Systematic Reviews Should Consider Effects From Both the Population and the Individual Perspective

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Risks of adverse health effects because of exposure to environmental factors or diet vary widely. People who smoke one to 10 cigarettes a day have a 2.6-fold higher risk of dying early and an 18.4-fold higher risk of lung cancer than nonsmokers.[1] In contrast, the risk of dying because of air pollution is only 1.08 times higher for a person living in a European city than for a person living in a rural area with an average annual 10 micrograms per cubic meter lower exposure to particulate matter (particulate matter with a diameter of ≤2.5 μm; $PM_{2.5}$).[2]

It may seem that the magnitude or relevance of the relative risk of air pollution is trivial in comparison with the relative risk of smoking. Some authors have even proposed that it would be better not to inform the public about very small environmental relative risks.[3] Nevertheless, interventions to reduce the effects of air pollution are considered at least as important as interventions to reduce smoking because, on the basis of the same relative risks, the number of people at the global level dying each year because of air pollution is estimated at 4.9 million and the number dying from smoking is estimated at 8.1 million.[4] Therefore, authors have argued that it is important to consider the effects of health determinants and health outcomes from a population perspective.[5]

Authors of systematic reviews summarize and synthesize the effects of exposures or interventions. Preferably, this will include judgments of the importance of these effects for an individual and a population. Systematic review authors typically present their results as the relative risk for the intervention or exposed group versus the control or unexposed group. The relative risk makes the effects of interventions easily comparable, but the impact is impossible to judge without knowledge of the baseline rate. A relative risk of 0.5 will result in a change in the risk of death of 0.25% if the baseline rate of death is 0.5%, but the same relative risk will result in a change of 25% if the baseline rate is 50%. That is why risk communication studies have revealed that effects of interventions are best understood as changes in absolute risks. To be able to calculate an absolute risk or risk difference, we need to know the baseline rate of the disease or event that is being measured.[6,7]

To explore the importance of a preventive effect from the population perspective, Rose put forward the "prevention paradox,"[8] according to which a small mean reduction in exposure for the entire population is more beneficial than a very large exposure reduction for only those who are at high risk. This paradox is especially relevant for decisions in which individual or population exposure reduction options exist, such as in lowering cholesterol or alcohol consumption.[9,10] However, it remains unclear how the relevance of a small reduction in the population mean risk should be judged by systematic reviewers or decision-makers.

Here we use Cochrane reviews to explore how presentation of effect sizes from the individual or population perspective can influence judgments about the importance of these effects and prevention strategies. We provide guidance for systematic review authors on how to consider the individual and the population perspective.

Judging the importance of effects can be confusing because people use different terms for the population perspective. Some use population risk, but this is inaccurate as there is only one risk that applies to both the individual and the group. Therefore, we use the term perspective because it is the perspective that changes the judgment. Here we use this as a public health perspective. We define the population perspective as the judgment of the impact of a risk or intervention for a group of individuals, similar to the concept of population health.[5] Usually this is expressed as the number of individuals affected by the risk or the intervention. From the population perspective, it is also possible to observe differences in the distribution of the risks or effects in the group, which is important for judging equity.

WAYS OF ACCOUNTING FOR THE INDIVIDUAL PERSPECTIVE

The individual perspective is typically used when considering the effects of a medical treatment. When the beneficial effects of an intervention outweigh the harmful effects, treatment effects will be judged as meaningful if they exceed a minimally important difference. The minimally important difference is defined as the smallest change in the outcome measure that is experienced as an improvement by individuals.[11] This typically involves the use of patient-reported outcomes that measure functioning or symptom burden or severity.[12] For other outcome measurements such as survival or mortality, it is unclear how people judge what degree of risk is meaningful; this may depend on individual preferences. For example, chemotherapy in early-stage breast cancer is associated with only a small increase in 5-year survival, and it is unclear whether such an increase would be judged as meaningful by patients.

The number needed to treat (NNT) metric has been developed to facilitate judgments of the effects of treatment, expressed as relative risks from the individual perspective. This measure is not better understood by patients than an absolute risk reduction. It also lacks a cutoff such as the minimally important difference to judge its relevance, and therefore it is not helpful in making a judgment about the importance or magnitude of an effect size from the individual perspective.[6,13] Presenting risks on a risk ladder that arranges several comparable risks in order of magnitude could be a helpful aid in communicating mortality risks.[13]

Prevention can be defined as an intervention to stop healthy people from experiencing future adverse health effects. From the individual perspective, judging the effects of prevention is more complicated. There is no minimally important difference that can help in this case because the intervention is applied to healthy people without symptoms or complaints. An individual will balance the costs of an intervention and the effort needed to implement it versus the intervention's future benefits.

