PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Time trends in educational inequalities in cancer mortality in Colombia, 1998-2012
AUTHORS	de Vries, Esther; Arroyave, Ivan; Pardo, Constanza

VERSION 1 - REVIEW

REVIEWER	Bjørn Heine Strand Norwegian Institute of Public Health
REVIEW RETURNED	13-Jul-2015

GENERAL COMMENTS	This is an interesting paper on trends on educational inequalities in cancer mortality in Colombia during 1998-2012. The paper is based on high quality data of large size, which is analysed properly using standard statistical methods. The paper is nicely written and easy to follow. I have only one major concern and some minor. The main concern is the strong focus on relative inequalities when discussing the time trends. As discussed at length in the inequalities research, recently in a discussion paper by Johan Mackeneback («Should we aim to reduce relative or absolute inequalities in mortality» http://eurpub.oxfordjournals.org/content/25/2/185.long): "In a context of rapidly declining mortality rates, it is extremely difficult to reduce relative inequalities in mortality. This is not only suggested by the near absence of empirically observed reductions of relative inequalities,1 but can also be underpinned by theoretical reasons. A reduction of relative inequalities in mortality requires larger relative reductions in mortality in lower than in higher socioeconomic groups." As cancer mortality rates are indeed declining in Colombia it might be better to focus on absolute inequalities when investigating time trends in inequalities. Therefore I would suggest figure 3 to also include development in SII over time (you could skip age specific results in figure 3 as they are not very informative due to the mathematical reason as described above - when rates decline, relative inequalities tend to increase). In results in the abstract and in results section it is decribed that RR_educ was stronger in women than in men, and showing RR=1.35 for women with primary versus basic education, and similar RR in men is 1.49. To me this seems like a larger RR for men than women? Furhermore, I do not see any formal test of this gender differenece (interaction Gender by SES)?

REVIEWER	Oscar Bernal

	University Andes, Colombia.
REVIEW RETURNED	14-Jul-2015

GENERAL COMMENTS	This study evaluates educational level, gender and Health Insurance coverage with Cancer mortality. However, the goal expressed is focused on educational level only and was: “In this paper we evaluate if the seemingly positive trend in cancer mortality by educational level…” and title. “Time trends in educational inequalities in cancer mortality in Colombia, 1998-2012. So I recommend to clarify the goal and change the title according to that. The relationship between healthcare insurance coverage showed contradictory results in the 2002-2007 period compare with 2007-2012. It is important to comment about other possible factors such as quality of care and propose new research. Changed over time and within periods of RRs is a mention but is not clear presented in the methodology and results. Age 20 is early to define highest educational level, taking in account that the average age to end secondary school is 18 years old and 23 for university http://www.mineducacion.gov.co/1621/articles-156179_recurso_7.unknown http://www.mineducacion.gov.co/sistemasdeinformacion/1735/articles-254702_libro_desercion.pdf How do you imputed values for educational level for individuals with missing educational information based on a information on age, sex marital status, region and urban/rural residence? Please include ethical consideration and confirm if this study has been presented to a ethical comity. Figure 1. Please write the source?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Bjørn Heine Strand
Institution and Country: Norwegian Institute of Public Health
Please state any competing interests or state ‘None declared’: None declared.

This is an interesting paper on trends on educational inequalities in cancer mortality in Colombia during 1998-2012. The paper is based on high quality data of large size, which is analysed properly using standard statistical methods. The paper is nicely written and easy to follow. I have only one major concern and some minor.

R/ We thank to the reviewer for the kind and positive comments on our manuscript. We have fully revised the paper to take into account the comments raised. Following the suggestions of the reviewer we have also prepared additional calculations to improve the understanding of the results. We hope you and the editor will find this revised version suitable for publication in BMJ Open.

1. The main concern is the strong focus on relative inequalities when discussing the time trends. As discussed at length in the inequalities research, recently in a discussion paper by Johan Mackenbach

(«Should we aim to reduce relative or absolute inequalities in mortality»): "In a context of rapidly declining mortality rates, it is extremely difficult to reduce relative inequalities in mortality. This is not only suggested by the near absence of empirically observed reductions of relative inequalities 1, but can also be underpinned by theoretical reasons. A reduction of relative inequalities in mortality requires larger relative reductions in mortality in lower than in higher socioeconomic groups."

R/ We thank the reviewer for this very true argument that we did not consider before. We tried to address this comment in several calculations to respond to this and further comments. Firstly, in order to improve the understanding of the declining pattern of the premature mortality rates for cancer we prepared an additional calculation of Estimated Annual Percent Change (EAPC) in ASMRs of cancer in Colombia for the whole studied period (1998-2012), not taking into account any joinpoints (and therefore different to that of Figure 2 which is done with joinpoints).

