Lifetime Socioeconomic Status, Historical Context, and Genetic Inheritance in Shaping Body Mass in Middle and Late Adulthood

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Genes

Obesity

Environment T1 → Environment T2 → Environment T3

Society

Genes → Obesity → Obesity
Research Questions

• Whether the genetic influence on body mass index (BMI) in middle or late adulthood depends on socioeconomic status (SES) at different life stages (e.g., childhood, young adulthood, and middle/late adulthood) and, particularly, changes in SES over the life course?

• How the influences of life-course SES, genetic factors, and their interaction on BMI differ across birth cohorts?
How Genes Interact with The Environment Influencing Obesity?

**Obesity Risk**

- **Adverse Condition**
- **Favorable Condition**

**Genetic Predisposition**
Life-course Perspectives

Source: Loucks et al. 2010
Data

Health and Retirement Study (HRS):
• Longitudinal study of Americans over age 50 conducted every two years from 1992 to 2012
• Genome-wide genotype data (more than 2 million genetic variants from each of 12,507 individuals)
• Accelerated multi-cohort longitudinal design
  - Assets and Health Dynamics among the Oldest Old (AHEAD) (born before 1924)
  - Children of Depression (CODA) (born 1924 to 1930)
  - HRS (born 1931 to 1941)
  - War Babies (WB) (born 1942 to 1947)
  - Early Baby Boomers (EBB) (born 1948 to 1953)
  - Mid Baby Boomers (MBB) (born 1954 to 1960)
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Key Variables

SES measures in HRS:
(1) Childhood SES: father’s occupation;
(2) Young adulthood SES: years of education
(3) Late adulthood SES: wealth

Accumulative advantage score: 0-3

SES mobility trajectories: stable and low, downwardly mobile,
stable and high, upwardly mobile.
Key Variables

• Genetic predisposition score (GPS)
  - Based on 32 single-nucleotide polymorphisms (SNPs) associated with BMI (Speliotes et al. 2010);

**Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index**

Obesity is globally prevalent and highly heritable, but its underlying genetic factors remain largely elusive. To identify genetic loci for obesity susceptibility, we examined associations between body mass index and ~2.8 million SNPs in up to 123,865 individuals with targeted follow-up of 42 SNPs in up to 125,931 additional individuals. We confirmed 14 known obesity susceptibility loci and identified 18 new loci associated with body mass index ($P < 5 \times 10^{-8}$), one of which includes a copy number variant near GPRCS3. Some loci (at MC4R, POMC, SH2B1 and BDNF) map near key hypothalamic regulators of energy balance, and one of these loci is near GIPR, an incretin receptor. Furthermore, genes in other newly associated loci may provide new insights into human body weight regulation.
Genetic Predisposition Score and Body Mass Index in the Health and Retirement Study

$b = .13 \ p < .001$
## Results

<table>
<thead>
<tr>
<th></th>
<th>Moderating Effects of SES on the Genetic Influence</th>
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</thead>
<tbody>
<tr>
<td>Sensitive Period</td>
<td>$P &gt; .05$</td>
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<tr>
<td>Social Accumulation</td>
<td>$P &lt; .05$</td>
</tr>
<tr>
<td>Social Mobility</td>
<td>$P &lt; .05$</td>
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</tbody>
</table>
Socioeconomic Differences in The Genetic Association with BMI (Social Mobility)

- **Stable and Low**: $b = .16$, $p = .000$
- **Downwardly Mobile**: $b = .18$, $p = .000$
- **Upwardly Mobile**: $b = .08$, $p = .000$
- **Stable and High**: $b = .07$, $p = .051$

![Graph showing the relationship between Genetic Predisposition Score (GPS) and Predicted Body Mass Index (kg/m²)].
Predicted BMI (kg/m$^2$)

**Genetic Predisposition Score (GPS)**

**AHEAD (Born Before 1924)**
- Stable and Low: $b = 0.14$, $p = 0.001$
- Stable and High: $b = -0.07$, $p = 0.850$

**CODA (Born 1924-1930)**
- Stable and Low: $b = 0.15$, $p = 0.000$
- Stable and High: $b = 0.00$, $p = 0.468$

**HRS (Born 1931-1941)**
- Stable and Low: $b = 0.16$, $p = 0.000$
- Stable and High: $b = 0.08$, $p = 0.020$

**WB (Born 1942-1947)**
- Stable and Low: $b = 0.17$, $p = 0.000$
- Stable and High: $b = 0.15$, $p = 0.001$
**AHEAD (Born Before 1924)**

