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Prevalence of Airflow Limitation Defined by Pre- and Post-Bronchodilator Spirometry in a Community-Based Health Checkup: The Hisayama Study

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Spirometry in health checkup may contribute to early diagnosis of chronic obstructive pulmonary disease (COPD) and asthma. Although post-bronchodilator airflow limitation is essential for definite diagnosis of COPD and post-bronchodilator normalization of airflow is suggestive of asthma, this test has not been prevailed in health checkup. The objective of this study was to estimate the prevalence of airflow limitation defined by pre- and post-bronchodilator spirometry in health checkup. Post-bronchodilator spirometry was conducted for participants with airflow limitation in a town-wide health checkup for residents aged 40 years and older in Hisayama, a town in the western part of Japan. The prevalence of pre- and post-bronchodilator airway limitation defined by $FEV_1/FVC < 70\%$ were estimated. A total of 2,232 participants underwent pre-bronchodilator spirometry. In males, the age of current smokers was significantly younger than those of never smokers and former smokers. In females, the ages of current- and former smokers were significantly younger than never smokers. The values of $\%FEV_1$ and %FVC in current smokers were significantly lower than those in former smokers and never smokers. Two hundred sixty nine subjects, 85% of total subjects with a pre-bronchodilator $FEV_1/FVC < 70\%$, completed post-bronchodilator spirometry. The prevalence of pre-bronchodilator airflow limitation was 14.6% in males and 13.7% in females, and the prevalence of post-bronchodilator airway limitation was 8.7% and 8.7%, respectively. Post-bronchodilator spirometry in health checkup would reduce the number of subjects with probable COPD to two-third. Recommendation for those examinees to take further evaluations may pave the way for early intervention.

Keywords: asthma; bronchodilator; chronic obstructive pulmonary diseases; prevalence; spirometry
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Introduction

Chronic obstructive pulmonary disease (COPD) is a major challenge to public health and socioeconomic burden particularly on countries of accelerated aging with a low birth rate including Japan (Bustacchini et al. 2011). Asthma is also a major disease involving a wide range of generation from infancy to elderly. Given that COPD and asthma is revealed by airway limitation in spirometry, involvement of spirometry to community-based health checkup may become an "easy access" improving early diagnosis. In spirometry, airflow can be assessed as forced expiratory volume in one second (FEV_1), while lung volume can be assessed as forced vital capacity (FVC). FEV_1/FVC lower than 70% indicates airflow limitation. Importantly, post-bronchodilator spirometry is essential for definite diagnosis of COPD to demonstrate airway limitation that is not fully reversible (Global Initiative for Chronic Obstructive Lung Disease 2014). Normalization of airflow by bronchodilator may indicate possible asthma. This test has not been prevailed in health checkups and the examinees with airflow limitation are recommended to have further evaluation

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including post-bronchodilator spirometry at pulmonary physician's clinics. However, a substantial proportion of examinees default further evaluation, which results in a useless cost of health checkup. In this regard, completion of post-bronchodilator spirometry at the health checkup may reduce the default evaluation and then improve cost-effectiveness. The relevance of post-bronchodilator spirometry in health checkup should be investigated.

The Hisayama Study is an ongoing population-based epidemiologic study for cardiovascular diseases and smoking-related diseases and their risk factors in the community in Hisayama, a town in the western part of Japan (Hata et al. 2013; Toyoda et al. 2013). The population of the town is approximately 8,300 and has been stable for more than the last 40 years. The age and occupational distributions of the Hisayama population have been almost identical to those of Japan as a whole from the 1960s to the present, based on data from the nation census (The Statistics Bureau of Japan 2010). In 2009, post-bronchodilator spirometry was conducted for participants with airflow limitation in a town-wide health checkup for residents aged 40 years and older. The objective of this study was to estimate the prevalence of airflow limitation defined by pre- and post-bronchodilator spirometry in a community-based health checkup.

