Evaluation of Small Airways Disease in asthma medical research: Application of Structural Equation Modeling (SEM) and Latent Transition Analysis (LTA)

Thomas Zwingers
Marco Pannacci
Agenda

• Study Design
• Small Airways Disease (SAD) in asthma
• Structural Equation Model
• Cross-sectional Model
• Longitudinal Model
• Summary
Study Design and Objectives

• Study Design: Multinational, multicenter, non-pharmacological intervention study with a cross-sectional and a longitudinal phase.

• Follow-up time: 1 year

• Major objectives:
  ➢ To evaluate which (combination of) clinical methods best assesses the abnormalities of small airways disease in asthma and their role in the clinical manifestations of asthma, both cross-sectionally and longitudinally.
Study Population

- Planned Sample Size: 900 patients (800 asthmatic patients + 100 healthy volunteers).

<table>
<thead>
<tr>
<th></th>
<th>No. of Asthmatic Patients</th>
<th>No. of Healthy Volunteers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screened Set</td>
<td>883</td>
<td>104</td>
</tr>
<tr>
<td>Evaluable Set</td>
<td>772</td>
<td>98</td>
</tr>
</tbody>
</table>
Asthma is a common long-term inflammatory disease of the airways of the lungs. It is characterized by variable and recurring symptoms, reversible airflow obstruction, and bronchospasm. There is no cure for asthma.

Poorly controlled inflammation in small airways may contribute to
• asthma exacerbations,
• air trapping,
• lung function decline, and
• irreversible structural changes

Source: https://en.wikipedia.org/wiki/Asthma
ASTHMA

Asthma Prevalence

• An estimated 300 million people worldwide suffer from asthma, with 250,000 annual deaths attributed to the disease.

• It is estimated that the number of people with asthma will grow by more than 100 million by 2025.

Categories of asthma severity

**Mild asthma:**
Well controlled with SABA or low dose ICS
⇒ GINA Steps 1 or 2

**Moderate asthma:**
Well controlled with low dose ICS/LABA
⇒ GINA Step 3

**Severe asthma:**
requires moderate or high dose ICS/LABA ± add on, or remains uncontrolled despite this treat
⇒ GINA Steps 4/5

Structural Equation Modeling (SEM)

SEM is a very general statistical modeling method.

It can be viewed as a combination of exploratory factor analysis, confirmatory factor analysis, path analysis or regression and others.

- Typical example: measurement of intelligence.

  - We can’t measure the concept of interest (intelligence, socio-economic status ..) directly

    ➔ latent variables.

  - However we can refer to observable indicators that are influenced by the latent variable, e.g scores obtained by a series of tests about linguistic or arithmetic abilities

    ➔ observed variables.
Structural Equation Modeling (SEM)

Structural Equation Models consist of

- a structural model representing the relationship between the latent variables of interest, and
- measurement models representing the relationship between the latent variables and their manifest or observable indicators
The Path Diagram describes the theoretical framework that forms the basis for specification of our initial model.

The rationale about hypotheses and directionality specifications in the diagram was built by the statisticians consulting the experts of the clinical team during two TC meetings.

**Observed variables** in the Path Diagram are represented with squares or rectangles; **latent variables** with circles; **hypothesized directional effects (causal relationships)** of one variable on another, with a line with a single arrowhead; correlations between variables with a curved line with two arrowheads.
Outcome of SEM model: Asthma clusters

Overall the clusters represent GINA severity stages predominantly, suggesting that SAD increases with asthma severity.

This analysis identifies specific asthma, not SAD, clusters.
**Statistical Analysis Plan - New approach**

*only the variables reflecting small airways disease and both small and large airways disease were considered for the SAD measurement model*

