PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Prevalence of atrial fibrillation and cardiovascular risk factors in a 63-65-year-old general population cohort: the Akershus Cardiac Examination (ACE) 1950 Study
AUTHORS	Berge, Trygve; Lyngbakken, Magnus; Ihle-Hansen, Haakon; Brynildsen, Jon; Pervez, Mohammad; Aagaard, Erika; Vigen, Thea; Kvisvik, Brede; Christophersen, Ingrid; Steine, Kjetil; Omland, Torbjorn; Smith, Paal; Rosjo, Helge; Tveit, Arnljot

VERSION 1 – REVIEW

REVIEWER	Lidia Staszewsky IRCCS - Istituto di Ricerche Farmacologiche "Mario Negri", Milan. Italy
REVIEW RETURNED	23-Feb-2018

GENERAL COMMENTS	This study results from the analysis of the baseline data from the Akershus Cardiac Examination (ACE) 1950 Study, an observational, prospective, longitudinal, population-based cohort study of subjects born in 1950. The first aim was to assess the sex specific prevalence of known and unknown AF; secondary aims were to investigate the prevalence of cardiovascular risk factors and their association with AF. Major comments 1) Study aims need to be consistent along all the manuscript (abstract, introduction, methods, ecc.) and need to follow a logical sequence: a) AF prevalence in all the study population and in women and men, b) gender differences in the frequency of CV risk factors and diseases d) AF associated variables. 2) Discussion: a) need to be shortened please consider your principal findings. b) In page 13, 3th paragraph please avoid the sentence " For this reason…… for AF." Also in page 14, 1st all the first paragraph. c) page 15. a) Clinical implications.: reference 23 need to be placed before the sentence "However, ….be justified." 3) Conclusion: need to be rephrased. Consider the structure of that written in the abstract or for example like the following: "AF prevalence in studied patients, 63-65 years old, resulted higher than expected and higher in men than in women. The frequency of cardiovascular risk factors and diseases was also significantly more frequent in men than in women; some modifiable risk factors but not gender resulted independently associated to AF."

	Minor comments 1) The present study report the results of a post-hoc analysis of the baseline data from the Akershus Cardiac Examination (ACE) 1950 Study an observational, prospective, longitudinal, population-based cohort study of subjects born in 1950, the study was not designed as a “cross-sectional study” but it is a “ cross sectional analysis”. So this concept need to be change along when it is considered along the MS 2) In page 5 I suggest to change the title BACKGROUND with INTRODUCTION 3) Could you please verify the definition of chronic kidney disease? To our knowledge to consider chronic, GFR need to be less than 60 ml/min/1.73 m2 with or without markers of kidney damage, on at least 2 separate occasions separated by a period of at least 90 days (see: ref https://www.nice.org.uk/guidance/cg182). 4) Page 8: Results. I think that to better present the study population you need to include in the “general cohort profile” the contents of the subtitle “Cardiovascular risk factors and diseases” and those of “Stroke risk factors”. 5) Page 11: Discussion – Strengths and limitations: I think that the screening participation rate was “acceptable” and not “relatively high” as considered by the authors. A study strength is the availability a 12 leads ECG in all enrolled patients (n=3706). 6) Page 13: 3th paragraph 3th sentence”: the comment …”with the obvious limitations in our cross sectional design”…. … 7) Page 14: The first paragraph is irrelevant. 8) Please verify reference 16, the original one is Heeringa J, van der Kuip DA, Hofman A, Kors JA, van Herpen G, Stricker BH, Stijnen T, Lip GY, Witteman JC. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. Eur Heart J. 2006 Apr;27(8):949-53. Epub 2006 Mar 9. PubMed PMID: 16527828.

REVIEWER	Ayodele Odutayo University of Toronto, Canada
REVIEW RETURNED	24-Feb-2018

GENERAL COMMENTS	Thank you for the opportunity to review the manuscript entitled “Prevalence of atrial fibrillation and cardiovascular risk factors in a 63-65-year-old general population cohort: the Akershus Cardiac Examination (ACE) 1950 Study” by Berge et al. The authors have conducted a cross-sectional study to estimate the prevalence of atrial fibrillation in a community dwelling cohort. The authors have also conducted ancillary analyses to examine risk factors associated with atrial fibrillation. Overall, the manuscript is clear and well written. This reviewer has very few concerns: 1. The selection of variables for inclusion in the logistic regression model based on univariate statistical significance can be problematic. This is because variables may not demonstrate statistical significance in univariable models but may have strong

	effects once confounders are controlled for (PMID: 8699212). Therefore, I would encourage the authors to at least consider a sensitivity analysis where all variables tested in the univariable setting are included in the final model. 2. Could the authors clarify in their methods how they distinguished between paroxysmal and permanent AF, give that only single time point ECG was performed? Was this based on medical records? 3. In table 4, the reference group for certain variables in unclear (e.g. physical activity). Can the authors clarify? 4. Do the authors have general characteristic data on the 2121 non-participants to compare with adults who participated. This would provide insight into the extent to which the sample is biased based on participant decisions to participate.

