What have we learned about eczema from routinely-collected health data?

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London School of Hygiene and Tropical Medicine
Why eczema?
Observational studies in dermatology

• The need for population-based studies
• Prolonged follow up times
• Large numbers to detect rare outcomes
• Cost and logistic implications
From individual patients to “ehealth”
Health records ‘An arsenal that the genius of English healers cannot fail to turn to account’

William Farr 1874

supplement to 35th annual report
of the Registrar General
“Routinely collected health data”

Data collected for non-research purposes and/or without an *a priori* research question in mind

Examples

Administrative or “claims” data

Medical record databases (EMR/EHR)

Disease registries (including cancer registries)
What have we learned about eczema from routinely-collected health data?

• Selected early life risk factors for eczema
• Long-term outcomes in people with eczema
• Particular challenges using routinely-collected health data for eczema
Search strategy to inform this talk

- PubMed
- EMBASE
- Web of Science
  - April 10, 2016 for studies using routinely collected data to identify cases of atopic dermatitis
- Map of systematic reviews of eczema,
  https://nottingham.ac.uk/research/groups/cebd/resources/eczema-systematic-reviews.aspx
Clues about early life exposures

*Does Caesarian section increase the risk of eczema?*

Data from West Midlands General Practice database (n=24,690, 7,758 with eczema)

-No increased risk observed with C Section OR 1.04 (0.98-1.10)

*McKeever, Am J Respir Crit Care Med 2002*

Clues about early life exposures

*Does exposure to antibiotics in utero or in the first year of life increase the risk of eczema?*

Data from West Midlands General Practice database (n=24,690)

<table>
<thead>
<tr>
<th>In utero antibiotics</th>
<th>Risk of eczema</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.02 (0.96–1.07)</td>
</tr>
<tr>
<td>2</td>
<td>1.02 (0.93–1.10)</td>
</tr>
<tr>
<td>≥2</td>
<td>1.12 (1.02–1.24)</td>
</tr>
</tbody>
</table>


*Infections and antibiotics in first year of life*

Bacterial infections HR 1.33, 1.14-1.56

≥3 antibiotics increased the risk of eczema HR 1.54 (1.39-1.70); adjusting for consultations 1.25, 1.12-1.40
Does exposure to antibiotics in the first year of life increase the risk of eczema?

German administrative health data (n=487)

**Infections and antibiotics in first year of life**

<table>
<thead>
<tr>
<th>RTI No antibiotics</th>
<th>RTI treated with antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR 0.69 (0.39-1.24)</td>
<td>Macrolides RR 2.15 (1.18–3.91)</td>
</tr>
<tr>
<td></td>
<td>Cephalosporines RR: 1.93 (1.07–3.49)</td>
</tr>
</tbody>
</table>

*Schmitt et al. Pediatric Allergy and Immunology 2010;21(2):292-300*
Does early life exposure to antibiotics increase the risk of eczema? A systematic review

Prenatal antibiotics

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Odds Ratio)</th>
<th>SE</th>
<th>Weight</th>
<th>Odds Ratio IV, Random, 95% CI</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Bisgaard 2009</td>
<td>-0.4308</td>
<td>0.3185</td>
<td>20.4%</td>
<td>0.65 [0.35, 1.21]</td>
<td></td>
</tr>
<tr>
<td>Dom 2010</td>
<td>0.5988</td>
<td>0.2399</td>
<td>0.0%</td>
<td>1.82 [1.14, 2.91]</td>
<td></td>
</tr>
<tr>
<td>Jedrychowski 2006</td>
<td>0.8329</td>
<td>0.4725</td>
<td>12.9%</td>
<td>2.30 [0.91, 5.81]</td>
<td></td>
</tr>
<tr>
<td>McKeever 2002b</td>
<td>0.157</td>
<td>0.0501</td>
<td>38.3%</td>
<td>1.17 [1.06, 1.29]</td>
<td></td>
</tr>
<tr>
<td>Sariachvili 2007</td>
<td>0.6419</td>
<td>0.2047</td>
<td>28.4%</td>
<td>1.90 [1.27, 2.84]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td></td>
<td>100.0%</td>
<td>1.30 [0.86, 1.95]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.11$; $\text{Chi}^2 = 10.89$, df = 3 ($P = 0.01$); $I^2 = 72%$

Test for overall effect: $Z = 1.26$ ($P = 0.21$)

Does early life exposure to antibiotics increase the risk of eczema? A systematic review

