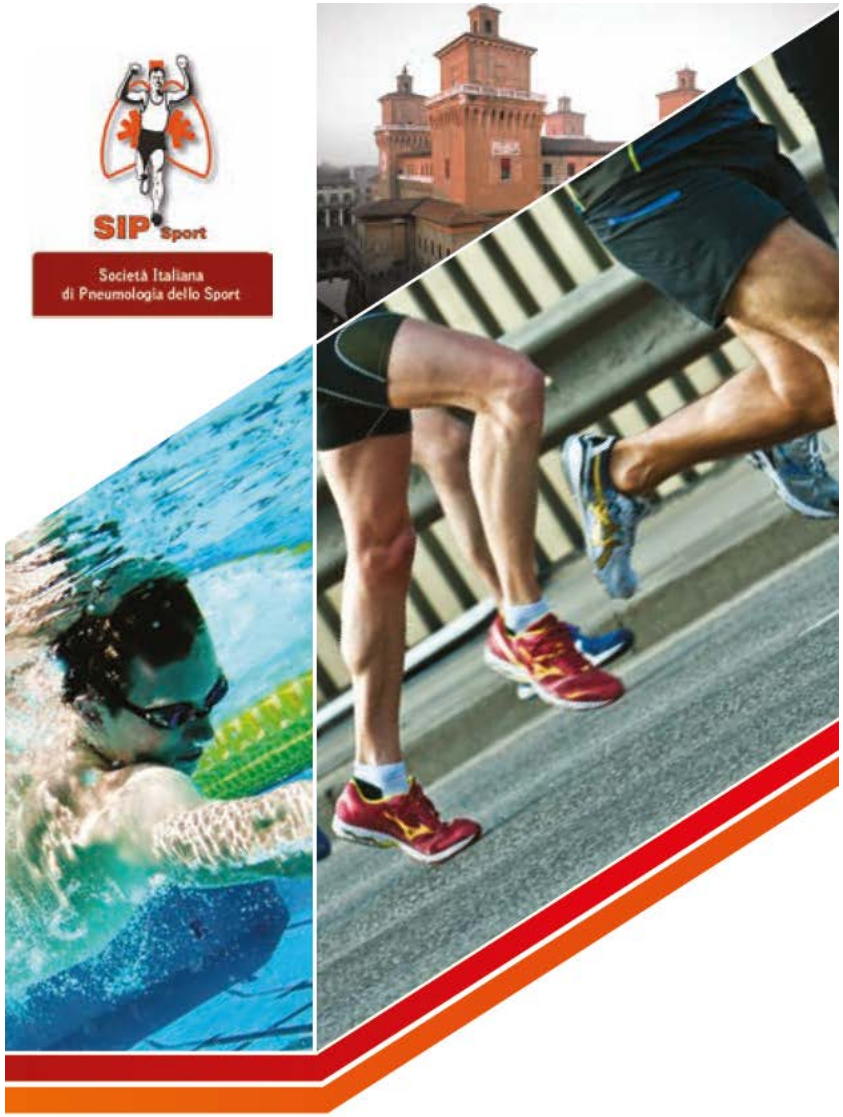

Asma, BPCO
ed Esercizio Fisico

Ferrara, 6 e 7 novembre 2015

Novita’ su patogenesi e trattamento dell’asma da sforzo

Matteo Bonini

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Imperial College London

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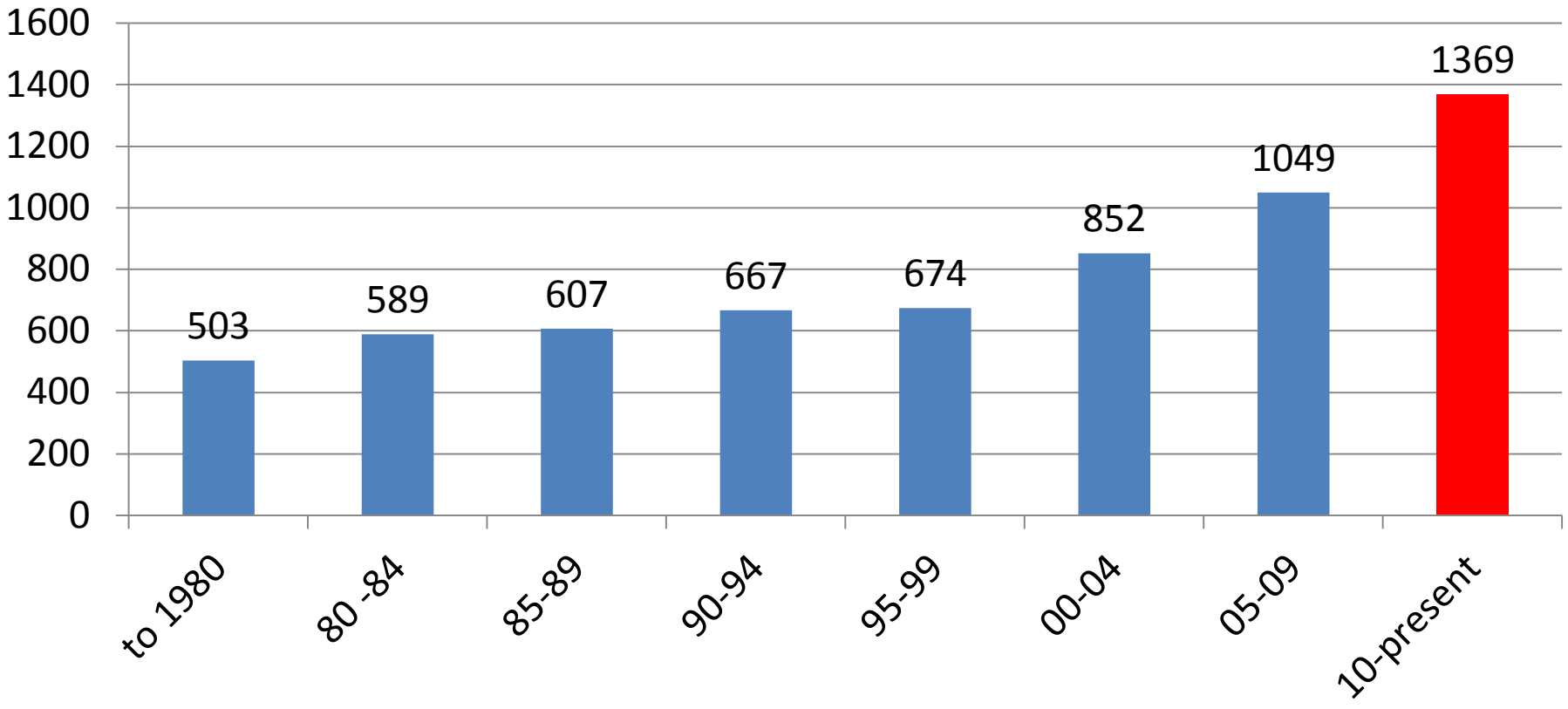
No. of publications



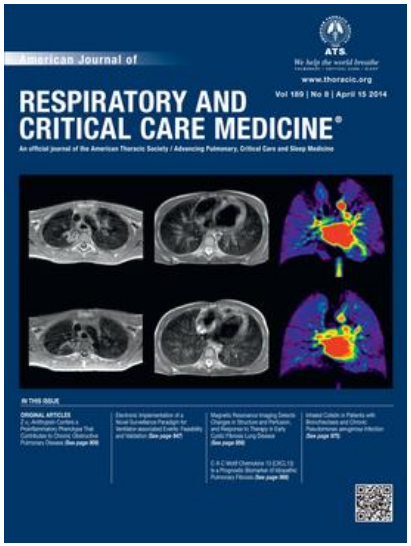
The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

Jeffrey M. Drazen, M.D., *Editor*

Asthma and Exercise-Induced Bronchoconstriction in Athletes

Louis-Philippe Boulet, M.D., and Paul M. O'Byrne, M.B.



American Thoracic Society Documents

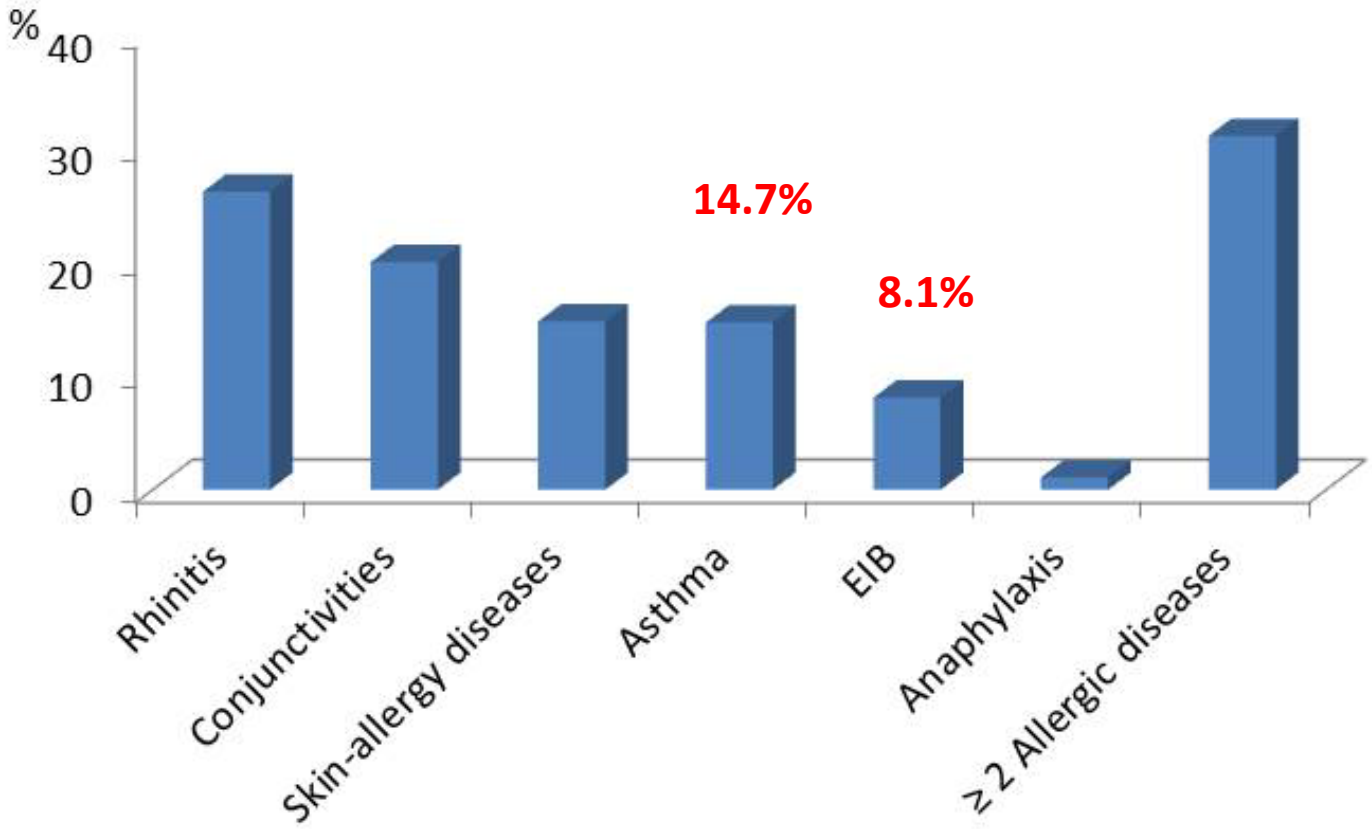
An Official American Thoracic Society Clinical Practice Guideline: Exercise-induced Bronchoconstriction

