

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Cohort profile: A Nation-wide cohort of Finnish military recruits born 1958
AUTHORS	Sormunen, Jorma; Arnold, M; Soerjomataram, Isabelle; Pukkala, Eero

VERSION 1 – REVIEW

REVIEWER	Esther de Vries Pontificia Universidad Javeriana, Bogotá, Colombia
REVIEW RETURNED	16-May-2017

GENERAL COMMENTS	<p>This is a first description of a new cohort which can be used to investigate risk factors for cancer development in male populations. The cohort described has a very high potential for future studies, as the population ages and will accumulate more events. Besides cancer, certainly other diseases will be studied. In short, a cohort (and a paper) with a lot of potential!</p> <p>My comments are mostly questions, to understand certain choices that were (or had to be) made:</p> <ul style="list-style-type: none"> - First of all: if Finns all get recruited, why is the cohort limited to the 1958 cohort and why did the authors not decide on a wider cohort (example born between 1950-1960)? Inclusion of more years would increase numbers....and presumably the data would be available? - The cohort does not include men who were categorized in the C and D categories, whereas they were examined at baseline according to the text. As the PID of these "C and D" men is presumably known, the C and D category could also have follow-up (albeit less detailed) and may provide an interesting contrasting group for cancer and other chronic diseases. Some of them may have the disease under study at baseline but presumably at 17-30 years of age very few of them would have cancer. Having information on these men would probably not help you with the PC but could provide even tobacco and alcohol information perhaps? - Similarly, the authors describe that the sample includes 74% of the men born in 1958. Are not all men drafted? So why not 100%? (perhaps excluding the C and D category depending on your answer on the previous point)? Could you please explain? - The 1958 cohort was examined between 1975 and 1989 - could you include some description of standardization of examination over such a long time period? Did changes in measuring the different variables of interest occur? - Authors describe prevalence of smoking and alcohol consumption at first measurement - did this prevalence change during the time of
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	<p>military service of respondents? Presumably, a 17 year old boy could be "taught" to drink and smoke during service? The exit data may be of more interest than the entry data but if I understand correctly the reported prevalences are for the entry data? Authors describe that "considering the relatively stable life (STYLE) habits in (THE) majority of (THE) population" but I wonder if this is true for 17 year olds entering military service. For the 30-year olds this may apply, but for a late-teenager?!?!?</p> <p>Minor comments:</p> <ul style="list-style-type: none"> - Since the objective of the paper is to describe the cohorts, I would advise against placing the HR in the abstract. In the results one may mention them (although they are not needed). Better to focus in the abstract - results section on numbers of cases (perhaps a few "big" ones in particular), number of follow-up and prevalence of PC, alcohol and tobacco. - Should you decide to present the HR results, make it a bit more clear. For example, it is not clear to me if both the overweight and obese groups miraculously had the same HR and 95% CI, or if you analysed the group of overweight and obesity as one group. I believe probably the latter, but to avoid confusion, better present as "overweight and obese, BMI>25". Results are presented as "an association" without the caution of a wide confidence interval (and not statistically significant). - Page 5, just before the section "cohort description": authors mention "a handful" (which I would interpret as 5) of cancers, which are actually 11 cancers listed! (at least 2 handfuls!) - Consider removing the HRs from the results: your objective is to describe the cohort, not to describe the associations observed. Moreover, you did not describe methodology of analyses etc. and results are not visible in any table. Alternatively, present a table with the number of cancer cases observed (for the important groups) so far in the linkage, if possible by some subgroups or duration of follow-up. - If you do not remove the HRs, consider how to present your results of the interaction. Of course, if you include an interaction term, the individual terms for smoking and alcohol may change, and anyway become uninterpretable, so the mention that they become insignificant (I presume the interaction was significant) does not imply that their effects became insignificant...? - Depending on the journal, include a brief description of the requirements for crosslinking these data in Finland. I know it is all within the rules and regulations, but this is not specified in the paper in its current form.
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REVIEWER	Rehab Auf Florida International University, USA
REVIEW RETURNED	17-May-2017

