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

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Version: 2 Date: 25 June 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: 1 Date: 4 May 2010

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 Revisoins:

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.

Thanks for the comment. We agree with Dr. Mozaffarian that we have not included or addressed all possible risk factors and/or clinical or community-based interventions to reduce cardiovascular diseases in Argentina. In fact, Dr. Mozaffarian has mentioned some community based interventions of proven benefit to populations. Nevertheless, the aim of our study was to build a model based on valid local population health data at individual level. As we mentioned in the “Methods” section, we have included in our model risk factors which fulfill all three following criteria:
• Sufficient evidence was available on the presence and magnitude of likely causal association with CHD and stroke from high-quality epidemiological studies,
• available interventions existed to modify exposure to the risk,
• data on risk factor exposure were available from nationally representative surveys not subjected to selection bias.

Unfortunately, information about seafood/omega-3 consumption in Argentina is not available nor was asked in the national survey where all data are derived to build the different models, therefore, failing to meet the third criterion for inclusion in our model. In this sense, we have recently conducted a systematic review of studies addressing nutritional habits associated with cardiovascular diseases in Argentina. We have found 7 subnational studies aimed to address this issue, and none of them included seafood consumption as an exposure. Only 2 studies included some exposures related to nutritional habits at a national level. The First National Survey or Risk Factors was carried-out in 2005 including people of both sexes older than 18. However, only fruits and vegetable consumption was addressed. In 2004-2005 another national survey, the National Survey of Nutrition and Health was conducted, focused on children, pregnant women and women between 18 and 49 years. Unfortunately, in the last group only two risk factors related to cardiovascular diseases were addressed: total caloric intake and cholesterol consumption. In addition, macronutrients distribution (proteins, fats, and carbohydrates) was available. We agree with Dr. Mozaffarian that seafood/omega-3 consumption could be modeled from other countries. However, Argentina is very different from other Latin American countries on nutritional habits. Our country ranks first in beef intake in the world, whereas consumption of seafood in Argentina is probably lower than in other Latin American countries. Since our study aimed to provide local decision makers with high quality evidence based on local data, modeling using data based on regional or international sources was not considered an appropriate option. On the other hand, we agree with the reviewer that interventions to increase seafood/omega-3 consumption could be especially relevant in our setting and this should be pursued in further local studies. In any case, our decision to use data solely retrieved from the national survey was mentioned as a limitation of our study.

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.

Please, see previous answer.

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.

Many thanks for the comment. Cardiovascular risk factors data were derived from de First National Survey of Risk Factors, as mentioned. For all risk factors included, available information allows us to stratify the entire population in two or three groups, according to the cardiovascular risk level. For instance, for blood pressure, population was divided in two groups: a high blood pressure and a non-high blood pressure strata.
For body weight, population was divided in three different groups: normal weight, overweight and obesity, based on their BMI. So, Population Attributable Risk (PAR) was estimated assuming that ‘prevalence’ of all groups but the lower risk group would be reduced to the normal reference or zero. However, we agree with Dr. Mozaffarian’s comment and we think that the paragraph mentioned could be confused. Please note that we have modified that paragraph.

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).

Thanks for the comment. The RRs in table 1 are for serving, not for adequate consumption. Please note that we have modified the Table. Nevertheless, we would like to highlight that this RR was used only for the “fine tuning” to calculate the absolute baseline risk, but no intervention was targeted towards F&V consumption. Hence the effect on the ICER is expected to be negligible. We have extensively discussed this limitation in the discussion section of the manuscript.

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.

Thanks for the comment. We would like to highlight that we actually used a RR for atorvastatin of 0.89 for CHD and 0.94 for stroke. We do that because this is the RR that statins are expected to achieve after the first year (see footnote in Gaziano et al.). However, we have changed these RRs in our new draft, according to the reviewer’ comment. For the polypill, we agreed with the reviewer’s recommendation and re-run our model including a RR for statins of 0.77 for CHD as suggested, based on Baigent et al, and 0.81 for stroke based on Lim SS et al, published in the Lancet.
series of 2007. For Aspirin we used a RR of 0.66 for CHD, in secondary prevention, and 0.78 for Stroke, from the same bibliographic source.

In this way we finally used in our model the following combination of RR: 0.66*0.77*0.66=0.34 for CHD and 0.51*0.81*0.78=0.32 for stroke in an aspirin-containing polypill. It is important to underline that we have included aspirin in our modified polypill strategy because we are targeting people with more than 20% of cardiovascular risk at 10 years, which may be comparable to a secondary prevention strategy.

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.

Thanks for the comment. We agree with the reviewer about the importance of these population-based interventions. As mentioned, we include interventions only if local data were available to model them. We would like to note that we have included this issue in the limitations of our study at the ‘Discussion’ section.

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.

