

Rôle des endotoxines de l'environnement intérieur dans les pathologies respiratoires

Olivier Michel

CHU Brugmann

Université Libre de Bruxelles

ENDOTOXIN ACTIVITY OF A HOUSE DUST EXTRACT

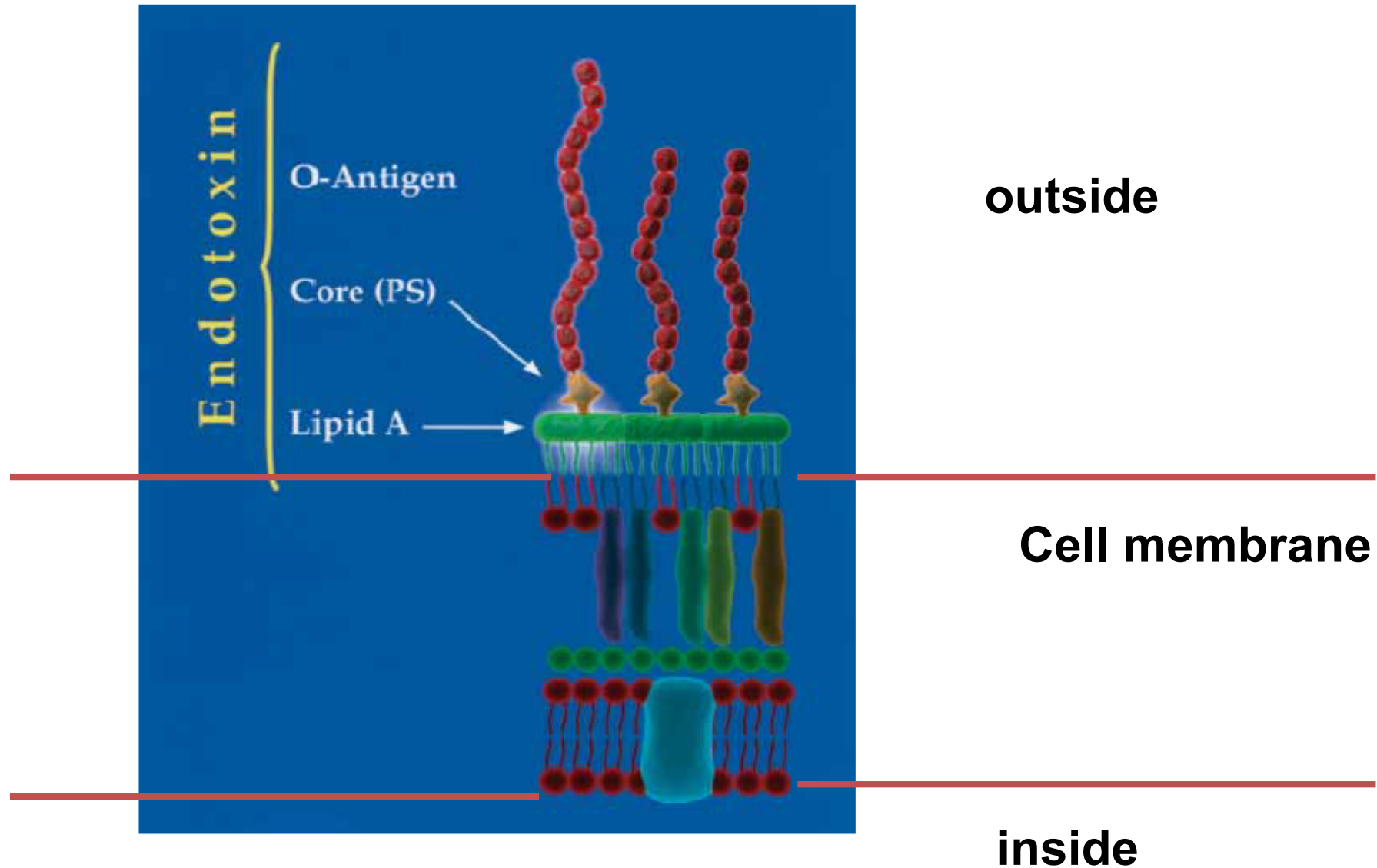
Abstract

A commercial dust extract has been demonstrated to contain endotoxin-like activity. The clinical significance of this finding is unclear, but any substance as biologically active as endotoxin must be seriously considered to have some action when it is injected into a living organism. Any study of the action of dust extract in clinical allergy must consider this potent substance.

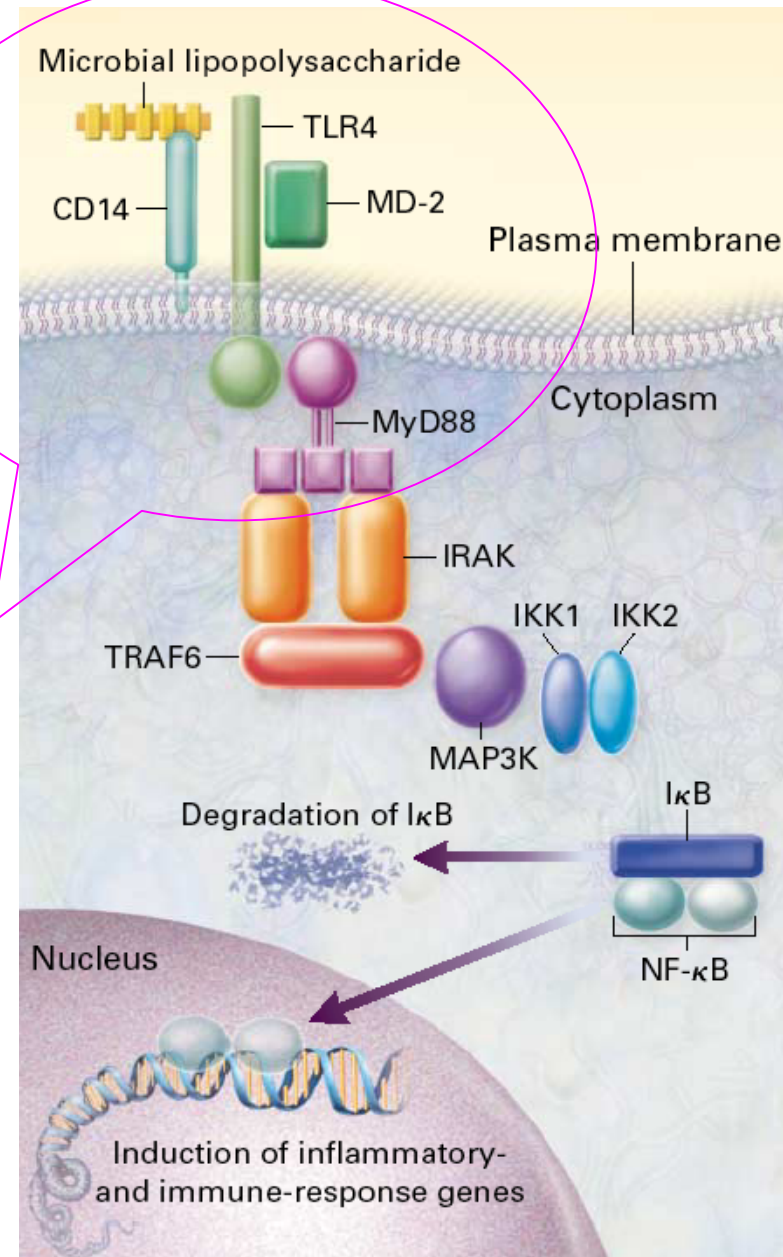
PETERSON RD, WICKLUNDS PE, GOOD RA.

J Allergy Clin Immunol. 1964 Mar-Apr;35:134-42.

Gram negative bacteria



The LPS receptor



*R Medzhitov, C Janeway.
N Engl J Med 2000; 343: 338-44*

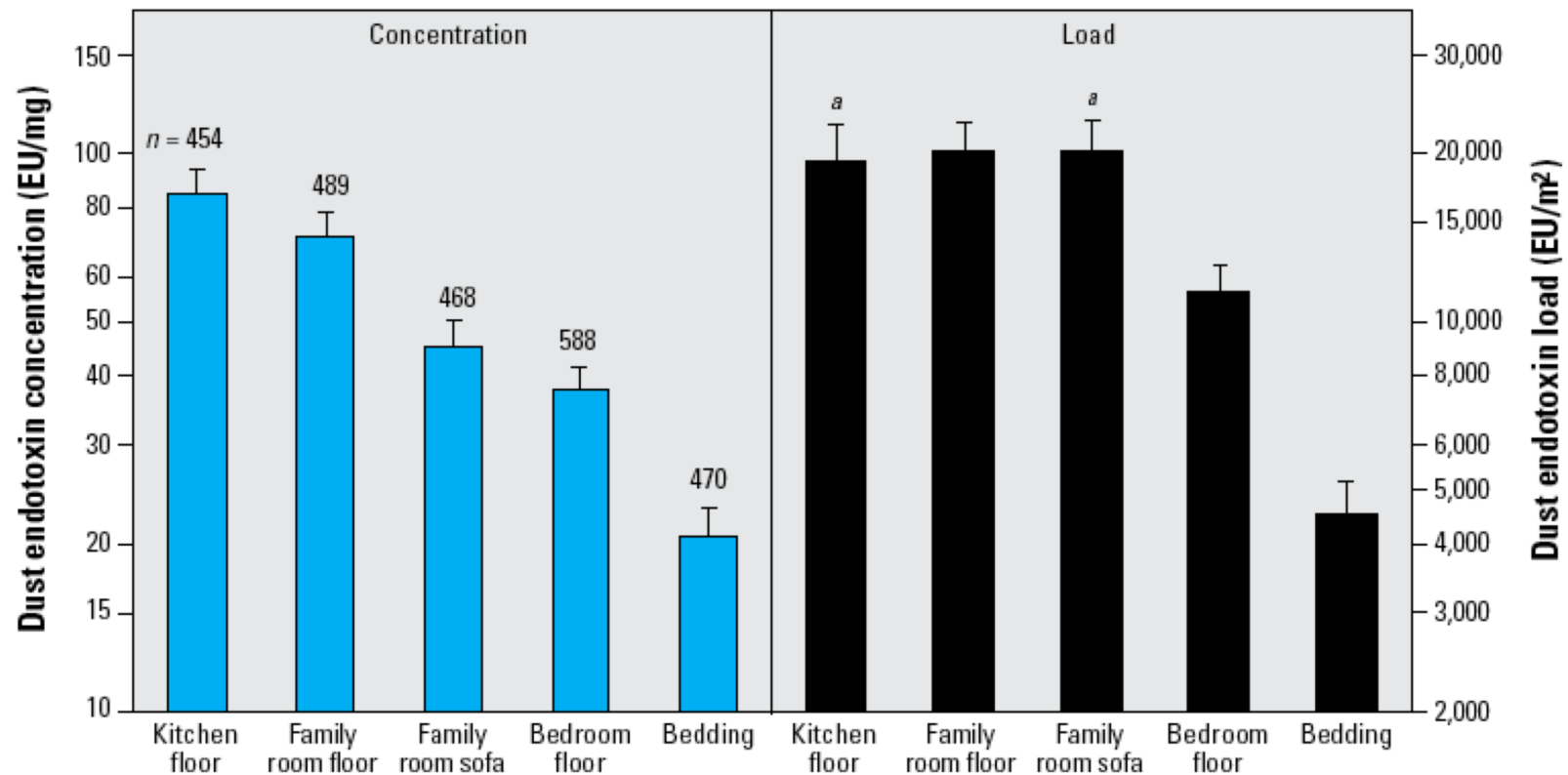
Endotoxin in house dust

Table 1. Endotoxin concentrations in house dust

Reference	<i>n</i>	Room	Location	Settled/ airborne dust	Endotoxin concentration (ng/g HD or ng/m ³ air)	Significant risk factor
Rylander & Malmberg (1992) ⁸⁹	8	Day-care center	Air	Airborne	0.43 ng/m ³	ND
	10	School	Air	(inhalable)	0.26 ng/m ³	
	36	Office	Air		0.06 ng/m ³	
Michel <i>et al.</i> (1992) ⁴⁹	28	Bedroom	Floor + mattress	Settled	2274 ng/g	Not related with the presence of cat
Preller <i>et al.</i> (1995) ²⁷	194	Living (pig farmers)	Air	Airborne (inhalable)	111 ng/m ³	Farming
Michel <i>et al.</i> (1996) ²⁸	69	Bedroom	Floor	Settled	1860 ng/g	Not related with Der p1
			Mattress	Settled	1780 ng/g	
Rizzo <i>et al.</i> (1997) ²⁹	20	Bedroom	Floor + mattress	Settled	1080 ng/g	ND
Douwes <i>et al.</i> (1998) ³⁰	25	Living	Floor	Settled	1730 ng/g	Built after 1970
		Bedroom	Floor	Settled	730 ng/g	
		Bedroom	Mattress	Settled	270 ng/g	
Wouters <i>et al.</i> (2000) ³¹	99	Living	Floor	Settled	601 ng/g	Storage of separated organic dust
		Kitchen	Floor	Settled	1344 ng/g	
Gereda <i>et al.</i> (2000) ³²	61	Living + bedroom	Floor + mattress	Settled	18,240 ng/g	ND
von Mutius <i>et al.</i> (2000) ³³	84	Kitchen farming Kitchen controls	Floor	Settled	14,300 ng/g	Farming
			Floor	Settled	3900 ng/g	
				Air inhalable	15 ng/m ³	
				Air respirable	0.7 ng/m ³	
Park <i>et al.</i> (2001) ³⁴	499	Living	Floor	Settled	7900 ng/g	Dog, cockroach
		Bedroom	Floor	Settled	6300 ng/g	
		Bedroom	Mattress	Settled	5000 ng/g	
Gereda <i>et al.</i> (2001) ³⁵	86	Living/bedroom	Floor + mattress	Settled	17,820 ng/g	Presence of animals
Heinrich <i>et al.</i> (2001) ³⁶	454	Living	Floor	Settled	1960 ng/g	Dog, cat, cockroach
Franci <i>et al.</i> (2001) ³⁷	100	Bedroom	Floor	Settled	1930 ng/g	ND
Bischof <i>et al.</i> (2002) ³⁸	405	Living	Floor	Settled	2 274 ng/g	Poor hygienic conditions

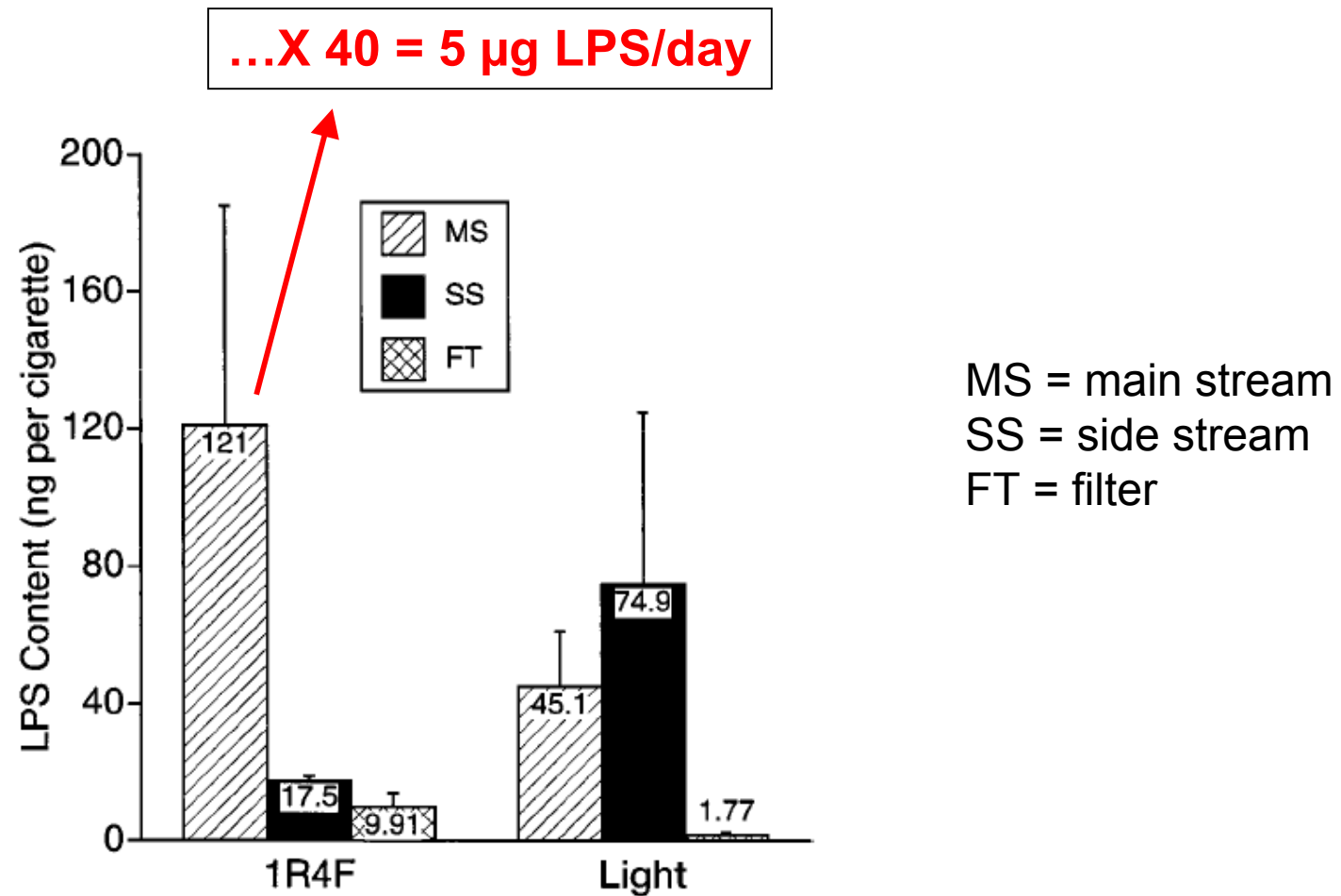
Data expressed in EU have been transformed to ng (1 ng = 10 EU).

