DETERMINING CAUSALITY IN OBESITY

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Obesity is a heterogeneous, complex disease


Energy in  >  Energy out
Going beyond the “big two” using observational data

- Risk factor identification
- Molecular approaches
- Systems science
- Causal Inference
Risk factor identification: From cell to society
### Gestational smoke exposure and childhood obesity

<table>
<thead>
<tr>
<th>Reference</th>
<th>Exposure</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al Mamum 2006</td>
<td>Yes vs. no</td>
<td></td>
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<tr>
<td>Bergmann et al. 2003</td>
<td>Yes vs. no</td>
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<tr>
<td>Boerschmann et al. 2010</td>
<td>≥ 1 cig/day vs. 0</td>
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<tr>
<td>Braun et al. 2010</td>
<td>Yes vs. no</td>
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<tr>
<td>Chen et al. 2006</td>
<td>Active vs. never</td>
<td></td>
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<tr>
<td>Chen et al. 2006</td>
<td>Current vs. never</td>
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<tr>
<td>Durmus et al. 2011b</td>
<td>Yes vs. no</td>
<td></td>
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<tr>
<td>Fasting et al. 2009</td>
<td>Yes vs. no</td>
<td></td>
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<tr>
<td>Gillman et al. 2008</td>
<td>Yes vs. no</td>
<td></td>
</tr>
<tr>
<td>Iliadou et al. 2010</td>
<td>1–9 cig/day vs. 0</td>
<td></td>
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<tr>
<td>Koupil and Toivanen 2008</td>
<td>Yes vs. no</td>
<td></td>
</tr>
<tr>
<td>Kuhle et al. 2010</td>
<td>&gt; 0–5 packs/day vs. none</td>
<td></td>
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<tr>
<td>Mendez et al. 2008</td>
<td>1st trimester vs. no</td>
<td></td>
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<tr>
<td>Mizutani et al. 2007</td>
<td>Early pregnancy vs. no</td>
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<tr>
<td>Oken et al. 2005</td>
<td>Early pregnancy vs. no</td>
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<tr>
<td>Tome et al. 2007</td>
<td>Yes vs. no</td>
<td></td>
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<tr>
<td>Widerøe et al. 2003</td>
<td>Yes vs. no</td>
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<td>Al Mamum et al. 2006</td>
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<td>Dubois and Girard 2006</td>
<td>Yes vs. no</td>
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<tr>
<td>Durmus et al. 2011b</td>
<td>Yes (cont) vs. no</td>
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<tr>
<td>Gillman et al. 2008</td>
<td>Yes vs. no</td>
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<tr>
<td>Montgomery and Ekholm 2002</td>
<td>Heavy vs. nonsmoker</td>
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<tr>
<td>Power and Jefferis 2002</td>
<td>Yes, after 4th month vs. no</td>
<td></td>
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<td>Yes, after 4th month vs. no</td>
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<tr>
<td>Power et al. 2010</td>
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<td>Reilly et al. 2005</td>
<td>Yes vs. no</td>
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<tr>
<td>Rooney et al. 2010</td>
<td>1–9 cig/day vs. 0</td>
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<tr>
<td>Salsberry and Reagan 2005</td>
<td>Yes vs. no</td>
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<td>Yes vs. no</td>
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<tr>
<td>Suzuki et al. 2009</td>
<td>Current vs. none/former</td>
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</tbody>
</table>
Leptin signaling pathway

Adipocytes

Leptin

Insulin

POMC CART

AgRP NPY

PC1 CPE

α-MSH

Melanocortin Receptors

CRH, TRH, Oxytocin, Histamine, Others

BDNF

TrkB Receptor

Hindbrain

MCH, Orexin, Galanin, GABA, Others

Hypothalamus

Y2 Receptor

Ghrelin

PYY, Others

GI Tract

Anabatic Effects

↑ Food Intake and/or ↓ Energy Expenditure

Catabolic Effects

↓ Food Intake and/or ↑ Energy Expenditure

Lean et al. The Lancet. 2010
Molecular epidemiology

Tools
- Biomarkers of response
- Epigenetics
- OMICS (e.g., metabolomics)