Jonathan P. Parsons, Teal S. Hallstrand, John G. Mastronarde, David A. Kaminsky, Kenneth W. Rundell, James H. Hull, William W. Storms, John M. Weiler, Fern M. Cheek, Kevin C. Wilson, and Sandra D. Anderson; on behalf of the American Thoracic Society Subcommittee on Exercise-induced Bronchoconstriction

Asthma, allergy and the Olympics: a 12-year survey in elite athletes

SPECIAL ARTICLE

Matteo Bonini[a,b], *Claudia Gramiccioni*[b,c], *Daniela Fioretti*[b], *Beate Ruckert*[d], *Monica Rinaldi*[b], *Cezmi Akdis*[d], *Antonio Todaro*[e], *Paolo Palange*[a], *Kai-Hakon Carlsen*[f], *Antonio Pelliccia*[e], *Guido Rasi*[g], *Sergio Bonini*[b,h], *on behalf of the AIDA and the Italian Unit of the GA2LEN Olympic Study*[*]



Curr Opin Allergy Clin Immunol 2015, 15:184–192

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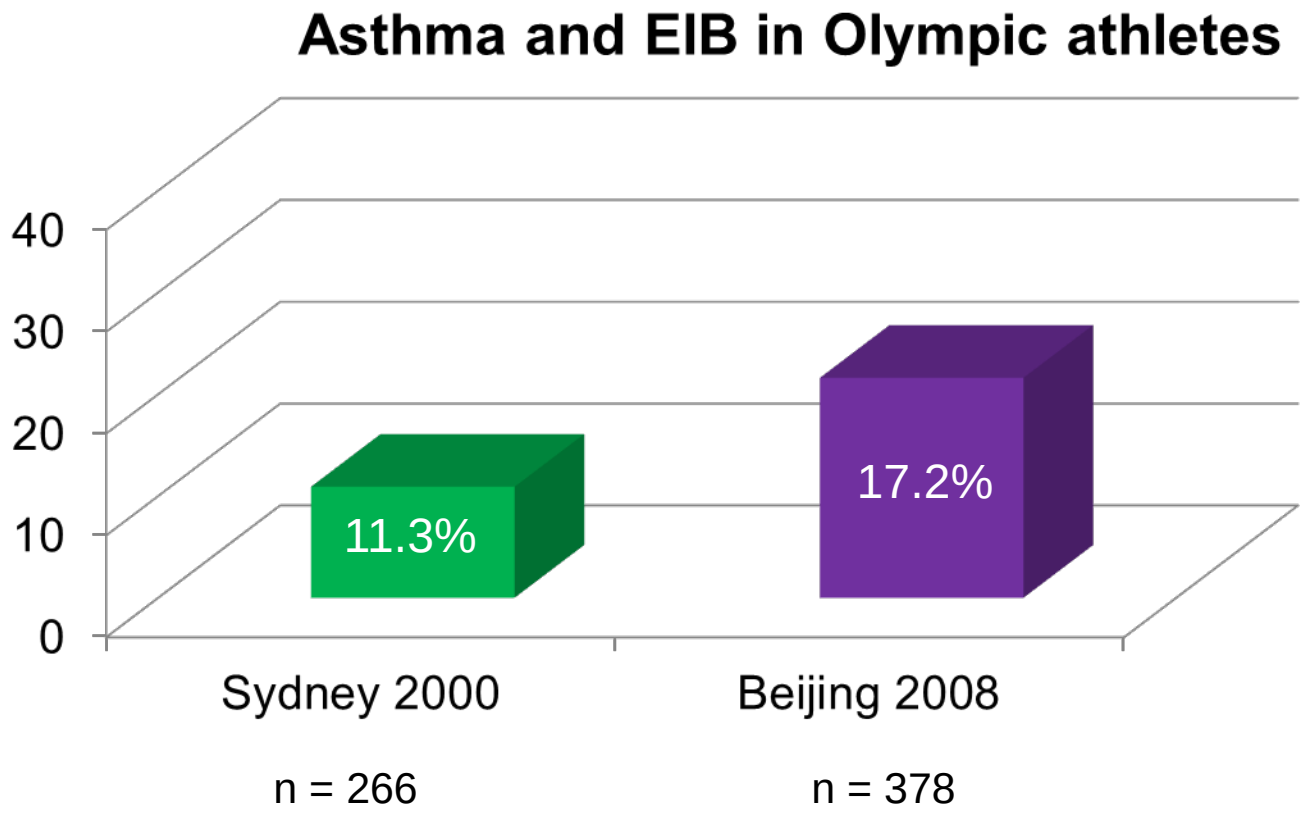
Matteo Bonini[a,b], *Claudia Gramiccioni*[b,c], *Daniela Fioretti*[b], *Beate Ruckert*[d], *Monica Rinaldi*[b], *Cezmi Akdis*[d], *Antonio Todaro*[e], *Paolo Palange*[a], *Kai-Hakon Carlsen*[f], *Antonio Pelliccia*[e], *Guido Rasi*[g], *Sergio Bonini*[b,h], *on behalf of the AIDA and the Italian Unit of the GA2LEN Olympic Study*[*]



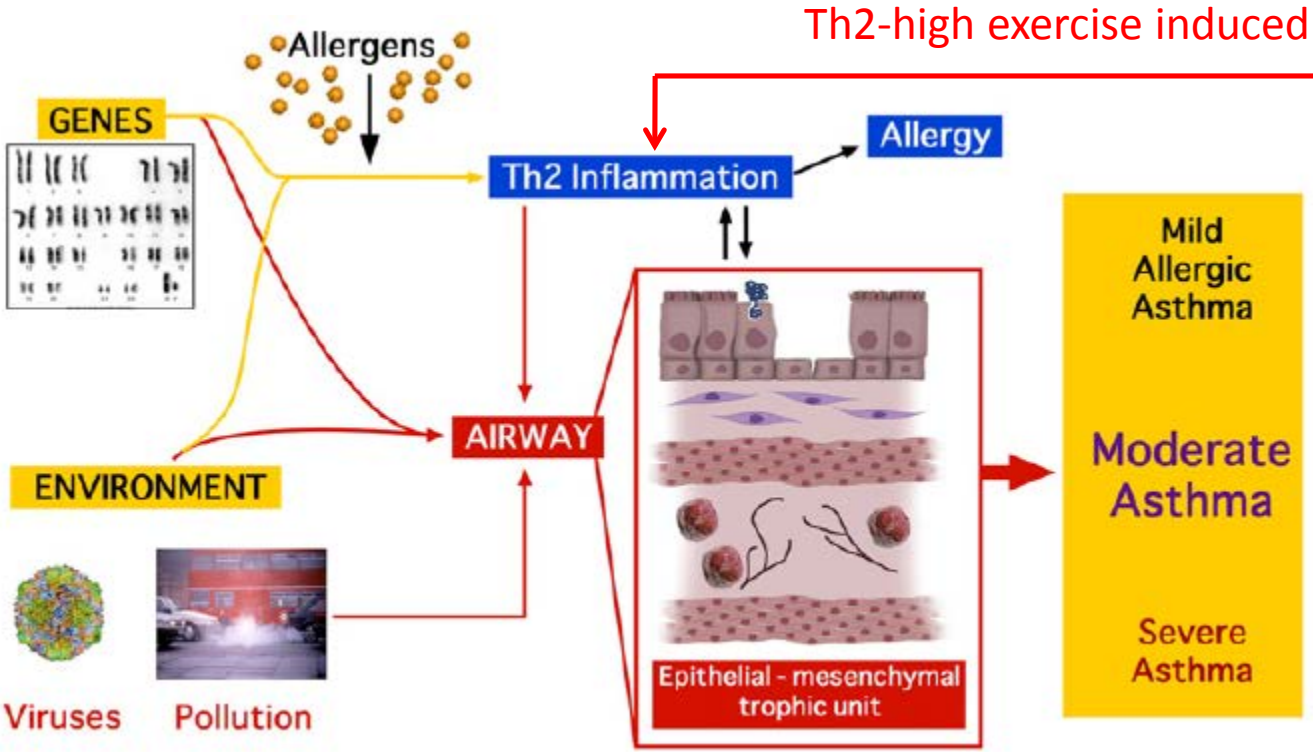
Curr Opin Allergy Clin Immunol 2015, 15:184–192

Current reviews of allergy and clinical immunology
(Supported by an unrestricted educational grant from Genentech, Inc. and Novartis Pharmaceuticals Corporation)

