Author's response to reviews

Title: Prostate-specific antigen (PSA) screening and follow-up investigations in Maori and non-Maori men in New Zealand

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Author's response to reviews: see over
Reply to the reviewers

We are very grateful to the three reviewers for their comments and suggestions that certainly have helped to improve the manuscript.
We have addressed reviewers’ comments point-by-point in the text below. Our replies are highlighted in bold italics script. The manuscript has been revised accordingly. All changes were tracked.

Many thanks.

Sincerely,

Zuzana Obertova on behalf of the authors

Reviewer 1: Ben Hudson

Reviewer’s report:
This paper casts light on an area of importance in public health and clinical practice, and builds on work already published by the authors. A clear research question is asked and an appropriate method has been used. The results are clearly presented and they inform the discussion. A few minor essential revisions regarding the Abstract, Methods and Discussion sections follow:

1. The abstract is clear and provides a good summary of the work. It would be useful to demonstrate in the Results section of the abstract that the differences observed between M#ori and non-M#ori were statistically significant – suggest include RRs with CIs here. 

2. Some results are presented in the Methods section – e.g. lines 130-131 and lines 172-173. These should be moved to the Results section. We would prefer to leave the text in lines 172-173 in the Methods section, just to illustrate for international readers the relative homogeneity of the non-Maori group.

3. In the Strengths and Limitations section at line 314 the authors mention that the study was “powered for the assessment of screening rates...” However, no power calculation is presented, and given the nature of the study and the lack of prior data its absence seems reasonable. This phrase should therefore be removed, but the subsequent comment on the lack of power to comment on referral and biopsy rates is important and should be retained.

4. At line 326 in the Conclusions the authors comment that their finding that M#ori men were more likely to have an elevated PSA than non-M#ori men suggests “that screening would be more effective for M#ori men”. Given the ongoing uncertainty about a mortality reduction with PSA screening and the clear harms associated with it, this statement is too strong and is not supported by the research findings – an equally valid interpretation could be that M#ori men are currently being protected from the harms of a form of screening that is yet to show clear benefits! A more neutral framing of the comment would be preferred.

We rephrased the text following reviewer’s suggestion.
5. At line 336 in the Conclusions, the authors propose that prostate cancer pathways “need to be organised so that men receive standardises (sic) evidence-based equitable care.” Are they sure that they mean standardized care? Again, given the uncertainty about the balance of benefit to harm with this form of screening, and the competing priorities that any individual man will bring to this decision, surely a standardised approach is undesirable? I suggest the authors consider advocating for an approach which ensures men are provided with clear and up to date information about the benefits and harms of screening and are supported in a process of shared decision making. (Note also the typos “caner” and “standardises” here).

*We rephrased the text following reviewer’s suggestion.*

**Reviewer 2: Manuel Zorzi**

**Reviewer’s report:**

I read with interest the paper by Obertova et al, that analyses the screening rates with PSA test and subsequent diagnostic workup in a population from New Zealand by ethnic group, Maori vs non-Maori. The authors found lower screening rates for Maori and for the patients of practices governed by Maori groups. This is a well conducted and properly reported study. I have only one major and some minor points to underline.

**Major Compulsory Revisions**

1. The authors found lower screening rates among the Maori, which is coherent with the epidemiological figures of lower incidence rates of- and higher mortality rates for prostate cancer. They also found that general practices conducted by Maori, that have a higher proportion of Maori patients, are characterized by lower rates of PSA prescription. However, the reported results regarding screening rates and type of practice (Maori vs nonM) does not allow to understand if and how much the lower screening rates among the Maori are associated with the ethnicity of the patient and/or with the prescription patterns of the Maori practices. I encourage the authors to carry out some multivariate analysis in order to disentangle the effect of patients’ ethnic group from that of the type of practice. This result is of primary interest mainly at a local level, because it could highlight the underlying reasons of the observed disparities and help to focus future efforts to reduce them.

*We certainly agree that it is important to elucidate the effect of ethnicity and prescription patterns. However, we are not sure whether a multivariate analysis would be help to clarify the issue. As shown in Figure 2 Maori men are less likely to be screened regardless of the characteristics of the practice, while only Maori provider practices have actually a more equal screening ratio by ethnicity. We also emphasised throughout the paper that GPs are the driving force behind screening patterns and it seems that for yet unknown reasons they are less likely to screen Maori men.*

**Minor Essential Revisions**

2. Lines 108-109: the last part of the sentence that starts on line 105 should be clarified. In its actual form, it seems to suggest that the effect of a high PSA screening rate on prostatic cancer incidence and mortality is entirely due to over-detection of indolent cancers. In fact, this is not the case, otherwise we would expect to observe only differences in mortality. PSA screening has been shown to produce a proportion of overdiagnosed cancers, as well as the diagnostic anticipation of a proportion of ‘truly aggressive’ cancers (i.e. not over-diagnosed) that determines an impact on mortality rates.
The sentence was changed following recommendations of Reviewer 2 and 3.
3. Lines 139-144: are there other Laboratories (in particular private Labs) whose records have not been available for this study? If so:
- are there estimates of their volume of PSA tests in the studied cohort?
- Is it possible to evaluate whether their coverage on Maori and non-Maori is different?