Materials and Methods

Study population, spirometry, and ethics

All registered residents aged 40 years and older were invited to participate in a town-wide health checkup including spirometry from June to August in 2009. Subjects completed a self-reported questionnaire on cigarette smoking. Individual height and weight were measured at the beginning of health checkup. Subjects with the following conditions were excluded from spirometry: current chest pain; had recent surgery of the eye, chest or the abdomen; had a recent history of pneumothorax; had a past history of lung resection, or refusal. Spirometry was performed under guidelines of the Japanese Respiratory Society (The Japanese Respiratory Society 2004) using a CHESTGRAPH HI-105 spirometer (Chest MI, Inc., Tokyo, Japan). Up to four tests were used to obtain satisfactory flow-volume loop recordings. Pulmonary physicians assessed the results by visual inspection to the loop recordings and excluded those without at least two satisfactory tests. Subjects with poor maneuver were excluded. The largest FVC and the largest FEV_1 from all acceptable maneuvers were selected. Subjects who had $FEV_1/FVC < 70\%$ were eligible for post-bronchodilator testing, in which spirometry was performed 15 min after inhalation of salbutamol (GlaxoSmithKline, Tokyo, Japan) via a metered-dose inhaler with a spacer, according to the procedure recommended (Pellegrino et al. 2005). Subjects with the following conditions were excluded from post-bronchodilator spirometry: had a recent history of ischemic heart attack, unstable arrhythmia requiring medications, or refusal. Subjects were also excluded if they had already taken a β_2-adrenergic bronchodilator to avoid exceeding doses, of if they had had a previous history of adverse reaction to salbutamol. The written informed consent for potential risk and benefit to use salbutamol inhaler was obtained from all subjects with post-bronchodilator spirometry. Subjects who had post-bronchodilator $FEV_1/FVC < 70\%$ were recommended to have further evaluations in the clinics of pulmonary medicine and to have adequate pharmacotherapy if necessary. Reference values for spirometric measures predicted were derived from Japanese criteria updated on 2014 (Kubota et al. 2014). The study was conducted according to the Declaration of Helsinki and approved by the Institutional Review Board for Clinical Research of Kyushu University (Approved #: 19-15 and 21-37), and written informed consent for medical research was obtained from the subjects.

Smoking status

We defined "never smokers" those individuals who declared that they never smoked before the study, "current smokers" those who declared active smoking, and "former smokers" those who declared that they quitted smoking before the study. Those who declared that they quitted smoking just before (< 1 month) the study were classified into current smokers. Pack-years were calculated as the number of packs of cigarettes smoked per day times how many years the participants smoked.

Statistical analysis

Results are presented as the mean ± standard deviation (SD). Differences in categorical variables were assessed by chi-square tests. Differences in continuous variables with normal distribution, such as age, the body mass index (BMI), FEV_1, FVC, FEV_1/FVC, and $\%FEV_1/FVC$, were assessed by means of analyses of variance with *post hoc* Tukey-Kramer's HSD tests. Differences in skewed continuous variable, such as pack-years, $\%FEV_1$, and FVC, were assessed by Kruskal-Wallis tests with *post hoc* Mann-Whitney *U*-tests. P values of less than 0.05 were considered to indicate statistical significance.

Results

Eligibility of participants

Flow diagram of the study population is shown in Fig. 1. A total of 2,251 subjects participated in the health checkup over the period from July to August 2009. All participants were Asians. Nineteen subjects were excluded from the study due to safety reasons, refusal or poor maneuver. Of the 2,232 subjects, 315 had a pre-bronchodilator FEV_1/FVC of less than 70% and 46 were excluded from post-bronchodilator spirometry due to safety reasons, refusal, or poor inhalation maneuver. Remaining 269 subjects, 85% of total subjects with a pre-bronchodilator FEV_1/FVC of less than 70%, completed post-bronchodilator spirometry.

Characteristics of the participants

The baseline characteristics of the 2,232 subjects eligible for the final analyses are shown in Table 1. In males, the age of current smokers was significantly younger than those of never smokers ($p < 0.001$) and former smokers ($p < 0.001$). The age of former smokers was significantly older than that of never smokers ($p < 0.001$). The BMI of current smokers was significantly lower than those of never smokers ($p < 0.05$) and former smokers ($p < 0.05$), while there was no significant difference between those of former smokers and never smokers. The pack-year of current smokers was significantly higher than that of former smok-

