



18-yr cumulative incidence of respiratory/allergic symptoms/diseases and risk factors in the Pisa epidemiological study

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ARTICLE INFO

Keywords:

Allergy
Asthma
COPD
Environmental & occupational health and epidemiology
Tobacco

ABSTRACT

Background: Few population-based studies on the effects of environmental exposure variation exist.

Aim: Assessing respiratory symptom/disease incidence related to risk factor exposure changes.

Methods: A longitudinal general population sample from two surveys (PISA2:1991–1993; PISA3:2009–2011; no. = 970), aged ≥ 20 years at baseline, completed a questionnaire on respiratory symptoms/diseases, risk factor exposure and performed spirometry. 18-year follow-up cumulative incidence of respiratory symptoms/diseases and longitudinal changes (persistence, incidence, remittance) in risk factor exposure were computed.

Results: Cumulative incidence values were: 3.2% (corresponding to a 1.8‰/year incidence rate), asthma; 6.6% (3.8‰/year), asthma attacks; 4.5% (2.6‰/year), wheeze; 31.7% (21.0‰/year), allergic rhinitis-AR; 7.6% (4.4‰/year), chronic obstructive pulmonary disease-COPD; 16.1% (9.7‰/year), usual cough; 18.5% (11.3‰/year), usual phlegm; 30.7% (20.1‰/year), dyspnoea 1+; 13.9% (8.3‰/year), airway obstruction. The following associations emerged among respiratory symptom/disease cumulative incidence and risk factor exposure changes: a two-to-five fold higher risk for COPD, phlegm, cough, dyspnoea, asthma attacks, airway obstruction in persistent smokers; a two-to-three fold higher risk for COPD in remittent smokers; a two-fold higher risk for AR, phlegm and a four-fold higher risk for asthma in subjects with persistent occupational exposure; a two-fold higher risk for cough, phlegm, dyspnoea, AR in subjects with incident occupational exposure; a two-fold higher risk for AR, asthma attacks, COPD in subjects with incident traffic exposure.

Conclusions: Our study showed noteworthy respiratory symptom/disease incidence values and indicated that life-style and environmental exposure changes can differently influence onset. This information could be useful for primary prevention strategies in order to reduce the chronic disease burden in the general population.

1. Introduction

There is evidence that prevalence rates of respiratory symptoms/diseases have continued to increase in the last decade [1–4].

Longitudinal epidemiological surveys on the general population can provide important data to better comprehend the risk factors associated with the incidence of respiratory symptoms/diseases in the *real life* setting, making it possible to assess their natural history and long-term outcomes after adjusting for age. Nevertheless, few population-based

longitudinal studies have taken into account the effects of changes in life-style and in environmental exposure (remittance, persistence and incidence) on symptom/disease incidence [5–7]; indeed, exposure at baseline or at any time have more frequently been analyzed [8–10].

Studies published in the last two decades showed high values of respiratory symptom/disease cumulative incidence in adult subjects at 10–20-year follow-up: asthma incidence ranged from 2% to 6% [5,9,11–13]. Higher values were found for allergic rhinitis (AR) incidence, ranging from 12% to 26% [14–16]. Wheeze incidence values ranged

Abbreviations: AR, allergic rhinitis; AO, airway obstruction; COPD, Chronic obstructive pulmonary disease; LLN, lower limit of normal; PI1, first Pisa survey; PI2, second Pisa survey; PI3, third Pisa survey.

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<https://doi.org/10.1016/j.rmed.2019.09.013>

Received 20 December 2018; Received in revised form 19 September 2019; Accepted 23 September 2019

Available online 24 September 2019

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from 3% to 7% in European cohorts [17–19].

A 1% cumulative incidence of chronic bronchitis was found in a ten-year follow-up of Swedish adults [20]. Values of 2% emerged from an English database about physicians' diagnosis of chronic obstructive pulmonary disease (COPD) [21]. Higher incidence values of COPD (chronic cough and chronic phlegm) symptoms were found in a Norwegian eleven-year adult follow-up study (9% and 16.5%, respectively) [5]. In the same study, cumulative incidence of dyspnoea ranging from 17.5% (grade 1) to 2% (grade 4) emerged [5]. Cumulative incidence of about 3% for the lower limit of normal (LLN)-defined COPD was found in European studies on adult subjects at a ten-twenty-year follow-up [22–24], reaching a value of 7.4% in a Swiss study [8].

According to the World Health Organization and many recent publications, the main environmental risk factors associated with lifetime increase of respiratory symptoms/diseases are tobacco use, air pollutants, occupational exposure and climate changes [25–28]. In 2017, data released by the Institute for Health Metrics and Evaluation indicated that, in Western Europe, 44.3% of COPD deaths were attributable to smoking habits, 15.3% to particulate matter and 7.9% to occupational exposure; 12.9% of asthma deaths were attributable to smoking habits and 2.7% to occupational exposure [29].

The purpose of our population-based study was to evaluate the 18-year follow-up regarding the cumulative incidence of respiratory symptoms/diseases related to variations (remittance, persistence and incidence) in smoking habits and in occupational/environmental exposures.

2. Materials and methods

2.1. Sample

Detailed information on population characteristics and methods are available elsewhere [1,30].

Briefly, a multistage stratified family-cluster random sample of the general population, living in Pisa, was investigated in three subsequent cross-sectional surveys: first survey (PI1) (1985–1988); second survey (PI2) (1991–1993); third survey (PI3) (2009–2011).

