Obstructive Sleep Apnea on the Job: A 2-Way Street
Daniel Schwartz, MA MSc
Emerging and Re-emerging Occupational and Environmental Exposure and Disease
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Disclosures
• I have no disclosures.

Roadmap
• Occupation as a Risk Factor for OSA, Motivations and Research Questions
• Understanding Meta-Analysis
• Meta-Prevalence of OSA in Commercial Drivers
• Meta-Analysis of Association Between Organic Solvent Exposure and OSA
• Limitations, Sources of Bias, and Discussion
• Questions

Obstructive Sleep Apnea and Occupation
• Involves a decrease or stoppage of airflow despite ongoing efforts to breathe during sleep.
• Well-defined risk factors – BMI, smoking, alcohol – each of which have occupational associations.
• Stealth disease that can go undetected; high prevalence, probably under reported
  • 4% in middle-aged men
  • 2% in middle aged women
• Research objectives
  1. Provide quantitative estimates of risk and association between occupational factors and OSA.
  2. Provide synthesis of the occupational literature on OSA, including the risks of commercial driving, and risks related to organic solvent exposure.
What is meta-analysis?

- A set of quantitative, statistical procedures used to systematically aggregate and combine the results of previous research.
- Can increase statistical power and precision in measuring a treatment effect.
- A means of identifying data gaps, and exploring sources of heterogeneity from multiple sources.
- Applicable to both observational/epidemiological data, and trial data.

Fixed Effects Model

- Assumes all study estimates are of a single underlying effect.
- Observed differences in measured effects are generated due to sampling error.
- Better terminology – "common effect" model.
- With an infinitely large sample for all studies, between-study differences would disappear.
- Heterogeneity ($I^2$) statistic
  - Measures the % variability due to between-study variability rather than within-study sampling error.

Fixed Effects Model Assumptions

Invoking a Fixed Effects Model
Assigning study weights in a fixed effects model

- Inverse variance method
  - I.e., larger, more precise estimates receive greater weight

\[ \text{Weight}_i = \frac{1}{(\text{standard error})^2} \]

Random Effects Model

- Assumes the true treatment/exposure effect is different from study to study.
- Pooled estimates capture the average treatment effect.
- Accounts for between-study differences in measurement AND error due to chance. Even if samples are infinitely large (eliminating variability due to chance), the observed study effects would vary because of real differences in treatment/exposure effects.
- Default model when large heterogeneity exists (i.e., high \( I^2 \)) between studies, and corresponding CI will be wider, i.e., claims of significance are more conservative.

Study weighting in a random effects model

- Inverse variance method
  - Within-study variance
  - Between-study from the overall treatment/exposure effect mean

\[ \text{Weight}_i = \frac{1}{(\text{standard error})^2} \]
Commercial Driver Meta-Prevalence Analysis

- Embase/PubMed query → June 2016
  - “Drivers” AND “sleep” AND “apnea”
  - “Commercial” AND “driver” AND “sleep” AND “apnea”

- Major inclusion criteria
  - Polysomnography-confirmed OSA

- Major exclusion criteria
  - OSA defined by paper survey of symptoms
  - Prevalence estimates based on pre-screened populations selecting for symptomatic patients
  - Case reports, conference papers, abstracts

Spectrum of Obstructive Sleep Apnea

Apneas

Respiratory effort related arousals

Hypopneas

12-channel Polysomnography

- A measure of OSA severity using 12-channel polysomnography.
- Count of the average # apneas + # hypopneas per hour
  - Apnea = complete cessation of airflow during sleep >= 10 s
  - Hypopnea = reduction in airflow, variably defined

Apnea-Hypopnea Index (AHI)

- AHI is a reproducible measurement of OSA severity, and is predictive of cardiovascular risk
- Hypopneas without apneas lead to similar expression of OSA, but are harder to measure and defined differently

- AASM 2001
  - Recommended - Abnormal respiratory event >= 10 sec with >=30% reduction of airflow AND >=4% oxygen desaturation.
  - Alternative - >=50% reduction in nasal pressure signal excursions AND associated with >=5% desaturation or arousal
  - Sleep Heart Health Study – stricter cut-off for desaturation >=4%
AHI is Predictive of Cardiovascular Risk

- Sleep Heart Health Study
- Graded association between AHI and HTN >140/90

<table>
<thead>
<tr>
<th>Variables</th>
<th>No. of Subjects</th>
<th>Adjusted OR (95% CI)</th>
<th>BMX OR (95% CI)</th>
<th>BMX OR (95% CI)</th>
<th>Odds Ratio to HR Risk Adjusted OR (95% CI)</th>
<th>Odds Ratio to BMX Risk Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0-4.9</td>
<td>1088</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>5-9.9</td>
<td>1731</td>
<td>1.07 (1.00-1.14)</td>
<td>1.08 (1.00-1.16)</td>
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</tr>
<tr>
<td>10-14.9</td>
<td>719</td>
<td>1.73 (1.60-1.88)</td>
<td>1.80 (1.63-1.98)</td>
<td>1.80 (1.63-1.98)</td>
<td>1.70 (1.51-1.90)</td>
<td>1.70 (1.51-1.90)</td>
</tr>
<tr>
<td>&gt;15</td>
<td>373</td>
<td>2.27 (2.12-2.46)</td>
<td>2.30 (2.15-2.48)</td>
<td>2.30 (2.15-2.48)</td>
<td>2.20 (2.01-2.41)</td>
<td>2.20 (2.01-2.41)</td>
</tr>
</tbody>
</table>