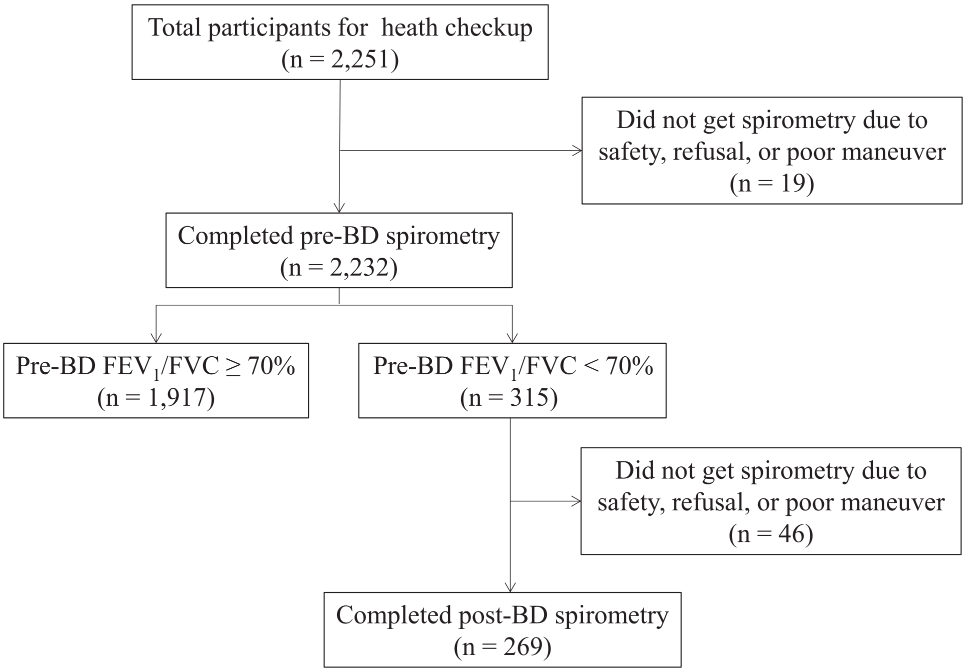
Total participants for heath checkup
(n = 2,251)
Did not get spirometry due to safety, refusal, or poor maneuver
(n = 19)
Completed pre-BD spirometry
(n = 2,232)
Pre-BD FEV1/FVC ≥ 70%
(n = 1,917)
Pre-BD FEV1/FVC < 70%
(n = 315)
Did not get spirometry due to safety, refusal, or poor maneuver
(n = 46)
Completed post-BD spirometry
(n = 269)

Fig. 1. Flow diagram of the study population.
BD, bronchodilator; FEV_1, forced expiratory volume in the one second; FVC, forced vital capacity.

ers ($p < 0.001$). In females, the ages of current smokers and former smokers were significantly younger than never smokers ($p < 0.001$, $p < 0.001$, respectively), while there was no significant difference between those of current smokers and former smokers. The BMI was not significantly different among never-, former-, and current smokers. The pack-year of current smokers was significantly higher than that of former smokers ($p < 0.001$).

Pre-bronchodilator spirometric analyses

The pre-bronchodilator spirometric measures are also shown in Table 1. Both in males and females, the values of FEV_1 and FVC and the FEV_1/FVC ratio were not significantly different among never smokers, former smokers, and current smokers. In males, the value of %FEV_1 in current smokers was significantly lower than those in former smokers ($p < 0.001$) and never smokers ($p < 0.05$). The value of %FVC in current smokers was also significantly lower than those in former smokers ($p < 0.05$) and never smokers ($p < 0.05$). The value of %FEV_1/FVC in current smokers was significantly lower than that in former smokers ($p < 0.01$), but it was similar to that in never smokers. The values of %FEV_1, %FVC, and %FEV_1/FVC did not significantly differ between former smokers and never smokers. In females, the values of %FEV_1 in current smokers and former smokers were significantly lower than that in never smokers ($p < 0.01$, $p < 0.001$, respectively). The values of %FVC in current smokers and former smokers were also significantly lower than that in never smokers ($p < 0.01$, $p < 0.001$, respectively). There was no significant difference in the values of %FEV_1 or %FVC between former smokers and current smokers. The values of %FEV_1/FVC were not significantly different among never smokers, former smokers, and current smokers in females.

Prevalence of pre- and post-bronchodilator airflow limitation

The prevalence of airflow limitation is shown in Table 2. In male subjects, the prevalence of airflow limitation defined by pre-bronchodilator FEV_1/FVC was 17.3% in never smokers, 13.6% in former smokers, 14.4% in current smokers, and 14.6% in total. There was no significant difference in the prevalence among never-, former- and current smokers ($\chi^2 = 1.53$, $p = 0.4653$). Applying the same criteria to post-bronchodilator FEV_1/FVC results, the prevalence of airflow limitation that is not fully reversible was 9.4% in never smokers, 8.5% in former smokers, 8.5% in current smokers, and 8.7% in total. Again, there was no significant difference in the prevalence among never smokers, former smokers and current smokers ($\chi^2 = 0.22$, $p = 0.8957$). In female subjects, the prevalence of airflow limitation defined by pre-bronchodilator FEV_1/FVC was 13.4% in never smokers, 19.7% in former smokers, 10.5% in current smokers, and 13.7% in total. There was no significant difference in the prevalence among never-, former- and current smokers ($\chi^2 = 3.22$, $p = 0.2002$). Applying the same criteria to post-bronchodilator FEV_1/FVC results, the prevalence of airflow limitation was 8.6% in never smokers, 10.4% in former smokers, 8.7% in current smokers, and 8.7% in total. There was no significant difference among never smokers, former smokers and current smokers ($\chi^2 = 0.51$, $p = 0.7759$).