Endotoxine dans l'habitat US



PS Thorne et al. Environ Health Perspect 2009

Endotoxin and cigarette smoke

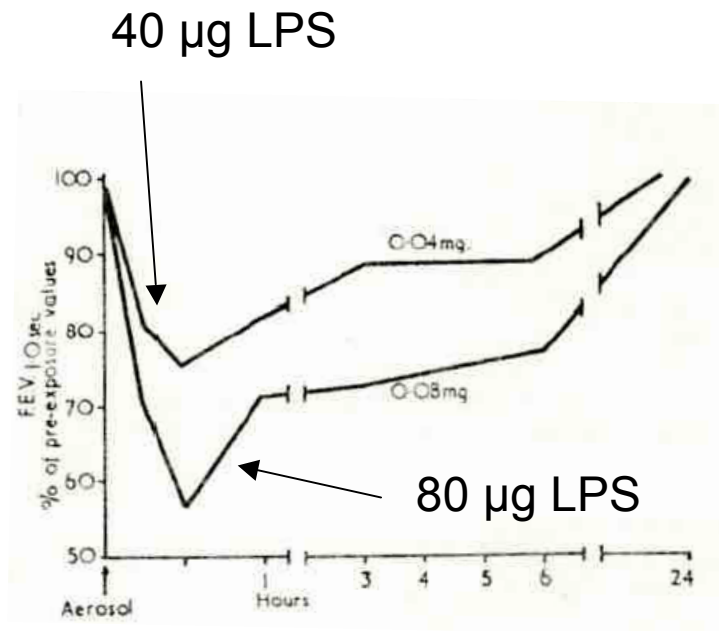


JD Hasday Chest 1999; 115: 829

Lung function response to LPS

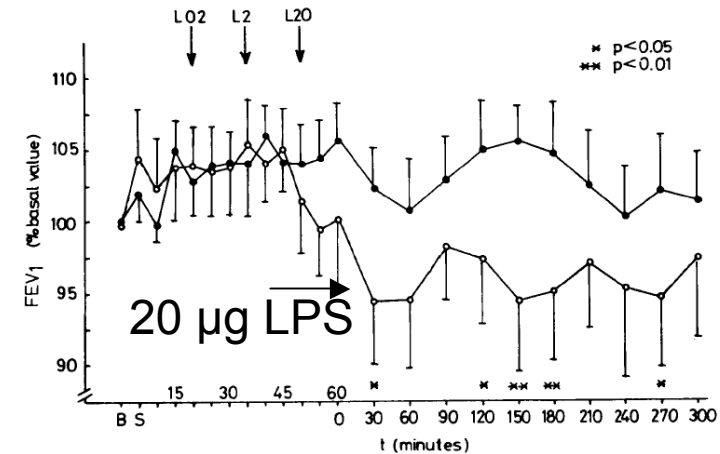
Chronic bronchitis

FEV₁ (100%)



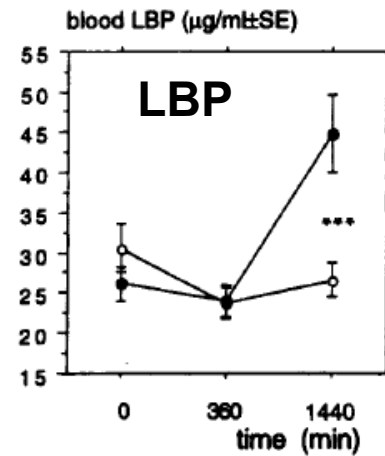
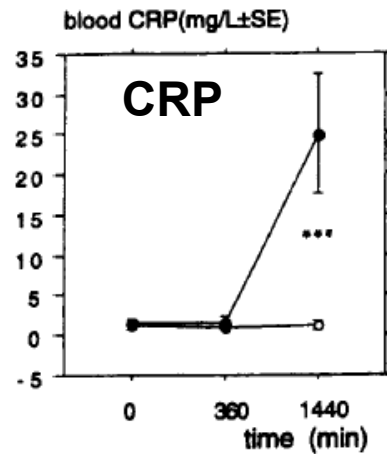
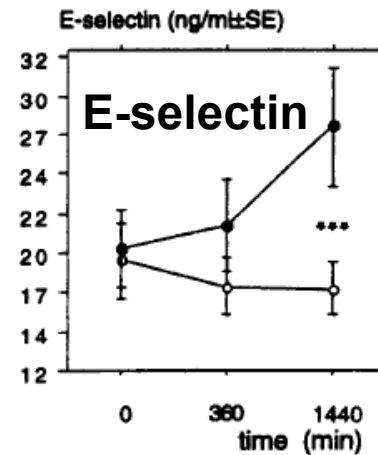
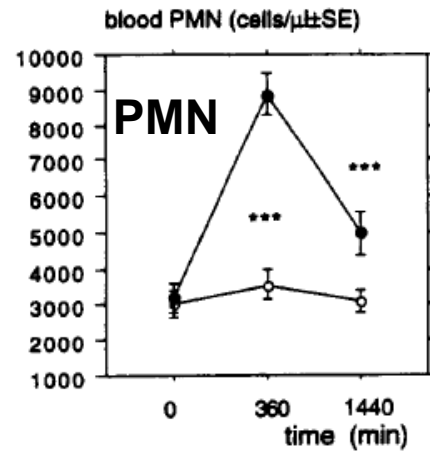
G Cavagna et al
Br J Ind Med 1969; 26:314-21

Asthma



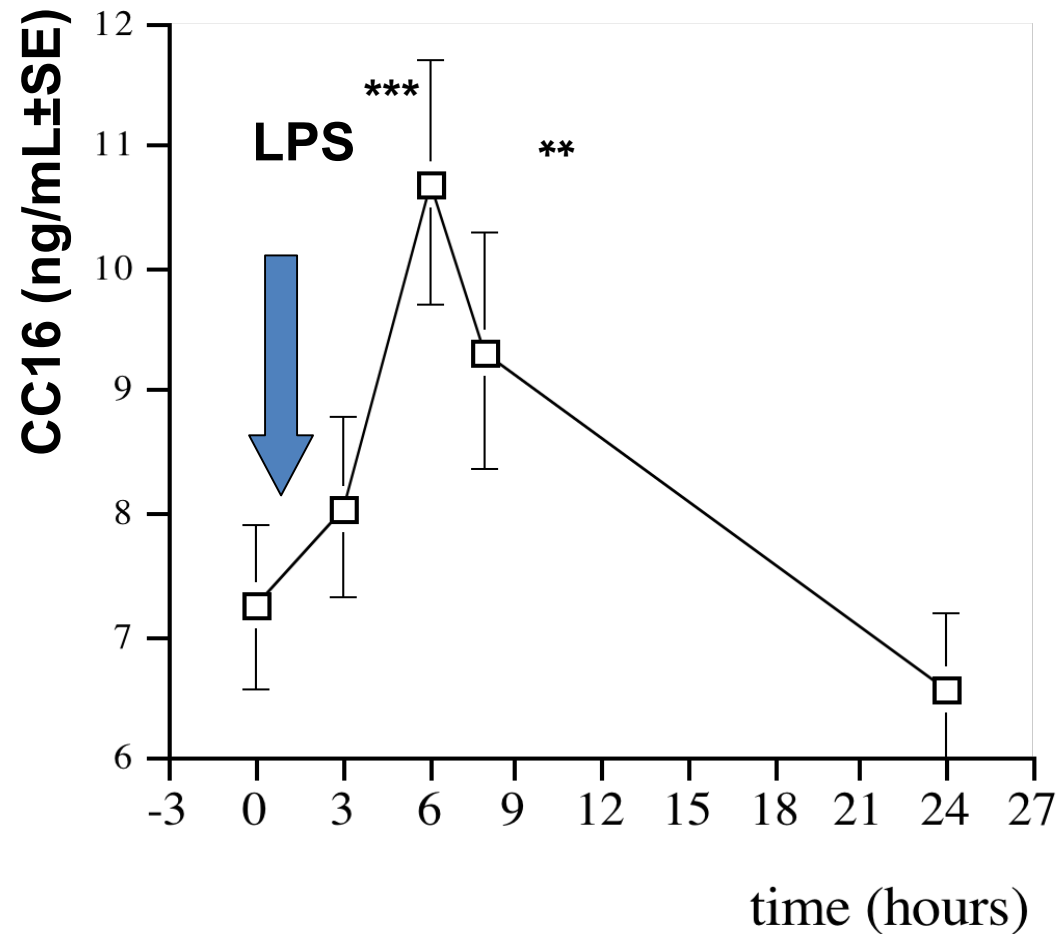
Michel et al
JAP 1989; 66: 1059-64

LPS: blood inflammation



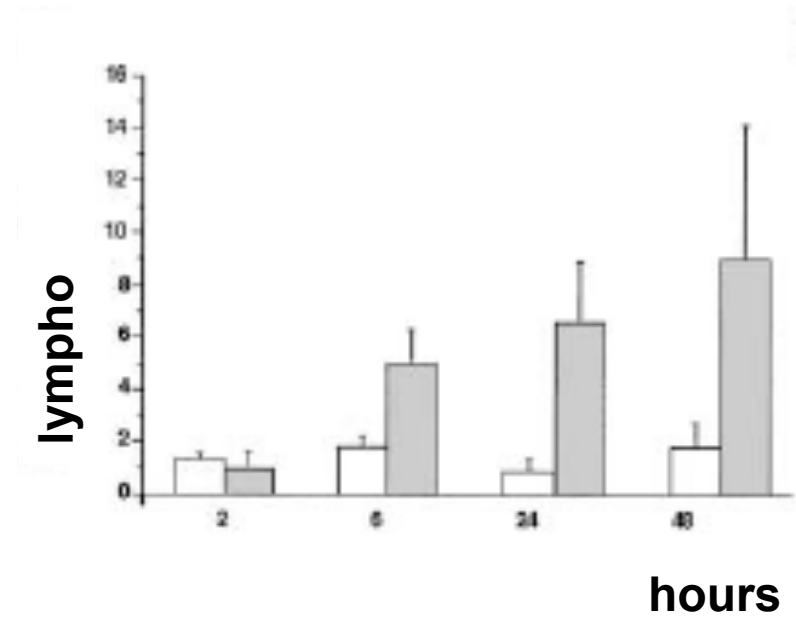
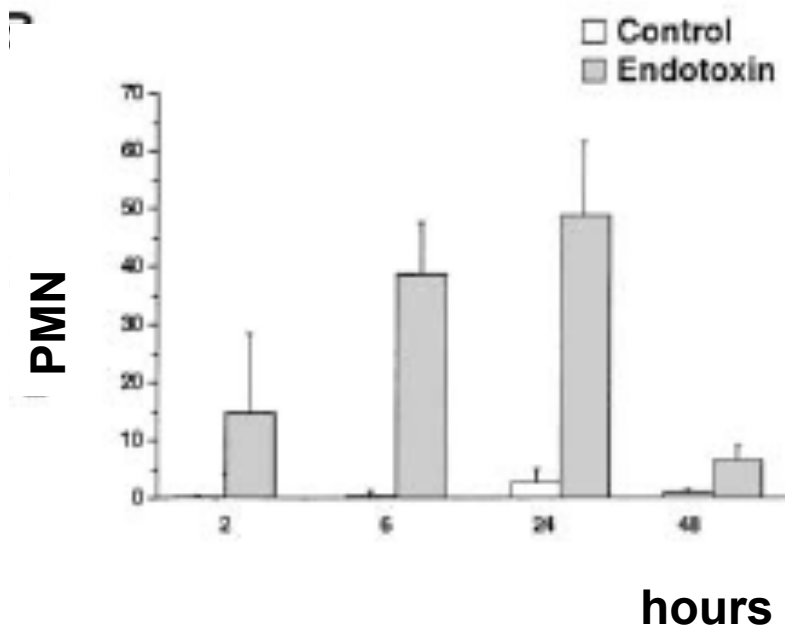
O Michel et JACI 2001; 107: 797-804

The clara cells are activated



Bronchial inflammation to LPS

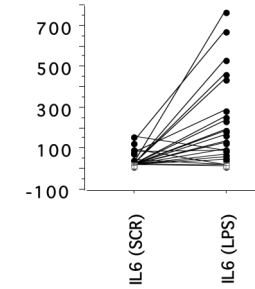
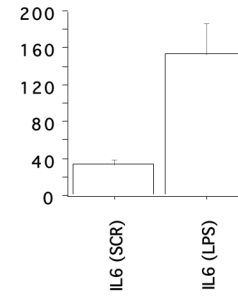
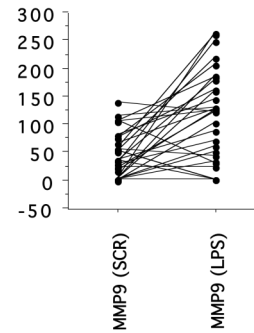
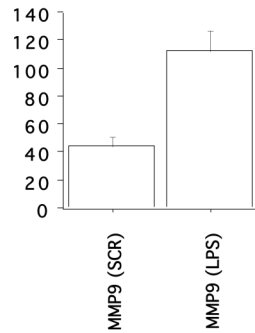
Lung segmental challenge (5 mcg LPS) and BAL



NP O'Grady et al AJRCCM:2001;163:1591-8

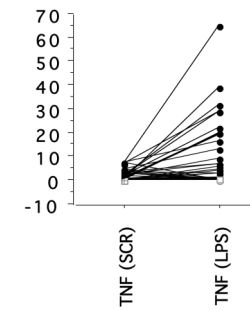
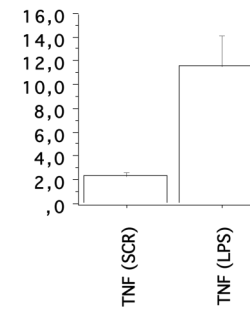
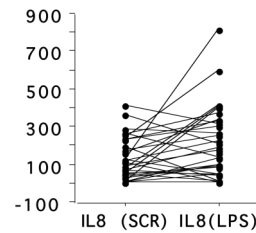
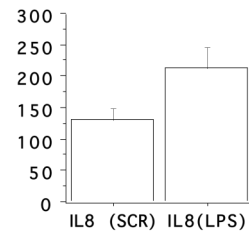
Bronchial inflammation to LPS