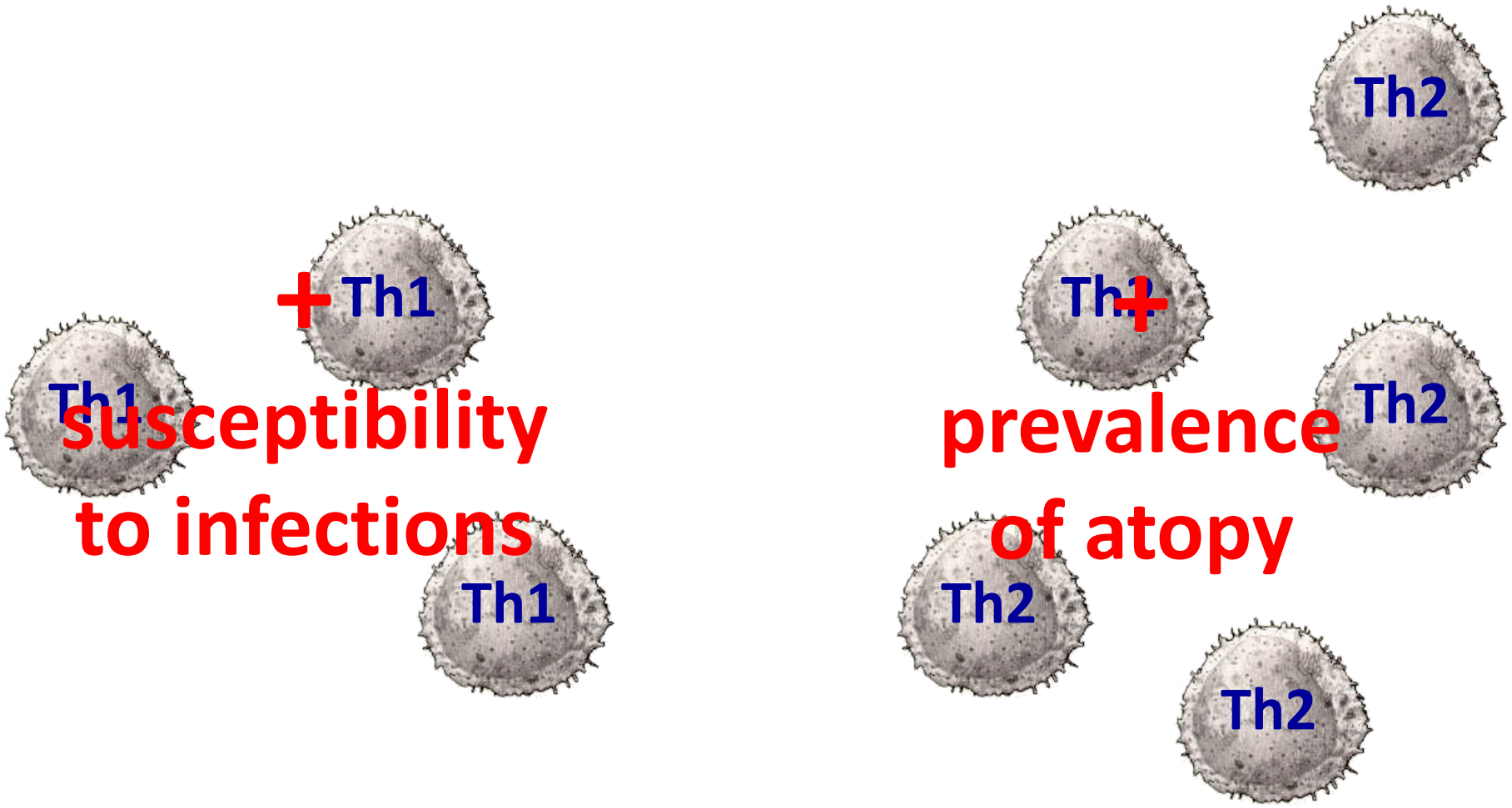
Series editors: Donald Y. M. Leung, MD, PhD, and Dennis K. Ledford, MD

Epithelium dysfunction in asthma

Stephen T. Holgate, MD, DSc *Southampton, United Kingdom*



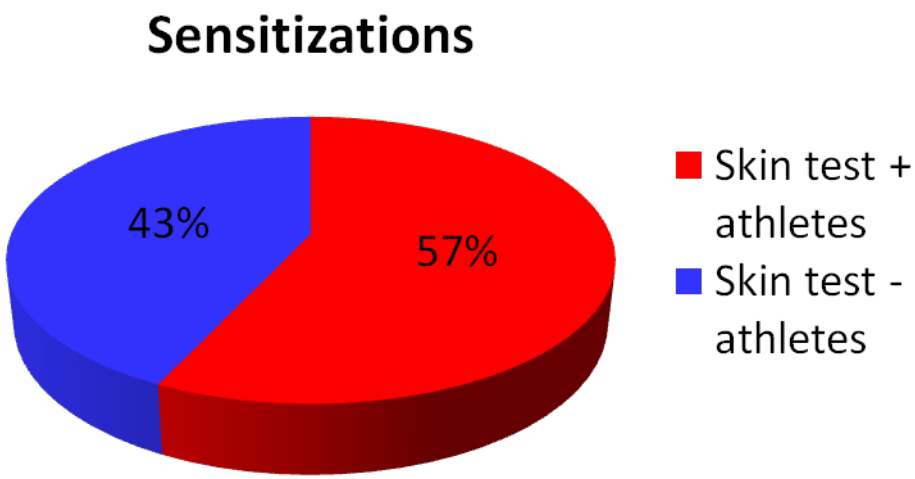
Effect of physical exercise on T helper sub-populations balance

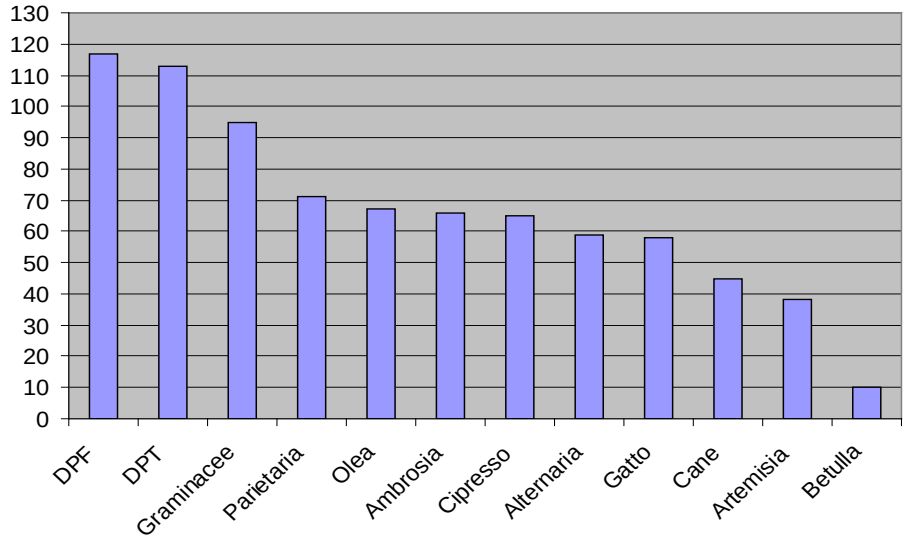


Asthma, allergy and the Olympics: a 12-year survey in elite athletes

SPECIAL ARTICLE

Matteo Bonini[a,b], *Claudia Gramiccioni*[b,c], *Daniela Fioretti*[b], *Beate Ruckert*[d], *Monica Rinaldi*[b], *Cezmi Akdis*[d], *Antonio Todaro*[e], *Paolo Palange*[a], *Kai-Hakon Carlsen*[f], *Antonio Pelliccia*[e], *Guido Rasi*[g], *Sergio Bonini*[b,h], *on behalf of the AIDA and the Italian Unit of the GA2LEN Olympic Study*[*]





Curr Opin Allergy Clin Immunol 2015, 15:184–192

Cytokine	A vsCTRL	AA vs NAA
IL-1ra	↓ < 0,0001 ↑	NS (0,9280)
IL-4	↓ < 0,05 ↑	NS (0,0784)
IL-6	↓ < 0,0001 ↑	NS (0,1882)
IL-7	↓ < 0,0001 ↑	NS (0,3663)
IL-8	↓ < 0,0001 ↑	NS (0,9875)
IL-12	↓ < 0,0001 ↑	NS (0,9093)
IL-10	↓ < 0,0001 ↑	NS (0,1366)
IL-13	NS (0,1659)	NS (0,9436)
IL-17	↓ < 0,0001 ↑	NS (0,3984)
Eotaxin	↓ < 0,0001 ↑	NS (0,9749)
IFN-gamma	↓ < 0,0001 ↑	NS (0,8752)
IP-10	↓ < 0,0001 ↑	NS (0,5584)
MCP-1	↓ < 0,0001 ↑	NS (0,5427)
MIP-1alfa	NS (0,0852)	NS (0,9187)
MIP-1beta	↓ < 0,0001 ↑	NS (0,2979)
RANTES	↓ < 0,05 ↑	NS (0,8690)

Cytokine serum profile in allergic and non-allergic top athletes

- AA = 41; NAA = 51; CTRL = 49
- Luminex assay
- For all cytokines measured, apart from IL-13 and MIP-1a, serum levels in athletes were significantly lower than in controls
- No differences were observed between allergic and non-allergic athletes
- The median value of the IFNg/IL-4 ratio was lower in athletes than in controls (33.0 vs. 37.9), particularly in the allergic ones (27.8)

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Current reviews of allergy and clinical immunology
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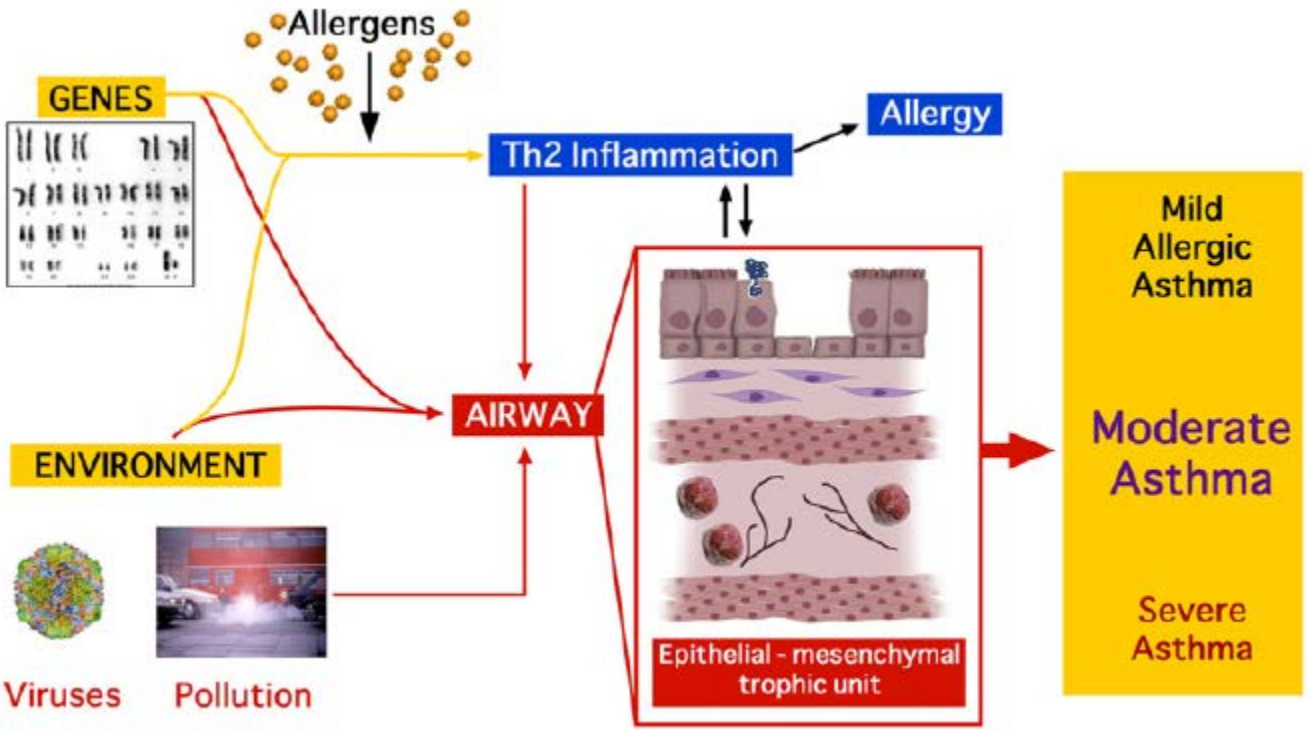
Epithelium dysfunction in asthma

