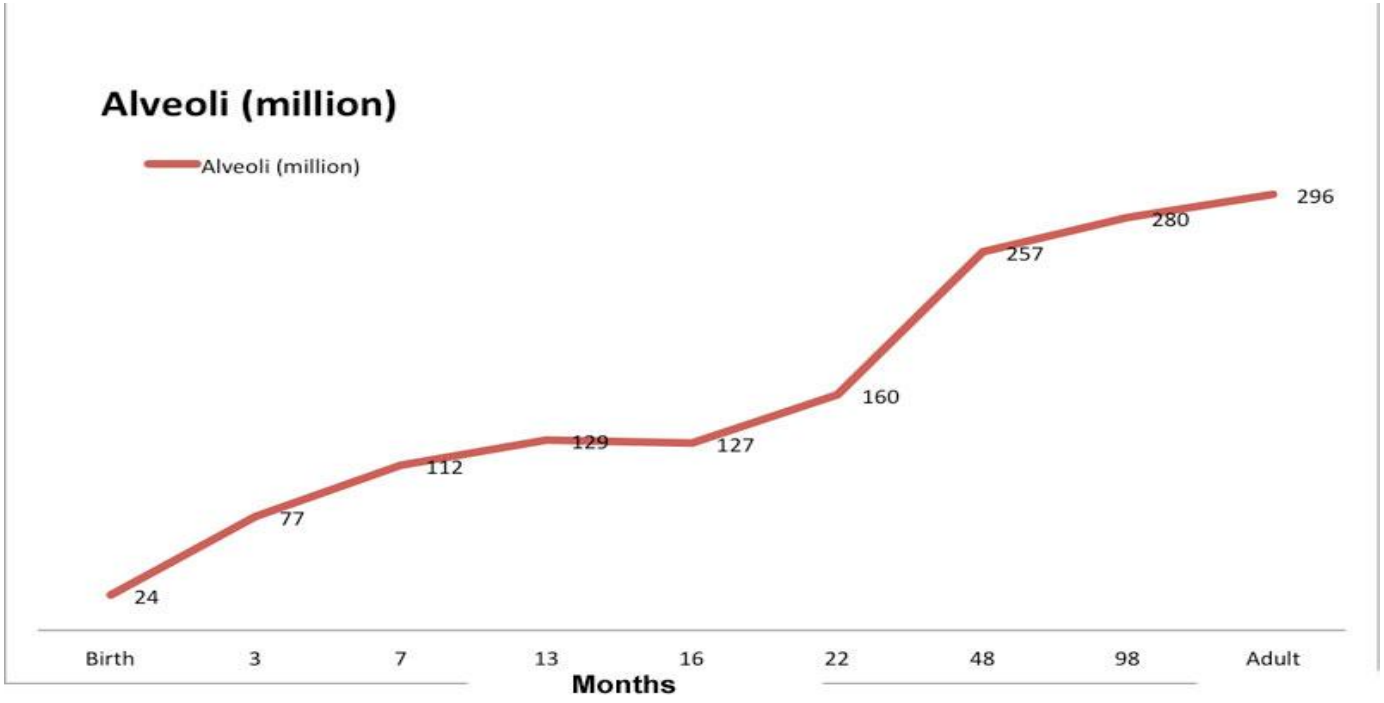
LA BPCO E' UNA MALATTIA PEDIATRICA !

Ricerca e Cura delle Malattie Respiratorie
ed allergiche del bambino
Mario La Rosa

BPCO: Una Malattia Pediatrica

Dopo la nascita, le dimensioni del polmone aumentano con le dimensioni del corpo, ma sono anche influenzate da età, sesso ed etnia.

[Quanjer et al. 2012].



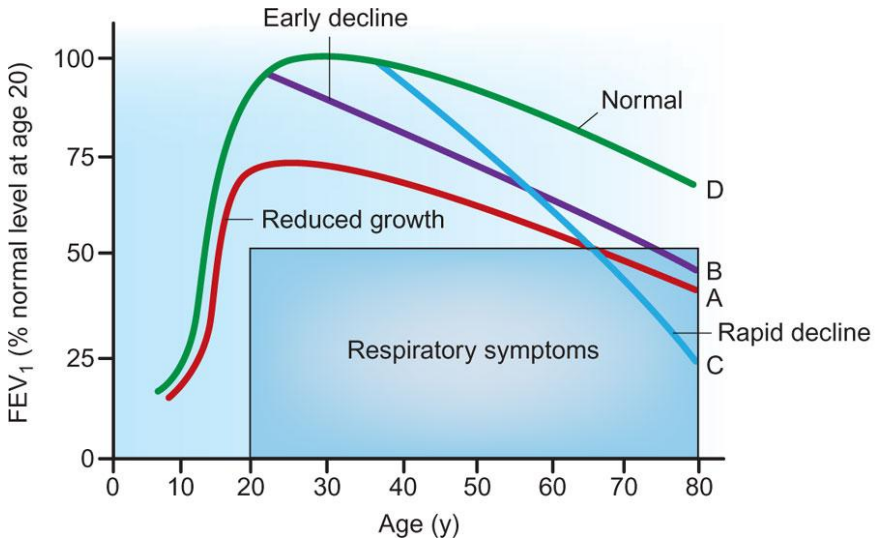
Data: Dunnill MS. Postnatal growth of the lung. Thorax 1962;17:329–333.

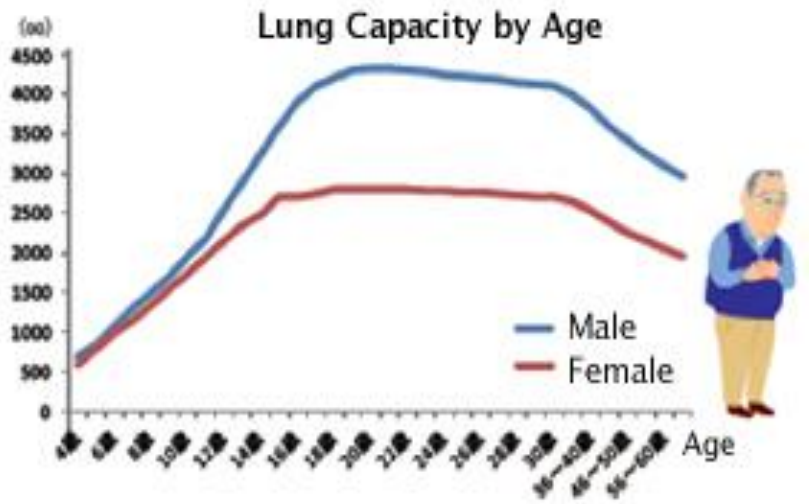
I volumi massimi polmonari sono raggiunti a circa 22 anni nei maschi e poco prima nelle femmine, raggiungendo un volume polmonare che è 30 volte maggiore rispetto alla nascita.

[Kohansal et al. 2009; Quanjer et al. 2012]

Anche in salute, FEV1 e FVC hanno un graduale declino dopo aver raggiunto il loro picco a causa di una progressiva perdita di elasticità del polmone.

[Quanjer et al. 2012].





BPCO: Una Malattia Pediatrica

Il concetto che la BPCO in età adulta non è semplicemente dovuta ad un accelerato declino della funzione polmonare con l'invecchiamento ,ma al mancato raggiungimento del picco di funzionalità respiratoria durante l'accrescimento è stato proposto diversi decenni fa.