MMP9
p < 0,001



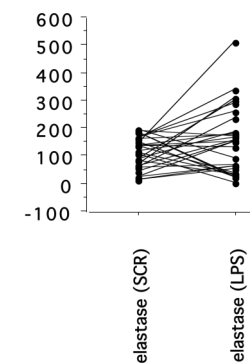
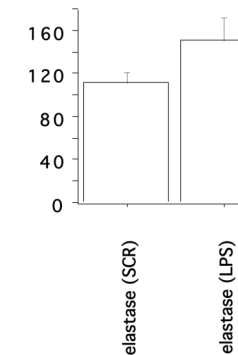
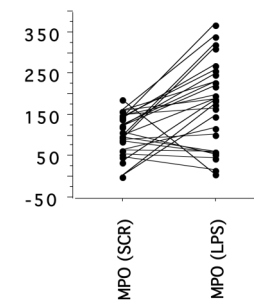
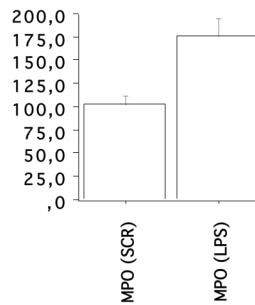
IL6
p < 0,001

IL8
p < 0,03



TNF
p < 0,001

MPO
p < 0.01

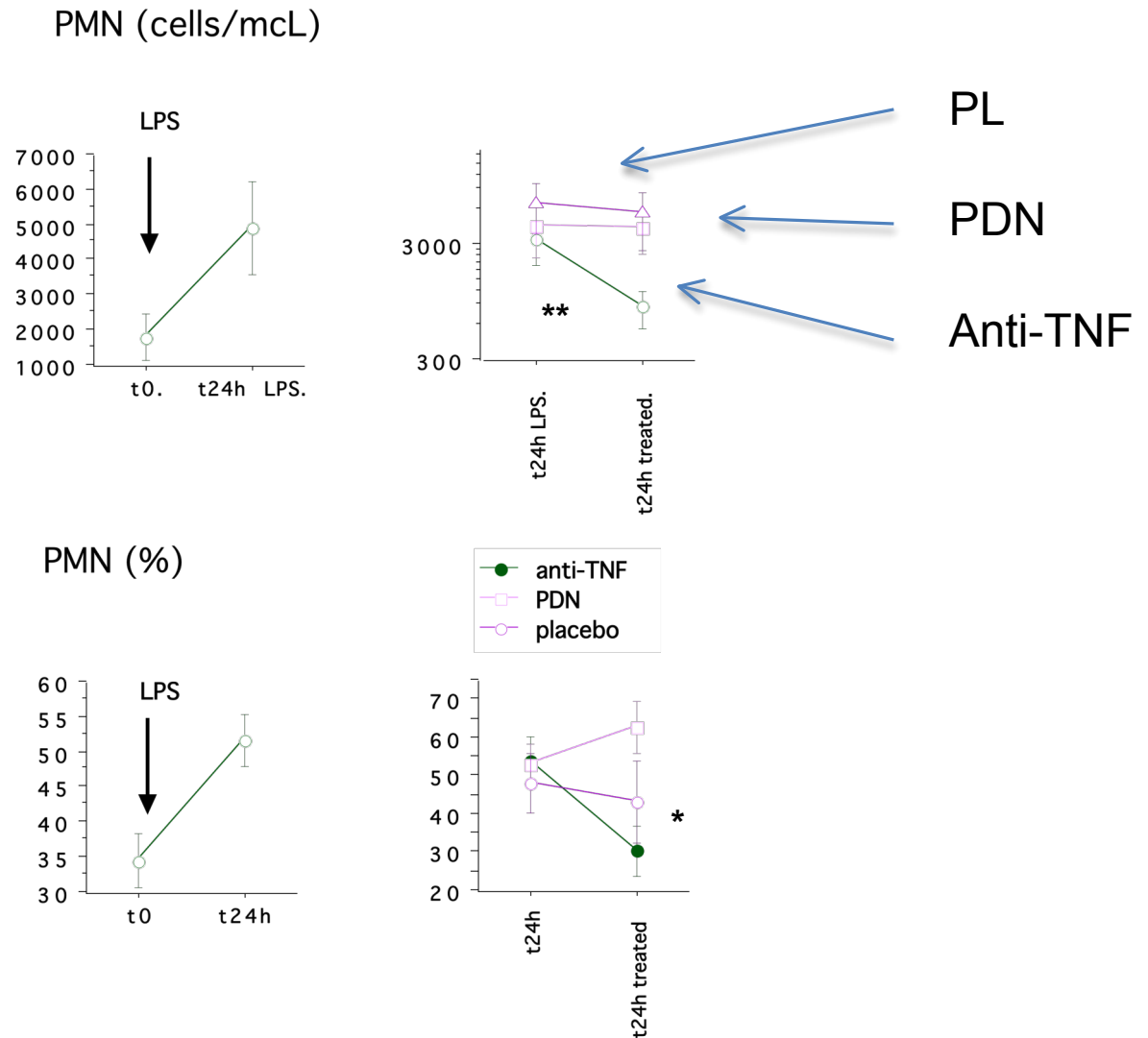


Elastase
p < 0,1

Effet d'un anti-TNF (humira) et de la prednisolone sur la neutrophilie bronchique induite par l'inhalation de LPS

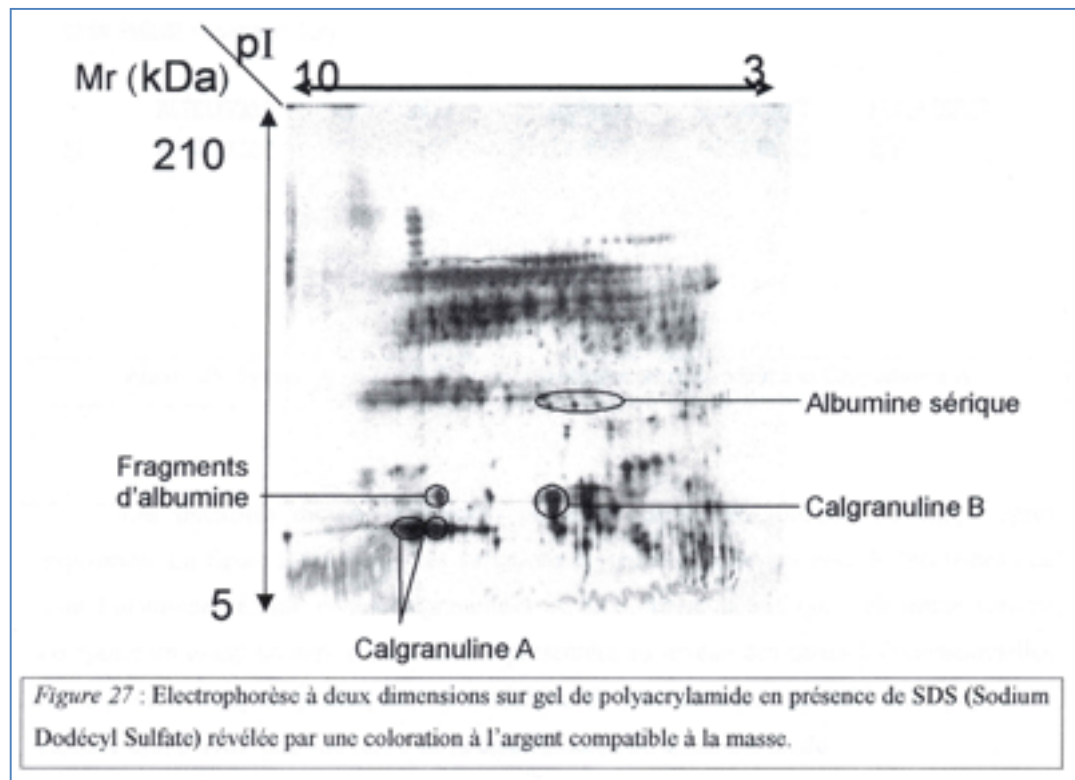
n = 24
volontaires
+ LPS
----- sputum

- placebo n = 8
- anti-TNF n = 8
- PDN n = 8



Proteomic of the induced-sputum supernatant (« sputome »)

Proteins separation by two-dimensional gel electrophoresis



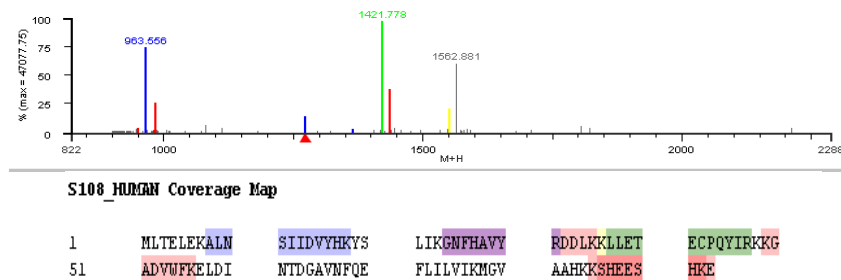
Ruddy Wattiez, PhD

Department of Proteomics
and Protein Biochemistry

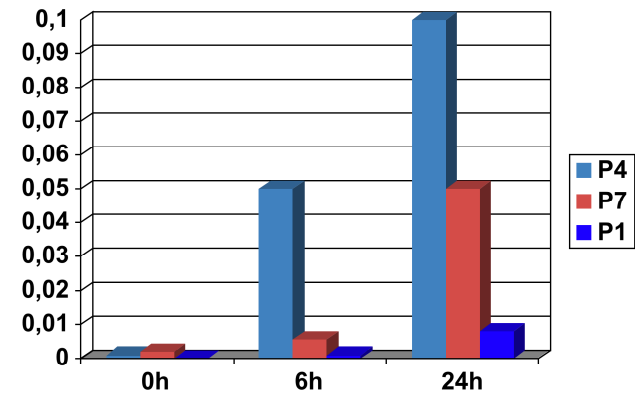
University of Mons-
Hainaut

Inflammatory proteins

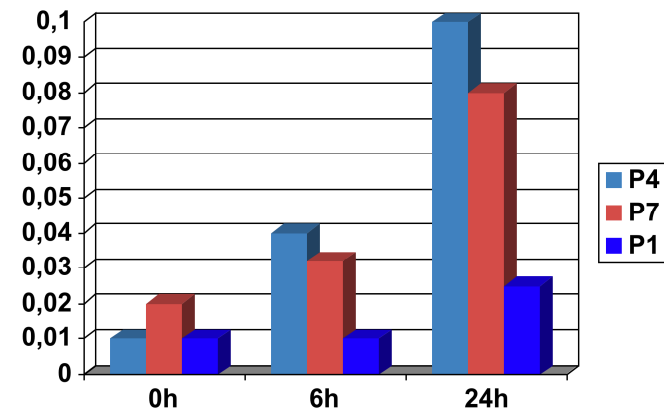
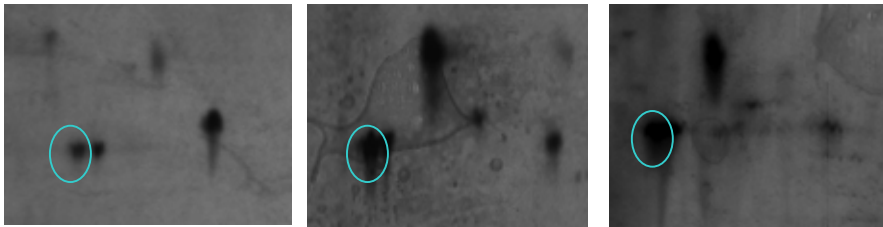
MALDI-TOF mass spectrometry



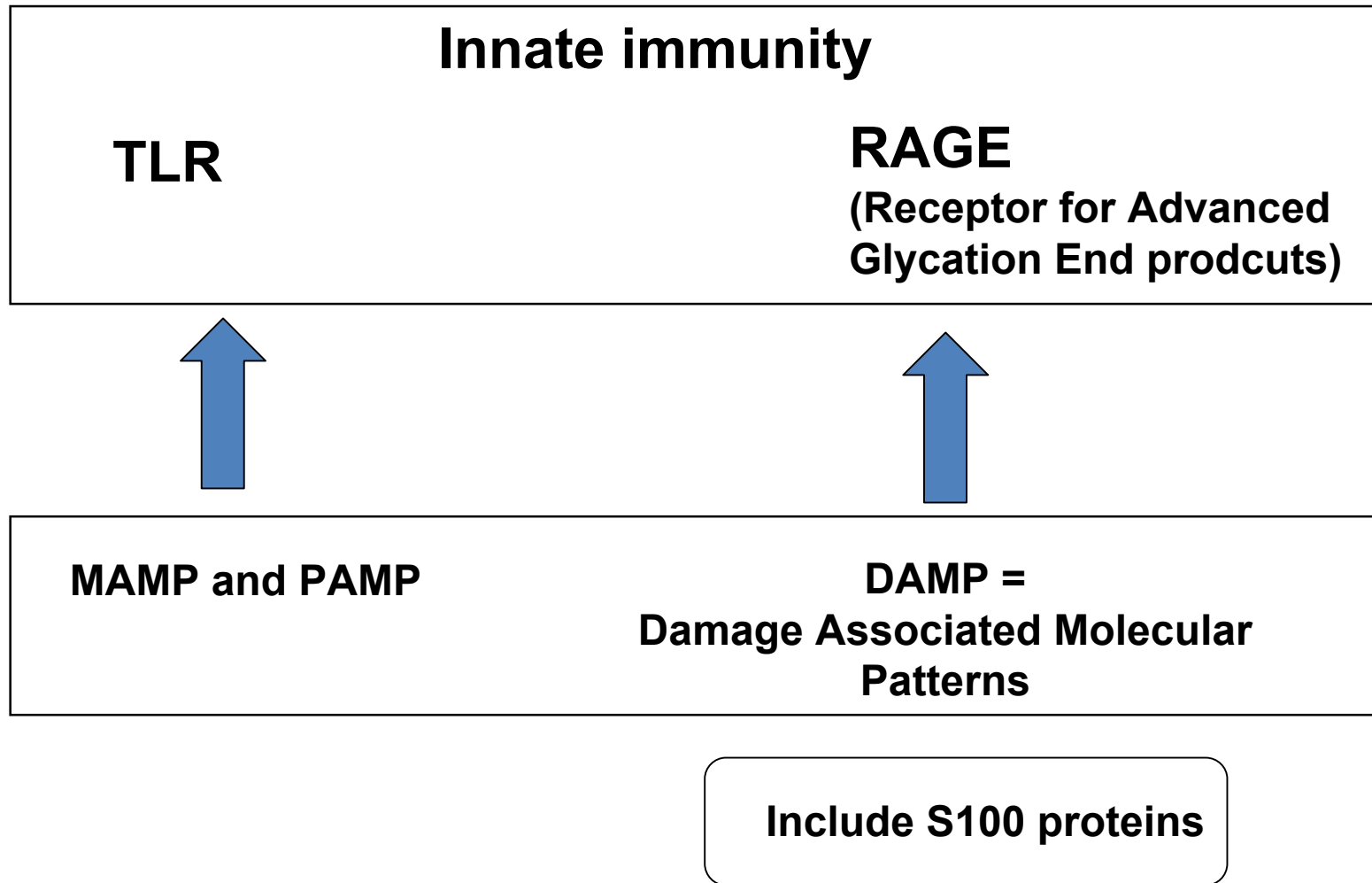
Calgranulin B



Calgranulin A



Fonctions of the calgranulines (S100A8)



