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Title

Trends in the prevalence of airflow limitation in a general Japanese population: the Hisayama Study

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ABSTRACT

Objectives Chronic airways disease, which is characterized by airflow limitation, is a major burden on public health. Reductions in environmental pollution in the atmosphere and workplace and a decline in the prevalence of smoking over recent decades may have affected the prevalence of airflow limitation in Japan. The present epidemiological study aimed to evaluate trends in the prevalence of airflow limitation and in the influence of risk factors on airflow limitation in a Japanese community.

Design Two series of cross-sectional surveys.

Setting Data from the Hisayama Study, a population-based prospective study which has been longitudinally conducted since 1961.

Participants A total of 1,842 and 3,033 residents aged ≥ 40 years with proper spirometric measurements participated in the 1967 and 2012 surveys, respectively.

Main outcome measures Airflow limitation was defined as forced expiratory volume in one second/forced vital capacity < 70% by spirometry. For each survey, the age-adjusted prevalence of airflow limitation was evaluated by sex. Odds ratios and population attributable fractions of risk factors on the presence of airflow limitation were compared between surveys.

Results The age-standardized prevalence of airflow limitation decreased from 1967 to 2012 in both sexes (from 26.3% to 16.1% in men, and from 19.8% to 10.5% in women). Smoking

was significantly associated with higher likelihood of airflow limitation in both surveys, although the magnitude of its influence was greater in 2012 than in 1967 (the multivariable-adjusted odds ratio was 1.63 (95% confidence interval 1.19-2.25) in 1967 and 2.26 (1.71-2.98) in 2012; $P = 0.007$ for heterogeneity). Accordingly, the population attributable fraction of smoking on airflow limitation was 33.4% in 2012, which was 1.5-fold higher than that in 1967 (21.1%).

Conclusions The prevalence of airflow limitation was decreased over 45 years in Japan, but the influence of smoking on airflow limitation increased with time.

ARTICLE SUMMARY

Strengths and limitations of this study

- The strengths of our study include the high participation rates and the use of spirometry for evaluating the exact prevalence of airflow limitation in both 1967 and 2012 surveys.
- One limitation was the difference in the instruments used for spirometry: a dry wedge bellows spirometer in 1967 vs a more sophisticated instrument in 2012.
- Another limitation was the possible decrease in airflow limitation due to the bronchodilators that have been used as standard therapies for COPD and asthma over the last decade in our country.

Keywords epidemiology; public health; chronic airways disease (thoracic medicine); epidemiology (thoracic medicine)

INTRODUCTION

Chronic obstructive pulmonary disease (COPD), which is characterized clinically by expiratory airflow limitation, is a major threat to the health of the respiratory system. COPD is caused by emphysematous destruction of the lungs through lifetime exposure to inhaled toxic gases and particles, and can lead to acute exacerbation of respiratory symptoms and airway function, ultimately progressing to respiratory failure.[1] In addition, COPD poses a great burden in terms of morbidity and premature mortality as well as in health care expenditures worldwide.[2] Therefore, it would be clinically and epidemiologically valuable to clarify the trends in the prevalence of airflow limitation and in the influence of risk factors on airflow limitation in individual communities.

A previous literature-based meta-analysis estimated that the prevalence of airflow limitation increased over two decades in both developed and developing regions, but these estimations were based on a statistical model.[3] Few studies have addressed the trends in the prevalence of airflow limitation over time based on the data from repeated community-based surveys, although the nationwide surveys in the U.S. showed a decreasing trend in the prevalence of airflow limitation.[4] Tobacco smoke, indoor and outdoor air pollutants, and occupational dust have been acknowledged as risk factors for airflow limitation,[5] but there has been no survey assessing the associations of risk factors with the prevalence of airflow

limitation in a time series manner. In recent decades, reduction of environmental pollution in the atmosphere and workplace and the reduction in smoking prevalence[6-10] may have affected the influence of these risk factors on airflow limitation.

The purpose of the present study was to evaluate trends in the prevalence of airflow limitation in Japan from 1967 to 2012 using cross-sectional surveys from a long-term community-based study, the Hisayama Study, with high participation rates and a consistent spirometric definition of airflow limitation. In addition, the magnitudes of the association of risk factors with airflow limitation were compared between surveys.

METHODS

study population

Since 1961, a population-based prospective study has been longitudinally conducted to investigate the distributions and associations of lifestyle-related diseases and their risk factors in the town of Hisayama, Japan. Details of this cohort study have been described elsewhere.[11] As part of an annual health examination, two series of cross-sectional surveys of airflow limitation with spirometry were performed in 1967 and 2012. In 1967, a total of 1,995 residents aged ≥ 40 years (89.0% of the whole population in this age group) consented to participate in an examination and underwent a comprehensive health assessment. Among

them, 151 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. The remaining 1,842 subjects (824 men and 1,018 women) with successfully measured pulmonary function were enrolled in the present study. Similarly, in 2012, 3,396 subjects participated in a health examination (participation rate, 72.6%). After excluding 6 subjects who refused to participate in the epidemiological research, and 357 subjects who were either unable or unwilling to submit to spirometric measurement, 3,033 subjects (1,340 men and 1,693 women) with proper spirometric measurements were enrolled in the study (online supplementary figure E1).

assessment and definition of airflow limitation

A dry wedge bellows spirometer was used in 1967 to obtain volume-time curves. Participants underwent spirometry several times until valid curves were obtained. Pulmonary physicians graphically evaluated and scrutinized the figures, and obtained the values of forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), and FEV_1/FVC. In the 2012 survey, spirometry was performed in line with the guidelines of the Japanese Respiratory Society.[12] Two to four measurements were performed using a CHESTGRAPH HI-105 electronic spirometer (Chest MI, Tokyo), in order to obtain satisfactory flow-volume

loops. Pulmonary physicians visually assessed the quality of the maneuvers and chose the finest loop, showing the highest sum of FEV_1 and FVC. FVC, FEV_1, and FEV_1/FVC were obtained from the selected curve. Bronchodilators were not used for any of the surveys.

There are two major, worldwide criteria for the definition of airflow limitation: the modified Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria with a fixed cut-off of FEV_1/FVC[13] and the American Thoracic Society / European Respiratory Society (ATS/ERS) criteria using age-, sex- and height-specific lower limits of normal (LLNs) for the cut-off of FEV_1/FVC.[14] We employed the GOLD criteria as the primary principle for airflow limitation and the ATS/ERS criteria as the secondary principle since it was not clear whether LLN values for recent Japanese non-smokers[15] were applicable to subjects studied half a century ago. The GOLD criteria-based airflow limitation was defined as FEV_1/FVC < 70%. We also used a modified definition of airflow limitation (i.e., FEV_1/FVC < 67%), because the dry wedge bellows spirometer has been reported to yield values 2-3% lower than those measured by a water-sealed spirometer or an electronic spirometer.[16,17] Among participants with airflow limitation, the severity was defined using the predicted FEV_1 value for a person of the same age, sex, and height using the equation for the Japanese population[15] as follows: mild, $FEV_1 \geq 80\%$ of predicted; moderate, $50\% \leq FEV_1 < 80\%$ of predicted; severe and very severe, $FEV_1 < 50\%$ of predicted. The ATS/ERS criteria-based

airflow limitation was defined as FEV_1/FVC < the 5th percentile (LLN), and the severity of airflow limitation was defined as follows: mild, $FEV_1 \geq 70\%$ predicted; moderate and moderately severe, $50\% \leq FEV_1 < 70\%$ predicted; and severe and very severe, $FEV_1 < 50\%$ predicted.

clinical evaluation and laboratory measurements

Each participant completed a self-administered questionnaire covering smoking habits, alcohol intake, medical history, and antihypertensive treatments. Smoking habits were categorized as never smokers or current/former smokers since airflow limitation could persist even after cessation of smoking. Alcohol drinking was defined as current or not. Body height and weight were measured in light clothing without shoes, and body mass index (BMI; kg/m^2) was calculated. Overweight and underweight were defined as BMI ≥ 25.0 kg/m^2 and BMI < 18.5 kg/m^2, respectively. Blood pressure was measured 3 times using a mercury sphygmomanometer in 1967 and an automated sphygmomanometer (BP-203 RVIIIB; Omron Healthcare, Kyoto) in 2012 in a sitting position after rest for at least 5 minutes; the average values were used in the analyses. Hypertension was defined as a systolic blood pressure ≥ 140 mmHg, a diastolic blood pressure ≥ 90 mmHg or current treatment with antihypertensive agents.

statistical analysis

The SAS software package version 9.4 (SAS Institute, Cary, NC, USA) was used to perform all statistical analyses. Baseline characteristics were shown as age-adjusted values by sex and by survey year using the analysis of covariance (ANCOVA) for continuous variables or by the direct method using the age distribution of the 1985 Japanese population as a standard.[18] They were compared between survey years using an ANCOVA, a Cochran–Mantel–Haenszel test, or a logistic regression model. The sex-specific prevalence of airflow limitation was estimated separately for each age group (40-49, 50-59, 60-69, and 70+ years), and as a whole adjusting for age by the direct method using the same standard population. The linear trend of airflow limitation across age groups in each survey year was tested using a logistic regression model. The same model was used for the test of secular trends in sex-specific and age-standardized prevalence of airflow limitation from 1967 to 2012. Among residents with airflow limitation, the sex-specific and age-standardized distribution of its severity was compared between survey years using an ordinal logistic regression model. The associations of potential risk factors with airflow limitation were estimated as adjusted odds ratios (ORs) with 95% confidence intervals (95% CIs) for each survey year by using multivariable-adjusted logistic regression models, wherein adjustment

was made for sex, age, smoking habits, overweight, underweight, hypertension, and living alone that were associated with airflow limitation or COPD in previous reports.[1,13,19-21] Multivariable-adjusted ORs with 95% CIs were calculated using data of subjects with no missing data (proportion of subjects excluded: 2.1% in 1967 and 0.07% in 2012). We tested whether these associations were changed over decades by including the interactions of risk factors and the survey years in the relevant statistical models. The contribution of each risk factor to airflow limitation was estimated as a population attributable fraction (PAF) in each survey using the multivariable-adjusted OR of each risk factor and its frequency among cases,[22] which represents the proportional reduction in population that would occur if each risk factor was eliminated. The 95% CIs of the PAFs were estimated in accordance with Greenland's method.[23]

As described above, the sensitivity analysis was performed using the ATS/ERS criteria for each survey year. Another sensitivity analysis was performed with the modified definition of airflow limitation, which was FEV_1/FVC of < 67%. A two-sided value of $P < 0.05$ was considered to indicate statistical significance.

participant involvement

There was no direct patient involvement in the development, design or conduct of the study.

ethical considerations

The study was approved by the Kyushu University Institutional Review Board for Clinical Research and written informed consent was obtained from the participants for the survey in 2012.

RESULTS

demographic and clinical characteristics

The demographic and clinical characteristics in 1967 and 2012 are summarized by sex in table 1, in which the mean values and the frequencies were adjusted for age. In both sexes, subjects in 2012 were older than those in 1967. The mean values of height, weight and BMI were higher in 2012 than 1967. The frequencies of drinking habits and living alone also increased over 45 years. The prevalence of hypertension decreased with time. For smoking habits, there was a downward trend in men, and an upward trend in women.

Table 1 Age-adjusted mean values or frequencies of demographic and clinical characteristics in 1967 and 2012 by sex

Variables	Men			Women		
	1967 (n=824)	2012 (n=1340)	*P*-value	1967 (n=1018)	2012 (n=1693)	*P*-value
Age (years)	55.0 (0.40)	63.1 (0.32)	<0.001	55.5 (0.37)	62.9 (0.29)	<0.001
Height (cm)	158 (0.21)	166 (0.16)	<0.001	146 (0.17)	153 (0.13)	<0.001
Weight (kg)	53.2 (0.32)	65.8 (0.25)	<0.001	47.4 (0.27)	53.6 (0.21)	<0.001
BMI (kg/m^2)	21.4 (0.10)	23.8 (0.08)	<0.001	22.3 (0.11)	22.8 (0.09)	<0.001
Degree of fatness						
Overweight (%)	7.6	31.5		17.0	22.0	
Normal weight (%)	84.9	64.6	<0.001	72.4	67.6	0.001
Underweight (%)	7.5	3.9		10.6	10.5	
Smoking habit (%)	83.6	79.8	0.08	13.9	20.6	0.003
Alcohol intake (%)	63.3	74.7	<0.001	4.1	40.1	<0.001
Hypertension (%)	57.3	47.7	<0.001	53.0	33.8	<0.001
Systolic blood pressure (mmHg)	147.0 (0.78)	130.7 (0.61)	<0.001	145.7 (0.65)	125.4 (0.50)	<0.001
Diastolic blood pressure (mmHg)	86.4 (0.44)	79.8 (0.34)	<0.001	83.8 (0.37)	74.0 (0.28)	<0.001
Antihypertensive medication (%)	13.6	29.3	<0.001	15.0	21.8	<0.001
Living alone (%)	1.3	4.5	<0.001	2.5	5.4	0.002

Age is given as the mean plus standard error. Other values are given as the age-adjusted mean (if appropriate) with standard errors in brackets for continuous variables and as age-adjusted percentages for dichotomized or categorical variables. *P* values denote the statistical significance

of the difference in each variable between 1967 and 2012. Overweight was defined as a body mass index ≥ 25.0 kg/m^2. Underweight was defined as a body mass index < 18.5 kg/m^2. Smoking habits were categorized as never smokers or current/former smokers. Alcohol intake was defined as current or not. Hypertension was defined as blood pressure ≥ 140/90 mmHg and/or current use of antihypertensive agents. Numbers of subjects with missing data were as follows: alcohol intake 20, hypertension 4, antihypertensive medication 10, and living alone 9 in men in 1967; height 1, body mass index 1, degree of fatness 1, and living alone 1 in men in 2012; smoking habit 2, alcohol intake 42, hypertension 3, antihypertensive medication 5, and living alone 25 in women in 1967; no missing data in women in 2012.

BMI, body mass index.

trends in the prevalence of airflow limitation

Among the 1,842 and 3,033 survey subjects in 1967 and 2012, 401 and 524 subjects had airflow limitation, respectively. The age-standardized prevalence decreased over the intervening decades (from 26.3% to 16.1% in men and 19.8% to 10.5% in women) (figure 1). Almost all age groups in both sexes, with the exception of 40-49 years in women, showed significant downward trends in the age-specific prevalence from 1967 to 2012 (figure 2). The prevalence of airflow limitation increased with age in both 1967 and 2012 (all $P < 0.001$ for trend). As shown in figure 3, there was a significant shift in the distribution of severity of airflow limitation in both men and women with airflow limitation; the proportions of moderate and severe/very severe airflow limitation decreased over time, while the proportion of mild airflow limitation increased ($P < 0.001$ for difference in both sexes). The sensitivity analyses using the ATS/ERS criteria (online supplementary figures E2-E4) or using the modified definition of airflow limitation (i.e., $FEV_1/FVC < 67\%$) in 1967 (online supplementary figures E5-E7) did not altered the results substantially.

trends in the associations of risk factors with airflow limitation

There was a significant positive association of smoking with airflow limitation in both surveys (OR = 1.63 (95% CI 1.19-2.24), $P = 0.003$ in 1967; OR = 2.26 (95% CI

1.71-2.98), $P < 0.001$ in 2012) (figure 4). In comparison, there was a stronger association between smoking and airflow limitation in 2012 than in 1967 ($P = 0.007$ for interaction). Consequently, the contribution of smoking to the estimated proportion of cases with airflow limitation—i.e., PAF—was 21.1% in 1967 and 33.4% in 2012 (a 1.5-fold increase). Overweight was negatively associated with airflow limitation in both surveys (OR = 0.65 (95% CI 0.42-0.98), $P = 0.04$ in 1967; OR = 0.66 (95% CI 0.52-0.85), $P = 0.001$ in 2012), and there was no statistically significant difference between them ($P = 0.84$ for interaction). Nevertheless, due to the 2-fold elevation in the proportion of overweight from 13.0% in 1967 to 26.8% in 2012, the potential of overweight for reducing the proportion of airflow limitation (PAF) was greater in 2012 than in 1967 (-4.1% in 1967 to -10.3% in 2012). For the associations of sex (men vs women) with airflow limitation, we found a significant difference between survey years, although neither association reached statistical significance. The other variables were not associated with airflow limitation, and made no significant contributions to the PAF. In the sex-specific analysis, the influence of each risk factor on airflow limitation was substantially similar between sexes (all $P > 0.06$ for heterogeneity), except for underweight in 1967 ($P = 0.002$ for heterogeneity) (online supplementary figure E8).

DISCUSSION

This longitudinal comparison of the prevalence of airflow limitation based on the GOLD criteria in Japan revealed a significant reduction from 1967 to 2012, consistently across age-groups in both men and women. Among participants with airflow limitation, the proportion with a moderate to severe level of the disorder decreased remarkably. Similar findings were observed with the ATS/ERS criteria. Moreover, both the relative association between smoking and airflow limitation and the PAF of smoking were compared and found to be stronger in 2012 than in 1967. This is the first study to evaluate trends in the prevalence of airflow limitation and in the influence of its risk factors in an Asian population on the basis of the data from repeated community-based surveys.