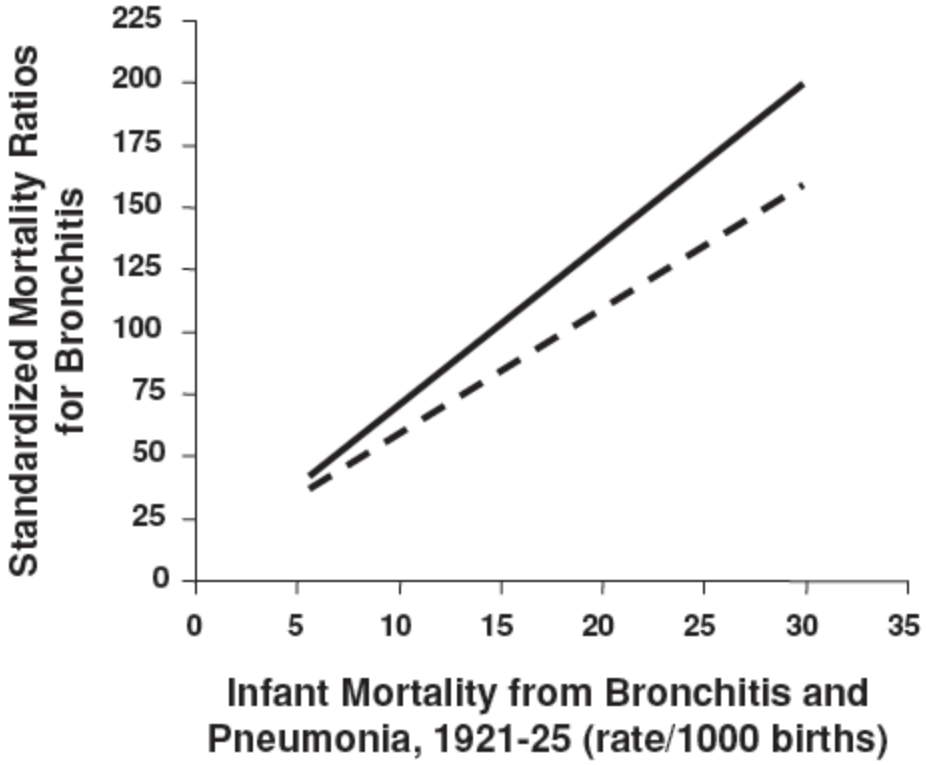
BMJ. 1991 Sep 21;303(6804):671-5.

Relation of birth weight and childhood respiratory infection to adult lung function and death from chronic obstructive airways disease.

Barker DJ[1], Godfrey KM, Fall C, Osmond C, Winter PD, Shaheen SO.

The fetal and infant origins of adult disease.

Barker DJ.



r= 0.71 ; p<0.01

Barker DP. Fetal and infant origins of adult disease. BMJ Books 1992; 343:52–53.

Early life influences on the development of chronic obstructive pulmonary disease

Janet Stocks and Samatha Sonnappa

COPD [Barker *et al.* 1991]. Evidence to support the concept of 'foetal programming', whereby insults during critical periods of development produce permanent structural, physiological or epigenetic changes with lifelong consequences [Miller and Marty, 2010; Barker, 2012], has also been provided by experimental animal models [Kallapur and Ikegami, 2006; Kramer *et al.* 2009; Shimoda and Semenza, 2011; Abbott and Winzer-Serhan, 2012; Hilgendorff *et al.* 2012; Magnani *et al.* 2012; Maritz and Mutemwa, 2012; Sutherland *et al.* 2012]. These studies have shown that insults to the developing lung during intrauterine or very early postnatal life lead to increased susceptibility to respiratory disease during both childhood and later life [Gluckman *et al.* 2008; Harding and Maritz, 2012].

Ther Adv Respir Dis

(2013) 7(3) 161–173

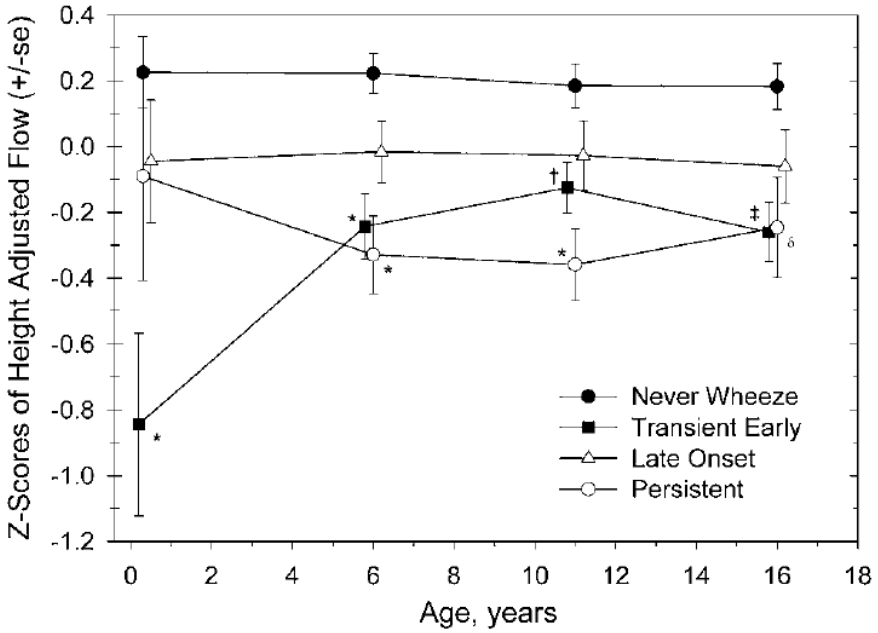
DOI: 10.1177/
1753465813479428

Outcome of Asthma and Wheezing in the First 6 Years of Life

Follow-up through Adolescence

Wayne J. Morgan*, Debra A. Stern*, Duane L. Sherrill, Stefano Guerra, Catharine J. Holberg, Theresa W. Guilbert, Lynn M. Taussig, Anne L. Wright, and Fernando D. Martinez

	Number (%)	Wheeze age 3	Wheeze age 6
Normals	425 (51)	–	–
Transient wheeze	164 (20)	+	–
Persistent wheeze	124 (15)	+	+
Late onset wheeze	113 (14)	–	+

