PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Prospective cohort study of fever incidence and risk in elderly persons living at home
AUTHORS	Yokobayashi, Kenichi; Matsushima, Masato; Watanabe, Takamasa; Fujinuma, Yasuki; Tazuma, Susumu

VERSION 1 - REVIEW

REVIEWER	Philippe Vanhems Lyon University Hospital Edouard Herriot Hospital Dept of Epidemiolgy and Infection Control
REVIEW RETURNED	26-Mar-2014

GENERAL COMMENTS	1. The authors did not discussed the vaccine issue. We don't know if vaccines (especially against flu or pneumococcus) were used. Vaccine is recommanded for elderly and it is not mentionned. The vaccine effectiveness in that population might be low but that can be alos a confounder of the outcome (fever or pulmonary infection). 2. A biais must be discussed toward more severe patients censured (hospitalized or deceased). 3. A description of antibiotics or antiviral drugs used might be interesting when fever was treated. The statistical power needs to be reported, even if this calculation is done after that the study was performed. Interesting study on an important public health issue Helpfull for care management of elderly in Japan Some limitations need to be fixed

REVIEWER	Seiji Bito NHO Tokyo Medical Center, Japan
REVIEW RETURNED	14-Apr-2014

GENERAL COMMENTS	I interpret the main aim of this study is to determine the associations between basic characteristics and health status, and fever events among community dwelling elderly people. The authors examined the epidemiology study with an appropriate method. I would be concerned about the clinical applications from their study. If I were one of the authors, I would state the following from the study: "Elderly residents with lower objective functional status are more likely to have fever at home. They should be measured their temperature more frequently." I may be suspicious, however, if this

	conclusion is clinically suggestive. The main methodological concern about interpreting the result is statistical procedures. The authors should adopt recurrent survival analysis because so many frail elderly patients recur fever events in observation periods. Some patients with high risk factors may have fever recurrence some days after the disappearance of fever. If recurrence data is available, the authors should receive help by statisticians for performing recurrent survival analysis. If recurrence data is not available, they should discuss how they interpret their results without recurrence data. Abstract: The authors should state clinical implication from the study in conclusion section. Introduction: - The contents of the second paragraph were somewhat redundant and does not have direct relevance of this study. Measurements: - The authors should indicate more clearly about outcomes of fever. How they evaluate the associations between fever and patients' outcomes? Discussion: - Some contents about the interpretation of the results are shown in the "strength" section. The authors should present their interpretations from their findings independently from the "strength" section.

REVIEWER	Dr Victoria Allgar University of York United Kingdom
REVIEW RETURNED	01-May-2014

GENERAL COMMENTS	Sample size was discussed but not formal calculation was undertaken. The CI for the primary endpoint is 2.4/1000 patient-days (95% CI, 2.1 to 2.7) was +/- 12.5% which is fairly wide, and could have been reduced with larger numbers. No account was made for the centre that the patients were recruited from. What analysis package was used?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name Philippe Vanhems
Institution and Country Lyon University Hospital
Edouard Herriot Hospital
Dept of Epidemiolgy and Infection Control
Please state any competing interests or state ‘None declared’: Non declared

1. The authors did not discuss the vaccine issue. We don't know if vaccines (especially against flu or

pneumococcus) were used. Vaccine is recommended for elderly and it is not mentioned. The vaccine effectiveness in that population might be low but that can be also a confounder of the outcome (fever or pulmonary infection).

Response)
Thank you very much for pointing out this important issue. We agree with your suggestion that the information on vaccine is important. However, we did not consider the confounding effect of vaccination. So we added the following comments in the discussion:

(Page15, Line16)
Another potential limitation is the lack of vaccination data. Japanese elderly people are arbitrarily vaccinated against such as pneumonia and influenza. These vaccines might be a confounder of fever and/or outcome.

2. A bias must be discussed toward more severe patients censured (hospitalized or deceased).

Response)
The point you raised is very helpful in improving our manuscript. We agree with the reviewer that the admission to hospital is likely to change the risk of fever. Therefore, we have considered hospital admission should be dealt as a competing risk event as well as death in the survival analyses. Instead of Kaplan-Meier methods, we adopted competing risk method to draw the cumulative incidence function curve in Figure. 2. In addition, Table 3 was revised by using competing-risks analyses in which both death and hospital admission were treated as competing risks. We had a major correction at the statistical analyses section as follows.

