PEER REVIEW HISTORY

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This paper was submitted to a another journal from BMJ but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open. The paper was subsequently accepted for publication at BMJ Open.

(This paper received three reviews from its previous journal but only two reviewers agreed to published their review.)

ARTICLE DETAILS

TITLE (PROVISIONAL)	Trends in the prevalence of airflow limitation in a general Japanese population: two serial cross-sectional surveys from the Hisayama Study
AUTHORS	Ogata, Hiroaki; Hirakawa, Yoichiro; Matsumoto, Koichiro; Hata, Jun; Yoshida, Daigo; Fukuyama, Satoru; Inoue, Hiromasa; Kitazono, Takanari; Ninomiya, Toshiharu; Nakanishi, Yoichi

VERSION 1 – REVIEW

REVIEWER	Jonathan Benzaquen Department of Pulmonary Medicine and Oncology, Université Côte d'Azur, CHU de Nice, University Hospital Federation OncoAge, 06001 Nice Cedex 1, France
REVIEW RETURNED	20-Jun-2018

GENERAL COMMENTS	The authors performed a descriptive analytical epidemiology work comparing the prevalence of obstructive airways disorder of a Japanese population in 1967 versus 2012 and its association with certain risk factors including smoking and pollution. The article is well written, the figures and the take-home messages are clear. The value of this work is high considering the frequency and the cost of this pathology, the evolution of the prevalence of smoking and changes in its sex ratio, and the pollution prevention campaigns implemented in Japan in recent decades. Here are some remarks: **Major remarks:** - Remark 1: In the introduction, the definition of COPD should be further clarified. Indeed, emphysema is not in itself a cause of COPD but is frequently associated with COPD. Concerning the COPD's risk factors, they are not limited to smoking and pollution, so I do not think that this definition should be exclusive. It would perhaps be more appropriate to specify that these both causes are largely majority in frequency, but without being exclusive (genetic causes such as the deficit in A1AT, other causes of emphysema...)

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	- Remark 2: In the introduction, concerning the definition of COPD, it is certainly necessary to specify that the diagnosis requires pulmonary function test including a bronchodilator reversibility test. It should then be remembered the limit of the study: the absence of post-bronchodilator measurement of the FEV1/FVC, implying that here is analyzed the prevalence of chronic obstructive airways disorder and not COPD which in its definition includes the fact that obstruction is non reversible (i.e post bronchodilator FEV1/FVC ratio 70%) Indeed, the transition between "defining COPD" and "clinical and epidemiological interest of the study" is confusing, and could lead readers to believe that the prevalence of COPD are here studied, which is not the case. It would therefore be interesting to explain that the obstructive airway disorder discovered in those patients, includes several diagnostic hypotheses that could be COPD, but could also be any other cause of chronic obstructive ventilatory disorder (especially asthma, but also bronchiectasis, etc, ...) - Remark 3: Concerning the discussion and conclusion, following the previous remarks, the conclusions regarding evolution of the epidemiology of COPD should also be moderated. The study actually evaluated evolution of the epidemiology of chronic obstructive ventilatory disorder (and not COPD stricto sensu), given the lack of reversibility test data at EFRs. **Minor remarks:** - Remark 1: Regarding the list of study limitations: it may be useful to indicate that you did not have access to a pulmonary function test with assessment of reversibility post bronchodilation. - Remark 2: Regarding the list of study limitations: It may also be interesting to note that you could not exclude patients with a restrictive ventilatory disorder associated to the obstructive one - Remark 3: Regarding the list of study limitations: Resulting from these first two remarks, you can also signal that it was not possible to associate the various respiratory diseases providing obstructive ventilatory disorder with the risk factors found. Indeed, the association of an "obstructive ventilatory disorder discovered with the pulmonary function test " associated with "certain identified risk factors" have been studied, without prejudging the etiology of the ventilatory obstructive disorder, regarding that the pneumological diagnosis was not known.