Epidemiological findings in regard to trends in the prevalence of airflow limitation are very limited. A literature-based meta-analysis of cross-sectional spirometric surveys showed that there was an increase in the prevalence of airflow limitation from the 1990s to 2010s in both developed and developing regions.[3] However, these estimations were calculated by using a statistical model on the basis of demographic changes over time. On the other hand, the results from the repeated nationwide National Health and Nutrition Examination Surveys demonstrated that there was a significant decrease in the prevalence of airflow limitation in the U.S. from 1988-1994 to 2007-2010, although it barely changed from 1971-1975 to 1988-1994.[4,24] This finding was in accord with ours. The reduction of

environmental pollution in both the atmosphere and workplace and the reduction in the smoking frequency may have decreased the prevalence of airflow limitation in the U.S. as well as in our population.[6-10]

Previous studies estimated the prevalence of airflow limitation in Japan in the 2000s as 16.2%-16.4% among men and 5.0%-5.8% among women.[25,26] The former range was similar to that in 2012 in the present study, while the latter was 2-fold lower. The discrepancy may be due to the difference in the participation rate, which would likely lead to a selection bias; the participation rate in our study was over 3-fold higher than those in the preceding studies. The prevalence of airflow limitation determined using the GOLD criteria has been reported to be higher than that based on the ATS/ERS criteria in elderly populations,[4,27] which was consistent with our study. However, other than ours, there has been no study estimating the prevalence of airflow limitation in Japan using the ATS/ERS criteria, and thus further studies are needed.

In the present study, the potentiating effects of smoking on airflow limitation were more pronounced in 2012 than in 1967. Cigarette smoking and chronic inhalational exposure to a polluted atmosphere both lead to COPD by the same mechanism—i.e., hazardous particles penetrating deep into the respiratory tract and eliciting neutrophilic inflammation and oxidative stress.[28] However, environmental, occupational, and household exposure to

hazardous pollutants has been steadily attenuated over the last several decades. This reduction in exposure to atmospheric pollutants could have increased the relative influence of smoking in recent years.[29] In turn, the prevention of tobacco use and the promotion of smoking cessation have become increasingly important public health concerns in order to prevent airflow limitation and COPD.

The present study showed that overweight was inversely associated with airflow limitation both in 1967 and 2012. Previous observational studies demonstrated that higher BMI was associated with lower FVC and therefore with higher FEV_1/FVC,[19,30] which probably reflected the decrease in excursion of the thoracic cage due to intra-abdominal and subpleural fat deposition.[31] Our present findings may also be explained by reverse causality; weight loss commonly occurs in COPD patients via muscle wasting and elevated energy metabolism.[20] The weaker association and smaller PAF among women than among men in 2012 can be explained by the relatively small number of female participants with airflow limitation. There was no evidence of a significant association between underweight and airflow limitation in either survey, but the influence of underweight on the airflow limitation was different between the sexes. The underlying explanation for this heterogeneity was unclear. It may merely reflect the play of chance.

In the present study, the magnitude of the association between male sex and the airflow limitation in 2012 was significantly greater than that in 1967, although the OR for each survey did not reach statistical significance. This heterogeneity may have been caused by residual confounding due to the greater amount and duration of tobacco smoking in men than women, considering the fact that the influence of smoking habits increased with time, as mentioned above. Nevertheless, based on the current evidence, it remains controversial whether the male sex is a risk factor for airflow limitation.[32-35] Further evaluation of this matter is warranted.

The strengths of our study include the high participation rates and the use of spirometry for evaluating the exact prevalence of airflow limitation in both surveys. One limitation was the difference in the instruments used for spirometry: a dry wedge bellows spirometer in 1967 vs a more sophisticated instrument in 2012. This limitation could have led to an overestimation of the prevalence of airflow limitation in 1967, since the dry wedge bellows spirometer has been reported to generate 2-3% smaller FEV_1/FVC values compared to the instrument used in 2012.[16] However, several other studies have reported that the dry wedge bellows spirometer exhibited comparable reliability to more sophisticated instruments.[36-39] Additionally, the sensitivity analyses using the 3% lower cut-off value for FEV_1/FVC in 1967 showed similar results. Hence, this potential bias did not appear to have

affected the present results. Another limitation was the possible decrease in airflow limitation due to the bronchodilators, such as short-acting β2 agonist, short-acting muscarinic antagonist, long-acting β2 agonist (LABA), long-acting muscarinic antagonist (LAMA), inhaled corticosteroids (ICS)/LABA, LABA/LAMA, and xanthine, that have been used as standard therapies for COPD and asthma over the last decade in our country. [40,41] However, the proportion of subjects who used bronchodilators was only 2.6% (n=80) in 2012, and thus the decrease in the prevalence of airflow limitation was unlikely by virtue of the effects of these medications.

In conclusion, over the past half century, the prevalence of airflow limitation has decreased significantly among the general Japanese population. However, more than 10% of men and women aged 40 years or older still exhibit airflow limitation. With respect to risk factors, the contribution of smoking to the occurrence of airflow limitation has become more pronounced over the previous 5 decades, which we speculated as a result of a reduction in the occupational exposures to indoor and outdoor air pollution. To accelerate the prevention of airflow limitation, therefore, further public efforts toward smoking cessation are mandatory.

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Competing interests

HI reports grants from Astellas, AstraZeneca, Boehringer-Ingelheim, ChugaiPharm, GlaxoSmithKline, Pfizer, MerckSharp&Dohme, Novartis, Teijin-Pharma, personal fees from Astellas, AstraZeneca, Boehringer-Ingelheim, Chugai-Pharm, GlaxoSmithKline, Kyorin, MerckSharp&Dohme, MeijiSeikaPharma, Novartis, Otsuka, Pfizer, Taiho, outside the submitted work. The other authors report no competing interests.

Patient consent

This manuscript does not contain personal medical information about each identifiable person.

Ethics approval

The study was approved by the Kyushu University Institutional Review Board for Clinical Research and written informed consent was obtained from the participants for the survey in 2012.

Data sharing statement

Due to data protection regulations of executive committee of the cohort and of the administration that support the cohort, the authors do not have the permission to share the data. No additional data are available.

Contributors

HO contributed to the study concept, data collection, interpretation of data, statistical analysis, and drafting of the manuscript. YH contributed to the study concept, data collection, interpretation of data, and revision of the manuscript. SF and KM contributed to the data collection, interpretation of data, and revision of the manuscript. JH, DY, HI, TK, and YN contributed to interpretation of data and revision of the manuscript. TN was the chief investigator of the Hisayama Study and contributed to the study concept, data collection, interpretation of data, revision of the manuscript, and acquisition of funding. All authors critically reviewed the manuscript and approved the final version.

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FIGURE LEGENDS

Figure 1 Trends in the age-adjusted prevalence of airflow limitation in 1967 and 2012 by sex.

Vertical bars indicate 95% confidence intervals. $^{*}P < 0.001$ vs 1967.

Airflow limitation was defined as forced expiratory volume in one second / forced vital capacity < 70% according to the Global Initiative for Chronic Obstructive Lung Disease criteria.

Figure 2 Trends in the prevalence of airflow limitation according to age groups in 1967 and 2012 by sex.

$^{*}P < 0.05$, $^{\dagger}P < 0.01$ vs 1967, $^{\ddagger}P$ for trend < 0.01.

Airflow limitation was defined as forced expiratory volume in one second / forced vital capacity < 70% according to the Global Initiative for Chronic Obstructive Lung Disease criteria.

Figure 3 Trends in the age-adjusted prevalence of airflow limitation according to severity in 1967 and 2012 by sex.

Airflow limitation was defined as forced expiratory volume in one second / forced vital capacity < 70% according to the Global Initiative for Chronic Obstructive Lung Disease

criteria.

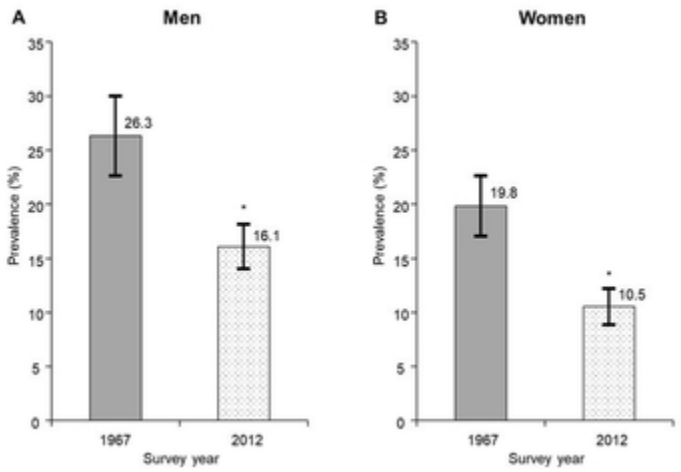
Figure 4 Multivariate-adjusted odds ratios and population attributable fractions of risk factors for airflow limitation in 1967 and 2012.

Airflow limitation was defined as forced expiratory volume in one second / forced vital capacity < 70%. Adjustments were made for sex, age, smoking habits, overweight*, underweight†, hypertension, and living alone. Horizontal bars indicate 95% CIs.

*For the analysis of overweight, the normal weight or underweight group was used as the reference group.

†For the analysis of underweight, the normal weight or overweight group was used as the reference group.

RF, risk factor; OR, odds ratio; CI, confidence interval; PAF, population attributable fraction.



Trends in the age-adjusted prevalence of airflow limitation in 1967 and 2012 by sex. Vertical bars indicate 95% confidence intervals. $^{*}P < 0.001$ vs 1967. Airflow limitation was defined as forced expiratory volume in one second / forced vital capacity < 70% according to the Global Initiative for Chronic Obstructive Lung Disease criteria.

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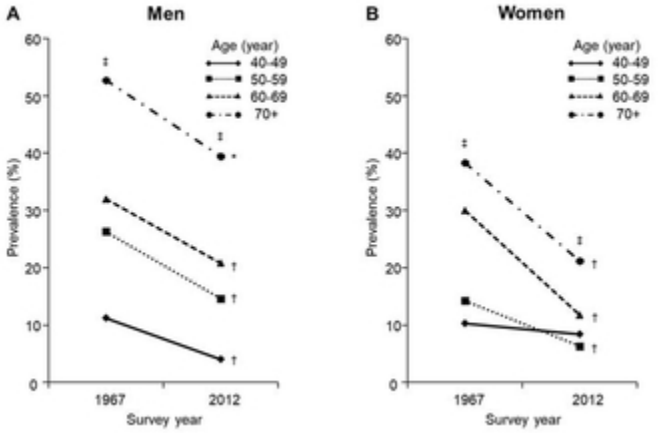

Trends in the prevalence of airflow limitation according to age groups in 1967 and 2012 by sex.
*P < 0.05, †P < 0.01 vs 1967, ‡P for trend < 0.01.
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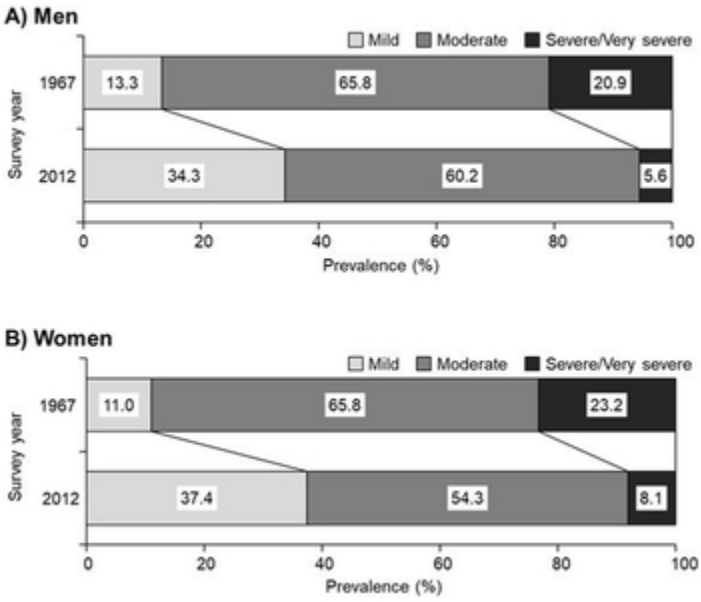

Trends in the age-adjusted prevalence of airflow limitation according to severity in 1967 and 2012 by sex. Airflow limitation was defined as forced expiratory volume in one second / forced vital capacity < 70% according to the Global Initiative for Chronic Obstructive Lung Disease criteria.

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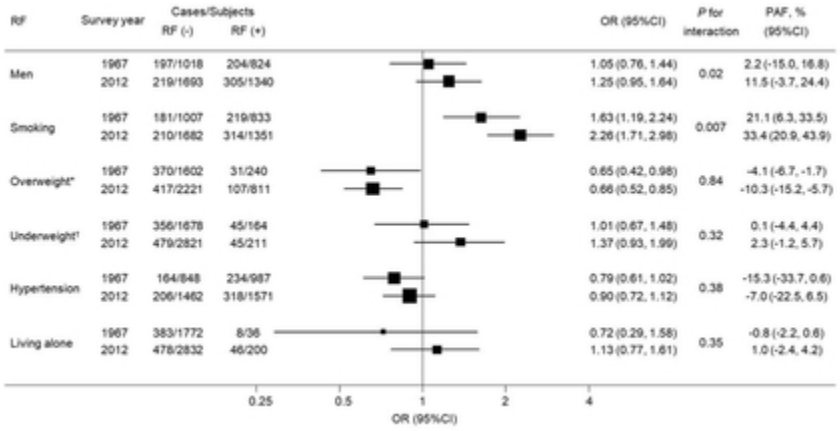

Multivariate-adjusted odds ratios and population attributable fractions of risk factors for airflow limitation in 1967 and 2012.

Airflow limitation was defined as forced expiratory volume in one second / forced vital capacity < 70%. Adjustments were made for sex, age, smoking habits, overweight*, underweight†, hypertension, and living alone. Horizontal bars indicate 95% CIs.

*For the analysis of overweight, the normal weight or underweight group was used as the reference group.

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RF, risk factor; OR, odds ratio; CI, confidence interval; PAF, population attributable fraction.

17x9mm (600 x 600 DPI)

Online Data Supplement

Figure E1 Selection of participants.

