Xª Reunión **Grupo EPOC FEMI**

Madrid, 12-13 marzo 2015

EPOC EN *NO FUMADORES*

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Guión

EPOC NO FUMADORES:

La práctica clínica: un caso

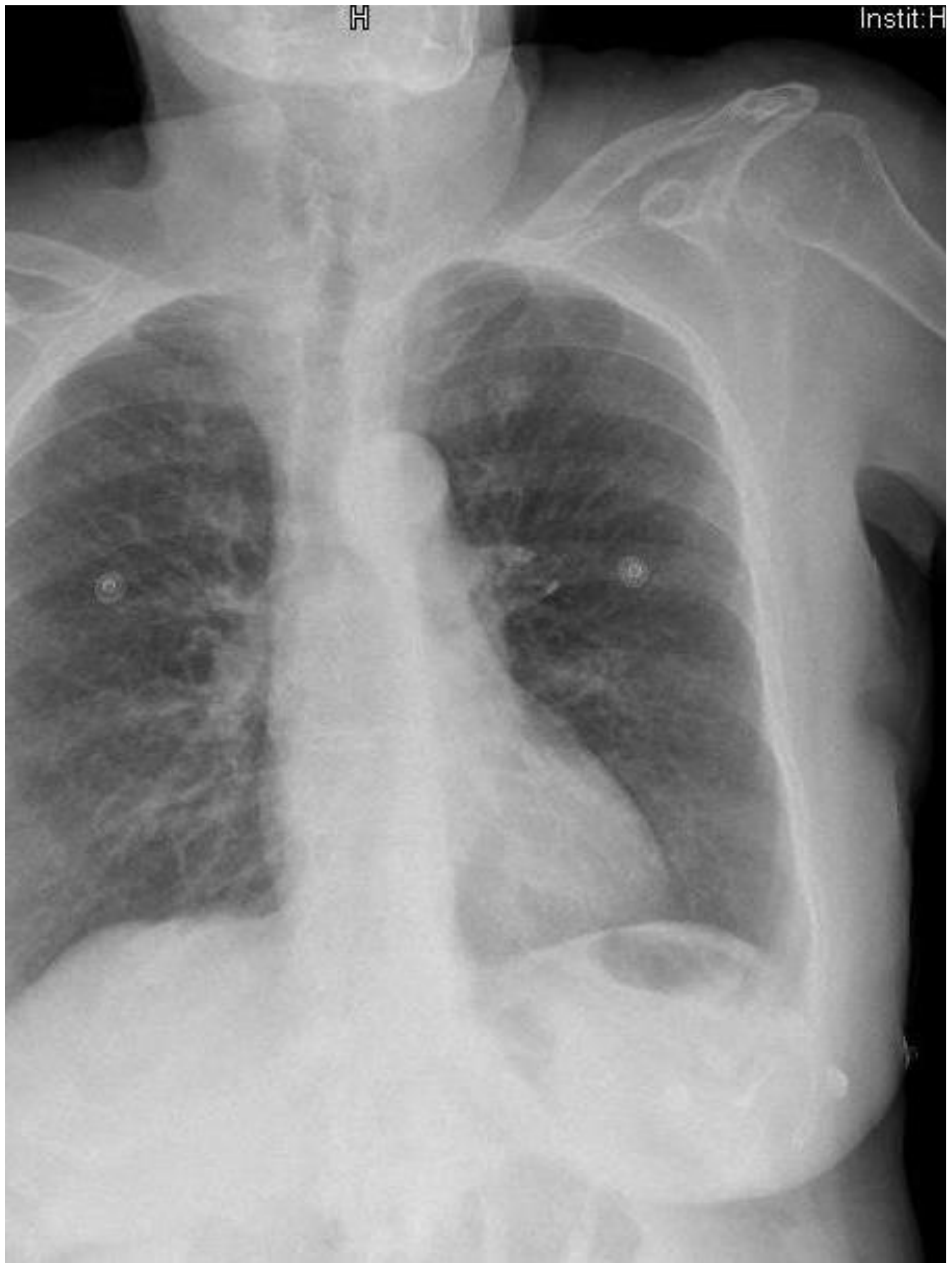
Guías de Práctica Clínica

Epidemiología

Patogenia

Factores de riesgo:
- Endógenos
- Exógenos

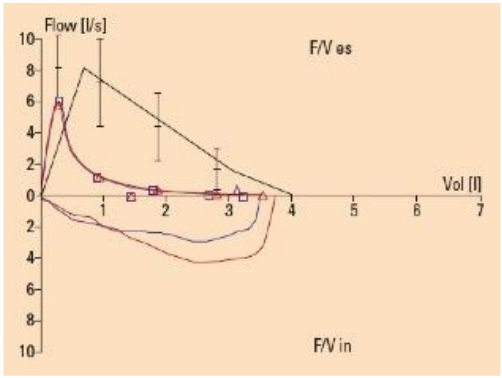
Consideraciones en la práctica



Antonia, de 71 años,

Disnea de grado 3 mMRC

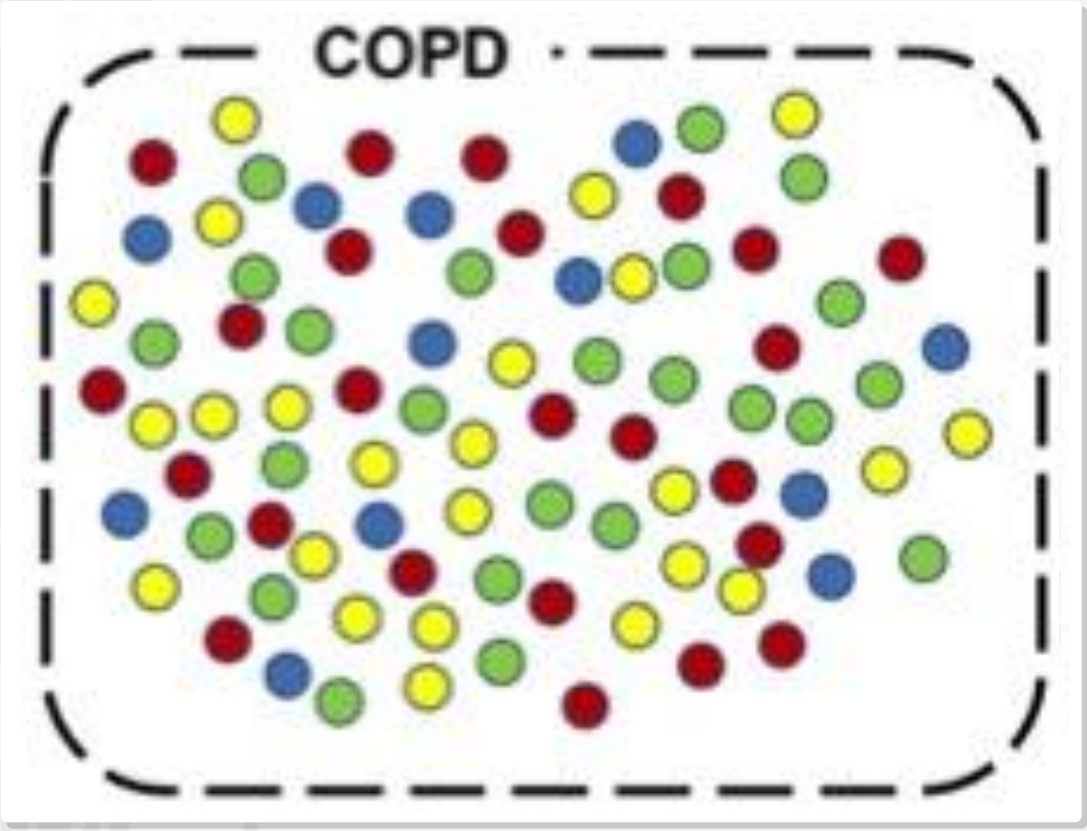
Tos habitual



Antonia puede tener una EPOC
aunque **nunca fumó**

Desenmascarar los otros casos de EPOC
no relacionados con el tabaco

EPOC: síndrome, no solo enfermedad por tabaco



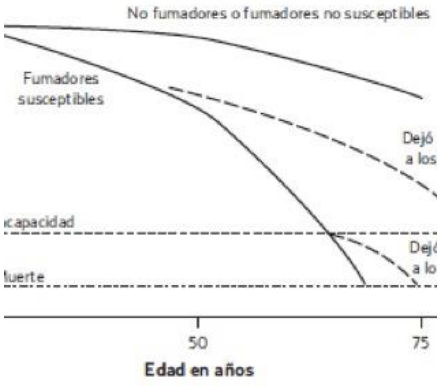
Tomado de Agustí A, Thorax 2014

Los casos de EPOC en no fumadores…

¿pueden tener unas características diferenciadas?