Stable and Low  \( b = .14 \) \( p = .001 \)

**CODA (Born 1924-1930)**

Stable and Low  \( b = .15 \) \( p = .000 \)

**HRS (Born 1931-1941)**

Stable and Low  \( b = .16 \) \( p = .000 \)

**WB (Born 1942-1947)**

Stable and Low  \( b = .17 \) \( p = .000 \)
Predicted BMI ($\text{kg/m}^2$) vs Genetic Predisposition Score (GPS)

- **AHEAD (Born Before 1924)**
  - Stable and High $b = -0.07$ $p = 0.850$

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Main Findings

1. The genetic influence on BMI in middle and late adulthood is smaller for **socioeconomically advantaged** individuals than **socioeconomically disadvantaged** ones.

2. Compensatory effects of **socioeconomic advantages** on the genetic influence are **less pronounced** in more recent birth cohorts than in earlier ones.
Conclusions

Society

Childhood SES ➔ Young Adulthood SES ➔ Late Adulthood SES

Genes ➔ BMI

SES = Socioeconomic Status

BMI = Body Mass Index
Thank you!
Distribution of the Genetic Predisposition Score by SES

- Childhood SES
- Young Adulthood SES
- Middle/Late Adulthood SES
<table>
<thead>
<tr>
<th></th>
<th>Sensitive Period</th>
<th>Social Accumulation</th>
<th>Social Mobility</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Genetic Predisposition Score (GPS)</td>
<td>.13(.05)**</td>
<td>.15(.04)***</td>
<td>.06(.07)</td>
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<td>GPS × Childhood SES</td>
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<td>GPS × Low SES</td>
<td>.02(.06)</td>
<td>.01(.06)</td>
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<tr>
<td>GPS × Medium SES</td>
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<td>−.01(.05)</td>
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<tr>
<td>GPS × High SES</td>
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<tr>
<td>GPS × Cumulative Advantage in SES (CAS)</td>
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<tr>
<td>GPS × CAS (=0)</td>
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<td>.08(.08)</td>
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<td>GPS × CAS (=1)</td>
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<td></td>
<td>.05(.08)</td>
</tr>
<tr>
<td>GPS × CAS (=3)</td>
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<td>GPS × SES Trajectory</td>
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<tr>
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<tr>
<td>Sample Size</td>
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<td>4,325</td>
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Socioeconomic Differences in The Genetic Association with BMI (Social Accumulation)

Predicted Body Mass Index (kg/m²) vs. Genetic Predisposition Score (GPS)

- Cumulative Advantage Score = 0 $b = .17$ $p = .000$
- Cumulative Advantage Score = 1 $b = .14$ $p = .000$
- Cumulative Advantage Score = 2 $b = .10$ $p = .000$
- Cumulative Advantage Score = 3 $b = .07$ $p = .071$
Gene-Environment Interaction Models

(a) Social Trigger/Compensation
High | Medium | Low

(b) Social Push
High | Medium | Low

(c) Differential Susceptibility
High | Medium | Low

Obesity Risk vs Genetic Predisposition to Obesity

Obesity Risk vs Genetic Sensitivity
Statistical Model

- **Level 1:**
  \[ \text{BMI}_{jit} = \beta_0 + \beta_1 \text{GPS}_{ji} + \beta_2 \text{SES}_{ji} + \beta_3 \text{Cohort}_{ji} \]
  \[ + \beta_4 (\text{GPS}_{ji} \times \text{SES}_{ji}) + \beta_5 (\text{GPS}_{ji} \times \text{Cohort}_{ji}) + \beta_6 (\text{SES}_{ji} \times \text{Cohort}_{ji}) \]
  \[ + \beta_7 (\text{GPS}_{ji} \times \text{SES}_{ji} \times \text{Cohort}_{ji}) + \sum_p \gamma_p C_{pji} + \sum_q \gamma_q C_{qjit} + \varepsilon_{jit}, \]

- **Level 2:**
  \[ \text{cov}(\text{BMI}_{jit_1}, \text{BMI}_{jit_2}) = \sigma^2 \rho_{|t_2-t_1|}, \]

- **Level 3:**
  \[ \beta_{0j} = \beta_0 + u_j \]