(Page 10, Line 9)
Statistical analyses
In contrast, only the first episode of fever was considered in survival analyses since some participants experienced hospital admissions hampering home medical care and stayed there, which may have an effect on risk of fever after the discharge from hospital. Therefore, we did not employ multiple failure-time data in the survival analyses. Instead we treated hospital admission as well as death as competing risk event of fever in the survival analyses using competing-risk method [18].
The cumulative incidence of first fever occurrence was determined using competing-risk method. Between-group comparisons of cumulative incidence were assessed using the method developed by PePe and Mori[19].
To evaluate an independent effect of care-need level, ADL, cognitive function and medical devices on the occurrence of fever event, competing-risks regression was employed considering death and hospital admission as competing risk [20].

3. A description of antibiotics or antiviral drugs used might be interesting when fever was treated.

Response)
We are very grateful for bringing an important point to our attention. We describe following sentence at the end of the result.

(Page12 , Line23)
Of the 229 events, 153 (67%) were treated in the home medical care setting using antimicrobial agents.

The statistical power needs to be reported, even if this calculation is done after that the study was

performed.

Response)
Thank you very much for giving us an important comment. This issue was discussed among us before beginning the research.
As we described in our pre-revised manuscript, we did not perform the exact sample size calculation. It was difficult to set up more than 5 centers at that time; however, we thought 5 centers would be sufficient for the estimation of fever incidence, the primary endpoint, with narrow 95% confidence interval, because we thought 350 participants would be recruited at least, which was estimated from the result of our previous retrospective cohort study and the scale of centers to be able to participate. In the case that the incidence is 4.0/1,000 person-day estimated from the data of nursing home and the number of participants is 350, we could observe 91,820 person-day and 367.28 events estimated based on our previous retrospective cohort study. As a result, the incidence would be 4.0/1,000 person-day with 95% confidence internal of 3.6-4.4 (around +-10% of point estimation).
The real situation was different; however, the incidence in this study was 2.5/1,000 person-day with 95% CI of 2.2-2.8, which was even narrower than that reported in our previous study (2.3/1000 patient-day with 95% CI, 1.8–2.9).
In addition to the primary outcome, we thought that the statistical power would be also sufficient in the comparison of care-need level because our previous retrospective cohort study revealed the statistically significance in spite of small sample size.

Interesting study on an important public health issue
Helpful for care management of elderly in Japan
Some limitations need to be fixed

We are very grateful for the reviewer’s favorable response. At the same time, thank you so much for your bringing many important points to our attention.

Reviewer: 2
Reviewer Name Seiji Bito
Institution and Country NHO Tokyo Medical Center, Japan
Please state any competing interests or state ‘None declared’: none declared

I interpret the main aim of this study is to determine the associations between basic characteristics and health status, and fever events among community dwelling elderly people. The authors examined the epidemiology study with an appropriate method. I would be concerned about the clinical applications from their study. If I were one of the authors, I would state the following from the study: "Elderly residents with lower objective functional status are more likely to have fever at home. They should be measured their temperature more frequently." I may be suspicious, however, if this conclusion is clinically suggestive.

Response)
Thank you very much for your suggestion. Actually, we were undecided whether to add more direct message to clinicians. We think that the reviewer encouraged us to do that. Therefore, we added the following comments in the discussion and conclusion.

(Page13, Line20)
Fever was significantly more likely to occur in wheelchair-bound or bedridden and moderate-severe cognitive impairment, which means health care providers should consider these conditions and should measure the temperatures of elderly residents with lower objective functional status more

frequently.

The main methodological concern about interpreting the result is statistical procedures. The authors should adopt recurrent survival analysis because so many frail elderly patients recur fever events in observation periods. Some patients with high risk factors may have fever recurrence some days after the disappearance of fever. If recurrence data is available, the authors should receive help by statisticians for performing recurrent survival analysis. If recurrence data is not available, they should discuss how they interpret their results without recurrence data.

Response)
Thank you so much for bringing this point to our attention.
First of all, we did not consider the duration of hospital admission when calculating the incidence density of fever: therefore, we fixed this error, which resulted in slightly higher incidence 2.5/1000 patient-days (95% CI: 2.2 to 2.8). The incidence density has already been calculated as multiple failure events.
Second, we discussed whether to perform survival analyses with multiple failure-time survival data. In the case that we consider multiple failure-time events, the duration of hospital admission will be too cumbersome to make modeling because some participants had long duration of hospital admission; therefore, we cannot incorporate it into the model. In contrast, in the case that only the first episode of fever is a failure event, we can deal with hospital admission as competing risk event. In this manuscript, therefore, we did competing-risks regression analyses for the first event of fever.