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</tr>
</thead>
<tbody>
<tr>
<td>Cohet 2004</td>
<td>0.3365</td>
<td>0.0744</td>
<td>10.4%</td>
<td>1.40 [1.21, 1.62]</td>
<td></td>
</tr>
<tr>
<td>Droste 2000</td>
<td>0.47</td>
<td>0.0986</td>
<td>8.2%</td>
<td>1.60 [1.32, 1.94]</td>
<td></td>
</tr>
<tr>
<td>Floistrup 2006</td>
<td>0.4886</td>
<td>0.1469</td>
<td>5.1%</td>
<td>1.63 [1.22, 2.17]</td>
<td></td>
</tr>
<tr>
<td>Folkard 2009</td>
<td>0.3523</td>
<td>0.0324</td>
<td>14.5%</td>
<td>1.42 [1.33, 1.51]</td>
<td></td>
</tr>
<tr>
<td>Sobko 2010</td>
<td>0.0619</td>
<td>0.1844</td>
<td>3.7%</td>
<td>1.06 [0.74, 1.53]</td>
<td></td>
</tr>
<tr>
<td>von Mutius 1999</td>
<td>0.4054</td>
<td>0.0986</td>
<td>8.2%</td>
<td>1.50 [1.24, 1.82]</td>
<td></td>
</tr>
<tr>
<td>Wickens 1999</td>
<td>0.207</td>
<td>0.2801</td>
<td>1.8%</td>
<td>1.23 [0.71, 2.13]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td></td>
<td></td>
<td><strong>51.8%</strong></td>
<td><strong>1.43 [1.36, 1.51]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 5.31, df = 6 (P = 0.50); I² = 0%
Test for overall effect: Z = 13.55 (P < 0.00001)

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<tr>
<th>Study or Subgroup</th>
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<th>Odds Ratio</th>
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</thead>
<tbody>
<tr>
<td>Celedon 2002</td>
<td>0.0953</td>
<td>0.5224</td>
<td>0.6%</td>
<td>1.10 [0.40, 3.06]</td>
<td></td>
</tr>
<tr>
<td>Farouqi 1998</td>
<td>0.7129</td>
<td>0.1466</td>
<td>5.0%</td>
<td>2.04 [1.52, 2.73]</td>
<td></td>
</tr>
<tr>
<td>Kummeling 2007</td>
<td>−0.06</td>
<td>0.1156</td>
<td>6.9%</td>
<td>0.94 [0.75, 1.18]</td>
<td></td>
</tr>
<tr>
<td>Kusel 2008</td>
<td>0.4055</td>
<td>0.3956</td>
<td>1.0%</td>
<td>1.50 [0.69, 3.26]</td>
<td></td>
</tr>
<tr>
<td>Mai 2010</td>
<td>0.2624</td>
<td>0.0791</td>
<td>9.9%</td>
<td>1.30 [1.11, 1.52]</td>
<td></td>
</tr>
<tr>
<td>McKeeve 2002a</td>
<td>0.392</td>
<td>0.0646</td>
<td>11.3%</td>
<td>1.48 [1.30, 1.68]</td>
<td></td>
</tr>
<tr>
<td>Saraiachvili 2007</td>
<td>0.0953</td>
<td>0.1604</td>
<td>4.5%</td>
<td>1.10 [0.80, 1.51]</td>
<td></td>
</tr>
<tr>
<td>Schmitt 2009</td>
<td>0.7655</td>
<td>0.2056</td>
<td>1.6%</td>
<td>2.15 [1.18, 3.91]</td>
<td></td>
</tr>
<tr>
<td>Su 2010</td>
<td>0.3001</td>
<td>0.2211</td>
<td>2.7%</td>
<td>1.35 [0.88, 2.08]</td>
<td></td>
</tr>
<tr>
<td>Wickens 2008</td>
<td>0.5365</td>
<td>0.1568</td>
<td>4.7%</td>
<td>1.71 [1.26, 2.33]</td>
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<td><strong>Subtotal (95% CI)</strong></td>
<td></td>
<td></td>
<td><strong>48.2%</strong></td>
<td><strong>1.40 [1.19, 1.64]</strong></td>
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Heterogeneity: Tau² = 0.03; Chi² = 25.60, df = 9 (P = 0.002); I² = 65%
Test for overall effect: Z = 4.14 (P < 0.0001)

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<tr>
<td>Total</td>
<td></td>
<td></td>
<td><strong>100.0%</strong></td>
<td><strong>1.41 [1.30, 1.53]</strong></td>
<td></td>
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Heterogeneity: Tau² = 0.01; Chi² = 31.69, df = 16 (P = 0.01); I² = 50%
Test for overall effect: Z = 8.56 (P < 0.00001)
Test for subgroup differences: Chi² = 0.07, df = 1 (P = 0.76), I² = 0%
What have we learned about eczema from routinely-collected health data?

