1958	-0.06	-1.68
1959	-0.56	1.11
1960	-0.32*	0.13
1961	-0.30*	0.73
1962	0.00	-0.58

* P < 0.05, ** P < 0.01

- BMI: 0.92 kg/m^2 higher in the 1957 cohort (exposed from 1.5 to 4.5 y), but 0.3 kg/m^2 lower in the 1960–1961 cohorts (exposed during pregnancy and infancy)
- Height: 1.7 and 1.3 cm lower in 1958 and 1959 cohorts by respectively

Reference Huang C, Li Z, Wang M, et al. Early life exposure to the 1959–1961 Chinese famine has long-term health consequences. J Nutr. 2010;140(10):1874–1878.

China Famine, 1959 – 61 (Study 2)

Study Design

- **Study Design:** Analysis of data from the 2002 Nationwide Nutrition and Health Survey
- **Sample size:** 7056 men and women (4363 exposed)

  Categorized according to their birth year:

  – 1959, 1960 and 1961 – famine years (study groups)

  – 1964 - no famine (control group)
- **Age at assessment:** 38-43 y
- **Outcomes measured:** Obesity and overweight prevalence, BMI

  – Did not explore gestation-timing specific effects

  – Confounded by age – all controls are younger than famine-exposed

Key Results

Group		Prevalence in female subjects (%)	
		Overweight	Obesity
Born in years of disaster	1959	30.78*	10.58*
	1960	32.41*	10.30*
	1961	32.35*	8.97
Born in year w/o disaster	1964	26.48	7.33

*Compared with control group born in 1964: $P < 0.05$.

- Females:

  – Mean BMI of women significantly higher in the three famine groups than that in the control group born in 1964 (P < 0.01)

  – Prevalence of overweight in women higher in the three famine groups (P < 0.01) and of obesity in the 1959 and 1960 groups. (P < 0.01)
- Males: No associations significant

Reference Yang Z, Zhao W, Zhang X, et al. Impact of famine during pregnancy and infancy on health in adulthood. Obes Rev. 2008;9(suppl 1):95S–99S.

China Famine, 1959 – 61 (Study 3)

Study Design

- **Study Design:** Used data from records of annual physical evaluations
- **Sample size:** 17,023 men and women (4056 gestational exposure)

  Categorized as:

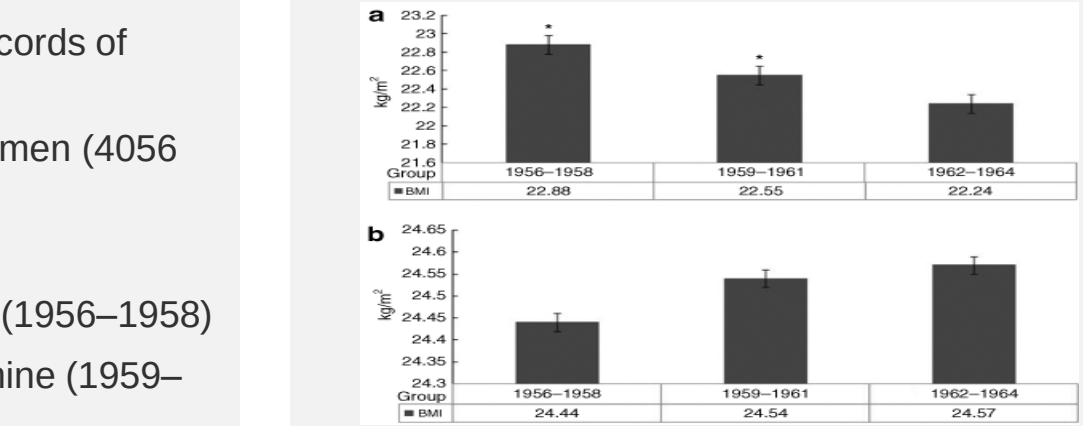
  – Toddler: born before the famine (1956–1958)

  – Gestational: born during the famine (1959–1961)

  – Control: born after the famine (1962–1964)
- **Age at assessment:** ~50 y
- **Outcomes measured:** Body weight, height, and BMI

  – Did not explore gestation-timing specific effects

Key Results



Comparison of BMI in (a) female subjects and (b) male subjects (M ± S.D.).
*$P < 0.05$ vs. control group

- Females: Body weight and BMI significantly higher in the toddler and gestational groups as compared to control

  – OR for overweight more pronounced in the toddler group (1.48) than in the gestational group (1.26)

  – OR for obesity in females significantly higher in the toddler group (1.46) than the control group
- No associations in males

Reference

Wang Y, Wang X, Kong Y, et al. The great Chinese famine leads to shorter and overweight females in Chongqing Chinese population after 50 years. Obesity. 2010;18(3):588–592

China Famine, 1959 – 61 (Study 4)

Study Design

- **Study Design:** Retrospective cohort study
- **Sample:** 12,065 men and women (1156 exposed in utero)
  - Adults born during the famine period were compared to those who were unexposed to the famine
- **Age at assessment:** 46-53 y (Mean 49.1 y)
- **Outcomes measured:** Stature, obesity
  - Did not explore gestation-timing specific effects

Key Results

- No significant differences in BMI or odds of obesity comparing any famine exposure group to the non-exposed group
- Lower odds of obesity in men exposed during both fetal development and infancy (adjusted OR = 0.72, p = 0.03)
- Exposure to famine during infancy associated with shorter stature

Reference

Wang P-X, Wang J-J, Lei Y-X, et al. Impact of Fetal and Infant Exposure to the Chinese Great Famine on the Risk of Hypertension in Adulthood. PLoS ONE. 2012; 7(11): e49720.