REVIEWER	Jean-Marie Degryse Université Catholique de Louvain Institute for Health and Society Belgium
REVIEW RETURNED	09-Aug-2018

GENERAL COMMENTS	This is a well written paper, that report the results of two population based cross-sectional studies in the same region in Japan aiming to assess the prevalence of airflow limitation. The authors observed a considerable decrease in prevalence from 1967 to 2012 in both sexes. Furthermore the association with

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	smoking was confirmed in both surveys although the association was more important in 2012 that in 1967. The findings concerning the prevalence appear to be robust and are confirmed after age-stratification, after using different accepted cut-off values (fixed versus LLN) and after correction for potential confounders and for the fact that different types of spirometers have been used to assess lung function in both surveys. The statistical methods appear to be adequate. The authors recognise a major limitation of their study: no post-bronchodilator values of FEV1/FVC are available, neither symptoms. A few issues remain to be clarified: 1 This is not a longitudinal study but a "repeated cross-sectional study" concerning different populations (different generations) 2. The authors should be more careful in using different terms with different meanings: Chronic airway disease is not the same as chronic obstructive airway disease, airflow limitation is not a synonym of airflow obstruction, and last but not least: airflow obstruction is not a synonym of COPD. Although airflow obstruction remains a hallmark of COPD, a more comprehensive assessment involving risk factors and symptoms is needed in order to establish such a diagnosis (refs) 3. Smoking habits were assessed by means of a self-administered questionnaire and categorized as never smokers and ever/current smokers, without further quantification of the number of pack years. The "stronger" association between the airflow limitation and current/ever smoking that was found in the second cross sectional study could be biased by a more intense and longer exposure to smoking. 4. A major issue remains the lack of data concerning the reversibility of the airflow obstruction that was diagnosed. Are any data available concerning the prevalence of asthma in Japan ? 5. p9 The ATS/ERS criteria (based on LLN cut-off values) were used as "secondary principle".. The argumentation to do so is not convincing. By the way did the authors use the GLI (universal) reference values in their sensitivity analysis ? 5. Table 1 shows some striking differences between the 1967 and 2012 populations: 1. The mean age (of man and woman) is considerable different, 2. The use of anti-hypertensive medication is considerable higher in 2012 (as well as the number of subjects with a "diagnosis" of hypertension . Smoking habits remained the same for men but increased in woman. It could be interesting to investigate cardiovascular morbidity and mortality rates in both populations.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1:

Reviewer Name: Jonathan Benzaquen
Institution and Country: Department of Pulmonary Medicine and Oncology, Université Côte d'Azur, CHU de Nice, University Hospital Federation OncoAge, 06001 Nice Cedex 1, France

<u>Comment 1:</u>

In the introduction, the definition of COPD should be further clarified. Indeed, emphysema is not in itself a cause of COPD but is frequently associated with COPD. Concerning the COPD's risk factors, they are not limited to smoking and pollution, so I do not think that this definition should be exclusive. It would

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perhaps be more appropriate to specify that these both causes are largely majority in frequency, but without being exclusive (genetic causes such as the deficit in A1AT, other causes of emphysema...)

Response 1:

We thank the reviewer for this comment. In accordance with the suggestion, we described the definition of COPD more precisely by including emphysema and obstructive bronchiolitis and by describing the risk factors more broadly in the INTRODUCTION section as follows: *"COPD is composed of a mixture of small airway disease (e.g., obstructive bronchiolitis) and parenchymal destruction (emphysema),"* (page 6, lines 5-6), and *"Tobacco smoke, indoor and outdoor air pollutants, and occupational dust have been acknowledged as major risk factors for airflow limitation along with genetic factors such as alpha1-antitrypsin deficiency, but there has been no survey assessing the associations of risk factors with the prevalence of airflow limitation in a time series manner"* (page 7, lines 1-5).