Opportunities
- Biologic pathways
- Phenotyping
- Innovative study designs
- Inform potential interventions

More work is needed to determine the public health relevance of associations with molecular markers of obesity
Societal policies and processes influencing the population prevalence of obesity

Systems science

Tools
- System dynamics
- Agent-based modeling
- Discrete event simulation

Opportunities
- Multilevel influences
- Dynamic relationships
- Evaluate interventions

Existing studies integrate across limited set of domains, few applications to childhood obesity

A systems model of childhood obesity

Cockrell Skinner & Foster J Obesity 2013
Example: dynamics of childhood obesity from community to epigenetics

Geisinger Health System
- 1288 communities in 37 counties of Pennsylvania
- Over 163,000 children aged 3-18

Conditional random forest analysis of 44 spatially correlated predictors of childhood obesity

Will assess obesogenic environments in relation to methylation of obesity-related genes in a subset

Nau et al. *Health & Place* 2015; Dunstan et al. *Clinical Epigenetics* in revision
Causal inference: Intervention framework for decision making
...in recent decades, our discipline’s robust interest in identifying causes has come at the expense of a more rigorous engagement with... the intent for us to intervene.
Causal inference approaches

Tools
- Potential outcomes framework
- Causal diagrams
- G methods

Opportunities
- Evaluate interventions
- Leverage longitudinal data
- Interpretable effect estimate
- Direct policy relevance
- Cost-benefit analyses

Few applications of G methods in environmental epidemiology

<table>
<thead>
<tr>
<th>Sample question</th>
<th>Risk factor</th>
<th>Intervention</th>
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<tbody>
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<td>What is the dose-response function for the association of the exposure with obesity?</td>
<td>Regression</td>
<td>G methods</td>
</tr>
<tr>
<td>How many cases of obesity could be prevented by a specific strategy to reduce the exposure?</td>
<td>Etiologic insight</td>
<td>Public health impact</td>
</tr>
</tbody>
</table>

Robins *Math Modeling* 1986; Taubman et al. *Int J Epidemiol* 2009
Example: interventions on childhood obesity

- All interventions
  (1 to 6 combined)

- Low-risk lifestyle intervention
  (1 + 4 + 6 combined)

- Low-risk lifestyle intervention
  (1 to 3 combined)

- Breastfeed exclusively for at least 6 months

- Eliminate fast-food consumption

- Watch TV for no more than one hour/day

- Eat at least 5 fruits and vegetables/day

- Eliminate SSB consumption

- Play at the playground everyday

- No intervention, natural course

Types of exposure reduction interventions

**Cap:** What is the expected change in $Y$ if we implemented an exposure limit on $X$?

**Shift:** What is the expected change in $Y$ if we reduced exposure to $X$ for all individuals?

**Ban:** What is the expected change in $Y$ if we eliminated exposure to $X$?
Example: evaluating exposure limits

Cumulative lung cancer mortality in the Colorado Plateau Uranium Miners cohort between 1950 and 2005 estimated under various occupational exposure guidelines for radon

Intervention | Risk difference | Lung cancer deaths avoided
---|---|---
≤2 Working-level months | -3.6 (-4.4, -2.8) | 149
≤1 Working-level months | -4.5 (-5.3, -3.7) | 187
≤0.33 Working-level months | -5.2 (-6.1, -4.3) | 216
Multicausality in an intervention framework

Two potential interventions to reduce NO\textsubscript{x} exposure

1) Mandate three-way catalytic converters
   \( \rightarrow \) Reduce exposure to NO\textsubscript{x}

2) Institute a congestion charge to limit driving trips in urban areas
   \( \rightarrow \) Reduce exposure to NO\textsubscript{x} as well as other traffic-related air pollutants and road traffic noise
   \( \rightarrow \) Increase physical activity
Bayesian g-formula

Extension to incorporate model stabilization techniques developed for mixtures applications

Advantages

- Useful with highly correlated and/or sparse data
- Incorporate toxicologic knowledge using informative priors
- Estimate effect of realistic interventions in the presence of multicausality and correlated exposures

Keil et al. Stat Methods Med Res In press
THANK YOU

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