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Reviewer Name: Lidia Staszewsky
Institution and Country: IRCCS - Istituto di Ricerche Farmacologiche "Mario Negri", Milan. Italy

This study results from the analysis of the baseline data from the Akershus Cardiac Examination (ACE) 1950 Study, an observational, prospective, longitudinal, population-based cohort study of subjects born in 1950. The first aim was to assess the sex specific prevalence of known and unknown AF; secondary aims were to investigate the prevalence of cardiovascular risk factors and their association with AF.

Major comments

1. **Study aims need to be consistent along all the manuscript (abstract, introduction, methods, ecc.) and need to follow a logical sequence: a) AF prevalence in all the study population and in women and men, b) gender differences in the frequency of CV risk factors and diseases d) AF associated variables.**

   We agree with the Reviewer and have tried to improve consistency by rephrasing several aspects of the manuscript. We also believe that our original distinction between objectives and primary/secondary measures in the abstract (according to the standard abstract style of BMJ Open) was unnecessary and potentially unclear in this observational study. Therefore, we suggest bringing this together in the abstract's 'Objectives'.

   Abstract:
   Objectives: To investigate the sex-specific prevalence of atrial fibrillation (AF), including subclinical AF found by screening ~~and cardiovascular risk factors~~ in a general population aged 63-65 years. The prevalence of cardiovascular risk factors and their association with AF will also be investigated.

   ~~**Primary measure:** Sex-specific prevalence of known and unknown (screen-detected) AF.~~

~~**Secondary measures:** Risk factors associated with AF and prevalence of cardiovascular risk factors in this age group.~~

Introduction, page 5, last paragraph:
The primary~~ aim~~ objective of this study was to investigate the sex-specific prevalence of self-reported and ECG-validated AF, including subclinical AF found by screening, in a contemporary population-based cohort aged 63-65 years. ~~We also wanted to identify variables associated with AF diagnosis in this age group and report~~Secondary objectives were to investigate the prevalence of~~ known~~ cardiovascular risk factors and their association with AF. ~~in a contemporary population-based cohort aged 63-65 years.~~

Furthermore, we have toned down the general cardiovascular findings of the full cohort (while maintained these in the Tables), and restructured (and shortened) both the Results and the Discussion chapter to improve consistency and readability. Some of these changes are presented further below in the subsequent comments from Reviewer #1.

2. **Discussion: a) need to be shortened please consider your principal findings. b) In page 13, 3th paragraph please avoid the sentence " For this reason…… for AF." Also in page 14, 1st all the first paragraph. c) page 15. a) Clinical implications.: reference 23 need to be placed before the sentence "However, ….be justified."**

We thank the Reviewer for this suggestion, and have rephrased the 'Principal findings' more in line with the main results.

Discussion, Principal findings, page 12:
The key results of this study were that we identified a high prevalence of verified AF, whereas single time point screening by 12-lead ECG identified only 0.3% new cases in an unselected contemporary population aged 63-65 years. Body size and cardiovascular comorbidity, but not sex, were independently associated with prevalent AF at this age. ~~Although a low burden of advanced CVD was reported, we identified a high burden of obesity and hypertension.~~

Furthermore, we have shortened the Discussion by removing paragraphs addressing general cardiovascular risk factors (hypertension and obesity). For consistency (and because the above-mentioned paragraphs have been deleted), the title "Risk factors for cardiovascular disease and stroke" has been changed to "Stroke risk in AF". Furthermore, we have deleted the paragraph on AF and physical activity. We have also omitted the sentence "For this reason….for AF". At last, reference 23 has been moved. In total, the Discussion is now shortened and more focused towards AF and our principal findings.

3. **Conclusion: need to be rephrased. Consider the structure of that written in the abstract or for example like the following: "AF prevalence in studied patients, 63-65 years old, resulted higher than expected and higher in men than in women. The frequency of cardiovascular risk factors and diseases was also significantly more frequent in men than in women; some modifiable risk factors but not gender resulted independently associated to AF."**

We agree with the Reviewer and have rephrased the conclusion. Moreover, this also improves consistency throughout the manuscript (in line with comment #1).