Stephen T. Holgate, MD, DSc *Southampton, United Kingdom*

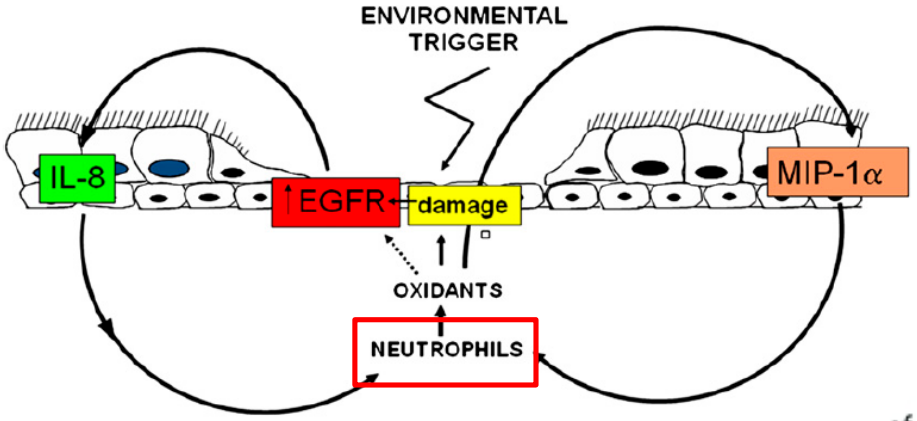


Physical exercise

Th2-low exercise induced asthma

Physical exercise as trigger on target organs

Potential role of epithelium damage in EIB



The Role of the Airway Epithelium and its Interaction with Environmental Factors in Asthma Pathogenesis

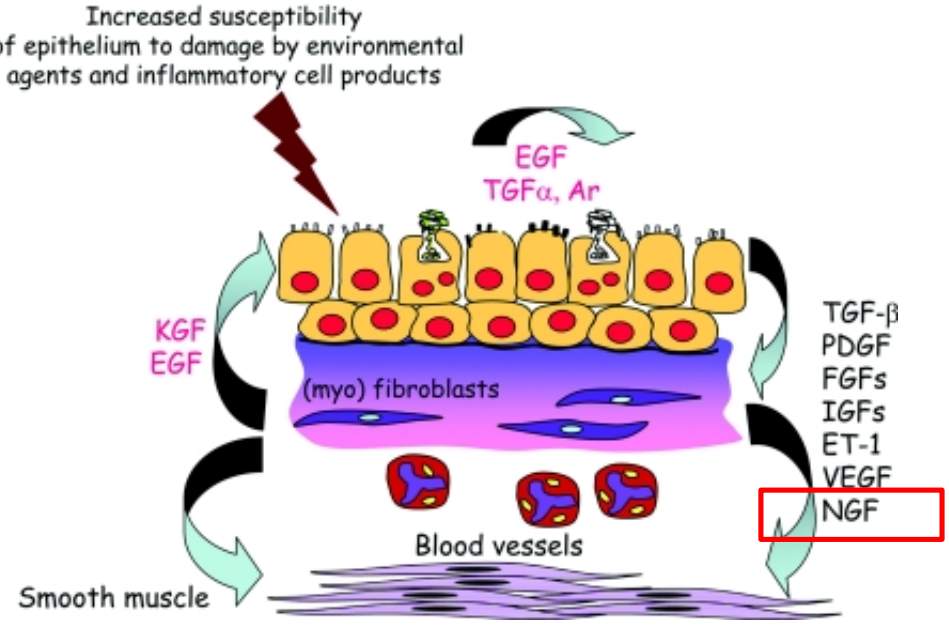
Stephen T. Holgate[1], Graham Roberts[1], Hasan S. Arshad[1], Peter H. Howarth[1], and Donna E. Davies[1]

Proc Am Thorac Soc Vol 6. pp 655–659, 2009
DOI: 10.1513/pats.200907-072DP
Internet address: www.atsjournals.org

A new look at the pathogenesis of asthma

Stephen T. Holgate,* Hasan S. Arshad,* Graham C. Roberts,*
Peter H. Howarth,* Philipp Thurner,† and Donna E. Davies*

Clin Sci (Lond). 2009 December 23; 118(Pt 7): 439–450.



Increased Nerve Growth Factor Serum Levels in Top Athletes

Matteo Bonini, MD, PhD,† Daniela Fioretti, PhD,† Vittorio Sargentini, MD,‡ Stefano Del Giacco, MD,§ Monica Rinaldi, PhD,† Carlo Tranquilli, MD,¶ and Sergio Bonini, MD†||*

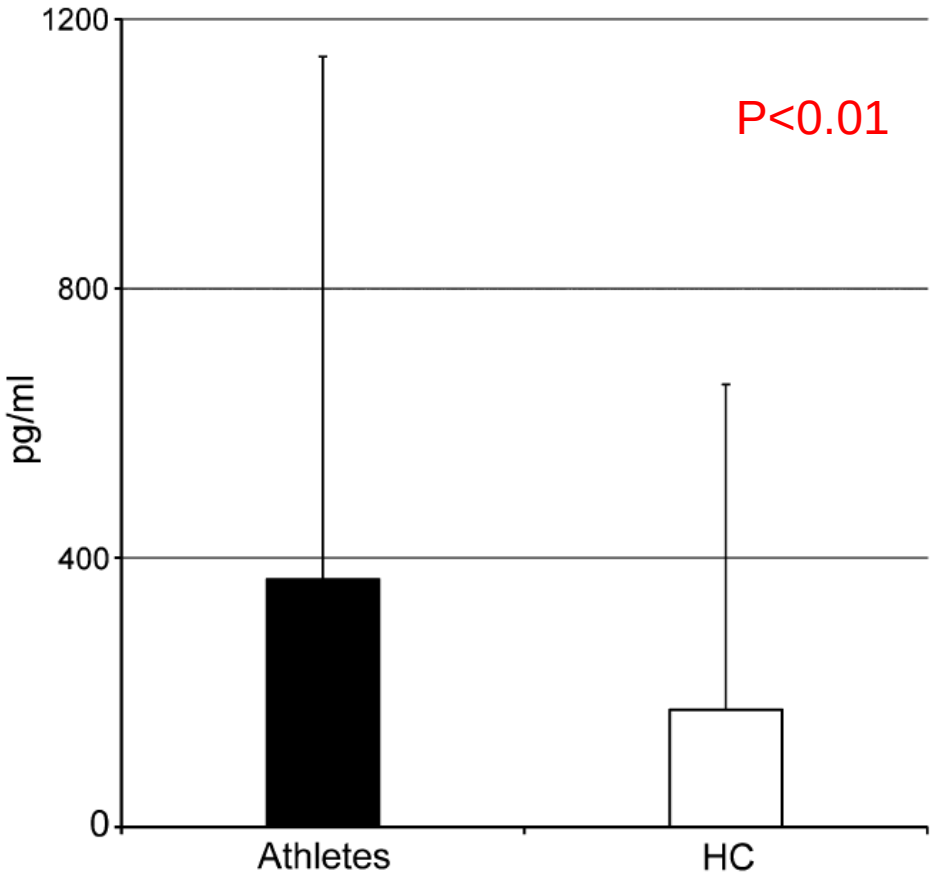
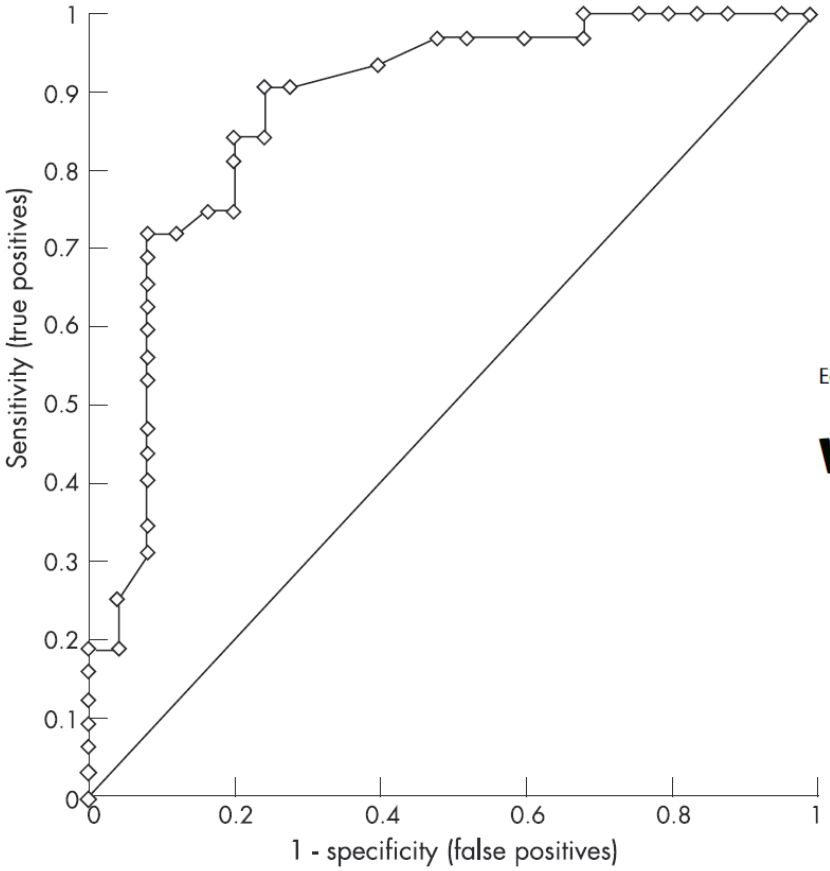


FIGURE 1. Nerve growth factor mean serum values in 96 athletes and 49 HC.

