Reviewer's report

Title: Estimation of the burden of cardiovascular disease attributable to modifiable risk factors and cost-effectiveness analysis of preventative interventions to reduce this burden in Argentina

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Reviewer: Dariush Mozaffarian

Reviewer's report:

The authors present a very important, comprehensive, and carefully done analysis of CVD burden due to modifiable risk factors in Argentina. Several major strengths are evident, in particular attention to several key methodologic issues in comparable risk estimation, use of joint exposure distributions and joint causal effects when possible, new cost-effectiveness analyses of specific interventions, and important sensitivity analyses. Several key issues remain to be addressed to improve this paper further.

Major Compulsory Revisions:

1. In considering approaches to improving population health, there has long been substantial bias toward emphasis on drug-based treatments, with little inclusion or evaluation of other population-based interventions. This analysis takes a step toward improving this historical bias by including physical inactivity, fruits and vegetables, and salt, but ignores several other key population risk factors, including in particular trans fat, low marine omega-3 (seafood), and low polyunsaturated fat (exchanged for saturated fat). A paper last year by Danaei et al. provides a framework for assessing these three factors, both in terms of causal RR’s and optimal distributions, and each of these 3 factors must be included in this analysis, both for estimating attributable burdens of disease and for evaluating specific interventions – the latter will be particularly novel and important. Surely data on seafood/omega-3 and total polyunsaturated fat intake are available. Individual-level data on trans fat may not be, but population-level estimates can be imputed from disappearance data on partially hydrogenated oils or consumption levels in other Latin American countries.

2. Page 5, Data Sources: Data on low marine omega-3 (seafood), low polyunsaturated fat (exchanged for saturated fat), and trans fat should be added.

3. Page 6, Estimating Mortality and Disability: Most risk factor exposures cannot be reduced to zero, but rather to optimal minimum risk distributions. This should be clarified, and the optimal minimum risk distributions used for each risk factor should be specified.

4. Table 1: What are the comparison categories for the RR’s for fruit and vegetable intake? The listed RR’s are not consistent with the published literature. For example, per 106g serving, the RR for fruits is 0.93 for CHD, 0.89 for stroke,
and the RR for vegetables is 0.89 for CHD, and 0.97 for stroke. So, the RR’s in the Table seem to correspond to the RR’s for a single serving change, not for adequate consumption (4.6 servings/d of fruits, 4.6 servings/d of vegetables).

5. Table 2: Based on Gaziano et al., the estimated CHD RR for a statin would be 0.64 (not 0.89 listed in the table); I am assuming the authors used 0.64. However, the more important point is that the RR reductions for both statin and polypill treatments are overestimates, which are based on prior published (but incorrect) literature that falsely estimates the effects of these drugs by evaluating their short-term effects on risk markers, rather than their true effects on disease outcomes in RCTs. (For BP this is less of a concern, as the BP-lowering effect appears to predict the disease reduction very closely.) Several meta-analyses are available on the effects of statin therapy and aspirin on actual disease outcomes in both primary and secondary prevention trials. Clearly this evidence should be used, rather than the extrapolations based on changes in risk markers. For example, combining primary and secondary populations, the actual RR’s for statin therapy are 0.77 for CHD and 0.83 for stroke (Baigent, Lancet 2005, Figure 2). In primary prevention, the actual RR for statin therapy is 0.72 for CHD (Baigent, Lancet 2005, Figure 5), and can be imputed to be ~0.85 for stroke (Baigent, Lancet 2005). The polypill estimate should then be derived by combining these estimates. Thus, for primary prevention the CHD RR should be 0.66 x 0.72 = 0.48, and the stroke RR should be 0.51 x 0.85 = 0.43. Aspirin reduces CHD risk by a RR of 0.88, with no effect on stroke, but is of unclear overall effectiveness for primary prevention due to excess bleeding risk (Lancet 2009;373:1849-60) and should therefore be excluded from the polypill.

6. Page 8, Interventions: Other population-wide interventions that must be evaluated include (a) eliminating industrial trans fat through legislation, and (b) adding marine omega-3 (EPA+DHA) through dietary fortification.

7. Polypill: The 50% disease detection and 50% compliance estimates for drug treatment of blood pressure and cholesterol are appropriate estimates of plausible maximum effectiveness. However, the 70% detection and 60% long-term compliance for the polypill strategy are dramatic (!) overestimates that cannot be justified by any empiric literature. If disease detection for a single risk factor is <=50% (as has been shown in many prior studies), then disease detection for multiple risk factors (as would be needed to identify those with estimated risk>20%) would be even lower, plausibly in the range of 25-35%. Similarly, long-term compliance with a polypill would be lower than compliance with a single pill, again plausibly in the range of 25-35%. 100% provider compliance is also unrealistic. Other polypill treatment cutpoints should be evaluated, including (a) those with estimated risk>10% and (b) everyone over age 55 as originally proposed by Wald and Law. Costs of side effects should also be included, that should be estimated to be at least 2-3 fold higher than what was seen in RCTs given that RCTs had strict inclusion/exclusion criteria to minimize side effects.

8. Page 7: How was the baseline absolute risk for no risk factors specifically estimated?
Minor Essential Revisions:

1. The introduction is too long, and some of this detail should be moved to the Discussion (for example, the entire top paragraph on page 4 can be moved). The primacy of lifestyle risk factors for CVD are also brought in too late. On page 3, the authors state that the “main risk factors for disease are hypertension, elevated BMI, and smoking” – this should immediately follow with the statement that, of course, elevated BMI is due to excess calories and insufficient activity, and that a large proportion of hypertension is due to these same lifestyle risks plus also poor diet quality.

2. Methods, page 5, first paragraph: Clinical efficacy of interventions cannot be (and was not herein) evaluated only using RCTs – this should be clarified in some detail here. (Such an approach would favor bias toward drug-based treatments that can be tested in such trials, vs. population-based interventions such as salt reduction, omega-3 fortification, trans fat elimination, whose effects cannot plausibly be tested in formal RCTs. Effects of these latter interventions can be directly estimated from causal RR’s from long-term observational studies, extended to quantify the effects of selected direct policy interventions that would assure compliance. Of note, the authors are also not assessing clinical efficacy of their drug interventions from RCTs. Currently, they are assessing effects of individual drugs on risk factors, and then extrapolating these effects to clinical efficacy, i.e., to effects on disease outcomes. This clearly should not be done in the cases for which there is direct evidence from RCTs of the effects of these drugs on disease outcomes in primary prevention populations. Similarly, the authors have no data for clinical efficacy of the polypill, that has not been evaluated for effects on disease outcomes in any RCTs.)

Level of interest: An article of outstanding merit and interest in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

'I declare that I have no competing interests'