HUMO DE TABACO

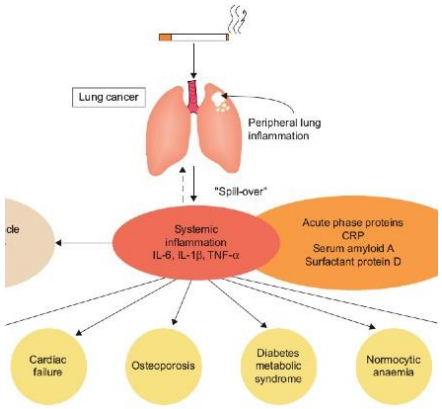
ESPIROMETRÍA



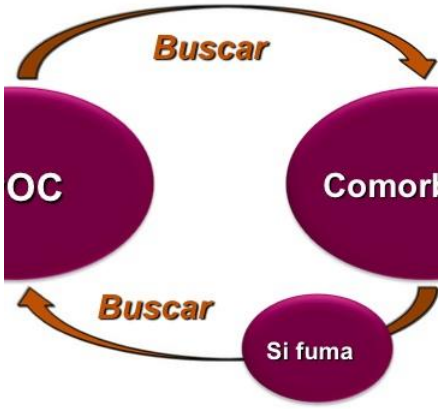
HISTORIA NATURAL

BIOMASA POLUCIÓN PROFESIONAL

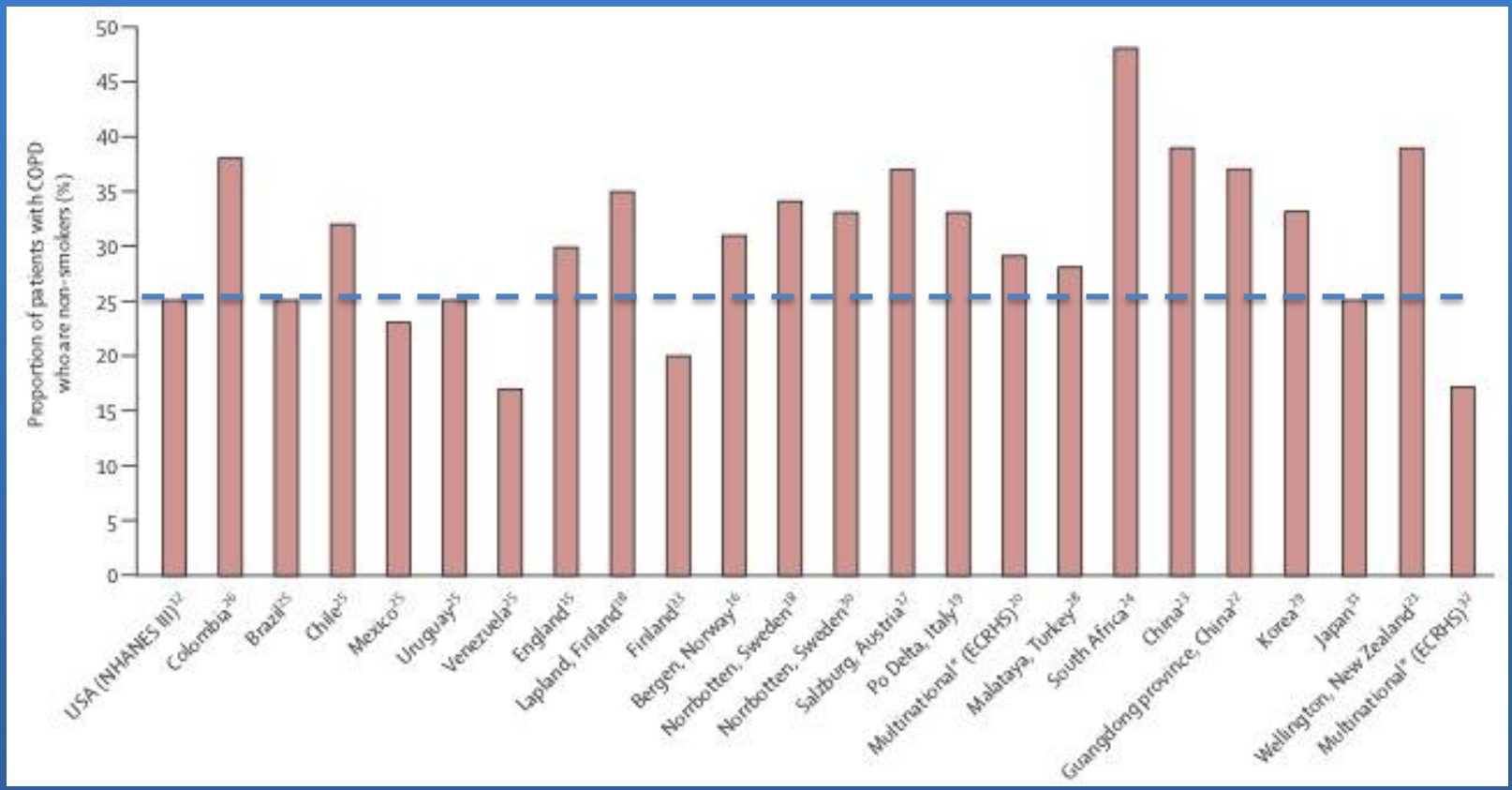
INFLAMACIÓN



COMORBILIDAD



Prevalencia de EPOC NO fumador en diferentes países



Salvi SS, Lancet 2009

PREVALENCIA DE EPOC NO FUMADORES

	País	Prevalencia EPOC	% EPOC No fumadores
Miravitlles, 2009	España	10,2	23,4
Shirtcliffe, 2007	Nueva Zelanda		38,8
Liu, 2007	China	9,4	36,7
Zhou, 2009	China	5,2	38,6
Viegi, 2000	Italia	18,3	33
Menezes, 2005	Brasil	15,8	25
	Chile	16,9	31,8
	Méjico	7,8	23,2
	Uruguay	19,7	25
	Venezuela	12,1	17
Caballero, 2008	Colombia	8,9	30,1
Gunen, 2008	Turquía		27,5
Kim, 2005	Corea	7,8	33
Lindberg, 2005	Suecia	12,2	33

Modificado de Calle M, 2010

¿Qué dicen las guías?

- Humo del tabaco
- Contaminación ambiental:
  - Combustión biomasa
  - Combustión calefacción
  - Polvo y sustancias químicas ocupacionales
  - Contaminación externa
- Factores de desarrollo pulmonar:
  - gestación
  - infancia
- Factores genéticos

GOLD-2013

- Humo de tabaco:activo/pasivo
- Exposición biomasa
- Antecedentes TBC
- Infecciones infancia
- Contaminación: ambiental / laboral
- Déficit alfa1-AT
- Factor genético
- Nivel socioeconómico
- Sexo

SEPAR-ALAT-2011

- Partículas nocivas y gases:
  - humo del tabaco
  - biomasa y calefacción
  - laboral
- Infecciones infancia
- Nivel socioeconómico
- Factores genéticos
- Sexo
- Edad

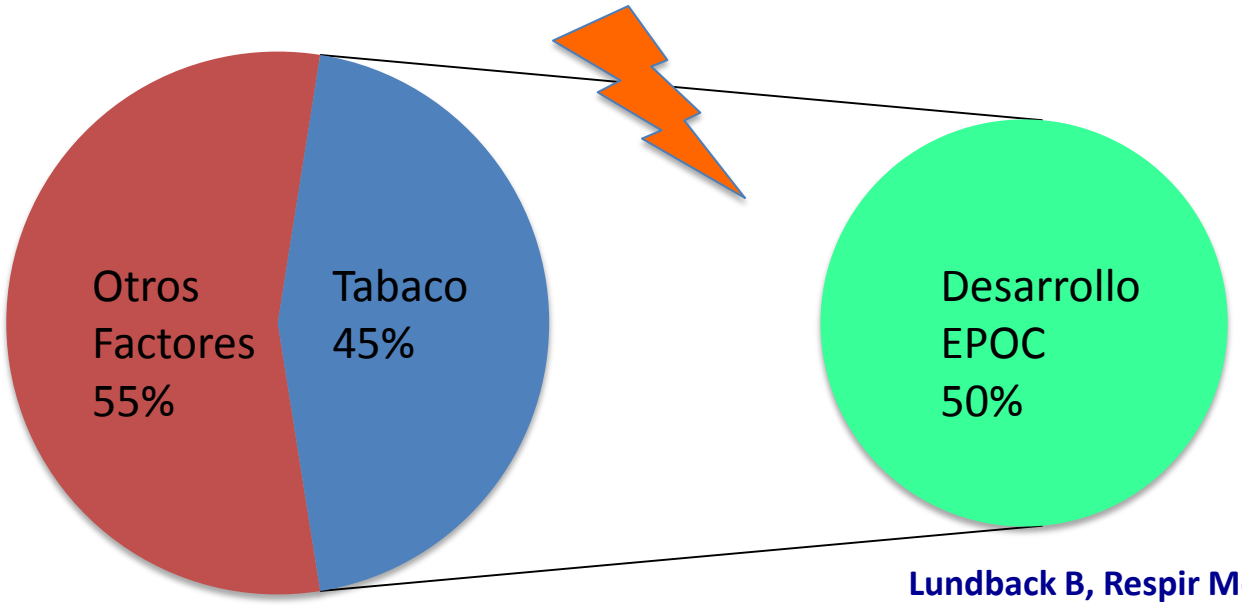
GesEPOC-2012-2014

Las Guías exponen unos factores de riesgo similares:

Humo de tabaco y otros / factores endógenos

Riesgo atribuible de factores y Patogenia de la EPOC

Interacciones con susceptibilidad individual



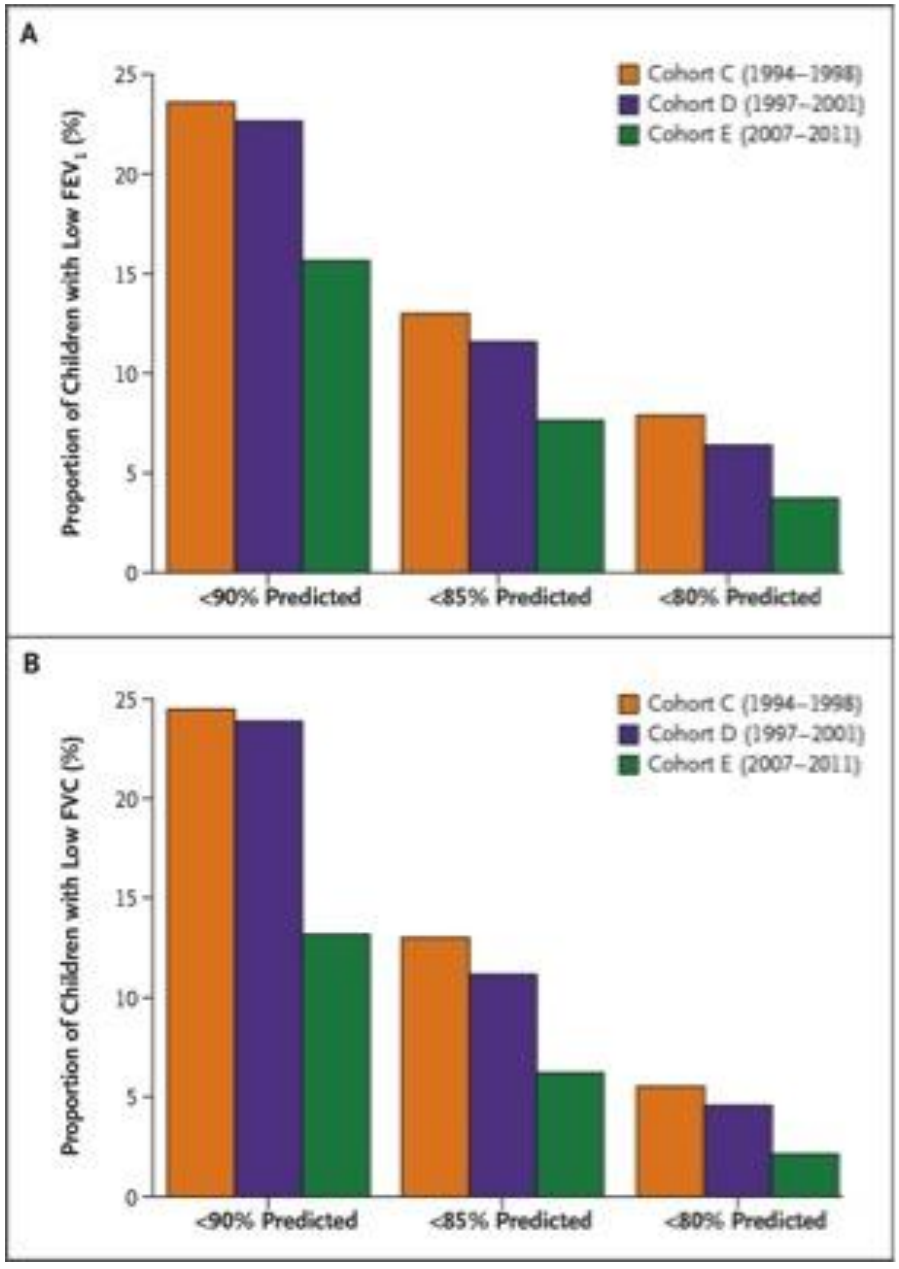
Lundback B, Respir Med 2003
Salvi SS, Lancet 2009

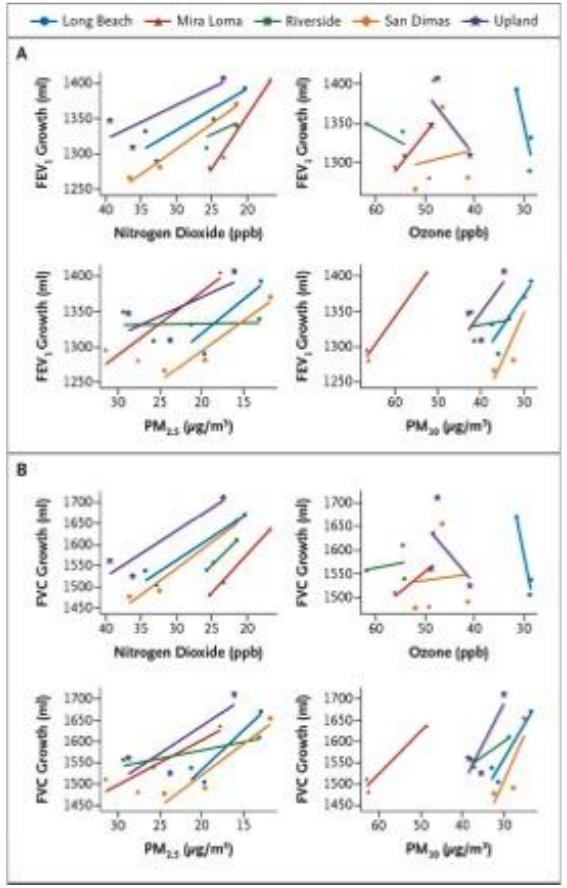
Interacciones entre factores de susceptibilidad individual y factores ambientales para condicionar el desarrollo de EPOC.

Factores de riesgo de EPOC en NO fumadores

Factores ambientales o exógenos	
Polución de ambientes interiores	Inhalación de humo de biomasa: residuos vegetales (madera, carbón vegetal, hierba seca, ramas) y residuos animales (como el estiércol)
Contaminación atmosférica	Partículas sólidas (diámetro ≤ 10 μm) Dióxido de nitrógeno y monóxido de carbono
Exposición ocupacional	Granjas de cultivo: granos de cereal, polvo orgánico e inorgánico Granjas de animales: polvo orgánico, amoníaco Exposición a polvo: minas de carbón y oro, fundición de hierro y acero, construcción, tunelación Exposición química: plástico, tejidos, caucho, goma, manipulación de pieles y productos alimenticios Exposición a contaminantes: reparación de automóviles y transporte
Nivel socioeconómico bajo	
Nivel educacional bajo	
Pobre estado nutricional	
Tuberculosis pulmonar tratada	
Infecciones de las vías respiratorias bajas de repetición en la infancia	
Estilo de vida sedentario	

Calle M, Arch Bronconeumol 2010 (modif)





Gauderman WJ, N Engl J Med 2015.

EPOC NO fumador **ocupacional**

Prevalencia varía: 1,1 – 40%
- Definición EPOC
- Edades de pacientes
- Métodos de estudio

Fracción EPOC atribuible **laboral**:
- 31,1% entre no fumadores
- Estimaciones 20-53%

Profesiones riesgo:
- maquinaria
- construcción
- algodón
- conductores autobús

Bang KM, Curr Opin Pulm Med 2015

Uso de Biomasa

Productos empleados:

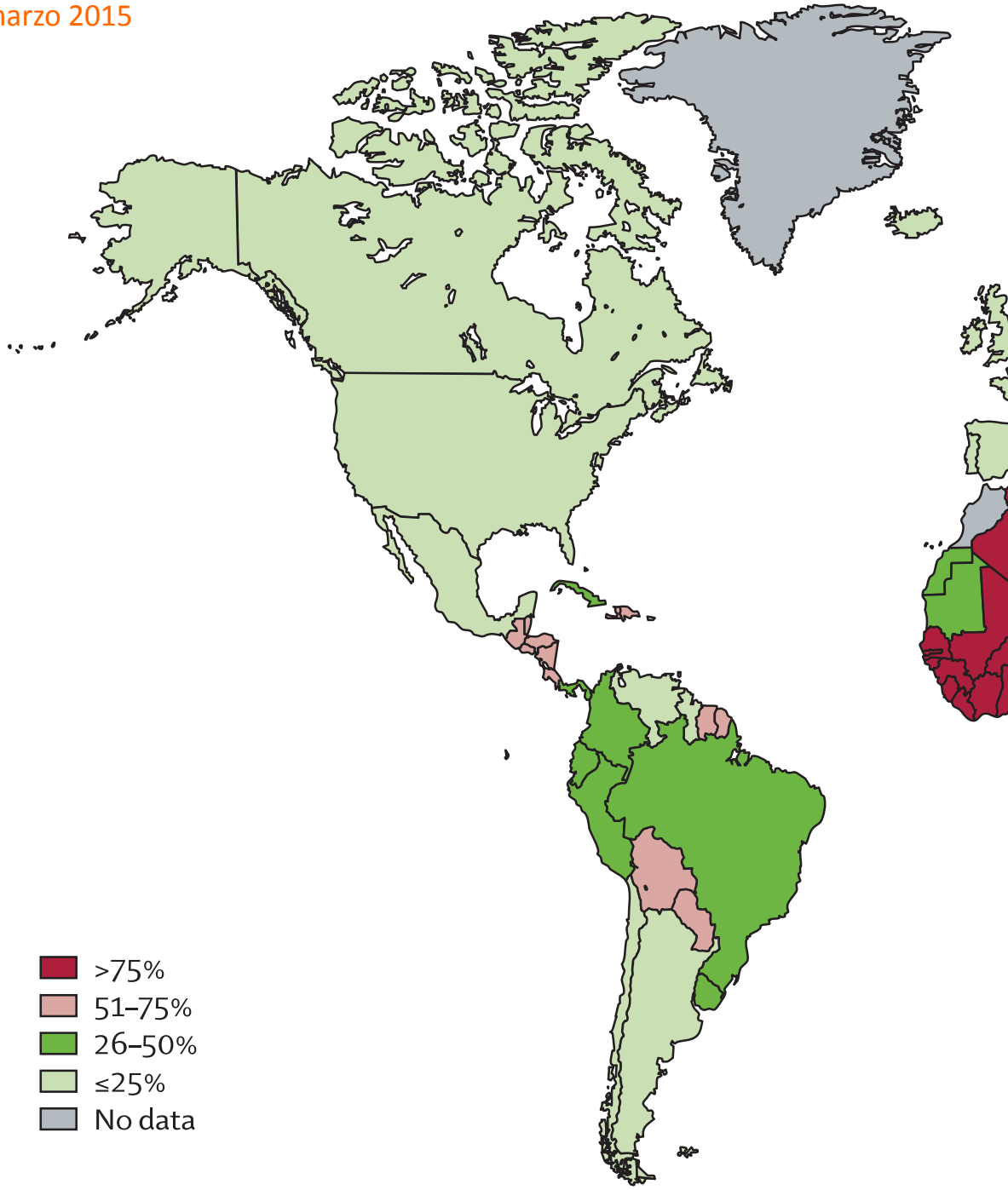
Leña

Hierba seca

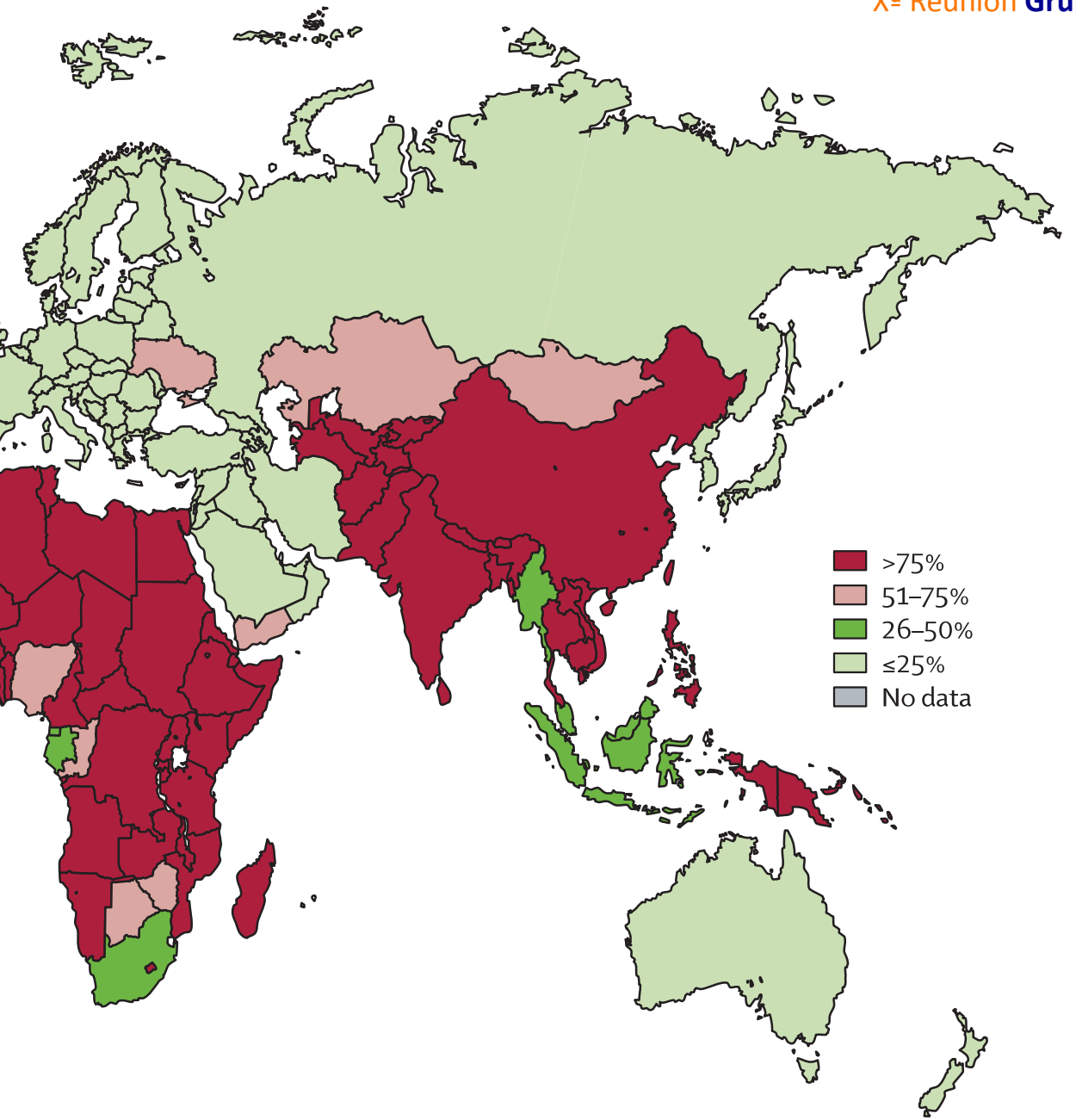
Carbón vegetal

Excrementos

Carbón



Uso de biomasa



Salvi SS, Lancet 2009

Riesgo proporcional: Tabaco vs No tabaco

1 Billón de habitantes
Tabaco

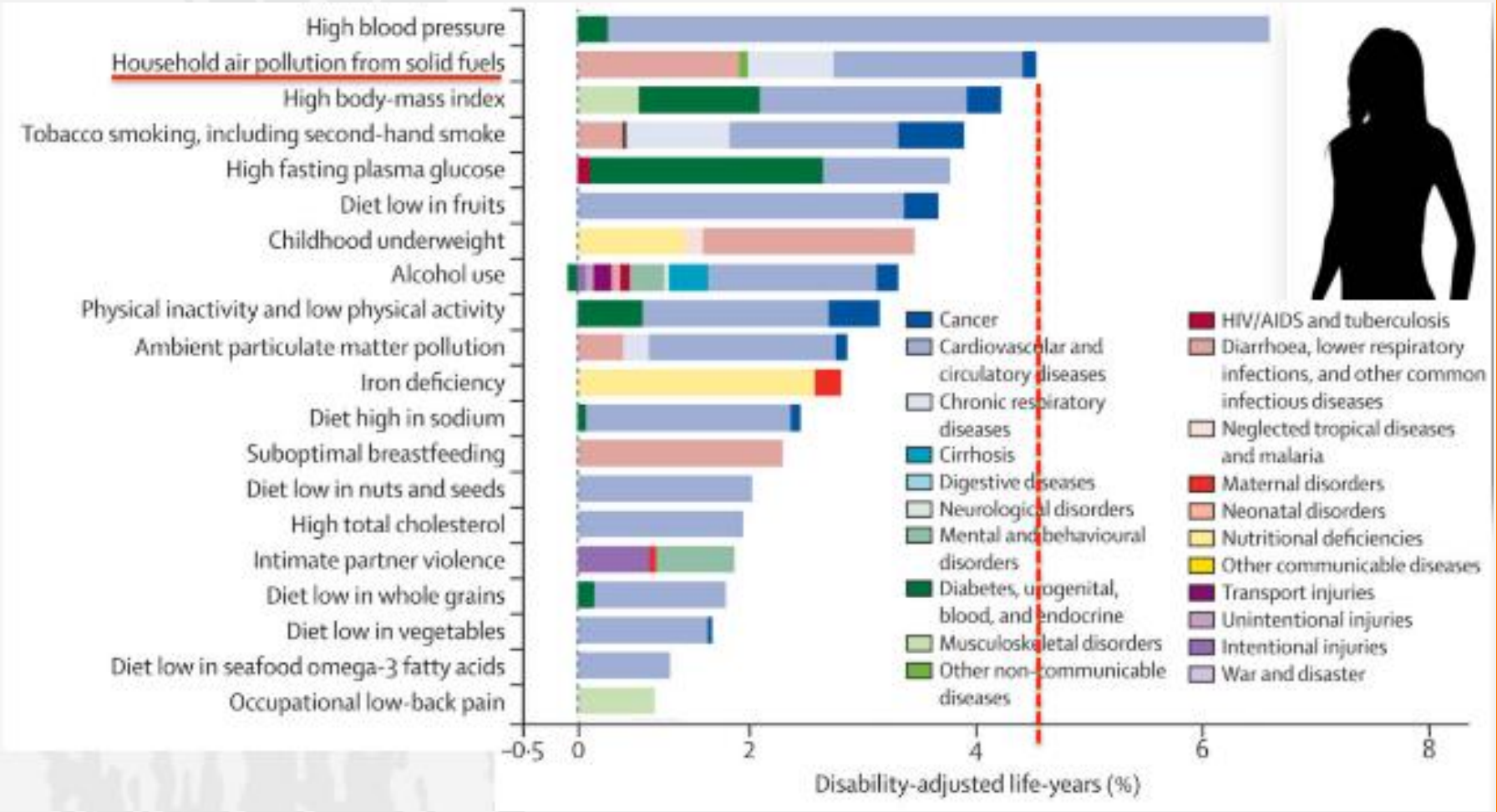
3 Billones de habitantes
No tabaco

	Controls	COPD patients	Univariate logistic regression		Multivariate logistic regression[#]	
			OR (95% CI)	p-value	OR (95% CI)	p-value
Subjects n	60	60				
Wood or charcoal smoke exposure	43 (72)	55 (92)				
Exposure length yrs	11±10	21±18	1.1 (1.0–1.1)	0.003	1.1 (1.0–1.1)[¶]	0.001
Exposure length quartiles						
0–7 yrs	22 (37)	8 (13)	1		1[¶]	
7–15 yrs	12 (20)	16 (27)	3.7 (1.2–11.0)	0.02	3.8 (1.2–12.1)	0.02
15–20 yrs	15 (25)	16 (27)	2.9 (1.0–8.6)	0.05	3.7 (1.2–11.5)	0.02
>20 yrs	11 (18)	20 (33)	5.0 (1.0–14.9)	0.004	6.7 (2.1–21.5)	0.001
Time from exposure yrs	58±10	52±17	0.97 (0.94–1.00)	0.03	0.97 (0.94–1.00)	0.02
Time from exposure in quartiles						
0–49 yrs	11 (18)	17 (28)	1			
50–55 yrs	17 (28)	12 (20)	0.5 (0.2–1.3)	0.15		
56–63 yrs	13 (22)	17 (28)	0.8 (0.3–2.4)	0.76		
>63 yrs	19 (32)	14 (23)	0.5 (0.2–1.3)	0.16		
Exposure intensity in summer h·day^{-1}	6±4	11±7	1.4 (1.2–1.7)	<0.0001		
Exposure intensity in summer in tertiles						
0–6 h·day^{-1}	33 (55)	9 (17)	1		1[¶]	
7–11 h·day^{-1}	23 (38)	18 (34)	2.9 (1.1–7.5)	0.03	2.9 (1.1–7.7)	0.03
12–24 h·day^{-1}	4 (7)	26 (49)	23.8 (6.6–86.2)	0.001	23.3 (6.3–85.7)	0.00
Exposure intensity in winter h·day^{-1}	8±8	15±7	1.1 (1.0–1.2)	0.002		
Exposure intensity in winter in tertiles						
0–6 h·day^{-1}	29 (48)	9 (17)	1		1[¶]	
7–11 h·day^{-1}	18 (30)	11 (21)	2.0 (0.7–5.7)	0.21	1.8 (0.6–5.4)	0.28
12–24 h·day^{-1}	13 (22)	33 (62)	8.2 (3.1–21.9)	0.00	8.1 (3.0–22.3)	0.00
Working as a cook[+]	9 (15)	14 (25)	1.9 (0.7–4.8)	0.18		
Indoor location of kitchen[+]	44 (73)	49 (89)	3.0 (1.1–8.3)	0.04		
