Uncovering Exposures Responsible for Birth Season – Disease Effects: A Global Study

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Purpose

• Two types of effects

• Latent (not readily apparent at birth)
  – Birth season effects

• Overt (readily apparent at birth)
  – Pharmacological drug exposure effects

• Develop informatics methods for using Electronic Health Record data to study these effects
Birth Season → Lifetime Disease Risk
## Demographics

<table>
<thead>
<tr>
<th>Location</th>
<th>Total Number of Patients</th>
<th>% Female</th>
<th>Age</th>
<th>Koppen-Geiger Climate</th>
<th>In- / Out-patient</th>
<th>OMOP CDM Version</th>
</tr>
</thead>
<tbody>
<tr>
<td>New York City: Columbia University Medical Center</td>
<td>1,749,400</td>
<td>54.67%</td>
<td>38 (22, 58)</td>
<td>Cfa</td>
<td>In-patient</td>
<td>V. 4</td>
</tr>
<tr>
<td>New York City: Mount Sinai Medical Center</td>
<td>1,169,599</td>
<td>58.03%</td>
<td>53 (36, 66)</td>
<td>Cfa</td>
<td>Both</td>
<td>None</td>
</tr>
<tr>
<td>Nashville, Tennessee: Vanderbilt University</td>
<td>3,051,997</td>
<td>51.07%</td>
<td>44 (25, 61)</td>
<td>Cfa</td>
<td>Both</td>
<td>None</td>
</tr>
<tr>
<td>Seattle, Washington</td>
<td>1,770,510</td>
<td>50.57%</td>
<td>48 (34, 64)</td>
<td>Csb</td>
<td>Both</td>
<td>None</td>
</tr>
<tr>
<td>Taiwan: All areas within Taiwan (99.99% of total population in Taiwan)</td>
<td>909,689</td>
<td>51.07%</td>
<td>35 (20, 50)</td>
<td>Aw</td>
<td>Both</td>
<td>V. 5</td>
</tr>
<tr>
<td>Suwon, South Korea: Ajou University School of Medicine</td>
<td>1,848,692</td>
<td>48.26%</td>
<td>42 (28, 57)</td>
<td>Dwa</td>
<td>Both</td>
<td>V. 4</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>10,499,887</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Factors Influencing Birth Month - Disease Relationships

- Culture
- Flu
- Climate
- Pollution

- Sunlight
- Moisture
- Fine Air Particulates
- Ozone (O3)
- Particulate Matter (PM 2.5)
- Carbon Monoxide (CO)
- Nitrogen Dioxide (NO2)
- Sulfur Dioxide (SO2)

- Relative Age in School
- Min. Temperature
- Max. Temperature
- Sunshine Hours
- Relative Humidity
- Rainfall in Inches
- Days of Precipitation
- PM 2.5
- Ozone (O3)
- Carbon Monoxide (CO)
- Nitrogen Dioxide (NO2)
- Sulfur Dioxide (SO2)
What is Relative Age?
Relative Age Effect

• Age relative to school grade – inadvertently affects the birth month distribution
  – Sports base their cutoff on Jan. 1
    • IOC
    • FIFA
    • AFC
    • CAF
    • CONCACAF
    • CONMEBOL
    • OFC
    • UEFA
    • Older children have the advantage in most competitive sports
Relative Age Effect


Adjusting for Relative Age

Raw Data

School Cutoff

Age (in months)

Birth Month

Adjusting for Relative Age

Attention deficit hyperactivity disorder
Relative Risk

CUMC − Seattle: R = 0.85
CUMC − Vanderbilt: R = 0.95
CUMC − MSH: R = 0.92
CUMC − Taiwan: R = 0.81
CUMC − Korea: R = 0.77

Mt. Sinai
Nashville
Seattle
Taiwan
S. Korea

Relative Age

Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sept
Oct
Nov
Dec

Birth Month

Adjusting for Relative Age

Attention deficit hyperactivity disorder
Relative Risk

CUMC − Seattle: R = 0.85
CUMC − Vanderbilt: R = 0.95
CUMC − MSH: R = 0.92
CUMC − Taiwan: R = 0.81
CUMC − Korea: R = 0.77

Mt. Sinai
Nashville
Seattle
Taiwan
S. Korea

Relative Age

Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sept
Oct
Nov
Dec

Birth Month
Adjusting for Relative Age

All Curves Are Adjusted

Difference from Avg. Age for Students in the Same Grade

Age (in months)

+6  0  -6

Jan  Feb  Mar  Apr  May  Jun  Jul  Aug  Sept  Oct  Nov  Dec
Un-Adjusted

Attention deficit hyperactivity disorder

CUMC−Seattle: R= −0.01  CUMC−Vanderbilt: R= −0.07  CUMC−MSH: R= 0.92
CUMC−Taiwan: R= 0.03  CUMC−Korea: R= 0.55
Adjusted