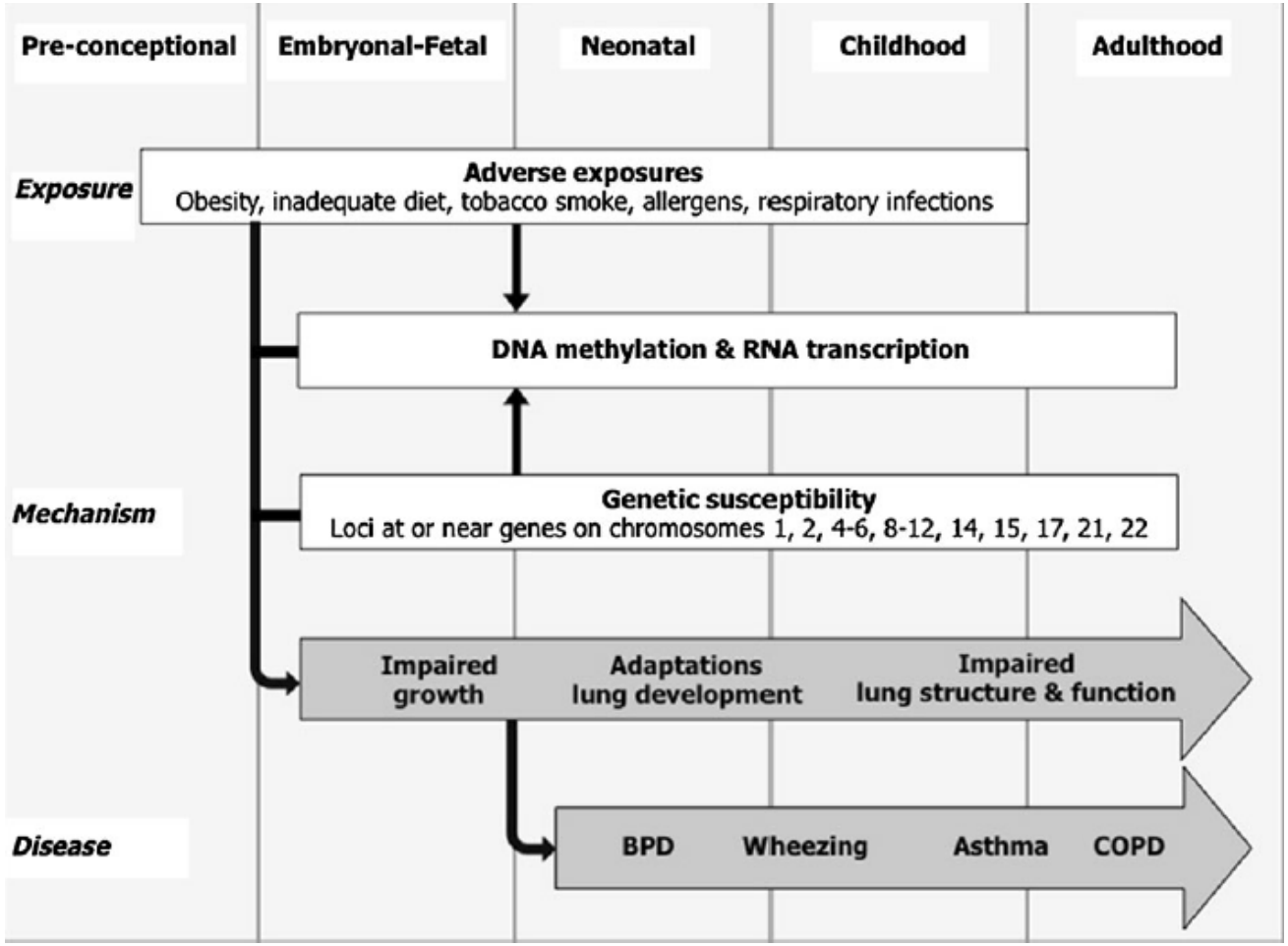


AMERICAN JOURNAL OF
Respiratory and Critical Care Medicine

Am J Respir Crit Care Med Vol 172. pp 1253–1258, 2005

Early origins of chronic obstructive lung diseases across the life course

Liesbeth Duijts · Irwin K. Reiss · Guy Brusselle · Johan C. de Jongste



Eur J Epidemiol (2014) 29:871–885

BPCO
Le
Origini

FATTORI DI RISCHIO DI BPCO

Janet Stocks and Samatha Sonnappa

Early life influences on the development of chronic obstructive pulmonary disease

Postnatal risk factors for COPD
Chronic lung disease of prematurity
Postnatal growth and nutrition
Postnatal exposure to environmental tobacco smoke
Environmental pollution
Childhood respiratory illness

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DOI: 10.1177/
1753465813479428

Maternal Smoke During Pregnancy

[…] in utero exposure to nicotine leads to smaller lungs with a reduced number of enlarged alveoli, alveolar changes suggestive of premature ageing and a low capillary density .

Semin Fetal Neonatal Med. 2012 Apr;17(2):67-72. doi: 10.1016/j.siny.2012.01.005. Epub 2012 Jan 23.

Maternal and fetal origins of lung disease in adulthood.

Harding R[1], Maritz G.

Maternal smoking of 10 cigarettes/day was found to increase risk of COPD in offspring by 1.7 (95% confidence interval, 1.2– 2.5).
Within families, the effect of maternal smoking of 10 cigarettes/day had the same effect on airflow limitation in the offspring as 10 years of personal smoking by the offspring .

Am J Respir Crit Care Med. 2004 Feb 15;169(4):479-87. Epub 2003 Nov 20.

Maternal and personal cigarette smoking synergize to increase airflow limitation in adults.

Upton MN[1], Smith GD, McConnachie A, Hart CL, Watt GC.

Maternal Smoke During Pregnancy

Table 4 Association between exposure to maternal smoking during and after pregnancy and children' lung function at 21 years by gender

	Males (n = 1185)			Females (n = 1224)		
Lung function tests	Never smoked	Smoked after	Smoked during ± after	Never smoked	Smoked after	Smoked during ± after
FVC (litre)	Ref	0.06 (0.08)	0.02 (0.05)	Ref	0.07 (0.05)	0.01 (0.04)
z-score	Ref	−0.05 (0.09)	0.12 (0.06)	Ref	0.14 (0.08)	0.05 (0.06)
FEV_1 (litre)	Ref	0.06 (0.06)	−0.04 (0.04)	Ref	0.06 (0.04)	−0.01 (0.03)
z-score	Ref	0.11 (0.09)	−0.17 (0.06)*	Ref	−0.05 (0.09)	−0.05 (0.06)
FEF_{25-75} (litre/s)	Ref	0.10 (0.11)	−0.16 (0.07)**	Ref	0.01 (0.08)	−0.06 (0.05)
z-score	Ref	0.06 (0.09)	−0.10 (0.06)	Ref	0.009 (0.08)	−0.03 (0.06)

The reference group (Ref) is children whose mothers never smoked. Values are regression coefficients (SE).
*$p<0.01$; **$p<0.05$.
FVC, forced vital capacity; FEF_{25-75}, forced expiratory flow between 25% and 75%; FEV_1, forced expiratory volume in 1 s

Results: In utero exposure to maternal smoking was associated with a reduction in FEV_1 and FEF_{25-75} in males (regression coefficient, −0.16; 95% CI, −0.30 to −0.02), after accounting for maternal smoking after pregnancy. At least part of the effect of in utero smoking on young adults' lung function was explained by the child's birth weight and subsequent asthma.
Conclusions: Adverse effects of antenatal smoking on development of airway growth may persist into early adulthood. Gender differences noted in this longitudinal cohort need to be explored further.

Maternal smoking during and after pregnancy and lung function in early adulthood: a prospective study

M R Hayatbakhsh,[1] S Sadasivam,[2] A A Mamun,[1] J M Najman,[1] G M Williams,[1] M J O'Callaghan[2]

Thorax 2009;**64**:810–814. doi:10.1136/thx.2009.116301

Low Birth Weight

La maggior parte degli studi epidemiologici hanno dimostrato che il basso peso alla nascita è associato ad aumentata morbilità cardiovascolare e respiratoria in età avanzata. I fattori responsabili del basso peso alla nascita sono il **parto pretermine** e il **ritardo di crescita intrauterino**.