• Selected early life risk factors for eczema

• Long-term outcomes in people with eczema

• Particular challenges using routinely-collected health data for eczema
Long-term outcomes in people with eczema

Overview of systematic reviews

Deckert et al. Allergy 2014;69:37-45

Eczema and cancer- decreased risk of glioma (pooled OR 0.69, 0.58-0.82), meningioma (0.75, 0.65-0.87) and acute lymphoblastic leukaemia (6 reviews)

Eczema and ADHD- increased risk (1 review)

Associations also observed in recent SRs

https://nottingham.ac.uk/research/groups/cebd/resources/eczema-systematic-reviews.aspx

Recent emerging evidence of associations in individual studies between eczema and cardiovascular disease, fractures, renal outcomes
Is eczema associated with cardiovascular outcomes?

- Mechanistic work suggests that eczema may be associated with increased platelet activation and decreased fibrinolysis.
- Cross-sectional studies in adults and US children suggest associations between eczema and acute vascular outcomes.

- *Is there convincing evidence to support these observations?*
- *Is the association causal?*
Is eczema associated with cardiovascular outcomes?

• German insurance data (n=1.2m)
• Associations observed with angina RR 1.17 (1.12-1.23) and PVD RR 1.15 (1.11-1.19) after adjusting for age, sex, SES, healthcare access
• Stronger associations with severe eczema
• No associations with MI and stroke
• No lifestyle factors available

Standl et al. J Inv Dermatol 2017
Is eczema associated with cardiovascular outcomes?

- Danish registry data (reference pop 145,372, mild AD 26,898, severe AD 2,527)
- Associations with stroke (1.51, 1.08-2.10), CVD death (1.46, 1.07-2.02) and MACE (1.53, 1.23-1.91) in severe eczema after adjusting for age and sex; none significant after adjusting for possible mediators

Anderson 2017 J Aller Clin Immunol
Is eczema associated with cardiovascular outcomes?

• Taiwan National Health Insurance database (n=20,323 AD patients and 20,323 comorbidity-matched subjects)
• HR=1.33 (1.12-1.59) increased incidence of ischemic stroke
• Gradient with increased severity
• Findings persisted after adjusting for confounders and mediators
Is eczema associated with cardiovascular outcomes?

- UK CPRD (n=469,453 eczema patients matched to 2.3m patients without eczema)
- Increased risk of acute coronary syndrome, stroke and coronary revascularisation in moderate and severe eczema
- Stronger associations with increased disease severity
Is eczema associated with cardiovascular outcomes?

• Signals from studies
• SR coming soon to summarise and meta-analyse key findings
• Routinely collected data allowed sufficient numbers and prospective follow up
• Many data sources lack lifestyle information, hence are subject to residual confounding
What have we learned about eczema from routinely-collected health data?

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• Particular challenges using routinely-collected health data for eczema
Particular challenges using routinely-collected health data for eczema

• Relapsing and remitting disease
• Non-specific terminology
• Validity of diagnostic algorithms
Are we measuring eczema?

• Develop and validate a diagnostic algorithm for atopic eczema that identifies cases based on medical record and pharmacy codes.
• The Health Improvement Network
• Sent survey to physicians of 100 children and 100 adults

Abuabara et al. JID 2017
### Algorithm ‘test characteristics’

<table>
<thead>
<tr>
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<th>PPV (%)</th>
<th>95%CI</th>
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<tbody>
<tr>
<td>One eczema code + at least 2 treatment codes (selection criteria)</td>
<td>177</td>
<td>154</td>
<td>87%</td>
<td>(81%-92%)</td>
</tr>
<tr>
<td>Two eczema codes + at least 2 treatment codes</td>
<td>86</td>
<td>79</td>
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<td>Two eczema codes + at least one steroid/TCI codes</td>
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Can routinely collected data be used to estimate burden related to eczema?

• Systematic review (in submission) assessing how studies using routinely collected data defined eczema

• Prevalence measured in 40/59 (68%) of studies- estimates ranged from 0.18% to 32.49%
Why are prevalence estimates so different?

• Different countries, ages etc.

• Terminology/measuring different things- studies including seborrheic and contact dermatitis codes reported higher prevalences- 10% vs. 5%

• Algorithms which included prescription data- median prevalence 16% if included compared to 4%

• One major caveat- Algorithms need to be context specific
Key issues to watch out for

Why were data collected?
  • Clinical care
  • Billing

Who is the population?
  • Selection bias
  • Generalisability

What information are we missing?
  • Limited data on disease severity
  • Mostly no “over the counter” drugs
  • Residual confounding
Pitfalls

• Changes in how diseases/drugs are coded
• Changes in healthcare systems leading to artefactual findings
• Ascertainment issues with repeated measures
What have we learned about eczema from routinely-collected health data?

- Selected early life risk factors for eczema
- Long-term outcomes in people with eczema
- Particular challenges using routinely-collected health data for eczema
New opportunities
Acknowledgements

- Wellcome Senior Clinical Fellowship
- British Skin Foundation Innovative award