GENERAL COMMENTS	<p>The study bears great potential as the authors describe it. It describes results from a large cohort that can be followed up for several years with link to medical records and cancer registry. However, there are several major concerns in connection to how the authors presented the study.</p> <p>1- It seems the authors are referring to BMI at baseline to examine its relation to later cancer incidence. However, the BMI during the years of follow up were not taken into consideration. If a person was overweight/obese at the service screening then became normal</p>
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	<p>weight for the rest of his life, it would not carry an equal risk as the person who continued as obese, if it would carry any risk at all.</p> <p>2- The methods and results require further clarification and elaboration. The data analysis was mentioned with the findings, this should have separate section. It was confusing to understand how they fit the referred to models.</p> <p>3- The authors presented two descriptive tables for the results, but did not present the most important part, which is the survival model (I assume this is how they estimated the HR). A table to summarize the models they fitted and corresponding HR would ease understanding their results.</p> <p>4- The authors stated in the abstract and results that in general high BMI increased the risk for cancer, while their reported HR does not support this contention (the confidence interval crosses the one, so the HR is statistically insignificant and can be attributed to random errors).</p> <p>5- It would have been ideal if they presented Kaplan Meir to compare overweight and obese to normal weight individuals risk to develop cancer.</p> <p>6- The authors did not present justification to the variables included in their model. For example, access to health service, fitness facilities, and income can play a major role in developing cancer. Why they did not consider such factors?</p> <p>7- Last point, since the age of the cohort is relatively young, genetic factors should be considered. Probably family history of similar cancer or different sites could be a good variable to consider such risk. I wonder if the authors can include this in their analysis and or provide explanation why the results stand with the exclusion of genetic factors (especially the estimated risk is very small and insignificant in the overall figure).</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Esther de Vries

Institution and Country: Pontificia Universidad Javeriana, Bogotá, Colombia Competing Interests: None declared

This is a first description of a new cohort which can be used to investigate risk factors for cancer development in male populations. The cohort described has a very high potential for future studies, as the population ages and will accumulate more events. Besides cancer, certainly other diseases will be studied. In short, a cohort (and a paper) with a lot of potential!

My comments are mostly questions, to understand certain choices that were (or had to be) made:

- First of all: if Finns all get recruited, why is the cohort limited to the 1958 cohort and why did the authors not decide on a wider cohort (example born between 1950-1960)? Inclusion of more years would increase numbers....and presumably the data would be available?

All Finnish males get recruited for national service, either military or civil service. Our team was the first civilians allowed to collect data on the military conscripts in the country. We would have collected more if we had the resources (funding) for the work which were very labour intensive. We were on a strictly limited budget which covered data collecting for 74% of one birth year cohort. Men born in 1958 did their military service mainly in the 1970s and these data were of good quality and available in a format (paper) that was accessible. This was the oldest full dataset that was available for research purposes.

- The cohort does not include men who were categorized in the C and D categories, whereas they were examined at baseline according to the text. As the PID of these "C and D" men is presumably known, the C and D category could also have follow-up (albeit less detailed) and may provide an interesting contrasting group for cancer and other chronic diseases. Some of them may have the disease under study at baseline but presumably at 17-30 years of age very few of them would have cancer. Having information on these men would probably not help you with the PC but could provide even tobacco and alcohol information perhaps?

Data on the men in classes C and D and their cancer incidence were collected as well. This part of the manuscript has been amended and clarified. They were so few, that their results would be uninformative.

- Similarly, the authors describe that the sample includes 74% of the men born in 1958. Are not all men drafted? So why not 100%? (perhaps excluding the C and D category depending on your answer on the previous point)? Could you please explain?

We were, as mentioned before, under financial constraints. We had funding to hire clerks to collect data on a random-sample of 74% of all men born in 1958.

- The 1958 cohort was examined between 1975 and 1989 - could you include some description of standardization of examination over such a long time period? Did changes in measuring the different variables of interest occur?