Attention deficit hyperactivity disorder

CUMC
Mt. Sinai
Nashville
Seattle
Taiwan
S. Korea

Relative Risk

Oldest
Average
Youngest

Difference from Avg. Age for Students in the Same Grade

CUMC–Seattle: R= 0.85  CUMC–Vanderbilt: R= 0.95  CUMC–MSH: R= 0.92

CUMC–Taiwan: R= 0.81  CUMC–Korea: R= 0.77
Relative Age and ADHD - Literature

• “Relative age, as an indicator of neurocognitive maturity, is crucial in the risk of being diagnosed with ADHD and receiving ADHD medication among children and adolescents. Our findings emphasize the importance of considering the age of a child within a grade when diagnosing ADHD and prescribing medication for treating ADHD” – Chen 2016

• “Relative age among classmates affects academic performance among boys and girls into puberty, as well as children’s risk of being prescribed stimulants for ADHD. This should be taken into account when evaluating children’s performance and behavior in school to prevent unnecessary stimulant prescribing.” – Zoega 2012

• “Since ADHD is an underlying neurological problem where incidence rates should not change dramatically from one birth date to the next, these results suggest that age relative to peers in class, and the resulting differences in behavior, directly affects a child's probability of being diagnosed with and treated for ADHD” – Evans 2006

• “CONCLUSIONS. ADHD diagnosis is likely to be influenced by a child's social and school environment as well as exogenous child characteristics. Concerns that increased pressures for school performance are associated with increased ADHD diagnoses may be justified.” – Schneider 2006
Attention Problems Are Due To School Cutoff Periods and Relative Age Effect

The Average Difference was 17.97% Between Peak High and Low Months!
Factors Influencing Birth Month - Disease Relationships

- Culture
- Flu
- Climate
  - Sunlight
  - Moisture
    - Relative Humidity
    - Rainfall in Inches
    - Days of Precipitation
- Pollution
  - Fine Air Particulates
  - Criteria Gases
    - PM 2.5
    - Ozone (O3)
    - Carbon Monoxide (CO)
    - Nitrogen Dioxide (NO2)
    - Sulfur Dioxide (SO2)

- Relative Age in School
- Min. Temperature
- Max. Temperature
- Sunshine Hours
- Birth Month
- Relative Risk
For Each Developmental Time-Point, Calculate A Summary Correlation Statistic Using the DerSimonian-Laird (DSL) Random-Effect Meta-Analytical Approach

List of Birth Month – Disease Relationships Tied to Culture/Flu/Climate/Pollutant Factor And Developmental Period
Compute Conception Month Using Birth Month and Average Gestation Period Per Site
Correlate Each Birth Month – Disease Risk Curve With Cumulative Trimester-Level Exposure and Entire Pregnancy-Level Exposure For Each Factor

Sum Exposure Across Each Trimester and Entire Pregnancy

\[ \sum_{i=1}^{3} (Exposure_i) \]
For Each Developmental Time-Point, Calculate a Summary Correlation Statistic Using the DerSimonian-Laird (DSL) Random-Effect Meta-Analytical Approach.
DerSimonian-Laird (DL or DSL) Meta-Analysis Statistic

• Approach for Estimating Variance Between Studies
  – Data from >4 sites required for accurate estimation of inter-study heterogeneity
  – DSL works well with large sample sizes (Jackson et al. 2010)

• Effect statistic: Pearson’s Correlation

• Effect sizes are weighted by sample size (i.e., N)

• “Random Effects” Approach
  – Variance of synthesized effect statistic based on idea that studies included in the analysis are a random sample of all possible studies that could have been included

• Implemented in R using the Schulze 2004 method
Relative Exposures Vary Across Study Sites
Results: Pooled Site-Wide Correlation
Third Trimester Sunlight and Diabetes

South Korea

Type 2 diabetes mellitus

Correlation Between Birth Month – Sunshine

Korea: $R = -0.94 \ P = 0$

NYC, Mt Sinai

Type 2 diabetes mellitus

Correlation Between Birth Month – Sunshine

MSH: $R = -0.9 \ P = 0$
Vitamin D

Sunlight

Vitamin D

Zhang et al. 2008

Risk of Gestational Diabetes

Clausen et al. 2008

T2DM in Offspring

Current Study
A First Trimester Exposure and Atrial Fibrillation

NYC, Columbia University

NYC, Mount Sinai Hospital

Nashville, Vanderbilt University

Seattle, University of Washington

Suwon S. Korea, Ajou University

Taiwan, Taipei Medical University

B Mechanistic Pathway

Fine Air Particulates (PM 2.5)

Risk of Gestational Hypertension

Miettola et al. 2013

High Blood Pressure in Offspring

Psaty et al. 1997

Risk of Atrial Fibrillation

Current Study
Summary of Studies

• Climate is important in understanding disease susceptibility

• Birth Month – Disease Relationships Are Correlated with Certain Exposures During Specific Trimesters Across All Sites

• Results Fit With Known Biological Developmental Pathways


https://www.nature.com/articles/s41598-017-04708-3
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Questions?

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