Prenatal Exposure to Undernutrition and Obesity Risk in Adulthood

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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**
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**

<table>
<thead>
<tr>
<th>Sex and body measure</th>
<th>Time of gestational exposure to famine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Late</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>0.8</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>0.5</td>
</tr>
<tr>
<td>BMI (%)</td>
<td>0.4</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>-1.8</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>0.1</td>
</tr>
<tr>
<td>BMI (%)</td>
<td>-2.1</td>
</tr>
</tbody>
</table>

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

**Reference**

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**

<table>
<thead>
<tr>
<th>Sex and body measure</th>
<th>Period of gestational exposure to famine (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 - 10</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>3.37</td>
</tr>
<tr>
<td>Waist (cm) circumference</td>
<td>1.82</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>1.06</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>3.98</td>
</tr>
<tr>
<td>Waist (cm) circumference</td>
<td>1.96</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>1.44</td>
</tr>
</tbody>
</table>

- 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**

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**

<table>
<thead>
<tr>
<th>Exposed groups</th>
<th>Intrauterine (n=169)</th>
<th>Infant (n=192)</th>
<th>Unexposed (n=188)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body mass index (kg/m²)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>24.6</td>
<td>25.4</td>
<td>25.2</td>
<td>0.4</td>
</tr>
<tr>
<td>Female</td>
<td>26.9</td>
<td>27.0</td>
<td>26.7</td>
<td>0.9</td>
</tr>
<tr>
<td><strong>Subscapular: triceps skinfold ratio</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.26</td>
<td>1.32</td>
<td>1.41</td>
<td>0.5</td>
</tr>
<tr>
<td>Female</td>
<td>1.01</td>
<td>0.93</td>
<td>0.88*</td>
<td>0.2</td>
</tr>
</tbody>
</table>

*P<0.05

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

**Reference**
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

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Reference

## 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

<table>
<thead>
<tr>
<th>Birth cohort</th>
<th>Rural sample</th>
<th>Urban sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>1957</td>
<td>0.92**</td>
<td>0.03</td>
</tr>
<tr>
<td>1958</td>
<td>-0.06</td>
<td>-1.68</td>
</tr>
<tr>
<td>1959</td>
<td>-0.56</td>
<td>1.11</td>
</tr>
<tr>
<td>1960</td>
<td>-0.32*</td>
<td>0.13</td>
</tr>
<tr>
<td>1961</td>
<td>-0.30*</td>
<td>0.73</td>
</tr>
<tr>
<td>1962</td>
<td>0.00</td>
<td>-0.58</td>
</tr>
</tbody>
</table>

*P < 0.05, **P < 0.01

- BMI: 0.92 kg/m² higher in the 1957 cohort (exposed from 1.5 to 4.5 y), but 0.3 kg/m² 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

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**

*Compared with control group born in 1964: \( P < 0.05 \).

<table>
<thead>
<tr>
<th>Group</th>
<th>Prevalence in female subjects (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overweight</td>
</tr>
<tr>
<td>Born in years of disaster</td>
<td></td>
</tr>
<tr>
<td>1959</td>
<td>30.78*</td>
</tr>
<tr>
<td>1960</td>
<td>32.41*</td>
</tr>
<tr>
<td>1961</td>
<td>32.35*</td>
</tr>
<tr>
<td>Born in year w/o disaster</td>
<td></td>
</tr>
<tr>
<td>1964</td>
<td>26.48</td>
</tr>
</tbody>
</table>

- **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**

## 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.).**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Females BMI</td>
<td>22.48</td>
<td>22.56</td>
<td>22.24</td>
</tr>
<tr>
<td>Males BMI</td>
<td>24.44</td>
<td>24.54</td>
<td>24.57</td>
</tr>
</tbody>
</table>

*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

China Famine, 1959 – 61 (Study 4)

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Key Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>• <strong>Study Design</strong>: Retrospective cohort study</td>
<td>• No significant differences in BMI or odds of obesity comparing any famine exposure group to the non-exposed group</td>
</tr>
<tr>
<td>• <strong>Sample</strong>: 12,065 men and women (1156 exposed in utero)</td>
<td>• Lower odds of obesity in men exposed during both fetal development and infancy (adjusted OR = 0.72, p = 0.03)</td>
</tr>
<tr>
<td>– Adults born during the famine period were compared to those who were unexposed to the famine</td>
<td>• Exposure to famine during infancy associated with shorter stature</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th></th>
<th>Famine in early childhood</th>
<th>Fetal-infant famine</th>
<th>Unexposed</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>76.2</td>
<td>78.5</td>
<td>77.0</td>
<td>0.08</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>169</td>
<td>169</td>
<td>170</td>
<td>0.03</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>93</td>
<td>94</td>
<td>91</td>
<td>0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.7</td>
<td>27.5</td>
<td>26.5</td>
<td>0.02</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Exposure to Ramadan</th>
<th>BMI (n = 12,856)</th>
<th>Weight, kg (n = 12,861)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>95% CI</td>
</tr>
<tr>
<td>Not in utero during Ramadan</td>
<td>0.00</td>
<td>Referent</td>
</tr>
<tr>
<td>In utero during Ramadan</td>
<td>-0.32*</td>
<td>-0.57, -0.06</td>
</tr>
<tr>
<td>Concealed during Ramadan</td>
<td>-0.37*</td>
<td>-0.71, -0.03</td>
</tr>
<tr>
<td>Ramadan in early gestation</td>
<td>-0.24</td>
<td>-0.53, 0.04</td>
</tr>
<tr>
<td>Ramadan in midgestation</td>
<td>-0.42**</td>
<td>-0.72, -0.13</td>
</tr>
<tr>
<td>Ramadan in late gestation</td>
<td>-0.43**</td>
<td>-0.74, -0.12</td>
</tr>
<tr>
<td>Born during Ramadan</td>
<td>-0.04</td>
<td>-0.40, 0.32</td>
</tr>
</tbody>
</table>

- P < 0.05; **P < 0.01. cβ, unstandardized regression coefficient

Among non-Muslims, no such associations observed

Reference

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