Type of exposure						
Not exposed	17 (28)	9 (15)	1		1[§]	
Wood smoke	13 (22)	11 (18)	1.6 (0.5–5.0)	0.42	1.8 (0.6–6.0)	0.33
Charcoal smoke	20 (33)	15 (25)	1.4 (0.5–4.1)	0.52	1.5 (0.5–4.6)	0.48
Wood and charcoal smoke	10 (17)	25 (42)	4.7 (1.6–14.1)	0.01	4.5 (1.4–14.2)	0.01

Data are presented as n (%), unless otherwise indicated. OR: odds ratio; CI: confidence interval. [#]: each line is a single adjusted model; [¶]: adjusted by smoking (since age was highly correlated with yrs of exposure); [+]: five values were missing from "working as a cook" and five from "indoor location of kitchen"; [§]: adjusted by age and smoking.

Orozco-Levi M, Eur Respir J 2006

Oportunidades de prevenir carga mundial de enfermedades



Lim SS. Lancet 2012

Factores de riesgo de EPOC en NO fumadores

Factores endógenos o del hospedador	
Factores genéticos	
Hiperreactividad bronquial	
Asma crónica	
Susceptibilidad autoinmune	
	de carbono
Exposición ocupacional	Granjas de cultivo: granos de cereal, polvo orgánico e inorgánico Granjas de animales: polvo orgánico, amoníaco Exposición a polvo: minas de carbón y oro, fundición de hierro y acero, construcción, tunelación Exposición química: plástico, tejidos, caucho, goma, manipulación de pieles y productos alimenticios Exposición a contaminantes: reparación de automóviles y transporte
Nivel socioeconómico bajo	
Nivel educacional bajo	
Pobre estado nutricional	
Tuberculosis pulmonar tratada	
Infecciones de las vías respiratorias bajas de repetición en la infancia	
Estilo de vida sedentario	

Calle M, Arch Bronconeumol 2010 (modif)

Factores genéticos

Factores genéticos y endógenos

Polimorfismos y mutaciones
- Inhibidores metaloproteinasas
- Alfa 1 antiquimiotripsina
- Glutation-S-transferasa
- Superóxido dismutasa
- Hidrolasa epóxido microsomial
- Hemooxigenasa 1
- Citocromo P4501A1
- TNF-α
- TNF-β
- Interleucina 13