Conclusion, page 17:
"The prevalence of known AF was higher than previously reported below the age of 65 years, and higher in men than in women. Single time point screening for AF revealed only a low number of previously unknown AF. Height, weight and comorbidity, but not sex, were independently associated with AF at this age."

Minor comments

1. **The present study report the results of a post-hoc analysis of the baseline data from the Akershus Cardiac Examination (ACE) 1950 Study an observational, prospective, longitudinal, population-based cohort study of subjects born in 1950, the study was not designed as a "cross-sectional study" but it is a " cross sectional analysis". So this concept need to be change along when it is considered along the MS**

   We thank the reviewer for this appropriate distinction; rather than referring to this study as a 'cross-sectional study', it is more precise to use the term 'cross-sectional analysis' of a cohort. We have changed this throughout the manuscript, as well as in the Abstract.

   Abstract, page 2:
   "**Design:** Cross-sectional ~~study~~ analysis of an observational, prospective, longitudinal, population-based cohort study ~~based on a prospective age cohort.~~"

   Strengths and limitations of this study, page 3:
   "This report is a cross-sectional ~~study~~ analysis of a limited age cohort~~group~~, making comparison to other study settings difficult."

   Methods, page 6, 1st paragraph:
   "…a cross-sectional ~~data from~~analysis of the baseline examination,…"

2. **In page 5 I suggest to change the title BACKGROUND with INTRODUCTION**

   This is changed as suggested.

3. **Could you please verify the definition of chronic kidney disease? To our knowledge to consider chronic, GFR need to be less than 60 ml/min/1.73 m2 with or without markers of kidney damage, on at least 2 separate occasions separated by a period of at least 90 days (see: ref https://www.nice.org.uk/guidance/cg182).**

   We thank the Reviewer for a good comment. This was discussed in the author group during the writing of the manuscript as well. Generally, repeated measurements are advisable, or even mandatory, for many diagnoses (i.e. suspected hypertension and diabetes), and, as pointed out by the Reviewer, it is mandatory for the diagnosis of chronic kidney disease. In our study setting, this was not feasible. As we only know that the eGFR was reduced at one point in time, it is more appropriate to use the term 'Reduced eGFR' in this context. We have re-phrased this in the

Methods chapter, as well as replaced ‘chronic kidney disease’ with ‘reduced eGFR’ throughout the manuscript (including Tables).

Methods, page 7, 3rd paragraph:
“Reduced eGFR (eGFR <60 mL/min/1.73 m^2), indicative of chronic kidney disease, was reported and used for the analyses~~defined as eGFR <60 mL/min/1.73 m^2~~.”

4. **Page 8: Results. I think that to better present the study population you need to include in the “general cohort profile” the contents of the subtitle “Cardiovascular risk factors and diseases” and those of “Stroke risk factors”.**

Thank you for a good suggestion in order to restructure the Results chapter. We have now included the content of “Cardiovascular risk factors and diseases” into the first paragraph; “General cohort profile”. We have kept “Stroke risk in AF” at the end of Results. In this way, a brief profile of the full cohort is presented first, followed by AF prevalence and further AF-related results (AF risk factors and stroke risk in AF). We believe this has improved the structure of the Results chapter.

For consistency, we have also omitted two sentences reporting detailed results regarding blood pressure levels, as the corresponding discussion points have been removed from the shortened Discussion chapter.

5. **Page 11: Discussion – Strengths and limitations: I think that the screening participation rate was “acceptable” and not “relatively high” as considered by the authors. A study strength is the availability a 12 leads ECG in all enrolled patients (n=3706).**

This is indeed a valid point. We initially described our participation rate as ‘relatively high’ in comparison to the general trend seen in Norway (as well as in other countries) of lower participation rates in present population studies, compared to the past. The Rotterdam Study had a truly high participation rate of 78% back in the early 1990s [1]. The Norwegian HUNT study, one of the largest population studies performed worldwide, has seen decreasing participation rates from 89% in the 1980s to 54% in the last wave; HUNT3, completed in 2008 [2].

Although no distinct definition of a high, moderate or low participation rate really exists, we agree that it may be more appropriate to label our participation rate as ‘acceptable’, as is the case for most present population-based studies. Furthermore, we appreciate the point made by the Reviewer, that the availability of 12-lead ECGs from all the participants is a strength of the study. We have emphasized this, and rephrased the relevant paragraph accordingly.