Even though good systematic reviews are missing, studies consistently report that people are willing to put effort into individual preventive action only if they expect considerable absolute risk reductions. For example, it has been shown that people are willing to take preventive cardiovascular disease medication only if it results in an absolute risk reduction of at least 30%[14,15]; such a desired risk reduction is much larger than the clinical effects of the medication. These findings are consistent with the theory of discounting, in which future costs or health risks are valued less than those faced today.[16]

WAYS OF ACCOUNTING FOR THE POPULATION PERSPECTIVE

From the population perspective, the difference between therapy and prevention seems less important. To make a judgment about treatment from the population perspective, the risk difference between the intervention and control groups should be used. This risk difference can then be expressed as the number of events that can be prevented for a given population, such as the number of people dying from a myocardial infarction or tuberculosis. The population can be the population of the country or jurisdiction in which the study has been performed. It can also be expressed for an average country size of 30 million, which will facilitate comparisons between countries.

Several attempts have been made to better express the impact of treatment at the population level. Heller and Dobson proposed that, by taking into account the incidence of a disease and the implementation of an intervention, one can calculate an NNT for a specific disease at the population level.[17] The population NNT is the number of individuals in the entire population for whom the intervention must be available to prevent one event. According to Smeeth and Ebrahim, it would be better to take decreases in effectiveness into account when health care trials are implemented. The community effectiveness NNT would thus be substantially larger than an NNT derived from a trial.[18]

With respect to prevention of health effects from environmental or lifestyle risk factors, the impact at the population level also depends on the prevalence of the exposure, in addition to the baseline rate and the relative risk.[19] The prevalence of the exposure and the relative risk of the effects of exposure are used to calculate the population-attributable fraction (AFp).[20] The assumption that all exposures can be avoided leads to a relative risk of intervention equal to 1 − AFp. This calculation is similar to those used for the global burden of disease due to risk factors.[4] Table 1 shows, as an instructional example, that reducing air pollution can have a higher impact on mortality at the population level than reducing smoking. It is important to note that this is a simplification that does not consider a time horizon and uncertainty. It is also assumed that all smokers can be turned into nonsmokers and that all air pollution can be decreased by three units of exposure, which is not the same as a well-defined intervention.[21]

Judged from the individual perspective, environmental risks such as those resulting from air pollution will hardly be relevant. Reducing $PM_{2.5}$ with three units of exposure (30 μg/m^3) could potentially reduce mortality by 30%. This would reduce the average absolute risk of mortality from 8.0 per 1000 to 6.6 per 1000. Relative to the individual expectations of the preventive interventions described earlier, this absolute risk reduction of less than 1.4 per 1000 will be only minimally relevant from the individual perspective.

Air pollution and mortality is an exceptional case because the baseline rate is high, and all individuals are exposed to polluted air. In the case of other risk factors, the resulting number of preventable events could be much lower. It is therefore important to make assumptions explicit and to model consequences, as in the earlier-described example.

SALT REDUCTION AND CARDIOVASCULAR DEATHS

Salt reduction in preventing cardiovascular deaths provides another good example to judge the relevance of results from the individual perspective and from the population perspective. From the individual perspective, there should be a substantial reduction in absolute mortality risk that will be balanced against the effort needed to decrease individual salt consumption. From the population perspective, a reduction in salt intake, albeit a small reduction, should lead to the prevention of a considerable number of deaths.

The Cochrane Library includes three reviews of the preventive effects of salt reduction.[22–24] In one review, Adler et al. synthesized randomized controlled trials that examined whether low-salt diets lead to reductions in cardiovascular events and mortality.[22] They found relative risks of cardiovascular disease mortality of 0.67 (95% confidence interval [CI] = 0.40, 1.12) among normotensive individuals and 1.00 (95% CI = 0.86, 1.15) among hypertensive individuals. The authors concluded that "there is insufficient power to confirm clinically important effects of dietary advice and salt substitution on cardiovascular mortality. They [the interventions] 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."[22] However, they did not provide a definition of "clinically important effects" and whether they considered these effects from the individual or the population perspective.

In another Cochrane review, He et al. synthesized randomized controlled trials of the effects of low-salt diets on blood pressure.[23] Their review showed that low-salt diets led to mean difference reductions of −4.18 millimeters mercury (95% CI = −5.18, −3.18) in systolic blood pressure and −2.06 millimeters mercury (95% CI = −2.67, −1.45) in diastolic blood pressure. The authors concluded that "there is high certainty evidence that a modest reduction in salt intake causes

TABLE 1— Hypothetical Comparison of the Effects of Reducing Smoking to Zero and Decreasing Air Pollution by Three Levels of Exposure From the Population Perspective

	Smoking	Air Pollution
Prevalence of exposure	0.137	0.85
RR of effects of exposure[a]	2.6	1.3
AFp[b]	0.18	0.18
Mortality base rate per 1000	8	8
RR of effects of intervention (1 − AFp)	0.82	0.82
Intervention mortality rate per 1000	6.6	6.6
Risk difference per 1000[c]	−1.44	−1.45
Number needed to treat	695	691
Deaths prevented per 30 million population	43 150	43 400

Note. AFp = population-attributable fraction; RR = relative risk.

