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Respiratory symptoms/diseases prevalence is still increasing: a 25-yr population study

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ABSTRACT

Background: Few epidemiological surveys on general population samples estimated changes in prevalence of respiratory symptoms/diseases over a long time interval; our study aims to quantify the temporal changes in the prevalence rates of asthma, allergic rhinitis and Chronic Obstructive Pulmonary Disease (COPD) after 25 years from baseline.

Methods: A general population sample participated in 3 cross-sectional surveys carried out in Central Italy (Pisa) in 1985–88 (n = 3865), 1991–93 (n = 2841), 2009–11 (n = 1620). 2276 (47%) subjects participated in at least 1 survey, 1723 (35.5%) in at least 2 surveys and 849 (17.5%) in all the 3 surveys. All subjects filled in a standardized questionnaire about health status and risk factors; a sub-sample performed spirometry.

Chi-square test was used to compare adjusted prevalence rates of respiratory symptoms/diseases and descriptive characteristics among the surveys. Generalised estimating equations (GEE) were used to analyze the association between respiratory symptoms/diseases and risk factors.

Results: There was an increasing trend in prevalence rates of all respiratory symptoms/diseases throughout the surveys: current asthma attacks (1st–3rd survey prevalence: 3.4–7.2%), allergic rhinitis (16.2–37.4%), usual phlegm (8.7–19.5%) and COPD (2.1–6.8%) more than doubled. The GEE model confirmed these increasing trends, indicating higher risk of having respiratory symptoms/diseases in the second and third surveys.

Conclusions: While asthma and allergic rhinitis increasing trends were confirmed, with respect to other international studies, also a COPD increasing prevalence rates was shown.

1. Introduction

Few studies assessed the temporal changes in prevalence of respiratory symptoms/diseases from cross-sectional studies repeated at interval of some years, but covering only certain age ranges (e.g., children and young adults up to 44 years of age) [1,2].

The prevalence of asthma increased worldwide after the second world war until the 1990s, without a clear temporal pattern thereafter [3]. Swedish studies showed an increase up to about 10% of asthma prevalence from 1996 to 2006 in general population samples (age range 20–69 yrs) [4,5]. Also the Italian phase of the European Community Respiratory Health Survey (ECRHS) (20–44 yrs) found increasing asthma prevalence up to 6.6% in 2010 [2].

The frequency of allergic rhinitis (AR) has also been increasing worldwide. The Italian and Swedish ECRHS samples estimated an AR increase up to 25.8% (in 2010) [2] and 31% (in 2008) [6], respectively.

Chronic Obstructive Pulmonary Disease (COPD), according to the World Health Organization, will rank 3rd among the death causes by 2030 worldwide [7]. A Canadian study showed that COPD

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Abbreviations list

AO	airway obstruction
AR	allergic rhinitis
ATS	American Thoracic Society
COPD	Chronic Obstructive Pulmonary Disease
95% CI	95% Confidence Interval
ECRHS	European Community Respiratory Health Survey
ERS	European Respiratory Society
FEV_1	forced expiratory volume in the first second
FVC	forced vital capacity
GEE	Generalised estimating equations
IMCA2	Indicators for Monitoring COPD and Asthma in the EU project
LLN	Lower Limit of Normal
OR	odds ratio
PI1	Pisa 1 survey
PI2	Pisa 2 survey
PI3	Pisa 3 survey

standardized prevalence increased from 7.8% to 9.5%, since 1991 to 2007, in adult subjects with age ≥ 35 yrs [1]. In Norway, an increasing adjusted prevalence of GOLD-defined COPD from 7% to 14% in nine years was shown (subjects with age ≥ 35 yrs) [8]. On the contrary, the Italian ECRHS study showed a stable prevalence of chronic bronchitis during the past decade (12.5%) [9].

We aim to quantify 25-yr temporal changes in the prevalence of asthma, AR and COPD symptoms/diagnoses in an Italian general population sample, by analyzing three subsequent cross-sectional surveys which include both cross-sectional (investigated only once) and longitudinal subjects (investigated at least two times).

2. Materials and methods

2.1. Study population and methods

Detailed information on population characteristics and methods were previously published [10,11].

A flow chart of the investigated population is presented in Fig. 1.

In 1985–1988, a general population sample of 3865 subjects (84% of the invited subjects) living in the urban and suburban area of Pisa, Central Italy, was investigated within the first Pisa survey (**PI1**) with the aim to assess the COPD natural history and the related risk factors. The sample was enrolled through a randomized, stratified, family cluster design, similar to the one previously used in the Po Delta Survey [12].