Discussion, Strengths and limitations, page 12:
“Strengths of this study include the unselected population-based design and~~ a relatively high participation rate.~~ complete, or nearly complete, data on all participants. For example, 12-lead ECGs were available from all 3706 participants. ~~Furthermore, the most important data variables were complete.~~

6. **Page 13: 3th paragraph 3th sentence": the comment …"with the obvious limitations in our cross sectional design"…. …**

   This sentence has been deleted, as part of shortening the Discussion.

7. **Page 14: The first paragraph is irrelevant.**

   We agree with the Reviewer that this paragraph (AF and level of physical activity; page 15 in revised version) is not particularly relevant. As part of shortening the Discussion, this paragraph has been removed.

8. **Please verify reference 16, the original one is Heeringa J, van der Kuip DA, Hofman A, Kors JA, van Herpen G, Stricker BH, Stijnen T, Lip GY, Witteman JC. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. Eur Heart J. 2006 Apr;27(8):949-53. Epub 2006 Mar 9. PubMed PMID: 16527828.**

   We thank the Reviewer for this good observation. We agree that the original prevalence publication by Heeringa et al. (2006) is more appropriate in this context, and have changed this accordingly.

Reviewer: 2
Reviewer Name: Ayodele Odutayo
Institution and Country: University of Toronto, Canada

Thank you for the opportunity to review the manuscript entitled "Prevalence of atrial fibrillation and cardiovascular risk factors in a 63-65-year-old general population cohort: the Akershus Cardiac Examination (ACE) 1950 Study" by Berge et al. The authors have conducted a cross-sectional study to estimate the prevalence of atrial fibrillation in a community dwelling cohort. The authors have also conducted ancillary analyses to examine risk factors associated with atrial fibrillation. Overall, the manuscript is clear and well written. This reviewer has very few concerns:

1. **The selection of variables for inclusion in the logistic regression model based on univariate statistical significance can be problematic. This is because variables may not demonstrate statistical significance in univariable models but may have strong effects once confounders are controlled for (PMID: 8699212). Therefore, I would encourage the authors to at least consider a sensitivity analysis where all variables tested in the univariable setting are included in the final model.**

   We thank the Reviewer for a relevant comment regarding our logistic regression model, raising the potentially problematic issue of omitting variables without statistical significance in univariate analysis, as these may have a relevant effect after controlling for other variables, due to confounding. The reference referred to by the reviewer was read with great interest [3].

We have performed an additional sensitivity analysis, a 'full-model fit', in which all candidate variables are put into the same model. This did not change our results substantially. The full model has been added below, and we suggest adding this as a Supplementary table and have added the following in the manuscript:

Methods, Statistical analysis, page 8:
"To assess the robustness of the model, we performed a sensitivity analysis in which all candidate variables were put into the same model."

Results, page 11, 1st paragraph:
"A sensitivity analysis, in which all independent variables were included, did not change the results (Supplementary table 2)."

	Univariate OR (95% CI)	p	Multivariate OR (95% CI) 'Original model'	p	Multivariate OR (95% CI) 'Complete model'	p
Male sex	2.73 (1.92 –	<0.0	1.00 (0.59 –	0.99	1.03 (0.61 –	0.92
Height per 10 cm	**1.90 (1.59 –**	**<0.0**	**1.67 (1.26 –**	**<0.0**	**1.62 (1.21 –**	**0.00**
Weight per 10 kg	**1.42 (1.29 –**	**<0.0**	**1.15 (1.01 –**	**0.03**	**1.16 (1.02 –**	**0.02**
Hypertension	**3.27 (2.15 –**	**<0.0**	**2.49 (1.61 –**	**<0.0**	**2.47 (1.59 –**	**<0.0**
Heart failure	**8.53 (4.71 –**	**<0.0**	**3.51 (1.71 –**	**0.00**	**3.37 (1.61 –**	**0.00**
Familial AF	**2.16 (1.55 –**	**<0.0**	**2.32 (1.63 –**	**<0.0**	**2.35 (1.64 –**	**<0.0**
Reduced eGFR	**2.87 (1.66 –**	**<0.0**	**2.56 (1.42 –**	**<0.0**	**2.43 (1.33 –**	**<0.0**
Coronary heart disease	2.88 (1.88 –	<0.0	1.56 (0.95 –	0.08	1.60 (0.96 –	0.07
History of stroke/TIA	2.09 (1.13 –	0.02	1.43 (0.74 –	0.29	1.49 (0.77 –	0.24
OSA	1.94 (1.17 –	0.01	1.11 (0.63 –	0.71	1.07 (0.60 –	0.82
Physical activity (low/normal						
Inactive	1.61 (1.10 –	0.02	1.38 (0.92 –	0.12	1.39 (0.92 –	0.12
High level	1.30 (0.88 –	0.19	1.20 (0.80 –	0.38	1.20 (0.79 –	0.39
Diabetes	1.24 (0.74 –	0.41	-	-	0.68 (0.39 –	0.19
Daily smoking	0.72 (0.44 –	0.20	-	-	0.94 (0.55 –	0.81
High alcohol consumption	0.81 (0.45 –	0.81	-	-	0.87 (0.34 –	0.78

