Contextual and Longitudinal Approaches for Understanding Risk Factors of AD/ADRD

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Longitudinal studies

- Offer unique opportunities to
  - Investigate life course exposures and processes
  - Formally test causal assumptions
  - Examine Repeated measures across multiple domains
Life course research

• More than repeated measures
• Theoretical models of temporal ordering of exposures and their interrelationships with respect to health and disease
• Life course epidemiology: study of long-term biological, behavioral, and psychosocial processes that link adult health and disease risk to physical or social exposures acting during gestation, childhood, adolescence, earlier in adult life, or across generations
Life course models

• Critical periods model
  • Exposures acting during a specific time period has lasting or lifelong effects on the structure or function of organs, tissue, and body systems which are not modified in any dramatic way later experiences
  • Also known as:
    • Biologic programming
    • Latency model
    • Fetal origins of adult disease hypothesis

Ben-Shlomo & Kuh. *Int J Epidemiol*, 2002; 31:285-93
Life course models

• Sensitive periods model
  • Time period when an exposure has a stronger effect on development and disease risk than it would at other times
  • Same exposure outside of the time period may still be associated but weaker than during sensitive period

Ben-Shlomo & Kuh. *Int J Epidemiol*, 2002; 31:285-93
Life course models

• Accumulation of risk model
  • Life course exposures gradually accumulate through episodes of illness and injury, adverse environmental conditions, and health damaging behaviors
  • As number, duration, and severity of exposures increase, there is increasing cumulative damage to biological systems
  • Exposures can be uncorrelated or correlated
Life course models

- Chains of risk
  - Special case of accumulation model
  - Sequence of linked exposures that lead to impaired function and increased disease risk because one experience or exposure tends to lead to another, and so on, and so on.
Study designs

• Longitudinal designs most appropriate
  • Repeated measures across the life course provide most accurate temporal sequence and intra-individual change over time

• Analytic approaches
  • Multilevel modeling (random effects modeling)
  • Structural equation modeling
  • Marginal structural modeling
  • Path analyses
National Longitudinal Study of Adolescent to Adult Health

### Participants
- **Adolescents in grades 7-12**
  - Wave I: 20,745 (1994-1995, 79%)
  - Wave II: 14,738 (1996, 88.6%)
  - Wave III: 15,197 (2001-2002, 77.4%)
  - Wave IV: 15,701 (2008, 80.3%)
  - Wave V: 12,300 (2016-2018)
  - Wave VI: 15,701 (2022-2024)
- **Transition to Adult Aged 18-26**
  - Wave I: 20,745
  - Wave II: 14,738
  - Wave III: 15,197
- **Young Adults Aged 24-32**
  - Wave IV: 15,701
  - Wave V: 12,300
- **Adults Aged 34-43**
  - Wave V: 12,300
- **Early Midlife Aged 39-49**
  - Wave VI: 15,701

### Data Collection
- **In-School Administration**:
  - Wave I: Students 90,118, School Admin 144
  - Wave II: Students 90,118, School Admin 144
  - Wave III: Partners 1,507
  - Wave IV: Young Adults Aged 24-32 15,701
  - Wave V: Adults Aged 34-43 12,300
  - Wave VI: Early Midlife Aged Goal: 13,694

- **Survey Administration**:
  - Wave I: Adolescents in grades 7-12 20,745, Parent 17,670
  - Wave II: Adolescents in grades 8-12 14,738
  - Wave III: Transition to Adult Aged 18-26 15,197
  - Wave IV: Young Adults Aged 24-32 15,701
  - Wave V: Adults Aged 34-43 12,300
  - Wave VI: Early Midlife Aged Goal: 13,694

- **Biomarker Data Collection**:
  - Urine: N = 14,012
  - Blood Spots: N = 14,687
  - Venous Blood: N ~ 5,000

- **Additional Data**:
  - Parent: 3,000
  - IIV Study ~100
Contextual Data Across The Life Course

• From external sources (i.e., Census, CDC, FBI, NCHS)
• At “local” level: county, neighborhood, Census tract and block group
• 10,000+ variables across Waves I-V (1994-2018) and planned for Wave VI
• Domains:
  • Socioeconomic, demographic, epidemiological, political, built, environment, climate, pollution
Contextual Data Ancillary Studies

**Neighborhood**
- Vital statistics
- ONE
- Political context
- Food Environment
- Air pollutants
- Sexual Minority Policy
- Health Context
- Income mobility

**School**
- Transcript
- Wave III EduContext
- Wave IV IPEDS
- Mobility report cards
Studies of life course neighborhood disadvantage and risk of AD/ADRD
• Neighborhoods important contextual determinants of health.

