How to consider effect sizes from the individual and from the population perspective

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Who is attending?

Poll 1
Individual AND population risk?

Environmental health risks are usually small

- Air pollution: concentration of particles smaller than 2.5 μm (PM$_{2.5}$) related to mortality
- RR for mortality 1.08 per 10 μg/m$^3$ PM$_{2.5}$ in outdoor air.
- Risk of dying increases with 8% per unit of exposure.

Poll 2: What does the audience think?
Risk
(Absolute) Risk

- The likelihood that an adverse event will happen in the future
- Related to time-frame: next year, next ten years
- Expressed as probability varying from 0 to 1 (0% to 100%)
  - 0 means it will not happen
  - 1 means it will happen
- Based on extrapolation from group findings in the past
- Risk is number of events / population at risk
- Risk is group based but applied at individual level
- My risk of dying next year is 2.4 % based on group findings
Relative Risk

Findings in health studies expressed as relative risk (RR)

- RR = Risk in intervention/exposed group divided by risk in control group

Relative risk is the average of a group

Can be easily compared in terms of strength but…

*Impact judgement impossible without knowledge of the baseline rate*

RR = 0.5

- Baseline rate 0.5 / 100 gives Absolute risk reduction 0.25 / 100
- Baseline rate 50 / 100 gives Absolute risk reduction 25 /100
RR and Population attributable fraction

AFp

• proportional reduction in mortality that would occur if exposure to a risk factor were reduced to alternative ideal exposure scenario

• Depends on RR and prevalence of exposure

• Only at population level

• Formula: \[ AFp = \frac{p (RR - 1)}{p (RR - 1) + 1} \]

RR = relative risk  P = proportion population exposed
**Risk difference**

Difference in risk between the intervention and control group

Also called

- Excess risk
- Attributable risk
- Absolute risk reduction

Risk difference is expressed as an absolute risk (probability)
Is there an Individual risk AND a Population ‘risk’?

• No
• All risks are group based and there is only one number
• What is different is the **perspective** from which you look at the numbers
Individual risk different from population ‘risk’?

• Yes

• The perspective that we take leads to a different interpretation of the relevance of a risk or relative risk

• A small risk for one individual is irrelevant from the individual perspective; it can’t be differentiated from background risk

• A small relative risk for many can add up to a substantial number of persons being affected in the population

• Also other arguments differ from individual and population perspective: costs, values, decision making process
Population perspective: Air pollution versus Smoking example
Air pollution and smoking

- RR mortality for persons exposed to PM$_{2.5}$ is 1.08
- RR mortality for persons who smoke is 2.6 (6 times larger)

Poll 3 How large is the global burden of disease form air pollution and from smoking?
Air pollution and smoking

RR mortality for PM$_{2.5}$ is 1.08
RR mortality for smoking is 2.6 (6 times larger)

Global burden of disease

- Outdoor air pollution 4.9 million
- Smoking 8.1 million
# Air pollution and smoking

<table>
<thead>
<tr>
<th></th>
<th>Scenario 1</th>
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<th>Scenario 2</th>
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<tbody>
<tr>
<td></td>
<td>Smoking</td>
<td>PM 2.5</td>
<td>Smoking</td>
<td>PM 2.5</td>
</tr>
<tr>
<td>Prevalence of exposure (proportion)</td>
<td>0.137</td>
<td>0.85</td>
<td>0.2</td>
<td>0.5</td>
</tr>
<tr>
<td>RR of effects of exposure</td>
<td>2.6</td>
<td>1.3</td>
<td>2.6</td>
<td>1.3</td>
</tr>
<tr>
<td>Population Attributable Fraction (AFp)</td>
<td>0.18</td>
<td>0.18</td>
<td>0.24</td>
<td>0.11</td>
</tr>
<tr>
<td>Yearly Mortality Rate per 1000</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Death pop 30 million</td>
<td>240000</td>
<td>240000</td>
<td>240000</td>
<td>240000</td>
</tr>
<tr>
<td>Death prevented</td>
<td>43,150</td>
<td>43,400</td>
<td>58,182</td>
<td>27,584</td>
</tr>
</tbody>
</table>
Warning: *Population* different meanings

Population can refer to

• Population ‘*risk*’
  – as the number of persons affected by exposure or intervention in a group
  – as in *Absolute Risk Reduction* or *Risk Difference*

• Better replaced by *Population perspective*
Warning: Population different meanings

1. Population *health*
   • focus on trying to understand the determinants of health of populations

2. Population *intervention at group level*
   • as in an intervention that is applied to a whole group of individuals as in environmental changes, legislation

3. Population *intervention for all individuals*
   • as in a health care intervention that is available to all individuals of a group such as screening
Warning: Population different meanings

4. Population *intervention with added value at the group level*
   - as in an intervention that is more effective if all individuals in a group get the intervention at the same time due to a group effect such as in vaccination or HIV testing

5. Population *intervention of high risk individuals vs decrease of population mean*
   - as in treating the whole population versus high risk individuals only (Rose’s prevention paradox)
Individual Perspective
Population Perspective
Therapy: Individual perspective

A patient with health complaints asks for help

- Judgement of Mean Difference: *Minimally Important Difference* (MID)
  - the smallest difference in score in the outcome of interest that informed patients perceive as important, either beneficial or harmful, and which would lead to consider a change in the management

- Example Back Pain: Pain killer effects
  - MID VAS Pain at least 15 score points (range 0-100)

- Problem with dichotomous outcomes / mortality (risk ladder?)
Prevention: Individual perspective

