Author's response to reviews

Title: Increased incidence of kidney diseases in general practice after a nationwide albuminuria self-test program

Authors:

Julia de Borst (juliadeborst@gmail.com)
Markus M.J. Nielen (m.nielen@nivel.nl)
Robert A Verheij (r.verheij@nivel.nl)
Francois G Schellevis (f.schellevis@nivel.nl)

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Author's response to reviews: see over
May 27, 2011

Dear Sir / Madam,

Please find enclosed the revised manuscript ‘Increased incidence of kidney diseases in general practice after a nationwide albuminuria self-test program’. We would like to thank the reviewers for the valuable suggestions, which improved the quality of the manuscript. A point-by-point response to the concerns of the referees is added to this cover letter. All changes in the revised manuscript are marked blue.

The next five weeks (until the first week of July) I will not be at NIVEL and will not be able to respond on e-mails. Please contact one of the co-authors, Robert Verheij (r.verheij@nivel.nl), for questions during this period.

We hope that you will find the manuscript suitable for publication, and look forward to hearing from you.

Yours sincerely, also on behalf of the co-authors

Mark Nielen, PhD
We would like to thank the reviewers for their useful comments, which has improved the quality of our paper. Changes are marked blue in the manuscript.

Reviewer: Anteo Di Napoli

MAJOR COMMENTS

1 Abstract: The authors did not report the study design in the methods or background section.
We added the following sentence to the methods section of the abstract: ‘Data were used from the Netherlands Information Network of General Practice (LINH), including a representative sample of general practices with a dynamic population of approximately 300.000 listed patients’

2 The 4-week moving average may be not adequate to model a pre-post study, especially when the intervention is so limited in time.
We agree with the reviewer that the 4-week moving average is not adequate for using in the Cox regression analyses. However, this method was only used to calculate the number of contacts with the GP for kidney diseases per 10,000 consultations per week in the year before and after the intervention. This first step of the analyses was performed to give more insight in the course of the number of kidney disease consultations per week. We have made a clearer distinction between this descriptive analysis and the statistical analyses in the methods section of the revised manuscript.

3 The model used for multivariate analysis is a survival time analysis. However, in this case we are not interested to the time to event, but to the occurrence or not of the event after self-test program. Consequently, I think the best analysis would be a Incidence Rate Ratio.
We agree that the most important outcome is whether or not a new event occurs. However, we had several reasons to prefer Cox regression above logistic regression analyses:
1) For this study we used a dynamic population. As a result, not all patients had a follow-up period of a whole year. Cox regression makes it possible to also include patients with incomplete follow-up. This not only results in a more precise estimate of the effect, but also prevents selection bias.
2) We expected that new events occurred earlier in the year after the intervention compared with the year before the intervention. Cox regression makes it possible to compare the number of newly detected cases with the time of occurrence.
3) With Cox regression Hazard ratio’s are calculated, which can be interpreted as an Incidence Rate Ratio (or as a Relative Risk). This makes it possible to compare the output of the regression analyses with the incidence rate ratio’s calculated in the revised table 2 (see also comments below).
Since both reviewers and the associate editor questioned the use of this technique, we have described in more detail why we have used Cox regression in the revised manuscript.

4 Given that target age for screening is an open issue, and the Dutch intervention was very comprehensive, age stratified analysis would be very interesting for the readers.
We agree with the reviewer that subgroup analyses would be very interesting. Therefore, we have added the results of stratified analyses to table 2. Incidence rates are calculated for both periods, stratified by age (18-45 years, 46-65 years and >65 years), the presence of hypertension (yes/no) and the presence of diabetes mellitus (yes/no). Furthermore we used these incidence rates to calculate incidence rate ratio’s (risk ratio’s). As a result, the revised table 2 is also more in line with the results presented in table 3.

5 The graph of figure 1 is reported only for the total GPs’ contacts. The authors should present the graph by type of visit and diagnosis, as they did for all the analyses they performed.
Figure 1 was added to the manuscript to give more insight in the course of the number of kidney disease consultations per week (see also response on comment 2). We agree that it would be interesting to present the graph by type of visit and diagnosis, however we prefer to focus on the results of the regression analyses instead of a more descriptive analysis. In the revised manuscript we have made a clearer distinction between the descriptive analysis (figure 1) and the regression analyses.
6 The results of tested interactions, one of the most important findings, are presented in an unclear way. The results of the interaction between fear of urinary disease (U27) and hypertension are not reported.

