Author's response to reviews

Title: Predicting mortality with biomarkers: a population-based prospective cohort study for elderly Costa Ricans

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Predicting mortality with biomarkers: a population-based prospective cohort study for elderly Costa Ricans

Luis Rosero-Bixby and William H Dow

Cover Letter to Editor

Thank you for the provisional acceptance of our manuscript, "Predicting mortality with biomarkers: a population-based prospective cohort study for elderly Costa Ricans.” This letter provides a point-by-point description of the changes made in response to the three referees’ comments. Our responses are in capital letters. And the changes made in the manuscript can be seen with the tracking option of MS Word.
Referee #1: Eleanor Brindle

Minor Essential Revisions
1. Line 73, spelling mistake: interleukin: DONE, LINE 79
2. Throughout the paper: CRP results are reported in units of ml/l; the convention is mg/l or mg/dl. Is this an error, or is there some justification?. CORRECTED IN TABLE 1 AND LINE 359: MG
3. Line 416: It’s not clear what “mortality presented before” refers to. 4. Line 420: Edit for clarity. CORRECTED IN LINES 418 AND 428
5. Line 442: Here it says the models in table 3 use 480 deaths, but the table 3 caption says 564 deaths. Please clarify. 564 DEATHS IS THE CORRECT NUMBER, LINE 444 CORRECTED
6. Line 597, spelling mistake: intervene. CORRECTED IN LINE 605
7. Line 657: Change the phrase to read “However, the great majority...” CORRECTED IN LINE 675.
8. Line 686, spelling mistake: inflammation. CORRECTED IN LINE 713
9. References: numbers 3 (line 750) and 11 (line 772) on the list appear to be missing page numbers. CORRECTED
10. References: the author list is incorrect for number 12 (line 773). 11. Figure 1: y-axes should be labeled. CORRECTED IN LINE 832
12. Figure 4: Moving the plot of functional markers (grip strength, etc.) to the upper left panel would make the order of panels in the figure match the order of discussion in the text. DONE, FIGURE 2 NOW

Discretionary Revisions.
1. In the introduction, the authors quite correctly note that most studies using biomarkers to predict mortality come from rich countries, and that we are lacking information on mortality in developing countries. Filling that gap is a key strength of this paper, but given the relatively good health of elderly Costa Ricans, it is hard to evaluate whether these results should be expected to be an anomaly. Can you comment on how mortality might be expected to compare in this sample versus other less developed countries? There is some mention of mortality in Taiwan in reference to the SEBAS study, but a more general comment on how Costa Rican mortality patterns in the elderly differ from those in other developing countries would be helpful. BECAUSE OF THE LACK OF RELIABLE DATA ON ADULT MORTALITY FOR DEVELOPING COUNTRIES WE CANNOT SAY MUCH ABOUT THIS. HOWEVER WE ADDED CAUTIONARY WORDS REGARDING EXTRAPOLATION OF THESE COSTA RICAN RESULTS TO OTHER CONTEXTS (SEE LINES 749-52)

2. I'm not sure that figure 1 is necessary. The text in the paragraph beginning at line 316 is probably adequate alone. WE MOVED FIG 1 AS AN ADDITIONAL FILE
3. The paragraph beginning at line 329 could be moved to the discussion section. WE CONSIDER THIS DATA AS AN IMPORTANT RESULT OF THIS RESEARCH AND PREFER TO KEEP IT IN THE RESULTS SECTION
Referee #2: Bernardo Hernández Prado

I would recommend to simplify the presentation as follows:

a) The introduction can be reduced from 3 to 2 pages eliminating some details, and without losing its original meaning. WE COULDN’T DO IT. EVERYTHING LOOKS IMPORTANT TO US.

b) In the section of results, mention only the CRELES mortality validity check, and move details and figure 1 (CRELES and Costa Rica life table) to an appendix (an option that PHM allows as additional material). DONE WE MOVED IT OUT AS ADDITIONAL FILE 1
c) Refer the main results of figure 3 only in the text (as it is in lines 397-405, page 19), and move figure 3 to an appendix. DONE WE MOVED IT OUT AS ADDITIONAL FILE 2
d) In figure 5, it is not clear to me the difference between the left and right charts, but I think the text refers to the one on the right. Keep only that. WE DROPPED THE LEFT PART OF THIS FIGURE (NUMBER 3 NOW)

Results are really interesting and can generate a lot of discussion. I think it is important to reinforce in the discussion 3 points that are crucial for the interpretation of this study:

1. What is the meaning of the biomarkers? Biomarkers may reflect a health condition, and in some cases they do not reflect a potential problem itself, but are indicators of a problem. The authors tackle this point in lines 446-446-452 (p. 21), talking about the interpretation, but I think it can be reinforced in the final discussion. WE ADDED TWO CAUTIONARY LINES (738-39) IN THIS REGARD (BIOMARKERS ARE JUST INDICATORS, NOT CAUSAL FACTORS)