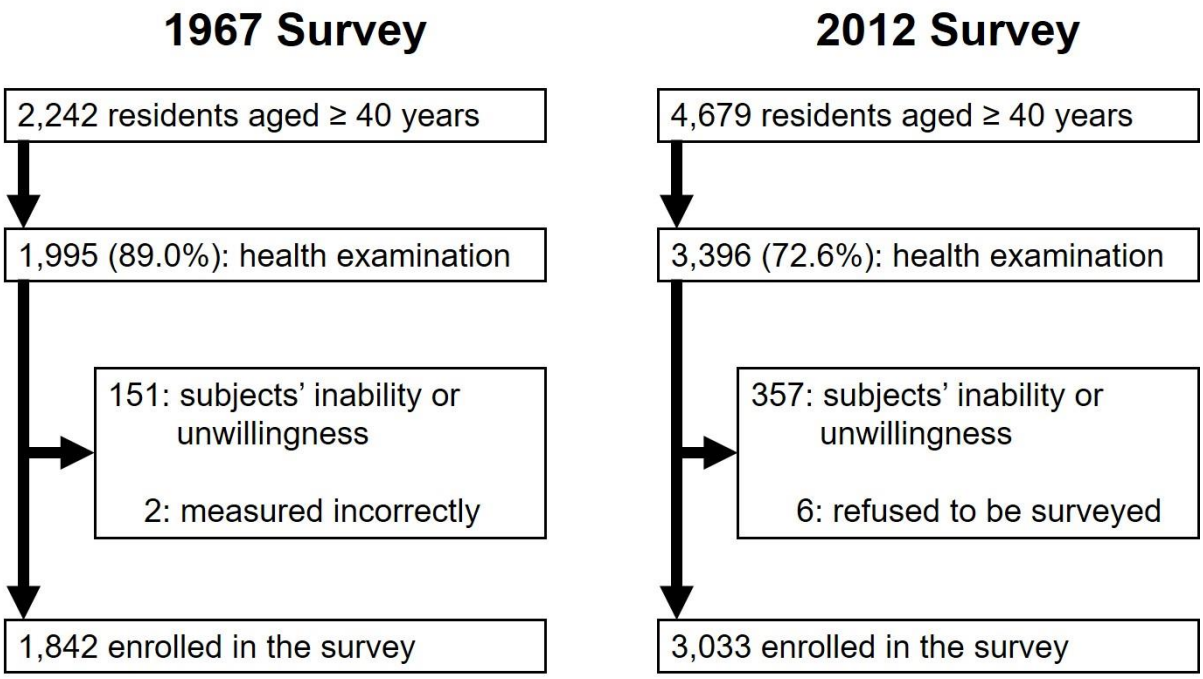
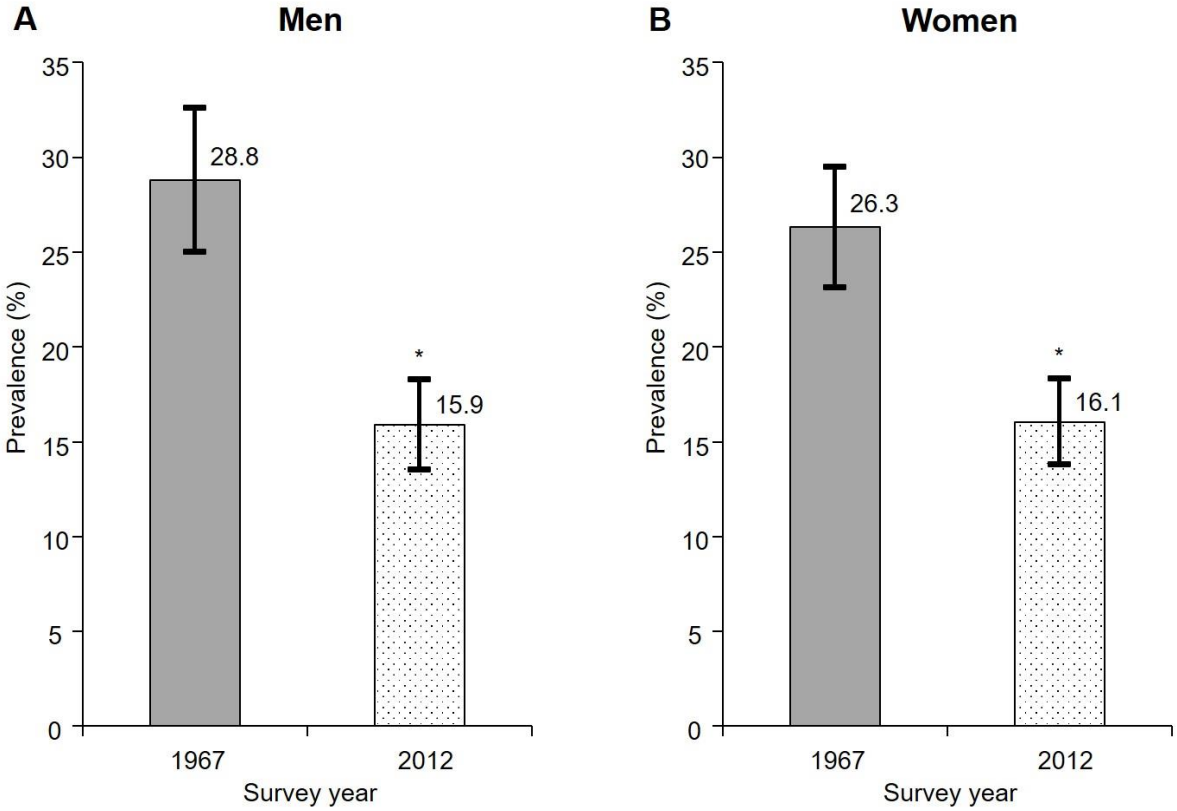


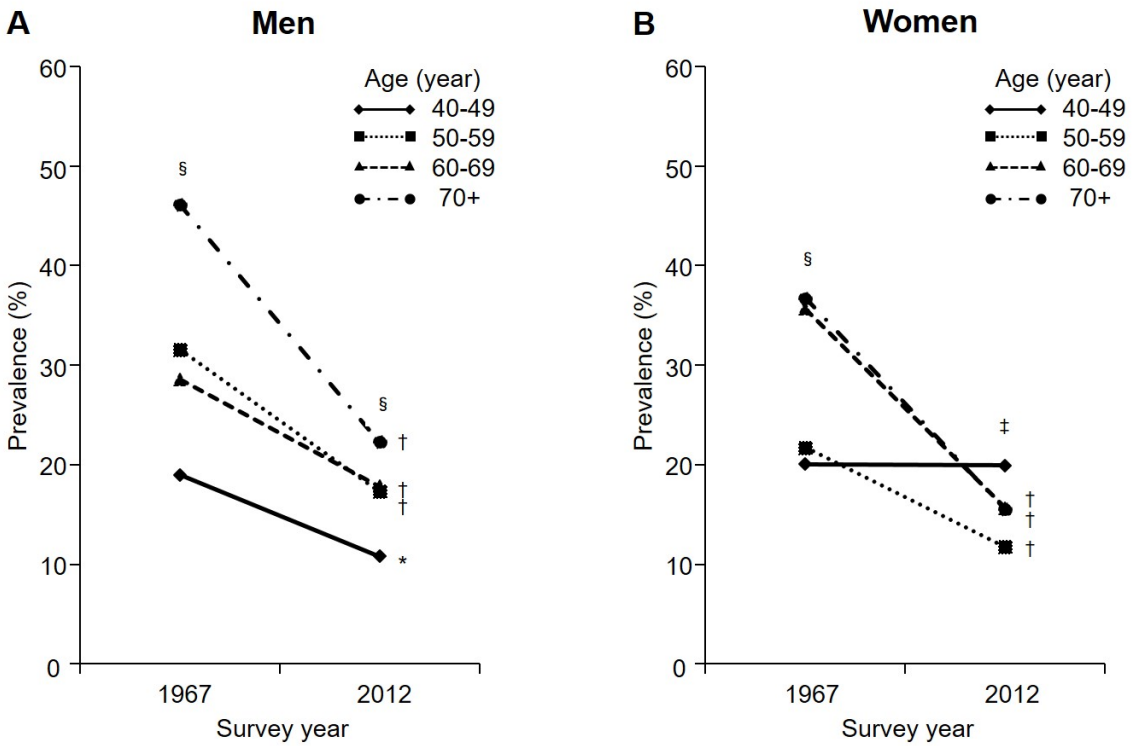
Figure E2 Trends in the age-adjusted prevalence of airflow limitation in 1967 and 2012 by sex.



Vertical bars indicate 95% confidence intervals. $^{*}P < 0.001$ vs 1967.

Airflow limitation was defined as forced expiratory volume in one second / forced vital capacity (FEV_1/FVC) < lower limit of normal for cut-off of FEV_1/FVC according to the American Thoracic Society / European Respiratory Society criteria.

Figure E3 Trends in the prevalence of airflow limitation according to age groups in 1967 and 2012 by sex.



*P < 0.05, †P < 0.01 vs 1967, ‡P for trend < 0.05, §P for trend < 0.01.

Airflow limitation was defined as forced expiratory volume in one second / forced vital capacity (FEV_1/FVC) < lower limit of normal for cut-off of FEV_1/FVC according to the American Thoracic Society / European Respiratory Society criteria.

Figure E4 Trends in the age-adjusted prevalence of airflow limitation according to severity in 1967 and 2012 by sex.

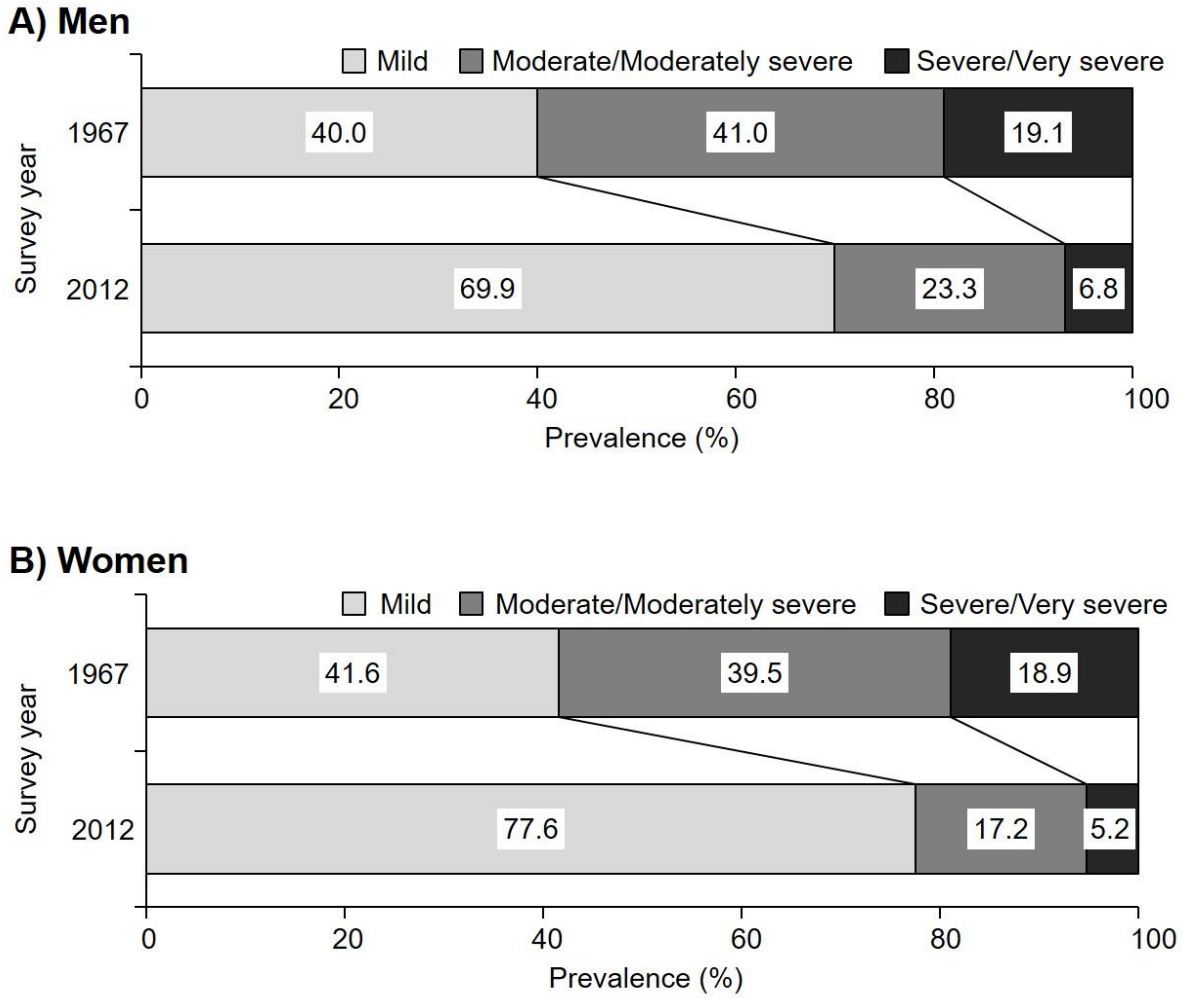


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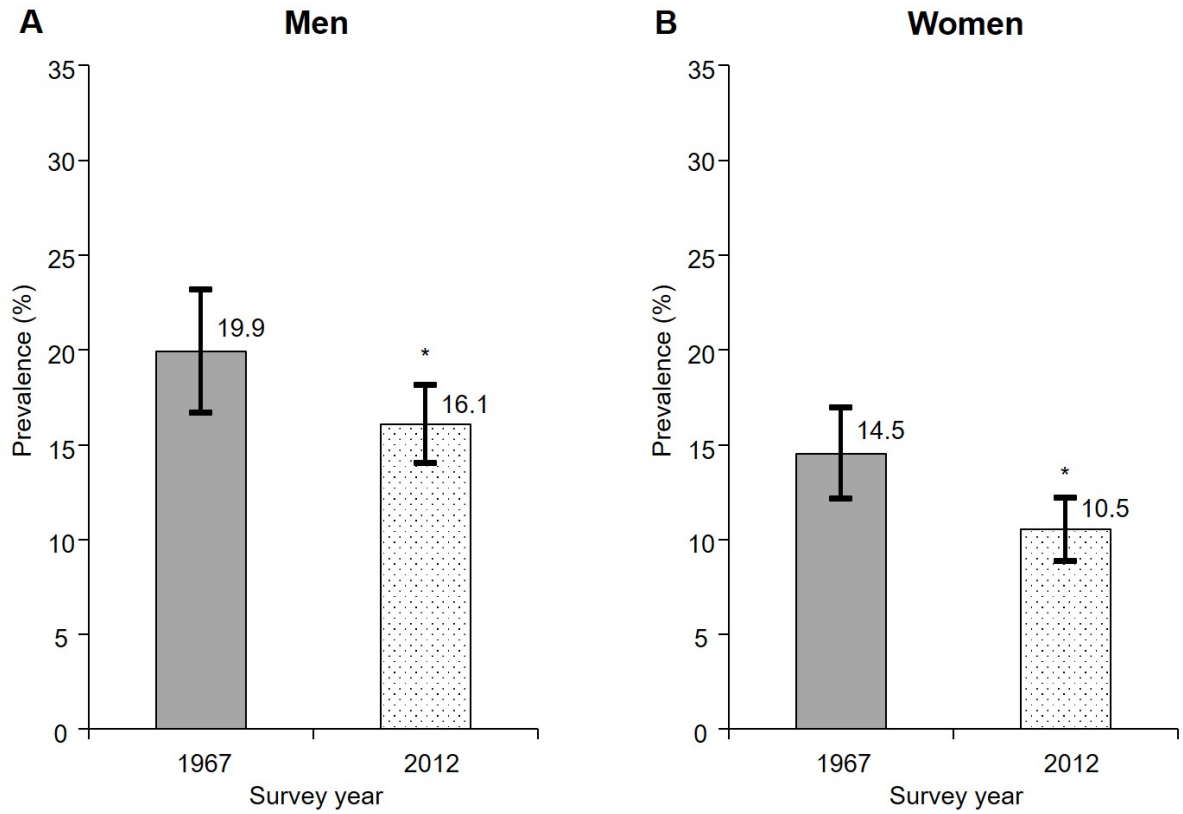
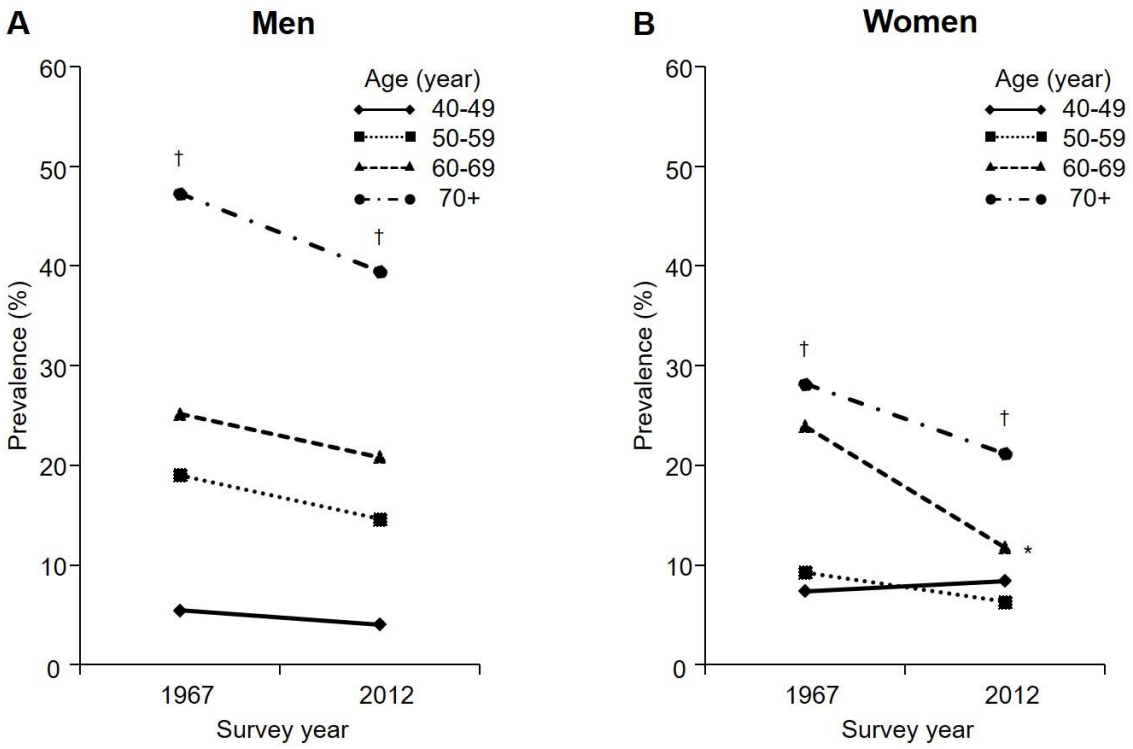
Figure E5 Trends in the age-adjusted prevalence of airflow limitation by sex.



Vertical bars indicate 95% confidence intervals. $^{*}P < 0.05$ vs 1967.

Airflow limitation was defined as forced expiratory volume in one second / forced vital capacity (FEV_1/FVC) < 67% in 1967 according to the modified Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria, and FEV_1/FVC < 70% in 2012 according to the GOLD criteria.

Figure E6 Trends in the prevalence of airflow limitation according to age groups by sex.



*P < 0.01 vs 1967, †P for trend < 0.01.

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Figure E7 Trends in the age-adjusted prevalence of airflow limitation by sex.