The Finnish Defense Forces have a very regulated training protocol for all military and medical personnel especially in relation to men's service class classification and measuring their physical condition. Over the 14-year period that these men completed their service there were no new classification or PC-measurement methods introduced in the FDF. We have amended the wording in the manuscript to clarify this.

- Authors describe prevalence of smoking and alcohol consumption at first measurement - did this prevalence change during the time of military service of respondents? Presumably, a 17 year old boy could be "taught" to drink and smoke during service? The exit data may be of more interest than the entry data but if I understand correctly the reported prevalences are for the entry data? Authors describe that "considering the relatively stable life (STYLE) habits in (THE) majority of (THE) population" but I wonder if this is true for 17 year olds entering military service. For the 30-year olds this may apply, but for a late-teenager?!?!?

As the health check-up was uniformly conducted at the beginning of the service we opted for using these data. We checked the data from the end of the service, and unfortunately only a very small amount of data on smoking and alcohol consumption had been collected at that time point.

Some men definitely increase/decrease their physical exercise, start smoking/stop smoking etc. but in big picture the changes are not a mainstream. Most men were at least 20 years old at the beginning of their military service, only a small percentage were 17year olds. Based on literature, only a quarter (26%) of those that smoke daily in their youth, were able to quit smoking later in life (Paavola et al. 2001). In addition the prevalence of leisure-time physical activity was very stable (from adolescence to adulthood), but smoking had the strongest level of continuity (Paavola et al. 2004).

Minor comments:

- Since the objective of the paper is to describe the cohorts, I would advise against placing the HR in the abstract. In the results one may mention them (although they are not needed). Better to focus in the abstract - results section on numbers of cases (perhaps a few "big" ones in particular), number of follow-up and prevalence of PC, alcohol and tobacco.

We have now adapted the text i.e. numbers and CI were removed from abstract, wording changed.

- Should you decide to present the HR results, make it a bit more clear. For example, it is not clear to me if both the overweight and obese groups miraculously had the same HR and 95% CI, or if you analysed the group of overweight and obesity as one group. I believe probably the latter, but to avoid confusion, better present as "overweight and obese, BMI>25". Results are presented as "an association" without the caution of a wide confidence interval (and not statistically significant).

Yes we analyzed them as one group. We have now clarified the text.

- Page 5, just before the section "cohort description": authors mention "a handful" (which I would interpret as 5) of cancers, which are actually 11 cancers listed! (at least 2 handfuls!)

We thank the reviewer for this comment. Wording in this chapter has been changed accordingly.

- Consider removing the HRs from the results: your objective is to describe the cohort, not to describe the associations observed. Moreover, you did not describe methodology of analyses etc. and results are not visible in any table. Alternatively, present a table with the number of cancer cases observed (for the important groups) so far in the linkage, if possible by some subgroups or duration of follow-up.

The wording and what is included in the chapter has been double-checked, however, we have left the HRs for this chapter.

- If you do not remove the HRs, consider how to present your results of the interaction. Of course, if you include an interaction term, the individual terms for smoking and alcohol may change, and

anyway become uninterpretable, so the mention that they become insignificant (I presume the interaction was significant) does not imply that their effects became insignificant...?

We have now verified the results, and also the explanation e.g. the wording.

- Depending on the journal, include a brief description of the requirements for crosslinking these data in Finland. I know it is all within the rules and regulations, but this is not specified in the paper in its current form.

The wording and what is included in the chapter has been checked. We have now included a brief description of the requirements for linkage of this cohort data with other databases in Finland, which were a permission from FDF and the National Institute of Health and Welfare in Finland. These permissions were obtained at the planning phase of this study.

Reviewer: 2

Reviewer Name: Rehab Auf

Institution and Country: Florida International University, USA Competing Interests: N/A

Dear Editor,

Thanks for the invitation to review this study.

The study bears great potential as the authors describe it. It describes results from a large cohort that can be followed up for several years with link to medical records and cancer registry. However, there are several major concerns in connection to how the authors presented the study.