• Cross-sectional studies suggest lower neighborhood socioeconomic status associated with metabolic syndrome, yet longitudinal associations unknown.

• Metabolic syndrome associated with dementias, particularly vascular dementia\(^1\)\(^-\)\(^2\).

Conceptual model
Constructing neighborhood disadvantage across the life course

• Used factor analysis to derive latent measure of disadvantage
• 5 factors retained based on factor loadings

<table>
<thead>
<tr>
<th>Neighborhood Indicators</th>
<th>Factor Loadings (Wave I)</th>
<th>Factor Loadings (Wave III)</th>
<th>Factor Loadings (Wave IV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% households below poverty</td>
<td>0.94</td>
<td>0.90</td>
<td>0.93</td>
</tr>
<tr>
<td>% households receiving public assistance</td>
<td>0.94</td>
<td>0.80</td>
<td>0.63</td>
</tr>
<tr>
<td>% adults w/out high school diploma</td>
<td>0.72</td>
<td>0.67</td>
<td>0.65</td>
</tr>
<tr>
<td>% Unemployed individuals</td>
<td>0.85</td>
<td>0.62</td>
<td>0.71</td>
</tr>
<tr>
<td>% Female-headed households</td>
<td>0.81</td>
<td>0.72</td>
<td>0.66</td>
</tr>
</tbody>
</table>
Evidence of neighborhood disadvantage as determinant of cognitive health

Sensitive periods of life when individuals are most vulnerable to influence of neighborhood disadvantage on cognitive health unknown

Early life social conditions (i.e., neighborhood environment) have lasting consequences for health
Marginal structural models for causal effects

Parental education, parental nativity, race/ethnicity, age, gender, baseline cognition, self-rated health, and BMI

\[ \text{Marginal Structural Model: } E[Y] = \beta_0 + \beta_g(N) \]

IPTW = \[
\frac{\text{Pr}(N = n)}{\text{Pr}(N = n | L)}
\]

N is neighborhood disadvantage at Wave I and L is the set of confounders

Y is the memory score and N is the operationalization of neighborhood disadvantage
<table>
<thead>
<tr>
<th></th>
<th>Expected Mean Difference</th>
<th>95% CI</th>
<th>Confidence Interval Difference (CLD)</th>
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</thead>
<tbody>
<tr>
<td><strong>Two-Level Disadvantage</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Level 1 vs Level 0</td>
<td>-1.11</td>
<td>(-2.23, 0.015)</td>
<td>2.25</td>
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<tr>
<td><strong>Three-Level Disadvantage</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 1 vs Level 0</td>
<td>-0.20</td>
<td>(-0.59, 0.19)</td>
<td>0.78</td>
</tr>
<tr>
<td>Level 2 vs Level 0</td>
<td>-1.10</td>
<td>(-2.19, -0.01)</td>
<td>2.18</td>
</tr>
<tr>
<td><strong>Five-Level Disadvantage</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 1 vs Level 0</td>
<td>-0.14</td>
<td>(-0.47, 0.19)</td>
<td>0.66</td>
</tr>
<tr>
<td>Level 2 vs Level 0</td>
<td>-0.24</td>
<td>(-0.73, 0.27)</td>
<td>1.00</td>
</tr>
<tr>
<td>Level 3 vs Level 0</td>
<td>-0.11</td>
<td>(-1.06, 0.85)</td>
<td>1.91</td>
</tr>
<tr>
<td>Level 4 vs Level 0</td>
<td>-1.09</td>
<td>(-3.21, 1.04)</td>
<td>4.25</td>
</tr>
</tbody>
</table>
Considerations

- Longitudinal approach depends on the research question and theoretical framework

**Methodological Challenges:**
- Loss to follow-up → selection bias
- Missing data
- Time-varying confounding
- Dependency of repeated measures
- Serial autocorrelation
Future Opportunities

• Wave VI currently in the field to include more contextual and cognitive measures

• Submission of an **Ancillary Study Proposal** to:
  1. Merges secondary data sources to Add Health respondent records that require unique identifiers (i.e., geocodes) for linkage
  2. Uses archived biospecimens collected by the Add Health study
     [https://addhealth.cpc.unc.edu/data/ancillary-studies/](https://addhealth.cpc.unc.edu/data/ancillary-studies/)