Proteomic of the BAL from smokers

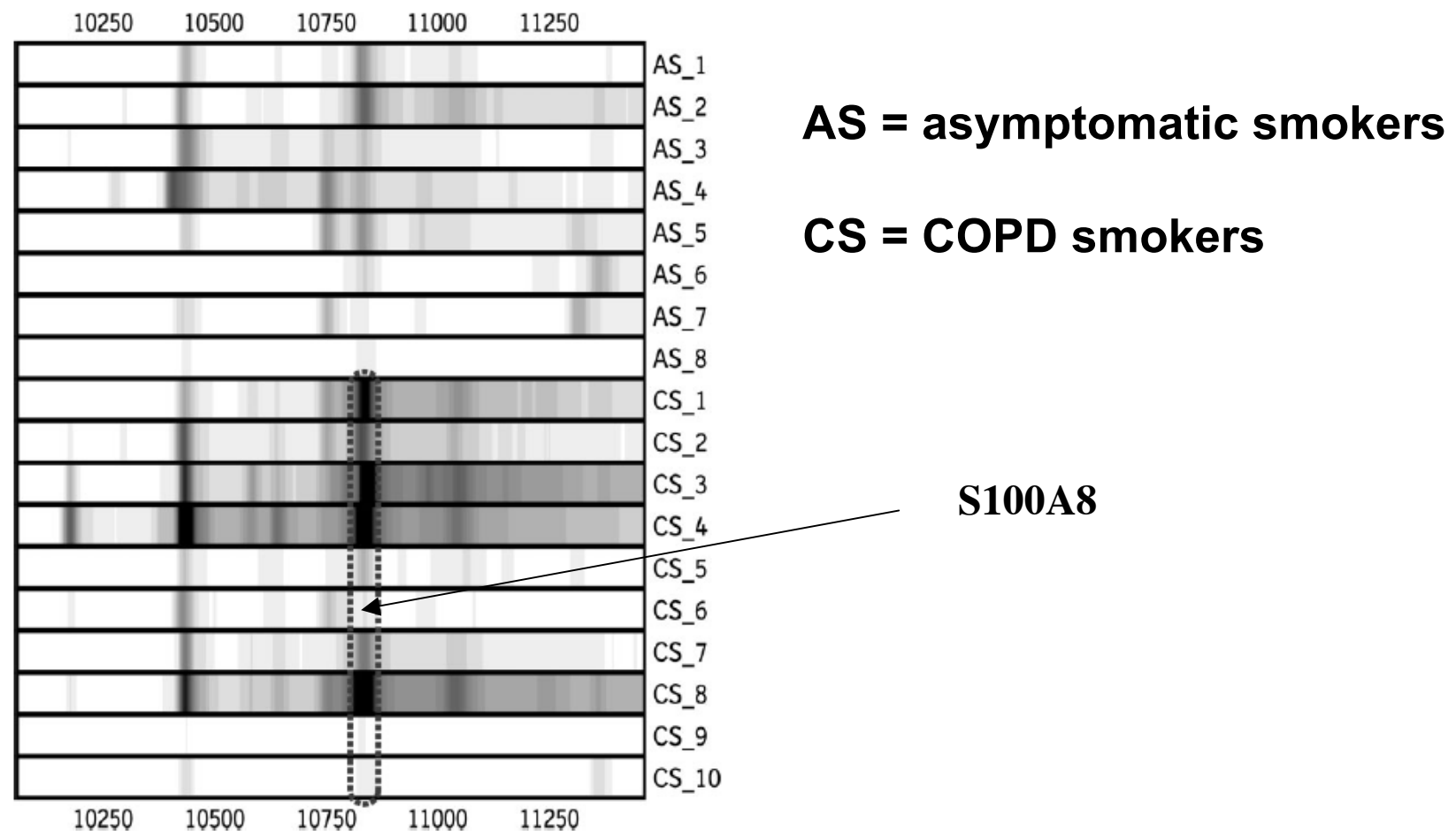
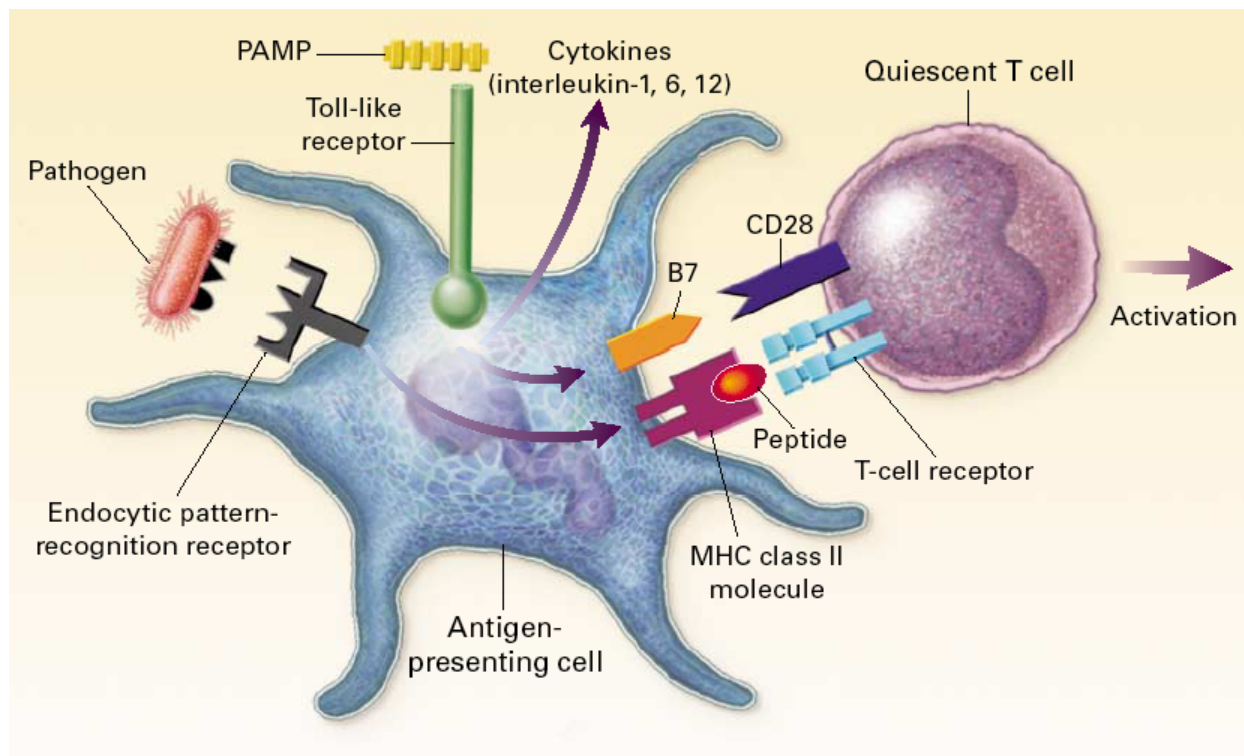


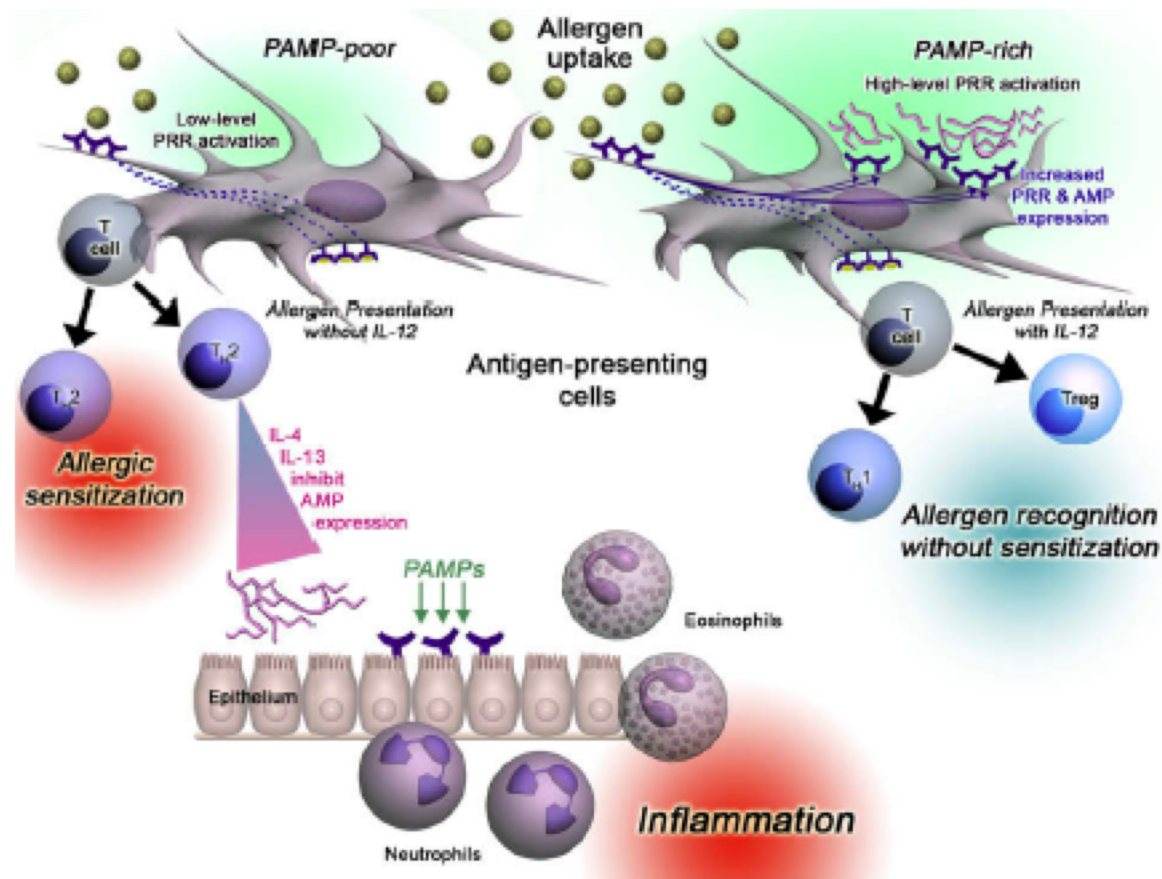
Figure 4. Differential display of proteins from BALF of smokers with COPD (CS) compared to AS on a WCX2 ProteinChip. S100A8 protein (10835 Da), which is up-regulated in the course of COPD, is indicated by a box.