Males Females
EAPC SE EAPC SE
Primary -0.29, 0.1523 -0.30 0.1430
Secondary -0.95* 0.2572 -0.42 0.3579
Tertiary -0.45 0.3147 -2.06* 0.3395
The highlighted results are statistically significant at the 0.05 level.
The results show that the reduction in ASMR is in facto not very strong. Indeed it is only significant for secondary educated men and tertiary educated women. All other groups tend to decline but these declines do not reach statistical significance. This is not “a context of rapidly declining mortality rates”.
On the other hand, CIs of the small but significant EAPCs by education level overlap, indicating that they do not differ significantly between them, and neither is some kind of tendency with a consistent increase or decrease within increasing educational level present in males. These characteristics contradict the condition hypothesized by Mackenbach of having “larger relative reductions in mortality in lower than in higher socioeconomic groups”.
But as explained, this reasoning applies to the whole period. On the contrary, what we showed in Figure 2 and Appendix-Figure 2 is, as the reviewer points out, a relatively stable pattern of inequalities. In fact the only significant reduction that we observed in RII (Appendix-Figure 2) was for women during the first half of the studied period, where we found a clearly divergent pattern between socioeconomic groups, following patterns as suggested by Mackenbach: A rapid significant decrease of ASMRs in the highest socioeconomic group (tertiary educated) and an opposed rapid significant increase of ASMRs among those with secondary education.
To take into account the reviewer comment we also calculated the absolute differences over time, see answer to comment #2.

2. As cancer mortality rates are indeed declining in Colombia it might be better to focus on absolute inequalities when investigating time trends in inequalities. Therefore I would suggest figure 3 to also include development in SII over time

R/ We thank the reviewer for this criticism which, in connection to the previous one, contributes to improve to the analyses and interpretation of the results.
In order to respond to this request we calculated trends in the Slope Index of Inequality (SII), which is indeed the “absolute version” of the Relative Index of Inequality (RII).

Figure: Sex-specific Slope Index of Inequality (RII) trends for premature (20-64 years) mortality in cancer, Colombia, 1998-2012

An essentially identical pattern is evident between these trends in SII with those presented in Appendix Figure 2 for RII. This is probably due to the fact that we described in the response above,

i.e., the decline in ASMRs is in general nuanced.
We suggest to add a comment on the results of this SII analysis to the paper in the discussion, without including the figure,to strengthen our rationale. The addition reads as follows:
In order to test that RII is a good indicator of changes in inequalities 2 we compared trends in relative and absolute measures of inequalities (RII and SII), which were almost identical (results not shown). Mackenbach hypothesized that, in the case of declining mortality rates, RIIs are exaggerating the differences 2, but this was clearly not the case in our study, probably because reductions in premature mortality rates of cancer were relatively smooth, not very strong and not very divergent between educational levels, with the exception of tertiary educated women. Among women we only found a clear reduction in inequalities during the period 1998-2004, owing to a clearly divergent pattern between educational levels: A rapid significant decrease of ASMRs in the higher socioeconomic group (tertiary educated) and an opposed rapid significant increase of ASMRs among those with secondary education. We have illustrated in previous work that these trends are most likely due to large changes in Cervical cancer mortality 3.

2.1. [Parenthesis:] you could skip age specific results in figure 3 as they are not very informative due to the mathematical reason as described above - when rates decline, relative inequalities tend to increase

R/ Although we largely agree with the reviewer in that rationale, we would like to put into consideration that the temporal trends of premature cancer age-standardized mortality rates are actually slowly reducing, as explained above. On the other hand, certainly premature cancer ASMRs trends tend to largely lessen from senior to young population, undoubtedly contributing to the huge increase of RII, as the reviewer points out. But, instead of skipping age specific results in figure 3, we suggest to clarify this issue directly in the paper. Now the final fragment of the third paragraph in the Explanation of results reads as follows:
"(…) Nevertheless we cannot discard that, at least partially, the huge inequalities in younger groups are due to the fact that, when rates are low, relative inequalities tend to show an increasing pattern 2."
However if the reviewers or the editors consider that removing this panel of the figure is necessary, we can re-consider our reasoning and omit the age-specific figure as well as this above suggested addition to the third paragraph.

3. In results in the abstract and in results section it is described that RR_educ was stronger in women than in men, and showing RR=1.35 for women with primary versus basic education, and similar RR in men is 1.49. To me this seems like a larger RR for men than women?