(Page 10, Line 9)
In contrast, only the first episode of fever was considered in survival analyses since some participants experienced hospital admissions hampering home medical care and stayed there, which may have an effect on risk of fever after the discharge from hospital. Therefore, we did not employ multiple failure-time data in the survival analyses. Instead we treated hospital admission as well as death as competing risk event of fever in the survival analyses using competing-risk method [18].

Abstract: The authors should state clinical implication from the study in conclusion section.

Response)
We agree with the reviewer that we should add the following comments in the conclusion section.

(Page4, Line1) Health care providers should measure the temperatures of elderly residents with lower objective functional status more frequently.

Introduction:
- The contents of the second paragraph were somewhat redundant and does not have direct relevance of this study.

Response)
We agree that the second paragraph was redundant, so we made this paragraph more concise. We also think this paragraph may have indirect relevance of this study, but we are afraid that readers from another country are not familiar with the Japanese home medical care system. Therefore we want to describe a bit of this system if we can.

Measurements:
- The authors should indicate more clearly about outcomes of fever. How they evaluate the associations between fever and patients' outcomes?

Response)
We must apologize that our expression is not appropriate. We describe following sentence at the top of the end-point.

(Page8 , Line14)
The end-points were onset of fever (≥37.5°C or ≥1.5°C above the individual's normal body temperature), diagnosis at onset and outcomes of fever (cured at home, hospitalized, death).

We wanted to state that our outcome (end-point) of this study was fever. However, according to above sentence, the meaning of outcome is obscure. Thus, we added following sentence instead of previous one.

(Page8 , Line14)
The end-points were onset of fever (≥37.5°C or ≥1.5°C above the individual's normal body temperature), diagnosis at onset and termination of fever (cured at home, hospitalized, death).

Discussion:
- Some contents about the interpretation of the results are shown in the "strength" section. The authors should present their interpretations from their findings independently from the "strength" section.

Response)
Thank you so much for pointing out this issue. Following the reviewer's suggestion, we stated our interpretations before the strength section.

Reviewer: 3
Reviewer Name Dr. Victoria Allgar
Institution and Country University of York
United Kingdom
Please state any competing interests or state 'None declared': None declared

Sample size was discussed but not formal calculation was undertaken. The CI for the primary endpoint is 2.4/1000 patient-days (95%
CI, 2.1 to 2.7) was +/- 12.5% which is fairly wide, and could have been reduced with larger numbers.

Response)
Thank you very much for giving us an important comment. This issue was discussed among us before beginning the research.
As we described in our pre-revised manuscript, we did not perform the exact sample size calculation. It was difficult to set up more than 5 centers at that time; however, we thought 5 centers would be sufficient for the estimation of fever incidence, the primary endpoint, with narrow 95% confidence interval, because we thought 350 participants would be recruited at least, which was estimated from the result of our previous retrospective cohort study and the scale of centers to be able to participate. In the case that the incidence is 4.0/1,000 person-day estimated from the data of nursing home and

the number of participants is 350, we could observe 91,820 person-day and 367.28 events estimated based on our previous retrospective cohort study. As a result, the incidence would be 4.0/1,000 person-day with 95% confidence internal of 3.6-4.4 (around +-10% of point estimation).
The real situation was different; however, the incidence in this study was 2.5/1,000 person-day with 95% CI of 2.2-2.8, which was even narrower than that reported in our previous study (2.3/1000 patient-day with 95% CI, 1.8–2.9).
In addition to the primary outcome, we thought that the statistical power would be also sufficient in the comparison of care-need level because our previous retrospective cohort study revealed the statistically significance in spite of small sample size.

No account was made for the centre that the patients were recruited from.

Response)
We should apologize that our description was ambiguous. We changed the following sentence in the methods section.

(Page8, Line6)
The participants comprised all patients aged ≥65 years who were medically managed at home by physicians at the above 5 center clinics.

What analysis package was used?

Response)
We added the analysis package in the statistical analysis section.

(Page11 , Line7)
Statistical analyses were carried out using STATA 12 (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP) .& 13 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP).

VERSION 2 – REVIEW

REVIEWER	Seiji Bito NHO Tokyo Medical Center, Japan
REVIEW RETURNED	17-Jun-2014

GENERAL COMMENTS	The revised version seems appropriate for publication.