Thanks for the comment. We understand the reviewer’s point of view. However we would like to explain our assumptions in more detail. Firstly, we would like to note that, as mentioned, we are targeting a high risk population (>20% risk of death at 10 years). In this sense, this population is comparable to a population in a secondary prevention setting, as has been addressed by Lim et al.


Since this people have more than one risk factor, and some of these risk factors are not ‘silent’ (for instance tobacco exposure, obesity, age, sex, etc.) it seems more likely that this special population could be detected in a more often than, say, hypertensive subjects. In this regard, we assumed that only 25% of all target population for antihypertensive treatment would be affected by the intervention (50% of detection and 50% of compliance). A similar approach was used for lipid lowering treatment. However,
for polypill strategy we assumed that 42% of the target population could be affected by the intervention (70% of detection and 60% of compliance) which seem to be more appropriate taking into account that this people are high risk and therefore more likely to be treated as compared to lower risk groups. On the other hand we assumed 100% of provider compliance for all these clinical interventions in order to maximize population effectiveness once subjects were detected, diagnosed and complied with provider recommendations. In any case, our model eventually excluded from the polypill intervention more than half of the potential targeted population. We would like to note that this assumption affected only the total number of DALYs, deaths and non fatal cases avoided, but not the Incremental Cost-Effectiveness Ratio of the pharmacological interventions.

Additionally, we have no included other cut off risk values in our analysis, since our multi-drug intervention (polypill) contains aspirin resembling a secondary prevention setting. Even though we think that bleeding risk would be small in this population (as compared to the benefit of cardiovascular risk reduction), we also believe that this analysis would not be appropriate for lower risk subjects, since our model doesn’t allow us to include bleeding events (this is a parsimonious model aimed to address several interventions). Please note that we have included these issues in our discussion.

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

Overall risk (derived from mortality rate and non-fatal event rate obtained after dividing mortality rate by lethality) was split by all possible risk factors combination. For instance, if we have only 2 possible combinations (one risk factor present or absent) we can estimate the basal risk for people without the risk factor, taking into account the prevalence of the risk factor and the associated relative risk using the following equation:

\[
\text{Basal risk} = \frac{\text{total risk}}{(\text{prevalence in subjects with the RF} \times \text{RR} + (1 - \text{prevalence people with the RF}))}
\]

In our model we split the absolute risk into 256 possible combinations of risk factors. We obtained the prevalence of these combinations from the National Survey of Risk Factors, and their respective RRs were derived multiplying all RRs associated to each risk factor presented in that particular stratum.

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.

Thanks for the comment. Please note that we have rewritten both the introduction and the discussion taking into account the suggestions of the reviewer.
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.)

Thanks for the comment. Please note that we have modified the first paragraph taking into account the reviewer’s comments.

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'

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: 1 Date: 25 March 2010

Reviewer: Rajeev Gupta

Reviewer's report:

Article: 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

General comments:
This is a secondary data analysis of the national health and economic data.

It addresses an important issue of cost effectiveness of various public health measures for prevention of cardiovascular diseases in a middle income country. The analyses performed are succinct and clinically relevant. However, there are certain short comings that have to be addressed before the article is accepted.

Major/minor essential revisions:

1. The introduction statement should be a one-liner giving the objective.

   Thanks for the comment. Please note that objectives were rephrased more clearly in the last paragraph.

2. The results section should provide data.

   Please note that we have now included the most relevant data (while most of the data are still left in their respective tables).

3. The conclusion statement should focus on the interventions that help (tobacco and BP control) and should not be a general statement as drug-supported interventions to reduce cholesterol and tobacco are not helpful.

   Thanks for the comment. Please note that we have modified the discussion section taking into account the reviewer’s comment.

4. Please shorten the introduction section, especially the first paragraph that is essentially a repetition of known facts.

   Please note that Introduction has been shortened.

5. Please provide the details of the statistical methods used.

   Please note that we have used a simulation model, not a statistical analysis. In this regard, model building, data sources and inputs, as well as assumptions are thoroughly described in the methods section.

6. Please reduce the statement on importance of risk factors.

   Thanks for the comment. We have modified our manuscript taking into account the reviewer’s comment.

7. This should be a one paragraph statement highlighting the positive and negative findings. Public health implications of this paper finding should be stressed.

   Thanks for the comment. Please note that we have modified the discussion section taking into account the reviewer’s comment.

Discretionary revisions:

8. The number of references is large, please reduce.

   Thanks for the comment. We would like to note that since this study is a secondary data analysis, the number of references is expected to be higher than is in primary studies. Nevertheless, since we have deleted some paragraphs of the introductory and discussion sections, we could take away some references as well.

9. Tables are too complex. Please describe salient findings in the results section.

   Thanks for the comment. As mentioned, we have included our salient findings in the Results section.
10. The second figure is not relevant.
   Please note that we have deleted the figure following the reviewer’s suggestion.

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

Quality of written English: Needs some language corrections before being published