R/ We are very grateful with the reviewer to notice this typo. The second paragraph of the results actually reads as follows:
The risk of dying was significantly and consistently higher among the lower educated. The RRs show clearly and statistically significantly increased risks of dying among the lower educated compared to the highest educated, this tendency was stronger in women (RRprimary=1.49; RRsecondary=1.22, both p<0.0001) than in men (RRprimary=1.35; RRsecondary=1.11 both p<0.0001).
In fact, because of this criticism we also noticed the mistake in the abstract of the results that currently reads as follows
Results: RR show increased risks of dying among the lower educated compared to the highest educated, this tendency was stronger in women (RRprimary 1.49; RRsecondary 1.22, both p<0.0001) than in men (RRprimary 1.35; RRsecondary 1.11, both p<0.0001).
To help clarify this confusion, we add this complementary figure in this response only (not to be included in the paper or the appendix):

Figure: Sex-specific Rate Ratio for premature (20-64 years) mortality in cancer, Colombia, 1998-2012

3.1. Furthermore, I do not see any formal test of this gender difference (interaction Gender by SES)?

R/ We thank the reviewer for this excellent suggestion. In order to respond we calculated Rate Ratios between sexes by educational levels, using as reference “men”, and the results were that, for all educational levels women have significant larger rate ratios, being slightly larger for secondary level.

Primary (women vs. men) 1.18 (1.16, 1.19), p<0.0001
Secondary (women vs. men) 1.26 (1.24, 1.28), p<0.0001
Tertiary (women vs. men) 1.18 (1.15, 1.22), p<0.0001

Despite this is out of the focus of the paper itself, we want to describe in this response one further issue: In results for studies into other causes of death we found an inverse relationship for essentially all other causes of premature death. i.e., men have significantly larger rate ratios for all educational levels than women, cancer is a clear exception to the rule. This contributes to strengthen our conclusion in regard to the huge effect of these gender disparities in cancer that are undoubtedly related to specific cancer types, opportunities for early detection and adequate treatment, and should be addressed in further papers on cancer site-specific issues.
Following the suggestion of introducing this additional test, and considering the implications of our findings, we finally added some statements along the paper in this regard.
In the results section:
In order to formally test this higher female risk, we calculated Rate Ratios between sexes by educational levels, using men as reference category. For all educational levels, women had significant larger rate ratios (results not shown).
In the discussion section:
The consistently higher RR for women than men are unique to cancer in Colombia, studies evaluating other causes of death consistently show a higher mortality risk for men 4 5, which also coincides with the usually lower life expectancy of men. This illustrates the high burden of certain cancers which are strongly SES related, probably mainly cervical and breast cancer, which, if diagnosed late, have a very poor prognosis even though early detection possibilities are ample.

Reviewer: 2
Reviewer Name: Oscar Bernal
Institution and Country: University Andes, Colombia.
Please state any competing interests or state ‘None declared’: None declared

1. This study evaluates educational level, gender and health insurance coverage with cancer mortality. However, the goal expressed is focused on educational level only and was: “In this paper we evaluate if the seemingly positive trend in cancer mortality by educational level…” and title. “Time trends in educational inequalities in cancer mortality in Colombia, 1998-2012”. So I recommend to clarify the goal and change the title according to that.

R/ The reviewer is correct in the inconsistency, for which we apologize. We suggest the following title and remaining the previously formulated goal (in the introduction):
Suggestion Title: “Time trends in educational inequalities in cancer mortality in Colombia, 1998-2012”

2. The relationship between healthcare insurance coverage showed contradictory results in the 2002-2007 period compared with 2008-2012. It is important to comment about other possible factors such as quality of care and propose new research.

R/ We already had the following paragraph included in the discussion section, we added the words highlighted in red.

Our results clearly illustrate that an almost complete coverage does not necessarily reduce inequalities in health 6 7. Particularly, having health insurance may be universal, but depending on income the type of health insurance is different (subsidized, contributory and special or exceptional regimes), with the wealthy population often buying additional private health assurance to ensure rapid and more broad access 8. The quality of care provided by the insurance (translating into early and timely diagnosis and adequate treatment) is not guaranteed with complete coverage, as seems to be the case: To warrant rights to get access to expensive treatments and medication, as usual in cancer, exceptional legal mechanisms are frequently launched in Colombia: Technical-scientific committees of health assurers, and an action for protection so-called “tutela” 8 9. A study shows that those affiliated to the contributory regime are more likely to warrant additional rights more efficiently 9, potentially increasing inequalities between regimes. Also, clear differences in gastric cancer survival by type of health insurance affiliation have been documented in a population-based Colombian study, clearly illustrating that, even though in theory there is access to care for all, this does not translate to equal outcomes 10.
In parallel with the increases in HIC, other changes in the Colombian health care system occurred, including increases in investments in care 11 12. Therefore, our results reflect the impact of the entire reform rather than only the increased coverage in health insurance. However, based on our analyses, it is safe to conclude that all these reforms have not resulted in reducing inequalities in cancer mortality. This is not unique to Colombia; in several countries, as diverse as Taiwan, Thailand and European countries, inequalities in health increased upon reaching almost universal coverage 13-18.