In this paper, subjects participating in both PI2 and PI3, aged ≥ 20 years at baseline, (no. = 970) were taken into account: the mean follow-up was eighteen years.

Information on symptoms/diseases and risk factors was obtained through standardized interviewer-administered questionnaires developed by CNR [1,31] on the basis on the National Heart Blood and Lung Institute questionnaire [32].

Moreover, objective data about respiratory troubles were collected through spirometry. In PI2, all subjects aged ≤ 75 were invited to perform spirometry (forced vital capacity-FVC- manoeuvre) according to the American Thoracic Society protocol [33], through a water-sealed spirometer (Baires, Biomedin) (participation rate 67%) [34]. In PI3, all subjects were invited to perform spirometry (FVC manoeuvre) according to the American Thoracic Society/European Respiratory Society protocol [35], through a hand-held ultrasonic spirometer (EasyOne Model 2001 Spirometer, NDD Medical Technologies) as recommended by the standard protocol of the EU-funded study on Indicators for Monitoring COPD and Asthma (IMCA2) (participation rate 55%).

At the time of PI2, Italian law did not require Ethical Committee approval. The protocol was approved by an Internal Review Board within the CNR Preventive Medicine Targeted Project. PI3 study protocol, patient information sheet, and consent form were approved by the Pisa University Hospital Ethics Committee (Prot. no. 23887, April 16, 2008).

2.2. Investigated respiratory symptoms/diseases

Since different questionnaires were used in PI2 and PI3, only the following comparable questions were used for these analyses:

- Asthma diagnosis, if the subjects reported asthma confirmed by a physician (PI2, PI3).
- Current asthma attacks, if the subjects reported attacks of shortness of breath with wheezing, apart from common colds, currently (PI2) or in the last 12 months (PI3).
- Wheeze, if the subjects reported wheeze, apart from common colds, lifetime (PI2) or in the last 12 months (PI3).
- Allergic rhinitis (AR) symptoms/diagnosis, if the subjects reported hay fever or other conditions causing runny or blocked nose, apart from common colds (PI2) or if the subjects reported hay fever or problems with sneezing or a runny or blocked nose, apart from common colds (PI3).
- Usual cough (or phlegm), if the subjects reported usual cough (or phlegm) apart from common colds (PI2, PI3).
- Dyspnoea, if the subjects reported grade 1 + dyspnoea (shortness of breath when hurrying on the level or walking up a slight hill) according to the modified Medical Research Council Dyspnoea Scale (PI2, PI3).
- COPD diagnosis, if the subjects reported chronic bronchitis or emphysema confirmed by a physician (PI2) or if the subjects reported chronic bronchitis, emphysema or COPD confirmed by a physician (PI3).
- LLN airway obstruction (AO_{LLN}) was detected using the ERS/ATS criterion: FEV_1/FVC percent predicted $< LLN$ [36]; the LLN was derived from population-specific prediction equations [37] (PI2, PI3). Considering that two different spirometers were used in PI2 and PI3, adjusted values of FEV_1 and FVC were used in PI3, as detailed elsewhere [1].

For each symptom or diagnosis, the 18-year follow-up regarding the cumulative incidence value was computed as the proportion of subjects who did not report the outcome of interest in PI2 ("population at risk") and who reported it in PI3 ("cumulative incidence" = "incident cases"/"population at risk") (more details are reported in the Supplemental material).

To compare our results with those of other studies performed using different follow-up periods, we estimated the incidence rate (IR), assumed to be linear, as follows: $IR = a / \{18 \times [b - (a/2)]\}$ where "a" refers to the incident cases and "b" to the population at risk at the start of the study [11,38].

2.3. Longitudinal environmental risk factors

Longitudinal changes of the main environmental risk factors for respiratory diseases were assessed.

Smoking habits were coded into 5 groups: "Never" (non-smoker subjects both in PI2 and PI3), "Persistent" (smoker subjects both in PI2 and PI3), "Incident" (subjects starting to smoke in the period between PI2 and PI3), "Remittent for < 18 years" (subjects who stopped smoking in the period between PI2 and PI3), "Remittent for ≥ 18 years" (subjects who had already stopped smoking before PI2).

Occupational exposure (self-reported exposure to dusts/fumes/gases at work) was codified into 4 groups: "Never" (unexposed subjects in both PI2 and PI3), "Persistent" (exposed subjects in both PI2 and PI3), "Incident" (subjects starting to be exposed in the period between PI2 and PI3), "Remittent" (subjects quitting exposure between PI2 and PI3).

Vehicular traffic exposure (self-reported exposure to vehicular traffic near home) was codified into 4 groups: "Never" (unexposed subjects in both PI2 and PI3), "Persistent" (exposed subjects in both PI2 and PI3), "Incident" (subjects starting to be exposed in the period between PI2 and PI3), "Remittent" (subjects quitting exposure between PI2 and PI3).

2.4. Statistical analyses

Statistical analyses were carried out using the Statistical Package for the Social Sciences (SPSS version 16.0). Comparisons among groups

were performed by the chi-square test for categorical variables and analysis of variance for continuous variables. The Fisher exact test was used in the case of cells with an expected frequency of less than 5.

Since the incidence values of respiratory symptoms/diseases, work exposure and smoking habits are different among adults and children/teenagers, only adult subjects were analyzed: a baseline age ≥ 20 years was set to be more comparable with other researches on respiratory outcome incidence in European general population samples like the European Community Respiratory Health (ECRHS) Survey [39] and the joint Nordic study on clinical respiratory epidemiology between Finland, Estonia, and Sweden (FinEsS) [40].