Comment 2:

In the introduction, concerning the definition of COPD, it is certainly necessary to specify that the diagnosis requires pulmonary function test including a bronchodilator reversibility test. It should then be remembered the limit of the study: the absence of post-bronchodilator measurement of the FEV_1/FVC, implying that here is analyzed the prevalence of chronic obstructive airways disorder and not COPD which in its definition includes the fact that obstruction is non reversible (i.e post bronchodilator FEV_1/FVC ratio 70%). Indeed, the transition between "defining COPD" and "clinical and epidemiological interest of the study" is confusing, and could lead readers to believe that the prevalence of COPD are here studied, which is not the case. It would therefore be interesting to explain that the obstructive airway disorder discovered in those patients, includes several diagnostic hypotheses that could be COPD, but could also be any other cause of chronic obstructive ventilatory disorder (especially asthma, but also bronchiectasis, etc, ...)

Response 2:

Thank you for your comments. We used the phrase "airflow limitation" rather than COPD as an outcome in order not to mislead readers into thinking that we studied nonreversible COPD. Therefore, in the INTRODUCTION, we provided general information on airflow limitation that consisted mainly of COPD. However, your point is very well taken, and we have decided to clarify the definitions of COPD in the INTRODUCTION section as follows: *"Chronic obstructive pulmonary disease (COPD), which is characterized by persistent respiratory symptoms and airflow limitation defined by post-bronchodilator spirometry"* (page 6, lines 2-3), and *"Pre-bronchodilator airflow limitation, which include chronic obstructive ventilatory disorders such as COPD, asthma, and bronchiectasis, is a well-used outcome in epidemiological studies without post-bronchodilator spirometry"* (page 6, lines 9-11). We also stated this limitation in the Discussion section as follows: *"Third, we did not have access to a pulmonary function test with assessment of airflow reversibility or post-bronchodilator FEV_1/FVC; some of the individuals with airflow limitation might have had chronic obstructive ventilatory disorders such as asthma rather than COPD. However, this limitation would not have changed our conclusion, because the prevalence of airflow limitation decreased in the present study despite the increasing trend in the prevalence of asthma in Japan"* (page 23, lines 10-16).

Comment 3:

Concerning the discussion and conclusion, following the previous remarks, the conclusions regarding evolution of the epidemiology of COPD should also be moderated. The study actually evaluated evolution of the epidemiology of chronic obstructive ventilatory disorder (and not COPD stricto sensu), given the lack of reversibility test data at EFRs.

Response 3:

We thank the reviewer for this comment. We realize that the airflow reversibility of each subject could not be assessed, and chronic obstructive ventilatory disorders other than COPD were included. Thus, we modified the sentence in the conclusion as follows: *"In conclusion, over the past half century, the prevalence of airflow limitation that included COPD as well as other chronic obstructive ventilatory disorders has decreased significantly among the general Japanese population*" (page 24, lines 12-14).

Comment 4:

Regarding the list of study limitations: it may be useful to indicate that you did not have access to a pulmonary function test with assessment of reversibility post bronchodilation.

Response 4:

We greatly appreciate the reviewer's concern. In accordance with your suggestion, we included the following statement of this limitation in the Discussion section (also see the response to comment 2 of

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Reviewer 1): *“Third, we did not have access to a pulmonary function test with assessment of airflow reversibility or post-bronchodilator FEV_1/FVC; some of the individuals with airflow limitation might have had chronic obstructive ventilatory disorders such as asthma rather than COPD. However, this limitation would not have changed our conclusion, because the prevalence of airflow limitation decreased in the present study despite the increasing trend in the prevalence of asthma in Japan”* (page 23, lines 10-16).