Epidemiological studies demonstrate that in-utero growth restriction and low birth weight are associated with **impaired lung function** and **increased respiratory morbidity** from infancy, throughout childhood and into adulthood. Chronic restriction of nutrients and/or oxygen during late pregnancy causes abnormalities in the airways and lungs of offspring, including *smaller numbers of enlarged alveoli* with *thicker septal walls and basement membranes*. The structural abnormalities and impaired lung function seen soon after birth persist or even progress with age. These changes are likely to cause lung symptomology through life and hasten lung aging.

Semin Fetal Neonatal Med. 2012 Apr;17(2):92-8. doi: 10.1016/j.siny.2012.01.006. Epub 2012 Jan 25.

Long term respiratory consequences of intrauterine growth restriction.

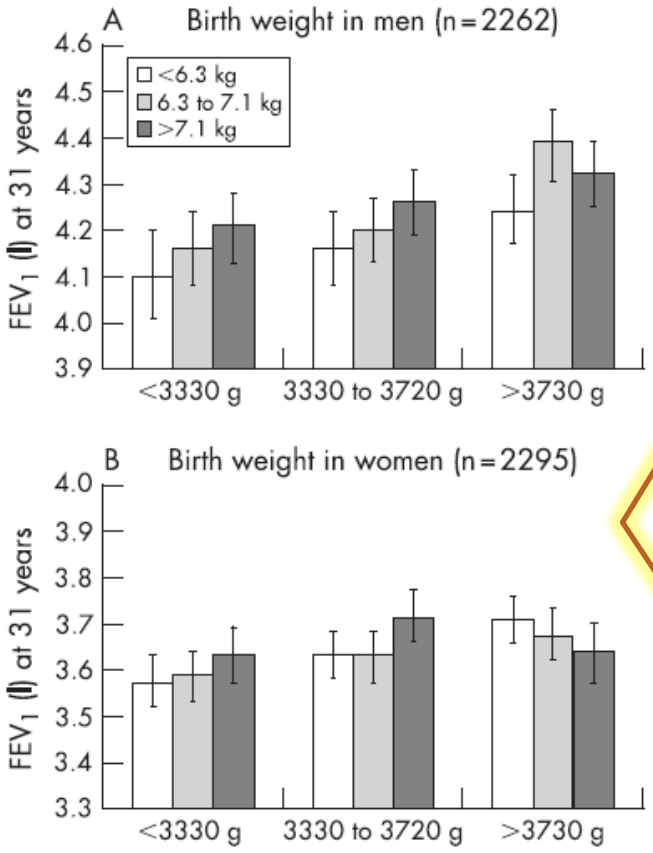
Pike K[1], Jane Pillow J, Lucas JS.

Low Birth Weight

Early growth and adult respiratory function in men and women followed from the fetal period to adulthood

Dexter Canoy, Juha Pekkanen, Paul Elliott, Anneli Pouta, Jaana Laitinen, Anna-Liisa Hartikainen, Paavo Zitting, Swatee Patel, Mark P Little, Marjo-Riitta Järvelin

Thorax 2007;**62**:396–402. doi: 10.1136/thx.2006.066241



RESULTS:
Adult FEV(1) and FVC increased linearly with higher birth weight in both men and women with no apparent threshold. […] **every 500 g higher birth weight was associated with a higher FEV(1) of 53.1 ml** (95% CI 38.4 to 67.7) **and higher FVC of 52.5 ml** (95% CI 35.5 to 69.4).

CONCLUSION:
Birth weight is continuously and independently associated with adult respiratory function. It is plausible that poor growth in early life may restrict normal lung growth and development, which could have long-term consequences on lung function later in life.

Il peso alla nascita è continuamente e indipendentemente associato alla funzione respiratoria dell'adulto.

POSTNATAL RISK FACTORS FOR COPD

Postnatal risk factors for COPD
Chronic lung disease of prematurity
Postnatal growth and nutrition
Postnatal exposure to environmental tobacco smoke
Environmental pollution
Childhood respiratory illness

Il parto pretermine, che corrisponde ad una durata della gestazione inferiore alle **37 settimane**, è la causa più comune di sviluppo polmonare anomalo con conseguenze sostanziali e per tutta la vita.

COPD. 2008 Feb;5(1):53-67. doi: 10.1080/15412550701815965.

COPD: a pediatric disease.

Bush A[1].

COPD
JOURNAL OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

CHRONIC LUNG DISEASE OF PREMATURITY

Infants born before **28 weeks' gestation** rarely survive without supplementary oxygen and ventilatory assistance, the iatrogenic effects of which may compound the disruption of lung development caused by preterm delivery *per se*. Exposure to hyperoxia, especially if combined with prenatal inflammation, results in the **disruption of alveolar development**, **reduced surface area for gas exchange**, **diffuse fibrosis** and **increased airway resistance.**

Therapeutic Advances in Respiratory Disease

Early life influences on the development of chronic obstructive pulmonary disease

Janet Stocks and Samatha Sonnappa

Ther Adv Respir Dis
(2013) 7(3) 161–173
DOI: 10.1177/1753465813479428

CHRONIC LUNG DISEASE OF PREMATURITY

Most longitudinal studies of lung function have reported evidence of **persistent airflow limitation** (reduced FEV1 and FEV1/ FVC) and/or **BHR** during childhood, adolescence and adulthood in survivors of preterm birth.

Semin Fetal Neonatal Med. 2012 Apr;17(2):73-6. doi: 10.1016/j.siny.2012.01.009. Epub 2012 Feb 1.

Long term respiratory outcomes of very premature birth (<32 weeks).

Greenough A[1].

Pediatr Pulmonol. 2013 May;48(5):449-55. doi: 10.1002/ppul.22619. Epub 2012 Jul 23.

Respiratory function at age 8-9 after extremely low birthweight or preterm birth in Victoria in 1997.

Hacking DF[1], Gibson AM, Robertson C, Doyle LW; Victorian Infant Collaborative Study Group (VICS).

Am J Respir Crit Care Med. 2010 Jul 15;182(2):237-45. doi: 10.1164/rccm.200912-1806OC. Epub 2010 Apr 8.

Lung function and respiratory symptoms at 11 years in children born extremely preterm: the EPICure study.

Fawke J[1], Lum S, Kirkby J, Hennessy E, Marlow N, Rowell V, Thomas S, Stocks J.