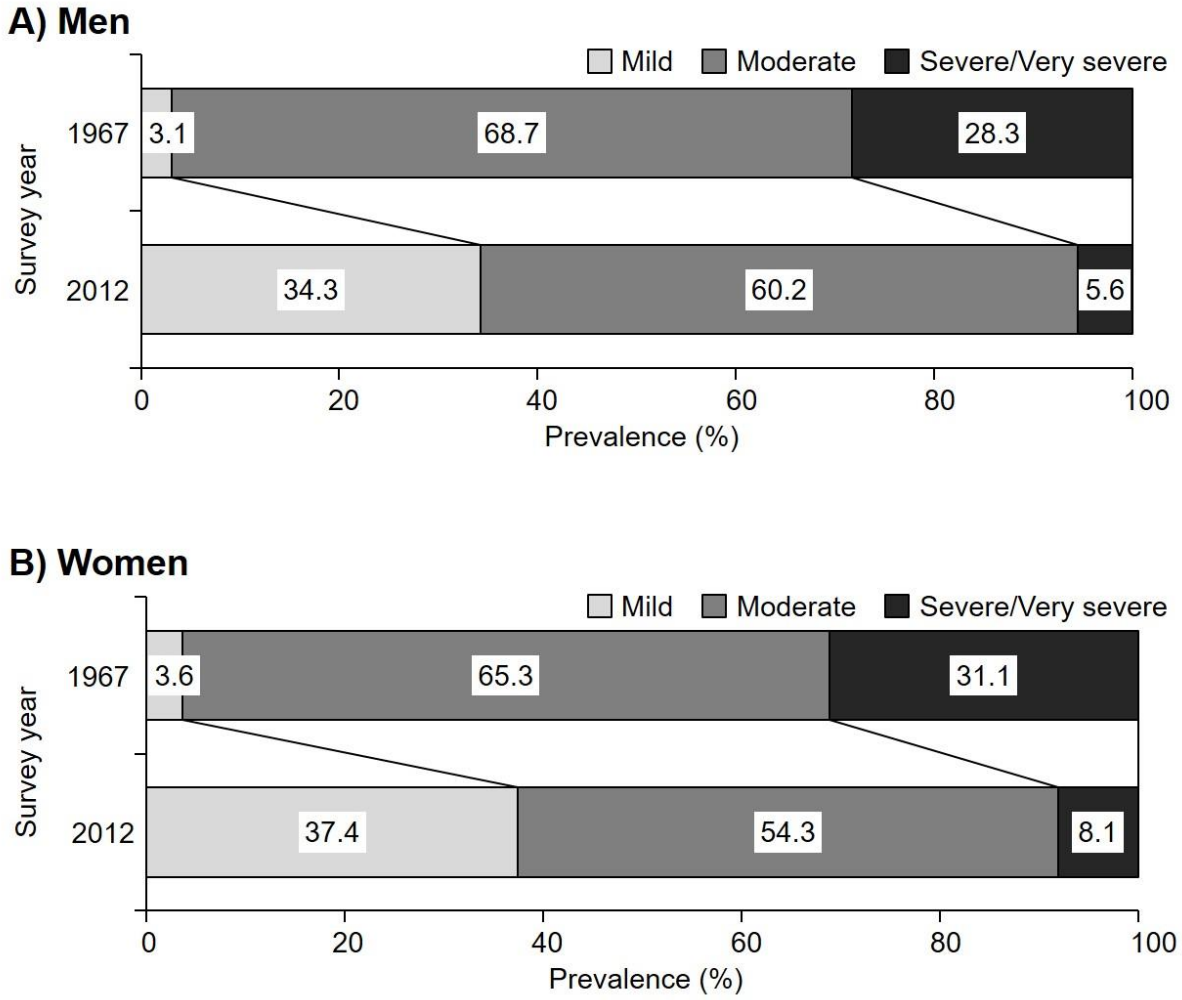

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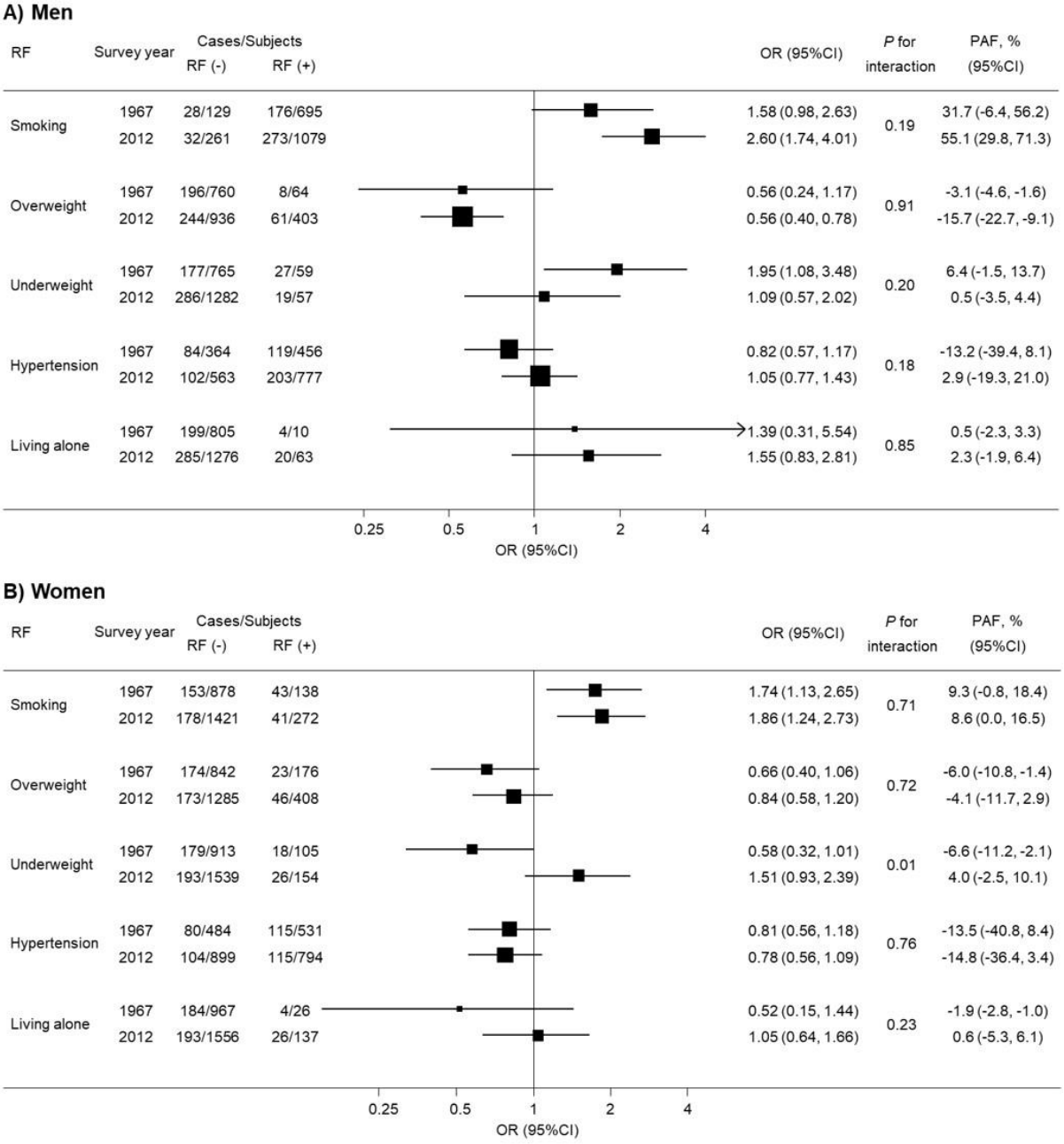
Figure E8 Multivariate-adjusted odds ratios and population attributable fractions of risk factors for airflow limitation in 1967 and 2012 by sex.



Airflow limitation was defined as forced expiratory volume in one second / forced vital

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*For the analysis of overweight, the normal weight or underweight group was used as the reference group.

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RF, risk factor; OR, odds ratio; CI, confidence interval; PAF, population attributable fraction.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3, 4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6, 7
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7, 8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	7, 8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8-10
Bias	9	Describe any efforts to address potential sources of bias	9
Study size	10	Explain how the study size was arrived at	7, 8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	11, 12
		(*b*) Describe any methods used to examine subgroups and interactions	11, 12
		(*c*) Explain how missing data were addressed	12
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	not appicable
		(*e*) Describe any sensitivity analyses	12
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7, 8
		(b) Give reasons for non-participation at each stage	7, 8
		(c) Consider use of a flow diagram	8, online supplementary figure E1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	13-15
		(b) Indicate number of participants with missing data for each variable of interest	15
Outcome data	15*	Report numbers of outcome events or summary measures	16
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	16, figure 2
		(*b*) Report category boundaries when continuous variables were categorized	11
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	16, 17
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	16, 17
Discussion			
Key results	18	Summarise key results with reference to study objectives	18
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	21, 22
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18-22
Generalisability	21	Discuss the generalisability (external validity) of the study results	21, 22
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	23

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Trends in the prevalence of airflow limitation in a general Japanese population: two serial cross-sectional surveys from the Hisayama Study

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Primary Subject Heading:	Respiratory medicine
Secondary Subject Heading:	Epidemiology, Public health, Smoking and tobacco
Keywords:	EPIDEMIOLOGY, PUBLIC HEALTH, Chronic airways disease < THORACIC MEDICINE, Epidemiology < THORACIC MEDICINE

Title

Trends in the prevalence of airflow limitation in a general Japanese population: two serial cross-sectional surveys from the Hisayama Study

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ABSTRACT

Objectives Chronic obstructive airway disease, which is characterized by airflow limitation, is a major burden on public health. Reductions in environmental pollution in the atmosphere and workplace and a decline in the prevalence of smoking over recent decades may have affected the prevalence of airflow limitation in Japan. The present epidemiological study aimed to evaluate trends in the prevalence of airflow limitation and in the influence of risk factors on airflow limitation in a Japanese community.

Design Two serial cross-sectional surveys.

Setting Data from the Hisayama Study, a population-based prospective study which has been longitudinally conducted since 1961.

Participants A total of 1,842 and 3,033 residents aged ≥ 40 years with proper spirometric measurements participated in the 1967 and 2012 surveys, respectively.

Main outcome measures Airflow limitation was defined as forced expiratory volume in one second/forced vital capacity < 70% by spirometry. For each survey, the age-adjusted prevalence of airflow limitation was evaluated by sex. Odds ratios and population attributable fractions of risk factors on the presence of airflow limitation were compared between surveys.

Results The age-standardized prevalence of airflow limitation decreased from 1967 to 2012 in both sexes (from 26.3% to 16.1% in men, and from 19.8% to 10.5% in women). Smoking

was significantly associated with higher likelihood of airflow limitation in both surveys, although the magnitude of its influence was greater in 2012 than in 1967 (the multivariable-adjusted odds ratio was 1.63 (95% confidence interval 1.19-2.25) in 1967 and 2.26 (1.71-2.98) in 2012; $P = 0.007$ for heterogeneity). Accordingly, the population attributable fraction of smoking on airflow limitation was 33.4% in 2012, which was 1.5-fold higher than that in 1967 (21.1%).

Conclusions The prevalence of airflow limitation was decreased over 45 years in Japan, but the influence of smoking on airflow limitation increased with time.

ARTICLE SUMMARY

Strengths and limitations of this study

- The strengths of our study include the high participation rates and the use of spirometry for evaluating the exact prevalence of airflow limitation in both 1967 and 2012 surveys.
- One limitation was the difference in the instruments used for spirometry: a dry wedge bellows spirometer in 1967 vs a more sophisticated instrument in 2012.
- Another limitation was the possible decrease in airflow limitation due to the bronchodilators that have been used as standard therapies for COPD and asthma over the last decade in our country.

Keywords epidemiology; public health; chronic airways disease (thoracic medicine); epidemiology (thoracic medicine)

INTRODUCTION

Chronic obstructive pulmonary disease (COPD), which is characterized by persistent respiratory symptoms and airflow limitation defined by post-bronchodilator spirometry, is a major threat to the health of the respiratory system. COPD is composed of a mixture of small airway disease (e.g., obstructive bronchiolitis) and parenchymal destruction (emphysema), and can lead to acute exacerbation of respiratory symptoms and airway function, ultimately progressing to respiratory failure.[1] In addition, COPD poses a great burden in terms of morbidity and premature mortality as well as in health care expenditures worldwide.[2] Pre-bronchodilator airflow limitation, which include chronic obstructive ventilatory disorders such as COPD, asthma, and bronchiectasis, is a well-used outcome in the epidemiological study without post-bronchodilator spirometry. Therefore, it would be clinically and epidemiologically valuable to clarify the trends in the prevalence of airflow limitation and in the influence of risk factors on airflow limitation in individual communities.

A previous literature-based meta-analysis estimated that the prevalence of airflow limitation increased over two decades in both developed and developing regions, but these estimations were based on a statistical model.[3] Few studies have addressed the trends in the prevalence of airflow limitation over time based on the data from repeated community-based surveys, although the nationwide surveys in the U.S. showed a decreasing trend in the

prevalence of airflow limitation.[4] 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 alpha$_1$-antitrypsin deficiency,[5] but there has been no survey assessing the associations of risk factors with the prevalence of airflow limitation in a time series manner. In recent decades, reduction of environmental pollution in the atmosphere and workplace and the reduction in smoking prevalence[6-10] may have affected the influence of these risk factors on airflow limitation.

The purpose of the present study was 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, the Hisayama Study, with high participation rates and a consistent spirometric definition of airflow limitation. In addition, the magnitudes of the association of risk factors with airflow limitation were compared between surveys.

METHODS

study population

Since 1961, a population-based prospective study has been longitudinally conducted to investigate the distributions and associations of lifestyle-related diseases and their risk

factors in the town of Hisayama, Japan. Details of this cohort study have been described elsewhere.[11] As part of an annual health examination, two serial cross-sectional surveys of airflow limitation with spirometry were performed in 1967 and 2012. 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 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. The remaining 1,842 subjects (824 men and 1,018 women) with successfully measured pulmonary function were enrolled in the present study. Similarly, in 2012, 3,396 subjects participated in a health examination (participation rate, 72.6%). After excluding 6 subjects who refused to participate in the epidemiological research, and 357 subjects who were either unable or unwilling to submit to spirometric measurement, 3,033 subjects (1,340 men and 1,693 women) with proper spirometric measurements were enrolled in the study (online supplementary figure E1).

assessment and definition of airflow limitation

A dry wedge bellows spirometer was used in 1967 to obtain volume-time curves. Participants underwent spirometry several times until valid curves were obtained. Pulmonary

physicians graphically evaluated and scrutinized the figures, and obtained the values of forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), and FEV_1/FVC. In the 2012 survey, spirometry was performed in line with the guidelines of the Japanese Respiratory Society.[12] Two to four measurements were performed using a CHESTGRAPH HI-105 electronic spirometer (Chest MI, Tokyo), in order to obtain satisfactory flow-volume loops. Pulmonary physicians visually assessed the quality of the maneuvers and chose the finest loop, showing the highest sum of FEV_1 and FVC. FVC, FEV_1, and FEV_1/FVC were obtained from the selected curve. Bronchodilators were not used for any of the surveys.