No, there are not. All tests ordered in the region, whether from the public or private sector are processed in the three laboratories mentioned in this paper.
4. Lines 142-144: what has been the geographical mobility of the studied population during 207-2010? Is it possible to evaluate whether it is different by ethnic group?

It is probable that there has been some mobility, but most men would move within the region. Mobility rates would be comparable between Maori and non-Maori men, even though the reasons for mobility may differ by ethnicity.
5. Lines 182-186 and Table 4: the description of the differences between Maori and non-Maori practices as in Table 4 has some limitations, e.g. the figure about the proportion of Maori men enrolled in Maori-practices is not available and it could be 21% as well as 99%. The authors could consider using different (or adding) data about the characteristics of the two groups of practices, in order to help the readers to better understand the differences.
Table 4 was excluded following recommendations of Reviewer 3. Some text was added for clarity.
6. Line 234: the authors should report if there are differences between Maori and non-M practices in terms of referral rates in case of elevated PSA result and of biopsy rates following referral. It is interesting to see if Maori practices are characterized only by a lower PSA prescription pattern or also by different referral rates of high PSA patients and biopsy rates after referral.

We agree that this is an important question to answer. However, we will not be able to do so with this dataset, since there were only 10 men (2 Maori) who had an elevated PSA result following screening in Maori provider practices. Future research might provide the answer.
Discretionary Revisions
7. Lines 93-94: please report the figures of screening rates in clear
We would prefer to keep the sentences as they are for the sake of brevity.
8. Lines 157-158: please report in clear the threshold values utilised for PSA test
Text was altered accordingly.
9. Tables 1, 2 and 3: I would replace the terms ‘from tested men’, ‘from screened men’ etc, with ‘% of tested men’ (or x 100 tested men), etc, or with something similar according to the editorial rules.
Text was altered accordingly.

Reviewer 3: Lauro Bucchi
Reviewer’s report:
I read with interest the manuscript of Obertova et al. (Prostate-specific antigen (PSA) screening and follow-up investigations in M#ori men and non-M#ori men in New Zealand: a cohort study) that was submitted for publication in BMC Family Practice. The paper would with an extensive revision provide an important insight into prostate cancer inequalities between M#ori men and
non-M\#ori men in New Zealand. I hope my English is sufficiently clear as to make my suggestions understandable.

**Discretionary Revisions**

105-109. The two interpretations suggested by the Authors for the comparatively low incidence and high mortality among M\#ori men are not alternative. They both point to a difference in screening rate. I would rephrase the sentence approximately as follows: It is unclear whether the low prostate cancer incidence and high mortality for M\#ori men are due to disparities in screening and biopsy rates, with later tumour stage at diagnosis for M\#ori men and over-detection of early-stage indolent cancers for non-M\#ori men.

*Text was altered accordingly.*

175-176. For sake of clarity, please replace <60 with 40-59 and <70 with 40-69.

*Text was changed accordingly.*

196. “... Northern Y Ethics ...”. I guess Y is a typing error. Please check.

*It is the correct designation of the Committee.*

222-229. The characteristics of practices with M\#ori and non-M\#ori providers are sufficiently described in the text. Table 4 seems rather unnecessary.

*Table 4 was excluded as advised.*

**Minor Essential Revisions**

122. Please give the total number of practices in the study area.

*The information was added to the text.*

122-123. Midland Cancer Network (MCN). I think that the DHBs of Waikato, Bay of Plenty, and Lakes – not the MCN – should be indicated as the geographical basis of the study. In other words, I would write “... enrolled in 31 general practices in the District Health Boards (DHBs) of ...”.

*The MCN was the initial geographical unit considered for the study, therefore we would prefer to keep it that way. However, we altered the text slightly, which may add some clarity.*

124. “... purposefully selected to ensure sufficient numbers ...”. Please, specify what approach was used to ensure sufficient numbers.