Multiple logistic regression models were used to estimate the effect of longitudinal changes in risk factor exposure on the cumulative incidence of symptoms/diseases and AO_{LLN} , adjusting for age, sex, body mass index (BMI), passive smoking, family history (at least one parent) of allergic rhinitis and/or respiratory diseases (asthma, chronic bronchitis or emphysema) at baseline (PI2). In the analyses concerning AR and asthma incidence, skin prick test positivity to house dust mites, pets, moulds or pollens was taken into account.

The odds ratio (OR) and 95% confidence interval (CI) were calculated. The significance level was set at 0.05.

3. Results

The descriptive characteristics of PI2 and PI3 participants are shown in Table 1: 56.1% were females, 31.6% had skin prick test positivity, 48.6% had family history of allergic diseases and 47.7% of respiratory diseases, and 54.7% reported passive smoking. A significantly higher percentage of obesity (29.2% vs 13.4%), vehicular traffic exposure (63.7% vs 35.7%) and a significantly lower percentage of smokers (16.2% vs 27.2%) were found in PI3 compared to PI2.

The eighteen-year follow-up cumulative incidence values for symptoms/diseases were as: 3.2%, asthma; 6.6%, asthma attacks; 4.5%,

Table 1

Descriptive characteristics of PI2-PI3 longitudinal subjects (no. = 970; males = 426; females = 544).

	PI2 (1991–1993)	PI3 (2009–2011)	p-value
Sex (%):			
males	43.9	43.9	
females	56.1	56.1	
Age (mean $\pm$ SD)	46.2 $\pm$ 13.2	64.0 $\pm$ 13.1	0.000
Age range	20–78	36–96	
BMI (mean $\pm$ SD)	25.9 $\pm$ 3.9	28.0 $\pm$ 4.5	0.000
BMI (%):			0.000
Underweight	0.7	0.3	
Normal weight	43.5	24.9	
Overweight	42.4	45.6	
Obese	13.4	29.2	
missing values		36.5	
Smoking habits (%):			0.000
Smokers	27.2	16.2	
Ex smokers	31.4	38.2	
Non smokers	41.3	45.6	
Occupational exposure (%)	44.8	45.6	0.749
Vehicular traffic exposure (%)	35.7	63.7	0.000
Positivity to SPT ^a (no. = 869) (%)	31.6	n.a.	
missing values (no. = 101)	10.4		
Family history (at least one parent) of respiratory diseases ^b (%)	47.7	n.a.	
Family history (at least one parent) of allergic diseases (%)	48.6	n.a.	
Passive smoking	54.7	n.c.	

SD: standard deviation; BMI: body mass index; SPT: skin prick test.

n.a. = not available; n.c. = not comparable.

In bold: statistically significant values.

^a Positivity (mean wheal diameter ≥ 3 mm than that of the negative control) to at least one allergen among house dust mites, pets, moulds, pollens.

^b Asthma or chronic bronchitis or emphysema.

wheeze; 31.7%, AR; 7.6%, COPD; 16.1%, usual cough; 18.5%, usual phlegm; 30.7% dyspnoea 1+; 13.9%, AO_{LLN} (Fig. 1). Significantly higher values of cumulative incidence of bronchitic/allergic symptoms/diseases were found in late-adults with respect to young-adults; no significant difference for asthma symptoms/diseases emerged (table e1 supplemental material).

The estimated incident rates (cases/1000/year) were the following: 1.8, asthma; 3.8, asthma attacks; 2.6, wheeze; 21.0, AR; 4.4, COPD; 9.7, usual cough; 11.3, usual phlegm; 20.1, dyspnoea 1+; 8.3, airway obstruction.

With regard to changes in risk factor exposure, the highest incidence value was shown by traffic exposure (38.2%), followed by occupational exposure (28.6%) and smoking habits (2.6%). The highest remittance value was found for smoking habits (28.7% for ≥ 18 years, 16.1% for < 18 years), followed by traffic exposure (10.1%) and occupational exposure (6.2%) (Fig. 2).

Incidence values of asthma symptoms/diseases and AR showed no significant associations with smoking habits. COPD incidence was significantly higher in persistent (12.8%) and remittent smokers (about 9%) with respect to the other categories; usual phlegm was significantly higher in persistent smokers (32.4%) (Table 2).

Incidence values of symptoms/diseases were significantly higher in persistent and incident occupational exposure: 7.1% and 3.9% for asthma, 40.0% and 37.6% for AR, 11.7% and 9.7% for COPD, 25.4% and 23.4% for usual phlegm, 17.3% and 20.3% for usual cough; dyspnoea incidence was higher in incident exposure (41.4%) (Table 3).

Asthma attacks incidence showed the highest value in incident traffic exposure (10.2%), whilst AR in persistent and incident traffic exposure (about 36% for both). Bronchitic symptoms/diseases showed no significant associations with traffic exposure (Table 3).

Multiple logistic regression analyses, after adjusting for anthropometric data, family history of allergic/respiratory diseases, passive smoking and atopy, showed significantly higher risks for asthma incidence in subjects with persistent occupational exposure (OR 4.4); a three-fold higher risk for asthma attacks incidence was found in persistent smokers (OR 2.7) and a two-fold higher risk in subjects with incident vehicular traffic exposure (OR 2.2); a 1.6/1.8-fold higher risk for AR incidence was observed in subjects with persistent and incident occupational exposure (OR 1.8 and OR 1.6, respectively) and with incident vehicular traffic exposure (OR 1.8) (Table 4a).