We agree with the reviewer that the results of the regression analyses are presented in an unclear way. In the revised manuscript we changed table 3. Per ICPC-code we report the hazard ratio with 95% confidence interval, followed by the p-values of the interaction with hypertension and diabetes mellitus, respectively. In case of a statistical significant interaction, the size of the effect is described in the text of the result section.

7 The discussion does not afford the main issues in screening for chronic diseases:
- Increase in incidence due to early diagnosis of asymptomatic people (the transformation of preclinical prevalence in screen detected incidence).
- The potential for over-diagnosis (a different phenomenon from the first one), i.e. the cases diagnosed by screening that would not be diagnosed for symptoms, because of death for other causes of the subject before symptom onset or because most of patients detected would have a low risk of progression to end stage renal disease.
- The limits of sensitivity and specificity of self dipstick testing as an initial screening for urine could determine an inaccurate identification of persons with false-positive results. As a consequence unaffected persons could be exposed to unnecessary and/or potentially harmful additional testing (i.e. renal biopsy) and to potentially adverse effects of ACE inhibitor or ARB therapy.
- The choice to invite all Dutch adults to self-test for screening. The authors should discuss the problem to screen for proteinuria also young persons and subjects without hypertension or diabetes. Probably a more selective focusing on high-risk groups could be more cost-effective. In fact lack of cost-effectiveness arises when the prevalence and incidence of proteinuria is very low and consequently the risk of renal disease progression is very low, too.
- The authors could discuss the limits and advantages of self testing in the real practice.
- The authors could discuss the limits and advantages of a spontaneous participation after mass campaign.

The aim of this study was to investigate the influence of the screening program on the number of GP contacts for urinary complaints and/or kidney diseases and the number of newly diagnosed patients with kidney diseases by the GP. The increased HRs we found in this study are caused by a combination of factors: 1) a direct result of participation in the campaign, 2) an indirect result of the campaign (see introduction) and 3) the ‘natural course’. We agree with the reviewer that main issues of screening could be described in more detail in the discussion section. However these issues are already described for this self-test program in a published paper (Nielen MM, Schellevis FG, Verhij RA: The usefulness of a free self-test for screening albuminuria in the general population: a cross-sectional survey. BMC Public Health 2009; 9:381). Since we think that it would improve the manuscript, we have added a summary of these main issues of this self-test program in the introduction and discussion section of the revised manuscript.

MINOR COMMENTS
I feel that the authors could add other reference to the bibliography of their paper. In particular, I suggest to add the following ones:

We would like to thank the reviewer for these suggestions. However, these papers describe the main issues of screening, which is not the focus of our paper (as we described in response on comment 7).
Reviewer: Susan Lynn Hogan

Major Compulsory Revisions

Methods
1. Second paragraph: 95% confidence intervals should be described for the person-time incidence rates, and then added to the results.
In the revised manuscript table 2 is changed (see also response on comment 4 reviewer 1). Since the association between newly detected kidney diseases and the period is the most important outcome, we have only added 95% confidence intervals to the Rate Ratio.

2. Last paragraph: The rational and definitions used for Cox regression analysis need to be better delineated and explained. Also a justification for use of a time-to-event analysis should be included since the timeframe is generally short for needing this type of modeling. The definitions for the start points, end points and censoring points need to be clearly stated in terms of the modeling requirements. The interaction terms used need to be specified. The methods should also state that 95% confidence intervals were used.
We agree with the reviewer that the use of Cox regression could be described in more detail. The reasons to prefer Cox regression above logistic regression analyses are described in the response to reviewer 1 (comment 3). Furthermore the use of 95% confidence intervals and interaction terms are described in more detail.

Results
3. First paragraph: Add absolute numbers for each the percents in the first paragraph.
We have changed the percentages into absolute numbers.

4. Second paragraph: The increased rates should be expressed as ‘increased by approximately 5 per 10,000 consultations to 25 to 30 per 10,000 consultations (use correct values- this is just an estimate/example). In the last sentence, reword some (a suggestion: ‘…in the first four weeks of period 2 to as high as an additional 10 per 10,000 consultations’).
We have changed this in the revised manuscript.

5. Third paragraph: 95% confidence intervals for the incidence rates are needed here and in Table 2. Due to changes in table 2 (see also response on comment 4 reviewer 1 and comment 1 reviewer 1), this paragraph of the results is rewritten. 95% confidence intervals are added to the presented rate ratio’s.

