Unanswered questions in tobacco harm reduction research

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Science is about never knowing everything

- Problems that need to be addressed
- Questions that need to be answered
- Answers create new questions
- New problems found → new efforts to solve them
Prejudice in tobacco harm reduction research

- Scientists more willing to look for problems rather than benefits
  - A lot of research about e-cigarettes being gateway TO smoking
  - Little research about e-cigarettes being gateway FROM smoking

- Funding focused mostly on searching for problems
  - Further motivation for scientists to look for problems

- Abstinence-only approach, denial for harm reduction potential
  - This approach has still not solved the smoking problem globally
  - Harm reduction as a strategy has been accepted in other areas

- Predisposition
  - It looks like smoking, it is used like smoking, so it must be bad
  - Associations assumed to have causal link
Example of predisposition

- E-cigarettes and myocardial infarction

**Table 2.** Univariate and Multivariable Associations Between E-cigarette Use and Myocardial Infarction of NHIS 2014 and 2016 Combined

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Unadjusted model</th>
<th>Adjusted model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>E-cigarette use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>ref</td>
<td></td>
</tr>
<tr>
<td>Former</td>
<td>0.79 (0.67, 0.94)</td>
<td>0.009</td>
</tr>
<tr>
<td>Some days</td>
<td>1.06 (0.79, 1.44)</td>
<td>0.665</td>
</tr>
<tr>
<td>Daily</td>
<td>1.69 (1.19, 2.39)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

**Conclusion (authors):** “Daily e-cigarette use, adjusted for smoking conventional cigarettes as well as other risk factors, is associated with increased risk of myocardial infarction.”

Increased risk clearly implies a **causal link** and **temporal definition of events** (e-cigarette use preceding infarction, which CANNOT be determined from this cross sectional study)
Inconsistent association

National Health Interview Survey (NHIS) 2016 and 2017

E-cigarette use and Coronary Heart Disease

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>E-cigarette use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never (referent)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily</td>
<td>1.52</td>
<td>0.91-2.53</td>
<td>0.109</td>
</tr>
<tr>
<td>Some days</td>
<td>1.19</td>
<td>0.73-1.92</td>
<td>0.481</td>
</tr>
<tr>
<td>Former</td>
<td>1.10</td>
<td>0.89-1.36</td>
<td>0.392</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily</td>
<td>1.67</td>
<td>1.41-1.98</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Some days</td>
<td>1.70</td>
<td>1.28-2.25</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Former</td>
<td>1.50</td>
<td>1.35-1.67</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Farsalinos, Polosa & Niaura (under review)
Association vs. causal inference

National Health Interview Survey (NHIS) 2016 and 2017

Taking prescribed anti-cholesterol medication and Coronary Heart Disease

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taking medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (referent)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2.05</td>
<td>1.65-2.55</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Having high cholesterol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (referent)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.42</td>
<td>1.15-1.75</td>
<td>0.001</td>
</tr>
</tbody>
</table>

**Conclusion (!!!!):** “Ever being prescribed anti-cholesterol medication, adjusted for having hypercholesterolemia as well as other risk factors, is associated with increased risk of coronary heart disease.”

**OBVIOUSLY NOT**

Example of predisposition

• Korea Ministry of Food and Drug Safety

“The Ministry of Food and Drug Safety Thursday dispelled the misconception of heat-not-burn cigarettes being healthier than ordinary cigarettes” (source: Korea Biomedical Review)
Example of predisposition

“The Ministry of Food and Drug Safety Thursday dispelled the misconception of heat-not-burn cigarettes being healthier than ordinary cigarettes” (source: Korea Biomedical Review)

(Schaller et al., Regul Toxicol Pharmacol 2016)
The end justifies the means?

• We don’t want people to become dependent on nicotine
  ◦ So, let’s create a message that helps our goal

• “No tobacco products are safe”
  ◦ No information on degree of risks
  ◦ “… the right to health information is independently related to the need to promote health literacy. This right should be respected whether or not harm reduction policies are judged advisable” (Kozlowski & Edwards, Tob Control 2005)
  ◦ Criticism that people think e-cigarettes are less harmful than smoking because this predicts future use
    • But this is true. Is it ethical to create misperceptions?

• WHO Ottawa Charter, 1986
  ◦ Empowerment in public health
  ◦ Ensure people’s access to information on public health issues
  ◦ Ensure people’s access to tools (products) that help them promote their health
Precautionary approach

- Past history of tobacco cigarettes is used to assume the effects of harm reduction products
  - Bans, severe restrictions, classify e-cigarette use as smoking, etc.

- Justified or an abuse of precaution?
  - “… precautionary approach, which in many cases could be described as misleading, originating from ideological opposition”
  - “the application of this principle justifies taking precautionary measures before “full scientific certainty” has been achieved, but there must be at least some evidence of risk or harm.” (Farsalinos & Le Houezec, Risk Manag Healthc Policy 2015)
  - The debate is about net harm or benefit, not about the absence of any harm

- Avoiding theoretical harms can cause harm to other population groups
  - Protecting kids vs. harming smokers
Do we know everything in THR science?

- Obviously not

- Products are new - We need decades to fully quantify the epidemiological effects of THR products
  - The same quote can be used for every new medication or any other new consumer product
  - There has never been any product which has been marketed after decades of epidemiological research (because this is impossible to happen)

- How can we deal with this?
Maybe follow other examples?

**ACE-inhibitors:** discovered in 1975, launched in 1981 (captopril)

2018: 10-30% higher risk of lung cancer compared to ARBs

**Editorial:** “Nonetheless, in an individual patient, concerns about the long term risk of lung cancer should be balanced against gains in life expectancy associated with use of ACEIs”
Prioritize research

- Seeking best possible information as soon as possible

- Long term epidemiological studies on young, healthy smokers
  - Time ++++
  - Cost ++++

- Short term follow-up in specific subpopulations
  - Examining subjects with established smoking-related disease
  - Secondary prevention
  - Look beyond disease outcomes (biomarkers of exposure/effect)

- Observational studies
  - Not the best quality evidence, but feasible and realistic
Prioritize research

• Seeking best possible information as soon as possible

• Clarify the chemistry profile of products
  ▫ Rapid
  ▫ Cheap (compared to clinical studies)

• Toxicological modeling
  ▫ Set standardized conditions and exposure levels that could have clinical context
  ▫ Compare with smoking

• Innovation – understand the product dynamics
  ▫ Improve the safety/risk profile of products
  ▫ Enhance the effectiveness in substituting smoking
  ▫ Change our conventional attitude towards research (RCTs, one product for all)
Outcome

- Population effects
  - Identify who is using THR products
  - Examine why they use THR products
  - Measure the impact of THR products on the smoking habit
  - Understand population perceptions and misperceptions
  - Address healthcare professionals misperceptions

- Finding the right balance
  - Measure intended (beneficial) and unintended (adverse) effects
  - Identify where the balance lies (benefit / risk ratio)

- Decisions based on the knowns
  - Not based on what we don’t know and what may theoretically happen, but on what we know and measure
  - Of course maintain a cautious approach and be ready to adjust recommendations
Decisions based on knowns

- Decisions based on the knowns
  - Of course, maintain a cautious approach
  - Focus on current knowledge, keep in mind the uncertainty in making decisions
  - Flexible framework to adjust to new evidence

- Truthful, evidence based information to everyone
  - Informed decisions require proper information
  - Proper information = current knowledge
THANK YOU