A significantly higher risk for cumulative incidence of bronchitic symptoms/diseases was shown in smokers and subjects with occupational exposure, as follows: increasing risk for COPD incidence ranging from OR 2.4 in remittent smokers ≥ 18 years to OR 5.4 in persistent

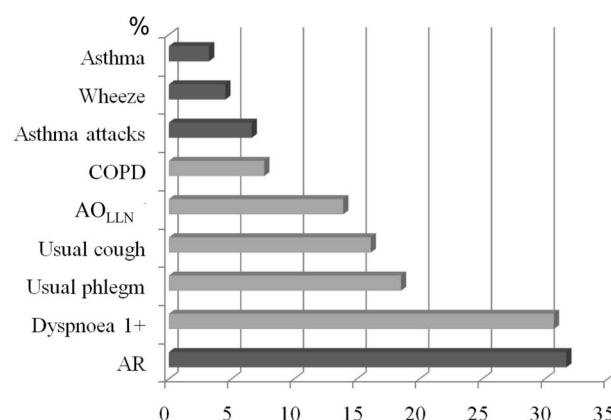


Fig. 1. 18-yr cumulative incidence of respiratory and allergic symptoms/diseases (%). COPD: Chronic Obstructive Pulmonary Disease; AO_{LLN} : Airway obstruction computed according to the lower limit of normal; AR: allergic rhinitis. In dark grey, asthma/allergic symptoms/diseases; in light grey, bronchitic symptoms/diseases.

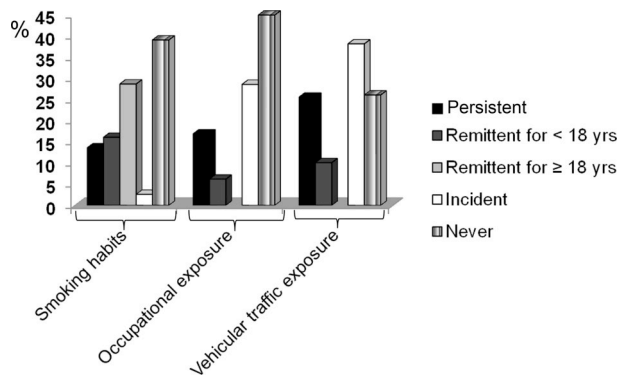


Fig. 2. Changes in environmental risk factor exposure from PI2 to PI3 (%). Remittent for <18 years: subjects stopping smoking between PI2 and PI3; Remittent for ≥18 years: subjects stopping smoking before PI2.

smokers; a three-fold higher risk for usual phlegm incidence in persistent smokers and a two-fold higher risk in subjects with persistent and incident occupational exposure (OR 1.8 and OR 1.5, respectively); a two-fold higher risk for usual cough and dyspnoea incidence in persistent smokers (OR 1.9 and OR 1.8, respectively) and in subjects with incident occupational exposure (OR 1.6 and OR 1.9, respectively); a three-fold higher risk for AO_{LLN} in persistent smokers (OR 2.7) (Table 4b).

Lastly, a two-fold higher risk of COPD emerged in subjects with incident vehicular traffic exposure (OR 2.4).

4. Discussion

Noteworthy 18-year follow-up cumulative incidence values of respiratory symptoms/diseases were found in an adult general population sample, living in an urban/suburban area in Central Italy.

Occupational and vehicular traffic exposure mainly influenced AR/asthma incidence, and smoking habits and occupational exposure mainly influenced COPD incidence.

4.1. Estimated incidence rates

In order to compare our findings about incidence values with those of

other European studies, we decided to estimate the annual incidence rates (cases/1000/year) in our population through the correction already applied by Ekerljung et al. [11] and Pallasaho et al. [38] (Table 5).

We found an asthma incidence rate of about 2 cases/1000/year in line with other findings [12,41], even though somewhat higher values were reported in the literature, especially in more recent follow-ups [11, 24,38,42]. The AR incidence rate was the highest (21 cases/1000/year), indicating that the worldwide increase of allergic respiratory diseases during the last 3 decades in industrialized countries is not over [14,16, 43]; this value is close to that of a recent publication on an European cohort (23.4/1000/year) [16]. Lower values emerged in studies only taking AR diagnosis into account (incidence rates ranging from 4.4 to 8.0) [42,44].

As regards COPD, an incidence rate of about 4 cases/1000/year was found in our population, slightly higher than the one observed in a Dutch cohort of general population aged ≥40 yrs (3 cases/1000/year) [45]; by contrast, lower values (1–2 cases/1000/year) were published in young adult European cohorts (20–44 years) [20,46]. Results of objective measurements (spirometry) pointed out an AO_{LLN} incidence rate of 8.3 cases/1000/year. This value is higher than the one observed in young adult cohorts (ranging from 1.4 to 3.5) [23,24], but slightly lower than the one found in older subjects (mean age about 70 years) (ranging from 8.9 to 11.7) [47,48].

The slight differences among the findings of the reported studies are likely due to the different periods of data collection and to the different definitions of “at risk population” (diagnosis with symptoms or only diagnosis or only symptoms).

Tables comparing our incidence cumulative values with those of other European studies were reported in the supplemental material (tables e2 and e3).