Contrôle de la réponse adaptative par le système inné

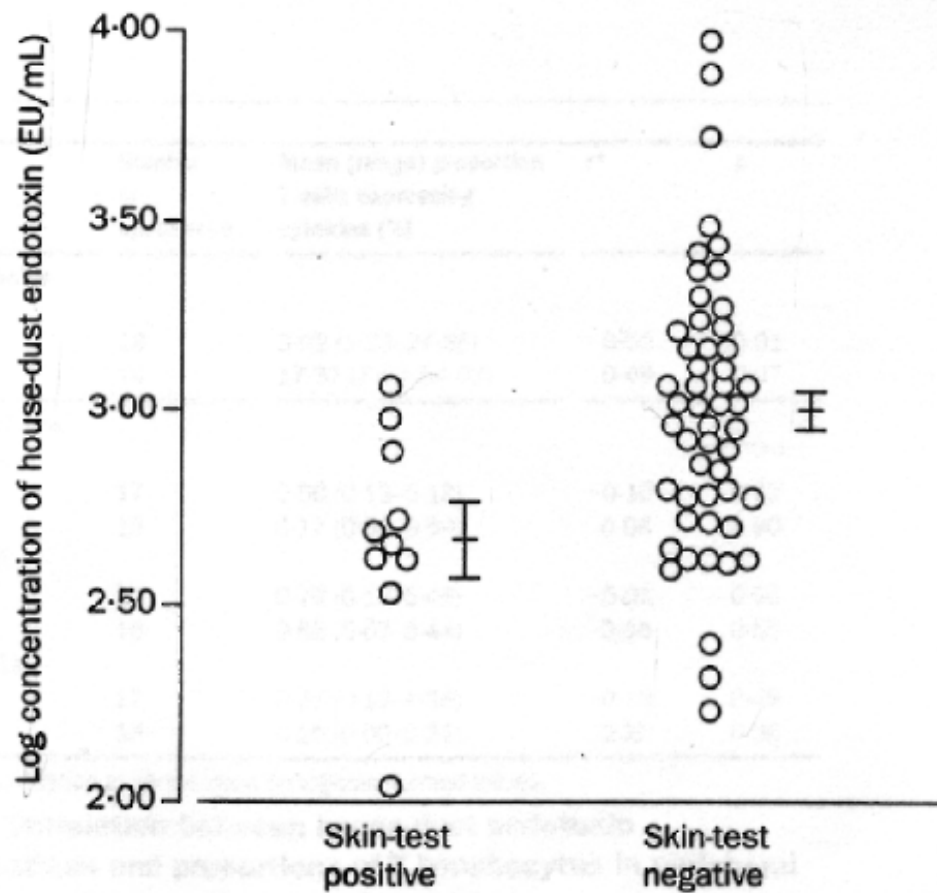


R Medzhitov, C Janeway. N Engl J Med 2000; 343: 338-44

Capteurs microbiens innés et allergies



Endotoxin and the positive skin tests to allergens in infants



JE Gerada et al
Lancet 2000; 355: 1680

Home endotoxin exposure in children

6-13 years n = 813

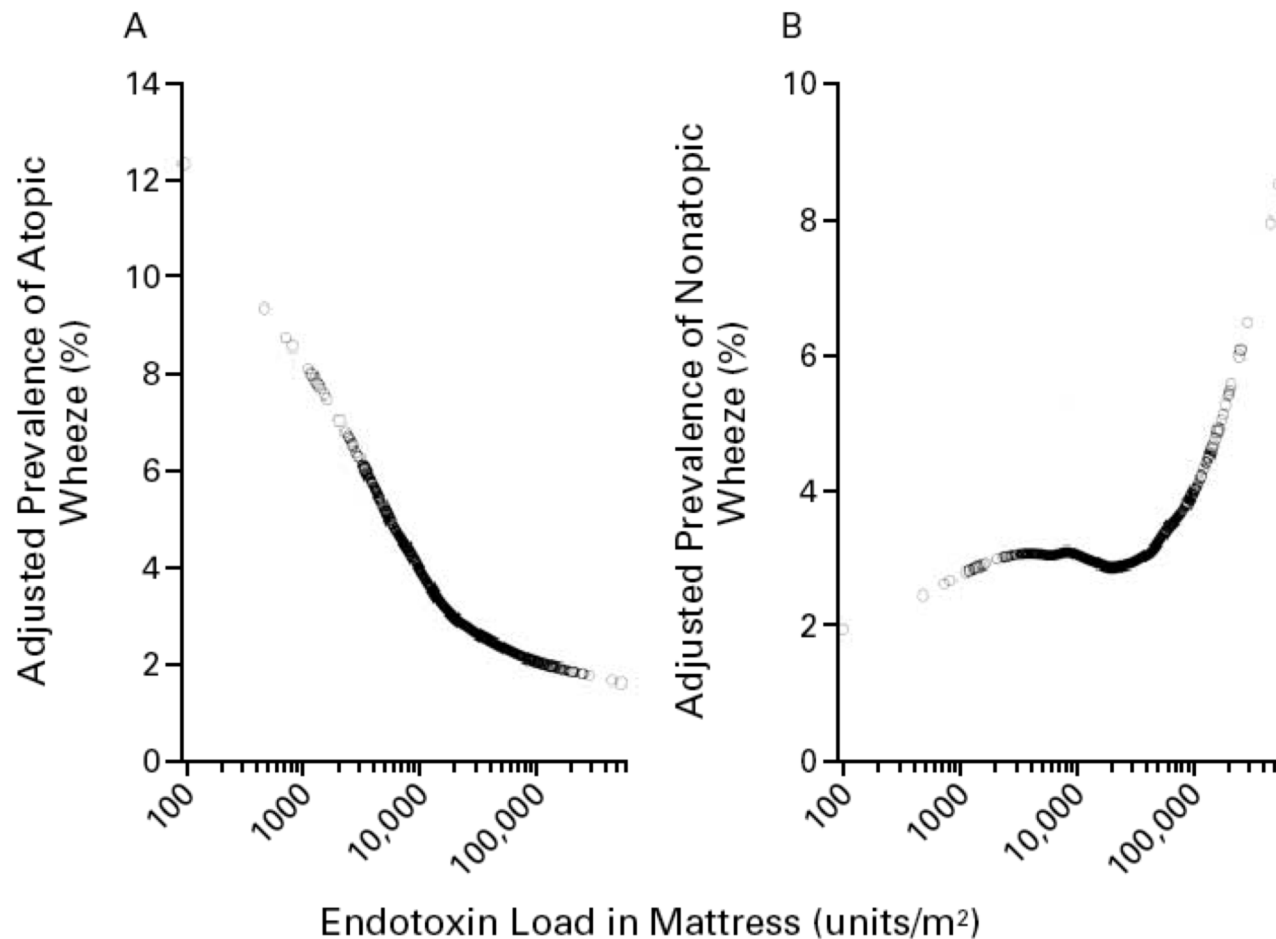
Clinical questionnaires

Endotoxin measurement from the bedding

HEALTH OUTCOME	TOTAL SAMPLE (N= 812)		CHILDREN FROM NONFARMING HOUSEHOLDS (N=493)	
	ENDOTOXIN LEVEL	ENDOTOXIN LOAD	ENDOTOXIN LEVEL	ENDOTOXIN LOAD
	adjusted odds ratio (95% CI)*			
Hay fever	0.58 (0.39–0.85)†	0.53 (0.35–0.81)†	0.79 (0.52–1.19)	0.56 (0.33–0.95)†
Sneezing and itchy eyes during previous yr	0.61 (0.43–0.86)†	0.50 (0.34–0.72)†	0.70 (0.47–1.05)	0.46 (0.28–0.76)†
Atopic sensitization‡	0.78 (0.60–1.01)	0.76 (0.58–0.98)†	0.80 (0.59–1.08)	0.73 (0.51–1.04)
Atopic asthma	0.73 (0.44–1.19)	0.48 (0.28–0.81)†	0.68 (0.39–1.19)	0.52 (0.25–1.07)
Nonatopic asthma	1.25 (0.62–2.51)	1.13 (0.57–2.26)	1.29 (0.62–2.68)	1.00 (0.46–2.21)
Atopic wheeze	0.89 (0.57–1.39)	0.62 (0.39–0.99)†	0.79 (0.46–1.33)	0.64 (0.33–1.25)
Nonatopic wheeze	0.97 (0.58–1.61)	1.14 (0.68–1.90)	1.36 (0.86–2.14)	1.82 (1.04–3.18)†

C Braun-Farlander et al NEJM 2002; 347: 869-77

Home endotoxin exposure in children

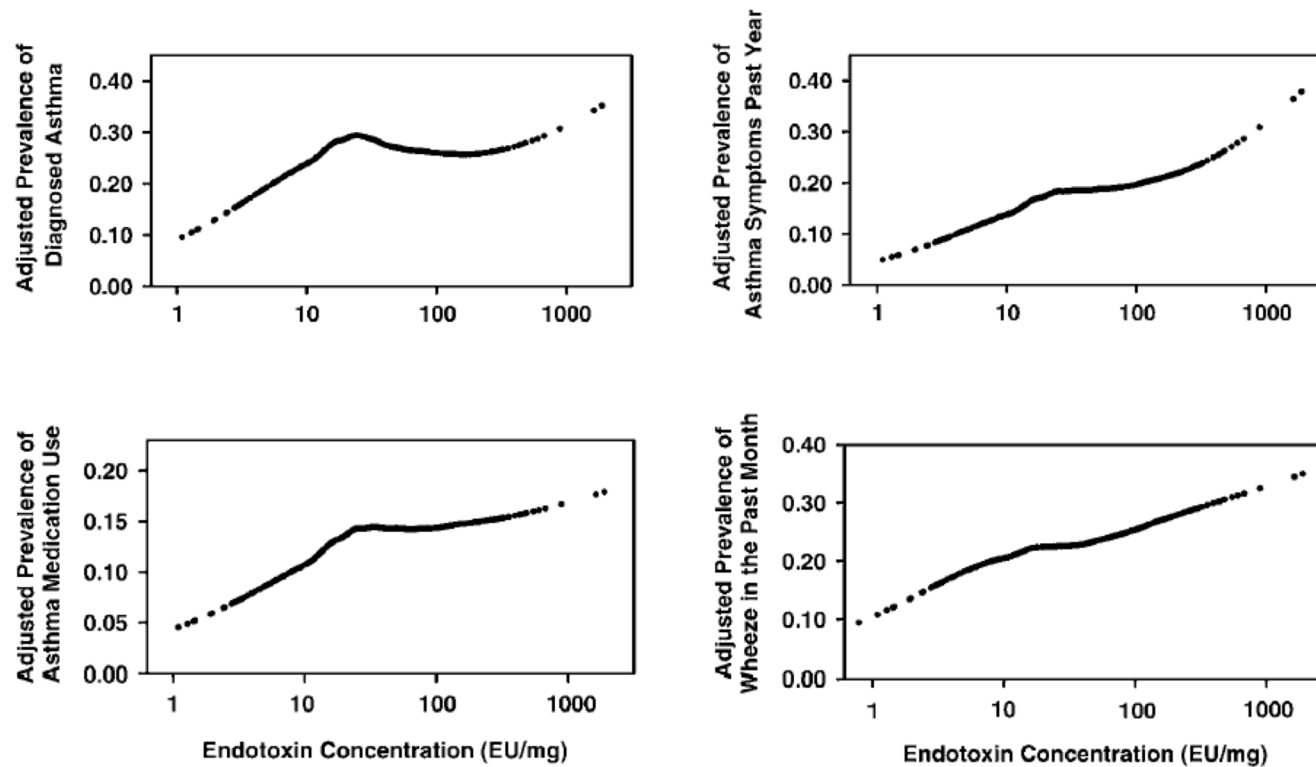


C Braun-Farlander et al NEJM 2002; 347: 869-77

Endotoxin exposure is a risk factor for asthma

831 housing units

2456 subjects evaluated by questionnaire



PS Thorne et al AJRCCM 2005; 172: 1371-77

Caractéristiques de l'habitat et risque d'asthme (UK)

LRC, Living room carpet; *LR*, living room; *MAT*, mattress; *BR*, bedroom; *RSP*, respirable suspended particles; *NO₂*, nitrogen dioxide; *HCHO*, formaldehyde.

TABLE III. Conditional logistic regression analysis of IPEADAM study key parameters

Indoor factor	Odds ratio (95% CI)	P value
Endotoxin (LRC)	1.88 (1.11-3.18)	.018*
Self-reported absence of dampness in home	0.36 (0.14-0.91)	.030*
Single-parent family	3.89 (1.25-12.1)	.019*
Redecoration in LR	3.15 (1.36-7.33)	.008*
Der p 1 (MAT) vs first quartile		
Second quartile	1.00 (0.36-2.80)	1.000
Third quartile	1.89 (0.73-4.89)	.190
Fourth quartile	0.98 (0.37-2.57)	.970
Self-reported dampness in kitchen and bathroom	2.72 (0.50-14.8)	.250
Time in residence	1.01 (0.77-1.34)	.930
No. of children in household		
2 vs 1	1.16 (0.54-2.48)	.710
3 or more vs 1	1.24 (0.59-2.60)	.570
Bedroom sharing	0.65 (0.34-1.25)	.2
Presence of smokers	1.09 (0.61-1.94)	.77
Furred pet ownership	1.22 (0.70-2.11)	.48
Gas cooking	0.69 (0.24-1.95)	.480
SolPM (LR)	1.18 (0.62-2.25)	.620
SolPM (BR)	1.64 (0.85-3.19)	.140
RSP (LR)	1.18 (0.80-1.74)	.400
NO ₂ (LR)	0.85 (0.51-1.44)	.550
NO ₂ (BR)	0.92 (0.49-1.71)	.790
HCHO (LR)		
Second tertile vs first tertile	0.82 (0.33-2.05)	.670
Third tertile vs first tertile	1.22 (0.49-3.07)	.670
HCHO (BR)		
Second tertile vs first tertile	1.26 (0.47-3.40)	.640
Third tertile vs first tertile	0.99 (0.39-2.52)	.980
Benzene (BR)	0.59 (0.26-1.31)	.190

G Tavernier et al JACI 2006; 117:656

Comparaison de la concentration en endotoxine dans la poussière chez l'asthmatique et le sujet normal

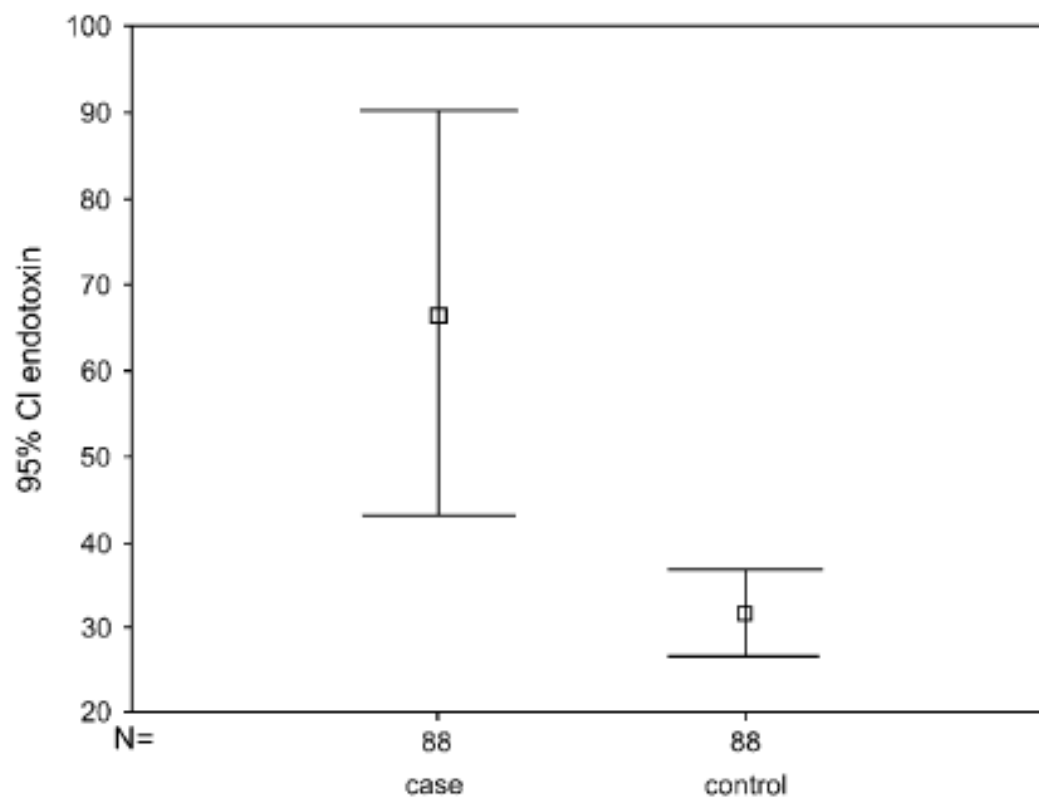
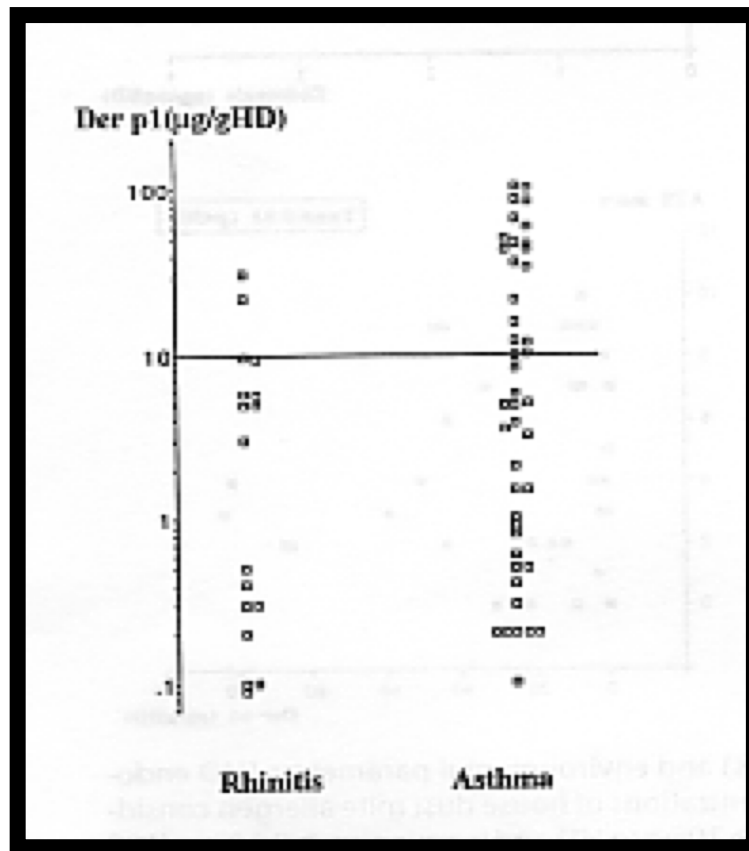


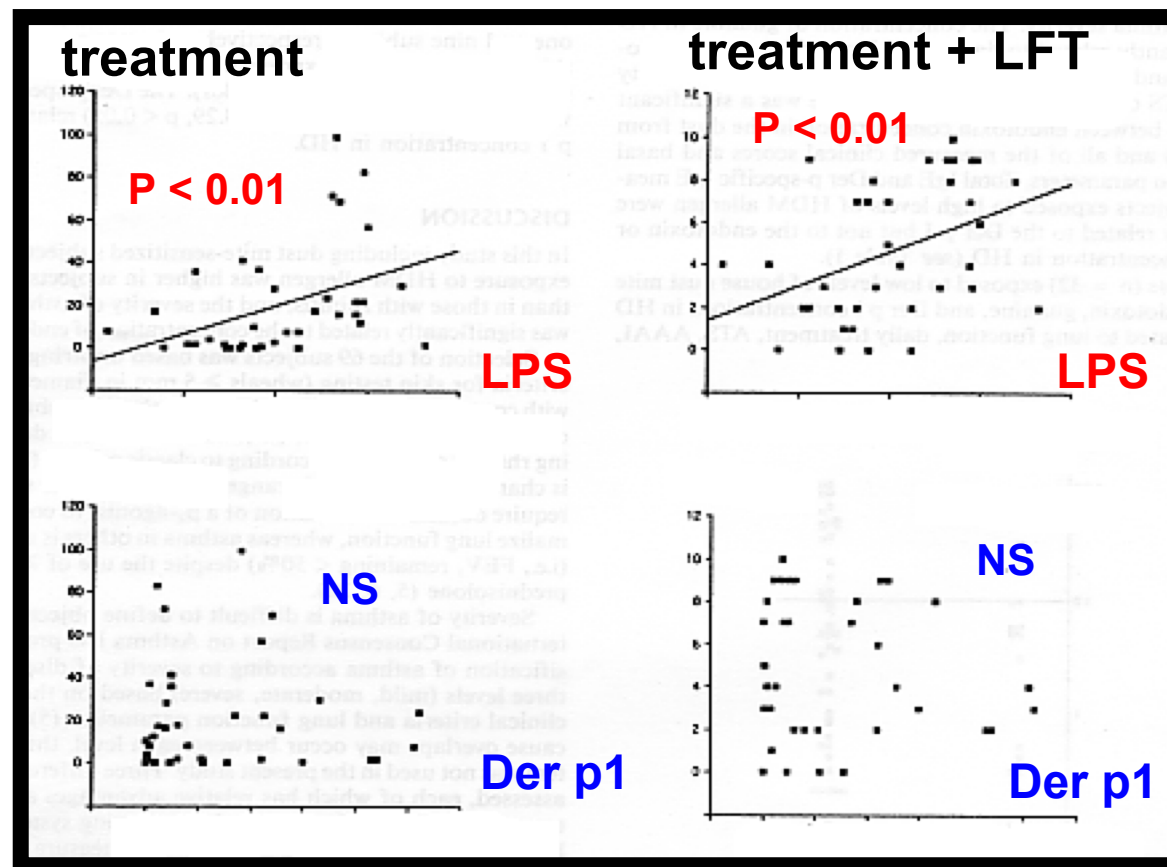
FIG 1. Comparison of the 95% CI of the levels of endotoxin (in endotoxin units per milligram of dust) measured in the living room dust of matched asthmatic and nonasthmatic children.

