Author's response to reviews

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

Authors:

Adolfo Rubinstein (arubinstein@iecs.org.ar)
Lisandro Colantonio (lcolantonio@iecs.org.ar)
Ariel Bardach (abardach@iecs.org.ar)
Joaquín Caporale (jcaporale@iecs.org.ar)
Sebastian García Martí (garciamarti@iecs.org.ar)
Karin Kopitowski (karin.kopitowski@hospitalitaliano.org.ar)
Andrea Alcaraz (andrea.alcaraz@gmail.com)
Luz Gibbons (luzgibbons@gmail.com)
Federico Augustovski (faugustovski@iecs.org.ar)
Andrés Pichòn Rivière (apichon@iecs.org.ar)

Version: 3 Date: 19 September 2010

Author's response to reviews: see over
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.

The exclusions of some dietary risk factors as those mentioned by the reviewer, as well as the reasons to do this, were stated as suggested in the section Selection of Risk Factors and also noted in the Discussion section of the manuscript as one of the limitations of the study.

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 for fruits and vegetables? For glycemia? etc.

Since the prevalence of risk factors was obtained from self-reports of participants
and not from direct measures, they were defined dichotomously or categorically (as
having or not having the risk factor) for the calculation of the PAR. This implies that
the risk of a particular risk factor behaves like an “all or none” phenomenon, which
is obviously not true given the continuous nature of this risk in all of the selected risk
factors. We agree with the reviewer that estimating the theoretical minimum risk
exposure distribution is the appropriate method to calculate PAR if this had been
possible with the data of the survey. However, this was also noted as a limitation of
the study.

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 all of the other risk factors, i.e. not per serving per day (that would be
equivalent to doing a proportional burden calculation per 5 mm Hg of SBP, or per 1
unit of BMI), but for moving the population from the current distribution of risk
(current F&V consumption) to absence of risk (everyone having F&V consumption
in the optimal distribution). After all, the point of comparable risk estimation is to
evaluate all risk factors comparably.

We agree with the reviewer. Unfortunately, consumption of vegetables and fruits
was ill-defined in the FASRF since the daily quantity of servings was not specified.
Therefore, we were bound to the two defined options as posed in the specific
question of the survey: more or less than five servings a week (rather than more or
less than five servings a day), which is clearly inappropriate based on WHO
recommendations. For this reason, we finally decided to exclude this risk factor for
further analysis and recalculated the proportional burden of disease and costs
attributable to the remaining cardiovascular risk factors as can be seen in the
Results sections and Table 5 and 6, and also noted as a limitation of the study. As
shown in Table 5, the effect of the exclusion of F&V from the analysis of the global
burden of CV disease was negligible (i.e selected risk factors including F&V
explained 77.4% of all CV events vs. 76.8% with its exclusion).

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.

We agree with the reviewer that there is not empirical evidence on higher population effectiveness of preventative interventions in subjects without clinical CVD. However, this high risk subset (> 20% risk in 10 years) is likely to have many risk factors, some of them not silent and therefore more prone to be detected and treated. Nevertheless, we changed the assumptions of the population effectiveness of the polypill in order to have more conservative and probably more realistic estimates, we run models with lower estimates: 50% detection, 50% patient compliance and 70% provider compliance, therefore reducing by more than half the population effectiveness of this intervention (from 42% to 17.5%). The revised results are incorporated in the manuscript (Result and discussion sections). Number of DALYs saved and percent of DALYs saved due to this interventions as well as its ICER, were also changed in table 7.

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.

As suggested by the reviewer, this point was now included in the discussion.

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).

As suggested by the reviewer, this limitation was also noted in the discussion.
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'