(*Clin J Sport Med* 2013;23:228–231)

Ventilation heterogeneity is a major determinant of airway hyperresponsiveness in asthma, independent of airway inflammation

Sue R Downie, Cheryl M Salome, Sylvia Verbanck, Bruce Thompson, Norbert Berend, Gregory G King



Treating the Small Airways

Respiration 2012;84:441–453
DOI: 10.1159/000343629

Omar S. Usmani

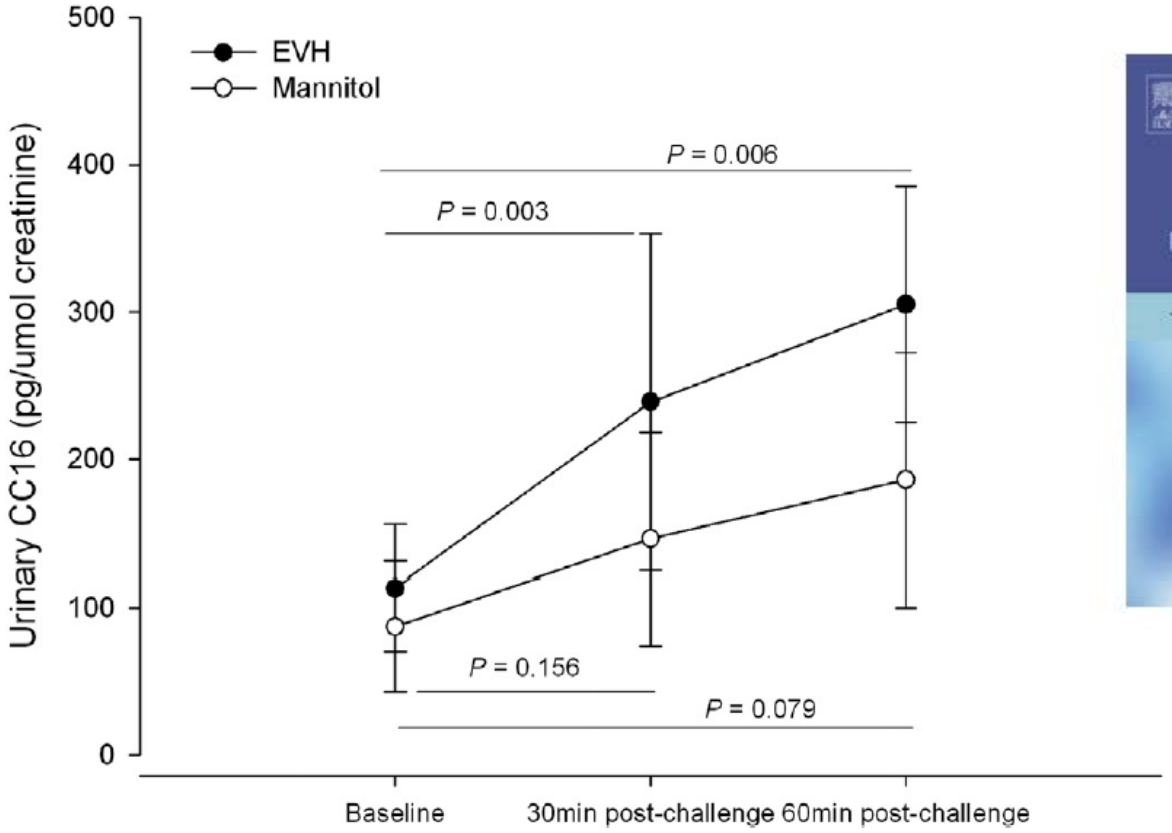
Editorials

Will the Small Airways Rise Again?

Thorax 2007;**62**:684–689.

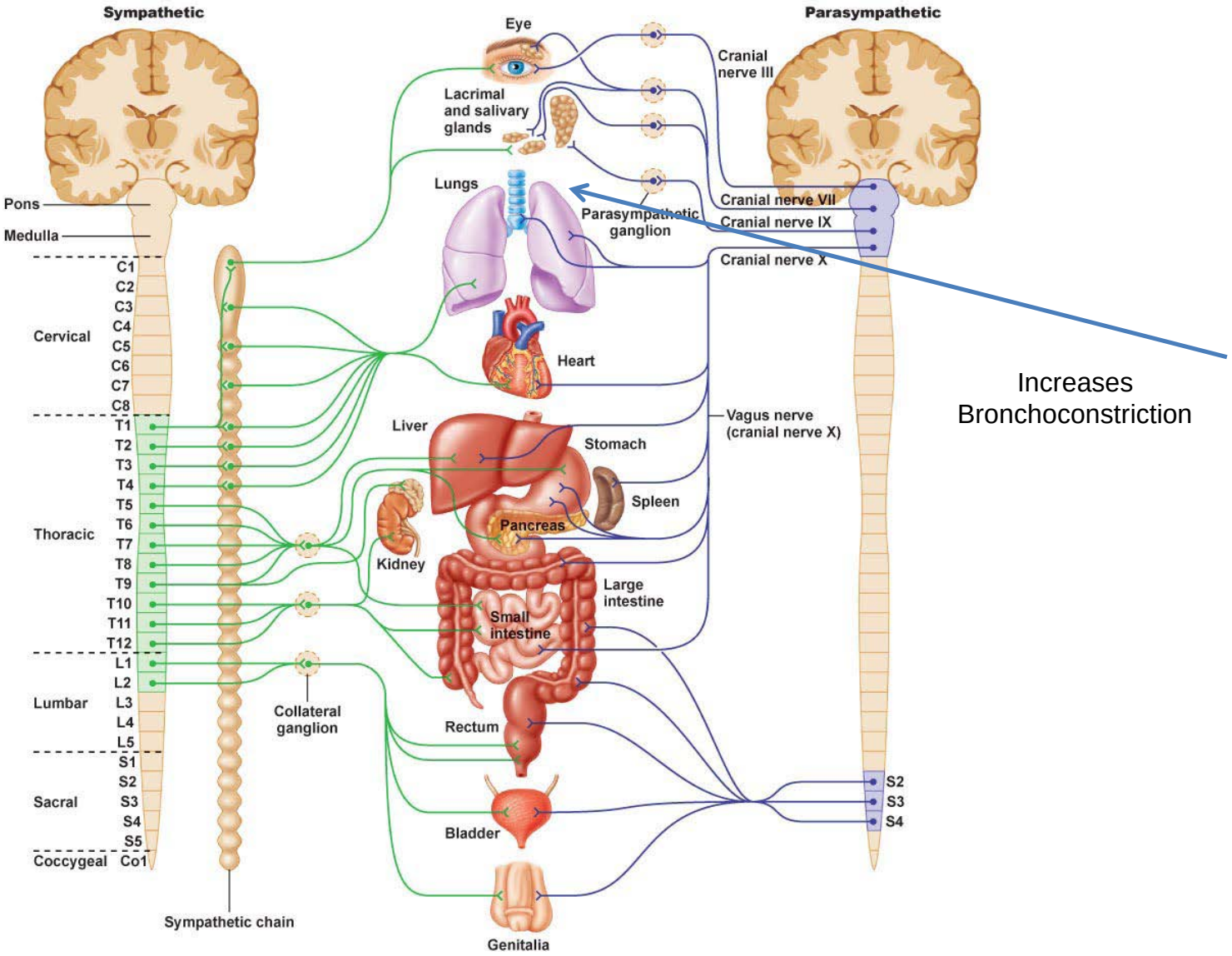
Urinary CC16 after challenge with dry air hyperpnoea and mannitol in recreational summer athletes

Pascale Kippelen [a,*], Ellen Tufvesson [b], Leena Ali [c], Leif Bjermer [b], Sandra D. Anderson [d]

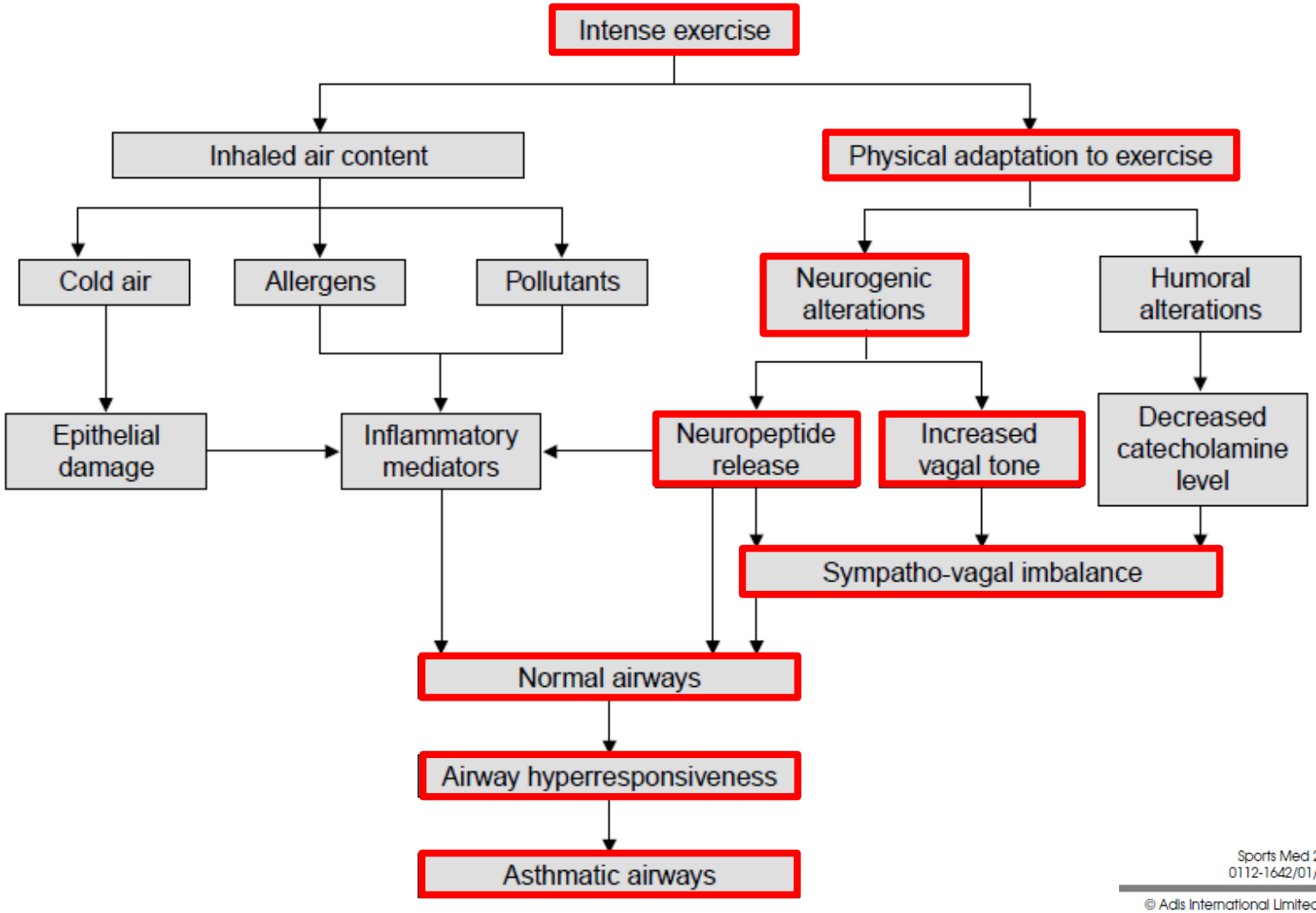


Respiratory Medicine (2013) **107**, 1837–1844

The autonomic nervous system



Prevalence and Mechanisms of Development of Asthma and Airway Hyperresponsiveness in Athletes

