

SUPPLEMENTARY INFORMATION

Incidence trends of airflow obstruction among European adults without asthma: a 20-year cohort study

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Internally-derived LLN equations

At each examination, pre-bronchodilator FEV₁/FVC values (corrected for the change in spirometer according to Bridevaux and colleagues [reference 41 in the manuscript]) were included in the LLN computations if obtained from normal putative subjects aged 25-64, who had provided valid lung function measurements during at least two consecutive examinations. Normal individuals were those who had reported none of the following conditions at the time of the measurement:

- chronic cough or phlegm;
- asthma-like symptoms [wheezing, nocturnal shortness of breath, shortness of breath at rest, shortness of breath following strenuous activities, nocturnal chest tightness] in the previous 12 months;
- use of medicines for breathing problems (in the ECRHS I-II-III and SAPALDIA I) or use of medicines for asthma (in the SAPALDIA II-III) in the previous 12 months;
- asthma (with or without a physician diagnosis) during a lifetime;
- smoking during lifetime.

Accordingly, 1,218 and 1,496 FEV₁/FVC values from 635 and 786 normal men and women in ECRHS, and 1,038 and 1,238 FEV₁/FVC values from 481 and 621 normal men and women in SAPALDIA were selected, respectively.

Three-level linear regression models (measurement: level 1 unit; subject: level 2 unit; centre: level 3 unit) were used to calculate the LLN equations separately for males and females in the ECRHS and SAPALDIA studies. The models had random intercept terms at levels 2 and 3, a random slope for age at level 2, an unstructured variance-covariance matrix of the random effects at level 2, a 1st order autoregressive error at level 1, and examination (1st, 2nd or 3rd measurement), the age × examination interaction term and height as fixed effects. Age was included as

a fixed effect in the model for males in ECRHS because the variance of the random slope was negligible. The LLN equations were computed as follows:

$$\text{LLN}(\text{examination}, \text{age}, \text{height}) = \text{FEV}_1/\text{FVC}^{\text{hat}} - z\text{-score}_{0.05} \cdot \sqrt{[\sigma_{(1)}^2 + \sigma_{(2)}^2 + \sigma_{(3)}^2]}$$

where:

- $\text{FEV}_1/\text{FVC}^{\text{hat}} = b_0 + b_1 \cdot \text{examination} + b_2 \cdot \text{age} + b_3 \cdot \text{age} \cdot \text{examination} + b_4 \cdot \text{height}$ is the predicted FEV₁/FVC obtained from the fixed part intercept (b_0 , b_1) and slope coefficients (b_2 - b_4 ; age is the age of a subject at a given examination and height is the height of a subject at the 2nd examination);
- $z\text{-score}_{0.05}$ is the 5th percentile of the z-score of FEV₁/FVC;
- $\sigma_{(1)}^2 = \sigma_{\text{residual}}^2 / (1 - \rho^2)$ is the variance at level 1 ($\sigma_{\text{residual}}^2$ is the residual variance and ρ is the 1st order autocorrelation coefficient);
- $\sigma_{(2)}^2 = \sigma_{\text{intercept}}^2 + \sigma_{\text{slope}}^2 \cdot \text{age}^2 + 2 \cdot \sigma_{\text{intercept, slope}} \cdot \text{age}$ is the variance at level 2 ($\sigma_{\text{intercept}}^2$, σ_{slope}^2 and $\sigma_{\text{intercept, slope}}$ are the components of the variance-covariance matrix of the random effects at level 2; $\sigma_{\text{slope}}^2 = \sigma_{\text{intercept, slope}} = 0$ for males in ECRHS);
- $\sigma_{(3)}^2$ is the variance at level 3.

The estimates of the fixed and random parameters were obtained using the restricted maximum likelihood (REML) method.

Year of age at AO onset

For each new case, the year of age at AO onset (t_{AO}) was estimated by linear interpolation as follows:

- FEV₁/FVC was obtained for each year of age (t) between the year of age at the last examination with normal spirometry (t_1) and the year of age at the subsequent examination with AO (t_2) assuming a linear decrease:

$$FEV_1/FVC(t) = FEV_1/FVC(t_1) + [FEV_1/FVC(t_2) - FEV_1/FVC(t_1)] \cdot [(t - t_1) / (t_2 - t_1)];$$

- LLN was obtained for each year of age (t) between t_1 and t_2 assuming a linear decrease:

$$LLN(t) = LLN(t_1) + [LLN(t_2) - LLN(t_1)] \cdot [(t - t_1) / (t_2 - t_1)];$$

- t_{AO} was the first year of age between t_1 and t_2 with $FEV_1/FVC(t_{AO}) < LLN(t_{AO})$.