A second cross-sectional survey (**PI2**) was carried out in 1991–1993. Beside those participating in PI1, new subjects were recruited: newborns, new spouses and subjects not available in PI1. There were 433 subjects lost to follow-up (dead or moved). Overall, 2841 subjects (69% of the invited subjects) were investigated. 2257 subjects participated in both PI1 and PI2 surveys, corresponding to a longitudinal participation rate of 58% (66% if those lost to follow-up were excluded from the computation) with a mean follow-up of 6 years.

A third cross-sectional survey (**PI3**) was carried out in 2009–2011 within the European IMCA2 (Indicators for Monitoring COPD and Asthma in the EU) project. Beside those participating in PI1 and/or PI2, new subjects were recruited: newborns, new spouses and subjects not available in PI1 and/or PI2. There were 1201 subjects lost to follow-up (dead or moved). Overall, 1620 subjects (69% of invited) were investigated. 1107 subjects participated in both PI2 and PI3 surveys, corresponding to a longitudinal participation rate of 39% (68% excluding lost to follow-up) with a mean follow-up of 18 years.

The same study protocol was used in PI1 and PI2. Information on respiratory symptoms/diseases and risk factors were obtained through a standardized interviewer-administered questionnaire developed by the National Research Council [13].

In PI2, a subsample (n = 1890) of subjects with age ≤ 75 years performed spirometry (forced vital capacity maneuver) according to the American Thoracic Society (ATS) protocol [14], thorough a water-sealed spirometer (Baires, Biomedin) [11].

As regards PI3, an interviewer-administered questionnaire on respiratory symptoms/diseases and risk factors was designed using questions from previously validated questionnaires [13,15,16] (http://ec.europa.eu/health/major_chronic_diseases/diseases/asthma/index_en.htm#fragment1). A subsample (n = 689) performed spirometry (forced vital capacity maneuver) according to the ATS/European Respiratory Society (ERS) protocol [17], through an hand-held ultrasonic spirometer (EasyOne Model 2001 Spirometer, NDD Medical Technologies).

Italian law didn't request the approval of Ethical Committee at the time of PI1/PI2. The protocol was approved by an Internal Revision Board within the Preventive Medicine Targeted Project of the Italian CNR. PI3 study protocol, patient information sheet and consent form were approved by the ethics committee of the Pisa University Hospital (Azienda Ospedaliero-Universitaria Pisana, Prot. no. 23887, April 16, 2008).

2.2. Statistical analyses

Detailed information on investigated respiratory outcomes are reported in the supplemental material.

Statistical Package STATA (Stata Statistical Software Release 9.0; StataCorp 2005, College Station, TX, USA) was applied: chi-square test and analysis of variance were used for comparing the symptoms/diseases prevalence and descriptive characteristics among the surveys.

Adjusted prevalence of symptoms/diseases was obtained through logistic regression models with respiratory symptoms/diseases as dependent variables and sex, age, smoking habits, educational level, occupational exposure to fumes/gases and area of residence as independent variables.

Chi square test and Cuzick test for trend were used to assess the linear trend among the 3 surveys.

Generalised estimating equations (GEE) with a logit link was used to analyze the association among respiratory symptoms/diseases and risk factors (sex, age, pack-years, educational level, occupational exposure, area of residence, survey); all risk factors were time-dependent, except for sex. GEE allowed to take into account data correlation for the serial observations on the same subjects (within-subject correlation); an unstructured working correlation was used.

COPD diagnosis was analyzed in the subsample of adult subjects (≥ 18 yrs).

P-values less than 5% were considered statistically significant.

3. Results

3.1. General characteristics

3865 subjects participated in PI1, 2841 in PI2, 1620 in PI3. 2276 participated in at least 1 survey (47%), 1723 in at least 2 surveys (35.5%) and 849 in all the 3 surveys (17.5%) (Table 1).

Descriptive characteristics and symptoms/diagnoses of participating subjects vs. those lost to follow-up are reported in the supplemental material (e-Table 1). A larger proportion of subjects