4.2. Risk factors for incidence of allergic/asthmatic diseases

We found significantly higher risks of asthma incidence and AR incidence in subjects with persistent occupational exposure: four-fold for asthma, two-fold for AR. A recent Northern European study reported a significantly higher risk of having rhinitis and asthma incidence among people sometimes engaged in welding (hazard ratio (HR) 1.5 for both diseases), with respect to people never engaged in welding [10]. A larger risk of developing asthma in subjects exposed to dusts/fumes was

Table 2
Symptom/disease incidence by longitudinal changes in smoking habits (%).

	Persistent ^b	Remittent for <18 years ^b	Remittent for ≥ 18 years ^b	Incident ^b	Never	p-value
No. ^a	124	149	257	25	353	
Asthma diagnosis	2.4	2.7	3.9	4.0	3.1	0.897
No.	125	144	255	23	353	
Asthma attacks	10.4	6.3	7.1	4.3	5.1	0.348
No.	91	99	212	23	327	
Wheeze	7.7	1.0	4.7	4.3	4.6	0.221
No.	107	132	230	21	279	
Allergic rhinitis	27.1	34.1	37.0	23.8	28.7	0.191
No.	125	147	250	24	366	
COPD	12.8	10.9	9.2	0.0	3.8	0.001
No.	105	127	248	23	347	
Usual phlegm	32.4	14.2	19.4	13.0	15.6	0.003
No.	94	123	241	24	334	
Usual cough	21.3	13.8	14.9	20.8	15.9	0.562
No.	111	124	237	23	301	
Dyspnoea 1+	36.0	29.8	33.3	21.7	27.6	0.337
No.	49	48	99	10	117	
AO _{LLN}	20.4	12.5	16.2	0.0	11.1	0.379

COPD: Chronic Obstructive Pulmonary Disease; AO_{LLN}: Airway obstruction computed according to the lower limit of normal.

In italic: borderline values; in bold: statistically significant values.

^a No. = population at risk.

^b Persistent: smokers at PI2 and PI3; Remittent for <18 years: quitters between PI2 and PI3; Remittent for ≥18 years: quitters before PI2; Incident: beginners between PI2 and PI3.

Table 3

Symptom/disease incidence by longitudinal changes in occupational exposure and vehicular traffic exposure (%).

	Persistent	Remittent	Incident	Never	p-value
<i>Occupational exposure</i>					
No. ^a	154	55	258	440	
Asthma diagnosis	7.1	0.0	3.9	1.8	0.008
No.	148	55	257	439	
Asthma attacks	8.1	5.5	7.0	5.9	0.765
No.	111	47	208	385	
Wheeze	3.6	2.1	6.3	4.2	0.609
No.	135	44	213	376	
Allergic rhinitis	40.0	22.7	37.6	26.6	0.003
No.	154	55	247	455	
COPD	11.7	0.0	9.7	5.9	0.005
No.	134	51	235	429	
Usual phlegm	25.4	5.9	23.4	15.2	0.001
No.	139	52	212	412	
Usual cough	17.3	5.8	20.3	14.8	0.050
No.	142	51	215	387	
Dyspnoea 1+	27.5	19.6	41.4	27.4	0.001
No.	63	20	102	138	
AO _{LLN}	15.9	15.0	16.7	10.9	0.541
<i>Vehicular traffic exposure</i>					
No.	227	93	348	239	
Asthma diagnosis	1.8	4.3	4.9	1.7	0.074
No.	227	89	344	239	
Asthma attacks	4.0	4.5	10.2	4.6	0.011
No.	187	75	300	189	
Wheeze	4.3	4.0	5.3	3.7	0.870
No.	193	78	297	200	
Allergic rhinitis	35.2	20.5	36.0	26.5	0.014
No.	231	92	349	239	
COPD	8.2	10.9	8.9	3.8	0.060
No.	216	86	328	220	
Usual phlegm	18.5	19.8	19.5	16.4	0.809
No.	204	82	319	211	
Usual cough	14.7	19.5	16.0	16.1	0.806
No.	195	82	308	210	
Dyspnoea 1+	31.3	30.5	32.8	27.1	0.590
No.	88	26	124	84	
AO _{LLN}	11.4	7.7	13.7	19.0	0.414

COPD: Chronic Obstructive Pulmonary Disease; AO_{LLN}: Airway obstruction computed according to the lower limit of normal.

In italic: borderline values; in bold: statistically significant values.

^a No. = population at risk

confirmed by a Swedish general population study showing an HR of 1.8; moreover, 9.4% of new-onset asthma cases were attributable to occupational exposure [12]. A recent official statement of the American Thoracic Society and of the European Respiratory Society reported that workplace exposure contributes to 16% of asthma incidence [49].

We also found an association between AR incidence and incident occupational exposure (a 1.6-fold higher risk), highlighting the need for strong and early preventive measures in workplaces still in the 21st century. Indeed, in a 7-year follow-up study performed on German adolescents, an increased risk for rhinitis symptoms onset (OR 1.5) emerged in those working in high-risk occupations (i.e. high exposure levels to chemicals/irritants/fumes and/or environmental tobacco smoke), with the highest incidence shown in the first ten months of work [7].

In Pisa, as in many other urban areas, vehicular traffic has been increasing in the last years. Traffic exposure incidence was related to a 1.8–2.2 fold higher risk of AR and asthma attack incidence, compared to non-exposure, adding new evidences to those reported in six European cohorts suggesting a deleterious effect of pollutants emitted by vehicular traffic on adult-onset asthma incidence [50]. Furthermore, there is evidence that people living in urban areas more frequently experience AR and bronchial asthma than those living in rural areas: one of the main determinants is the increased presence of outdoor air pollutants, from energy consumption and vehicles exhaust emissions, able to promote airway sensitization [26,43].