As a result of the interpolation process, the incident cases were aged 26 or older.

Reshaped datasets

When computing the IRs of AO, we used a reshaped dataset by age (“long” format) for each sex. The “original” dataset, which contains one record for each subject, was reshaped by replicating each individual record in as many records as the number of age years from the subject’s first participation in ECRHS or SAPALDIA (or from age 25 if his/her age at the first study was <25) to the end of follow-up (or to age 64 if his/her age at the end of follow-up was >64). The end of follow-up was the calendar year of AO onset for the incident cases, and the calendar year of the last examination for the remaining subjects. The “new” record of a subject at a given age contained the subject’s age and health indicator at that age (i.e. the dummy variable indicating if he/she was an incident case at that age). Therefore, a subject contributed one person-year to the denominator of the IR for each age year without AO, and one unit to the numerator and one person-year to the denominator of the IR for the age year when he/she developed AO. When estimating the trends in AO incidence as a function of lifetime pack-years among ever smokers, reshaping was carried out by pack-years instead.

Stability of AO

We evaluated how many incident cases of AO at ECRHS/SAPALDIA II had one of the following conditions at ECRHS/SAPALDIA III:

- pre-bronchodilator $FEV_1/FVC < LLN$;
- pre-bronchodilator $FEV_1/FVC \geq LLN$ AND ever smoking (≥ 10 pack-years) AND key respiratory symptoms for COPD (chronic cough, chronic sputum production, dyspnoea, shortness of breath following strenuous activity in the last 12 months);
- pre-bronchodilator $FEV_1/FVC \geq LLN$ AND self-reported diagnosis of chronic bronchitis, emphysema or COPD;
- pre-bronchodilator $FEV_1/FVC \geq LLN$ AND father and/or mother with a diagnosis of chronic bronchitis, emphysema or COPD.

Among the incident cases of AO at the 2nd examination, the subjects who had fulfilled at least one of these conditions at the 3rd examination were: 57/93 (61.3%) males and 44/66 (66.7%) females.

Table S1. Brand of the spirometers* used by study, centre and examination.

Study	Country	Centre	1 st examination	2 nd examination	3 rd examination
ECRHS	Belgium	Antwerp City	SensorMedics (D)	Jaeger Masterscope	NDD EasyOne
		Antwerp South	SensorMedics (D)	Jaeger Masterscope	NDD EasyOne
	Estonia	Tartu	Jaeger Masterscope	Jaeger Masterscope	NDD EasyOne
	France	Bordeaux	Vitalograph	Vitalograph	NDD EasyOne
		Grenoble	Biomedin	Biomedin	NDD EasyOne
		Montpellier	Biomedin	Biomedin	NDD EasyOne
		Paris	Biomedin	Biomedin	NDD EasyOne
	Germany	Erfurt	Jaeger Masterscope	Jaeger Masterscope	NDD EasyOne
		Hamburg	Jaeger Masterscope	Jaeger Masterscope	NDD EasyOne
	Iceland	Reykjavik	SensorMedics (D)	SensorMedics (D)	NDD EasyOne
	Italy	Pavia	Biomedin	Biomedin	NDD EasyOne
		Turin	Biomedin	Biomedin	Biomedin
		Verona	Biomedin	Biomedin	Biomedin
	Norway	Bergen	SensorMedics (D)	SensorMedics (D)	NDD EasyOne
	Spain	Albacete	Biomedin	Biomedin	NDD EasyOne
		Barcelona	Biomedin	Biomedin	NDD EasyOne
		Galdakao	Biomedin	Biomedin	NDD EasyOne
		Huelva	Biomedin	Biomedin	NDD EasyOne
		Oviedo	Biomedin	Biomedin	NDD EasyOne
	Sweden	Gothenburg	SensorMedics (D)	SensorMedics (D)	NDD EasyOne
		Umea	SensorMedics (D)	SensorMedics (D)	NDD EasyOne
		Uppsala	SensorMedics (D)	SensorMedics (D)	NDD EasyOne
	United Kingdom	Ipswich	Biomedin	Biomedin	NDD EasyOne
		Norwich	Biomedin	Biomedin	NDD EasyOne
SAPALDIA	Switzerland	Aarau	SensorMedics (H)	SensorMedics (H)	NDD EasyOne
		Basel [†]	SensorMedics (H)	SensorMedics (H)	NDD EasyOne
		Davos	SensorMedics (H)	SensorMedics (H)	NDD EasyOne
		Geneva	SensorMedics (H)	SensorMedics (H)	NDD EasyOne
		Lugano	SensorMedics (H)	SensorMedics (H)	NDD EasyOne
		Montana	SensorMedics (H)	SensorMedics (H)	NDD EasyOne
		Payerne	SensorMedics (H)	SensorMedics (H)	NDD EasyOne
		Wald	SensorMedics (H)	SensorMedics (H)	NDD EasyOne

* SensorMedics (D) is a volume-displacement spirometer and SensorMedics (H) is a heated-wire spirometer.