Biafra, Nigeria, 1967 – 70

Study Design

- **Study Design:** Cross sectional survey
- **Sample:** 1339 (exposed 292)

  Categorized as:

  – Born before (exposed to famine in early childhood)

  – Born during (exposed to famine in fetal life and in infancy)

  – Born immediately after (uncategorized)

  – Born after 1971 (unexposed)
- **Age at assessment:** 36-44 y (Mean age of fetal exposure group 40.5 y)
- **Outcome measured:** Anthropometric measures

  – Did not explore gestation-timing specific effects

Key Results

	Famine in early childhood	Fetal-infant famine	Unexposed	P-value
Weight (kg)	76.2	78.5	77.0	0.08
Height (cm)	169	169	170	0.03
Waist circumference (cm)	93	94	91	0.001
BMI (kg/m^2)	26.7	27.5	26.5	0.02

Fetal-infant exposure to famine was associated with increased waist circumference (+3 cm, P<0.001), and increased risk of overweight (OR 1.41; 95% CI 1.03-1.93) as compared to people born after the famine

Reference Hult M, Tornhammar P, Ueda P, et al. Hypertension, Diabetes and Overweight: Looming Legacies of the Biafran Famine. PLoS ONE. 2010; 5(10): e13582

Indonesia: Ramadan

Study Design

- **Study Design:** Analysis of data from Indonesian Family Life Survey
- **Sample:** 14,120 (11,380 exposed in utero)
  - Muslims who were in utero during Ramadan
  - Muslims who had not been in utero during Ramadan
  - Non-Muslims
- **Age at assessment:** >18y (Mean age 34.6 y)
- **Outcomes measured:** Height, Weight, BMI

Key Results

Association Between Having Been in Utero During Ramadan and Weight and BMI in Muslims

Exposure to Ramadan	BMI[b] (*n* = 12,856)		Weight, kg (*n* = 12,861)	
	β[c]	95% CI	β[c]	95% CI
Not in utero during Ramadan	0.00	Referent	0.00	Referent
In utero during Ramadan	−0.32*	−0.57, −0.06	−0.85*	−1.54, −0.17
Conceived during Ramadan	−0.37*	−0.71, −0.03	−1.42**	−2.32, −0.53
Ramadan in early gestation	−0.24	−0.53, 0.04	−0.64	−1.41, 0.13
Ramadan in midgestation	−0.42**	−0.72, −0.13	−0.93*	−1.72, −0.14
Ramadan in late gestation	−0.43**	−0.74, −0.12	−1.06*	−1.88, −0.25
Born during Ramadan	−0.04	−0.40, 0.32	−0.32	−1.28, 0.64

- P < 0.05; **P < 0.01. [c] β,unstandardized regression coefficient

Among non-Muslims, no such associations observed

Reference

Van Ewijk RJ, Painter RC, Roseboom TJ. Associations of Prenatal Exposure to Ramadan with Small Stature and Thinness in Adulthood: Results From a Large Indonesian Population–Based Study. Am J Epidemiol. 2013 Apr 15;177(8):729-36.

Summary

The Dutch Famine (3 studies)

- Increased obesity risk/adiposity in adult offspring exposed to the famine in utero (3 studies)
- Early gestation more critical than late gestation (2 studies)
- Stronger effects in women as compared to men (2 studies)

The Great Chinese Famine (4 studies)

- Higher body weights and BMI in female subjects born during the famine when compared to those born outside the famine period (2 studies)
- No association between famine exposure and obesity risk (1 study)
- Decrease in BMI of subjects exposed to the famine (1 study)

Other food shortages (4 studies)

- *Leningrad*: No significant association with obesity risk
- *Holocaust*: Higher BMI in males in exposed group
- *Nigeria*: Increased waist circumference and risk of overweight in those exposed to the famine
- *Ramadan*: Those exposed to the fast during conception or in utero had lower BMI than those who weren't exposed. The lowest BMI was observed following mid-gestation and late- gestation exposure.

Conclusions

- Most studies have serious methodological challenges
- None of the famine studies able to distinguish food shortages from other stresses of famine and war
  - Study of births in relation to Ramadan suggestive of need to do so
- Women tend to be more vulnerable than men
- Some suggestion that risk of obesity is increased following early-gestation exposure to famine