The value of stratified economic analysis in cohort-level models: A case study on interventions for obstructive sleep apnea

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Disclosure

No actual or potential conflict of interest in relation to this topic or presentation.
Cohort-Level Modelling

• Many “cohort-level” models in economic evaluation
• All rely on an *Homogeneity* assumption
  • Aggregate, based on identifying similarities between individuals
• Subgroup effects may exist that is largely ignored in such models
Objective

To illustrate the importance of conducting stratified economic analysis to incorporate subgroup effects through the example of treatments for obstructive sleep apnea.

Stratified vs Partly stratified vs Non-stratified analyses
Obstructive Sleep Apnea (OSA)

- Relatively common disorder characterized by the narrowing and collapse of the upper airway during sleep
  - Severity categorized by apnea-hypopnea index (AHI):
    
    | Mild | Moderate | Severe |
    |------|----------|--------|
    | 0    | 5        | 15     |
    | 15   | 30       | 30     |
  - If left untreated, there is significant morbidity and mortality consequences
OSA Treatment Reviewed

PAP devices (e.g., CPAP)

Oral appliances (i.e., MAD)

Weight Loss*

No treatment

Surgery (MMA ± GTA)

Additional interventions considered:
Exploratory analyses- ePAP, positional therapy

CADTH conducted an Optimal Use review to address the question of “which treatment- for whom?”

CPAP = continuous positive airway pressure; ePAP = exploratory positive airway pressure; GTA = Genial tubercle advancement; MAD = mandibular advancement devices; MMA = Maxillomandibular advancement

*Only suitable in patients who are overweight
Economic Model Structure

AHI = apnea hypopnea index; MI = myocardial infarction

Positive relationship

Negative relationship
External Validation

Survival curve

A. Wisconsin Sleep Cohort Study

B. Busselton Study
Non-stratified Analysis

No stratification by natural history or by treatment effect
Modelling OSA Natural History

• All-cause mortality: based on Canadian lifetables for general population (age- and gender-specific)
  Also impacted by AHI:
  
  RR (severe OSA vs no OSA*) = 1.6
  RR (moderate OSA vs. no OSA*) = 1.2
  RR (mild OSA vs. no OSA*) ~ 1

• Cardiovascular event: based on Framingham risk equation
  Predictive equation of probability of MI or stroke based on gender, age, systolic blood pressure, smoking status, total cholesterol, HDL, diabetes status and ECG
  Also indirectly impacted by AHI, RR incident hypertension:

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>1.19</td>
<td>1.37</td>
</tr>
<tr>
<td>Moderate</td>
<td>1.61</td>
<td>1.79</td>
</tr>
<tr>
<td>Severe</td>
<td>1.66</td>
<td>1.90</td>
</tr>
</tbody>
</table>
Partly Stratified Analysis

Stratify by natural history but not by treatment effects
Summary of Partly Stratified Analysis

*Considerable parameter uncertainty at baseline AHI value 22 to 30 as no strategy emerged as most likely cost-effective at prob>60% (CPAP was most likely cost-effective at 25≤AHI≤27)

