SUPPLEMENTARY MATERIAL

Manuscript title

Airway responsiveness to methacholine and incidence of COPD: an international prospective cohort study

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METHODS

Definition of COPD based on the GOLD clinical criteria

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines for the diagnosis, management and prevention of COPD identify a set of key indicators for considering a diagnosis of COPD, which includes a history of symptoms, a history of exposure to air pollution, a family history of COPD and early life risk factors (1). According to the guidelines an individual older than 40 years of age with any of key indicators should be diagnosed as COPD if spirometry confirms the presence of persistent airflow limitation.

For sensitivity analysis we repeated the main analysis using a definition of COPD based on the GOLD clinical criteria (labelled $COPD_{clinical}$). Incidence of $COPD_{clinical}$ was defined as a combination of a post-BD FEV_1/FVC <lower limit of normal (LLN) (2) at the 3rd examination with at least one of:

a) **history of symptoms**: either shortness of breath after strenuous activity in the last 12 months; or dyspnoea (trouble with breathing); or chronic cough, or chronic sputum production (usual cough or phlegm on most days for as long as 3 months during winter);

b) **history of air pollution exposures**: either having smoked ⩾10 pack-years (3,4); or reporting occupational exposures to vapours, dust, gas or fumes over lifetime;

c) **family history of COPD and/or childhood risk factors:** either reporting that biological parents ever had chronic bronchitis, emphysema, or COPD (the latter was only available in ECRHS); or reporting a serious respiratory infection within 5 years of age.

As in the main analysis, we excluded subjects with a pre-BD FEV_1/FVC <LLN (2) at the 2nd examination.

Alternative indicator of airway responsiveness in ECRHS

The method originally used to calculate the methacholine dose-response slope was different between ECRHS and SAPALDIA.

In ECRHS the "least-squares" slope was developed by Chinn et al to account for systematic differences in the dose delivered by different Mefar nebulizers (5). It was calculated by regressing percentage fall in FEV_1 on $\log_{10}$ dose using all FEV_1 measurements (except post-saline FEV_1) and then reciprocally transformed (100 / [DRS + 10]) (5). For the sake of consistency across the centres, only the doses of methacholine up to 1 mg were considered to derive the slope.

In SAPALDIA, the "two-point" method by O'Connor et al. was used (6,7). To improve consistency between studies (as described in the manuscript), we calculated the two-point slope also for ECRHS and conducted a pooled analysis. Unlike the least-squares slope, the two-point slope does not require mathematical transformations and is therefore easier to interpret.

For sensitivity analysis we repeated the main analysis using the transformed least-squares slope as an alternative indicator of responsiveness. This analysis was carried out only for the ECRHS cohort and, unlike the main analysis, it included all ECRHS centres (regardless of the maximum cumulative dose of methacholine reached). The results of this analysis are reported in Table E4.

TABLES

Table E1: Brands of the spirometers used by study and centre.*

Study	Country	Centre	1st examination	2nd examination	3rd examination
ECRHS	Belgium	Antwerp South	SensorMedics (D)	Jaeger Masterscope	NDD Easyone
		Antwerp City	SensorMedics (D)	Jaeger Masterscope	NDD Easyone
	Germany	Erfurt	Jaeger Masterscope	Jaeger Masterscope	NDD Easyone
	Spain	Galdakao	Biomedin	Biomedin	NDD Easyone
	France	Bordeaux	Vitalograph	Vitalograph	NDD Easyone
		Grenoble	Biomedin	Biomedin	NDD Easyone
		Montpellier	Biomedin	Biomedin	NDD Easyone
		Paris	Biomedin	Biomedin	NDD Easyone
	Italy	Pavia	Biomedin	Biomedin	NDD Easyone
		Turin**	Biomedin	Biomedin	Biomedin
		Verona**	Biomedin	Biomedin	Biomedin
	Iceland	Reykjavik	SensorMedics (D)	SensorMedics (D)	NDD Easyone
	Norway	Bergen	SensorMedics (D)	SensorMedics (D)	NDD Easyone
	Sweden	Gothenburg	SensorMedics (D)	SensorMedics (D)	NDD Easyone
		Umea	SensorMedics (D)	SensorMedics (D)	NDD Easyone
		Uppsala	SensorMedics (D)	SensorMedics (D)	NDD Easyone
	Australia	Melbourne	Fleish	SensorMedics (D)	NDD Easyone
SAPALDIA	Switzerland	Basel***	SensorMedics (H)	SensorMedics (H)	NDD Easyone
		Wald	SensorMedics (H)	SensorMedics (H)	NDD Easyone
		Davos	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
		Aarau	SensorMedics (H)	SensorMedics (H)	NDD Easyone
		Geneva	SensorMedics (H)	SensorMedics (H)	NDD Easyone

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

** Turin and Verona were not included in the analysis of COPD incidence because post-BD spirometry was not carried out

*** Subjects from Basel aged 20–44 in 1991 participating in ECRHS (n=854), who were also part of the larger sample recruited for SAPALDIA (n=1111, age 18–60), are considered as part of SAPALDIA throughout the analyses

Table E2. Multiple regression coefficients with 95% CIs for the association between increasing airway responsiveness and decline in FEV_1.*