Comment 5:

Regarding the list of study limitations: It may also be interesting to note that you could not exclude patients with a restrictive ventilatory disorder associated to the obstructive one

Response 5:

We greatly appreciate the reviewer’s concern. We agree that subjects with a restrictive ventilatory disorder associated with the obstructive one (e.g., combined pulmonary fibrosis and emphysema (CPFE)) might exist, but the prevalence of CPFE is small, as reported in the COPDGene Study. However, we appreciate your point, and we have added the following sentences as a limitation in the DISCUSSION section*: “Fourth, airflow limitation could also include a restrictive ventilatory disorder associated with an obstructive disorder, such as combined pulmonary fibrosis and emphysema (CPFE). However, in a recent epidemiologic study, subjects with CPFE were found to make up only 5-10% of total COPD cases. Thus, this limitation may not have altered our conclusions”* (page 23, line 16-page 24, line 2).

Comment 6:

Regarding the list of study limitations: Resulting from these first two remarks, you can also signal that it was not possible to associate the various respiratory diseases providing obstructive ventilatory disorder with the risk factors found. Indeed, the association of an "obstructive ventilatory disorder discovered with the pulmonary function test " associated with "certain identified risk factors" have been studied, without prejudging the etiology of the ventilatory obstructive disorder, regarding that the pneumological diagnosis was not known.

Response 6:

As suggested, the factor associated with airflow limitation in the present study was smoking, which is a risk factor not only for COPD but also for various other respiratory diseases, such as asthma and pulmonary fibrosis. Therefore, we included the following limitation in the DISCUSSION section: *“Fifth, airflow limitation could include several types of obstructive disorders, and thus we should be cautious about concluding that individual risk factors affect all of the diseases providing airflow limitation”* (page 24, lines 2-4).

Reviewer 2:

Reviewer Name: Jean-Marie Degryse
Institution and Country: Université Catholique de Louvain, Institute for Health and Society, Belgium

Thank you for your useful suggestions. We have attempted to address all the points you raise as follows:

Comment 1:

This is not a longitudinal study but a “repeated cross-sectional study” concerning different populations (different generations)

Response 1:

You are correct: the design of the present study consisted of two serial cross-sectional surveys. To clarify this, we now mention the study design in the ABSTRACT: *“Design Two serial cross-sectional surveys”* (page 3, line 8). We also added a mention in the INTRODUCTON: *“to evaluate trends in the prevalence of airflow limitation in Japan from 1967 to 2012 using two serial cross-sectional surveys concerning different generations from a long-term community-based study”* (page 7, lines 8-10). And we added the following phrase in the METHODS: *“two serial cross-sectional surveys of airflow limitation with spirometry were performed in 1967 and 2012”* (page 8, lines 2-3). Finally, to further underscore this point, we deleted the word “longitudinal” from the sentence in the DISCUSSION section as follows: *“The present comparison of the prevalence of airflow limitation based on the GOLD criteria in Japan revealed*

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a significant reduction from 1967 to 2012, consistently across age-groups in both men and women" (page 19, lines 3-5).

Comment 2:

The authors should be more careful in using different terms with different meanings: Chronic airway disease is not the same as chronic obstructive airway disease, airflow limitation is not a synonym of airflow obstruction, and last but not least: airflow obstruction is not a synonym of COPD. Although airflow obstruction remains a hallmark of COPD, a more comprehensive assessment involving risk factors and symptoms is needed in order to establish such a diagnosis (refs)

Response 2:

We thank the reviewer for this comment. We changed the phrase *"chronic airways disease"* to *"chronic obstructive airway disease"* (page 3, line 2). To inform readers that "airflow limitation" in our paper did not mean airflow obstruction evaluated with radiological findings or clinical symptoms, we added the following sentence to the METHODS section: *"Airflow limitation was pathophysiologically assessed with spirometry and without any radiological measurements or clinical symptoms"* (page 9, lines 9-10). To further clarify this point, the following statement was included in the INTRODUCTION section (also see the response to comment 2 of Reviewer 1): *"Chronic obstructive pulmonary disease (COPD), which is characterized by persistent respiratory symptoms and airflow limitation defined by post-bronchodilator spirometry"* (page 6, lines 2-3).