A healthy person with no complaints undergoes an intervention

- MID does not help because there are no complaints
- Judgement: balancing future benefits against current harms/costs
- At which risk levels will persons take preventive medication eg statins?
  - 30% absolute risk reduction over 5 years, 18 mo life exp increase (Trewby 2002)
  - 42 months CVD-free life gain for life long statin therapy (Jaspers 2018)
  - These expectations exceed clinical effects for most risk groups
Prevention: Population perspective

*How many lives will be saved if we eliminate this exposure?*

<table>
<thead>
<tr>
<th></th>
<th>Air Pollution</th>
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<tbody>
<tr>
<td>Prevalence of exposure (%)</td>
<td>0.85</td>
</tr>
<tr>
<td>RR of effects of exposure</td>
<td>1.30</td>
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<tr>
<td>Population Attributable Fraction (AFp)</td>
<td>0.18</td>
</tr>
<tr>
<td>Baseline Mortality Rate per 1000</td>
<td>8.00</td>
</tr>
<tr>
<td>Mortality Population 30 million</td>
<td>240 000</td>
</tr>
<tr>
<td>Death prevented per 30 million persons</td>
<td>-43 400</td>
</tr>
</tbody>
</table>
Therapy: Population perspective:

*How many lives do we save if we implement this intervention for all?*

- There is no MID
- Judgement: The population impact number (Heller 2000)
  - “the number of those in the whole population among whom one event will be prevented by the intervention”
- Example Aspirin for stroke

<table>
<thead>
<tr>
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<th>Aspirin</th>
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<tbody>
<tr>
<td>Absolute risk reduction*</td>
<td>0.031</td>
</tr>
<tr>
<td>Proportion of stroke population treated†</td>
<td>0.70</td>
</tr>
<tr>
<td>Number needed to treat</td>
<td>33</td>
</tr>
<tr>
<td>Disease impact number</td>
<td>46</td>
</tr>
<tr>
<td>Population impact number ‡</td>
<td>35 450</td>
</tr>
</tbody>
</table>

*From a systematic review.† Comprises those for whom treatment can be provided base vary according to economic and geographical setting.‡ Annual rate of first cerebral infarction taken as 1.3/1000 (0
Cochrane Reviews
Reducing salt in diet two reviews

Adler et al 2014: Salt reduction for prevention of CVD, RCTs
- CVD Mortality (No certainty assessed)
- Normotensive: RR 0.67 (0.45 to 1.01), 3 RCTs n=2656
- Hypertensives: RR 0.76 (0.57 to 1.01), 5 RCTs n=3397

Conclusion: ‘insufficient power to confirm clinically important effects on cardiovascular mortality’

He et al 2013: Effect of salt reduction on blood pressure
- SBP MD -4.18 (-5.18 to -3.18), 33 RCTs n=3206 (High certainty)
- DBP MD -2.06 (-2.67 to -1.45), 34 RCTs n=3220 (High certainty)

Conclusion: ’causes significant and, from population viewpoint, important falls in blood pressure, leading to reduction in CVD mortality’
Does salt reduce CVD mortality?

Poll 4: Does salt reduction in diet reduce CVD mortality?
Conclusions He et al

- A longer-term modest reduction in salt intake of 4.4 g/d on average, causes significant and, from a population viewpoint, important falls in BP in individuals with both raised and normal BP.

- These results provide further strong support for a reduction in population salt intake which will result in a lower population BP and, thereby, a reduction in strokes, heart attacks and heart failure.

- A modest reduction in salt intake lowers BP and, therefore, would reduce cardiovascular risk. It was estimated that a reduction of 6 g/d in salt intake would reduce stroke by 24% and coronary heart disease by 18% (He 2003). This would prevent ≈35,000 stroke and coronary heart disease deaths a year in the UK and ≈2.5 million deaths worldwide.
**My conclusion He et al**

*Convert reduction of SBP to reduction in CVD mortality*

- Absolute Risk Reduction -4 mm SBP $\approx$ CVD mortality rate - 0.27/1000 (13% decrease) (Lewington 2002)

- Population 30 million: 7 966 death prevented

*Individual perspective:*

It will be difficult to motivate individuals to reduce salt intake based on this reduction in CVD mortality.

*Population perspective:*

The benefits should be balanced against the costs. Salt reduction is probably best achieved through a population level intervention that does not require individual effort. These interventions should be evaluated with an ITS design. (McLaren 2016)
Conclusion Adler et al

- There is *insufficient power to confirm clinically important effects* of dietary advice and salt substitution *on cardiovascular mortality* in normotensive or hypertensive populations.

- The intervention generally required considerable efforts to implement and *would not be expected to have an effect on the burden of cardiovascular disease commensurate with their costs*.

- Trials *need to assess population level (e.g. workplace, institutional, regulatory) interventions that might be more likely to lead to sustained reductions* in salt intake and which would provide evidence relevant to current public health guidelines.
My conclusion Adler et al

We don’t know if salt reduces CVD mortality due to imprecision of the direct evidence. Probably low to very low quality evidence.

A large trial would be needed to assess the relevant effects on mortality (n=25 000). If not possible modelling is the alternative.

From individual perspective:
• results trivial; 0.0026 % absolute risk reduction in mortality

From population perspective:
• Number saved RR = 0.67 baseline 0.0026 = 53 600 population 30 million
• Results compatible with substantial? number of death prevented
Conclusion

• All reviews should formulate the implications for practice of the effects of the intervention both from the individual and the population perspective
  – Provide assumptions and calculations for the numbers affected in the population

• All reviews that use *surrogate outcomes* should provide an estimate of the effect on the *clinically relevant outcomes* based on modelling
  – Provide assumptions and calculations

• More research needed on relevance of effects of both preventive interventions and therapy from both the individual and the population perspective.