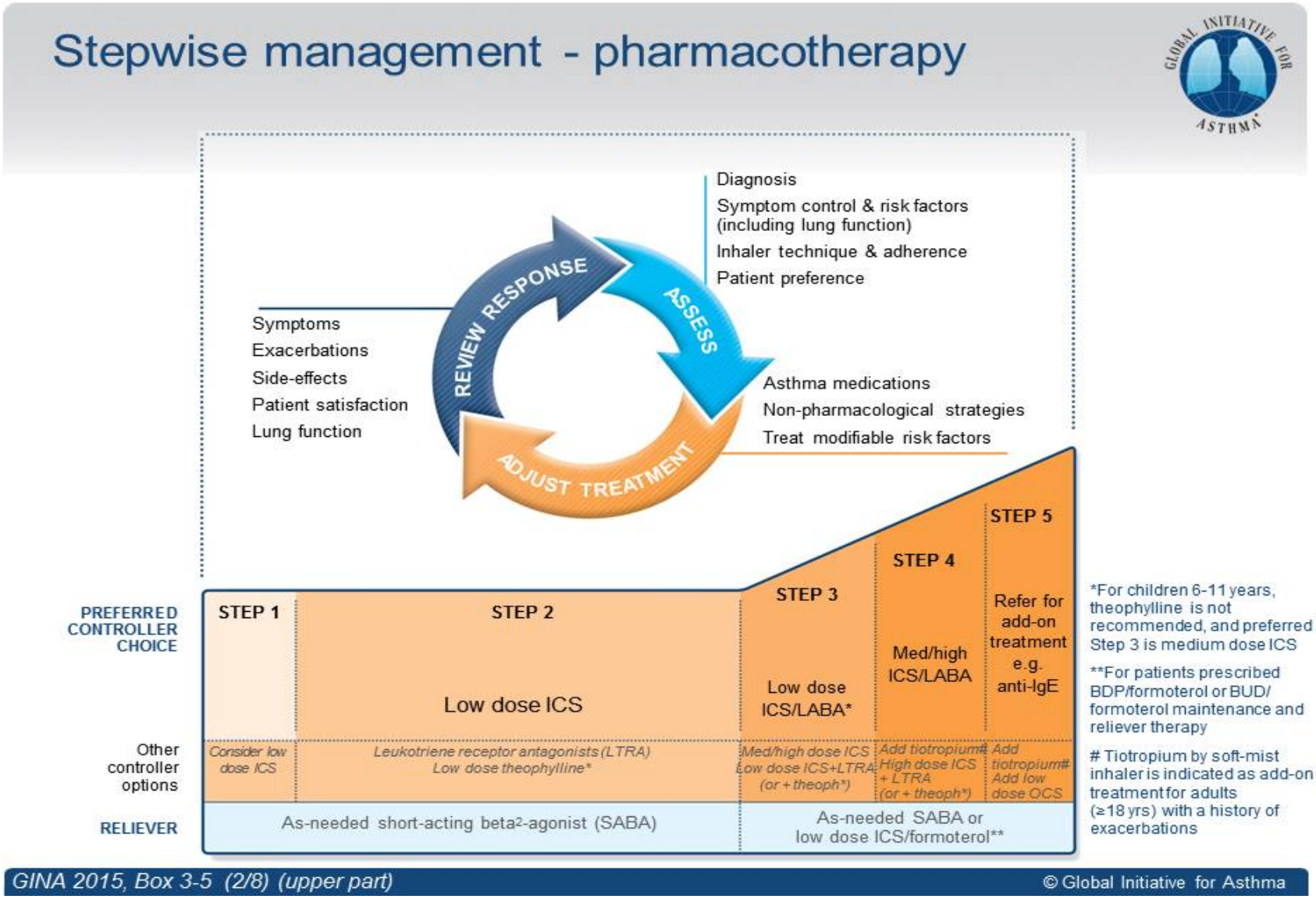


Sports Med 2001; 31 (8): 601-616
0112-1642/01/0008-0601/$22.00/0

Management of EIB

- The two main principles of treating exercise-induced bronchospasm consist in:
  - reversing the bronchial obstruction induced by exercise with bronchodilators
  - preventing it either by the chronic use of controller drugs in subjects with asthma or by administering, just before exercise, drugs which have been shown to be able to inhibit symptoms as well as the decrease of pulmonary function parameters

Management of EIB with asthma



Management of EIB without asthma

Treatment

Drugs

Beta-2 agonists (short-acting)

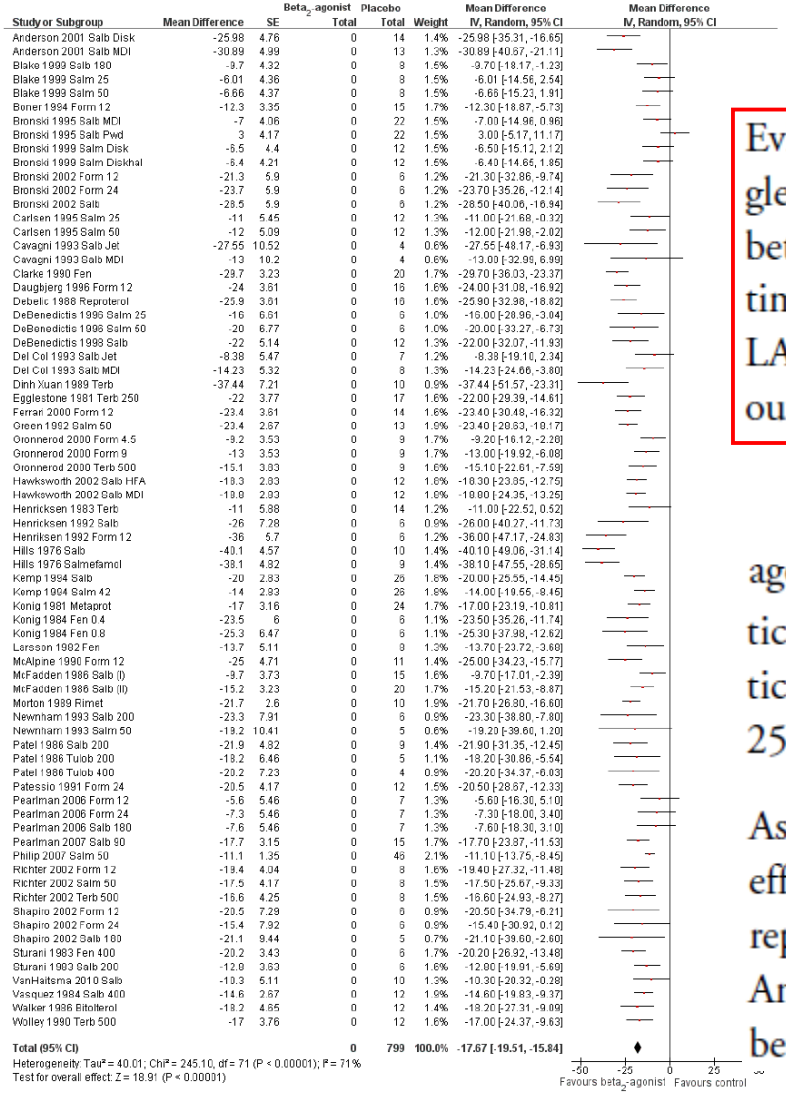
Prevention

Drugs	Time of administration
Beta-2 agonists (short-acting)	15 min before exercise
Beta-2 agonists (long-acting)	60 min before exercise
Cromons	15 min before exercise
Leukotriene modifiers	60 min before exercise

Beta$_2$-agonists for exercise-induced asthma

Matteo Bonini[1,2,3], Corrado Di Mambro[4], Moises A Calderon[3], Enrico Compalati[5], Holger Schünemann[6], Stephen Durham[3], Giorgio W Canonica[5]