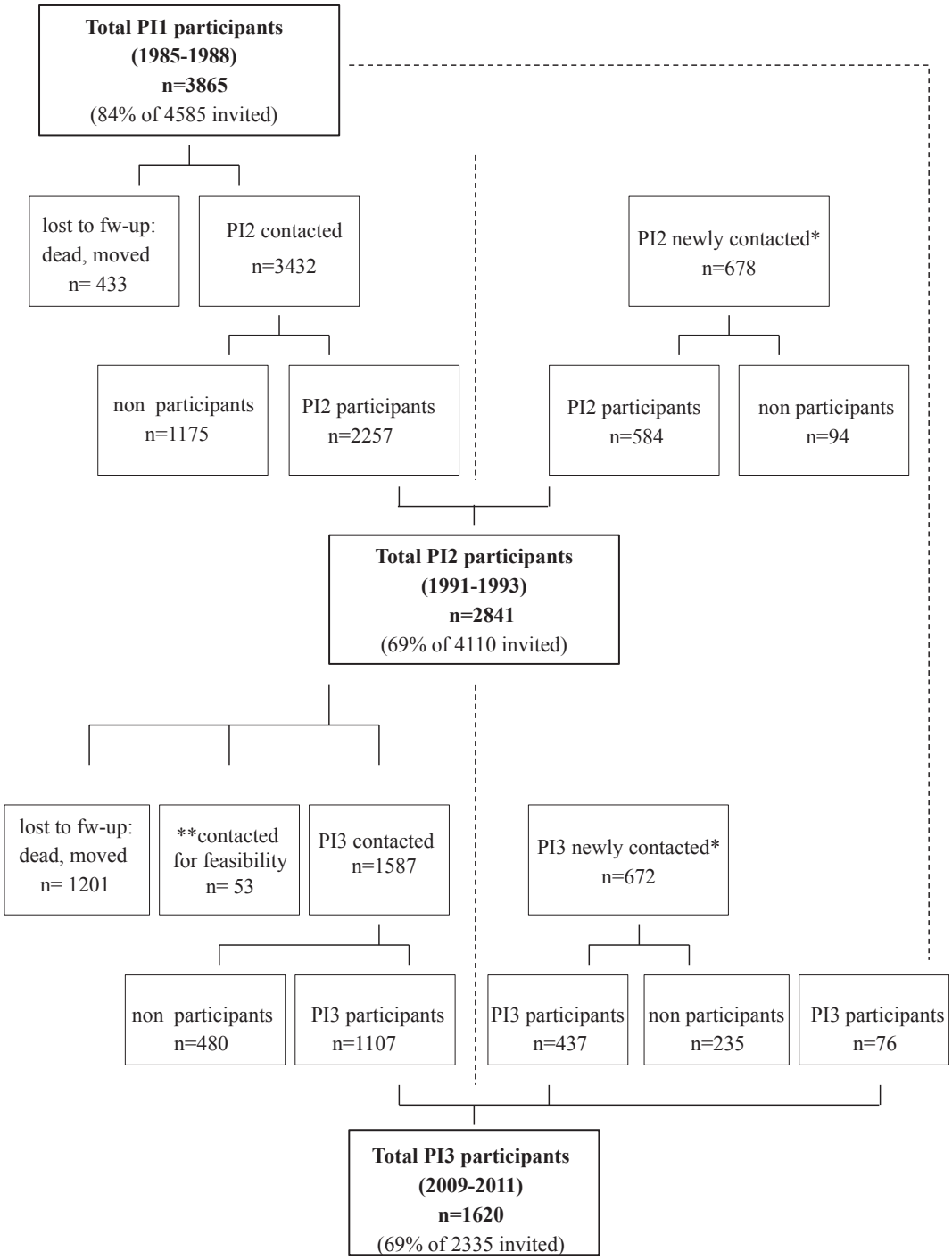

Fig. 1. Flow chart of the participation in the Pisa study. Legend: PI1 = Pisa 1 survey; PI2 = Pisa 2 survey; PI3 = Pisa 3 survey; fw-up = follow-up. * newborns, new spouses or subjects not available in PI1/PI2. **subsample of subjects recruited for a feasibility study collecting a limited number of information.

living in the urban area, with a high level of education, a higher prevalence of asthma symptoms and COPD diagnosis and a lower prevalence of allergic rhinitis were lost to follow-up in PI2, as compared to PI1; a larger proportion of older subjects, with a lower level of education, a higher work exposure, a higher urban residence and a higher prevalence of asthma symptoms and COPD symptoms/diagnosis were lost to follow-up in PI3, as compared to PI2.

Descriptive characteristics and risk factors for the investigated subjects are reported in Table 2. Mean age of the participants significantly increased in the 3 surveys (from 44 yrs in PI1, through 48 in PI2, to 56.2 yrs in PI3), without gender difference. There were more ex-smokers and less current smokers (32.9% and 20.2%, respectively) and higher educational level (13.1% of subjects with more than 13 years of school) in PI3 than in PI1/PI2. Prevalence of work exposure significantly increased in the 3 surveys (from 38.0% in PI1 to 44.1% in PI3); in PI3 there was a reduction of subjects living in urban than in suburban area (from 46.1% in PI1 to 40.1% in PI3).