Relationship between house dust endotoxin content and allergic asthma



n = 69
SPT + (HDM)
Rhinitis/asthma

Relationship between house dust endotoxin content and allergic asthma



Endotoxin, atopy and the risk of severe asthma

Association between endotoxin, atopy, and the risk to be kept at home more than 3 times / year for a chest illness

Controls = non asthmatic children

Cases = asthmatics

	Models with bedroom endotoxin ^a		
	β	s.e.	P-value
Controls			
Atopic	-0.11	1.33	0.94
Non-atopic	-0.06	0.54	0.92
Cases			
Atopic	1.05	0.36	<0.01
Non-atopic	0.08	0.30	0.80

International comparisons of concentration of endotoxin in home dust. Relationship with the clinical risks

Study location	Dust sampling location	n	Endotoxin (EU/mg)	Associations with endotoxin
Rural New Zealand Wickens et al, 2002 ³⁷	Living room dust from farm homes	94	7.4 GM	} Endotoxin ↓ on farms } ↑ Exposure to poultry ↑ endotoxin } No difference with pet } No association with allergic disease
	Living room dust from nonfarms	188	11.6 GM	
Saxony-Anhalt, Germany Gehring et al, 2001 ²⁴ Bischof et al, 2002 ³⁰	Living room floor	405	22.7 (1-1200) GM (max-min)	↑ Endotoxin ↓ sensitization allergens Association strengthened with increasing degree of sensitization
Rural European Community Braun-Fahrlander et al, 2002 ⁴	Bedding from farm homes	319	37.8 (14.4-88.9) GM (5%-95%)	} ↑ Endotoxin ↓ hay fever } ↑ Endotoxin ↓ atopic asthma } ↑ Endotoxin ↑ nonatopic wheeze
	Bedding from nonfarm homes	493	22.8 (8.2-62.9) GM (5%-95%)	
US National Survey Thorne et al, 2005 ²⁹	Bedroom floor	588	35.3 (5.0-260) GM (5%-95%)	↑ Endotoxin ↑ asthma symptoms ↑ Endotoxin ↑ wheezing
Greater Boston area Park et al, 2001 ³² Phipatanakul et al, 2004 ²⁵	Bedroom floor	323	63 (2-761) GM (max-min)	↑ Endotoxin ↑ wheezing, 1st year life ↑ Endotoxin ↓ eczema, 1st year life
Northern Manhattan, South Bronx, NYC†	Bedroom floor	301	75.9 (1.2-3388) GM (max-min)	↑ Endotoxin ↑ wheezing, 2nd year life ↑ Endotoxin ↓ eczema, 1st year life
Metropolitan Denver Gereda et al, 2001 ³⁸ Gereda et al, 2000 ³	Multiple locations	86	178.2 GM	↓ Endotoxin for allergen sensitized Pets in home ↑ endotoxin Central air-conditioning ↓ endotoxin

MS Perzanowsli et al JACI 2006; 117: 1082-9

Association between endotoxin and atopy – rural environment

Table 1. Association between endotoxin and atopy – studies conducted in a rural environment

Author, year, country, acronym	Design, numbers, age	Setting	Definition of exposure; units	Outcome measures	Finding	Endotoxin protective, no effect or a risk for atopy	Comment
Braun-Fahrlander [43], 2002, Austria, Germany, Switzerland, ALEX	Cross-sectional survey, <i>N</i> = 814, 6–13 years	Rural, farming and non-farming	Dust from child's mattress; EU/mg and EU/m ²	Atopy (slgE)	Endotoxin levels were inversely related to atopic sensitization, OR 0.76 (0.58–0.98)	Protective	Also protective for hayfever but high levels were associated with an increase in non-atopic wheeze. In the multivariate analysis, exposure to farming in 1st year of life and endotoxin were independent protective factors
Ege [44], 2007, Schram-Bijkerk [46], 2006, Europe, PARSIFAL	Cross-sectional survey, <i>N</i> = 8263, 5–13 years	Children of farmers and Rudolf Steiner schools and controls	Dust from child's mattress; EU/mg and EU/m ² , <i>N</i> = 440 with endotoxin	Atopy (slgE), (<i>N</i> = 2086)	Endotoxin was inversely related to atopic sensitization, OR 0.38	Protective	No effect of endotoxin on asthma or current wheeze. Endotoxin effects were independent of farming exposures
Wickens [47], 2005, New Zealand	Cross-sectional, <i>N</i> = 293, 7–10 years	Rural, farming and non-farming	Dust from living room floor; EU/g and EU/m ²	Atopy (spt)	No association with atopy	No effect	Increased prevalence of allergic disease on farms; endotoxin levels were lower on farms
Perkins [41], 2006, UK	Cross-sectional, <i>N</i> = 4767, School-age children	Rural, farming and non-farming	Dust from living room floor; EU/mg (<i>N</i> = 879)	Atopy (spt) (<i>N</i> = 879)	No association with atopy, OR 0.94 (0.59–1.49)	No effect	Unpasteurized milk was associated with less atopy, irrespective of farming status
Eduard [48], 2004, Norway	Nested study of symptomatic farmers and controls, <i>N</i> = 2253, mean age 46 years	Farmers	Personal sampling of endotoxin exposure during farming tasks (<i>N</i> = 1614)	Atopy (slgE)	No association with atopy, OR 0.82 (0.58–1.2)	No effect	Higher endotoxin exposure was associated with non-atopic asthma and inversely associated with atopic asthma
Portengen [49], 2005, The Netherlands	Cross-sectional, adults, <i>N</i> = 162	Pig farmers	Personal exposure; EU/m ³	Atopy (slgE)	Strong inverse association between airborne endotoxin and atopy, OR 0.03 (0–0.3)	Protective	Higher endotoxin was associated with an increase in airway hyperresponsiveness

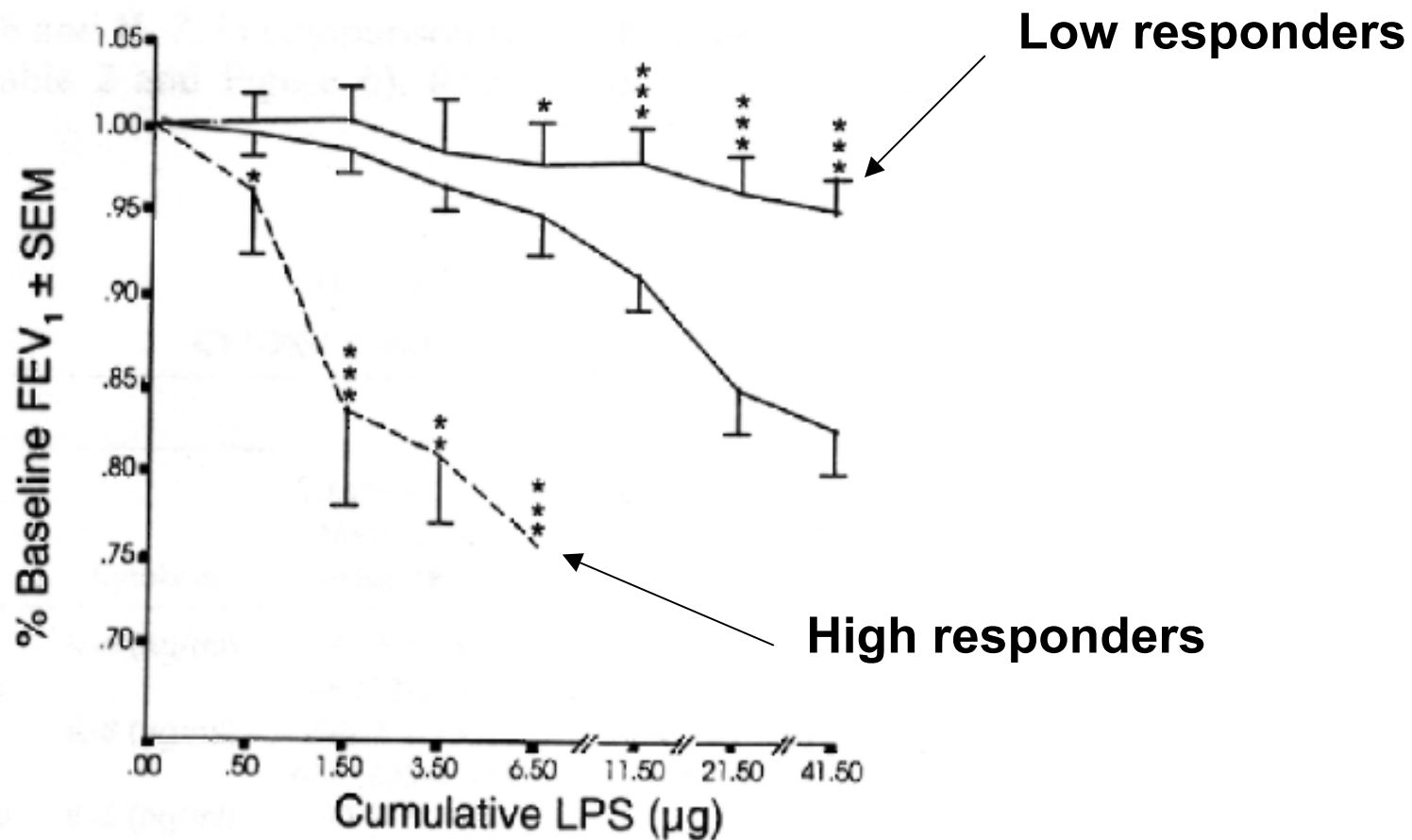
Association between endotoxin and atopy – urban environment

Table 2. Association between endotoxin and atopy – studies conducted in an urban environment

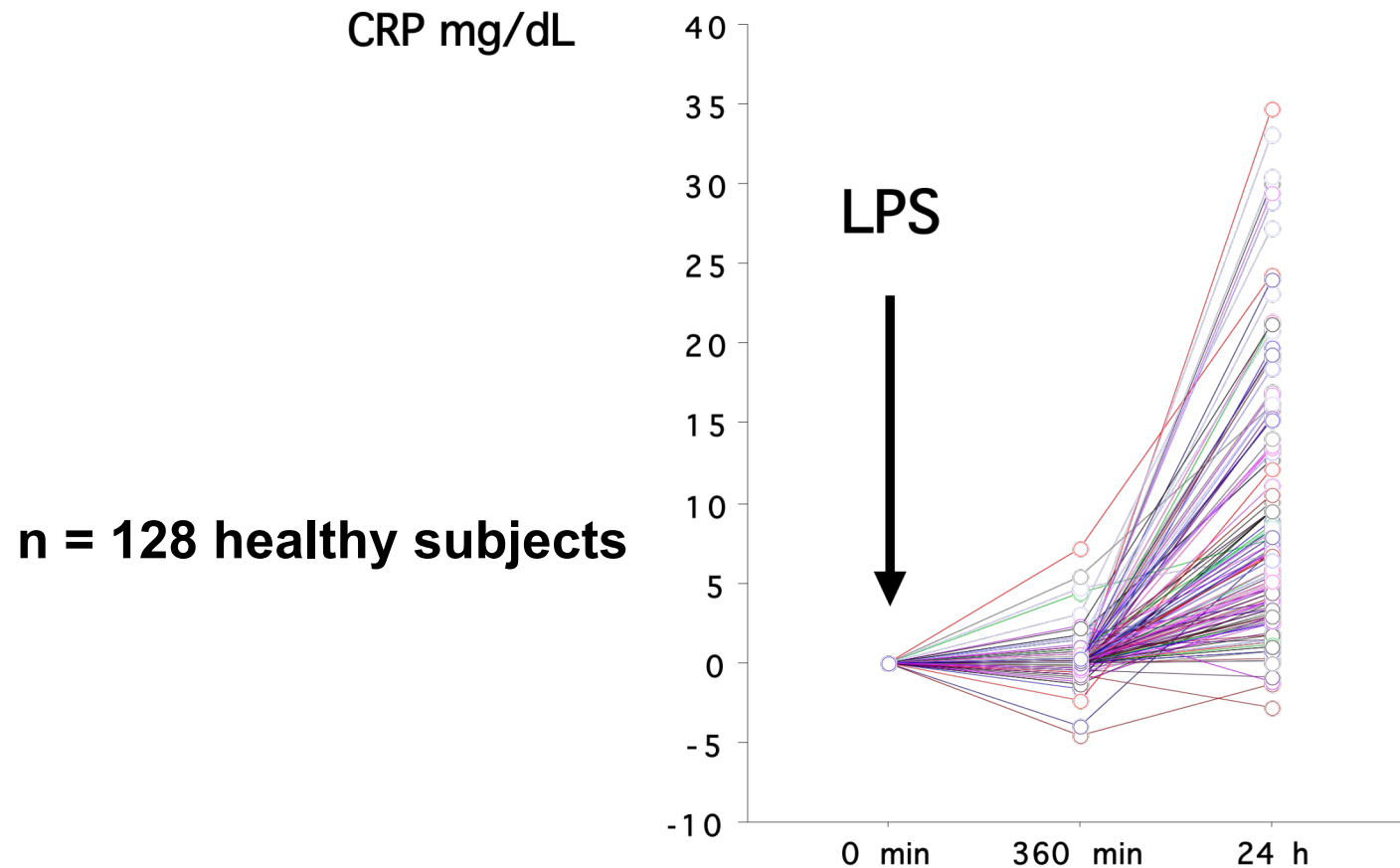
Author, year, country, acronym	Numbers, design, age	Definition of exposure; units	Outcome measures	Finding	Endotoxin protective, no effect or a risk for atopy	Comment
Gereda [50], 2000, USA	N = 61, wheezing infants, cohort, age 6–24 months	Domestic exposure (1 sample from living room floor, kitchen floor, sofa, bedroom floor and cot mattress); EU/mL	Atopy (spt)	Endotoxin levels were lower in the homes of children with allergies than those without	Protective	Only 10 children were atopic
Bolte [51], 2003, Germany, LISA	N = 2000, population-based birth cohort, age 2 years	Dust from mothers mattress at age 3 months; EU/g	Atopy (slgE)	No association with atopy when analysed in quartiles of exposure, e.g. OR 0.85 (0.54–1.35)	No effect	Increased repeated wheeze at higher exposures
Douwes [52], 2006, the Netherlands, PIAMA	N = 696 (287 with IgE), intervention arm of PIAMA, high-risk children, age 1 and 4 years	Dust from infants mattress and living room floor at age 3 months; EU/m ²	Atopy (slgE)	Levels in living room floor were not associated with atopy, OR ~1	No effect	Levels in mattress were low and not associated with any outcome. High levels in living room floor were protective for wheeze
Lau [53], 2005, Germany, MAS90	N = 153, age 10 years	Dust from child's mattress age 10 years; EU/mg	Atopy (slgE)	No association with atopy	No effect	This results is mentioned only in the discussion and is not the focus of the paper
Bottcher [54], 2003, Estonia and Sweden	N = 108 from Estonia, N = 111 from Sweden, age 2 years	Dust from infants mattress and a carpet in first year of life; EU/mg	Atopy (spt)	High endotoxin was protective in Sweden, OR 0.48 (0.35–0.9), no effect in Estonia	Protective/no effect	Endotoxin levels were generally higher in Estonia where prevalence of allergy is low compared with Sweden where prevalence is high
Gehring [55], 2002, Germany, INGA	N = 444 (nested atopy case-control study), age 5–10 years	Dust from living room floor; EU/m ²	Atopy (slgE)	Higher endotoxin was protective, OR 0.8 (0.67–0.97)	Protective	No effect seen on asthma, hayfever or eczema
Gehring [59], 2007, Europe, Airallerg (combining GINI, LISA, PIAMA, Bamse)	Nested case control for atopy within each cohort, age 2–4 years	Dust from child's mattress and living room floor at age 3 months; EU/m ² and EU/g (exposure was measured 1–4 years after sensitization was measured)	Atopy (slgE)	Higher endotoxin was protective when all populations were combined	Protective	Increasing mattress dust was also protective; this remained the only significant factor after mutual adjustment
Nicolaou [56], 2006, Cyprus	Asthma case control, N = 128, age 15–16 years	Dust from child's mattress; EU/m ² and EU/g	Atopy (spt)	Higher endotoxin was associated with an increase in risk of atopy on skin test, OR 1.6 (1–2.4)	Risk	
El-Sharif [57], 2006, Palestine	N = 109, nested case-control study within ISAAC, age 6–12 years	Dust from child's mattress and living room floor; EU/g	Atopy (spt)	Endotoxin concentrations were higher in the living room floor amongst non-atopic controls, OR 0.02 (0.002–0.3)	Protective	
Gehring [30], 2004, Germany	N = 350, nested case-control study within ECRHS, age 25–50 years	Dust from living room floor; EU/m ² and EU/g	Atopy (slgE)	Higher endotoxin was protective against more severe allergy, OR 0.72 (0.56–0.92)	Protective	Adults rather than children indicating that current exposure as well as early life exposure may be important