THE COCHRANE COLLABORATION®



Study or Subgroup	Mean Difference	SE	Beta$_2$-agonist Total	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Anderson 2001 Salb Disk	-25.98	4.76	0	14	1.4%	-25.98 [-35.31, -16.65]
Anderson 2001 Salb MDI	-30.89	4.99	0	13	1.3%	-30.89 [-40.67, -21.11]
Blake 1999 Salb 180	-9.7	4.32	0	9	1.5%	-9.70 [-18.17, -1.23]
Blake 1999 Salm 25	-6.01	4.36	0	9	1.5%	-6.01 [-14.56, 2.54]
Blake 1999 Salm 50	-6.66	4.37	0	9	1.5%	-6.66 [-15.23, 1.91]
Boner 1994 Form 12	-12.3	3.35	0	15	1.7%	-12.30 [-18.87, -5.73]
Bronski 1995 Salb MDI	-7	4.06	0	22	1.5%	-7.00 [-14.96, 0.96]
Bronski 1995 Salb Pwd	3	4.17	0	22	1.5%	3.00 [-5.17, 11.17]
Bronski 1999 Salm Disk	-6.5	4.4	0	12	1.5%	-6.50 [-15.12, 2.12]
Bronski 1999 Salm Diskhal	-6.4	4.21	0	12	1.5%	-6.40 [-14.66, 1.86]
Bronski 2002 Form 12	-21.3	5.9	0	6	1.2%	-21.30 [-32.86, -9.74]
Bronski 2002 Form 24	-23.7	5.9	0	6	1.2%	-23.70 [-35.26, -12.14]
Bronski 2002 Salb	-28.5	5.9	0	6	1.2%	-28.50 [-40.06, -16.94]
Carlsen 1995 Salm 25	-11	5.45	0	12	1.3%	-11.00 [-21.68, -0.32]
Carlsen 1995 Salm 50	-12	5.09	0	12	1.3%	-12.00 [-21.98, -2.02]
Cavagni 1993 Salb Jet	-27.55	10.52	0	4	0.6%	-27.55 [-48.17, -6.93]
Cavagni 1993 Salb MDI	-13	10.2	0	4	0.6%	-13.00 [-32.99, 6.99]
Clarke 1990 Fen	-29.7	3.23	0	20	1.7%	-29.70 [-36.03, -23.37]
Daugbjerg 1996 Form 12	-24	3.61	0	16	1.6%	-24.00 [-31.08, -16.92]
Debelic 1988 Reproterol	-25.9	3.61	0	16	1.6%	-25.90 [-32.98, -18.82]
DeBenedictis 1999 Salm 25	-16	6.61	0	6	1.0%	-16.00 [-28.96, -3.04]
DeBenedictis 1999 Salm 50	-20	6.77	0	6	1.0%	-20.00 [-33.27, -6.73]
DeBenedictis 1999 Salb	-22	5.14	0	12	1.3%	-22.00 [-32.07, -11.93]
Del Col 1993 Salb Jet	-8.38	5.47	0	7	1.2%	-8.38 [-19.10, 2.34]
Del Col 1993 Salb MDI	-14.23	5.32	0	8	1.3%	-14.23 [-24.66, -3.80]
Dinh Xuan 1989 Terb	-37.44	7.21	0	10	0.9%	-37.44 [-51.57, -23.31]
Egglestone 1981 Terb 250	-22	3.77	0	17	1.6%	-22.00 [-29.39, -14.61]
Ferrari 2000 Form 12	-23.4	3.61	0	16	1.6%	-23.40 [-30.48, -16.32]
Green 1992 Salm 50	-23.4	2.87	0	13	1.9%	-23.40 [-29.03, -17.77]
Gronnerod 2000 Form 4.5	-9.2	3.53	0	9	1.7%	-9.20 [-16.12, -2.28]
Gronnerod 2000 Form 9	-13	3.53	0	9	1.7%	-13.00 [-19.92, -6.08]
Gronnerod 2000 Terb 500	-15.1	3.83	0	9	1.6%	-15.10 [-22.61, -7.59]
Hawksworth 2002 Salb HFA	-18.3	2.93	0	12	1.8%	-18.30 [-23.85, -12.75]
Hawksworth 2002 Salb MDI	-18.9	2.93	0	12	1.8%	-18.90 [-24.35, -13.25]
Henricksen 1983 Terb	-11	5.88	0	14	1.2%	-11.00 [-22.52, 0.52]
Henricksen 1992 Salb	-26	7.28	0	6	0.9%	-26.00 [-40.27, -11.73]
Henriksen 1992 Form 12	-36	5.7	0	6	1.2%	-36.00 [-47.17, -24.83]
Hills 1976 Salb	-40.1	4.57	0	10	1.4%	-40.10 [-49.06, -31.14]
Hills 1976 Salmefamol	-38.1	4.82	0	9	1.4%	-38.10 [-47.55, -28.65]
Kemp 1994 Salb	-20	2.83	0	26	1.8%	-20.00 [-25.55, -14.45]
Kemp 1994 Salm 42	-14	2.93	0	26	1.8%	-14.00 [-19.56, -8.45]
Konig 1981 Metaprot	-17	3.16	0	24	1.7%	-17.00 [-23.19, -10.81]
Konig 1984 Fen 0.4	-23.5	6	0	6	1.1%	-23.50 [-35.26, -11.74]
Konig 1984 Fen 0.8	-25.3	6.47	0	6	1.1%	-25.30 [-37.98, -12.62]
Larsson 1982 Fen	-13.7	5.11	0	9	1.3%	-13.70 [-23.72, -3.68]
McAlpine 1990 Form 12	-25	4.71	0	11	1.4%	-25.00 [-34.23, -15.77]
McFadden 1986 Salb (I)	-9.7	3.73	0	15	1.6%	-9.70 [-17.01, -2.39]
McFadden 1986 Salb (II)	-15.2	3.23	0	20	1.7%	-15.20 [-21.53, -8.87]
Morton 1999 Rimet	-21.7	2.6	0	10	1.9%	-21.70 [-26.80, -16.60]
Newnham 1993 Salb 200	-23.3	7.91	0	6	0.9%	-23.30 [-38.80, -7.80]
Newnham 1993 Salm 50	-19.2	10.41	0	5	0.6%	-19.20 [-39.60, 1.20]
Patel 1986 Salb 200	-21.9	4.82	0	9	1.4%	-21.90 [-31.35, -12.45]
Patel 1986 Tulob 200	-18.2	6.46	0	5	1.1%	-18.20 [-30.86, -5.54]
Patel 1986 Tulob 400	-20.2	7.23	0	4	0.9%	-20.20 [-34.37, -6.03]
Patessio 1991 Form 24	-20.5	4.17	0	12	1.5%	-20.50 [-28.67, -12.33]
Pearlman 2006 Form 12	-5.6	5.46	0	7	1.3%	-5.60 [-16.30, 5.10]
Pearlman 2006 Form 24	-7.3	5.46	0	7	1.3%	-7.30 [-18.00, 3.40]
Pearlman 2006 Salb 180	-7.6	5.46	0	7	1.3%	-7.60 [-18.30, 3.10]
Pearlman 2007 Salb 90	-17.7	3.15	0	15	1.7%	-17.70 [-23.87, -11.53]
Philip 2007 Salm 50	-11.1	1.35	0	46	2.1%	-11.10 [-13.75, -8.45]
Richter 2002 Form 12	-19.4	4.04	0	8	1.6%	-19.40 [-27.32, -11.48]
Richter 2002 Salm 50	-17.5	4.17	0	8	1.5%	-17.50 [-25.67, -9.33]
Richter 2002 Terb 500	-16.6	4.25	0	8	1.5%	-16.60 [-24.93, -8.27]
Shapiro 2002 Form 12	-20.5	7.29	0	6	0.9%	-20.50 [-34.79, -6.21]
Shapiro 2002 Form 24	-15.4	7.92	0	6	0.9%	-15.40 [-30.92, 0.12]
Shapiro 2002 Salb 180	-21.1	9.44	0	5	0.7%	-21.10 [-39.60, -2.60]
Sturani 1983 Fen 400	-20.2	3.43	0	8	1.7%	-20.20 [-26.92, -13.48]
Sturani 1983 Salb 200	-12.0	3.63	0	6	1.6%	-12.00 [-19.91, -5.69]
VanHaltsma 2010 Salb	-10.3	5.11	0	10	1.3%	-10.30 [-20.32, -0.28]
Vasquez 1984 Salb 400	-14.6	2.67	0	12	1.9%	-14.60 [-19.83, -9.37]
Walker 1986 Bitolterol	-18.2	4.65	0	12	1.4%	-18.20 [-27.31, -9.09]
Wolley 1990 Terb 500	-17	3.76	0	12	1.6%	-17.00 [-24.37, -9.63]
Total (95% CI)			**0**	**799**	**100.0%**	**-17.67 [-19.51, -15.84]**

Heterogeneity: Tau² = 40.01; Chi² = 245.10, df = 71 (P < 0.00001); I² = 71%
Test for overall effect: Z = 18.91 (P < 0.00001)

Mean Difference IV, Random, 95% CI

-50 -25 0 25

Favours beta$_2$-agonist Favours control

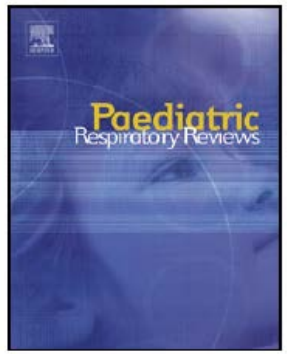
Evidence emerging from the meta-analysis of 45 short-term (single administration) studies shows that both short- and long-acting beta$_2$-agonists administered as preventive treatment (within the time-effect period set at one hour for SABA and at 12 hours for LABA) prevent exercise-induced asthma, as shown by the primary outcomes related to the FEV_1 fall.

... secondary outcomes considered show that the beta$_2$-agonist preventive effect is also documented by the number of participants protected (complete protection detectable in 68% of participants) and by other pulmonary function variables (PEF, FEF 25%-75%, MEF 50%)

As far as they concern secondary outcomes related to safety, side effects were assessed in 55 trials (Figure 5). Among these, 42 arms reported no adverse event for either active or placebo treatment. Analysis of the remaining 13 trials showed no significant difference between beta$_2$-agonists and placebo.

Beta-2 agonists for exercise-induced bronchoconstriction in children

Matteo Bonini



The analysis of the pediatric studies highlights that the beta2-agonist acute preventive effect, is significant, although highly heterogeneous. It is also interesting to note that all the trials which failed to prove a significant beta2-agonist effect compared to placebo were performed in children. Only two papers addressed the efficacy and safety of a chronic beta-2 agonist treatment in children, preventing from any general conclusive statement.

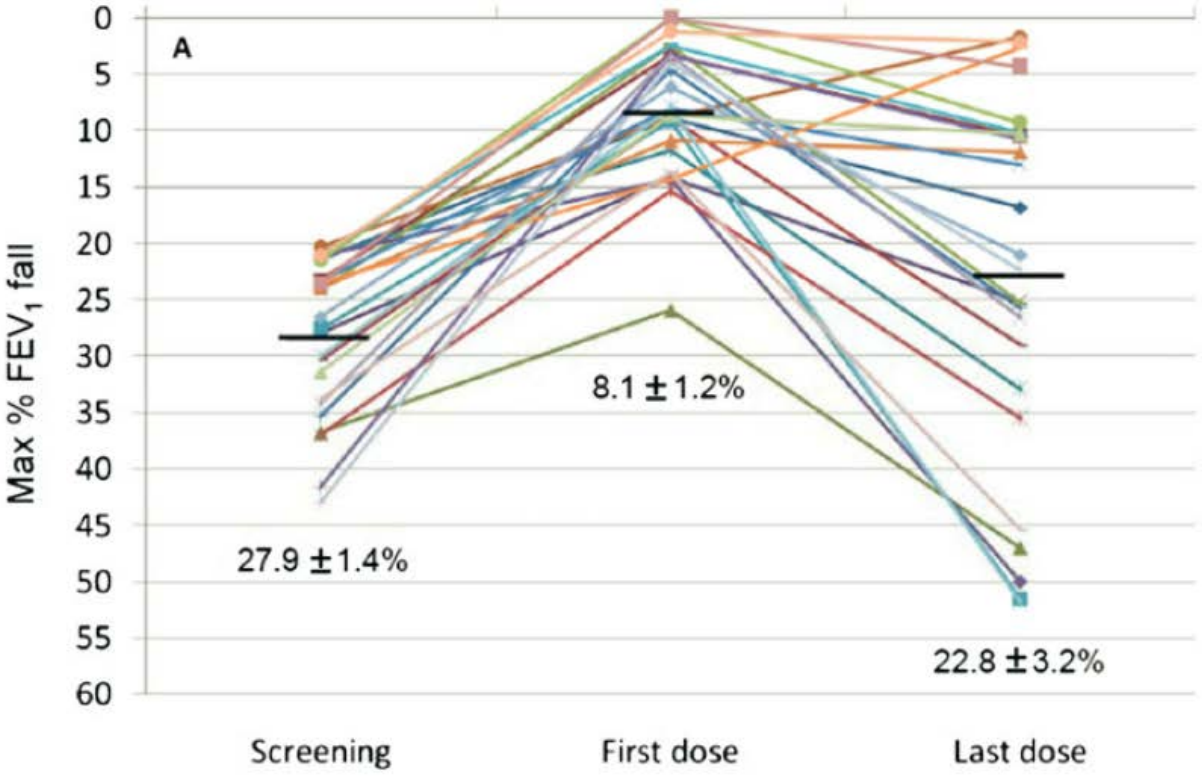
Cochrane Corner

THE COCHRANE COLLABORATION®

Loss of Salmeterol Bronchoprotection against Exercise in Relation to ADRB2 Arg16Gly Polymorphism and Exhaled Nitric Oxide