3.2. Respiratory symptoms/diseases prevalence rates

The adjusted prevalence (%) rate of respiratory symptoms/

Table 1
Number of participants in the three surveys of the Pisa study.

	Participants	
	n	%
only PI1	1532	31.6
only PI2	307	6.3
only PI3	437	9.0
at least one survey	*2276*	*47.0*
PI1-PI2	1389	28.7
PI2-PI3	258	5.3
PI1-PI3	76	1.6
at least two surveys	*1723*	*35.5*
PI1-PI2-PI3 (i.e. all the three surveys)	849	17.5
Total	4848	100.0

PI1 = Pisa 1 survey; PI2 = Pisa 2 survey; PI3 = Pisa 3 survey.

diseases and airway obstruction (AO) is reported in Fig. 2a–b (the crude prevalence is reported in the supplemental material, e-table 2). The prevalence rates of all the respiratory symptoms/diseases tended to increase. Current asthma attacks (1st–3rd survey prevalence: 3.4–7.2%), AR symptoms/disease (16.2–37.4%), usual phlegm (8.7–19.5%) and COPD (2.1–6.8%) more than doubled from PI1 to PI3. AO prevalence rates increased from PI2 (10.8%) to PI3 (21.1%).

3.3. Factors affecting prevalence

The multivariate models confirmed higher risks for having respiratory symptoms/diseases in PI2 and PI3 than in PI1 (Tables 3 and 4). In particular, there were significantly higher risks for asthma (odds ratio - OR 1.34, 95% Confidence Interval - 95% CI 1.09–1.66) and asthma attacks (OR 1.90, 95% CI 1.46–2.47) in PI3, and for AR in PI2 (OR 1.26, 95% CI 1.13–1.40) and PI3 (OR 2.98, 95% CI 2.58–3.44) (Table 3). Also, there were significantly higher risks for COPD (OR 1.24, 95% CI 1.02–1.52 and OR 1.46, 95% CI 1.14–1.85, respectively) in PI2 and PI3 and for usual phlegm in PI3 (OR 1.48, 95% CI 1.25–1.75); usual phlegm showed a borderline significance in PI2 (OR 1.13, 95% CI 0.99–1.29). AO showed a significantly higher risk in PI3 with respect to PI2 (OR 1.78, 95% CI 1.40–2.27) (Table 4).

Other significant associations were shown: asthma, asthma attacks and AR with work exposure; asthma attacks with heavy smoking (≥ 24 pack/years) (Table 3); COPD symptoms/diagnosis with older age, male gender, work exposure and smoking; usual cough with a low educational level; AO with older age and smoking (Table 4). Urban living with AR and COPD symptoms/diagnosis (Tables 3 and 4).

4. Discussion

4.1. Prevalence rate trends

We showed that the prevalence of asthma attacks, AR and COPD increased over a quarter of century across the millennium in an Italian general population sample made of subjects participating in 1–3 surveys. We have confirmed the worldwide increasing trend in allergic diseases/symptoms [3] and added new evidences to the conflicting results about COPD trends [1,4,8,9,19,20].

Our asthma increasing trend (from 6.7% to 7.8%), although not statistically significant, is close to that reported by the U.S. Department of health and human services (from 7.3% in 2001 to 8.4% in 2010) [21]. Other international studies confirmed this increasing trend: a Japanese study (from 5.1% to 6.7% for lifetime asthma and from 1.5% to 3.4% for current asthma, since 1999 to 2006) [22]; an Italian study (from 4.1% in 1991 to 6.6% in 2010 for current asthma) [2]; two Swedish studies (from 9.4% in 1996 to 11.6% in 2006 and from 7.6% in 1996 to 9.3% in 2007 for physician-diagnosed asthma) [4,5].

Further, our study showed a significantly increasing trend of current asthma attacks from 1991–1993 to 2009–2011 (from 3.4% to

Table 2
Mean age, sex and prevalence rates of risk factors in the three surveys of the Pisa study.