Déficit A1AT

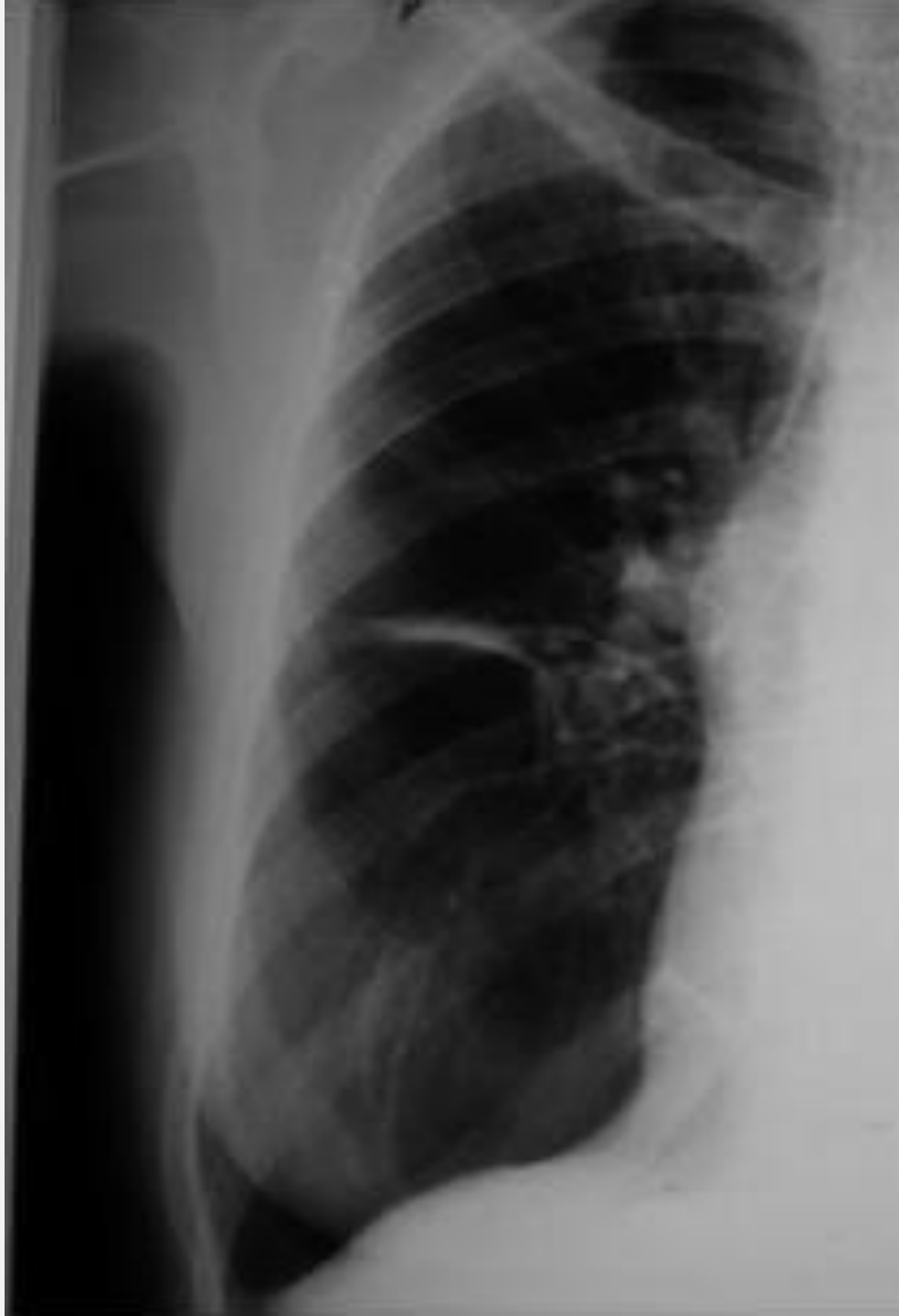
Sexo

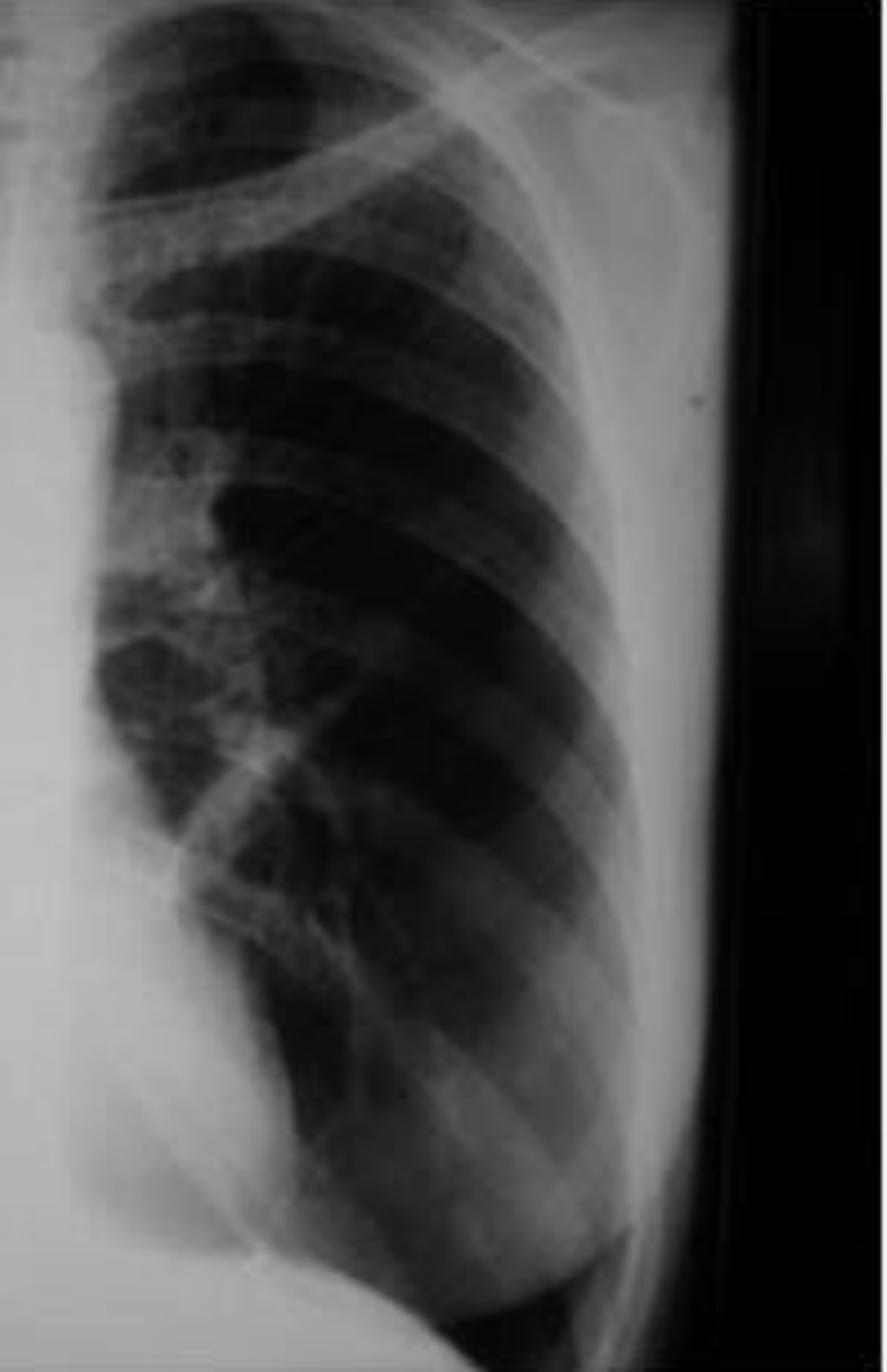
Edad

Hiperreactividad bronquial

Asma bronquial crónica

Calle M, Arch Bronconeumol 2010





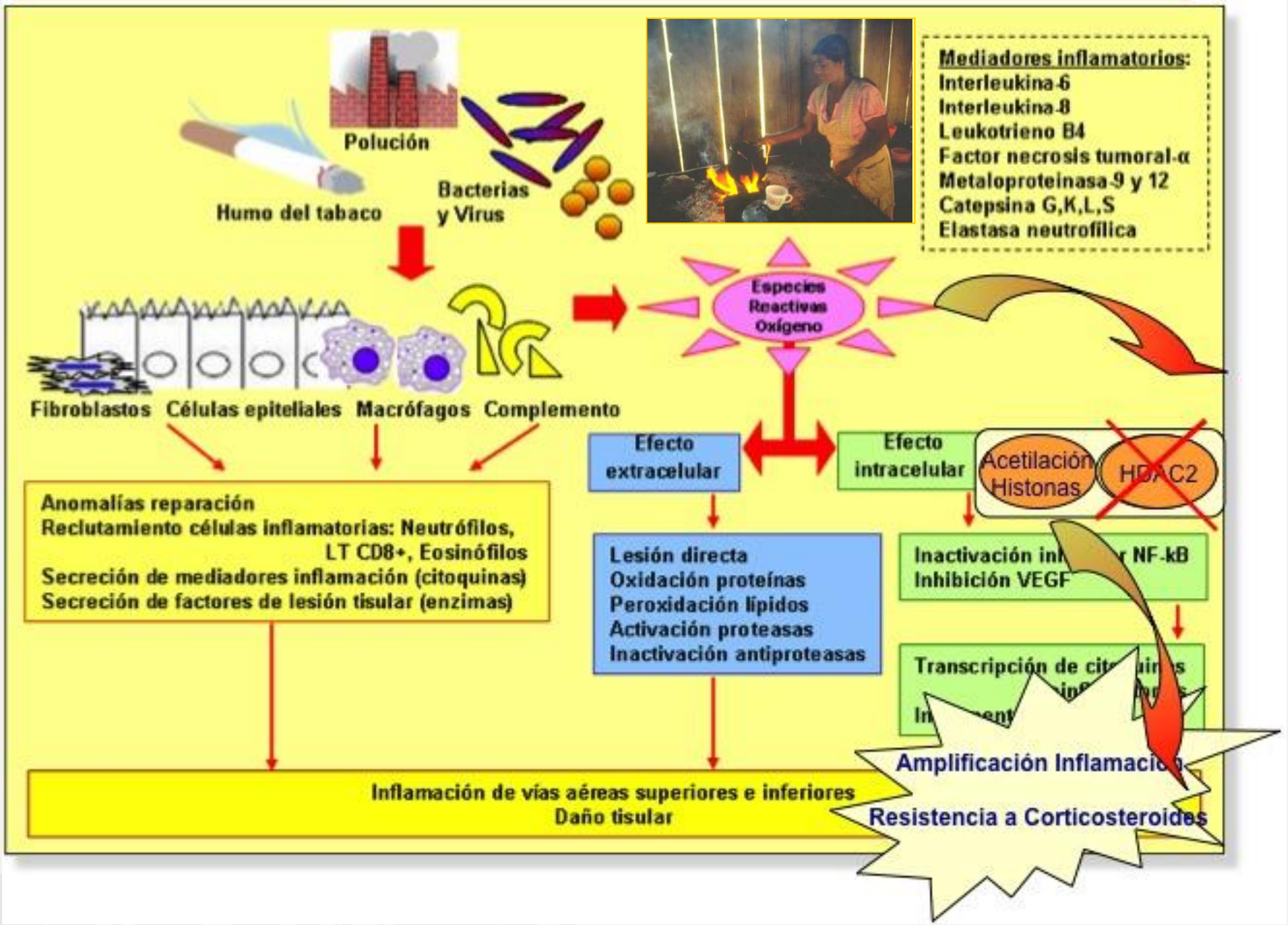
Factores genéticos

Déficit de A1AT, homocigotos ZZ:
En España se estiman 12000,
Diagnosticados 500

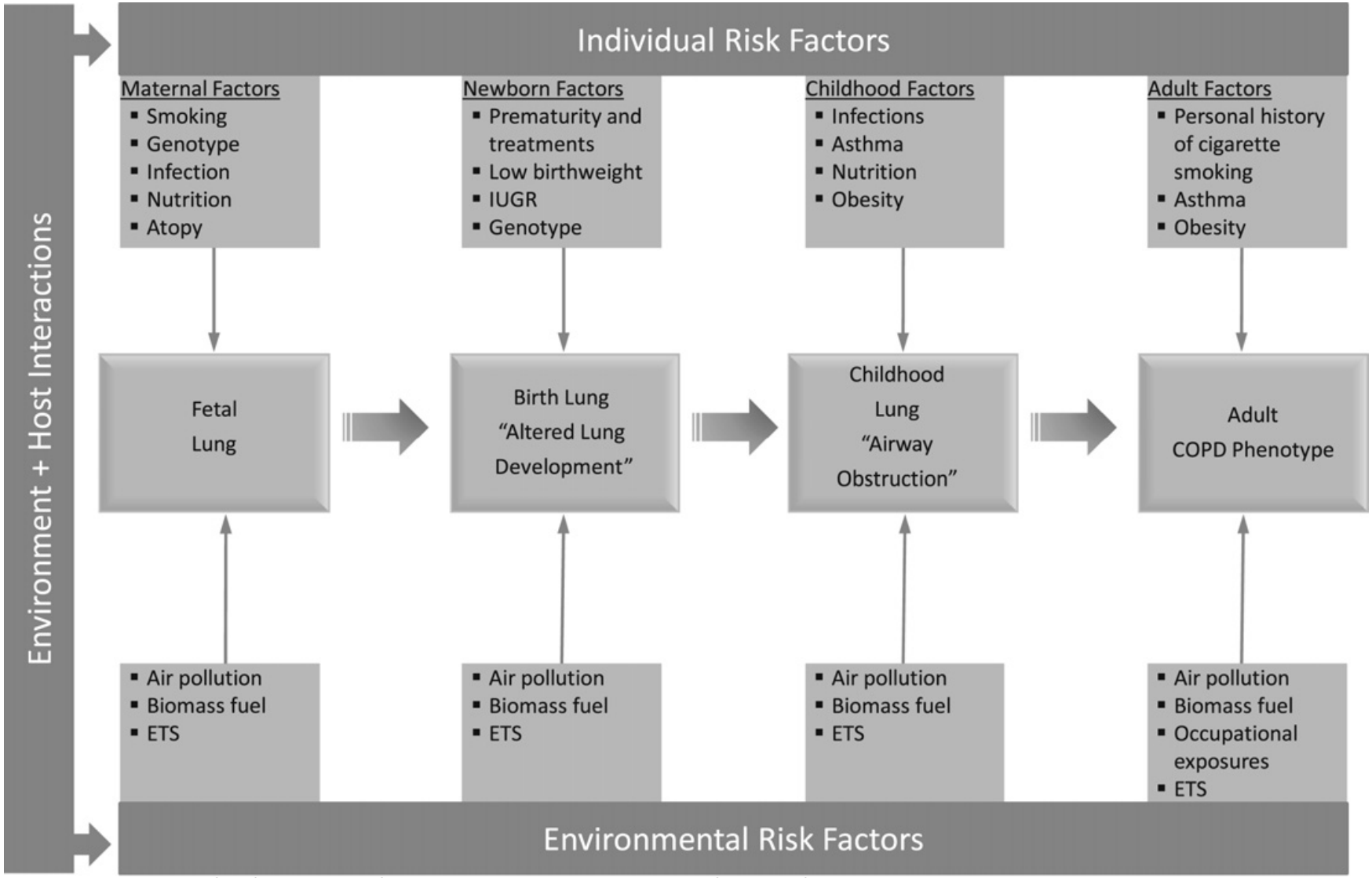
<10% casos graves son diagnosticados

1-2% casos de EPOC

Antón E, Arch Bronconeumol 2007


Polución
Humo del tabaco
Bacterias y Virus
Mediadores inflamatorios:
Interleukina-6
Interleukina-8
Leukotrieno B4
Factor necrosis tumoral-α
Metaloproteinasa-9 y 12
Catepsina G,K,L,S
Elastasa neutrofílica
Especies Reactivas Oxígeno
Fibroblastos
Células epiteliales
Macrófagos
Complemento
Efecto extracelular
Efecto intracelular
Acetilación Histonas
HDAC2
Anomalías reparación
Reclutamiento células inflamatorias: Neutrófilos, LT CD8+, Eosinófilos
Secreción de mediadores inflamación (citoquinas)
Secreción de factores de lesión tisular (enzimas)
Lesión directa
Oxidación proteínas
Peroxidación lípidos
Activación proteasas
Inactivación antiproteasas
Inactivación inh r NF-kB
Inhibición VEGF
Transcripción de cit s
In
Amplificación Inflamac
Inflamación de vías aéreas superiores e inferiores
Daño tisular
Resistencia a Corticosteroides

Patogenia de la EPOC: interacciones de factores



ETS: enviromental tobacco smoke; IUGR: intrauterine growth retardation

Narang I, Seminars in Fetal Neonatal Med 2012

Factores de riesgo de EPOC en NO fumadores

Una combinación que interactúa peligrosamente

DISTRIBUCIÓN FENOTIPOS EN EPOC POR TABACO VS BIOMASA

	BIOMASA (n=122)	TABACO (n=377)	p
Edad (años)	76,2	70,6	<0,0001
Varones	41,8%	91,2%	<0,0001
IMC	29,4	28,0	0,01
GOLD 2	60,6%	38,4%	<0,0001
GOLD 4	3,3%	17,9%	0,0001
BODE 0-2	63,1%	44,3%	0,01
Charlson>1	40,9%	45,1%	0,48
ICC	13,1%	9,8%	0,39
Arteriopatía MMII	1,6%	7,7%	0,03
DM2	18,0%	13,0%	0,22
IRC	4,9%	2,4%	0,27
Tumor sólido	5,7%	8,7%	0,38
Fenotipo Mixto	21,3%	5,0%	<0,0001
Fenotipo enfisema	31,9%	45,9%	0,009

Golpe R, Arch Bronconeumol 2014

American Thoracic Society Documents

An Official American Thoracic Society Public Policy Statement: Novel Risk Factors and the Global Burden of Chronic Obstructive Pulmonary Disease

Mark D. Eisner, Nicholas Anthonisen, David Coultas, Nino Kuenzli, Rogelio Perez-Padilla, Dirkje Postma, Isabelle Romieu, Edwin K. Silverman, and John R. Balmes, on behalf of the Environmental and Occupational Health Assembly Committee on Nonsmoking COPD

THIS OFFICIAL STATEMENT OF THE AMERICAN THORACIC SOCIETY (ATS) WAS APPROVED BY THE ATS BOARD OF DIRECTORS, MARCH 2010

CONTENTS

***Rationale*: Although cigarette smoking is the most important cause of chronic obstructive pulmonary disease (COPD), a substantial proportion of COPD cases cannot be explained by smoking alone.**
***Objectives*: To evaluate the risk factors for COPD besides personal cigarette smoking.**
***Methods*: We constituted an *ad hoc* subcommittee of the American Thoracic Society Environmental and Occupational Health Assembly. An international group of members was invited, based on their scientific expertise in a specific risk factor for COPD. For each risk factor area, the committee reviewed the literature, summarized the evidence, and developed conclusions about the likelihood of it causing COPD. All conclusions were based on unanimous consensus.