Comment 3:

Smoking habits were assessed by means of a self-administered questionnaire and categorized as never smokers and ever/current smokers, without further quantification of the number of pack years. The "stronger" association between the airflow limitation and current/ever smoking that was found in the second cross sectional study could be biased by a more intense and longer exposure to smoking.

Response 3:

We agree that this point requires clarification. Based on the national survey in Japan, the number of cigarettes smoked per day among smokers has remained unchanged in both men and women since the 1950s, whereas the trends in the duration of smoking are unknown. On the other hand, the frequency of current smokers significantly decreased in both sexes, whereas the frequency of ever smokers increased in the present study, suggesting that the frequency of smoking cessation has increased in recent years. Given these findings, we believe that neither the intensity nor the duration of smoking increased from 1967 to 2012, and consequently the stronger influence of smoking on airflow limitation in 2012 would not come from the increased the intensity or duration of smoking. As per the suggestion, we showed the frequency of current and ever smokers separately in Table 1, and stated this point in the RESULTS section as follows: *"For smoking habits (current or ever smoking), there was a downward trend in men, and an upward trend in women, although the frequency of ever smokers significantly increased in both sexes (from 11.5% in 1967 to 44.1% in 2012 for men, and from 1.7% in 1967 to 11.6% in 2012 for women; $P < 0.001$ in both sexes)"* (page 14, lines 10-14). We added the following sentences as a limitation in the DISCUSSION section: *"Lastly, we were unable to investigate the effects of intensity or duration of smoking on airflow limitation due to the lack of data concerning the number of pack years of cigarette smoking in 1967. However, in Japan, it has been reported that the number of cigarettes smoked per day has remained unchanged among smokers of both sexes (about 20 per day in men and about 15 per day in women) since the 1950s. In addition, the frequency of ever smokers who stopped smoking significantly increased in both sexes in the present study. Thus, we believe that the amount of smoking did not increase from 1967 to 2012"* (page 24, lines 4-11).

Comment 4:

A major issue remains the lack of data concerning the reversibility of the airflow obstruction that was diagnosed. Are any data available concerning the prevalence of asthma in Japan?

Response 4:

We wish to thank the reviewer for this comment. As reported by Fukutomi *et al.,* the prevalence of asthma is increasing in Japan. In accordance with your suggestion, we included the following statement of this limitation in the Discussion section, with reference to the study of Fukutomi *et al.* (also see the response to comment 2 of Reviewer 1): *"Third, we did not have access to a pulmonary function test with assessment of airflow reversibility or post-bronchodilator FEV_1/FVC; some of the individuals with airflow limitation might have had chronic obstructive ventilatory disorders such as asthma rather than COPD. However, this limitation would not have changed our conclusion, because the prevalence of airflow limitation decreased in the present study despite the increasing trend in the prevalence of*

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asthma in Japan" (page 23, lines 10-16).

Comment 5:

p9 The ATS/ERS criteria (based on LLN cut-off values) were used as "secondary principle". The argumentation to do so is not convincing. By the way did the authors use the GLI (universal) reference values in their sensitivity analysis?

Response 5:

We appreciate the reviewer's comment on this point. Initially, we considered that the reference equations of LLN for contemporary subjects would not be applicable for subjects in the past, because height and weight, which are components of LLN, have changed greatly over the last half century. In keeping with your comment, however, we decided to treat these criteria equally, as we now describe in the METHODS: *"We employed both the GOLD criteria and the ATS/ERS criteria"* (page 9, lines 14-15).