Even mild OSA is associated with a significantly elevated risk of hypertension after adjustments for relevant confounder variables.

Commercial Driver Meta-Prevalence Analysis

- 18 full-text articles eligible
- Defined OSA cut-offs
  - AHI >5 mild disease
  - AHI >15 moderate-severe
- Study size range from N = 32 to N = 2342
- High heterogeneity warranted use of a random effects model

There is a significant burden of even mild OSA amongst the commercial driver population.

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<th>AHI&gt;5</th>
<th>AHI&gt;15</th>
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<td>41% (95% CI 26.56%)</td>
<td>15% (95% CI 12.19%)</td>
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Other pooled estimates among the adult male population, mild OSA AHI>5 > 22% (Franklin and Lindberg, 2015)
Solvent Exposure and OSA Meta-Analysis

- Meta-analysis to determine summary relative risk rather than prevalence.
- Similar search strategy as earlier \( \rightarrow \) "occupational AND exposure AND sleep AND apnea"
- Major inclusion criteria
  - Summaries of risk including relative risk (RR), odds ratio (OR), standardized incidence ratios (SIR) with respect to solvent exposure and OSA risk.
  - Risk estimates for occupations characterized by solvent exposure (dry cleaning, painting, print shop work, etc).
  - OSA definable by sleep study, or ICD-based diagnostic code of OSA.
- Major exclusion criteria
  - Abstracts, reviews, commentaries, case reports

Solvent Exposure and OSA Meta-Analysis

- 542 abstracts screened; 7 full-text papers eligible.
- All bibliography title-reviewed leading to inclusion of 1 additional article.
- 8 full-text articles meeting criteria.
- Confounder adjusted and matched results selected over unadjusted:
  - Age
  - BMI
  - Smoking
  - Sex
- High heterogeneity prompting use of random effects model.
- Diverse methods of OSA definition; diverse study designs including case-control, and population-based designs.

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Schwartz et al 2017

Random Effect Summary Relative Risk
2.38 (95% CI 0.89 – 6.32)
Heterogeneity statistic $I^2$ 93.8%

### Table 1: Subgroup Analysis of Exposure to Solvent and OSA

<table>
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<tr>
<th>Analysis</th>
<th>No. of Cases</th>
<th>No. of Results</th>
<th>RR Summary</th>
<th>95% CI</th>
<th>p =</th>
<th>$p^2$</th>
</tr>
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<tbody>
<tr>
<td>All studies</td>
<td>217</td>
<td>8</td>
<td>2.38</td>
<td>0.89 – 6.32</td>
<td>0.03</td>
<td>90.6%</td>
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<td>Case-control (Goulden et al., 1987; Lape et al., 1987)</td>
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LR, lower bound of 95% confidence interval; OSA, occupational sleep apnea; RR, random effects model; CI, upper bound.
Take Home Points - Prevalence of OSA Amongst Commercial Drivers

- Pooled prevalence of 15% of moderate-severe OSA. 40% of mild OSA.
- By random effects model.
- PSG-confirmed OSA represents a principle strength. Bias minimized by including only asymptomatic patients.
- Variable estimates seen, based on population under study, PSG method, cut-offs.

Mechanisms of OSA pathogenesis
- Abnormal sleep/wake cycles
- Stress
- High rates of obesity and hypertension

Arnold et al., 2017

Key Points - Organic Solvents and OSA

- Pooled relative risk demonstrates a 1.38-fold increase in risk of OSA compared to referents, though our 95% CI did not exclude absence of effect.
- Considerable heterogeneity borne out in our statistics, and across studies, variability in OSA assessment, study design, and airflow analysis. Earlier studies may be more limited in capturing hypopneas, which are critical in measuring extent of disease.
- Trichloroethane, aromatic hydrocarbons, methycyclohexane.
- Considerable degree of variability limits causal inferences.

Multiple Choice Question

Which of the following are true regarding meta-analysis models?
A. A random effects model assumes variability is generated from within-study sampling error only.
B. A random effects model assumes variability is generated from within-study sampling error and between-study variability.
C. A random effects pooled estimate attempts to measure a common underlying treatment effect.
D. A random effects pooled estimator captures the average treatment effect of potentially several true effect measures.
E. B & D

References