THE HARVARD MEDICAL SCHOOL

Matteo Bonini[1], Perdita Permaul[1], Tejaswini Kulkarni[1], Shamsah Kazani[1], Alex Segal[1], Christine A. Sorkness[2], Michael E. Wechsler[1], and Elliot Israel[1]



Am J Respir Crit Care Med Vol 188, Iss. 12, pp 1407–1412,

CLINICAL RESEARCH STUDY

The American Journal of Medicine (2010) 123, 322-328

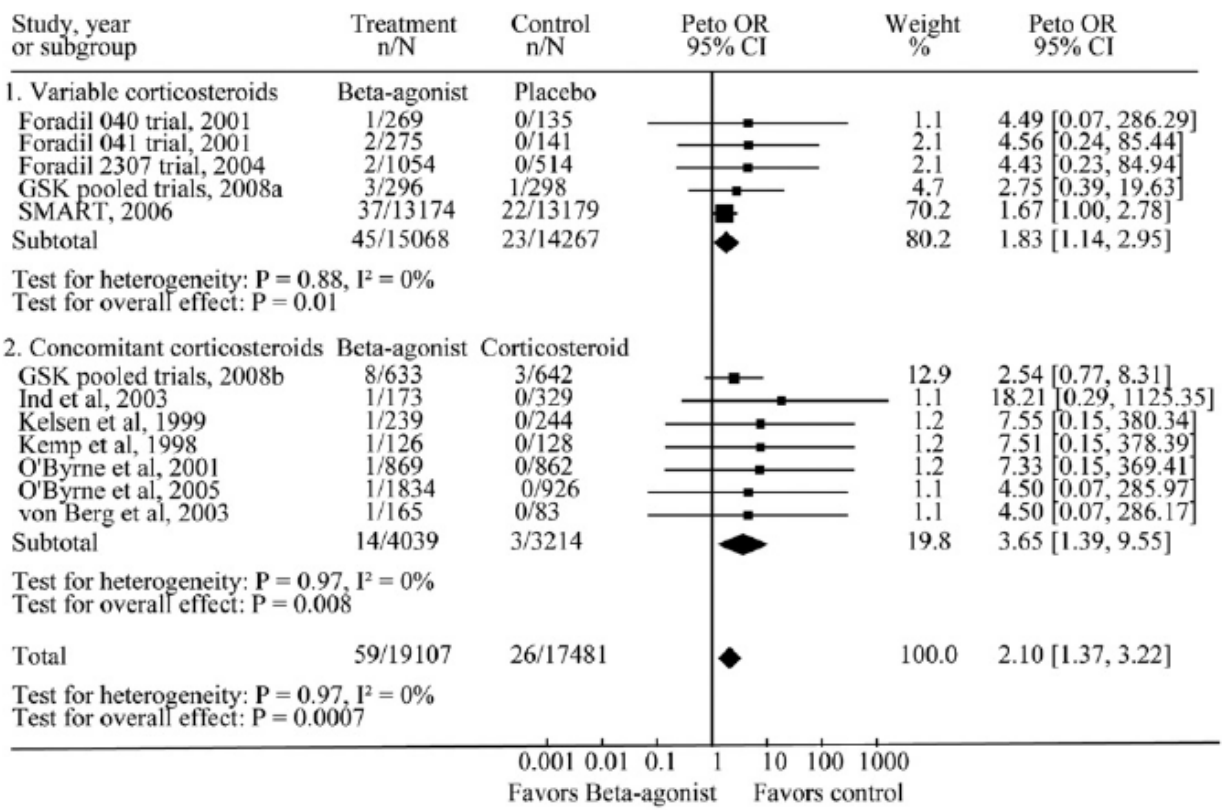
THE AMERICAN JOURNAL of MEDICINE®

Long-acting Beta-Agonists with and without Inhaled Corticosteroids and Catastrophic Asthma Events

Shelley R. Salpeter, MD, FACP,[a,b] Andrew J. Wall, MD,[a,b] Nicholas S. Buckley[c]

[a]Stanford University School of Medicine, Stanford, Calif; [b]Santa Clara Valley Medical Center, San Jose, Calif; [c]California Institute for Technology, Pasadena.

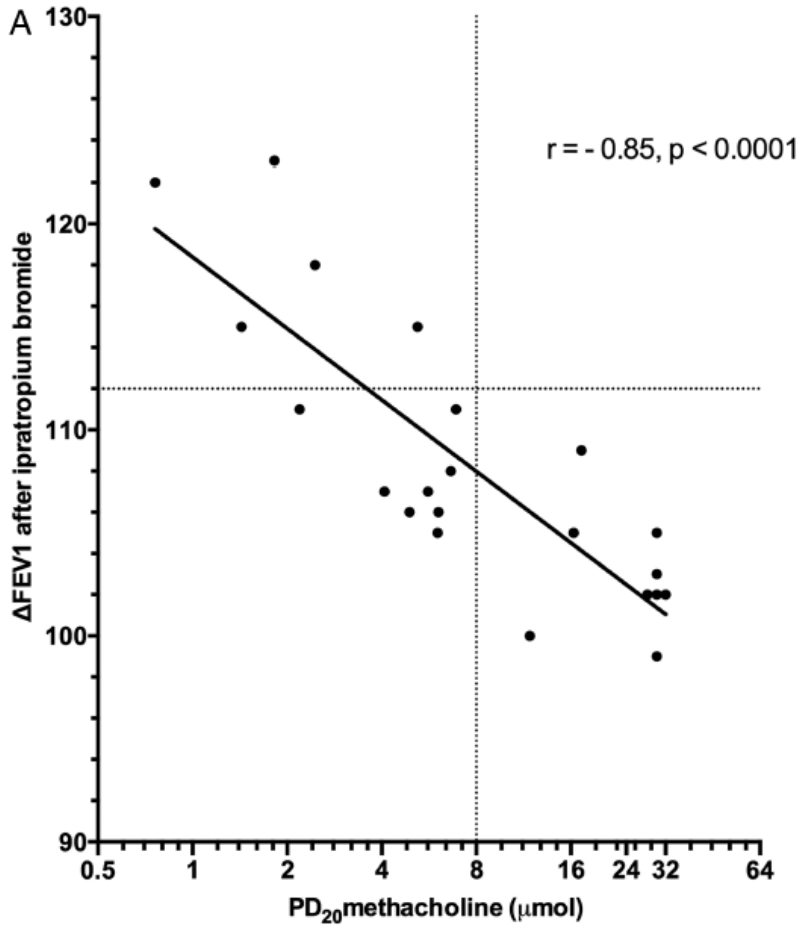
Figure 2 Effect of long-acting β-agonists on asthma intubations and deaths.

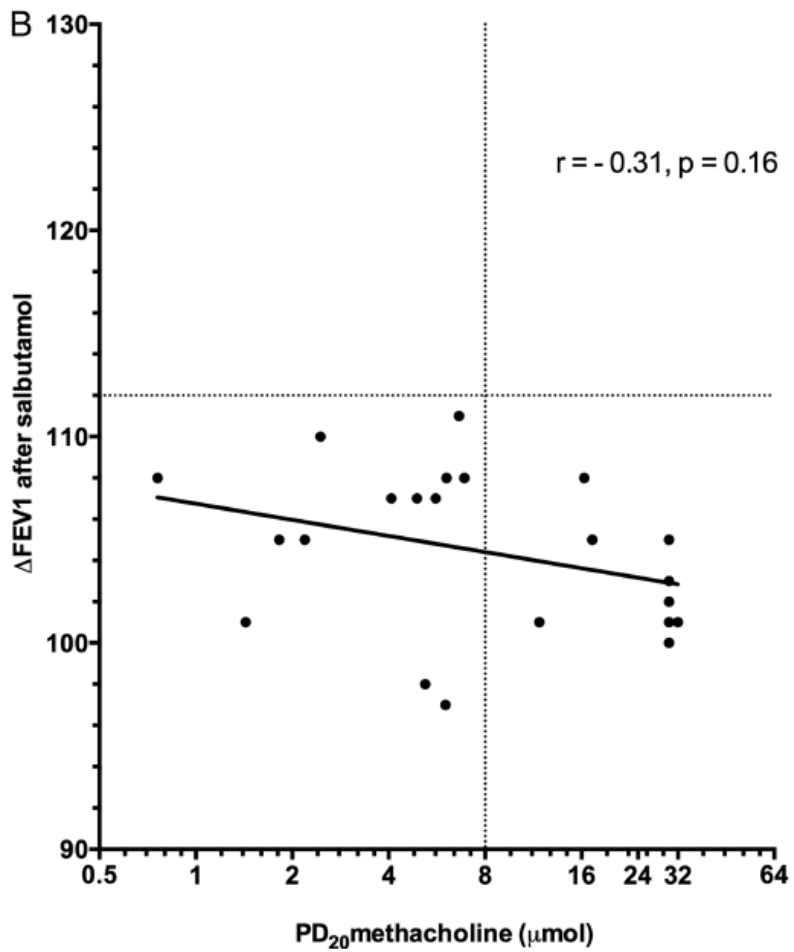


Increased bronchial parasympathetic tone in elite cross-country and biathlon skiers: a randomised crossover study

J Stang,[1] M Couto,[2,3] K-H Carlsen,[1,4,5] T Stensrud[1]

To cite: Stang J, Couto M, Carlsen K-H, *et al*. *Br J Sports Med* 2015;**49**:56–61.





2015 WADA anti-doping rules

Treatment	WADA rules	Notes
Antihistamines	Permitted	Second generation molecules should be preferred to avoid side effects
Leukotriene modifiers	Permitted	
Inhaled steroids	Permitted	
Immunotherapy	Permitted	SCIT should not be performed before or after physical exercise
β2 agonists	Inhaled *Salbutamol* *(max 1600 mcg/24H)* *Formoterol (max 54 mcg/24H) and Salmeterol* All others prohibited in and out competition	The presence in urine of salbutamol >1000 ng/mL or formoterol >40 ng/mL is presumed not to be an intended therapeutic use of the substance and will be considered as an Adverse Analytical Finding
Systemic steroids	Prohibited in competition	
Ephedrine, methylephedrine	Prohibited in competition	A concentration in urine greater than 10 ug/ml represent an adverse analytical findings

REVIEW ARTICLE

Airway dysfunction in elite athletes – an occupational lung disease?

O. J. Price[1], L. Ansley[1], A. Menzies-Gow[2,3], P. Cullinan[2,3] & J. H. Hull[1,2,3]

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In the meantime, it is our opinion that the evidence is currently sufficient to afford elite athletes the same considerations for their airway health as other individuals with potential and relevant occupational exposures.

Allergy **68** (2013) 1343–1352