	PI1	PI2	PI3	p-value*	p-value trend**
Study period	1985–1988	1991–1993	2009–2011		
N	3865	2841	1620		
Age, yrs (mean ± SD)	44.0 ± 21.3	48.0 ± 20.6	56.2 ± 18.3	<0.001	<0.001
Age range, yrs	4–97	8–97	18–103		
Sex (%):					
Male	47.6	45.3	47.3	0.157	0.949
Female	52.4	54.7	52.7		
Smoking habits (%):					
Smokers	26.8	23.2	20.2	<0.001	0.241
Ex smokers	19.4	27.6	32.9		
Non smokers	53.8	49.2	46.9		
Educational level (%):					
≤8 yrs	82.6	75.6	54.9	<0.001	<0.001
9-13 yrs	14.6	20.7	32.0		
>13 yrs	2.8	3.7	13.1		
Work exposure (%):					
Yes	38.0	41.8	44.1	<0.001	<0.001
No	62.0	58.2	55.9		
Residence (%):					
Urban	46.1	46.5	40.1	<0.001	<0.001
Suburban	53.9	53.5	59.9		
N	3673	2671	1612		
Pack-years (%)§:					
≥24	14.5	17.0	17.9	<0.001	<0.001
8–24	14.7	15.3	17.9		
≤7	14.2	15.4	17.1		
0	56.6	52.3	47.2		

PI1 = Pisa 1 survey; PI2 = Pisa 2 survey; PI3 = Pisa 3 survey.
* Chi-square test.
** Cuzick test for trend.
§ pack-years were categorized on the basis of the tertiles distribution.