3. Changed over time and within periods of RRs is a mention but is not clear presented in the methodology and results.

R/ As explained above (see “Editorial comments”), we added an additional table (see supplementary appendix: “Appendix-Table 2. Rate ratio in premature cancer mortality by educational level by 5-years periods and separately for men and women at 20–64 years, Colombia 1998-2012”), in order to improve the understanding of the differences in rate ratios and relative index of inequalities between those three periods analysed in the paper. , we finally added these statements in the results section: We also found a consistent and slight increase in rate ratios from first, to second, and then to the third period (appendix-table 2) among both men and women and for primary and secondary education compared to higher educated, but the Confidence Intervals overlap indicating the differences do not reach statistical significance.

4. Age 20 is early to define highest educational level, taking in account that the average age to end secondary school is 18 years old and 23 for university
http://www.mineducacion.gov.co/1621/articles-156179_recurso_7.unknown
http://www.mineducacion.gov.co/sistemasdeinformacion/1735/articles-254702_libro_desercion.pdf

R/ We thank to the reviewer for the enquiry. Certainly this applies to what is usually called educational attainment, which refers to the highest educational level achieved (finished with a diploma) by an individual. Using that approach, for instance, an individual who studied some years in the university,

but did not finish, is categorised in “secondary education”. In the category “tertiary” are included only those who graduated as of post-secondary education. That is the clustering that we used in previous studies 3-5 in which, of course, we defined the lower age threshold in 25 years old.
In this study, in order to have comparable measurements during the whole study period (in 2008 there were changes in the DANE databases in the achieved educational level question) we are using another classification for educational level in which both individuals of the previous examples are categorized as “tertiary”, the person who finished or that who did not, i.e., completed or uncompleted tertiary (and so on with the other educational levels). If we consider that the average age to end secondary school is 18 years, we can trust that most of the individuals began their post-secondary education, are below the level of 20 years old (regardless if they graduated from it), and that is why we used 20 years as threshold. We verified this assumption in two ways: Firstly: The distribution of population by educational level (completed or uncompleted) show increasing proportions of population by tertiary level up to 20 years, but essentially the same proportions as of this age, clearly suggesting that almost 100% of population who began post-secondary education did so before the age of 20. Secondly, we ran models using as thresholds 20 and 25 years yielding almost identical estimates.
In summary we think we can improve the paper following the guideline of the reviewer by adding more precise information about the threshold used directly in the paper. The sub-section of the paper so-called “Education level criteria” reads currently as follows:
Educational level was defined as the highest level in which the individual has been enrolled during his life (i.e. the person accessed but not necessarily graduated this level), and was categorized in three groups based on the highest educational level accessed by the deceased: (a) Primary school or less, (b) Secondary school, and (c) Tertiary (post-secondary education). In previous papers educational level has been used, based on the highest educational level attained (i.e. completed) by the deceased 3 4 but this category is restricted to the period 1998-2007. In our calculations we found both approaches to be similar in terms of the results yielded.

5. How do you imputed values for educational level for individuals with missing educational information based on information on age, sex marital status, region and urban/rural residence?

R/ The imputations done by using IVEWare are obtained by fitting a sequence of polytomous logit regression model (because the response variable of the imputation is categorical) and inferring values for missing data from the corresponding predictive distributions. Two additional common features in the imputation process are incorporated: restriction to a relevant subpopulation for some variables and logical bounds or constraints for the imputed values. The restrictions involve subsetting the sample individuals that satisfy certain criteria while fitting the regression models. The bounds involve drawing values from a truncated predictive distribution. Additional information of the procedure followed by the software is available elsewhere 19.

6. Please include ethical consideration and confirm if this study has been presented to an ethical committee

R/ We added this statement after the “Competing interests statement”
Ethics committee approval: This article is based on secondary analysis of data on deaths and population counts in aggregate form made publically available by the National Statistics Office in Colombia. Ethical approval for this study was not required.

7. Figure 1 Please write the source

R/ We thank to the reviewer for this observation. We added the source of to the caption of the figure which now reads as follows:
Source: Annual reports of the Ministry of Health and Social Protection to the Congress of the Republic 6of Colombia

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Multiply Imputing Missing Values Using a Sequence of Regression Models. Survey Methodology 2001;27(1):85-95.

VERSION 2 – REVIEW

REVIEWER	Bjørn Heine Strand Norwegian Institute of Public Health.
REVIEW RETURNED	21-Aug-2015

GENERAL COMMENTS	The reviewer completed the checklist but made no further comments.

REVIEWER	Oscar Bernal U Andes, Bogota Colombia
REVIEW RETURNED	22-Aug-2015

GENERAL COMMENTS	The reviewer completed the checklist but made no further comments.