A Simpson, FD Martinez CEA 2010

Individual responsiveness to LPS



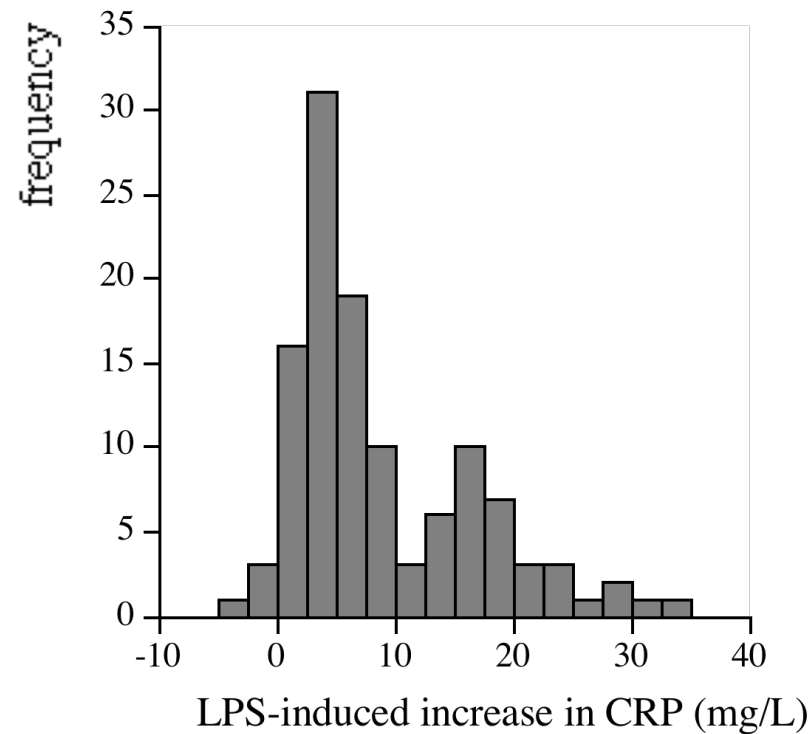
Individual responsiveness to LPS



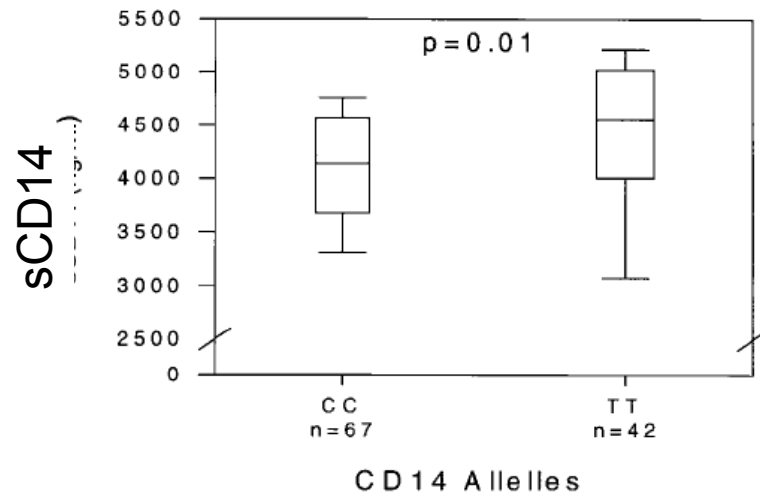
O Michel et al JACI 2003, 112: 923-9

Individual responsiveness to LPS

Bi-modal distribution of the LPS responsiveness



Genetic variants in the CD14 gene and at



nSPT

*the mean) by CD14/-159 genotypes in skin
test-positive white children at age 11 yr*

CD14/-159 Genotypes	n	Mean Number of Positive Skin Tests
CC	44	2.77 (2.24-3.31)
CT	82	2.74 (2.37-3.11)
TT	37	1.78 (1.38-2.18)
P = 0.0063		

**M Baldini, F Martinez. AJRCMB
1999;20:976-983.**

CD14 polymorphisms

	pollens allergy		total
	yes	no	
CD14-159CC	17	19	36
CD14 - 159CT/TT	16	66	82
total	33	85	118

Chi = 8.21
p = 0.004

Association between CD14 genotype and allergy

Table 3. Summary of studies on relationship between CD14 genotype and allergic outcomes

Study	Population	Outcome measure	Association	Risk allele	Comment
Baldini [68]	481 children from 4 ethnic groups in Tucson Children's respiratory study	Atopy	No association (data not shown)	None	TT children with allergies are 'less allergic' and have higher sCD14
		Total IgE in children with positive skin tests	Lower in TT group, TT 81 (52-128) vs. CC 168 (107-264), $P=0.02$	C	
		Number of positive skin tests in atopic children	Fewer in TT group, TT 1.78 (1.4-2.2) vs. CC 2.77 (2.2-3.3), $P=0.006$	C	
Sengler [75]	German children from MAS90 study, $N=558$	Asthma, rhinitis, eczema, polysensitization, IgE	No association, e.g. number of positive skin tests in atopic children TT 2.93 vs. CC 2.44	None	Control were not tested for asthma
Heinzmann [73]	Asthma case-control study, children, $N=352$	Asthma	No association with CD14 genotype, e.g. T allele carried by 46% of controls and 48% of asthmatics	None	
Leung [79]	Chinese children asthma case control, $N=350$	Total IgE in atopic children	Higher in CC genotype, TT 2.58 vs. CC 2.82 (log scale), $P=0.02$	C	
Kabesch [74]	German children from ISAAC study $N=2048$	Total IgE, number of positive skin tests, asthma, rhinitis, eczema	No association, e.g. asthma present in 11% of CC and 11% TT	None	Higher sCD14 in TT group
O'Donnell [71]	Cohort of Australian children, $N=305$, followed from age 8 years to age 25 years	Atopy	Associated with CC genotype in childhood OR 2.0 (1.1-3.9), $P=0.04$	C	CC associated with atopy and AHR in childhood, with much of the effect lost by adulthood
		AHR	Associated with CC genotype at age 8 years, with trend at other time-points OR 2.6 (2.1-5.6) $P=0.02$	C	
Wang [80]	Taiwanese children with asthma, $N=190$	High IgE in children with asthma	T allele associated with high IgE, OR 1.56 (1.03-2.36) $P=0.03$	T	In haplotype analysis effect was only seen in those with a particular haplotype containing a microsatellite marker
Woo [81]	Asthma and food allergy case control, $N=175$	Non-atopic asthma, food allergy	Higher frequency of T allele relative to controls, OR 2.7 (0.9-8.0) for non-atopic asthma	T	Lower rate of T allele in controls than in other published studies (39%)
Litonjua [78]	High risk birth cohort, $N=379$	Eczema	More common in carriers of T, OR 2.3 (1.4-3.8)	T	
		Total IgE	Lower in CC	T	
Gao [82]	British $N=300$ and Japanese $N=200$ asthma case control	Asthma, atopy	No association	None	
		Total IgE in British	Higher in CC, TT 21.9 vs. CC 79.4, $P=0.02$	C	
Ober [77]	Hutterites, $N=693$, founder population	Positive skin tests	More common in T allele carriers, $P=0.009$	T	
Koppelman [72]	Dutch adults with asthma and their spouses, $N=317$	Total IgE in subjects with positive skin tests	Higher in CC group, CC 163 (105-253) vs. TT 106 (67-168)	C	
		Number of positive skin tests	Higher in CC group	C	
		Hayfever	More common in CC group, OR 1.8 (1.1-3.0)	C	
		MD asthma	No association	None	
Buckova [83]	Case control Czech adults with asthma or rhinitis, $N=882$	Asthma, rhinitis, total IgE, lung function	No association	None	
		Sensitization to moulds	Associated with C allele	C	
Kedda [76]	Australia, adults, asthma case control, $N=1011$	Asthma, atopy	No association	None	Did meta-analysis and found no association
Sharma [84]	Case-control study of adults with atopic asthma from India, $N=414$	Atopic asthma, higher IgE	C allele present in 48% of cases and 38% of controls	C	
Lachheb [85]	Case-control study of children with asthma, Tunisia, $N=434$	Asthma	TT less likely to have asthma, OR 1.6 (1.2-2.2)	C	OR for asthma in C allele carriers was 1.6

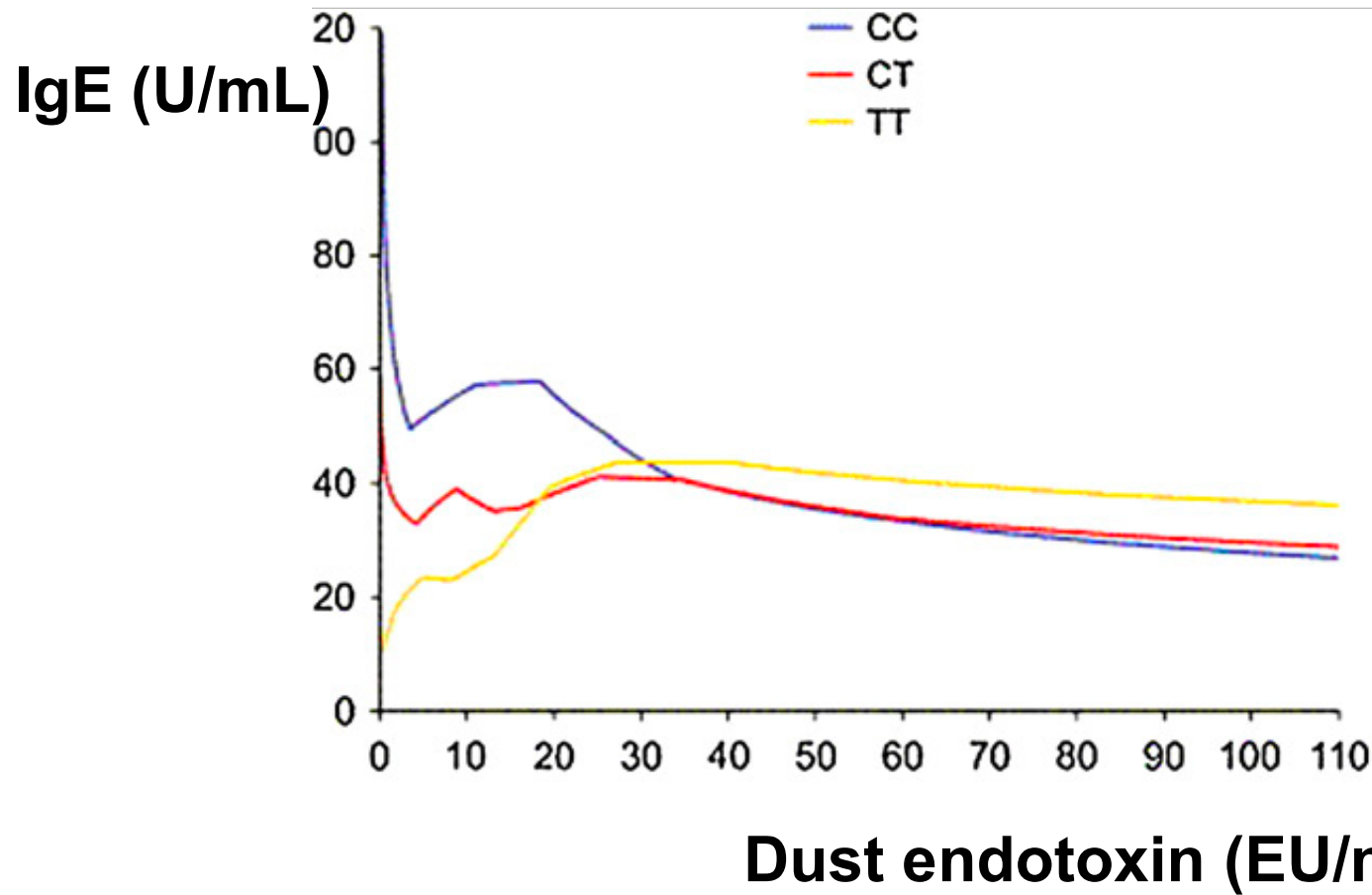
A Simpson, FD Martinez CEA 2010

Interaction between endotoxin and CD14 genotype

Table 4. Summary of studies reporting interaction between measured endotoxin exposure and CD14 genotype