When calculating LLN, we used the reference equations for the Japanese population that were reported by Kubota *et al.* in 2014. These equations were derived using the lambda, mu, and sigma method, which was also used by the ERS GLI Task Force, since the population used for calculating the GLI reference equations did not include Japanese. Therefore, we modified the statements in the METHODS section as follows: *"When calculating LLN, we used the reference equations for the Japanese population that were reported by the Clinical Pulmonary Functions Committee of the Japanese Respiratory Society (JRS) in 2014. Those equations were derived using the lambda, mu, and sigma method employed by the ERS Global Lung Function Initiative (GLI) Task Force, since the GLI reference group did not include Japanese subjects"* (page 9, line 15-page 10, line 2). We also added the following sentence: *"Regarding the ATS/ERS criteria-based airflow limitation, we also calculated LLN using the reference equations for the Japanese population that were reported by the ERS GLI Task Force in 2012"* (page 10, lines 13-15).

In addition, we performed sensitivity analyses using LLN with the GLI reference equations, as suggested. The results are summarized in the Supplementary Materials (online supplementary figures E8-E10). Moreover, we modified the following sentence in the METHODS section: *"As described above, the analysis was also performed using the ATS/ERS criteria with the JRS or GLI reference equations for each survey year*" (page 13, lines 6-7). In the RESULTS section, we added this passage: *"The results of the analyses were not substantially changed according to whether the ATS/ERS criteria with the JRS reference equations (online supplementary figures E2-E4), the GLI reference equations (online supplementary figures E5-E7), or the modified definition of airflow limitation (i.e., $FEV_1/FVC < 67\%$) from 1967 (online supplementary figures E8-E10) was used"* (page 17, lines 11-15).

Comment 6:

Table 1 shows some striking differences between the 1967 and 2012 populations: 1. The mean age (of man and woman) is considerable different, 2. The use of anti-hypertensive medication is considerable higher in 2012 (as well as the number of subjects with a "diagnosis" of hypertension. Smoking habits remained the same for men but increased in woman. It could be interesting to investigate cardiovascular morbidity and mortality rates in both populations.

Response 6:

We greatly appreciate the reviewer's interest. We too considered that it would be interesting to investigate the trends in all-cause, pulmonary or cardiovascular morbidity and mortality rates in both populations. Actually, we have reported the secular trends in the incidence and mortality of cardiovascular diseases in another project (see reference #11). In addition, deaths from all-cause, and respiratory diseases will be assessed as a future work because, at the moment, the analysis of these issue is beyond the scope of the present paper.

Correction of Typographical Error

We wish to express our appreciation to the reviewers for their insightful comments on our paper. The comments have helped us to significantly improve this research.

We would appreciate it if the editors and the reviewers could accept our sincere apology for an unfortunate typing error: the health assessment participation rate in 1967 was not 89.0% but 88.0%, although the number of the subjects enrolled in the present study was correct. We deeply regret the oversight. We modified the sentences in the METHODS section as follows: *"In 1967, a total of 1,973 residents aged ≥ 40 years (88.0% of the whole population in this age group) consented to participate in*

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an examination and underwent a comprehensive health assessment. Among them, 129 subjects who were either unable or unwilling to submit to a measurement of pulmonary function, and 2 subjects in whom spirometric measurements were performed incorrectly were excluded" (page 8, lines 3-8). We also modified the online supplementary figure E1.

VERSION 2 – REVIEW

REVIEWER	J.BENZAQUEN Department of Pulmonary Medicine, Pasteur University Hospital (Nice) FHU Oncoage
REVIEW RETURNED	24-Sep-2018

GENERAL COMMENTS	The authors performed a descriptive analytical epidemiology work comparing the prevalence of obstructive airways disorder of a Japanese population in 1967 versus 2012 and its association with certain risk factors including smoking and pollution. The article is well written, the figures and the take-home messages are clear. The value of this work is high considering the frequency and the cost of this pathology, the evolution of the prevalence of smoking and changes in its sex ratio, and the pollution prevention campaigns implemented in Japan in recent decades.

REVIEWER	Jean-Marie Degryse Université Catholique de Louvain, Institute of Health and Society, Brussels Belgium
REVIEW RETURNED	17-Sep-2018

GENERAL COMMENTS	The authors responded adequately to all comments.

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