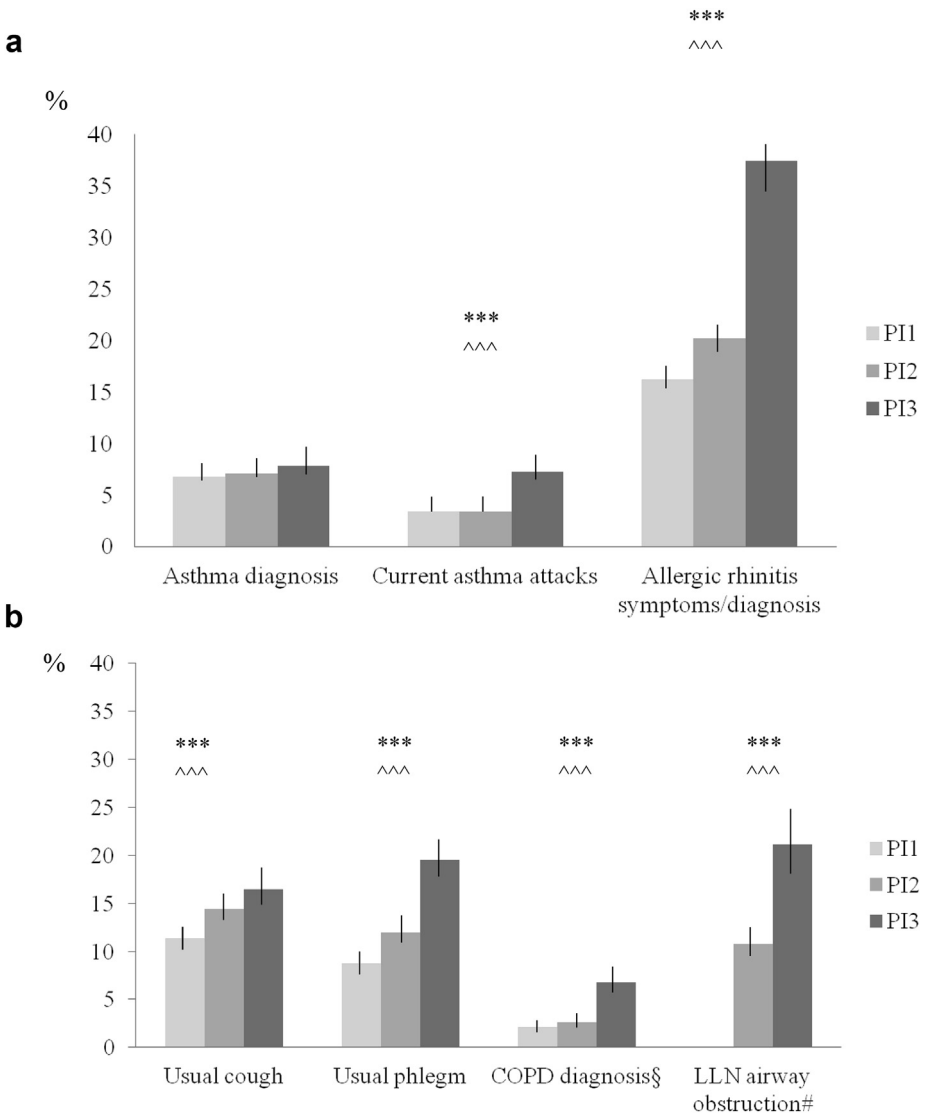

Fig. 2. **a**. Adjusted prevalence of asthma and allergic rhinitis symptoms/diagnosis in the three surveys of the Pisa study. Legend: PI1 = Pisa 1 survey; PI2 = Pisa 2 survey; PI3 = Pisa 3 survey.*** p-value < 0.001 among the three surveys, by chi square test. ^^^ p-value < 0.001 by chi-square test for trend. **b**. Adjusted prevalence of COPD symptoms/diagnosis and airway obstruction° in the three surveys of the Pisa study. Legend: PI1 = Pisa 1 survey; PI2 = Pisa 2 survey; PI3 = Pisa 3 survey. ° airway obstruction values available in PI2 and PI3 surveys. § diagnosis of COPD or emphysema or chronic bronchitis computed only in adult subjects. # Lower Limit of Normal (LLN) according to American Thoracic Society (ATS)/ European Respiratory Society (ERS) criterion [18]: forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) < 5th percentile of the predicted value. *** p-value < 0.001 among the three surveys, by chi square test. ^^^ p-value < 0.001 by chi-square test for trend.

7.2%), confirming the results of Italian (from 5.7% in 1998 to 8.5% in 2010) [2] and Swedish studies (from 3.2% in 1996 to 4.1% in 2007) [5].

AR increasing prevalence was confirmed (from 16.2% in 1985–1988, through 20.2% in 1991–1993, to 37.4% in 2009–2011). A similar increase was shown in the Swedish (from 22% in 1990 to 31% in 2008) [6] and in the Italian ECRHS samples (from 16.8% in 1991–1993 to 25.8% in 2007–2010) [2].

Repeated cross-sectional studies reported inconsistent results for COPD symptoms/diagnosis trend so far. The Italian ECRHS sample showed a stable prevalence of chronic bronchitis during the past decade (12.5%) [9]; on the contrary, our data highlight an increasing trend in COPD diagnosis (reported as COPD or chronic bronchitis or emphysema diagnosis), in line with a Canadian study where the standardized COPD prevalence increased from 7.8% to 9.5%, from 1991 to 2007 [1]. In Norway, an increasing adjusted prevalence of GOLD-defined COPD from 7% to 14% in nine years was shown [8]. Instead, a Spanish study reported a decreasing trend from 9.1% to 4.5% in the prevalence of COPD defined according to the old ERS guidelines over a 10 year period [20].

As regards COPD symptoms, our study showed an increasing trend in the adjusted prevalence of usual cough and usual phlegm. In Norway an increase of chronic cough from 9.6% (1972) to 13.1% (1998/1999) was shown in nine years [23]. On the contrary, a Swedish study showed a reduction in the prevalence of long-standing cough and phlegm (from 12.4% to 10.1% and from 19.0% to 15.0%, respectively) over a 10 year period [4].

As regards AO, the same prevalence (10.8%) previously found in a general population sample living in North Italy (11%) was observed in PI2 [24]. Such prevalence is slightly lower than those reported in the NHANES general population sample (aged 20–79 yrs): 15.6% in 1988–1994 [25] and 13.5% in 2007–2010 [26]. Moreover, our data are very close to those (12.4%) observed in volunteers (mean age 51.0 yrs) who underwent a spirometry testing during the 2004–2009 ERS Congresses [27].

Table 3
Risk factors for asthma/allergic rhinitis symptoms/diagnoses: OR and 95% CI.

	Asthma diagnosis	Attacks of asthma	Allergic rhinitis
Survey:			
PI1	1.00	1.00	1.00
PI2	1.08 (0.94–1.25)	0.88 (0.71–1.10)	**1.26 (1.13–1.40)**
PI3	**1.34 (1.09–1.66)**	**1.90 (1.46–2.47)**	**2.98 (2.58–3.44)**
Age	1.000 (0.991–1.001)	**1.010 (1.003–1.020)**	**0.996 (0.992–0.999)**
Sex:			
Females	1.00	1.00	1.00
Males	1.00 (0.80–1.26)	0.91 (0.69–1.21)	0.90 (0.78–1.04)
Work exposure:			
No	1.00	1.00	1.00
Yes	**1.23 (1.03–1.46)**	**1.27 (1.01–1.60)**	**1.37 (1.22–1.55)**
Pack-years:			
0	1.00	1.00	1.00
≤7	1.05 (0.82–1.36)	1.30 (0.92–1.85)	1.08 (0.92–1.28)
8–24	0.97 (0.73–1.27)	1.23 (0.86–1.74)	0.89 (0.75–1.06)
≥24	1.23 (0.92–1.64)	**2.04 (1.47–2.84)**	0.88 (0.73–1.07)
Educational level:			
>13 yrs	1.00	1.00	1.00
9-13 yrs	0.79 (0.52–1.19)	0.83 (0.47–1.47)	0.88 (0.69–1.13)
≤8 yrs	1.12 (0.75–1.67)	1.28 (0.75–2.18)	**0.75 (0.59–0.96)**
Area:			
Suburban	1.00	1.00	1.00
Urban	0.89 (0.73–1.10)	1.10 (0.87–1.40)	**1.19 (1.05–1.35)**