Airflow limitation was pathophysiologically assessed with spirometry and without any radiological measurements or clinical symptoms. There are two major, worldwide criteria for the definition of airflow limitation: the modified Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria with a fixed cut-off of FEV_1/FVC[13] and the American Thoracic Society / European Respiratory Society (ATS/ERS) criteria using age-, sex- and height-specific lower limits of normal (LLNs) for the cut-off of FEV_1/FVC.[14] We employed both the GOLD criteria and the ATS/ERS criteria. 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.[15] 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.[15,16] The GOLD criteria-based airflow limitation was defined as $FEV_1/FVC < 70\%$. We also used a modified definition of airflow limitation (i.e., $FEV_1/FVC < 67\%$), because the dry wedge bellows spirometer has been reported to yield values 2-3% lower than those measured by a water-sealed spirometer or an electronic spirometer.[17,18] Among participants with airflow limitation, the severity was defined using the predicted FEV_1 value for a person of the same age, sex, and height using the equation for the Japanese population[15] as follows: mild, $FEV_1 \geq 80\%$ of predicted; moderate, $50\% \leq FEV_1 < 80\%$ of predicted; severe and very severe, $FEV_1 < 50\%$ of predicted. The ATS/ERS criteria-based airflow limitation was defined as $FEV_1/FVC <$ the 5th percentile (LLN), and the severity of airflow limitation was defined as follows: mild, $FEV_1 \geq 70\%$ predicted; moderate and moderately severe, $50\% \leq FEV_1 < 70\%$ predicted; and severe and very severe, $FEV_1 < 50\%$ predicted. 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.[16]

clinical evaluation and laboratory measurements

Each participant completed a self-administered questionnaire covering smoking habits, alcohol intake, medical history, and antihypertensive treatments. Smoking habits were categorized as never smokers or current/former smokers since airflow limitation could persist even after cessation of smoking. Alcohol drinking was defined as current or not. Body height and weight were measured in light clothing without shoes, and body mass index (BMI; kg/m^2) was calculated. Overweight and underweight were defined as BMI $\geq$ 25.0 kg/m^2 and BMI < 18.5 kg/m^2, respectively. Blood pressure was measured 3 times using a mercury sphygmomanometer in 1967 and an automated sphygmomanometer (BP-203 RVIIIB; Omron Healthcare, Kyoto) in 2012 in a sitting position after rest for at least 5 minutes; the average values were used in the analyses. Hypertension was defined as a systolic blood pressure $\geq$ 140 mmHg, a diastolic blood pressure $\geq$ 90 mmHg or current treatment with antihypertensive agents.

statistical analysis

The SAS software package version 9.4 (SAS Institute, Cary, NC, USA) was used to perform all statistical analyses. Baseline characteristics were shown as age-adjusted values by sex and by survey year using the analysis of covariance (ANCOVA) for continuous variables or by the direct method using the age distribution of the 1985 Japanese population as a

standard.[19] They were compared between survey years using an ANCOVA, a Cochran–Mantel–Haenszel test, or a logistic regression model. The sex-specific prevalence of airflow limitation was estimated separately for each age group (40-49, 50-59, 60-69, and 70+ years), and as a whole adjusting for age by the direct method using the same standard population. The linear trend of airflow limitation across age groups in each survey year was tested using a logistic regression model. The same model was used for the test of secular trends in sex-specific and age-standardized prevalence of airflow limitation from 1967 to 2012. Among residents with airflow limitation, the sex-specific and age-standardized distribution of its severity was compared between survey years using an ordinal logistic regression model. The associations of potential risk factors with airflow limitation were estimated as adjusted odds ratios (ORs) with 95% confidence intervals (95% CIs) for each survey year by using multivariable-adjusted logistic regression models, wherein adjustment was made for sex, age, smoking habits, overweight, underweight, hypertension, and living alone that were associated with airflow limitation or COPD in previous reports.[1,13,20-22] Multivariable-adjusted ORs with 95% CIs were calculated using data of subjects with no missing data (proportion of subjects excluded: 2.1% in 1967 and 0.07% in 2012). We tested whether these associations were changed over decades by including the interactions of risk factors and the survey years in the relevant statistical models. The contribution of each risk

factor to airflow limitation was estimated as a population attributable fraction (PAF) in each survey using the multivariable-adjusted OR of each risk factor and its frequency among cases,[23] which represents the proportional reduction in population that would occur if each risk factor was eliminated. The 95% CIs of the PAFs were estimated in accordance with Greenland's method.[24]

As described above, the analysis was also performed using the ATS/ERS criteria with the JRS or GLI reference equations for each survey year. Another sensitivity analysis was performed with the modified definition of airflow limitation, which was FEV_1/FVC of < 67%. A two-sided value of $P < 0.05$ was considered to indicate statistical significance.

participant involvement

There was no direct patient involvement in the development, design or conduct of the study.

ethical considerations

The study was approved by the Kyushu University Institutional Review Board for Clinical Research, and written or oral informed consent was obtained from all the participants. In addition, we are applying an opt-out methodology to announce that the study is ongoing

and to provide the opportunity of refusal through the official website according to the ethical guidelines for medical and health research involving human subjects in Japan.[25]

RESULTS

demographic and clinical characteristics

The demographic and clinical characteristics in 1967 and 2012 are summarized by sex in table 1, in which the mean values and the frequencies were adjusted for age. In both sexes, subjects in 2012 were older than those in 1967. The mean values of height, weight and BMI were higher in 2012 than 1967. The frequencies of drinking habits and living alone also increased over 45 years. The prevalence of hypertension decreased with time. 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).

Table 1 Age-adjusted mean values or frequencies of demographic and clinical characteristics in 1967 and 2012 by sex

Variables	Men			Women		
	1967 (n=824)	2012 (n=1340)	*P*-value	1967 (n=1018)	2012 (n=1693)	*P*-value
Age (years)	55.0 (0.40)	63.1 (0.32)	<0.001	55.5 (0.37)	62.9 (0.29)	<0.001
Height (cm)	158 (0.21)	166 (0.16)	<0.001	146 (0.17)	153 (0.13)	<0.001
Weight (kg)	53.2 (0.32)	65.8 (0.25)	<0.001	47.4 (0.27)	53.6 (0.21)	<0.001
BMI (kg/m^2)	21.4 (0.10)	23.8 (0.08)	<0.001	22.3 (0.11)	22.8 (0.09)	<0.001
Degree of fatness						
Overweight (%)	7.6	31.5		17.0	22.0	
Normal weight (%)	84.9	64.6	<0.001	72.4	67.6	0.001
Underweight (%)	7.5	3.9		10.6	10.5	
Smoking habit (current/ever) (%)	83.6	79.8	0.08	13.9	20.6	0.003
Current smoker (%)	72.1	35.7	<0.001	12.2	9.0	<0.001
Ever smoker (%)	11.5	44.1	<0.001	1.7	11.6	<0.001
Alcohol intake (%)	63.3	74.7	<0.001	4.1	40.1	<0.001
Hypertension (%)	57.3	47.7	<0.001	53.0	33.8	<0.001
Systolic blood pressure (mmHg)	147.0 (0.78)	130.7 (0.61)	<0.001	145.7 (0.65)	125.4 (0.50)	<0.001
Diastolic blood pressure (mmHg)	86.4 (0.44)	79.8 (0.34)	<0.001	83.8 (0.37)	74.0 (0.28)	<0.001
Antihypertensive medication (%)	13.6	29.3	<0.001	15.0	21.8	<0.001
Living alone (%)	1.3	4.5	<0.001	2.5	5.4	0.002

Age is given as the mean plus standard error. Other values are given as the age-adjusted mean (if appropriate) with standard errors in brackets

for continuous variables and as age-adjusted percentages for dichotomized or categorical variables. *P* values denote the statistical significance of the difference in each variable between 1967 and 2012. Overweight was defined as a body mass index ≥ 25.0 kg/m^2. Underweight was defined as a body mass index < 18.5 kg/m^2. Smoking habits were categorized as never smokers or current/former smokers. Alcohol intake was defined as current or not. Hypertension was defined as blood pressure ≥ 140/90 mmHg and/or current use of antihypertensive agents. Numbers of subjects with missing data were as follows: alcohol intake 20, hypertension 4, antihypertensive medication 10, and living alone 9 in men in 1967; height 1, body mass index 1, degree of fatness 1, and living alone 1 in men in 2012; smoking habit 2, alcohol intake 42, hypertension 3, antihypertensive medication 5, and living alone 25 in women in 1967; no missing data in women in 2012.

BMI, body mass index.

trends in the prevalence of airflow limitation

Among the 1,842 and 3,033 survey subjects in 1967 and 2012, 401 and 524 subjects had airflow limitation, respectively. The age-standardized prevalence decreased over the intervening decades (from 26.3% to 16.1% in men and 19.8% to 10.5% in women) (figure 1). Almost all age groups in both sexes, with the exception of 40-49 years in women, showed significant downward trends in the age-specific prevalence from 1967 to 2012 (figure 2). The prevalence of airflow limitation increased with age in both 1967 and 2012 (all $P < 0.001$ for trend). As shown in figure 3, there was a significant shift in the distribution of severity of airflow limitation in both men and women with airflow limitation; the proportions of moderate and severe/very severe airflow limitation decreased over time, while the proportion of mild airflow limitation increased ($P < 0.001$ for difference in both sexes). 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.

trends in the associations of risk factors with airflow limitation

There was a significant positive association of smoking with airflow limitation in both surveys (OR = 1.63 (95% CI 1.19-2.24), $P = 0.003$ in 1967; OR = 2.26 (95% CI 1.71-2.98), $P < 0.001$ in 2012) (figure 4). In comparison, there was a stronger association between smoking and airflow limitation in 2012 than in 1967 ($P = 0.007$ for interaction). Consequently, the contribution of smoking to the estimated proportion of cases with airflow limitation—i.e., PAF—was 21.1% in 1967 and 33.4% in 2012 (a 1.5-fold increase). Overweight was negatively associated with airflow limitation in both surveys (OR = 0.65 (95% CI 0.42-0.98), $P = 0.04$ in 1967; OR = 0.66 (95% CI 0.52-0.85), $P = 0.001$ in 2012), and there was no statistically significant difference between them ($P = 0.84$ for interaction). Nevertheless, due to the 2-fold elevation in the proportion of overweight from 13.0% in 1967 to 26.8% in 2012, the potential of overweight for reducing the proportion of airflow limitation (PAF) was greater in 2012 than in 1967 (-4.1% in 1967 to -10.3% in 2012). For the associations of sex (men vs women) with airflow limitation, we found a significant difference between survey years, although neither association reached statistical significance. The other variables were not associated with airflow limitation, and made no significant contributions to the PAF. In the sex-specific analysis, the influence of each risk factor on airflow limitation was substantially similar between sexes (all $P > 0.06$ for heterogeneity), except for underweight in 1967 ($P = 0.002$ for heterogeneity) (online supplementary figure E11).

DISCUSSION

The present comparison of the prevalence of airflow limitation based on the GOLD criteria in Japan revealed a significant reduction from 1967 to 2012, consistently across age-groups in both men and women. Among participants with airflow limitation, the proportion with a moderate to severe level of the disorder decreased remarkably. Similar findings were observed with the ATS/ERS criteria. Moreover, both the relative association between smoking and airflow limitation and the PAF of smoking were compared and found to be stronger in 2012 than in 1967. This is the first study to evaluate trends in the prevalence of airflow limitation and in the influence of its risk factors in an Asian population on the basis of the data from repeated community-based surveys.

Epidemiological findings in regard to trends in the prevalence of airflow limitation are very limited. A literature-based meta-analysis of cross-sectional spirometric surveys showed that there was an increase in the prevalence of airflow limitation from the 1990s to 2010s in both developed and developing regions.[3] However, these estimations were calculated by using a statistical model on the basis of demographic changes over time. On the other hand, the results from the repeated nationwide National Health and Nutrition Examination Surveys demonstrated that there was a significant decrease in the prevalence of

airflow limitation in the U.S. from 1988-1994 to 2007-2010, although it barely changed from 1971-1975 to 1988-1994.[4,26] This finding was in accord with ours. The reduction of environmental pollution in both the atmosphere and workplace and the reduction in the smoking frequency may have decreased the prevalence of airflow limitation in the U.S. as well as in our population.[6-10]

Previous studies estimated the prevalence of airflow limitation in Japan in the 2000s as 16.2%-16.4% among men and 5.0%-5.8% among women.[27,28] The former range was similar to that in 2012 in the present study, while the latter was 2-fold lower. The discrepancy may be due to the difference in the participation rate, which would likely lead to a selection bias; the participation rate in our study was over 3-fold higher than those in the preceding studies. The prevalence of airflow limitation determined using the GOLD criteria has been reported to be higher than that based on the ATS/ERS criteria in elderly populations,[4,29] which was consistent with our study. However, other than ours, there has been no study estimating the prevalence of airflow limitation in Japan using the ATS/ERS criteria, and thus further studies are needed.

In the present study, the potentiating effects of smoking on airflow limitation were more pronounced in 2012 than in 1967. Cigarette smoking and chronic inhalational exposure to a polluted atmosphere both lead to COPD by the same mechanism—i.e., hazardous

particles penetrating deep into the respiratory tract and eliciting neutrophilic inflammation and oxidative stress.[30] However, environmental, occupational, and household exposure to hazardous pollutants has been steadily attenuated over the last several decades. This reduction in exposure to atmospheric pollutants could have increased the relative influence of smoking in recent years.[31] In turn, the prevention of tobacco use and the promotion of smoking cessation have become increasingly important public health concerns in order to prevent airflow limitation and COPD.

The present study showed that overweight was inversely associated with airflow limitation both in 1967 and 2012. Previous observational studies demonstrated that higher BMI was associated with lower FVC and therefore with higher FEV_1/FVC,[20,32] which probably reflected the decrease in excursion of the thoracic cage due to intra-abdominal and subpleural fat deposition.[33] Our present findings may also be explained by reverse causality; weight loss commonly occurs in COPD patients via muscle wasting and elevated energy metabolism.[21] The weaker association and smaller PAF among women than among men in 2012 can be explained by the relatively small number of female participants with airflow limitation. There was no evidence of a significant association between underweight and airflow limitation in either survey, but the influence of underweight on the airflow

limitation was different between the sexes. The underlying explanation for this heterogeneity was unclear. It may merely reflect the play of chance.

In the present study, the magnitude of the association between male sex and the airflow limitation in 2012 was significantly greater than that in 1967, although the OR for each survey did not reach statistical significance. This heterogeneity may have been caused by residual confounding due to the greater amount and duration of tobacco smoking in men than women, considering the fact that the influence of smoking habits increased with time, as mentioned above. Nevertheless, based on the current evidence, it remains controversial whether the male sex is a risk factor for airflow limitation.[34-37] Further evaluation of this matter is warranted.

The strengths of our study include the high participation rates and the use of spirometry for evaluating the exact prevalence of airflow limitation in both surveys. On the other hand, some potential limitations should be noted. First, there was a difference in the instruments used for spirometry: a dry wedge bellows spirometer in 1967 vs a more sophisticated instrument in 2012. This limitation could have led to an overestimation of the prevalence of airflow limitation in 1967, since the dry wedge bellows spirometer has been reported to generate 2-3% smaller FEV_1/FVC values compared to the instrument used in 2012.[17] However, several other studies have reported that the dry wedge bellows spirometer

exhibited comparable reliability to more sophisticated instruments.[38-41] Additionally, the sensitivity analyses using the 3% lower cut-off value for FEV_1/FVC in 1967 showed similar results. Hence, this potential bias did not appear to have affected the present results. Second, there was a possibility of decrease in airflow limitation due to the bronchodilators, such as short-acting β2 agonist, short-acting muscarinic antagonist, long-acting β2 agonist (LABA), long-acting muscarinic antagonist (LAMA), inhaled corticosteroids (ICS)/LABA, LABA/LAMA, and xanthine, that have been used as standard therapies for COPD and asthma over the last decade in our country.[42,43] However, the proportion of subjects who used bronchodilators was only 2.6% (n=80) in 2012, and thus the decrease in the prevalence of airflow limitation was unlikely by virtue of the effects of these medications. 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.[44] 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.[45] Thus, this limitation may not have altered our conclusions. 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. Lastly, we were unable to investigate the effects of intensity or duration of smoking on airflow limitation due to 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.[46] In addition, the frequency of ever smokers who stopped smoking significantly increased in both sexes in the present study. Thus, we believe that the intensity or duration of smoking did not increase from 1967 to 2012.

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. However, more than 10% of men and women aged 40 years or older still exhibit airflow limitation. With respect to risk factors, the contribution of smoking to the occurrence of airflow limitation has become more pronounced over the previous 5 decades, which we speculated as a result of a reduction in the

occupational exposures to indoor and outdoor air pollution. To accelerate the prevention of airflow limitation, therefore, further public efforts toward smoking cessation are mandatory.

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Competing interests

HI reports grants from Astellas, AstraZeneca, Boehringer-Ingelheim, ChugaiPharm, GlaxoSmithKline, Pfizer, MerckSharp&Dohme, Novartis, Teijin-Pharma, personal fees from Astellas, AstraZeneca, Boehringer-Ingelheim, Chugai-Pharm, GlaxoSmithKline, Kyorin, MerckSharp&Dohme, MeijiSeikaPharma, Novartis, Otsuka, Pfizer, Taiho, outside the submitted work. The other authors report no competing interests.

Patient consent

This manuscript does not contain personal medical information about each identifiable person.

Ethics approval

The study was approved by the Kyushu University Institutional Review Board for Clinical Research, and written or oral informed consent was obtained from all the participants. In addition, we are applying an opt-out methodology to announce that the study is ongoing and to provide the opportunity of refusal through the official website according to the ethical guidelines for medical and health research involving human subjects in Japan.[25]

Data sharing statement

Due to data protection regulations of executive committee of the cohort and of the administration that support the cohort, the authors do not have the permission to share the data. No additional data are available.

Contributors

HO contributed to the study concept, data collection, interpretation of data, statistical analysis, and drafting of the manuscript. YH contributed to the study concept, data collection, interpretation of data, and revision of the manuscript. SF and KM contributed to the data collection, interpretation of data, and revision of the manuscript. JH, DY, HI, TK, and YN contributed to interpretation of data and revision of the manuscript. TN was the chief investigator of the Hisayama Study and contributed to the study concept, data collection, interpretation of data, revision of the manuscript, and acquisition of funding. All authors critically reviewed the manuscript and approved the final version.

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FIGURE LEGENDS

Figure 1 Trends in the age-adjusted prevalence of airflow limitation in 1967 and 2012 by sex.

Vertical bars indicate 95% confidence intervals. $^{*}P < 0.001$ vs 1967.

Airflow limitation was defined as forced expiratory volume in one second / forced vital capacity < 70% according to the Global Initiative for Chronic Obstructive Lung Disease criteria.

Figure 2 Trends in the prevalence of airflow limitation according to age groups in 1967 and 2012 by sex.

$^{*}P < 0.05$, $^{\dagger}P < 0.01$ vs 1967, $^{\ddagger}P$ for trend < 0.01.