2. We should keep in mind that it is a population of elderly people with special characteristics, as mentioned in pages 30 and 31. What is the meaning of this indicators for elderly people? Having an excessive BMI is a risk factors the same way it is in early ages, or does it suggest a better present state of health? WE HAVE ADDED CAUTIONARY WORDS REGARDING EXTRAPOLATION OF THESE COSTARICAN RESULTS TO OTHER CONTEXTS (SEE LINES 749-52)

3. The baseline measure was collected in 2005, and follow-up in 2010. But we have little information on biomarkers or risk factors for cardiovascular disease before that. Could it be a confounder? I think the possible role of health conditions (reflected in different biomarkers) earlier in time is worthy to be discussed. WE HAVE ADDED IN LINES 625-28 A MENTION ABOUT THIS ISSUE (EARLIER CONDITIONS). THE RELATED ISSUE OF SURVIVAL-SELECTION IS ALSO NOW ADDRESSED IN LINES 699-706 IN RESPONSE TO COMMENTS OF ANOTHER REVIEWER.

Minor Essential Revisions

Some formal points to be considered:

1. Page 11, line 207: write complete DHEAS the first time, as all other acronyms are presented. DONE IN LINE 213

2. Page 19, lines 401-402, present correlation coefficients as numbers between -1 and 1 (e.g. r=0.95 instead of r= 95%). DONE IN LINES 404-407. Same in figure 3. TO AVOID CLUTTER THE FIGURE WE KEEP NUMBERS PER 100 WITH A NOTE EXPLAINING THAT R-COEFFICIENTS ARE MULTIPLIED BY 100

3. Page 25, line 530. “figure 6 compares the death RR estimated with the model for CV mortality (full, red dots) with those obtained in all-cause mortality (hollow, blue symbols).
From which of the all-cause mortality models were there obtained? Specify. EXPLAINED IN LINE 534
4. Table 2, some numbers are in red. Do they have a special meaning or was it a printing issue? CORRECTED, ALL ARE BLACK NOW
5. Figure 2. Set label of Y axis (I think death RR) 6. Figure 5, labels are missing in left chart CORRECTED FIGURES 1 AND 3 (see comment d above).
Referee #3: Martin Tobias

Excellent paper, but could be improved by a little more discussion of the following points: Study cannot tease apart effects of national income versus effects of age. Do the findings reflect a middle rather than a high income population? Or do they simply reflect an old versus a middle aged population?

WE AGREE WITH THE REVIEWER THAT IT IS DIFFICULT TO KNOW WHETHER ANOMALIES IDENTIFIED IN THESE DATA ARE DUE TO STUDYING A LOWER INCOME POPULATION THAN IN MANY OTHER STUDIES, OR SIMPLY DUE TO STUDYING AN OLDER POPULATION THAN MANY OTHER STUDIES. HOWEVER, WE DO NOTE THAT THE AGE INTERACTIONS IN THE MODELS SHOW THAT RELATIONSHIPS ARE GENERALLY SIMILAR AMONG BOTH ADULTS AGES 80+ AND THOSE AGES 60-79 (WITH THE EXCEPTION OF BMI), SUGGESTING THAT THIS IS UNLIKELY TO BE REFLECTING SOLELY AGE EFFECTS. CLEARLY MORE RESEARCH WILL BE NEEDED FROM OTHER SETTINGS TO BETTER UNDERSTAND THE ISSUES RAISED IN THIS PAPER.

Justify / explain in more detail why SES wasn't adjusted for, and why this is OK (would the findings have differed if confounding by SES was controlled? Was there confounding anyway?)

DONE. SEE LINES 618-623

To what extent could the findings reflect selection of survivors? What proportion of deaths occurred in Costa Rica at younger ages? Would a sensitivity analysis be helpful to confirm that selection bias could not have been quantitatively important?

WE ADDRESS THIS COMPLICATED ISSUE IN LINES 694-701

The model was not a good predictor of the outcome - the authors themselves describe the fit as 'lousy'. Given this, is the model not limited in its ability to evaluate the performance of individual biomarkers as predictors of the outcome (especially cardiovascular mortality, which is further constrained by relatively small number of deaths)? More discussion of model goodness of fit and consequential predictive ability might be helpful for the reader

WE ARGUE THAT THE CONFIDENCE INTERVALS AROUND EACH BIOMARKER IS MORE IMPORTANT THAN THE OVERALL GOODNESS OF FIT. THIS IS PARTICULARLY THE CASE SINCE MORTALITY IS EXTREMELY WELL-MEASURED IN THIS POPULATION (AS ARE THE BIOMARKERS), INDICATING THAT MEASUREMENT ERROR IS UNLIKELY TO BE CAUSING SUBSTANTIAL DETERIORATION OF GOODNESS OF FIT. TO THE EXTENT THAT GOODNESS OF FIT IS POOR, OUR PRIMARY CONCERN IS THAT THIS MAY BE CAUSED BY WEAKNESS IN THE TRUE RELATIONSHIP BETWEEN MORTALITY AND EACH OF THESE BIOMARKERS IN THIS POPULATION. WE ALSO ADDRESS THE ISSUE OF THE EXPLANATORY VALUE OF BIOMARKERS IN LINES 564-566