<table>
<thead>
<tr>
<th>Small</th>
<th>Large</th>
<th>Both</th>
<th>Systemic effects</th>
<th>Patient-reported outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>% fall in FVC at PC20</td>
<td>R20 (kPa L-1 s-1)</td>
<td>PC20 (mg/mL)</td>
<td>WBC</td>
<td>Asthma Control Test (ACT)</td>
</tr>
<tr>
<td>R5-20 (kPa L-1 s-1)</td>
<td>FENO single flow (50ml/s)</td>
<td>PD20 (mg)</td>
<td>Neutrophils</td>
<td>Mini asthma quality of life questionnaire</td>
</tr>
<tr>
<td>X5 (kPa L-1 s-1)</td>
<td>Sputum</td>
<td>PD20 &amp; PC20 categories</td>
<td>Monocytes</td>
<td>Asthma control questionnaire (ACQ-6)</td>
</tr>
<tr>
<td>AX (Hz kPa L-1 s-1)</td>
<td>FEV1 %pred</td>
<td>FEV1/FVC (L/sec)</td>
<td>Lymphocytes</td>
<td>Bronchial Hyperresponsiveness Questionnaire (BHQ)</td>
</tr>
<tr>
<td>Scond*VT in liter</td>
<td>IVC %pred</td>
<td>Eosinophils</td>
<td>EuroQol-5D-5L</td>
<td></td>
</tr>
<tr>
<td>Sacin*VT in liter</td>
<td></td>
<td>Basophils</td>
<td>EuroQol VAS (respondent’s self-rated health)</td>
<td></td>
</tr>
<tr>
<td>RV %pred</td>
<td>FENO multiple flows (100, 150, 350, other)</td>
<td>Phadiatop test</td>
<td>Total number of hospital admission days in the past 12 months before V1</td>
<td></td>
</tr>
<tr>
<td>RV / TLC %pred</td>
<td></td>
<td></td>
<td>Number of asthma-specific emergency room or urgent care visits</td>
<td></td>
</tr>
<tr>
<td>FRC %pred</td>
<td></td>
<td></td>
<td>Number of unscheduled consultations visits due to symptoms worsening</td>
<td></td>
</tr>
<tr>
<td>FEF50%/FVC</td>
<td></td>
<td></td>
<td>Total number of Unscheduled tests for asthma</td>
<td></td>
</tr>
<tr>
<td>FEF25-75%/FVC</td>
<td></td>
<td></td>
<td>Number of exacerbation in the last year</td>
<td></td>
</tr>
</tbody>
</table>
## Study Population

<table>
<thead>
<tr>
<th></th>
<th>No. of Asthmatic Patients</th>
<th>No. of Healthy volunteers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Evaluable Set</strong></td>
<td>772</td>
<td>98</td>
</tr>
<tr>
<td><strong>SAD SEM Analysis</strong>*</td>
<td>761</td>
<td>Not used</td>
</tr>
</tbody>
</table>

*We lost only 6 patients with no data for small airways disease variables and we excluded 5 patients that were outliers (based on the model indicators for outliers detection).*
Clinical SAD SEM – Cross Sectional Model

Model Fit:
Root Mean Squared Error of Approximation (RMSEA): 0.048
Comparative Fit Index (CFI): 0.990
SAD SEM model based clustering

Clinical SAD SEM Score

<table>
<thead>
<tr>
<th>SAD Group</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>452</td>
<td>59</td>
</tr>
<tr>
<td>2</td>
<td>312</td>
<td>41</td>
</tr>
</tbody>
</table>

Clinical SAD SEM Groups

- 1
- 2
## Relationship between Clinical SAD (SEM) groups and GINA classes

<table>
<thead>
<tr>
<th>Clinical SAD SCORE</th>
<th>Gina 1</th>
<th>Gina 2</th>
<th>Gina 3</th>
<th>Gina 4</th>
<th>Gina 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (n)</td>
<td>-0.143 (134)</td>
<td>-0.035 (83)</td>
<td>-0.048 (205)</td>
<td>0.071 (296)</td>
<td>0.239 (46)</td>
</tr>
<tr>
<td>Anova p-value</td>
<td>&lt;.0001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

![Mean Clinical SAD SCORE](image-url)
Clinical SAD SEM – Longitudinal Model

Latent Transition Analysis

VISIT 1

VISIT 3
Clinical SAD SEM – Latent Transition Analysis

**VISIT 1**

SAD Groups  
G1 = 59%  
G2 = 41%

14 patients move from G1 to G2  
28 patients move from G2 to G1

**VISIT 2**

SAD Groups  
G1 = 61%  
G2 = 39%

14 patients move from G1 to G2  
9 patients move from G2 to G1

**VISIT 3**

SAD Groups  
G1 = 60%  
G2 = 40%

27 patients move from G1 to G2  
36 patients move from G2 to G1
We were able to define a score that reflects the amount of physiological small airways impairment.

The score associated significantly with measures of asthma control, disease instability and asthma severity as defined by GINA stages.

SAD appears to be clinically meaningful as suggested by the association of physiologic parameters of SAD with asthma severity, asthma control and health care utilization.

We can detect asthma subtypes based on small airways dysfunction.