*We over-sampled practices with high proportion of Maori men. We added text in the Result section.*

127. “... population of 680,000 ...”. Does this number include males and females of all ages? If so, I suggest the Authors to give only the number of males aged 40+ years living in the study area, and to modify the statement “... of whom 24% are of M\#ori ethnicity”. Probably, this figure applies to the whole population of both sexes, since “The estimated proportion of M\#ori men aged 40+ years residing in the MCN region in 2010 was 14.4%” (Results section, 204-205).

*Text was altered following suggestions of Reviewer 1 and 3.*

128-129. What is the Authors’ comment on Figure 1? They probably concluded that the two populations were closely comparable. This should be stated.

*Text was altered accordingly.*

130-131. “... 24.5% of the estimated overall population ...”. Perhaps the Authors meant “... of total males aged 40+ years in the study area”. Please clarify.

*Text was altered accordingly.*
135-138. Baseline data. I suggest to indicate here all of the data provided by the general practices, including symptoms and biopsies, and not the only data the demographic information.

The information on baseline data was shifted to the section on study population.

136. “… identification code …”. Please clarify whether the code provided by the general practices was the NHI code (line 141). If so, please use the same terminology.

Text was altered accordingly.

139-140. In lines 135-136, it reads that all practices used the Healthtech Medtech software for recording patient data, clinical notes, and laboratory results. So, I don’t understand why PSA test results were obtained with record linkage with three (external) laboratories. I suppose that PSA test results, in fact, were not recorded (or not completely) in the practices’ files. Please clarify.

The computer systems of the practices and laboratories were not inter-connected, therefore we needed to cross-validate information on PSA tests and biopsy from the practices with laboratory data in order to be sure that data are complete.

143. “…three community laboratories…” It is not clear whether these three laboratories were the only ones in the study area or – at least – the only ones that were used by the 31 general practices for their patients.

Text was altered accordingly.

151. Please provide at this point of the ‘Data sources’ section the statistical references no. 21 and 23 (what data were taken and with which objective). They currently appear the Results section. Most journals do not accept that references are cited in the Results section.

We altered this section according to Reviewer 1, and would prefer to keep the references in the Results section.

163. Please clarify the meaning of the term ‘relevant time period’. Does it mean the three years prior to 2010 or the year 2010?

Text was altered accordingly.

165. “… men with an elevated PSA result (both screened and not screened) …”. I don’t understand what the term ‘not screened’ means. Does it mean ‘PSA-tested for non-screening purposes’? If so see below: lines 200-204.

This was an oversight, we deleted the irrelevant text.

166-168. “Biopsy data from practice records were cross-referenced with laboratory records to ascertain data completeness”. Did the Authors mean that biopsy information was cross-checked with ‘pathology’ records? And what items of information were checked for completeness? Please clarify.

Text was altered accordingly.

172-173. NZ European or other European. Does NZ European indicate a New Zealand citizen of European origin? The term ‘other European’ is totally obscure to me. I apologize my ignorance. Please clarify for me and for those potential readers who are not familiar with New Zealand demographics.

Text was altered for the sake of simplicity.

173-174. Please move the entire sentence “Patient who … personal information” to line 171, after the term ‘records’.

Text was altered accordingly.
... governed by M#ori groups ...”. Sorry, I don’t know anything of the New Zealand health care system. What is a “M#ori group”? Please clarify.

**Text was altered and more explanation added in the next sentence.**

180. “... have a special focus on M#ori patients ...”. Please clarify what this sentence specifically means.

**Text was altered and more explanation added.**

191. “... and cancer ...”. Probably, Authors intended to write ‘prostate cancer detection rate’. **Text was altered accordingly.**

196. “... M#ori consultation ...”: This is interesting. Why the consultation was deemed necessary?

205. Reference no. 21: see above: line 151. **As mentioned above, we would prefer to keep the references in the Results section.**

208. Reference no. 23: see above: line 151. **As mentioned above, we would prefer to keep the references in the Results section.**

219-220. Can the authors provide some information about the frequency of repeat PSA testing among M#ori and non-M#ori men who were not referred? **The rate of repeat PSA testing was 9.1% for referred and 15.4% for non-referred Maori men, and 36.4% for referred and 48.3% for non-referred non-Maori men.**

Discussion. I suggest that this section be shortened.