**
***Measurements and Main Results*: The population-attributable fraction for smoking as a cause of COPD ranged from 9.7 to 97.9%, but was less than 80% in most studies, indicating a substantial burden of disease attributable to nonsmoking risk factors. On the basis of our review, we concluded that specific genetic syndromes and occupational exposures were causally related to the development of COPD. Traffic and other outdoor pollution, secondhand smoke, biomass smoke, and dietary factors are associated with COPD, but sufficient criteria for causation were not met. Chronic asthma and tuberculosis are associated with irreversible loss of lung function, but there remains uncertainty about whether there are important phenotypic differences compared with COPD as it is typically encountered in clinical settings.**
***Conclusions*: In public health terms, a substantive burden of COPD is attributable to risk factors other than smoking. To prevent COPD-related disability and mortality, efforts must focus on prevention and cessation of exposure to smoking and these other, less well-recognized risk factors.**

Keywords: pulmonary disease, chronic obstructive; pulmonary emphysema; chronic bronchitis; respiratory function tests; genetics; diet; asthma; air pollution; air pollution, indoor; tobacco smoke pollution; biomass; occupational exposure; occupational diseases; diet; nutritional status; tuberculosis

EXECUTIVE SUMMARY

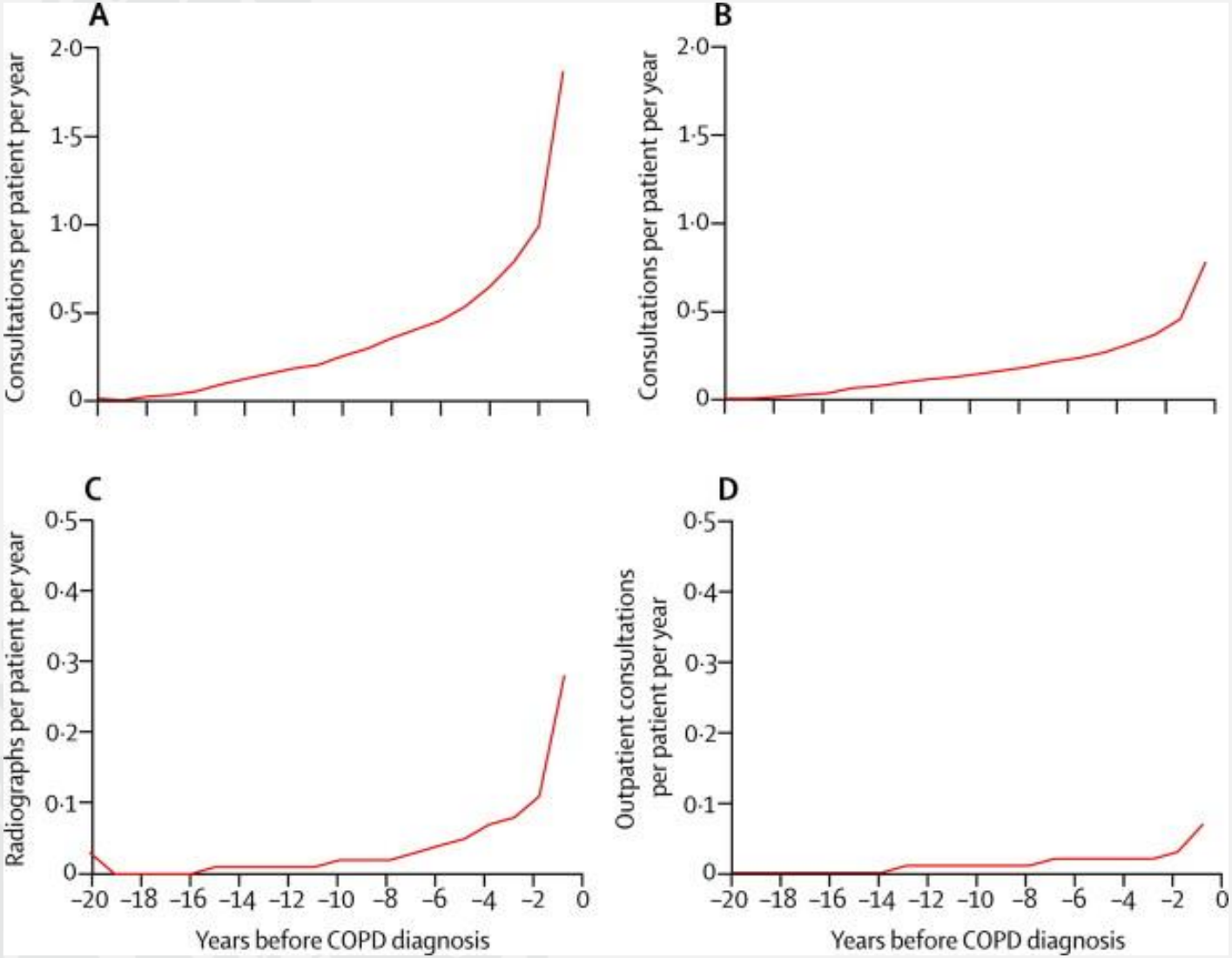
Cigarette smoking is the most important single causal factor for developing chronic obstructive pulmonary disease (COPD). The view that cigarette smoking is the *sole* meaningful factor in the epidemiology and natural history of COPD, however, is a misconception. Our review indicates that a substantial proportion of COPD cases cannot be explained by smoking, especially among younger persons, females, and residents of developing countries. We reviewed the literature to evaluate the impact of novel, less traditional risk factors for COPD. Strong evidence implicates several rare genetic syndromes (such as α_1-antitrypsin deficiency) and occupational exposures as causes of COPD. Traffic and other outdoor pollution, secondhand smoke, biomass smoke, and dietary factors are likely causes of COPD, although the evidence is not sufficient to infer a causal relationship for these risk factors. Chronic asthma and tuberculosis are likely causes of lung function decrement and irreversible airway obstruction. It remains uncertain, however, whether the clinical features and natural history of these diseases, when accompanied by irreversible airway obstruction, are the same as COPD as it is typically encountered in clinical settings. In research terms, further prospective studies with adequate numbers of nonsmokers and rigorous control for confounding variables are needed to establish the causal effects of outdoor pollution, secondhand smoke, biomass smoke, dietary factors, chronic asthma, and tuberculosis on COPD causation. In public health terms, a substantive burden of COPD is attributable to risk factors other than smoking. To prevent COPD-related disability and mortality, efforts must focus on prevention and cessation of exposure to smoking and these other, less well-recognized risk factors.