Airflow limitation was defined as forced expiratory volume in one second / forced vital capacity < 70% according to the Global Initiative for Chronic Obstructive Lung Disease criteria.

Figure 3 Trends in the age-adjusted prevalence of airflow limitation according to severity in 1967 and 2012 by sex.

Airflow limitation was defined as forced expiratory volume in one second / forced vital capacity < 70% according to the Global Initiative for Chronic Obstructive Lung Disease

criteria.

Figure 4 Multivariate-adjusted odds ratios and population attributable fractions of risk factors for airflow limitation in 1967 and 2012.

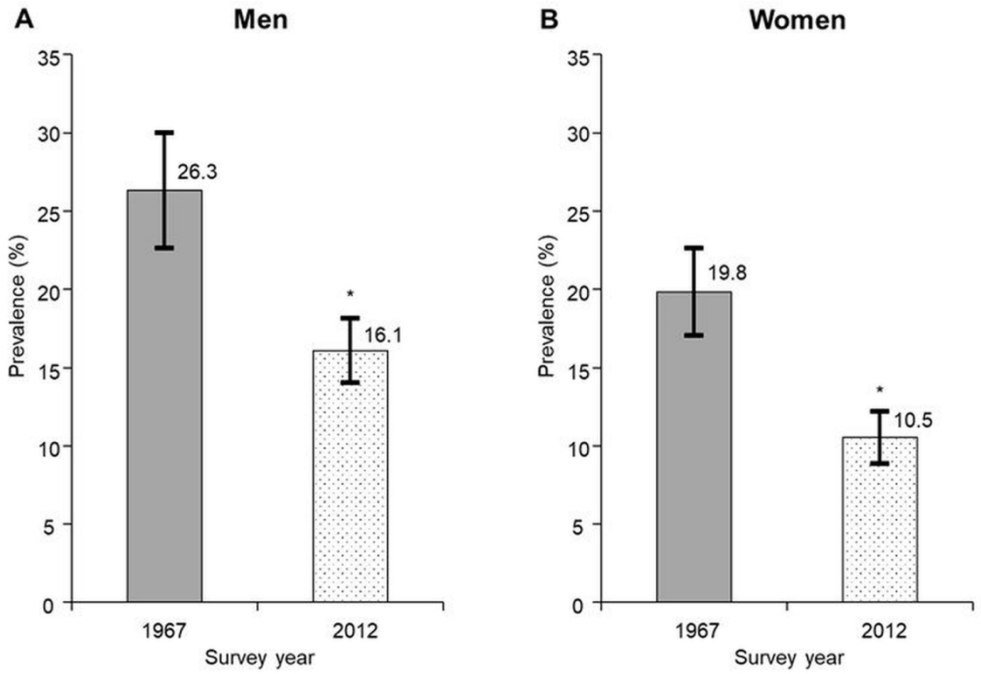
Airflow limitation was defined as forced expiratory volume in one second / forced vital capacity < 70%. Adjustments were made for sex, age, smoking habits, overweight*, underweight†, hypertension, and living alone. Horizontal bars indicate 95% CIs.

*For the analysis of overweight, the normal weight or underweight group was used as the reference group.

†For the analysis of underweight, the normal weight or overweight group was used as the reference group.

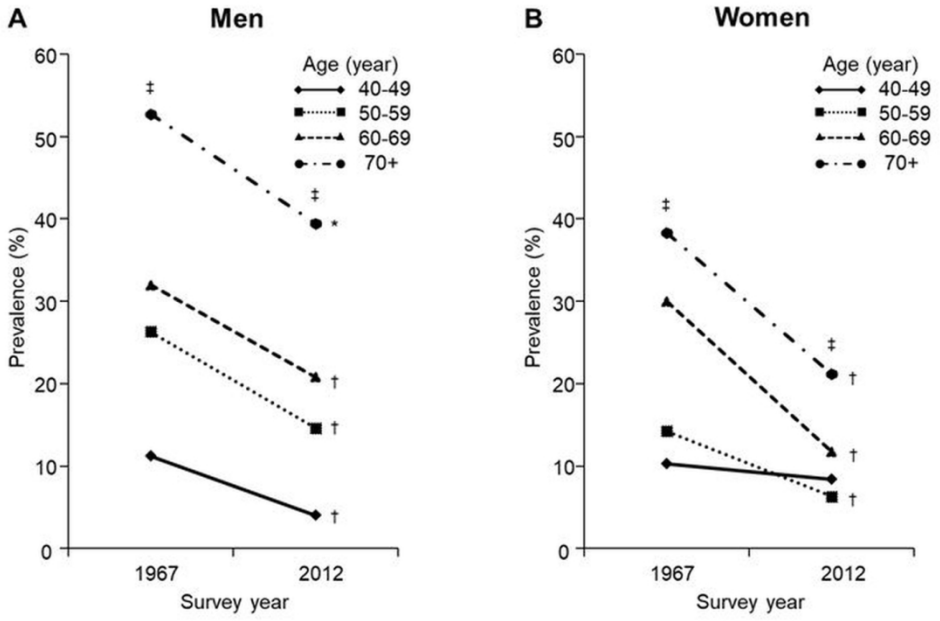
RF, risk factor; OR, odds ratio; CI, confidence interval; PAF, population attributable fraction.

attributable fraction.



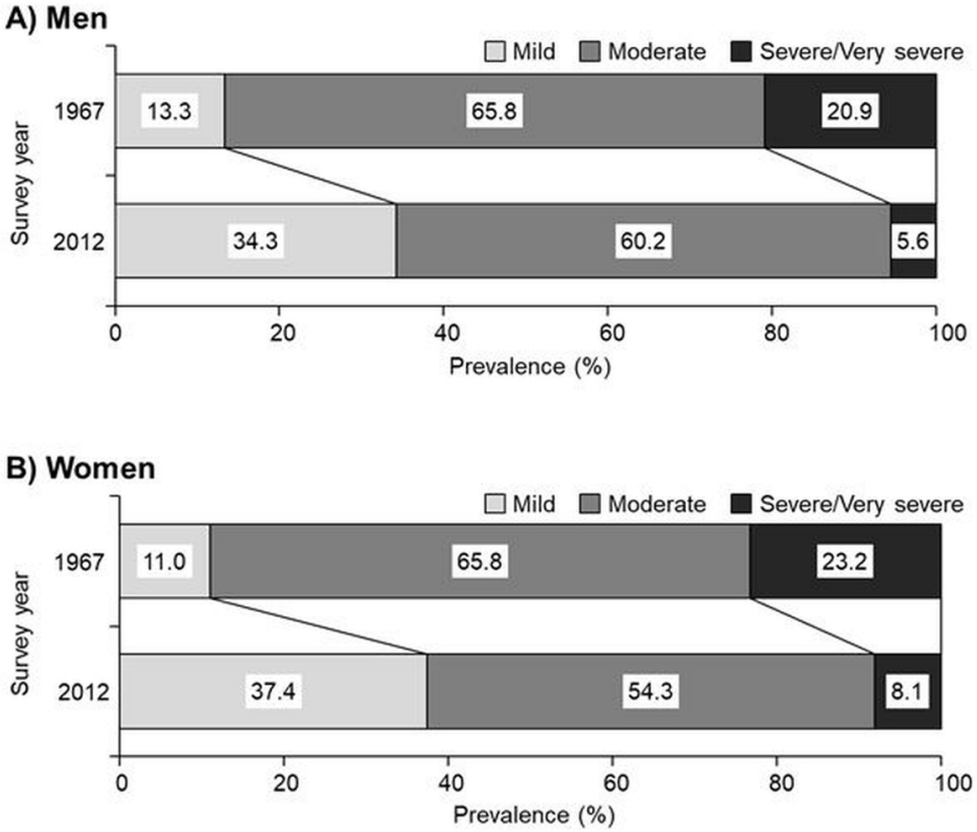
Trends in the age-adjusted prevalence of airflow limitation in 1967 and 2012 by sex. Vertical bars indicate 95% confidence intervals. $^{*}P < 0.001$ vs 1967. Airflow limitation was defined as forced expiratory volume in one second / forced vital capacity < 70% according to the Global Initiative for Chronic Obstructive Lung Disease criteria.

131x90mm (300 x 300 DPI)



Trends in the prevalence of airflow limitation according to age groups in 1967 and 2012 by sex. *P < 0.05, †P < 0.01 vs 1967, ‡P for trend < 0.01. Airflow limitation was defined as forced expiratory volume in one second / forced vital capacity < 70% according to the Global Initiative for Chronic Obstructive Lung Disease criteria.

130x90mm (300 x 300 DPI)



Trends in the age-adjusted prevalence of airflow limitation according to severity in 1967 and 2012 by sex. Airflow limitation was defined as forced expiratory volume in one second / forced vital capacity < 70% according to the Global Initiative for Chronic Obstructive Lung Disease criteria.

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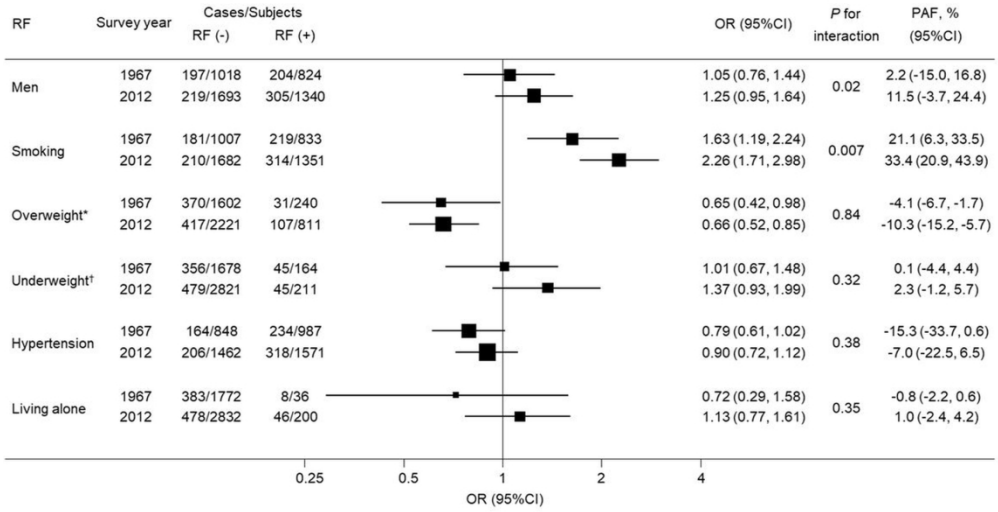

Multivariate-adjusted odds ratios and population attributable fractions of risk factors for airflow limitation in 1967 and 2012. Airflow limitation was defined as forced expiratory volume in one second / forced vital capacity < 70%. Adjustments were made for sex, age, smoking habits, overweight*, underweight†, hypertension, and living alone. Horizontal bars indicate 95% CIs. *For the analysis of overweight, the normal weight or underweight group was used as the reference group. †For the analysis of underweight, the normal weight or overweight group was used as the reference group. RF, risk factor; OR, odds ratio; CI, confidence interval; PAF, population attributable fraction.

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Online Data Supplement

Figure E1 Selection of participants.

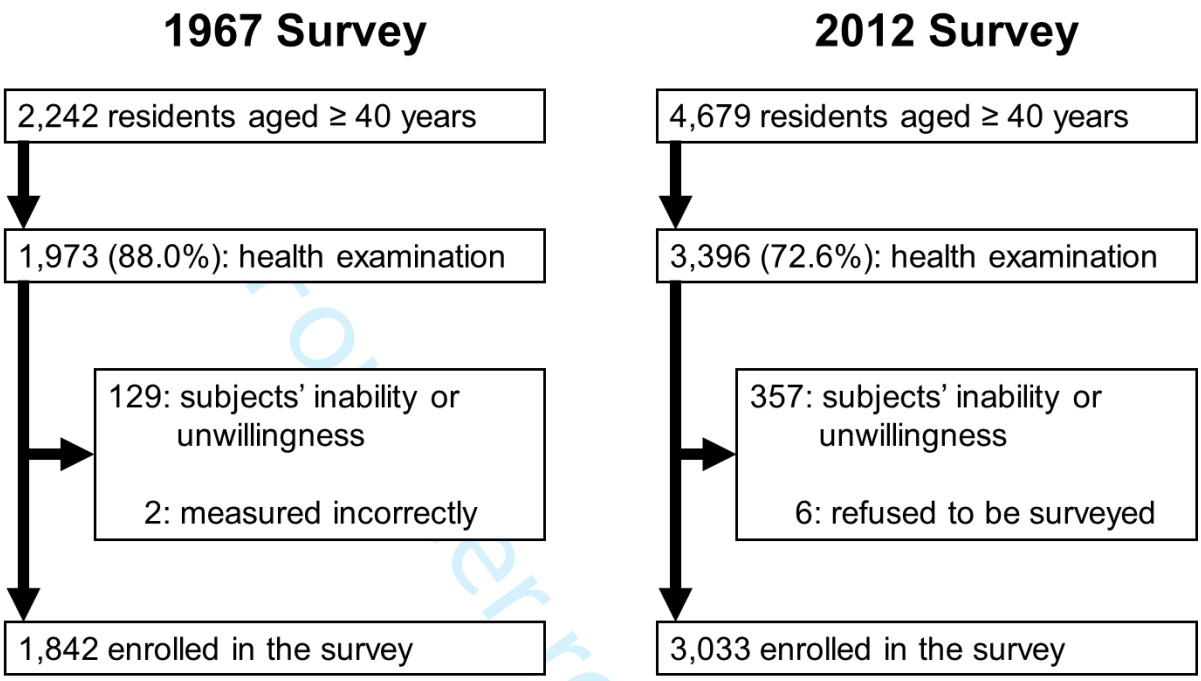
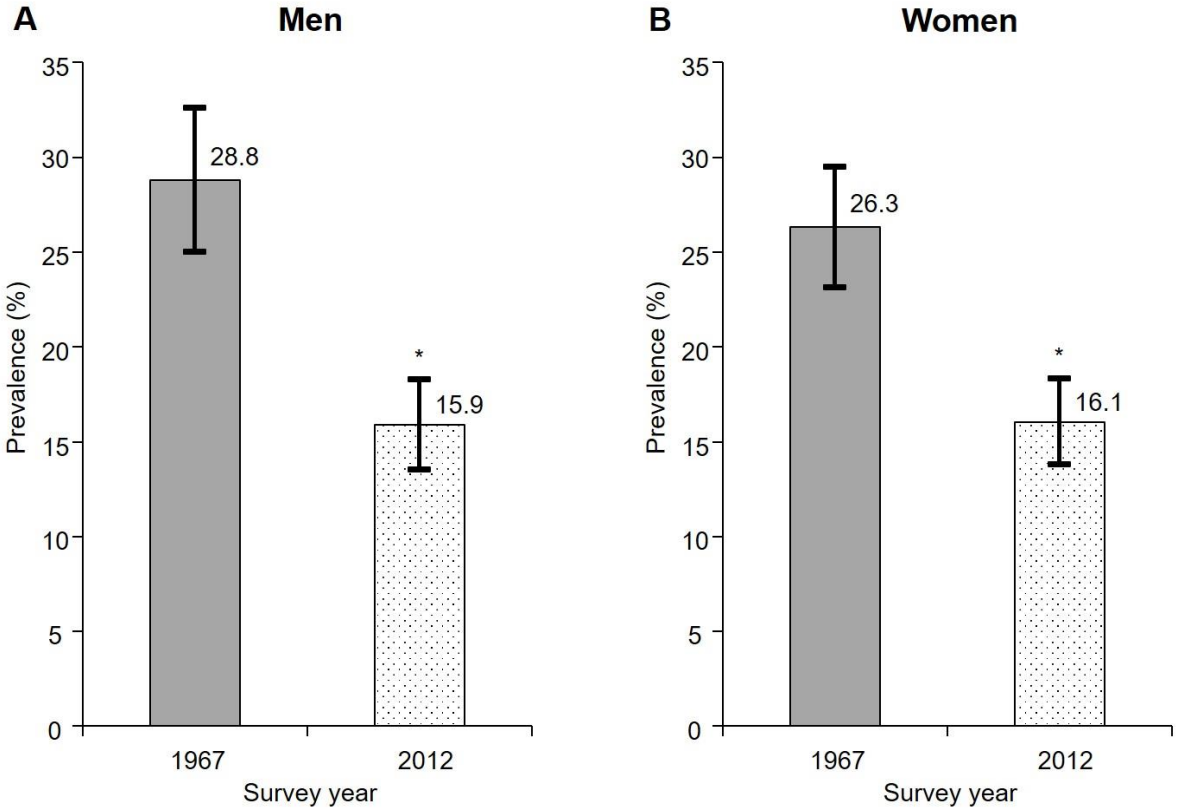


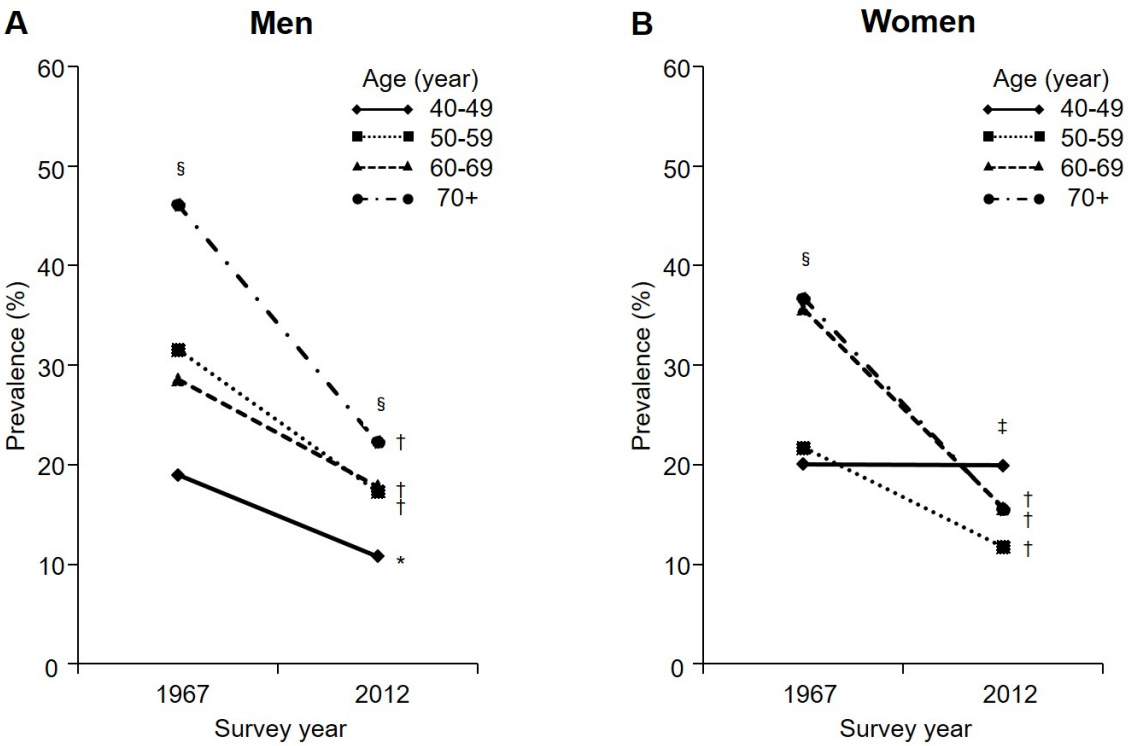
Figure E2 Trends in the age-adjusted prevalence of airflow limitation in 1967 and 2012 by sex.