6. Paragraph four: More explicit results and explanations for the interaction results are needed. First, the absolute values and percents in these subgroups should be described (and possibly also provided in the table). After this information, then the hazard ratios can be provided, with reference for each hazard to what the reference or comparison group is defined as. The results would likely be easier to follow if hazard ratios and 95% confidence intervals for the subgroups were provided in a table. This information could be added in a separate section within Table 2 after the significant interaction terms are given.
We agree with the reviewer that the results of the regression analyses are presented in an unclear way. In the revised manuscript we changed table 3 (see response on comment 6 reviewer 1). The HRs of the subgroups are described in more detail in the text of the manuscript. We have chosen not to include this in the table, because it makes the table more difficult to read.

7. Table 2: add 95% confidence intervals and summary measures by diabetes hypertension or the absence of these two
See response on comment 4 reviewer 1 and comment 1 reviewer 1.

8. Figure: The figure will be easier to interpret with dashed references lines displayed to show the differences highlighted in the text. Also, the x-axis could be limited to range from 15 to 45 per 10,000 to more clearly show the variations in the numbers across time.
We added dashed reference lines to the graph and changed the scale of the x-axis.

Discussion
9. The discussion should provide a statement of public health relevance and benefit of this study particularly since the results are from a nationwide parent study. It would also be useful to include some thoughts on the potential impact of these results beyond this study and on the results may or may not translate to other programs/countries (generalizability). There are no cost/benefit estimates, at the very least, some mention of the importance of this for future studies.

The introduction and discussion are changed in the revised manuscript (see response on comment 7 reviewer 1).

Specific Essential Minor Revisions/Comments:
10. Background; First paragraph first sentence. It is not clear from the references that chronic kidney disease has been included in with cardiovascular disease and diabetes mellitus as a lifestyle-related disease. A slight difference in wording can clarify this for the introduction.
We have changed the first sentence of the introduction in the revised manuscript.

11. Third paragraph: ‘a large number of probably false positive test results was found’ needs to be more clearly stated in the context of the program’s results and impact. It would be helpful to provide a summary of the actual increases in diagnoses of kidney diseases, hypertension and diabetes found in the program and already published.
The introduction and discussion are changed in the revised manuscript (see response on comment 7 reviewer 1).

12. Fourth paragraph: remove the double use of ‘self-test’ in the first sentence.
We have removed this in the revised manuscript.

13. Methods; First paragraph, first sentence: include ‘urinary’ before ‘complaints’ in all instances throughout the paper (in many cases, just ‘complaint’ or ‘complaints’ is used.
We have changed this in the revised manuscript.

14. Discussion; Typos – 5th line change ‘chance on’ to ‘chance of’; second to last line on page 11 change ‘cancer screening increased with’ to ‘cancer screening increased by’; last line of middle paragraph on page 12 change ‘It is unknown to which extend’ to ‘It is unknown to what extent’.
We have changed this in the revised manuscript.
Comments from the Associate Editor

The Reviewers’ comments are very consistent with each other. In particular: 1) the use of COX regression is questioned and I agree with them that time to event is not the most important thing to be modeled. Rather, the probability of the event is more relevant. 2) The presentation of some of the results is incomplete. 3) The discussion about false positives over diagnosis etc. is inadequate.

We have responded on all comments and revised the manuscript.

1) Copy-editing
We recommend that you copyedit the paper to improve the style of written English. If this is not possible, you may need to use a professional copyediting service. Examples are those provided by the Manuscript Presentation Service (www.biomedes.co.uk), International Science Editing (http://www.internationalscienceediting.com) and English Manager Science Editing (http://www.sciencemanager.com). BioMed Central has no first-hand experience of these companies and can take no responsibility for the quality of their service.

We agree with the editor that the style of written English could be improved. Therefore, we have edited the manuscript where needed.

2) Acknowledgements
Please include an Acknowledgements section between the Authors’ contributions section and Reference list. Please acknowledge anyone who contributed towards the study by making substantial contributions to conception, design, acquisition of data, or analysis and interpretation of data, or who was involved in drafting the manuscript or revising it critically for important intellectual content, but who does not meet the criteria for authorship. Please also include their source(s) of funding.

3) Ethics
Please include a statement in the ethics section regarding the study’s exemption from ethical approval in the Netherlands.

We added this to the methods section of the revised manuscript.