CHRONIC LUNG DISEASE OF PREMATURITY

Table 5 Mean and SD of z-scores of lung function measures adjusted for age, gender and height at age 14–17 years, with CIs for the difference of means (premature – term), unadjusted and adjusted for maternal smoking in pregnancy and social status

	25–32 weeks (n=42)		Term (n=4105)		Difference (95% CI) (unadjusted)	Difference (95% CI) (adjusted)	p Value for adjusted analysis
	Mean	SD	Mean	SD			
FEV_1	−0.186	0.850	0.001	1.004	−0.186 (−0.494 to 0.121)	−0.145 (−0.534 to 0.244)	0.464
FVC	−0.151	1.034	−0.004	1.002	−0.148 (−0.452 to 0.156)	−0.041 (−0.427 to 0.346)	0.836
FEF_{25-75}	−0.438	0.899	0.011	1.001	−0.449 (−0.753 to −0.145)	−0.382 (−0.768 to 0.005)	0.053
FEV_1/FVC	−0.195	1.117	0.010	0.995	−0.205 (−0.517 to 0.106)	−0.150 (−0.535 to 0.236)	0.446
FEF_{25-75}/FVC	−0.260	1.006	0.013	1.000	−0.274 (−0.581 to 0.034)	−0.338 (−0.723 to 0.046)	0.084
	33–34 weeks (n=49)		Term (n=4105)		Difference and 95% CI (unadjusted)	Difference and 95% CI (adjusted)	p Value for adjusted analysis
	Mean	SD	Mean	SD			
FEV_1	−0.022	1.135	0.001	1.004	−0.023 (−0.304 to 0.259)	−0.059 (−0.348 to 0.231)	0.691
FVC	0.169	0.905	−0.004	1.002	0.173 (−0.109 to 0.454)	0.127 (−0.161 to 0.415)	0.386
FEF_{25-75}	−0.279	1.143	0.011	1.001	−0.290 (−0.572 to −0.009)	−0.289 (−0.577 to −0.001)	0.049
FEV_1/FVC	−0.401	1.104	0.010	0.995	−0.411 (−0.693 to −0.130)	−0.379 (−0.666 to −0.092)	0.010
FEF_{25-75}/FVC	−0.415	0.984	0.013	1.000	−0.428 (−0.709 to −0.147)	−0.397 (−0.683 to −0.110)	0.007
	35–36 weeks (n=129)		Term (n=4105)		Difference and 95% CI (unadjusted)	Difference and 95% CI (adjusted)	p Value for adjusted analysis
	Mean	SD	Mean	SD			
FEV_1	0.057	0.859	0.001	1.004	0.057 (−0.120 to 0.234)	0.094 (−0.089 to 0.276)	0.315
FVC	0.095	0.956	−0.004	1.002	0.099 (−0.077 to 0.274)	0.119 (−0.060 to 0.299)	0.191
FEF_{25-75}	−0.077	0.877	0.011	1.001	−0.088 (−0.263 to 0.087)	−0.056 (−0.235 to 0.124)	0.543
FEV_1/FVC	−0.079	1.047	0.010	0.995	−0.089 (−0.267 to 0.088)	−0.062 (−0.243 to 0.119)	0.502
FEF_{25-75}/FVC	−0.137	0.957	0.013	1.000	−0.151 (−0.326 to 0.024)	−0.133 (−0.311 to 0.045)	0.143

FEF_{25-75}, forced expiratory volume at 25–75% of FVC; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity.

ORIGINAL ARTICLE

Effect of late preterm birth on longitudinal lung spirometry in school age children and adolescents

Sarah J Kotecha,[1] W John Watkins,[2] Shantini Paranjothy,[2] Frank D Dunstan,[2] A John Henderson,[3] Sailesh Kotecha[1]

Thorax 2012;**67**:54–61. doi:10.1136/thoraxjnl-2011-200329

Postnatal risk factors for COPD

Chronic lung disease of prematurity

Postnatal growth and nutrition

Postnatal exposure to environmental tobacco smoke

Environmental pollution

Childhood respiratory illness

Thorax. 2009 Jan;64(1):62-6. doi: 10.1136/thx.2008.101543. Epub 2008 Nov 10.

Effect of breastfeeding duration on lung function at age 10 years: a prospective birth cohort study.

Ogbuanu IU[1], Karmaus W, Arshad SH, Kurukulaaratchy RJ, Ewart S.

Eur Respir J. 2012 Apr;39(4):985-91. doi: 10.1183/09031936.00037011. Epub 2011 Aug 18.

Breastfeeding is associated with increased lung function at 18 years of age: a cohort study.

Soto-Ramírez N[1], Alexander M, Karmaus W, Yousefi M, Zhang H, Kurukulaaratchy RJ, Raza A, Mitchell F, Ewart S, Arshad SH

N Engl J Med. 2010 May 13;362(19):1784-94. doi: 10.1056/NEJMoa0907441.

Maternal vitamin A supplementation and lung function in offspring.

Checkley W[1], West KP Jr, Wise RA, Baldwin MR, Wu L, LeClerq SC, Christian P, Katz J, Tielsch JM, Khatry S, Sommer A.

Am J Respir Crit Care Med. 2011 May 15;183(10):1336-43. doi: 10.1164/rccm.201010-1596OC. Epub 2011 Feb 4.

Vitamin D deficiency causes deficits in lung function and alters lung structure.

Zosky GR[1], Berry LJ, Elliot JG, James AL, Gorman S, Hart PH.

Breastfeeding is associated with increased lung function at 18 years of age: a cohort study

N. Soto-Ramírez*, M. Alexander*, W. Karmaus*, M. Yousefi*, H. Zhang*, R.J. Kurukulaaratchy#,¶, A. Raza#,¶, F. Mitchell#,¶, S. Ewart+ and S.H. Arshad#,¶

TABLE 2 Effect of breastfeeding on forced vital capacity (FVC) at 18 yrs of age by height#

	Height cm				p-value+
	160	170	180	190	
Breastfeeding months¶					
Not breastfeeding	4.62	5.29	5.95	6.47	
<2	4.71	5.30	5.88	6.51	0.25
2–3	4.75	5.34	5.93	6.46	0.32
⩾4	4.85	5.38	5.92	6.62	0.04

Data are presented as litres, unless otherwise stated. #: n=586; ¶: adjusted for height (cm), sex, maternal smoking during pregnancy, birth weight (kg) and maternal body mass index (kg·m^{-2}); +: the interaction between breastfeeding and height.

Among 808 breastfed children, 49% were breastfed for 4 months. At 18 yrs of age the augmenting effect of breastfeeding on FVC was reduced with increased height. Linear mixed models identified that breastfeeding duration was associated with increased FVC. Path analysis suggested a direct effect of breastfeeding on FVC at 10 yrs of age, but an indirect effect at 18 yrs of age via FVC at 10 yrs of age. Although inversely related to breastfeeding, a higher weight gain in infants led to taller adolescents and, in turn, resulted in increased FVC.

Eur Respir J 2012; 39: 985–991
DOI: 10.1183/09031936.00037011

Una maggiore durata dell'allattamento al seno contribuisce alla salute dei polmoni durante l'infanzia e l'adolescenza.

Postnatal growth and nutrition

Vitamin A, D or E deficiency seems to have greatest effect on alveolar rather than airway development, with evidence that postnatal supplementation may potentially improve lung structure both in animal studies and humans

Am J Respir Crit Care Med. 2011 May 15;183(10):1336-43. doi: 10.1164/rccm.201010-1596OC. Epub 2011 Feb 4.

Vitamin D deficiency causes deficits in lung function and alters lung structure.

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J Nutr Biochem. 2013 Jan;24(1):137-45. doi: 10.1016/j.jnutbio.2012.03.010. Epub 2012 Jul 23.

Vitamin A deficiency disturbs collagen IV and laminin composition and decreases matrix metalloproteinase concentrations in rat lung. Partial reversibility by retinoic acid.

Esteban-Pretel G[1], Marín MP, Renau-Piqueras J, Sado Y, Barber T, Timoneda J.