@ $\lambda$ = $50,000/QALY

*Clinical Definition

- **Mild**
- **Moderate**
- **Severe**

*No treatment, MAD*, MMA*
Non-stratified Treatment Effect

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Mean reduction in AHI</th>
<th>Mean reduction in BP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Compared to “no treatment”</td>
<td></td>
</tr>
<tr>
<td>PAP-based therapy</td>
<td><strong>NMA</strong></td>
<td>NMA</td>
</tr>
<tr>
<td></td>
<td>-25.27</td>
<td>-2.5</td>
</tr>
<tr>
<td></td>
<td>(-22.03, -28.52)</td>
<td>(-1.5, -3.5)</td>
</tr>
<tr>
<td>MAD</td>
<td><strong>NMA</strong></td>
<td>NMA</td>
</tr>
<tr>
<td></td>
<td>-15.20</td>
<td>-2.1</td>
</tr>
<tr>
<td></td>
<td>(-10.91, -19.50)</td>
<td>(-0.8, -3.4)</td>
</tr>
<tr>
<td>Surgery</td>
<td><strong>Probability</strong> (by baseline AHI)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;30</td>
<td></td>
</tr>
<tr>
<td></td>
<td>30&lt;AHI&lt;60</td>
<td></td>
</tr>
<tr>
<td></td>
<td>60&lt;AHI&lt;90</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AHI&gt;90</td>
<td></td>
</tr>
<tr>
<td>Cure (AHI &lt;5)</td>
<td>0.557</td>
<td>0.458</td>
</tr>
<tr>
<td></td>
<td>0.28</td>
<td>0.195</td>
</tr>
<tr>
<td></td>
<td>-3.5 (-19, 11)</td>
<td></td>
</tr>
<tr>
<td>Success (AHI &lt;15 and 50% ↓ in baseline AHI)</td>
<td>0.836</td>
<td>0.88</td>
</tr>
<tr>
<td></td>
<td>0.727</td>
<td>0.707</td>
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## Stratified Treatment Effect

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<td></td>
<td>Stratified by baseline AHI</td>
<td></td>
</tr>
<tr>
<td>PAP-based therapy MA</td>
<td>Mild: -2.4 (-3.7, -1.1)</td>
<td>NMA -2.5 (-1.5, -3.5)</td>
</tr>
<tr>
<td></td>
<td>Moderate: -13.7 (-16.1, -11.2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe: -33.0 (-39.8, -33.0)</td>
<td></td>
</tr>
<tr>
<td>MAD MA</td>
<td>Mild: -7.8 (-16.4, -1.1)</td>
<td>NMA -2.1 (-0.8, -3.4)</td>
</tr>
<tr>
<td></td>
<td>Moderate: -10.7 (-14.6, -6.9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe: -8.0 (-16.0, 0.0)</td>
<td></td>
</tr>
<tr>
<td>Surgery Probability</td>
<td>&lt;30</td>
<td>0.557</td>
</tr>
<tr>
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Fully Stratified Analysis

*Stratify by natural history and by treatment effect*

![Graph showing probability cost-effective vs willingness to pay threshold for different treatment options: No Treatment, PAP, MAD, and Surgery.]

**Baseline AHI**

- **Mild OSA**: 60
- **Severe OSA**
Summary of Fully Stratified Analysis

@ $\lambda = 50,000/QALY

Clinical Definition

- Mild
- Moderate
- Severe

No treatment MAD MMA PAP MMA

CADTH
Subgroup: Overweight/Obese patients

- Rationale: Clinical experts and inclusion criteria from clinical review inclusion suggest lifestyle is a suitable option for patients who are overweight/obese

- Results: Lifestyle emerges as the most likely cost-effective interventions for patients with mild OSA

\[ \lambda = $50,000/\text{QALY} \]
Discussion

• By ignoring heterogeneity in patient characteristics or in treatment effects, different results reached.
  • Observed uncertainty in CEAC driven by heterogeneity.

• In this example, value of conducting stratified analyses arose when:
  • Heterogeneity in natural history,
  • Differential treatment effects by subgroups,
  • Clinical criteria exist regarding the suitability of a treatment.

• In reality, heterogeneity can be with any type of parameter inputs.
Challenge with Stratification

• Challenge remains with cohort-level models given the potentially large number of analysis required
  Independent: $\sum n_m$
  Dependent: $\prod n_m$
  $n =$ number of dimensions
  $m =$ number of levels within dimension

  Solution: Patient-level microsimulation

• How does one select which variables to factor with respect to heterogeneity in stratified analyses?
Conclusions

- Different economic findings when factoring patient-specific characteristics, with potential implication to policy-making.

At $\lambda = $50,000/QALY:

- **Non-stratified analysis:** MMA
- **Partly-stratified analysis:**
  - No Treatment: MAD, MMA
  - Subgroup: Overweight/Obese
  - Lifestyle: MAD, MMA, PAP, MMA
- **Stratified analysis:**
  - No Treatment: MAD, MMA, PAP, MMA