PI1 = Pisa 1 survey; PI2 = Pisa 2 survey; PI3 = Pisa 3 survey.
OR and 95% CI from the multivariate generalised estimating equations.
Statistically significant values are represented in bold.

We noted quite high AO prevalence (21.1%) in PI3. Since Gerbase et al. found systematically lower values for forced vital capacity (FVC) and forced expiratory volume in the first second (FEV_1) measured by the NDD spirometer [28], we compared the performance of the NDD spirometer to that of a water-sealed spirometer (Collins, Stead-Wells), similar to the one used in PI2: underestimated values, more for FEV_1 than for FVC, were found. Thus, we hypothesized that NDD overestimated AO as assessed by FEV_1/FVC. By adjusting the values of FEV_1 and FVC measured in PI3 for the observed coefficient of variation (see supplemental material), AO prevalence reduced from 21.1% to 13.6%, yet confirming a significant increase in AO prevalence with respect to PI2 (+25.9%) (e-fig. 1).

NDD spirometer was used in large epidemiological surveys (BOLD, PLATINO), assuming that it provides accurate results and does not need daily calibration [29]. However, according to our results, comparison between NDD and conventional spirometers is advisable to check whether correction factors are to be introduced.

4.2. Factors affecting prevalence

Through the use of GEE model, a higher risk of having respiratory symptoms/diseases in the second and third surveys with respect to the first one was shown. This may be due to cumulative exposures to various risk factors over a long time period.

COPD symptoms/diagnosis and AO increased with aging, as found by others [8,30].

Heavy smoking and work exposure were associated with asthma symptoms/diagnosis; male gender, smoking, and work exposure with COPD symptoms/diagnosis. These results are in line with a WHO report showing that the most important risk factors for chronic respiratory diseases are tobacco use, air pollutants and occupational exposure [31].

Our results also pointed out that subjects with low levels of education were more than twice as likely to report COPD symptoms/diagnosis than those with high levels [32].

Urban living was a risk factor for AR and COPD symptoms/diagnosis. Beside confirming our previous findings obtained through a geographic information system approach [33], the current data are in line with our previous observation that urban living is associated with higher bronchial hyper-responsiveness [34] and in agreement with an ATS statement highlighting the importance of outdoor/indoor pollution for COPD development that, with other

Table 4
Risk factors for COPD symptoms/diagnoses and airway obstruction°: OR and 95% CI.

	Usual cough	Usual phlegm	COPD*	LLN airway obstruction#
Survey:				
PI1	1.00	1.00	1.00	
PI2	1.11 (0.98–1.25)	***1.13 (0.99–1.29)***	**1.24 (1.02–1.52)**	1.00
PI3	1.10 (0.93–1.30)	**1.48 (1.25–1.75)**	**1.46 (1.14–1.85)**	**1.78 (1.40–2.27)**
Age	**1.015 (1.011–1.019)**	**1.019 (1.014–1.023)**	**1.050 (1.042–1.058)**	**1.022 (1.013–1.031)**
Sex:				
Females	1.00	1.00	1.00	1.00
Males	0.94 (0.80–1.11)	**1.36 (1.15–1.61)**	**1.55 (1.17–2.05)**	0.76 (0.57–1.01)
Work exposure:				
No	1.00	1.00	1.00	1.00
Yes	**1.25 (1.10–1.44)**	**1.40 (1.22–1.62)**	**1.81 (1.46–2.24)**	1.22 (0.95–1.57)
Pack-years:				
0	1.00	1.00	1.00	1.00
≤7	**1.85 (1.51–2.27)**	**1.80 (1.44–2.24)**	1.26 (0.83–1.91)	**1.81 (1.27–2.57)**
8–23	**2.66 (2.19–3.22)**	**2.67 (2.19–3.26)**	**2.25 (1.62–3.14)**	**2.16 (1.54–3.02)**
≥24	**4.44 (3.64–5.40)**	**4.64 (3.80–5.67)**	**4.45 (3.30–5.99)**	**2.69 (1.89–3.84)**
Educational level:				
>13 yrs	1.00	1.00	1.00	1.00
9-13 yrs	1.25 (0.87–1.79)	0.97 (0.70–1.37)	1.24 (0.66–2.31)	0.94 (0.57–1.55)
≤8 yrs	**1.57 (1.11–2.21)**	1.11 (0.80–1.53)	1.39 (0.77–2.51)	1.06 (0.65–1.73)
Area:				
Suburban	1.00	1.00	1.00	1.00
Urban	***1.14 (0.99–1.31)***	**1.30 (1.12–1.49)**	**1.54 (1.25–1.90)**	0.86 (0.67–1.11)