Postnatal growth and nutrition
VITAMINA D

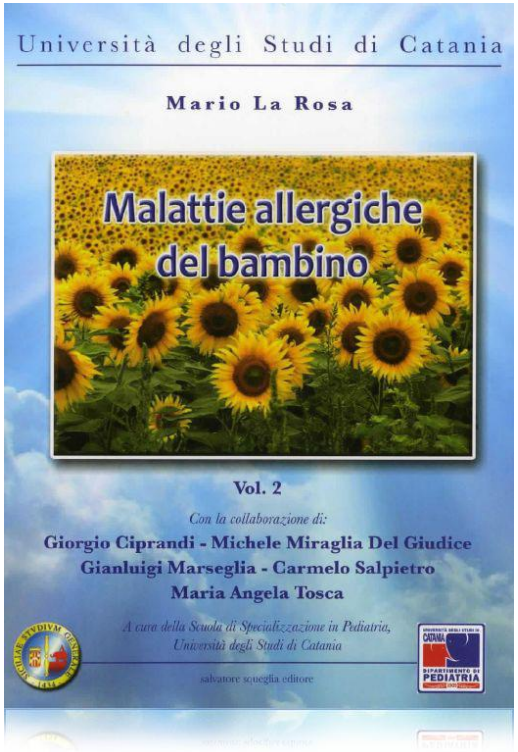
LA VITAMINA D E LA SUA FUNZIONE IMMUNO-MEDIATA

Giuseppe Fabio Parisi, Maria Calenducci, Agnese Castro, Mario La Rosa

Introduzione

Il crescente interesse sulle funzioni della vitamina D è dovuto alle numerose e recenti osservazioni che le vedono attribuire un ruolo non solo nella regolazione del metabolismo del calcio ma anche nella modulazione del sistema immunitario.

Diversi studi dimostrano, infatti, che la vitamina D interagisce con quasi tutte le cellule del sistema immunitario (linfociti T attivati CD4+ e CD8+, linfociti B, neutrofili, cellule presentanti l'antigene, macrofagi) e svolge un ruolo determinante nella prevenzione dei processi infiammatori e delle malattie infettive.



There have been numerous studies looking at vitamin D status in association with various lung diseases focusing on asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF), and respiratory infections.

Vitamin D and Chronic Lung Disease: A Review of Molecular Mechanisms and Clinical Studies[1,2]

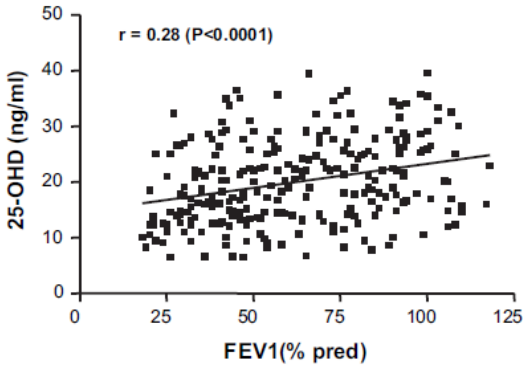
James D. Finklea,[3] Ruth E. Grossmann,[5] and Vin Tangpricha[4–6]*

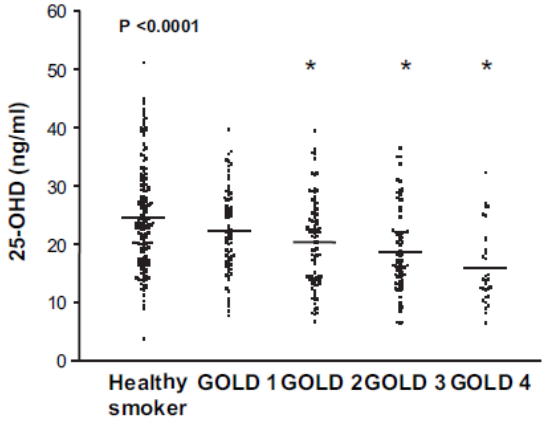
©2011 American Society for Nutrition. Adv. Nutr. 2: 244–253, 2011; doi:10.3945/an.111.000398.

Anche nella terra degli Ulivi?

Vitamin D deficiency is highly prevalent in COPD and correlates with variants in the vitamin D-binding gene

Wim Janssens,[1] Roger Bouillon,[2] Bart Claes,[3] Claudia Carremans,[1] An Lehouck,[1] Ian Buysschaert,[3] Johan Coolen,[4] Chantal Mathieu,[5] Marc Decramer,[1] Diether Lambrechts[3]





RESULTS:
In patients with COPD, 25-OHD levels correlated significantly with forced expiratory volume in 1 s (FEV(1)) (r=0.28, p<0.0001). Compared with 31% of the smokers with normal lung function, as many as 60% and 77% of patients with GOLD (Global Initiative for Obstructive Lung Disease) stage 3 and 4 exhibited deficient 25-OHD levels <20 ng/ml (p<0.0001). Additionally, 25-OHD levels were reduced by 25% in homozygous carriers of the rs7041 at-risk T allele (p<0.0001). Notably, 76% and 100% of patients with GOLD stage 3 and 4 homozygous for the rs7041 T allele exhibited 25-OHD levels <20 ng/ml.

CONCLUSIONI:
La carenza di vitamina D si associa frequentemente alla BPCO e correla con la gravità della stessa. I dati giustificano la supplementazione di vitamina D nei pazienti con BPCO grave, soprattutto in quelli che trasportano varianti a rischio come la rs7041.

Thorax 2010;**65**:215—220. doi:10.1136/thx.2009.120659

Postnatal risk factors for COPD

- *Chronic lung disease of prematurity*
- *Postnatal growth and nutrition*
- ***Postnatal exposure to environmental tobacco smoke***
- *Environmental pollution*
- *Childhood respiratory illness*




Thorax. 2000 Dec;55(12):1063-7.

Pediatric origins of adult lung diseases. 4. Tobacco related lung diseases begin in childhood.

Le Souëf PN[1].

Respirology. 2003 Sep;8(3):266-85.

The effect of parental smoking on lung function and development during infancy.

Stocks J[1], Dezateux C.

Ci sono difficoltà riconosciute nel separare gli effetti dell' esposizione al fumo di tabacco pre- e post-natale, dal momento che quasi tutte le donne che fumano durante la gravidanza continuano a farlo dopo la nascita del bambino.

Postnatal exposure to environmental tobacco smoke

[…] Not all children who are exposed to pre- or postnatal tobacco smoke have diminished lung function or increased respiratory morbidity, reflecting, at least in part, differences in maternal and foetal genetic susceptibility.

Tai, A.S.N., Tran, H., Roberts, M., Clarke, N., Wilson, J.W., Robertson, C.F. Pediatric origins of adult chronic obstructive pulmonary disease (COPD): childhood asthma. *Am J Respir Crit Care Med*. 2010;181:A2275.

Several, though not all, studies have reported a protective effect of the infant and/or maternal GSTT1 nonnull genotype in children of smoking mothers, with respect to lung function, airway reactivity and respiratory morbidity.

Schultz, E., Devadason, S., Khoo, S., Zhang, G., Bizzintino, J., Martin, A. *et al. (2010)* The role of GSTP1 polymorphisms and tobacco smoke exposure in children with acute asthma. *J Asthma 47: 1049– 1056*.