[†] The subjects from Basel participating in ECRHS, who were also recruited for SAPALDIA, were considered as part of SAPALDIA throughout the present analysis.

Table S2. Selection of the subjects at risk for AO by study and centre.

Study	Country	Centre	Males			Females		
			Participants*	Eligible subjects†	Subjects at risk for AO‡	Participants*	Eligible subjects†	Subjects at risk for AO‡
ECRHS	Belgium	Antwerp City	156	118	58	195	153	68
		Antwerp South	179	157	88	174	142	91
	Estonia	Tartu	73	44	5	117	86	18
	France	Bordeaux	166	115	26	166	124	30
		Grenoble	217	189	109	201	186	106
		Montpellier	197	166	58	209	173	46
		Paris	259	204	91	301	247	106
	Germany	Erfurt	282	234	87	286	261	80
		Hamburg	397	335	80	407	357	87
	Iceland	Reykjavik	228	215	159	240	214	128
	Italy	Pavia	142	119	70	122	99	58
		Turin	95	82	38	94	76	32
		Verona	134	126	66	135	119	57
		Norway	Bergen	343	311	195	338	307
	Spain	Albacete	141	135	58	176	166	67
		Barcelona	107	82	27	120	78	36
		Galdakao	175	150	89	156	127	73
		Huelva	104	101	60	103	90	54
		Oviedo	120	99	56	125	104	49
	Sweden	Gothenburg	242	212	91	263	234	97
		Umea	201	178	105	212	189	94
		Uppsala	224	161	88	215	159	79
	United Kingdom	Ipswich	163	144	72	194	168	78
		Norwich	136	114	52	201	161	74
				4,481	3,791	1,828	4,750	4,020
SAPALDIA	Switzerland	Aarau	326	283	196	327	295	207
		Basel†	376	337	157	371	330	160
		Davos	201	165	106	243	215	131
		Geneva	274	234	106	255	227	100
		Lugano	253	223	140	336	316	199
		Montana	200	170	119	199	186	125
		Payerne	359	316	151	397	359	198
		Wald	408	381	273	423	393	284
					2,397	2,109	1,248	2,551
TOTAL			6,878	5,900	3,076	7,301	6,341	3,192

* Subjects aged ≥ 25 years at the ECRHS - stage 2 or SAPALDIA I (baseline), who were born in 1945 or later.

† Subjects who had valid lung function measurements at baseline and who reported never having been diagnosed with asthma at baseline.

‡ Subjects who had pre-bronchodilator $FEV_1/FVC \geq LLN$ at baseline, who participated and had valid lung function measurements at ECRHS/SAPALDIA I-II or ECRHS/SAPALDIA I-II-III, and who reported not having been diagnosed with asthma at the follow-up.

Table S3. Main characteristics of the subjects at risk for AO by study.

	Males		Females	
	ECRHS	SAPALDIA	ECRHS	SAPALDIA
N° of subjects	1,828	1,248	1,788	1,404
Age at baseline (years), mean (range)	35 (25-48)	36 (25-46)	35 (25-47)	36 (25-46)
Subjects who participated and had valid lung function measurements at all examinations, %	52.3	70.0	56.0	66.3
Duration of the follow-up (years)*, mean (range)	14 (1-20)	16 (1-20)	14 (1-20)	16 (1-20)
Ever smokers at baseline and/or follow-up, %	67.3	63.9	58.2	54.4
N° of lifetime pack-years among ever smokers, median (IQR)	19 (9-32)	22 (9-36)	11 (4-21)	13 (5-26)
Pre-bronchodilator FEV ₁ /FVC(%), mean $\pm$ s.d.				
1 st examination (baseline)	79.7 $\pm$ 4.8	80.0 $\pm$ 5.5	83.7 $\pm$ 5.0	82.6 $\pm$ 5.4
2 nd examination	78.1 $\pm$ 5.2	76.1 $\pm$ 5.9	79.8 $\pm$ 5.4	77.4 $\pm$ 5.8
3 rd examination	76.6 $\pm$ 5.4	73.6 $\pm$ 5.4	76.9 $\pm$ 5.2	75.5 $\pm$ 5.1

IQR: interquartile range; s.d.: standard deviation.

