conclusions, as the association between E and D could be discovered in all subgroups selected for the study.

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Is representativeness the right question?

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We agree completely that representative studies are immensely valuable for describing disease patterns, quantifying the burden of disease[1] and generating risk stratification models.[2] Given representativeness is time- and place-specific,[3] these all need regular updates and more representative studies. For example, the SCORE (Systematic COronary Risk Evaluation) system for predicting fatal cardiovascular disease (CVD) uses the same risk factors in different models for high- and low-CVD-risk European countries,[4] but over time countries may, also, be promoted from high to low risk.[5] Clearly, such risk prediction models are not scientific models that describe nature consistently across space and time,[6] but they are immensely useful for service planning, targeting treatment and saving lives. Conversely, experimental studies, such as animal models and randomized controlled trials (RCTs), do not require representativeness to test scientific models.[6]

On the other hand, whether observational epidemiological studies, representative or not, are useful for generating hypotheses or testing causal factors in scientific models is less clear. First, these represent the triumph of hope over experience.[7] Second, as was pointed out over 20 years ago, nearly all possible hypotheses have already been generated.[8] Third, some potentially relevant hypotheses may not be readily observed for conceptual or practical reasons. The current paradigm may exclude some hypotheses as impossible, making them imperceptible. Apart from well-known biases inherent in observational studies, causal factors may be invariant in commonly studied populations, expensive or difficult to measure, affected by preclinical disease or hidden within the (mis)classification of diseases by symptom rather than cause. Fourth, as a discipline we have not generally thought through the hierarchy of studies to refute a hypothesis. Our current methods, using the Bradford-Hill viewpoints as a touchstone, are much more focused on corroborating hypotheses, with an RCT as the pinnacle of corroboration. However, even something as simple as 'field' epidemiology may refute hypotheses. For example, the existence of populations with low birthweight and low rates of heart disease casts doubt on a major role of birthweight in heart disease.[9]

Given these issues if we want to make progress in identifying causal processes in population health, assuming it is possible,[10] rather than focusing on representativeness in studies used to generate or test (corroborate) hypotheses, it might be more useful to look for better ways to generate and screen plausible hypotheses, before we test them in suitable studies.[11] Other methods of generating hypotheses about the drivers of population health are not obvious, but include using general mechanistic principles, starting with effective treatments and taking advantage of mechanistic insights from genetics or RCTs which include potential mediators. Not only do we need to move on from the debate about representativeness, we need to move onto some different questions.

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Representativeness

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We were recently invited, along with several other authors, to comment on the paper by Rothman *et al.*[1] on representativeness.[2] The journal editors also commented on Rothman's paper[3] and took the opportunity to comment on our paper[2] as well as two recent papers of ours published in another journal.[4,5] We don't wish to revive or unnecessarily prolong this debate (the various authors are largely in agreement in any case), but we would like to reply in order to correct some misrepresentations of our work. We can identify many, and it is not possible to respond to all of them in a brief letter.

Ebrahim and Davey Smith claim we 'suggest that non-representative populations produce only weak bias in exposure-disease associations'. In fact, we argued that 'each population, including a selected study population, has its own confounding pattern', and that 'there is no reason to believe that control of confounding can be more easily achieved in a population-based cohort than in a restricted cohort'. Either situation can be associated with bias, and there is no a priori reason to believe that one is always or usually more biased than the other (e.g. in a study of smoking and lung cancer, a restricted population such as British doctors may be less confounded than a general population sample).

In our two recent papers we explored the effects of selection through a 'simulation study'[4] and an 'empirical study' of an internet-based birth cohort.[5] In the simulation study, we considered a simplified scenario including an exposure E, an outcome D and a determinant R of both the selection S and the outcome. We simulated scenarios in which selection introduces bias and concluded that the bias is very small (a true relative risk for the exposure-outcome association of 1.00 becomes 1.02) in situations in which all relative risks involved are 2.0 or 0.5, and modest (a true relative risk of 1.00 becomes 1.16) when all relative risks are 4.0 or 0.25. We argued that 'it is unlikely that multiple and independent important disease risk factors would affect the sample selection' (this sentence quoted by Ebrahim and Davey Smith) and that 'it is indeed reasonable to consider R as a vector resulting from the combination of a set of correlated risk factors, all moderately associated with S' (this part not quoted by Ebrahim and Davey Smith who instead suggested that we missed the point that multiple risk factors may play a role). It is important to emphasize the term 'independent' in the above quote: risk factors tend to cluster together, so selection processes which are biased with respect to one risk factor may be biased with respect to others in the same cluster; but, for precisely this reason, the total bias from the cluster of associated risk factors is usually not much greater than the bias from one factor alone—in either case, our estimates apply for the range of relative risks that we considered.