GENETIC SUSCEPTIBILITY

L'importanza degli “eventi di vita precoci” ha notevoli implicazioni per la ricerca dei geni di suscettibilità nei confronti della BPCO.

COPD: A Pediatric Disease

Andrew Bush

COPD: Journal of Chronic Obstructive Pulmonary Disease, 5:53–67
ISSN: 1541-2555 print / 1541-2563 online

DOI: 10.1080/15412550701815965

GENETIC SUSCEPTIBILITY

ADAM33 is expressed in the developing lung during *branching morphogenesis*, increases throughout gestation, and persists into adult life, suggesting that it may have a role in the developmental regulation of *airway calibre*. Polymorphisms in the ADAM33 have been associated with impaired early life lung function. Now it has been shown that polymorphisms in ADAM33 are implicated in the severity of COPD.

Am J Respir Crit Care Med. 2005 Jul 1;172(1):55-60. Epub 2005 Apr 1.

Polymorphisms in a disintegrin and metalloprotease 33 (ADAM33) predict impaired early-life lung function.

Simpson A[1], Maniatis N, Jury F, Cakebread JA, Lowe LA, Holgate ST, Woodcock A, Ollier WE, Collins A, Custovic A, Holloway JW, John SL.

Another gene linking early lung function, asthma and COPD is the **beta-receptor**. A recent study genotyped the polymorphisms at positions 16 and 27 in more than 1100 people with a variety of respiratory problems, including asthma and COPD, as well as a control population (102**).** The Arg 16 homozygotes had an increased risk of COPD, asthma, and wheeze.

J Hum Genet. 2006;51(11):943-51. Epub 2006 Sep 1.

Beta2-adrenergic receptor polymorphisms are associated with asthma and COPD in adults.

Matheson MC[1], Ellis JA, Raven J, Johns DP, Walters EH, Abramson MJ.

GENETIC SUSCEPTIBILITY

Another illustration of an association between genes important in lung growth and also later susceptibility to COPD concerns **FGF-1, FGF-2** and their receptor **FGF1-R. FGFs** are important in lung growth. […] Human airway smooth muscle cells were shown to proliferate when exposed to FGF1 and 2. In vivo*, there* was cytoplasmic expression of FGF-2 in epithelium, and nuclear localization in airway smooth muscle cells, in COPD patients when compared with controls.

J Pathol. 2005 May;206(1):28-38.

Chronic obstructive pulmonary disease is associated with enhanced bronchial expression of FGF-1, FGF-2, and FGFR-1.

Kranenburg AR[1], Willems-Widyastuti A, Mooi WJ, Saxena PR, Sterk PJ, de Boer WI, Sharma HS.

The effects of **GSTM** polymorphisms in mother and child, and early lung function and symptoms, have been discussed. GSTT1 deficiency is associated with an accelerated decline in lung function, a known risk factor for COPD, in middle aged men, and a combination of polymorphisms in all three GST genes were associated with accelerated decline in lung function.

Am J Respir Crit Care Med. 2002 Sep 1;166(5):710-6.

Effects of glutathione-S-transferase M1, T1, and P1 on childhood lung function growth.

Gilliland FD[1], Gauderman WJ, Vora H, Rappaport E, Dubeau L.

Postnatal risk factors for COPD

- *Chronic lung disease of prematurity*
- *Postnatal growth and nutrition*
- *Postnatal exposure to environmental tobacco smoke*
- ***Environmental pollution***
- *Childhood respiratory illness*

Environ Res. 2012 Jan;112:111-7. doi: 10.1016/j.envres.2011.10.012. Epub 2011 Nov 30.

Impaired lung function in individuals chronically exposed to biomass combustion.

da Silva LF[1], Saldiva SR, Saldiva PH, Dolhnikoff M; Bandeira Científica Project.

Am J Respir Crit Care Med. 2009 Apr 1;179(7):579-87. doi: 10.1164/rccm.200803-388OC. Epub 2009 Jan 16.

Improvements in PM10 exposure and reduced rates of respiratory symptoms in a cohort of Swiss adults (SAPALDIA).

Schindler C[1], Keidel D, Gerbase MW, Zemp E, Bettschart R, Brändli O, Brutsche MH, Burdet L, Karrer W, Knöpfli B, Pons M, Rapp R, Bayer-Oglesby L, Künzli N, Schwartz J, Liu LJ, Ackermann-Liebrich U, Rochat T; SAPALDIA Team.

Durante lo sviluppo, il polmone è altamente suscettibile ai danni da esposizione agli **inquinanti ambientali.**
L'associazione tra l'esposizione acuta e cronica ad inquinanti ambientali e sintomi respiratori, così come la funzione polmonare ridotta, è ben descritta in bambini e adulti.

Environmental pollution

School children in rural India, where use of biomass is common, also have significant reductions in lung function and increased incidence of asthma when compared with nonexposed peers.

Ann N Y Acad Sci. 2008 Oct;1140:209-17. doi: 10.1196/annals.1454.015.

Domestic fuels, indoor air pollution, and children's health.

Padhi BK[1], Padhy PK.

A direct link between childhood exposure to PM and increased vulnerability to adult respiratory disease is provided by studies showing an association between life-long biomass smoke exposure and development of COPD in noncigarette-smoking women.

Proc Am Thorac Soc. 2009 Dec 1;6(7):564-9. doi: 10.1513/pats.200905-026RM.

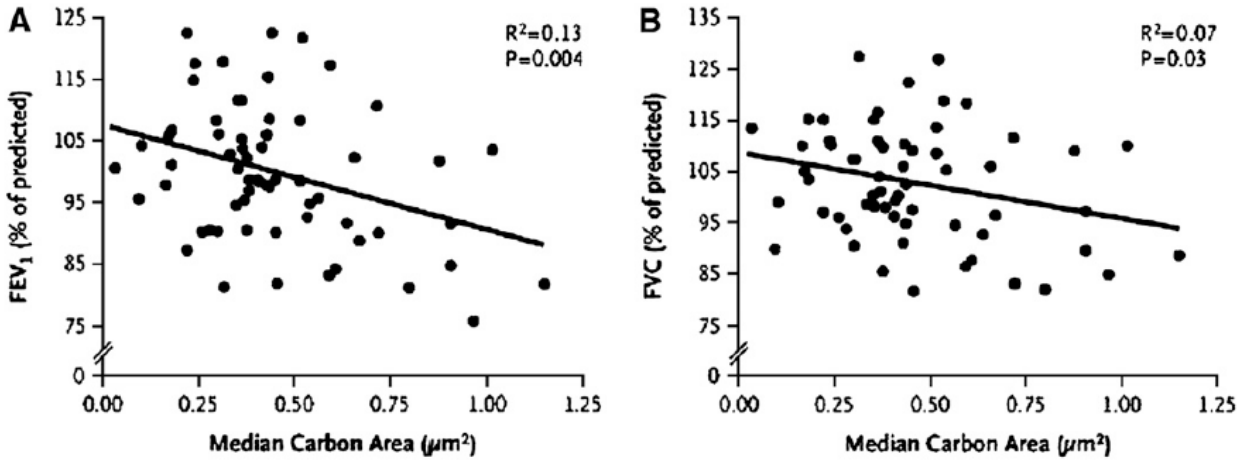
Particulate matter exposure in children: relevance to chronic obstructive pulmonary disease.