2. Could the authors clarify in their methods how they distinguished between paroxysmal and permanent AF, give that only single time point ECG was performed? Was this based on medical records?

We thank the Reviewer for a highly relevant question. The classification of AF was made along with the validation of the self-reported diagnoses, which was performed for all self-reported cases

of AF (n=193), as well as all previously unknown cases of AF (n=12), after the baseline examinations were completed.

Medical records at the two study sites (hospitals) were used, along with available ECGs (in hospital records as well as the study baseline ECG). As an example; if AF was found in the study ECG, this was classified as persistent/permanent only if recent medical records supported this classification. In some cases (i.e. if there were doubts whether the participant had a paroxysmal or persistent AF), a repeat ECG was performed within a few days; this was not according to protocol, but was done as a clinical follow-up of our study participants. This information may also have been used to ascertain the diagnosis in the consequent validation.

We cannot rule out the possibility that some cases have been misclassified (e.g. a case of persistent AF may truly be a case of paroxysmal AF), but we believe that this procedure provided us with reasonably accurate data for AF classification. We have added the following in the Methods and Discussion section:

Methods, page 6, last paragraph:
"Available information in the medical records including ECGs, as well as the study ECG, was used to classify AF as paroxysmal vs. persistent/permanent."

Discussion; Strengths and limitations, page 13, 1st paragraph:
"Furthermore, classification of AF as paroxysmal or persistent/permanent was made based on available ECGs and medical records, and we cannot rule out that some individuals may have been misclassified."

3. **In table 4, the reference group for certain variables in unclear (e.g. physical activity). Can the authors clarify?**

In this study, level of physical activity (PA) was classified into "inactive", "low", "medium" or "high" PA, based on a previously validated model, as described in Supplementary table 1 (method) and Table 1 (results).

Both sedentary lifestyle and high level of physical activity have been suggested as risk factors for AF [4]. Accordingly, in the logistic regression model (Table 4), we wanted to assess the potential association between these groups ("inactivity" and "high PA") and prevalent AF, and we used the "low" and "medium" PA, combined together (60% of the cohort; ref. Table 1), as the reference group.

We have tried to clarify this, by adding information in the table text itself, as well as in the caption below the table (see revised manuscript).

4. **Do the authors have general characteristic data on the 2121 non-participants to compare with adults who participated. This would provide insight into the extent to which the sample is biased based on participant decisions to participate.**

Unfortunately, we do not have any information about this group, as the Regional Ethics Committee approval does not allow for the collection of any registry data from non-participants. However, we may, at a later point in this cohort study (upon ethical approval) consider applying for group-level registry data for the non-participants. This would add important knowledge towards any selection bias that may have occurred, as well as the external validity of this cohort.

References:

1. Heeringa, J., et al., Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. Eur.Heart J., 2006. **27**(8): p. 949-953.
2. Krokstad, S., et al., Cohort Profile: the HUNT Study, Norway. Int J Epidemiol, 2013. **42**(4): p. 968-77.
3. Sun, G.W., T.L. Shook, and G.L. Kay, Inappropriate use of bivariable analysis to screen risk factors for use in multivariable analysis. J Clin Epidemiol, 1996. **49**(8): p. 907-16.
4. Morseth, B., et al., The ambiguity of physical activity, exercise and atrial fibrillation. Eur J Prev Cardiol, 2018: p. 2047487318754930.

VERSION 2 – REVIEW

REVIEWER	Lidia Staszewsky IRCCS - Istituto di Ricerche farmacologiche "Mario Negri", Milano. Italy
REVIEW RETURNED	28-Mar-2018

GENERAL COMMENTS	In this version the MS was changed according to the reviewer's observations. I have not further comments for the authors.