252-257. As stated above, it would be interesting to assess the rate of repeat PSA testing among M#ori men compared with non-M#ori men. **We replied to the reviewer above but since we mentioned that higher proportion of non-Maori men was tested previously in lines 246-248 we feel that the information would be repetitive.**

263-278. I suggest to shorten this paragraph, which deals with general problems encountered in delivering PSA screening, not with the problem of screening inequalities between M#ori men and non-M#ori men. **Although the section does not directly address inequalities it discussed potential reasons for variations in screening practices, and variation in practice often reinforces inequalities.**

279-282. If needed, please modify the sentence taking into consideration the probability of M#ori men being screened in M#ori provider practices versus non-M#ori provider practices (see above, 230-234). **Overall, Maori men were less likely to be screened in both Maori and other provider practices, just the magnitude of difference was slightly larger for other provider practices.**

282-284. This sentence is unnecessary. Uncertainties about the benefits and harms of PSA screening applies to non-M#ori men as well as to M#ori men. Moreover, it seems to me that the study is based on the assumption that differences in screening rates have an impact on both incidence and mortality (Introduction). **Text was deleted.**

33-58. The Abstract, which is well-structured, should be modified according to above suggestions. **Since no major changes were made to the results or their interpretation we feel that the abstract does not need to be altered (except for the changes suggested by Reviewer 1).**

Major Compulsory Revisions
I don’t think this is a cohort study (i.e., an incidence study). The term follow-up is commonly used to indicate assessment for a positive screening test result. However, follow-up for a positive test result is not a longitudinal design, since screen-detected cancers are considered to be already present at the time of testing. This is the reason why patients with positive PSA test results were “followed-up” in this study (like in many others) a for a relatively short time period. The study reports the prevalence of PSA testing and the detected prevalence of cancer, and this is equivalent to saying that it is a cross-sectional study. In any case, the title I suggest is “Prostate-specific antigen (PSA) screening and follow-up investigations in M#ori and non-M#ori men in New Zealand”. By implication, the term ‘cohort’ should be replaced throughout the manuscript.

We deleted the title section following the reviewer’s suggestion. However, we kept the word “cohort” in text since it relates to the cohort of men aged 40+ years, which was examined for screening and follow-up investigations.

The Authors correctly identified the patients who were PSA-tested for non-screening purposes, that is, men with previous positive tests, biopsies, and symptoms (Methods section, 160-164). As consequence, it is not clear why they excluded only the 1006 patients with previous prostate cancer and the 774 with unknown ethnicity. Men with previous symptoms and biopsies cannot be retained in the study, because it can be safely assumed that they were not tested for screening purposes.

We retained those tested for other reasons in the baseline since the number was not large and since symptoms were not assessed for the total cohort but only for men with elevated PSA results, we preferred not to overestimate screening rates even more than they potentially already were.

The screening rate for M#ori men was 11.2% compared with 22.6% for non-M#ori men...”. These figures are the same as those reported in Table 2 but they differ from those reported in Table 1, i.e., 13.0% and 26.9%. One hypothesis that can be raised is that the latter figures include men who were not tested for screening purposes. If this is the case, they should be excluded from the study.

These percentages are shown for the reader to assess for themselves the overall PSA testing rate, therefore we would prefer to keep the numbers in Table 1.

Table 3. I recommend to modify this Table. First, the rationale for stratifying the results by age is unclear, and the numbers are too small. So, I suggest removing the <70/70+ years strata and leaving only the totals with the M-H age-adjusted RR.

We agree with the reviewer that the numbers are small. However, prostate cancer care pathways are largely dependent on age, and 70 years is a common threshold for ceasing screening, not offering full diagnostic workup (mainly biopsy) and treatment options are also limited above this age. Although we did not discuss these age-related issues in the manuscript we would prefer to keep the information in for the readers.

Second, I suggest providing an essential outcome measure such as the detection rate of cancer, which is 4/557 or 7.1 per 1000 M#ori men and 23/6786 or 3.4 per 1000 non-M#ori men. The prevalence of disease was two-greater for M#ori men – despite the fact that they were younger.

We added information about detection rate from men with elevated PSA results, since this is the group considered at risk, rather than the total screened population.
230-234. To show whether the probability of M#ori men being screened relative to non-M#ori men differs between M#ori provider practices and non-M#ori provider practices, the Authors should add two ratios to those in Table 2: those for the two pools of practices. 

We added information accordingly.

249-250. The rate of follow-up (46% vs 38%, Table 3) and the positive predictive of biopsy (57% vs 62%) were similar between M#ori men and non-M#ori men, but not the detection rate of cancer (see above).

The detection rate from men with elevated PSA result was similar but we agree that because of a higher proportion of Maori men with elevated PSA result, Maori men seem to be more at risk of prostate cancer, but we will never know the outcomes unless the referral rates are approaching 100% for men with elevated PSA results.

294-296. After separating the subjects who were tested for screening purposes from those who were tested due to symptoms and disease monitoring, the latter should be excluded from the study (see above). I don’t see the rationale for comparing the true screening rates with the rates of clinical testing.

Although we retained men who had a PSA test due to other reasons than screening in the baseline, we do not think we compare screening rates and testing due to other reasons.