Table 4a

Longitudinal risk factors for asthma/allergic symptom/disease incidence: OR and 95% CI.

	Asthma diagnosis	Asthma attacks	Wheeze	Allergic rhinitis
<i>Smoking habits:</i>				
never	1.0	1.0	1.0	1.0
persistent	0.7 (0.2–3.0)	2.7 (1.1–6.4)	1.7 (0.6–4.7)	0.9 (0.5–1.6)
remittent for <18 years	1.1 (0.3–3.6)	1.5 (0.6–3.8)	0.2 (0.0–1.4)	1.1 (0.7–1.9)
remittent for ≥18 years	1.0 (0.4–2.7)	1.4 (0.7–3.1)	1.0 (0.4–2.6)	1.0 (0.7–1.6)
incident	–	0.9 (0.1–7.6)	0.8 (0.1–7.1)	0.7 (0.2–2.1)
<i>Occupational exposure:</i>				
never	1.0	1.0	1.0	1.0
persistent	4.4 (1.4–13.6)	1.1 (0.5–2.6)	0.5 (0.1–1.7)	1.8 (1.1–3.0)
remittent	–	0.8 (0.2–2.9)	0.3 (0.0–2.6)	0.7 (0.4–1.9)
incident	1.8 (0.7–4.8)	0.9 (0.5–1.9)	1.0 (0.4–2.4)	1.6 (1.1–2.4)
<i>Vehicular traffic exposure:</i>				
never	1.0	1.0	1.0	1.0
persistent	1.3 (0.3–5.1)	0.6 (0.2–1.6)	1.0 (0.3–2.9)	1.5 (0.9–2.5)
remittent	2.4 (0.5–10.2)	0.6 (0.2–2.2)	0.8 (0.2–3.9)	0.8 (0.4–1.6)
incident	2.6 (0.8–8.2)	2.2 (1.0–4.5)	1.5 (0.6–3.7)	1.8 (1.2–2.8)

A logistic regression model for each considered outcome was used to estimate the effect of longitudinal changes in risk factor exposure (smoking habits, occupational exposure and vehicular traffic exposure) on respiratory symptom/disease incidence, controlling for baseline factors closely related to the onset of respiratory symptom/disease (age, sex, body mass index -BMI, passive smoking, positivity to skin prick test, family history of allergic rhinitis and family history of respiratory diseases (asthma, chronic bronchitis or emphysema)).

In italic: borderline values; in bold: statistically significant values.

Persistent smoking was a risk factor for asthma attack incidence (OR 2.7); this relationship with asthma symptoms onset is consistent with earlier findings found in an Italian adult general population showing that baseline smoking habits were a strong predictor of asthma (OR 2.03) only when the definition of the outcome was expanded to include a new onset of asthma symptoms (wheezing) in addition to new-onset asthma diagnosis [9]. Moreover, previous studies performed in Northern Europe showed significant associations between persistent smokers and incidence of wheezing (OR 2.0) [5] and between current smokers and incidence of wheezing (OR 2.6) and attacks of breathlessness (OR 2.1) [19].

4.3. Risk factors for incidence of COPD symptoms/diagnosis

Smoking is the main risk factor for COPD occurrence and exacerbations. In our study, persistent smokers had an elevated risk of developing COPD, usual phlegm, usual cough and dyspnoea. Similar results have been shown in other European cohorts: smokers had a higher risk of incidence for COPD (OR 4.40), chronic productive cough (RR 2.4) and grade 1 dyspnoea (OR 1.5) in the Finnish [51], Swedish [20] and Norwegian cohorts [5], respectively.

Moreover, our results highlighted that the longer the period of abstinence from smoking, the lower the risk of COPD incidence; these findings are in line with a previous Danish 25-year follow-up study on the general population [6] and with a recent US survey showing that the prevalence of COPD and productive cough was higher in current smokers and ex-smokers who have abstained for < 10 years compared to smokers who have abstained for ≥ 10 years [52]. A recent Italian study reported that the more cigarettes were smoked per day and the younger the age of quitting smoking, the more years of life were gained with

Table 4b

Longitudinal risk factors for bronchitic symptom/disease incidence: OR and 95% CI.