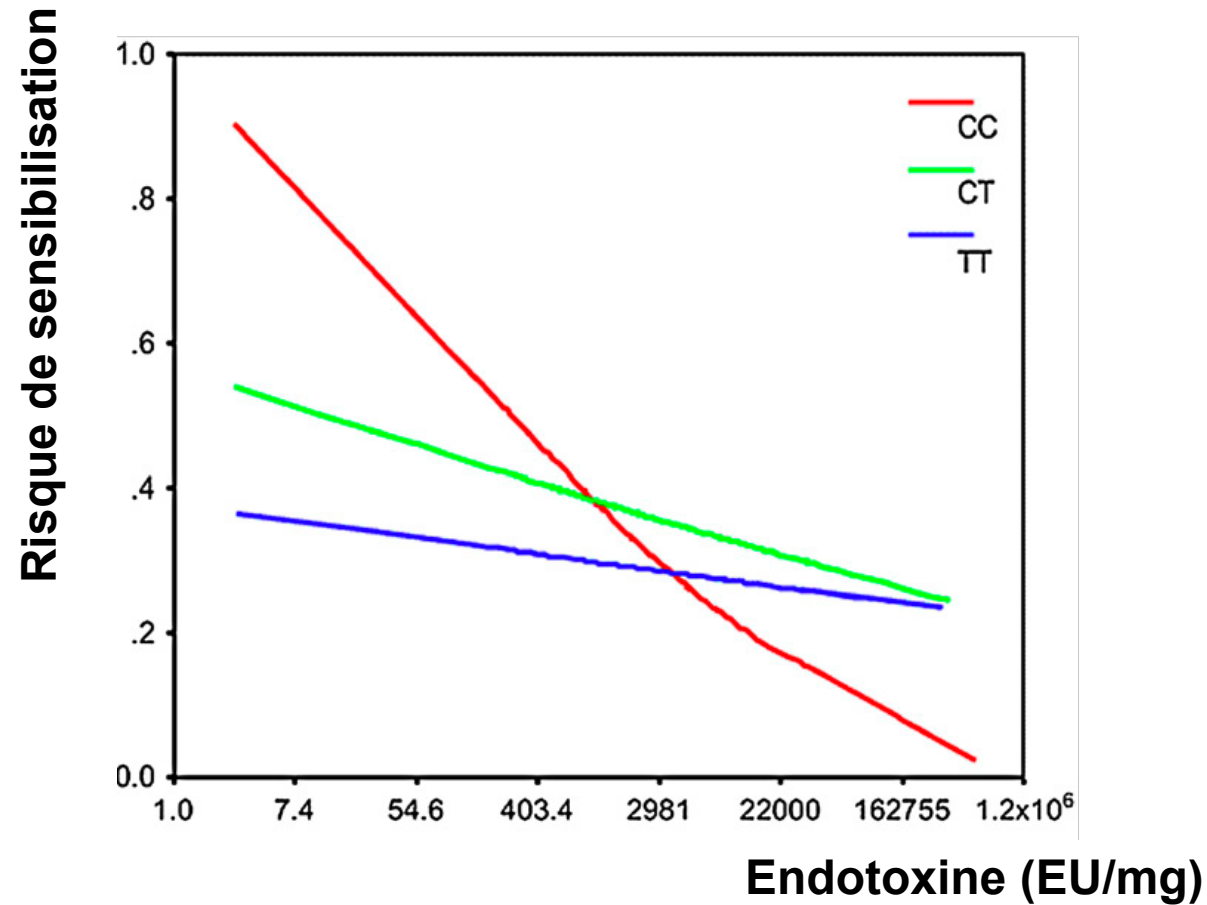
Author, year, acronym, country	Design, age, numbers	Ethnic group	Definition of exposure; units	Relationship between CD14 genotype and outcome	Relationship between Endotoxin and outcome	Interaction between CD14 genotype and endotoxin
Simpson [70], 2006, MAAS, UK	Population based birth cohort study, age 5 years, N = 442	Mixed European ancestry only	Living room floor, GM 2856 EU/m ² (16.1 EU/mg)	AS: NA A: NA E: NA	AS: increasing endotoxin associated with decreased AS A: NA E: NA	AS: In CC only higher endotoxin associated with decreased risk of AS A: In CC only higher endotoxin associated with increased risk of non-atopic wheeze E: In CC only higher endotoxin associated with decreased risk of eczema
Zambelli-weiner [86], 2005, BAGS, Barbados	Asthmatic probands and their families, N = 443 (adults and children)	Of African descent/ European admixture	Living room composite endotoxin load – dichotomous (75th percentile), GM 23 144 EU/m ²	AS: NA A: TT protective E: NR	AS: NA A: NA E: NR	AS: NR A: more common in TT with high endotoxin (i.e. at high exposures C allele is protective) E: NR
Williams [88], 2006, WHEALS mothers, USA	Mothers of population based birth cohort (young adults > 21 years), N = 517	All races analysed together	Dust from the home at age 1 month (child), GM 16.2 EU/mg	AS: TT had lower total IgE A: NR E: NR	AS: NA A: NR E: NR	AS: In CC only, higher Endotoxin associated with lower total IgE A: NR E: NR
Williams [89], 2008, WHEALS, USA	Population based birth cohort study, age 1 year N = 90	All races analysed together, stratified	Dust from the home at age 6 month (child), GM 18.2 EU/mg	AS: A: NR E: NR	AS: A: NR E: NR	AS: In CC only, higher Endotoxin associated with lower total IgE A: NR E: NR
Eder [87], 2005, ALEX, Germany and Austria	Children living on farms and local controls, N = 624	NR	Dust from child's mattress, GM in tertiles (2nd tertile 12 495–30 046 EU/m ²)	AS: NA A: NR E: NR	AS: high exposure protective A: NR E: NR	AS: C allele protective in the highest endotoxin tertile only A: NR E: NR

Association du taux d'IgE avec l'exposition aux endotoxine selon les polymorphismes du CD14

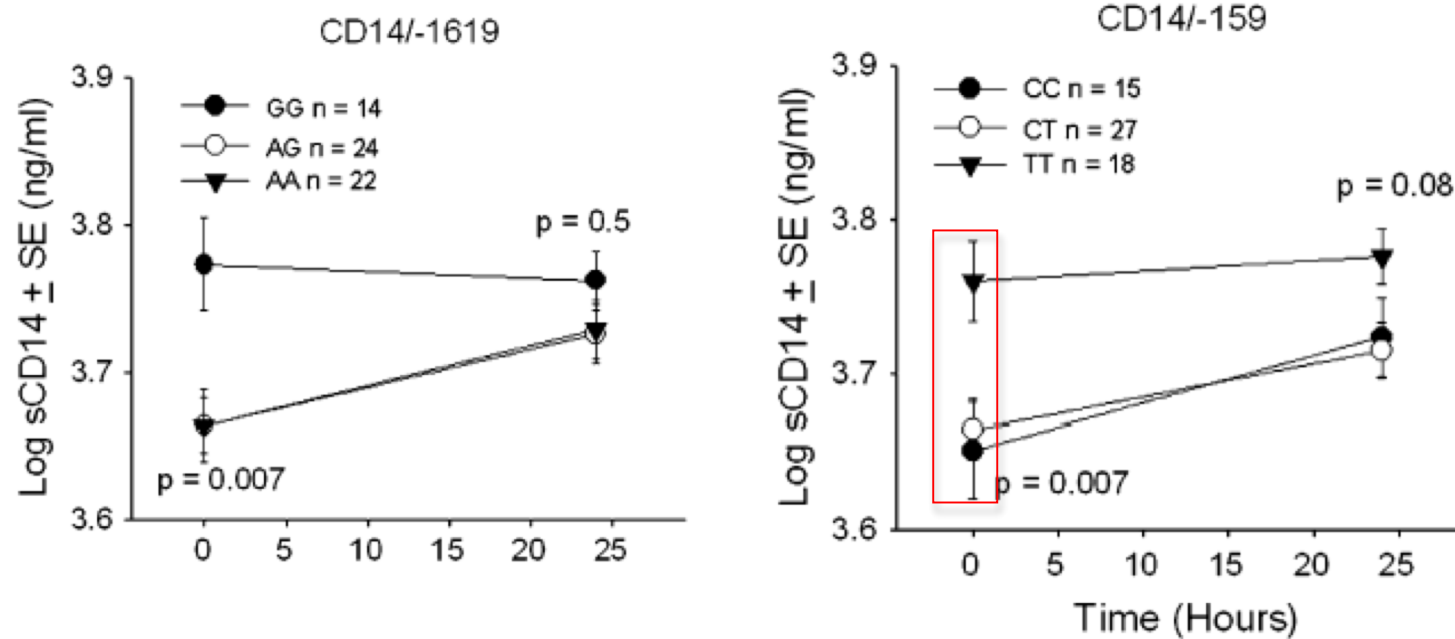


William LK et al JACI 2006; 118: 851

Association du taux d'IgE avec l'exposition aux endotoxine selon les polymorphismes du CD14

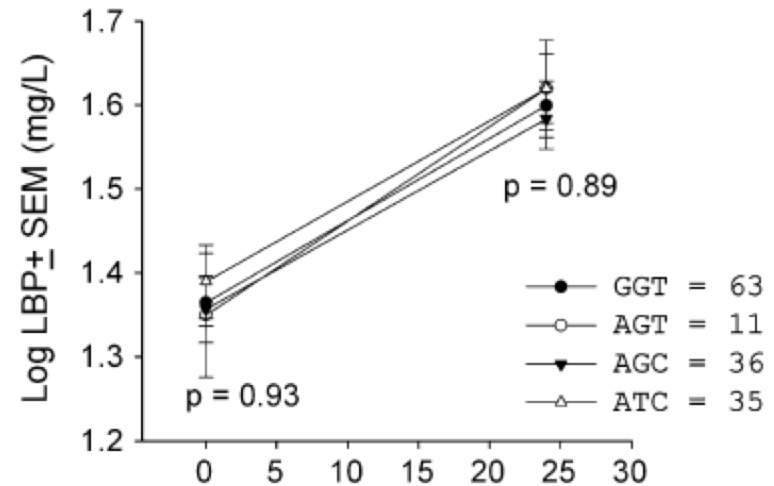
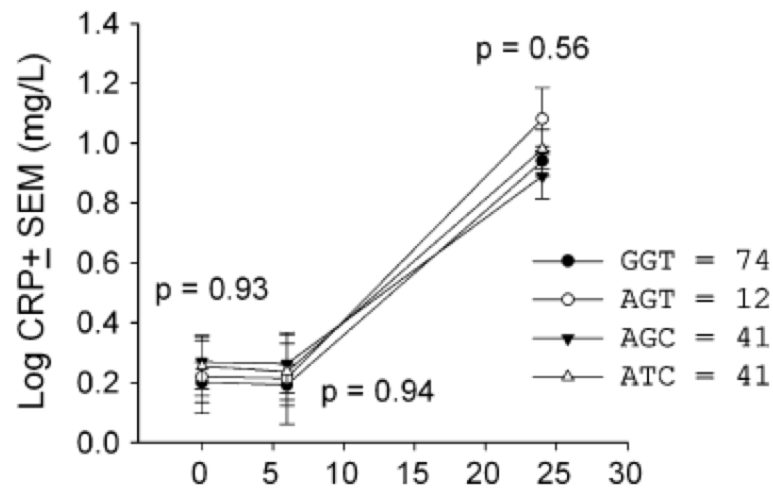


CD14 promotor polymorphisms **and** inhaled endotoxin modulates the sCD14



TD LeVan, O Michel et al JACI 2008; 121: 434-440

Association of CD14 haplotypes with LPS-induced systemic inflammation



Innate Immunity in Heart, Lung and Blood Disease Programs for Genomic Applications

Name	toll-like receptor 4 isoform D
Source PGA	InnateImmunity
Chromosome	chr9 (+) (chr9:113920245-113930888)
Accession	NM_138557
SNPs	44

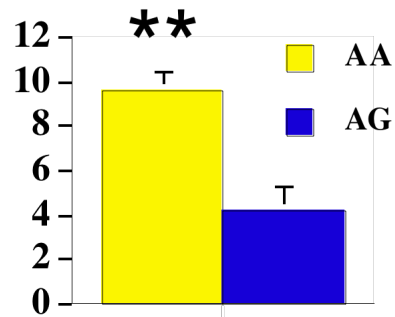
The most frequent are: -896, -1196, -1607, -2026, -137

***Ref: Immunity in Heart, Lung, and Blood Diseases.
Innate Immunity PGA, NHLBI Program for Genomic Applications,
URL: www.innateimmunity.net/IIPGASNPs/TLR4/index_html***

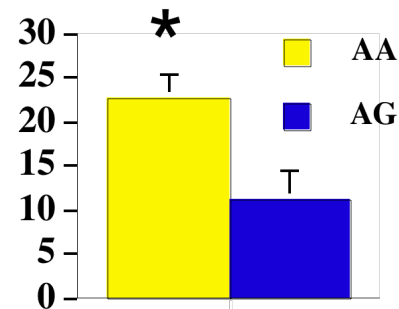
Tlr-4 polymorphism and the LPS responsiveness

The LPS response was lower in subjects +896 AG of Tlr-4 gene

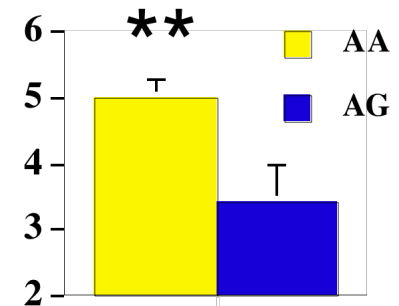
Δ CRP (mg/L \pm SE)



Δ LBP (mg/L \pm SE)



Δ WBC (*1000 cells/ μ L \pm SE)



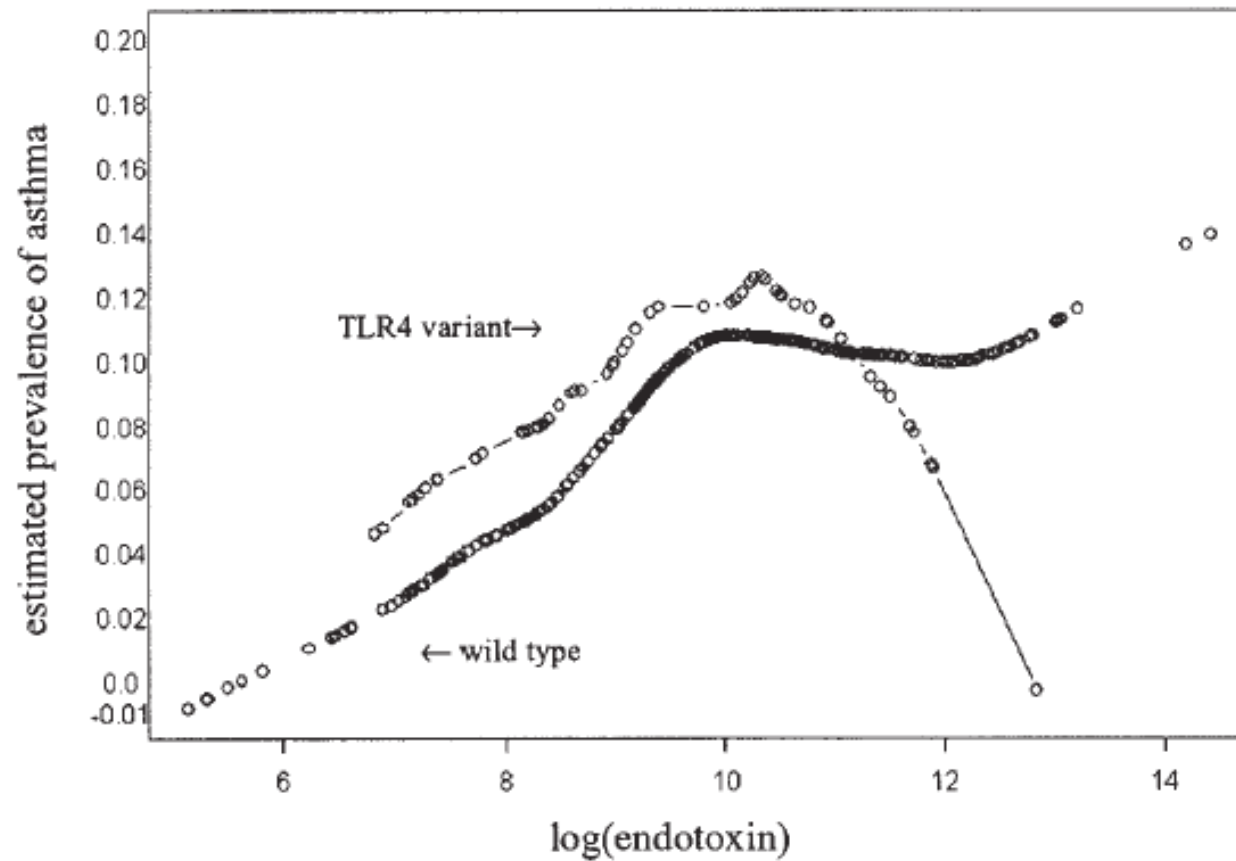
Michel, T LeVan, D Stern, M Dentener, J Thorn, D Gnat, L Beijer, P Cochaux, PG Holt, FD Martinez, R Rylander. J Allergy Clin Immunol 2003, 112: 923-9

LPS receptor gene : summary

LPS GENE STUDY SUMMARY

	TLR4-1607 TT	TLR4-896AA	TLR4-2026AA	CD14-159 CC
	Chi-2 p	Chi-2 p	Chi-2 p	Chi-2 p
Sexe	0,55 ns	0,61 ns	5,41 ns	1,48 ns
SPT	6,36 0,042	0,09 ns	2,04 ns	6,05 0,014
RAST g1, t3	5,91 0,0521	0,18 ns	0,97 ns	8,77 0,0031
CRP resp (>10)	2,47 ns	7,29 0,007	1,37 ns	2,04 ns
WBC resp (>4000)	3,07 ns	4,25 0,039	0,45 ns	0,31 ns

Relationship between endotoxin exposure and the prevalence of asthma, in regard with TLR4 polymorphism



M Werner et al JACI 2003;112:323

Conclusions

The effects of endotoxin exposure on allergic diseases are influenced by:

1. The timing of exposure
2. The pre-existence of a disease
3. The polymorphisms of the endotoxin receptor