Table 1. The subjects' characteristics and the pre-bronchodilator spirometric measures.

Sex	Males (n = 951)			Females (n = 1,281)		
Smoking status	NS n = 190	FS n = 491	CS n = 270	NS n = 1,138	FS n = 86	CS n = 57
Age (years)	63.9 ± 11.2	67.4 ± 10.4*	58.5 ± 10.5*,†	64.3 ± 11.2	57.2 ± 11.2*	55.9 ± 9.8*
BMI (kg/m^2)	23.5 ± 2.9	23.4 ± 2.9	22.8 ± 2.9*,†	22.8 ± 3.6	23.1 ± 3.8	22.3 ± 3.9
Pack-years		31.8 ± 22.9	39.6 ± 20.0†		9.9 ± 13.5	22.0 ± 11.7†
FEV$_1$ (L)	2.18 ± 0.65	2.18 ± 0.62	2.17 ± 0.63	2.16 ± 0.64	2.01 ± 0.61	2.05 ± 0.53
%FEV$_1$ (%)	79.8 ± 28.4	81.1 ± 26.5	73.2 ± 24.7*,†	111.0 ± 40.3	93.1 ± 32.0*	93.0 ± 25.5*
FVC (L)	2.88 ± 0.78	2.86 ± 0.75	2.86 ± 0.79	2.86 ± 0.78	2.67 ± 0.75	2.69 ± 0.67
%FVC (%)	82.3 ± 26.8	82.4 ± 24.6	76.4 ± 24.2*,†	115.8 ± 38.6	99.1 ± 31.3*	98.2 ± 25.9*
FEV$_1$/FVC (%)	75.5 ± 7.2	76.1 ± 7.0	75.5 ± 6.6	75.6 ± 7.1	75.0 ± 7.7	75.8 ± 7.5
%FEV$_1$/FCV (%)	96.3 ± 9.5	97.9 ± 9.5	95.2 ± 8.7†	95.4 ± 9.3	93.3 ± 10.0	94.1 ± 9.0

Values are expressed as the mean ± SD.

NS, never smokers; FS, former smokers; CS, current smokers; BMI, body mass index; FEV$_1$, forced expiratory volume in one second; FVC, forced vital capacity.

Pack-years were calculated based on the number of cigarettes smoked per day and the number of years that the subjects had smoked.

*$P < 0.05$, vs. NS.

†$P < 0.05$, vs. FS.

Table 2. The prevalence of airflow limitation defined by FEV$_1$/FVC < 70%.

Sex	Males (n = 951)			Females (n = 1,281)		
Smoking status	NS	FS	CS	NS	FS	CS
Pre-BD FEV$_1$/FVC < 70%/subjects	33/190	67/491	39/270	153/1,138	17/86	6/57
Total		139/951			176/1,281	
Post-BD FEV$_1$/FVC < 70%/subjects	18/27	42/57	23/36	98/132	9/12	5/5
Total		83/120			112/149	
Pre-BD prevalence (%)	17.3	13.6	14.4	13.4	19.7	10.5
Total (%)		14.6			13.7	
Post-BD prevalence (%)	9.4	8.5	8.5	8.6	10.4	8.7
Total (%)		8.7			8.7	

FEV$_1$, forced expiratory volume in one second; FVC, forced vital capacity; BD, bronchodilator; NS, never smokers; FS, former smokers; CS, current smokers.

Discussion

In this study, the prevalence of airflow limitation defined by pre-bronchodilator FEV$_1$/FVC < 70% was 14.6% in males and 13.7% in females, and the prevalence of post-bronchodilator airway limitation was 8.7% and 8.7%, respectively. The post-bronchodilator values are consistent with those estimated as the prevalence of COPD in a previous epidemiological study in Japan (Fukuchi et al. 2004). National institutes of USA reported the prevalence of COPD on a nationally representative sample of US adults aged 40-79 years: the prevalence of pre-bronchodilator airway limitation was 24.1% in males and 16.7% in females, while post-bronchodilator airway limitation was 11.4% and 5.4%, respectively (Tilert et al. 2013). These results suggest that post-bronchodilator spirometry would reduce the number of subjects with probable COPD to one-third to two-third in health checkup. Intensive recommendation for those examinees to take further evaluations may improve early intervention and efficacy of health checkup.