	Slope group, by quintiles (% × μmol^{-1})	ΔFEV_1 (mL/year)	p_{int}***	ΔFEV_1% (%/year)	p_{int}***
Overall (n=4200)	<0.44	0	-	0	-
	0.44–0.73	-0.1 (-2.5, 2.4)		0.01 (-0.06, 0.08)	
	0.74–1.12	-1.5 (-4.0, 1.0)		-0.01 (-0.08, 0.06)	
	1.13–1.84	0.4 (-2.1, 2.9)		0.08 (0.01, 0.15)	
	≥1.84	-1.0 (-3.6, 1.6)		0.08 (0.01, 0.16)	
Non-smoker (n=1880)	<0.44	0	0.53	0	0.29
	0.44–0.73	1.7 (-2.0, 5.3)		0.07 (-0.04, 0.17)	
	0.74–1.12	-1.1 (-4.8, 2.6)		-0.01 (-0.11, 0.10)	
	1.13–1.84	-0.3 (-4.0, 3.5)		0.05 (-0.06, 0.16)	
	≥1.84	-1.5 (-5.3, 2.3)		0.05 (-0.06, 0.16)	
Smoker** (n=2187)	<0.44	0		0	
	0.44–0.73	-1.0 (-4.5, 2.6)		-0.01 (-0.11, 0.09)	
	0.74–1.12	-1.5 (-5.0, 2.2)		-0.00 (-0.10, 0.10)	
	1.13–1.84	1.7 (-1.8, 5.3)		0.12 (0.02, 0.22)	
	≥1.84	0.7 (-3.0, 4.4)		0.15 (0.04, 0.25)	
No asthma (n=3223)	<0.44	0	0.56	0	0.55
	0.44–0.73	0.0 (-2.7, 2.7)		0.02 (-0.05, 0.10)	
	0.74–1.12	-0.9 (-3.6, 1.8)		0.01 (-0.07, 0.08)	
	1.13–1.84	1.2 (-1.6, 3.9)		0.10 (0.02, 0.18)	
	≥1.84	-0.7 (-3.7, 2.3)		0.08 (-0.00, 0.16)	
Asthma (n=977)	<0.44	0		0	
	0.44–0.73	0.2 (-6.3, 6.6)		-0.02 (-0.21, 0.17)	
	0.74–1.12	-3.4 (-9.6, 2.7)		-0.07 (-0.25, 0.11)	
	1.13–1.84	-2.9 (-8.9, 3.1)		-0.03 (-0.21, 0.15)	
	≥1.84	-1.7(-7.1, 3.6)		-0.03 (-0.09, 0.23)	

* regression coefficients represent the mean difference between groups of subjects with increasing airway responsiveness and the reference category. Adjusted for study, sex, education, FEV_1 predicted, age, BMI, BMI^2, ΔBMI, history of asthma/asthma-like symptoms (when applicable), history of active smoking (when applicable), second-hand smoking, and occupational exposures to vapours, gas, dusts or fumes.

** also adjusted for lifetime pack-years (data not available for 133 subjects)

*** p-values for the interactions between slope group and stratification variable

Table E3: Incidence rate ratios (IRRs) with 95% CIs for the association between increasing airway responsiveness and the development of $COPD_{LLN}$, stratified by study.*

	ECRHS	SAPALDIA	
Slope group, by quintiles (% × μmol^{-1})	IRR (95% CIs)	IRR (95% CIs)	p_{int}**
No. of subjects	1638	2099	
<0.44	1.0	1.0	
0.44–0.73	1.80 (0.32, 10.16)	1.65 (0.25, 10.92)	
0.74–1.12	2.90 (0.58, 14.58)	4.02 (1.15, 18.05)	0.27
1.13–1.84	3.96 (1.06, 14.80)	9.39 (1.47, 34.78)	
≥1.84	7.49 (2.27, 24.69)	9.95 (2.45, 40.41)	

* Adjusted for sex, education, FEV_1 predicted, age, BMI, history of asthma/asthma-like symptoms, history of active smoking, second-hand smoking, and occupational exposures to vapours, gas, dusts or fumes

** p-value for the interaction between slope group and study

Table E4: Incidence rate ratios (IRRs) with 95% CIs for the association between increasing airway responsiveness and the development of $COPD_{LLN}$: sensitivity analyses on the airway responsiveness indicator.*

Mean two-point slope between the 1st and 2nd examinations (% × μmol^{-1})		Transformed least-squares slope at the 1st examination (log_{10}(mg) × %$^{-1}$)**	
Group, by quartiles	IRR (95% CIs)	Group, by quintiles	IRR (95% CIs)
No. of subjects	3041		2199
<0.56	1	≥9.3	1
0.56–0.90	5.01 (0.95, 26.34)	8.4–9.2	1.33 (0.43, 4.18)
0.91–1.49	10.17 (2.96, 34.88)	7.6–8.3	2.80 (1.00, 7.89)
≥1.50	16.70 (4.14, 67.42)	6.2–7.5	3.00 (1.16, 7.77)
		<6.2	4.10 (1.56, 10.80)

* adjusted for study (only analysis on the two-point slope), sex, education, FEV_1 predicted, age, BMI, history of asthma/asthma-like symptoms, history of active smoking, second-hand smoking, and occupational exposures to vapours, gas, dusts or fumes

** decreasing values correspond to increasing airway responsiveness; analysis on the ECRHS cohort alone

Table E5: Incidence rate ratios (IRRs) with 95% CIs for the association between increasing airway responsiveness and the development of $COPD_{LLN}$: sensitivity analysis adjusted for use of inhaled/oral medication for asthma at the 1st examination.

Slope group, by quintiles (% × μmol^{-1})	IRR (95% CIs)*
No. of subjects	851
<0.44	1
0.44–0.73	1.25 (0.19, 8.34)
0.74–1.12	2.02 (0.50, 8.08)
1.13–1.84	5.09 (1.43, 18.07)
≥1.84	3.47 (1.14, 10.53)

* analysis on subjects with asthma/asthma-like symptoms, adjusted for study, sex, education, FEV_1 predicted, age, BMI, history of active smoking, second-hand smoking, occupational exposures to vapours, gas, dusts or fumes, and current use of inhalers, aerosols or tablets for asthma at the 1st examination

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ECRHS III

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