	COPD	Usual phlegm	Usual cough	Dyspnoea	AO _{LLN}
Smoking habits:					
never	1.0	1.0	1.0	1.0	1.0
persistent	5.4 (2.3–12.5)	2.9 (1.7–5.1)	1.9 (1.0–3.5)	1.8 (1.1–3.0)	2.7 (1.0–7.4)
remittent	3.3 (1.4–7.7)	0.8 (0.5–1.6)	1.0 (0.5–1.9)	1.5 (0.9–2.4)	1.1 (0.4–3.4)
for <18 years					
remittent	2.4 (1.2–5.1)	1.1 (0.7–1.7)	1.0 (0.6–1.7)	1.3 (0.9–2.0)	1.2 (0.5–2.8)
for ≥18 years					
incident	–	0.8 (0.2–3.0)	1.7 (0.6–5.1)	0.9 (0.3–2.8)	–
Occupational exposure:					
never	1.0	1.0	1.0	1.0	1.0
persistent	1.9 (0.9–4.1)	1.8 (1.1–3.2)	1.4 (0.8–2.6)	1.3 (0.8–2.0)	2.0 (0.8–5.2)
remittent	–	0.4 (0.1–1.3)	0.4 (0.1–1.4)	0.8 (0.4–1.7)	1.3 (0.3–5.4)
incident	1.6 (0.9–3.0)	1.5 (1.0–2.4)	1.6 (1.0–2.5)	1.9 (1.3–2.8)	1.1 (0.5–2.6)
Vehicular traffic exposure:					
never	1.0	1.0	1.0	1.0	1.0
persistent	1.7 (0.7–3.9)	1.0 (0.6–1.7)	0.7 (0.4–1.3)	1.0 (0.6–1.6)	0.4 (0.2–1.1)
remittent	2.6 (0.9–7.0)	1.1 (0.6–2.2)	1.1 (0.6–2.2)	1.0 (0.6–1.9)	0.4 (0.1–1.8)
incident	2.4 (1.1–5.2)	1.3 (0.8–2.0)	0.9 (0.6–1.5)	1.2 (0.8–1.8)	0.5 (0.2–1.2)

A logistic regression model for each considered outcome was used to estimate the effect of longitudinal changes in risk factor exposure (smoking habits, occupational exposure and vehicular traffic exposure) on respiratory symptom/disease incidence, controlling for baseline factors closely related to the onset of respiratory symptom/disease (age, sex, body mass index -BMI, passive smoking, family history of allergic rhinitis and family history of respiratory diseases (asthma, chronic bronchitis or emphysema)).

COPD: Chronic Obstructive Pulmonary Disease; AO_{LLN}: Airway obstruction computed according to the lower limit of normal.

In italic: borderline values; in bold: statistically significant values.

cessation [53].

These findings highlight the importance of early smoking cessation in the fight against COPD symptoms/diagnosis in the general population.

The relationship between smoking habits and bronchitic conditions was also confirmed by the results of objective measurements (spirometry), pointing out a three-fold higher risk of developing AO_{LLN} in persistent smokers. In a Swiss cohort, baseline heavy smoking was related to a higher risk for AO fixed ratio incidence (RR 1.5) [54]. More recently, in an elderly Swedish cohort, a significant effect of current smoking for both fixed ratio (RR 1.8) and LLN criteria (RR 2.2) was observed [48].

Persistent and incident occupational exposures were significantly associated with cumulative incidence of usual phlegm, usual cough and dyspnoea, confirming results of other general population cohorts. A Norwegian 11-year community cohort study found that exposure to workplace gases/fumes was significantly related to incident phlegm in women (OR 1.42) [55], and North-American authors reported that, during an approximately 3-year follow-up, subjects working in specific occupations (as mechanics and in other repair occupations and in cleaning and building services) had significantly higher risks of developing chronic phlegm and cough [17]; occupational exposure to dust/fumes at any time in a person's life was a significant risk factor for attacks of dyspnoea (OR 1.4) and dyspnoea grade 3 (OR 2.1) in an 11-year follow-up of a Norwegian cohort [56].

Lastly, COPD incidence was significantly related to incident vehicular traffic exposure (OR 2.4); this finding is in line with a recent

literature review of longitudinal studies reporting that outdoor air pollution has long-term effects on lung function, with higher pollution exposure leading to more rapid lung function decline in general population cohorts, possibly contributing to the development of COPD [57].

4.4. Limits and strengths

The use of questionnaires for collecting symptom/disease data might be a limitation because it is potentially affected by a reporting bias, as it relies upon individual memory. Nevertheless, the standardized questionnaire is one of the main investigation tools in respiratory epidemiology [58,59]. Moreover, we also applied an objective respiratory outcome (lung function), not affected by this potential bias.

It is to be pointed out that in PI3 there were some differences in the questionnaire used, but only comparable or identical questions to PI2 ones were chosen.

Spirometry was performed using different instruments in PI2 and PI3; a correction factor was derived to overcome this limit and to permit comparison between the studies, as previously reported [1].

Sensitivity analyses were performed to assess some potentially critical aspects of our study.

Firstly, since less than 50% of the original sample performed spirometry in both surveys (no. = 368), a comparison of cumulative incidence rates and frequencies of longitudinal risk factors between the subsample of subjects performing spirometry and the whole sample was performed: no difference was found allowing the generalizability of results about AO incidence to the whole Pisa sample.

Secondly, a comparison of the baseline characteristics and health status of subjects who were followed-up (PI2&PI3 participants) with those of subjects who were not (only PI2 participants) was performed: older age, lower prevalence of allergic/respiratory disease familiarity, higher prevalence of non-smokers and of COPD symptoms/disease were found in only PI2 participants than in PI2&PI3 participants. Thus, the incidence values were computed in a sample of younger healthy subjects, with a possible conservative estimate of the reported incidence values. This possible conservative estimate occurrence was confirmed by a recent article showing that, among long-term participants in population surveys, disease prevalence rates tend to be slightly lower than for the total baseline population, suggesting that subjects who continue to participate in a study are healthier than those who quit [60].

A strength of our population-based study is to have applied, over an eighteen-year follow-up, the same study design, sampling frame and study protocol in repeated cross-sectional surveys on general population samples living in the same area. Moreover, a general population sample spanning from early adulthood to late adulthood (elderly people) was analyzed, with a vast amount of individual qualitative and quantitative data.

Finally, our findings are consistent with those from other international studies, adding new evidences about changes in risk factor exposure and lifetime habits associated with symptom/disease onset in a general population sample.