Investigators in the UK reported the prevalence of pre-bronchodilator airflow limitation on a cross-sectional analysis of persons aged 40-95 years in England and Wales: the prevalence was 26.3% in males and 18.6% in females (Scholes et al. 2014). Fukuchi et al. (2004) reported the prevalence of pre-bronchodilator airflow limitation on 2,343 subjects aged 40 years and older who were demographically matched to the Japanese general population: the prevalence of airflow limitation was 16.4% in males and 5.0% in females. The prevalence of pre-bronchodilator airway limitation in males in the present study was comparable with that in the previous report in Japan but lower than those in the USA and the UK, while the prevalence in females was comparable with those in the USA and the UK but markedly higher than that in the previous report in Japan. The discrepant results in females between the studies in Japan might be partly derived from the difference in the study designs that the previous study was based on a population-matched sample while the present study was on a community-based sample. Accumulation of studies with similar design, in addition to studies on workplace-based health checkups, would provide better understanding for this issue.

The present study has several limitations. The study did not intend to discriminate between COPD and asthma. In previous studies, current smoking increased the prevalence of airflow limitation and the incidence of COPD (Kojima et al. 2007; Kohansal et al. 2009), while there is no significant association between smoking and the prevalence of airflow limitation in the present study. The documentation of not-fully reversible airflow limitation is a functional definition of COPD, which, however, does not preclude chronic asthma or asthma with airway remodeling. It is possible that the high prevalence of airflow limitation in never smokers was largely derived from subjects with undiagnosed asthma. In our prior study in Hisayama, 75% of subjects aged 40 years and older with physician-diagnosed asthma were never smokers (Matsumoto et al. 2015). As another possibility, the composition of age and age-specific factors in the examinees might affect the outcome. The proportion of the aged 4th and 5th decades, belonging to a working population and having high probability of current smoking, was less than that of the aged older, probably due to the inconvenience to have a community-based health checkup. Despite that the number of those middle-aged populations in Hisayama was comparable with that of the aged 6th decade, the participants of health checkup were only one-third to a half of the aged 6th decade. It is possible that the middle-aged participants might have some phenotype that prone to accompany with airflow limitation. With this regard, the mean age of groups (never smokers, former smokers and current smokers) showed a difference of up to 9 years old with each other. It is well known that FEV_1 and FVC decrease with age, raising a concern to compare directly these groups in which the mean age differs. This concern is particularly important in case that values of FEV_1 and FVC in some group are lower than those in the other group when the ages in the former group are older than the latter's. In the present study, however, the spirometric measures were lower in current smokers than in never smokers, despite that the current smokers were younger than the never smokers, which keeps logical relevance in negative impacts of current smoking on spirometric measures. Additionally, the low %FVC, less than 80%, in the male current smokers was unexpected in this study. We have used, for the first time, the reference values for spirometric measures that were derived from Japanese criteria updated on 2014. There might be some regional heterogeneity in relationships between anthropometric measures and spirometric measures, at least in males. Next, a small sample size of female current smokers and former smokers makes it unfeasible to provide the comprehensive understanding for the relationship between potential airflow limitation and smoking. Finally, the study did not investigate the impact of environmental cigarette smoking on the prevalence of airflow limitation in never smokers. Increasing exposure to environmental cigarette smoking is associated with increasing prevalence of respiratory symptoms that are common in COPD (Janson et al. 2001; Larsson et al. 2003; Yin et al. 2007). Many of never smokers with potential airflow limitation were females. Given that a majority of female never smokers had lived as housewives in Hisayama, partner's smoking might affect their pulmonary function.

In summary, the prevalence of airflow limitation defined by pre-bronchodilator $FEV_1/FVC < 70\%$ was 14.6% in males and 13.7% in females, and the prevalence of post-bronchodilator airway limitation was 8.7% and 8.7%, respectively. These results suggest that post-bronchodilator spirometry in health checkup settings would reduce the number of subjects with probable COPD to two-third and then reduce the default evaluation.

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Author Contributions

S.F., K.M., and H.I. designed the study, collected data, and wrote the initial drafts of manuscript. K.K., N.N., Y. T.-A., T.N., and Y.I. collected data. Y.K. (Kaneko) constructed the database. Y.K. (Kiyohara) and Y.N. advised the designing of study. All authors read and approved the final manuscript.

Conflict of Interest

The authors declare no conflict of interest.

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