Grigg J[1].

Particulate Matter Exposure in Children

Relevance to Chronic Obstructive Pulmonary Disease

Jonathan Grigg[1]



and cigarette smoke (50, 52)–associated COPD. A putative sequence is that chronic exposure to PM (*1*) reduces attainment of maximal lung function in childhood, (*2*) accelerates lung function decline in adulthood, (*3*) stimulates airway mucus production, and (*4*) impairs pulmonary innate immunity. If exposure to PM during childhood is high, then symptoms suggestive of COPD will develop early. For example, chronic

Proc Am Thorac Soc Vol 6. pp 564–569, 2009
DOI: 10.1513/pats.200905-026RM
Internet address: www.atsjournals.org

Postnatal risk factors for COPD

- *Chronic lung disease of prematurity*
- *Postnatal growth and nutrition*
- *Postnatal exposure to environmental tobacco smoke*
- *Environmental pollution*
- ***Childhood respiratory illness***

Eur Respir J. 2013 Jun;41(6):1371-7. doi: 10.1183/09031936.00005512. Epub 2012 Nov 8.

Age and height dependence of lung clearance index and functional residual capacity.

Lum S[1], Stocks J, Stanojevic S, Wade A, Robinson P, Gustafsson P, Brown M, Aurora P, Subbarao P, Hoo AF, Sonnappa S.

L'associazione tra infezioni respiratorie durante l'infanzia e le malattie polmonari croniche dell' età avanzata è da tempo riconosciuta.
Tuttavia, l'incapacità di misurare regolarmente la funzione polmonare nei bambini al di sotto di 6 anni ha reso impossibile determinare se la funzione polmonare ridotta preceda le infezioni respiratorie precoci o viceversa.

Childhood respiratory illness

It has been reported that lower respiratory tract infections, especially those associated with **respiratory syncytial virus (RSV)**, are associated with abnormal lung function at follow up.

Pediatr Infect Dis J. 2007 Nov;26(11):1019-24.

Lung function in prematurely born infants after viral lower respiratory tract infections.

Broughton S[1], Sylvester KP, Fox G, Zuckerman M, Smith M, Milner AD, Rafferty GF, Greenough A.

However, several studies have shown that children hospitalized as a result of RSV tend to have abnormal lung function before as well as after such infections.

Thorax. 2011 Jun;66(6):468-73. doi: 10.1136/thx.2010.148023. Epub 2011 Mar 28.

Lung function prior to viral lower respiratory tract infections in prematurely born infants.

Drysdale SB[1], Wilson T, Alcazar M, Broughton S, Zuckerman M, Smith M, Rafferty GF, Johnston SL, Greenough A.

Arch Dis Child. 2002 Nov;87(5):417-20.

Reduced lung function both before bronchiolitis and at 11 years.

Turner SW[1], Young S, Landau LI, Le Souëf PN.

Childhood respiratory illness

Considerable evidence now exists that diminished airway function, associated with a suboptimal intrauterine environment (e.g. maternal smoking, IUGR) may be present from birth and that such children are more likely to wheeze with subsequent viral infections.

Semin Fetal Neonatal Med. 2012 Apr;17(2):92-8. doi: 10.1016/j.siny.2012.01.006. Epub 2012 Jan 25.

Long term respiratory consequences of intrauterine growth restriction.

Pike K[1], Jane Pillow J, Lucas JS.

Pediatr Pulmonol. 2011 Jan;46(1):75-82. doi: 10.1002/ppul.21327. Epub 2010 Sep 16.

The relationship between infant lung function and the risk of wheeze in the preschool years.

Pike KC[1], Rose-Zerilli MJ, Osvald EC, Inskip HM, Godfrey KM, Crozier SR, Roberts G, Clough JB, Holloway JW, Lucas JS; Southampton Women's Survey Study Group.

Semin Fetal Neonatal Med. 2012 Apr;17(2):112-8. doi: 10.1016/j.siny.2012.01.002. Epub 2012 Jan 21.

Early origins of chronic obstructive pulmonary disease.

Narang I[1], Bush A.

Adverse Childhood Experiences and COPD

Purpose: Adverse childhood experiences (ACEs) before age 18 have been repeatedly associated with several chronic diseases in adulthood such as depression, heart disease, cancer, diabetes, and stroke. We examined sex-specific relationships between individual ACEs and the number of ACEs with chronic obstructive pulmonary disease (COPD) in the general population.

Materials and methods: Data from 26,546 women and 19,015 men aged ≥18 years in five states of the 2011 Behavioral Risk Factor Surveillance System were analyzed. We used log-linear regression to estimate prevalence ratios (PRs) and their corresponding 95% confidence intervals (CIs) for the relationship of eight ACEs with COPD after adjustment for age group, race/ethnicity, marital status, educational attainment, employment, asthma history, health insurance coverage, and smoking status.

Results: Some 63.8% of women and 62.2% of men reported ≥1 ACE. COPD was reported by 4.9% of women and 4.0% of men. In women, but not in men, there was a higher likelihood of COPD associated with verbal abuse (PR =1.30, 95% CI: 1.05, 1.61), sexual abuse (PR =1.69, 95% CI: 1.36, 2.10), living with a substance abusing household member (PR =1.49, 95% CI: 1.23, 1.81), witnessing domestic violence (PR =1.40, 95% CI: 1.14, 1.72), and parental separation/divorce (PR =1.47, 95% CI: 1.21, 1.80) during childhood compared to those with no individual ACEs. Reporting ≥5 ACEs (PR =2.08, 95% CI: 1.55, 2.80) compared to none was associated with a higher likelihood of COPD among women only.

Conclusion: ACEs are related to COPD, especially among women. These findings underscore the need for further research that examines sex-specific differences and the possible mechanisms linking ACEs and COPD. This work adds to a growing body of research suggesting that ACEs may contribute to health problems later in life and suggesting a need for program and policy solutions.

Sex-specific relationships between adverse childhood experiences and chronic obstructive pulmonary disease in five states

Timothy J Cunningham[1]
Earl S Ford[1]
Janet B Croft[1]
Melissa T Merrick[2]
Italia V Rolle[3]
Wayne H Giles[1]

International Journal of COPD 2014:9 1033–1043

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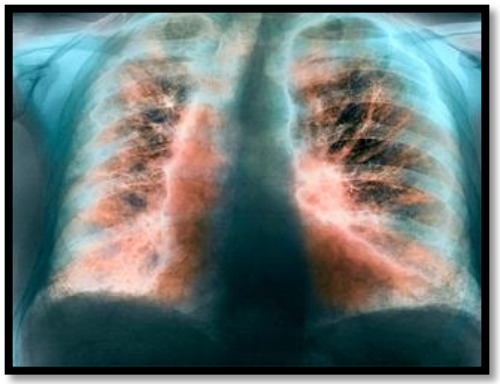

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CONCLUSIONI

Conclusioni

- Non è più plausibile considerare la BPCO come la malattia dell'anziano fumatore

- Rappresenta il frutto di influenze genetiche e soprattutto ambientali **precoci** che dovrebbero essere intercettate dal pediatra :

  a)se possibile curate

  b) comunque favorire il raggiungimento del più alto picco di funzionalità polmonare possibile .