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

Version: 2 Date: 2 August 2010

Reviewer: Dariush Mozaffarian

Reviewer's report:

This important and generally well-written paper is improved, but several of the major compulsory revisions have not been addressed or, if they could not be addressed due to methodologic limitations, were not adequately described in the manuscript.

Major Compulsory Revisions:

1. Page 5-6, Selection of Risk Factors: In their response letter, the authors describe in detail why they excluded other dietary factors that would meet their causal criteria, including consumption of (1) trans fat, (2) low marine omega-3 (seafood), and (3) low polyunsaturated fat (exchanged for saturated fat). The exclusions of these specific individual dietary factors that would meet criteria for causal effects, and the reasons for their exclusion (including the authors attempts to obtain data on these risk factors), should be specified in the manuscript (i.e., in Selection of Risk Factors). It would also be helpful to note in the Discussion the importance of obtaining future national-level data on these and other dietary risk factors for future work.

2. Page 7, Estimating Mortality and Disability: The authors have not corrected the prior incomplete description that they computed the disease reduction if risk factors “had been reduced to zero.” The correct and more clear statement would be if risk factors were reduced to the optimal minimum risk distribution. If the authors truly wish to define risk factors dichotomously (an artificial definition that ignores the continuous nature of nearly every risk factor that they examined), then this definition, and its limitations, should be specified here. Also, as previously indicated, the optimal minimum risk distributions used for each risk factor should be specified in a Table, e.g., in a new column in Table 1 or in a new Table. For example, what was the optimal minimum risk distribution used for BP? It cannot be “absence of hypertension”- what does this mean: did they assume everyone in the population had a SBP of 129/79 exactly? Similarly, what is the optimal minimum risk distribution used used for fruits and vegetables? For glycemia? etc.

3. Table 6: The calculation of proportional burden requires data on (a) the current distribution of exposure and (b) the alternative optimal minimum risk distribution. The proportional burden calculation for F&V should be done similarly to that for
4. The authors do not provide compelling arguments for not revising their dramatically optimistic rates of 70% detection, 60% long-term patient compliance, and 100% provider compliance for the polypill strategy. As previously noted, to identify individuals with >20% risk would require population screening of a much larger number of individuals (presumably nearly the entire adult population to be complete) for all of the risk factors needed to make this calculation, which would include smoking, BP, lipids, and glucose levels. As previously noted, if population screening for a single risk factor is <=50% (as has been shown in many prior studies), then population screening for multiple risk factors (which would need to be measured to make the calculation of >20% risk) would be much lower. Similarly, compliance with a polypill would be less than compliance with any monotherapy. There is no empiric evidence that, among populations without clinical CHD, those with higher calculated risk are more compliant than those with lower calculated risk; indeed, there is reasonable evidence that such calculations do not improve patient compliance to any large extent. The polypill calculations must be revised to reflect these realities, with more reasonable estimated rates of detection (plausibly in the range of 25-35%), long-term compliance (plausibly in the range of 25-35%), and provider compliance (plausibly up to 50-70%). This may not change the ICER, but the DALYS saved and percent of DALY saved (key results in Table 7) would be substantially more accurate. The authors can then note in the Methods text that far more optimistic estimates of detection, long-term patient compliance, and provider compliance (such as they originally used) do not appreciably alter the ICER.

5. The Discussion should note that other polypill treatment cutpoints were not evaluated, including (a) those with estimated risk>10% and (b) everyone over age 55 as originally proposed by Wald and Law, and that ICERs would likely be far higher for these populations.

6. I previously noted that costs of side effects of the polypill should be included, particularly because such side effects would be estimated to be at least 2-3 fold more common than what has been seen in RCTs, given that RCTs had strict inclusion/exclusion criteria to minimize side effects. In their response, the authors state that they did not include such costs for “parsimony” (perhaps they mean “simplicity”?), and that they have included these issues in the Discussion. I did not find any substantive discussion of these issues in the manuscript. These limitations – (1) the lack of inclusion of side effects of the polypill, (2) the likelihood that such side effects would be much more common in a population-wide approach targeting those with risk >20% compared to what has been seen in RCTs, and (3) that ignoring these side effects in their analysis would overestimate the ICER of the polypill strategy, perhaps substantially –
should be added to the Discussion (i.e., page 18).

**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’