5. Conclusion

In conclusion, our study showed noteworthy values of new onset of respiratory symptoms/diseases in a general population sample living in Central Italy, in line with other European studies. Furthermore, it indicated that changes in lifestyle and in environmental exposure can differently influence symptom/disease onset: changes in occupational and traffic exposure were mainly related to AR/asthma incidence and changes in smoking habits and occupational exposure were mainly related to COPD incidence.

This information could be useful for primary prevention strategies in order to reduce the burden of chronic diseases in the general population.

Table 5

Comparison of respiratory disease incidence rates between different studies.

	Reference	Country	Population (sample size and baseline age)	Follow-up period	Incidence rate (cases/1000/year)
Asthma diagnosis	Torén et al., 2004 [41]	5 Northern Europe countries	no. = 14731 20–44 yrs	1989–1999 10 yrs	2.2
	Ekerlung et al., 2008 [11]	Sweden	no. = 4479 20–69 yrs	1996–2006 10 yrs	3.9
	Torén et al., 2011 [12]	Western Sweden	no. = 18087 16–75 yrs	1990–2008 18 yrs	1.4
	Pallasaho et al., 2011 [38]	Finland	no. = 4302 20–69 yrs	1996–2007 11 yrs	3.7
	Gallmeier et al., 2014 [42]	Germany	no. = 924 21–47 yrs	1990–2010 20 yrs	3.1
	Traulsen et al., 2018 [24]	Denmark	no. = 742 20–44 yrs	2003–2012 9 yrs	5.8
	Maio et al.	Italy	no. = 970 20–78 yrs	1991–2009 18 yrs	1.7
Allergic rhinitis	Matheson et al., 2011 [44]	22 European countries	no. = 8486 20–44 yrs	1991–2000 ~9 yrs	7.0–8.0
	Gallmeier et al., 2014 [42]	Germany	no. = 924 21–47 yrs	1990–2010 20 yrs	4.4
	Burte et al., 2018 [16]	6 European countries	no. = 1533 age mean $\pm$ SD: 43.4 $\pm$ 8.9 yrs	2000–2011 11 yrs	23.4
	Maio et al.	Italy	no. = 970 20–78 yrs	1991–2009 18 yrs	21.0
COPD or CB	Afonso et al., 2011 [45]	the Netherlands	no. = 185325 ≥ 40 yrs	2000–2007 mean follow-up 3.4 yrs	2.9
	Holm et al., 2012 [46]	5 Northern Europe countries	no. = 15919 fw-up age mean $\pm$ SD: 39.8 $\pm$ 7.3 yrs	1989–1999 10 yrs	1.9
	Holm et al., 2014 [20]	Western Sweden	no. = 11407 20–50 yrs	1993–2003 10 yrs	0.9
	Maio et al.	Italy	no. = 970 20–78 yrs	1991–2009 18 yrs	3.2
AO _{LLN}	Luoto et al., 2016 [48]	Sweden	no. = 984 60–95 yrs	2001–2007 ~6 yrs	11.7
	Terzikhan et al., 2016 [47]	the Netherlands	no. = 14619 age mean $\pm$ SD: 65.8 $\pm$ 10.4 yrs	1989–2014 median fw-up 10.7 yrs	8.9
	Lytras et al., 2018 [23]	12 European countries	no. = 3343 20–44 yrs	1991–2010 20 yrs	1.4
	Traulsen et al., 2018 [24]	Denmark	no. = 742 20–44 yrs	2003–2012 9 yrs	3.5
	Maio et al.	Italy	no. = 417 20–78 yrs	1991–2009 18 yrs	8.3

SD: standard deviation; COPD: Chronic Obstructive Pulmonary Disease; CB: chronic bronchitis; AO_{LLN}: Airway obstruction computed according to the lower limit of normal.

Authors' contributions

Conception and design and acquisition of data: SM, SB, LC, FP, MS, AA, GV; Analysis and interpretation of data: SM, SB, SLG, VM, GV; drafting the manuscript for important intellectual concepts: SM, SB, SLG, GV; final approval: SM, SB, LC, FP, MS, AA, SLG, VM, GV.

Declaration of competing interest

“18-yr cumulative incidence of respiratory/allergic symptoms/diseases and risk factors in the Pisa epidemiological study” by Sara Maio, Sandra Baldacci, Laura Carrozzi, Francesco Pistelli, Marzia Simoni, Anna Angino, Stefania La Grutta, Vito Muggeo, Giovanni Viegi.

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

These analyses were performed within the PhD Doctorate course in Economical, Statistical, Psychological and Sociological Sciences of University of Palermo, Italy (cycle XXXI).

This work was supported in part by the CNR-ENEL (Italian Electric Power Authority) ‘Interaction of Energy Systems with Human Health and Environment’ Project (1989), by the Italian National Research Council Targeted Project ‘Prevention and Control Disease Factors-SP 2’ (Contract No. 91.00171.PF41; 1991), by the Italian Ministry of Labour and Social Security (Contract No. 587–1997; 1997), by the Italian Medicines Agency (AIFA), within the independent drug research program (Contract No. FARM8YRYZC; 2010), by the European Commission (Grant Agreement 2005121 - IMCA II) and by the National Institute for the Insurance of Occupational Injuries (INAIL) in the framework of the Call on Research and Collaboration 2016–2018 (project No 04/2016: BEEP).

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.rmed.2019.09.013>.

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