PI1 = Pisa 1 survey; PI2 = Pisa 2 survey; PI3 = Pisa 3 survey.
° airway obstruction values available in PI2 and PI3 surveys.
* diagnosis of COPD or emphysema or chronic bronchitis computed only in adult subjects.
# Lower Limit of Normal (LLN) according to American Thoracic Society (ATS)/European Respiratory Society (ERS) criterion [18]: forced expiratory volume in the first second (FEV_1)/forced vital capacity (FVC) < 5th percentile of the predicted value.
OR and 95% CI from the multivariate generalised estimating equations.
Statistically significant values are represented in bold. Borderline values are represented in italics.

risk factors, differently affect pulmonary function throughout life span [35]. A recent review of scientific evidences has clearly shown that urban outdoor pollution affects respiratory health worldwide, causing increase in the prevalence of respiratory symptoms/diseases both in children and adults [36].

4.3. Limitations and strengths

A limitation of this study is the use of questionnaire for collecting data on respiratory symptoms/diseases, potentially affected by a reporting bias, as it relies upon individual memory; nevertheless, the standardized questionnaire is one of the main investigation tool in respiratory epidemiology [37,38]. In addition, we used objective respiratory outcomes (lung function) not affected by such potential bias. Indeed, AO and reported COPD symptoms/diagnosis were associated with the same risk factors (survey, age and pack-years).

It is to point out that in PI3 some differences in the protocol and in the used questionnaire exist, but only comparable or identical questions were chosen.

Spirometry was performed using different instruments in PI2 and PI3: a water-sealed spirometer and a device that uses an ultrasonic sensor. This could partly explain the large difference in AO prevalence between the two surveys (10.8% PI2, 21.1% PI3). As already described, using the NDD spirometer, the AO is likely overestimated, but a correction factor can be derived from comparison of NDD with a standard spirometer.

Our sample was made of two main components: a) subjects investigated only once; b) subjects investigated twice/three times. The latter were slightly over 50% of the sample; these subjects aged during the surveys, possibly determining an overestimation of the diseases prevalence. On the other hand, comparing the characteristics of subjects included in follow-up surveys *vs*. those lost to follow-up, results showed that a larger proportion of sick subjects, exposed to risk factors for respiratory symptoms/diseases (urban residence, work exposure) were lost to follow-up, resulting in a possible underestimation of diseases prevalence. It is to point out that among long-term participants in population surveys the disease prevalence tend to be slightly lower than for the total baseline population [39]. It is plausible that subjects who continue to participate in a study may be healthier than those who quit [39], thus partially contrasting the effect of the increase in symptoms/diseases prevalence due to aging.

Sensitivity analyses were performed to verify the appropriateness of using our database to assess the prevalence trend: a) e-Table 3 shows that subjects investigated only at one survey (cross-sectional) had the same respiratory increasing trends of symptoms/diseases as the whole sample (longitudinal plus cross-sectional subjects); b) e-Table 4 shows that there is no significant difference in terms of adjusted prevalences of respiratory symptoms/diseases among subjects participating in only one survey and subjects participating in at least 2 surveys.

Thus, we are confident that our study shows consistent results as those of repeated cross-sectional studies on completely different samples.

A strength of our study is to have applied, over a 25-year follow-up, the same study design, sampling frame and study protocol in subjects living in the same area. In all the 3 surveys, questions were derived from validated international questionnaires, which already had passed the scrutiny of independent reviewers.

Another strength of the present study is the consistency of our results with those from other international studies.

At last, the added value of our study is to have analyzed a general population sample with a large age range from childhood to the elderly.

5. Conclusion

In conclusion, an increase in the prevalence of respiratory symptoms/diseases rates from 1985 to 2011 in a general population sample living in Central Italy has been shown. Current asthma attacks, AR, usual phlegm and COPD almost doubled. New information on a wide age span have been added, in particular for COPD and AO trends.

Conflicts of interest

None.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.rmed.2015.11.006.

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