Vertical bars indicate 95% confidence intervals. $^{*}P < 0.001$ vs 1967.

Airflow limitation was defined as forced expiratory volume in one second / forced vital capacity (FEV_1/FVC) < the lower limit of normal for the cut-off of FEV_1/FVC according to the American Thoracic Society / European Respiratory Society criteria using the Japanese Respiratory Society reference equations.

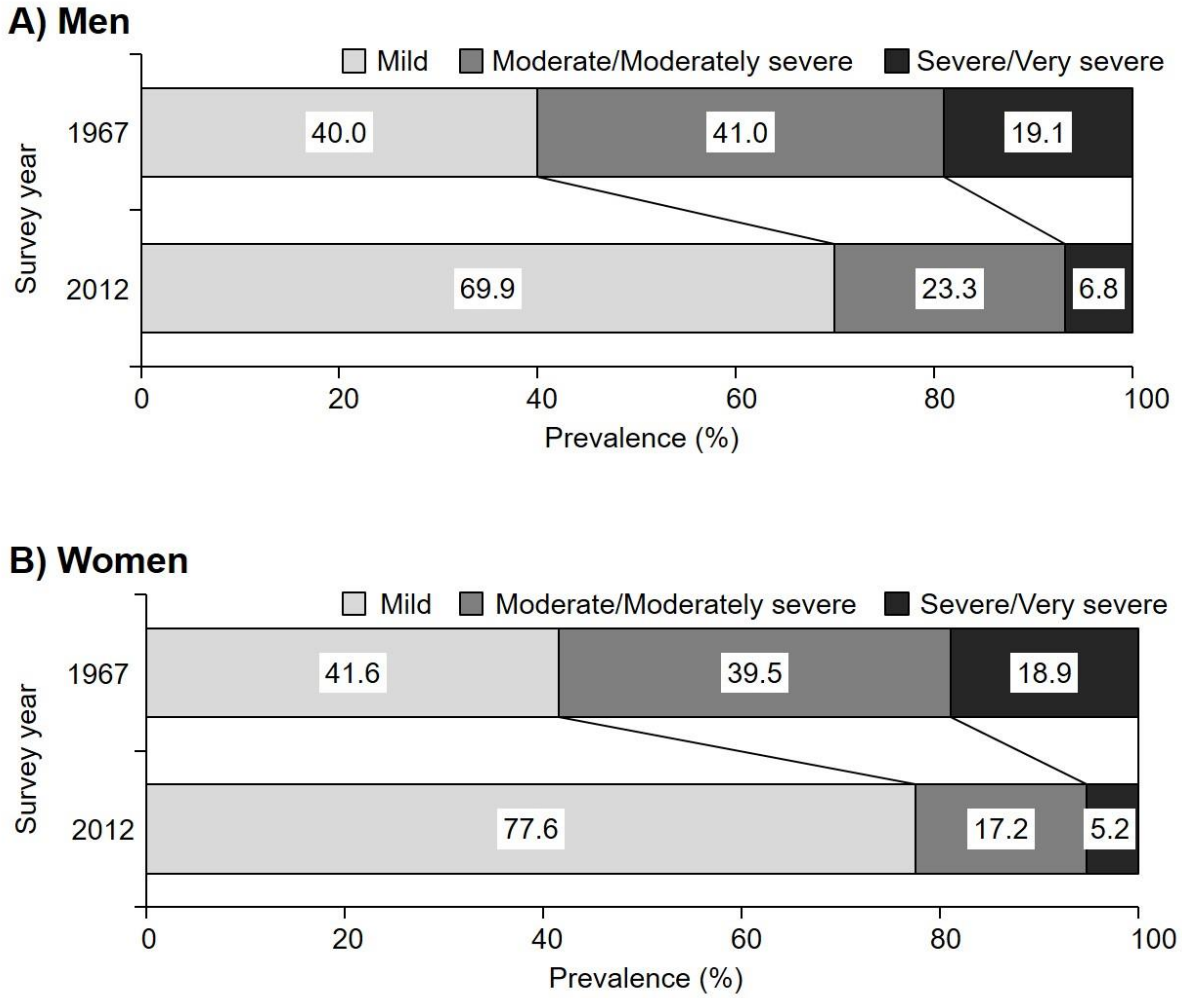
Figure E3 Trends in the prevalence of airflow limitation according to age groups in 1967 and 2012 by sex.



*P < 0.05, †P < 0.01 vs 1967, ‡P for trend < 0.05, §P for trend < 0.01.

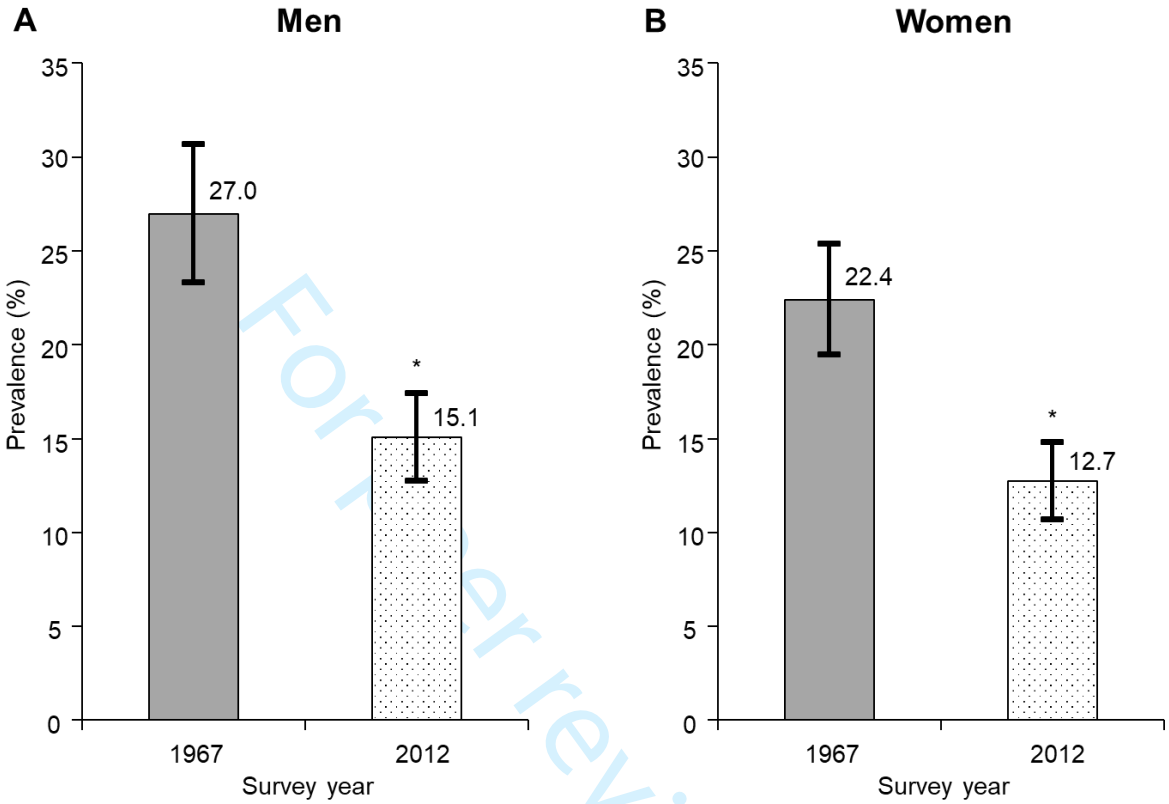
Airflow limitation was defined as forced expiratory volume in one second / forced vital capacity (FEV_1/FVC) < the lower limit of normal for the cut-off of FEV_1/FVC according to the American Thoracic Society / European Respiratory Society criteria using the Japanese Respiratory Society reference equations.

Figure E4 Trends in the age-adjusted prevalence of airflow limitation according to severity in 1967 and 2012 by sex.



Airflow limitation was defined as forced expiratory volume in one second / forced vital capacity (FEV_1/FVC) < the lower limit of normal for the cut-off of FEV_1/FVC according to the American Thoracic Society / European Respiratory Society criteria using the Japanese Respiratory Society reference equations.

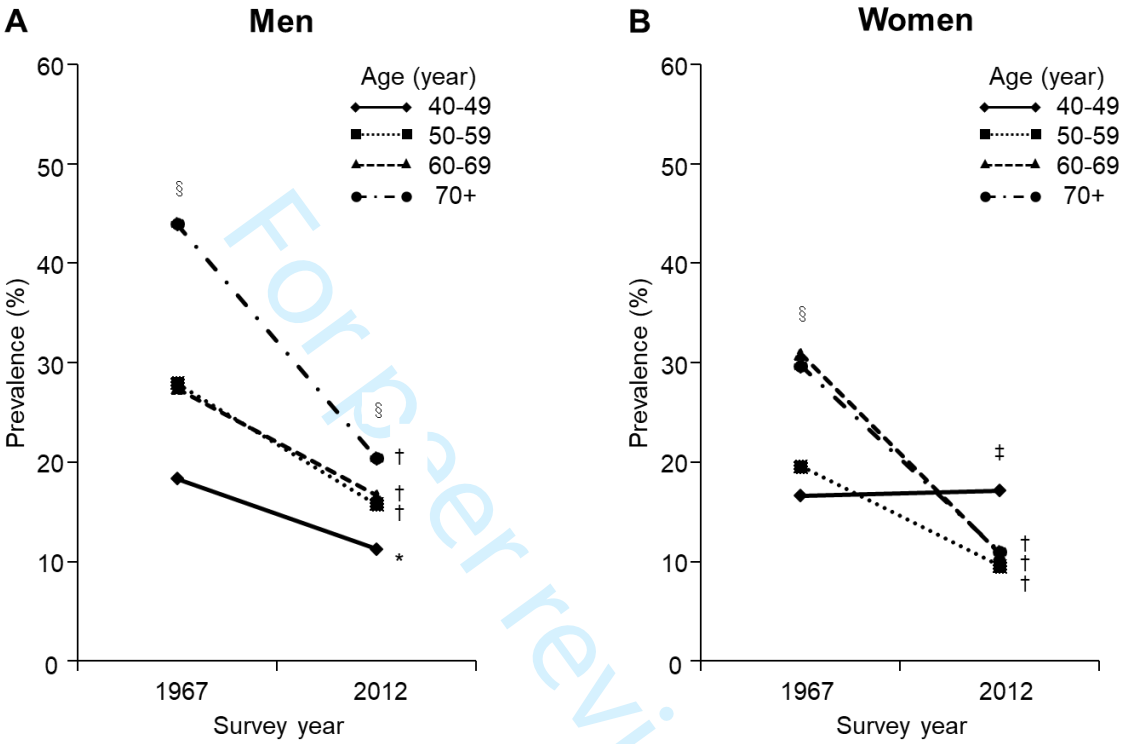
Figure E5 Trends in the age-adjusted prevalence of airflow limitation by sex.



Vertical bars indicate 95% confidence intervals. $^{*}P < 0.001$ vs 1967.

Airflow limitation was defined as forced expiratory volume in one second / forced vital capacity (FEV_1/FVC) < the lower limit of normal for the cut-off of FEV_1/FVC according to the American Thoracic Society / European Respiratory Society criteria using the Global Lung Function Initiative reference equations.

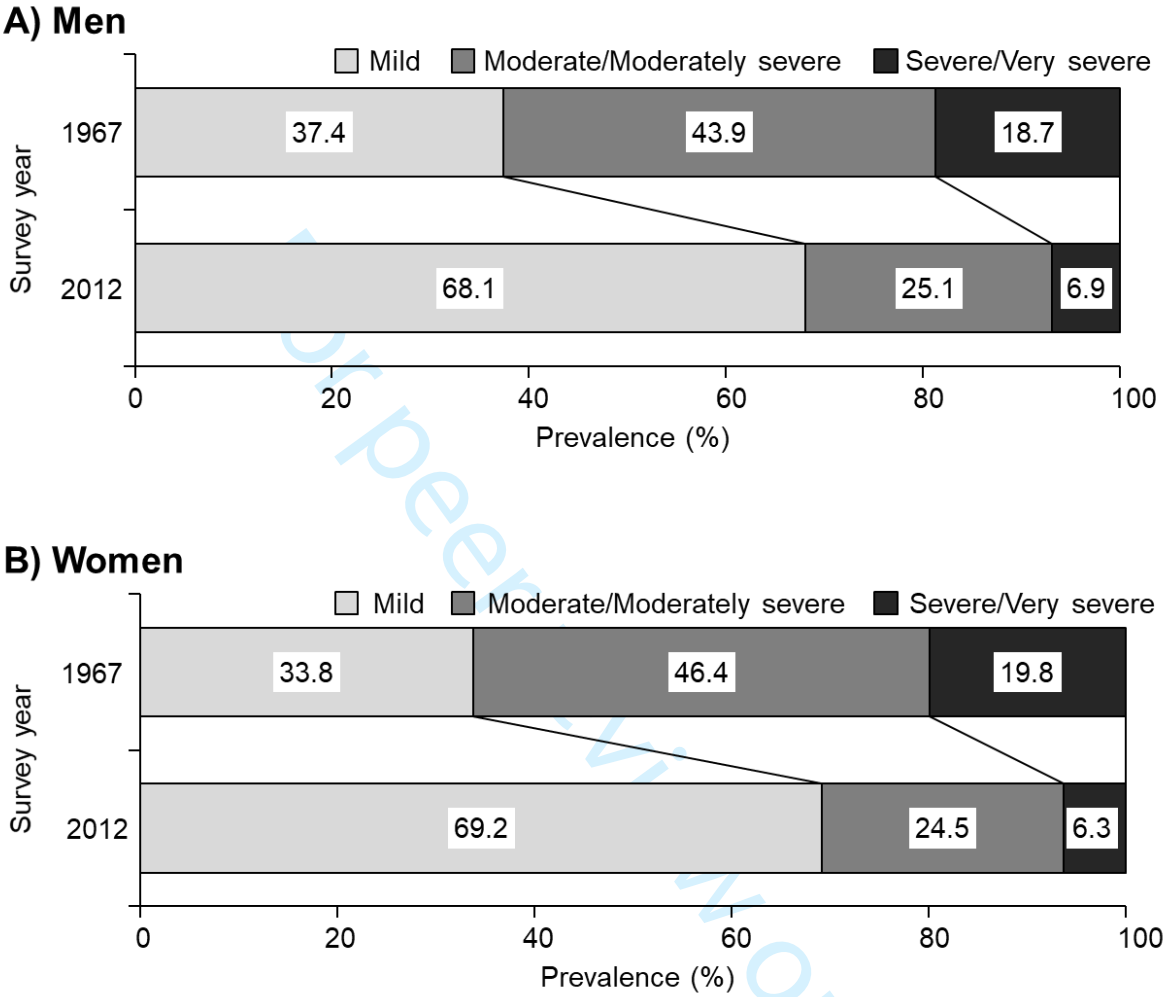
Figure E6 Trends in the prevalence of airflow limitation according to age groups in 1967 and 2012 by sex.