[a]Chen and Hoek[2] reported a pooled relative risk for mortality of 1.08 per 10 μg/m^3. Three levels of exposure lead to a risk of 1.3 (1.08^3).
[b]AFp = p(RR − 1)/p(rr − 1) + 1 (Rothman et al.[20]).
[c]RD = BR × (RR − 1) (Newcombe and Bender[19]).

significant and, from a population viewpoint, important falls in BP [blood pressure]." Although He et al. were clear about the perspective, they did not define "important falls in BP."

One way to judge the relevance of a blood pressure reduction from the population perspective is to model what the reduction would mean for mortality.[25] We used the meta-analysis of cohort studies on blood pressure and mortality by Lewington et al. to make these calculations (Table 2).[26] In this simplified model, we assumed that effects on stroke, ischemic heart disease, and other vascular disorders would be independent and could be averaged over all age categories. We calculated that this change in blood pressure would reduce the mortality risk for an average person from 0.65 per 1000 to 0.57 per 1000, which would probably be judged as trivial from the individual perspective. At the population level, it would lead to a number of preventable deaths that seems modest relative to the effects of reducing air pollution. A decision-maker would balance the number of preventable deaths against other factors important in decision-making such as costs and other burdens associated with the intervention.

The authors make seemingly contradictory conclusions in these reviews. When transformed to the same metric and judged from the same perspective, the review by He at al. yields a relative risk for mortality of approximately 0.86 (Table 2). This is well within the confidence interval of the review by Adler et al. It is difficult to judge whether the almost 8000 deaths prevented outweigh the costs of an intervention aimed at individual salt reduction. Adler et al. are probably correct in pointing out that implementing a reduced-salt diet might be too demanding for an individual given that only 10% of salt consumption is the result of individually added salt. However, salt reduction implemented at the population level (e.g., by reducing salt in food products) could be an alternative that does not require individual effort.

Population-level interventions[27] for dietary salt reduction were studied in another Cochrane review.[24] The authors evaluated whether interventions such as food product reformulation (i.e., food companies putting less salt in food products) and public information and education campaigns, among others, were effective in reducing salt intake. They included 15 studies, 10 of which provided quantitative data. The authors concluded that population-level interventions can influence dietary salt consumption but that there are large variations in effects, probably related to context and intervention components. They called for better evaluation studies.

From these reviews, we can conclude that it is highly unlikely that reduction of salt implemented either at the individual level, as a reduced-salt diet, or at the population level, as food product reformulation, will lead to effects on cardiovascular disease events or mortality that are relevant from the individual perspective. However, from the population perspective and based on modeling, salt reduction may lead to an important number of preventable deaths. Stating the perspective clearly and modeling the results from the population perspective makes

TABLE 2— Hypothetical Effects of Salt Reduction on Blood Pressure and Cardiovascular Mortality From the Population Perspective

	Cause-Specific Mortality			
	Stroke	Ischemic Heart Disease	Other Vascular	Total
Prevalence of "exposure" to BP[a]	1	1	1	
Reduction of systolic BP (mm Hg) with low-salt diet	4.2	4.2	4.2	
RR of mortality that relates to 4.2-mm BP reduction[b]	0.84	0.88	0.86	
Mortality base rate per 1000	0.47	1.00	0.50	
Intervention mortality rate per 1000	0.39	0.88	0.43	
Risk difference per 1000[c]	−0.08	−0.12	−0.07	
Number needed to treat	13 084	8239	14 764	
Deaths prevented per 30 million population	2293	3641	2032	7966

Note. BP = blood pressure; RR = relative risk.

[a]Prevalence of blood pressure is set at 1 because everyone is exposed.
[b]Conversion based on hazard ratios per 20-mm decrease in systolic BP provided by Lewington et al.[26]
[c]RD = BR × (RR-1) (Newcombe and Bender[19])

seemingly contradictory results compatible. These reviews also highlight the need for evidence from trials of individual and population-based interventions, as well as observational studies, to evaluate the importance of population-based public health interventions.

CONCLUSIONS

Here we have presented options for systematic reviewers to present risks from the individual and the population perspective. The individual perspective on the effects of therapy is best expressed by comparison with the minimally important difference or absolute risks ranked on a risk ladder. For preventive interventions, the individual perspective is best provided by the absolute risk decrease that considers the baseline risk. The literature suggests that an absolute risk decrease of 300 per 1000 can be used as a rule of thumb for relevance to individuals. The population perspective is best provided by presenting the NNT to prevent one event or the number of events or deaths at a concrete population level (e.g., an average country size of 30 million inhabitants).

The population perspective is dominant for questions addressing public health topics. When making judgments about the relevance of an effect size, we recommend that systematic reviewers clearly state and define whether they are taking an individual or population perspective. Information from different perspectives will help policymakers come to transparent and well-founded decisions. Policymakers must also weigh the trade-offs of reducing risks for a population even when individuals may see no benefit from a particular intervention. Both perspectives should be considered to recognize effects that are important from the population perspective. AJPH

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CONFLICTS OF INTEREST

None of the authors have conflicts of interest to declare.

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