1- It seems the authors are referring to BMI at baseline to examine its relation to later cancer incidence. However, the BMI during the years of follow up were not taken into consideration. If a person was overweight/obese at the service screening then became normal weight for the rest of his life, it would not carry an equal risk as the person who continued as obese, if it would carry any risk at all.

In addition to describing the cohort, the aim of this current study was to evaluate the lifestyle habits and PC measured during military service (i.e. at young age) and whether this has any effects in cancer incidence later in life. Some men definitely increase/decrease their physical exercise, start smoking/stop smoking or gain/lose weight etc. but in big picture the changes are not a mainstream (see further discussion on this topic in answer to previous reviewer). The effects of PC at young age to cancer incidence have been studied in some other papers, but never in as large a cohort as this. In the future, we plan to link the cohort to survey data collected after the military survey for about 2% of the cohort. Such a linkage will give information on the stability of BMI and physical activity after military service.

2- The methods and results require further clarification and elaboration. The data analysis was mentioned with the findings, this should have separate section. It was confusing to understand how they fit the referred to models.

We thank the reviewer for this comment. We have now added a separate sub-section entitled 'statistical methods'. This is placed before the 'Results – Findings to date' - section.

3- The authors presented two descriptive tables for the results, but did not present the most important part, which is the survival model (I assume this is how they estimated the HR). A table to summarize the models they fitted and corresponding HR would ease understanding their results.

At this point we opted to focus the paper to describing the 'cohort profile'. We agree with the reviewer that presenting the survival or overall mortality of the cohort is very interesting, and we will do that at a later stage, when the cohort is older. At the moment there are only very limited number of deaths, as such we have reported only the risk of being diagnosed with a cancer (i.e. the hazard represents the risk ratio of being diagnosed with cancer rather than died from cancer). We have clarified this in the method section.

4- The authors stated in the abstract and results that in general high BMI increased the risk for cancer, while their reported HR does not support this contention (the confidence interval crosses the one, so the HR is statistically insignificant and can be attributed to random errors).

We thank the reviewer for this comment. Following reviewer 1's advise we have now retained reporting of the Hazard Ratio and the CI in the abstract. We also believe that statistical significance should not be the only criterion to report interesting and relevant findings. We reported this finding because the result suggests a higher cancer incidence in overweight and obese men. In line with the reviewer comments, we have now added a text indicating that the finding is not statistically significant.

5- It would have been ideal if they presented Kaplan Meir to compare overweight and obese to normal weight individuals risk to develop cancer.

For the current manuscript we decided not to present a Kaplan-Meier curve for these two groups mostly due to the small number of cancer cases. In this future this might change.

6- The authors did not present justification to the variables included in their model. For example, access to health service, fitness facilities, and income can play a major role in developing cancer. Why they did not consider such factors?

Finland is a country where everyone has a universal access to public, free (or affordable) healthcare, which is of good quality. As such, income doesn't have a big effect on access to healthcare. Fitness facilities are similarly distributed throughout the municipalities for a nominal/free price to all those that are willing to use them. In addition to that we didn't have access of the socio-economic status of the men after military service at this point. We have added text to clarify this.

7- Last point, since the age of the cohort is relatively young, genetic factors should be considered. Probably family history of similar cancer or different sites could be a good variable to consider such risk. I wonder if the authors can include this in their analysis and or provide explanation why the results stand with the exclusion of genetic factors (especially the estimated risk is very small and insignificant in the overall figure).

In Finland it is indeed possible to trace the parents and sibling of persons born 1958 and check if they have had cancer. We have now added a comment on the possibility to add data on familial history of cancer in our discussion.

VERSION 2 – REVIEW

REVIEWER	Esther de Vries Pontificia Universidad Javeriana Colombia
REVIEW RETURNED	27-Jul-2017
GENERAL COMMENTS	Congratulations to the author on a very satisfactory reply to both reviewers comments and a very interesting cohort - which certainly will result in very useful studies in the (near) future.