*P < 0.05, †P < 0.01 vs 1967, ‡P for trend < 0.05, §P for trend < 0.01.

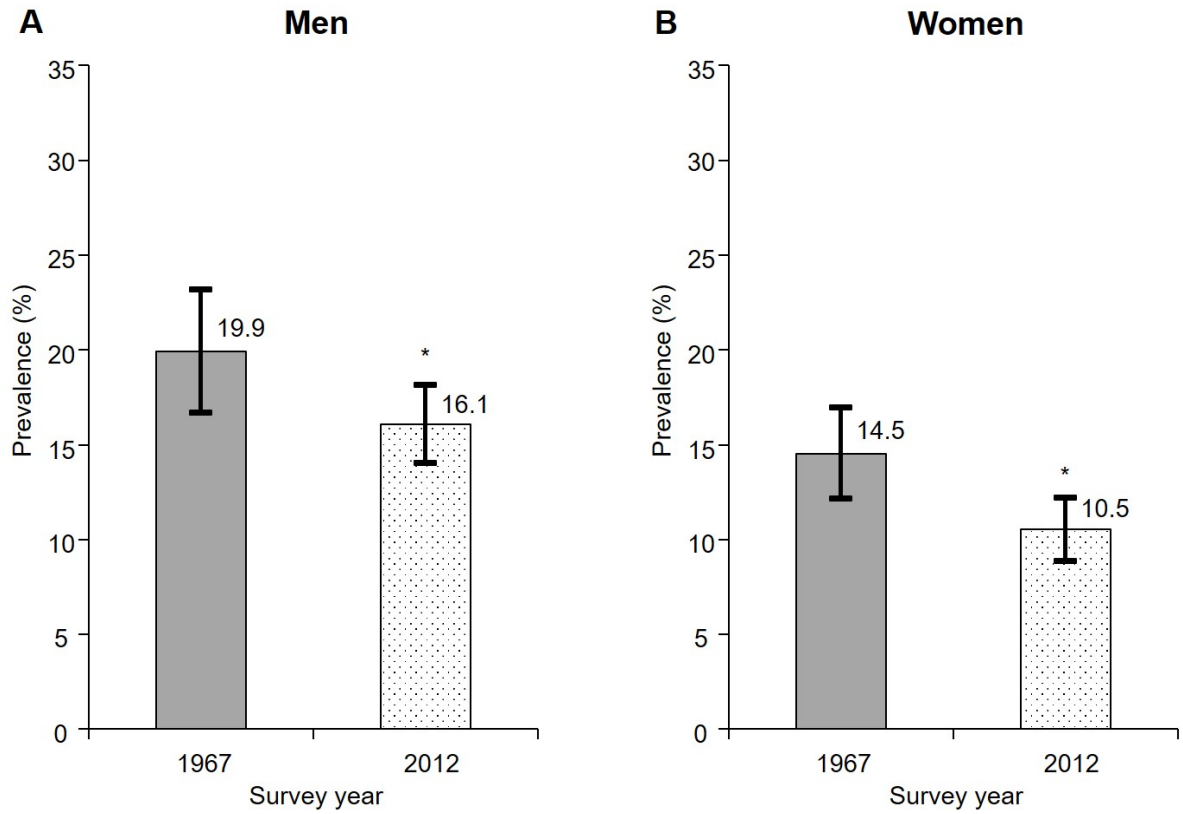
Airflow limitation was defined as forced expiratory volume in one second / forced vital capacity (FEV_1/FVC) < the lower limit of normal for the cut-off of FEV_1/FVC according to the American Thoracic Society / European Respiratory Society criteria using the Global Lung Function Initiative reference equations.

Figure E7 Trends in the age-adjusted prevalence of airflow limitation according to severity in 1967 and 2012 by sex.



Airflow limitation was defined as forced expiratory volume in one second / forced vital capacity (FEV_1/FVC) < the lower limit of normal for the cut-off of FEV_1/FVC according to the American Thoracic Society / European Respiratory Society criteria using the Global Lung Function Initiative reference equations.

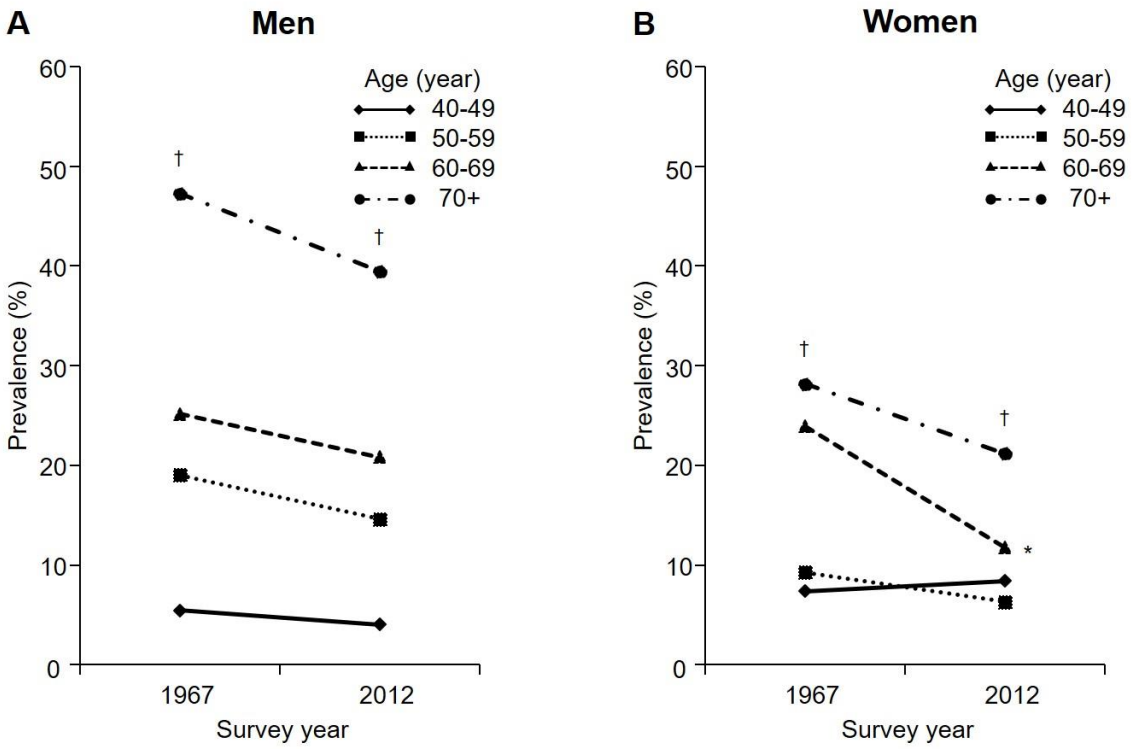
Figure E8 Trends in the age-adjusted prevalence of airflow limitation by sex.



Vertical bars indicate 95% confidence intervals. $^{*}P < 0.05$ vs 1967.

Airflow limitation was defined as forced expiratory volume in one second / forced vital capacity (FEV_1/FVC) < 67% in 1967 according to the modified Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria, and FEV_1/FVC < 70% in 2012 according to the GOLD criteria.

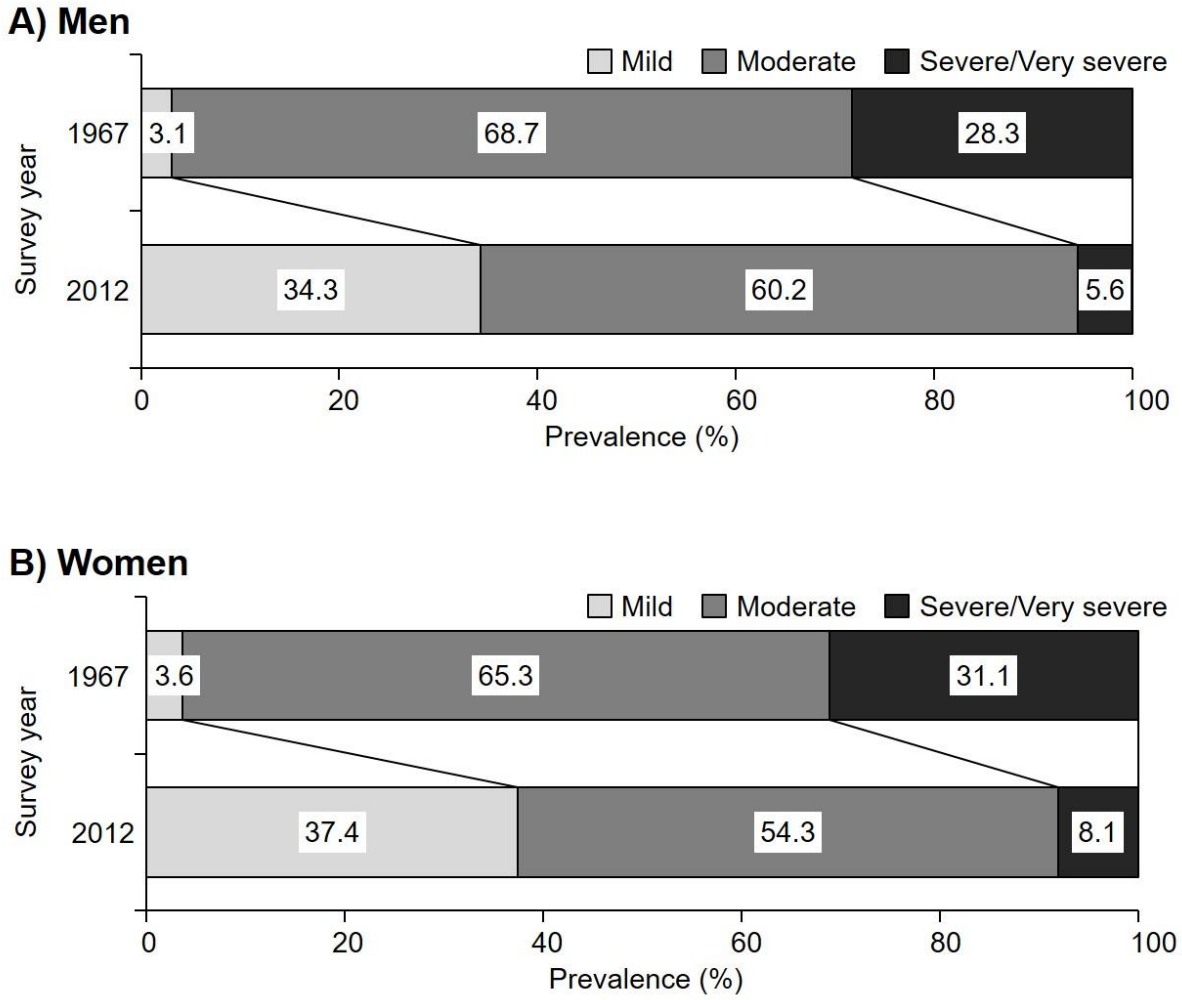
Figure E9 Trends in the prevalence of airflow limitation according to age groups by sex.



*P < 0.01 vs 1967, †P for trend < 0.01.

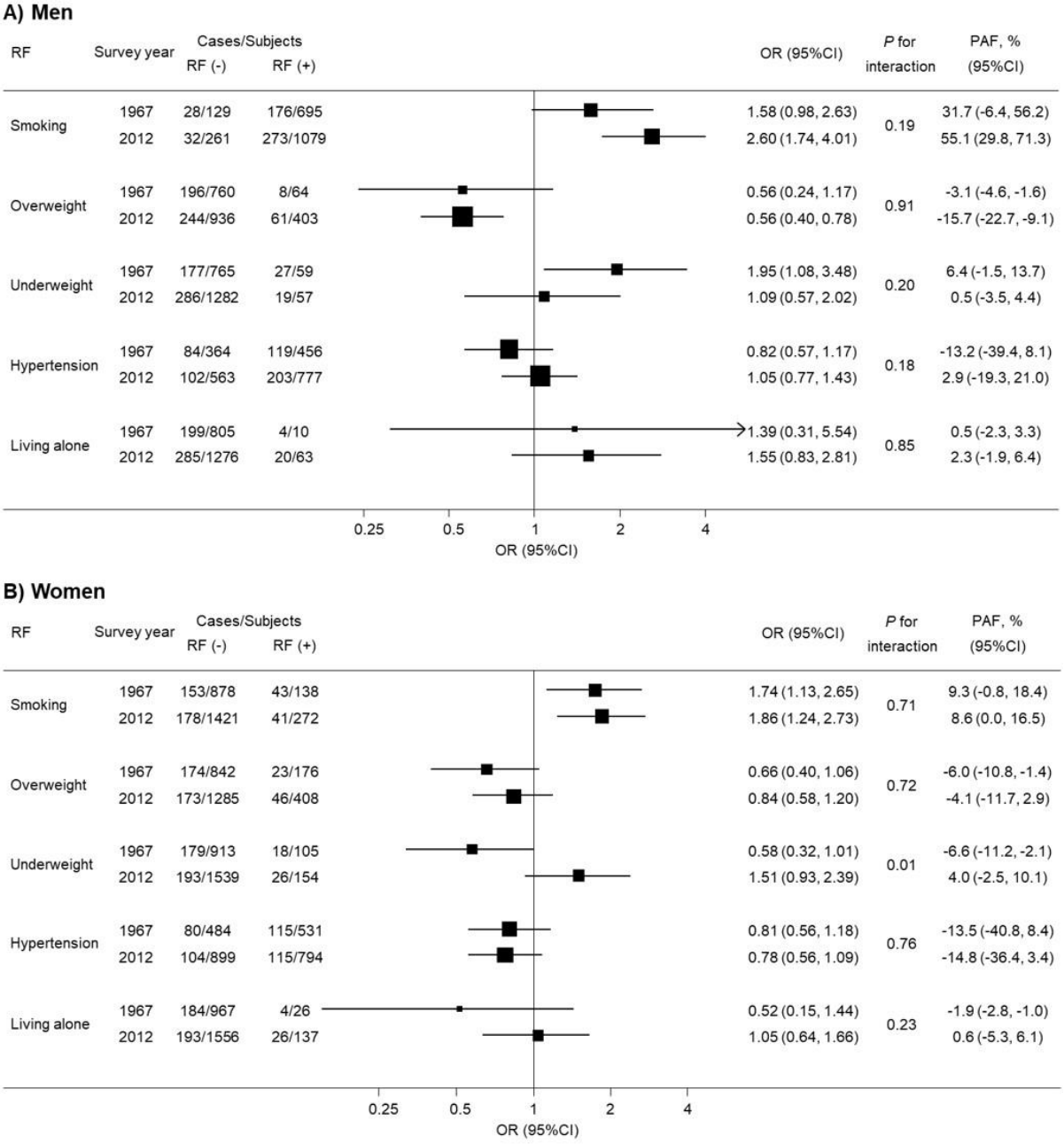
Airflow limitation was defined as forced expiratory volume in one second / forced vital capacity (FEV_1/FVC) < 67% in 1967 according to the modified Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria, and FEV_1/FVC < 70% in 2012 according to the GOLD criteria.

Figure E10 Trends in the age-adjusted prevalence of airflow limitation by sex.



Airflow limitation was defined as forced expiratory volume in one second / forced vital capacity (FEV_1/FVC) < 67% in 1967 according to the modified Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria, and FEV_1/FVC < 70% in 2012 according to the GOLD criteria.

Figure E11 Multivariate-adjusted odds ratios and population attributable fractions of risk factors for airflow limitation in 1967 and 2012 by sex.



Airflow limitation was defined as forced expiratory volume in one second / forced vital

capacity < 70%. Adjustments were made for sex, age, smoking habits, overweight*, underweight†, hypertension, and living alone. Horizontal bars indicate 95% CIs.

*For the analysis of overweight, the normal weight or underweight group was used as the reference group.

†For the analysis of underweight, the normal weight or overweight group was used as the reference group.

RF, risk factor; OR, odds ratio; CI, confidence interval; PAF, population attributable fraction.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3, 4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6, 7
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7, 8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	7, 8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8-10
Bias	9	Describe any efforts to address potential sources of bias	9
Study size	10	Explain how the study size was arrived at	7, 8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	11, 12
		(*b*) Describe any methods used to examine subgroups and interactions	11, 12
		(*c*) Explain how missing data were addressed	12
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	not appicable
		(*e*) Describe any sensitivity analyses	12
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7, 8
		(b) Give reasons for non-participation at each stage	7, 8
		(c) Consider use of a flow diagram	8, online supplementary figure E1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	13-15
		(b) Indicate number of participants with missing data for each variable of interest	15
Outcome data	15*	Report numbers of outcome events or summary measures	16
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	16, figure 2
		(*b*) Report category boundaries when continuous variables were categorized	11
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	16, 17
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	16, 17
Discussion			
Key results	18	Summarise key results with reference to study objectives	18
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	21, 22
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18-22
Generalisability	21	Discuss the generalisability (external validity) of the study results	21, 22
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	23

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.