* The end of the follow-up was the estimated calendar year of AO onset for the incident cases and the calendar year of the last examination for the remaining subjects.

Table S4. Main characteristics of the eligible subjects* included or excluded from the analyses (ECRHS study).

	Males		Females	
	Included [†]	Excluded [‡]	Included [†]	Excluded [‡]
N° of subjects	2,079	1,712	2,147	1,873
Age at baseline (years), mean (range)	35 (25-48)	35 (25-47)	35 (25-47)	35 (25-47)
Ever smokers at baseline and/or follow-up, %	67.6	69.7	58.8	61.1
N° of lifetime pack-years among ever smokers, median (IQR)	19 (9-32)	15 (7-25)	11 (4-21)	10 (4-18)
Pre-bronchodilator FEV ₁ /FVC(%) at the 1 st examination (baseline), mean ± s.d.	78.5 ± 6.0	78.5 ± 6.5	82.5 ± 6.2	83.1 ± 6.2

IQR: interquartile range; s.d.: standard deviation.

* Subjects who had valid lung function measurements and reported never having been diagnosed with asthma at the ECRHS I - stage 2 (baseline).

[†] Eligible subjects who participated in ECRHS II or ECRHS II-III, and who had valid lung function measurements and reported information on asthma at the follow-up.

[‡] Eligible subjects who did not participate in ECRHS II-III, or who did not have valid lung function measurements or did not report information on asthma at the follow-up.

Table S5. Main characteristics of the eligible subjects* included or excluded from the analyses (SAPALDIA study).

	Males		Females	
	Included [†]	Excluded [‡]	Included [†]	Excluded [‡]
N° of subjects	1,385	724	1,587	734
Age at baseline (years), mean (range)	36 (25-46)	36 (25-46)	36 (25-46)	36 (25-46)
Ever smokers at baseline and/or follow-up, %	64.1	72.6	55.6	64.4
N° of lifetime pack-years among ever smokers, median (IQR)	21 (9-35)	19 (9-32)	13 (5-26)	14 (7-22)
Pre-bronchodilator FEV ₁ /FVC(%) at the 1 st examination (baseline), mean $\pm$ s.d.	79.0 $\pm$ 6.7	79.3 $\pm$ 7.0	81.7 $\pm$ 6.4	81.6 $\pm$ 6.9

IQR: interquartile range; s.d.: standard deviation.

* Subjects who had valid lung function measurements and reported never having been diagnosed with asthma at SAPALDIA I (baseline).

[†] Eligible subjects who participated in SAPALDIA II or SAPALDIA II-III, and who had valid lung function measurements and reported information on asthma at the follow-up.

[‡] Eligible subjects who did not participate in SAPALDIA II-III, or who did not have valid lung function measurements or did not report information on asthma at the follow-up.

Table S6. Incidence of AO by study.

	Males				Females			
	ECRHS	SAPALDIA	p-value	Pooled cohorts	ECRHS	SAPALDIA	p-value	Pooled cohorts
Overall incidence rate								
N° of incident cases	124	84	-	208	98	96	-	194
person-years at risk	25,358	20,178	-	45,536	25,816	22,319	-	48,135
cases/1,000/year (95%CI)	4.6 (3.5-5.8)	4.1 (2.7-5.5)	0.56	4.4 (3.5-5.3)	3.7 (2.8-4.5)	4.1 (2.8-5.3)	0.60	3.8 (3.1-4.6)
Incidence rate among never smokers								
N° of incident cases	23	16	-	39	28	33	-	61
person-years at risk	8,499	7,595	-	16,094	11,005	10,446	-	21,451
cases/1,000/year (95%CI)	2.5 (1.4-3.7)	2.1 (0.9-3.3)	0.59	2.3 (1.5-3.2)	2.5 (1.5-3.4)	2.9 (1.7-4.1)	0.55	2.7 (1.9-3.4)
Incidence rate among ever smokers								
N° of incident cases	100	68	-	168	70	63	-	133
person-years at risk	16,785	12,583	-	29,368	14,784	11,873	-	26,657
cases/1,000/year (95%CI)	5.6 (4.2-7.1)	5.3 (3.4-7.1)	0.72	5.5 (4.3-6.6)	4.6 (3.3-5.8)	5.0 (3.4-6.7)	0.82	4.8 (3.8-5.8)

APPENDIX

ECRHS STUDY

ECRHS I

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