This document has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

Am J Respir Crit Care Med Vol 182. pp 693–718, 2010
DOI: 10.1164/rccm.200811-1757ST
Internet address: www.atsjournals.org

Oportunidades perdidas de diagnosticar EPOC

Frecuencia media de oportunidades perdidas para diagnosticar la EPOC (N=38.859)



Jones RCM. Lancet Respir Med 2014

Oportunidades perdidas de diagnosticar EPOC

Frecuencia media de oportunidades perdidas para diagnosticar la EPOC (N=38.859)

	0–5 years (n=38 859)	6–10 years (n=22 286)	11–15 years (n=9351)	16–20 years (n=1167)
Lower respiratory consultation	32 900 (85%)	12 856 (58%)	3943 (42%)	95 (8%)
Lower respiratory prescribing consultation	26 472 (68%)	10 627 (48%)	3185 (34%)	31 (3%)
Prescribed oral steroids	15 498 (40%)	3869 (17%)	928 (10%)	1 (<1%)
Prescribed antibiotics	21 364 (55%)	8656 (39%)	2544 (27%)	1 (<1%)
Chest radiography	14 675 (38%)	3366 (15%)	648 (7%)	19 (2%)
Outpatient consultation	4237 (11%)	1645 (7%)	364 (4%)	0 (0%)
Admitted to hospital	881 (2%)	220 (1%)	53 (1%)	3 (<1%)

Data are n (%). Shows the number and proportion of patients who had one or more of each event in each 5-year period.
COPD=chronic obstructive pulmonary disease.

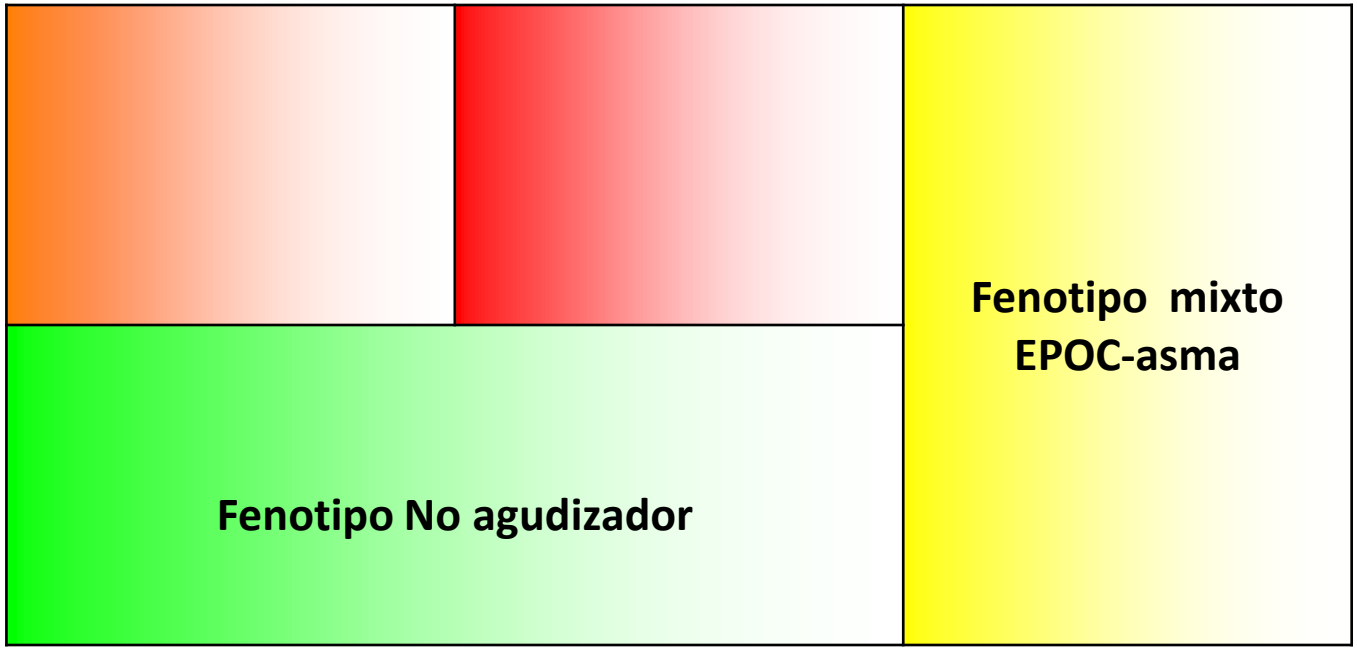
Jones RCM. Lancet Respir Med 2014

FENOTIPOS PROPUESTOS POR GesEPOC

Clasificación de mayoría EPOC NO fumadores

Fenotipo agudizador (≥2 agudizaciones/año)

Fenotipo no agudizador (<2 agudizaciones/año)

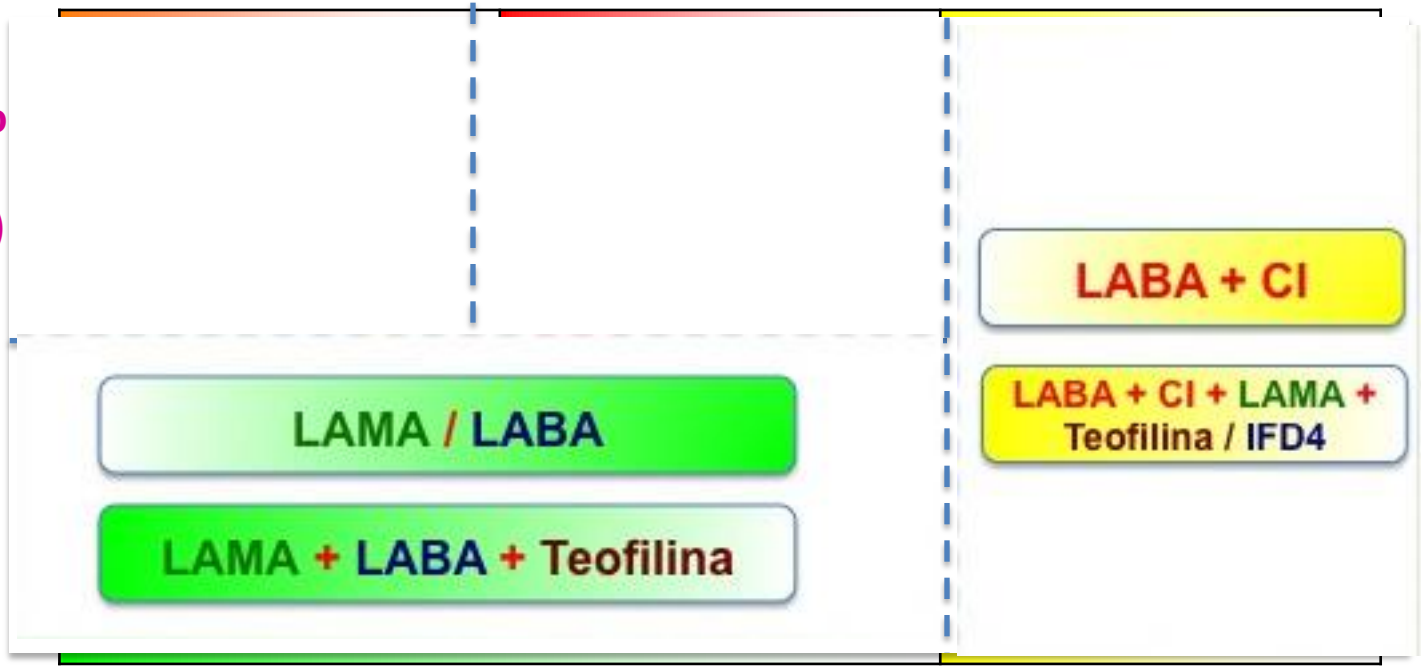


Fenotipo enfisema

Fenotipo Bronquitis crónica

TRATAMIENTO FARMACOLÓGICO DE LA EPOC

Tratamiento de mayoría EPOC NO fumadores



LAMA: antimuscarínico de acción larga
LABA: agonista Beta2 de acción larga
CI: corticoide inhalado
IFD4: Roflumilast

Nunca ha fumado

Mujer anciana

Exposición doméstica

Bajo nivel E-S-E

Hiperreactividad

Tos crónica
Disnea 2-3

Amplía tu mente: puedes tener delante a un paciente EPOC

Gracias