

Letter to the Editor

Opposite effects of allergy prevention depending on *CD14* rs2569190 genotype in 3 intervention studies

To the Editor:

Several birth cohort studies aimed at preventing the development of asthma by reducing the amount of exposure to inhalant allergens found no effects or even opposite effects on atopy development.¹⁻³ The Dutch Prevention and Incidence of Asthma and Mite Allergy (PIAMA) study investigated whether the use of mite allergen-impermeable mattress covers (IMCs) reduced the risk of asthma and allergy in high-risk children. No effect was found, despite lower allergen levels on the children's mattresses.¹ The Dutch Prevention of Asthma in Children (PREVASC) study and Canadian Childhood Asthma Primary Prevention Study (CAPPS) assessed the effectiveness of a multifaceted intervention program for primary prevention of asthma in high-risk children, including the use of mattress covers. A meta-analysis of the PREVASC study, CAPPS, and the Isle of Wight study showed a decreased risk of asthma with multifaceted interventions in the first 5 years of life.⁴ Although this effect was still observed in CAPPS at 7 years of age, the prevalence of atopy was not reduced.² A possible explanation might be that the interventions simultaneously reduced microbial exposure in the children's mattresses, which are important reservoirs of bacteria and microbial products.⁵ This would support the hypothesis that binding

of microbial antigens to innate immune receptors skews the immune system toward a T_H1 response, favoring a nonallergic immune response. A common functional single nucleotide polymorphism in the innate receptor *CD14* (rs2569190) has been shown to interact with the level of microbial exposure in the development of atopy.⁶⁻⁸ Therefore we studied whether the rs2569190 genotype modifies the intervention effects on the development of asthma and allergy in the PIAMA, CAPPS, and PREVASC birth cohorts.

We compared distributions of doctor-diagnosed asthma and symptoms of asthma (wheeze, dyspnea, or use of inhaled corticosteroids) in the last 12 months, atopy (≥ 1 positive skin prick test response to common inhalant allergens), and total IgE levels in the active intervention groups with those in the placebo and control groups stratified by the CC/CT versus TT genotype of rs2569190 in white children. Outcomes were measured at ages 8, 7, and 6 years for the PIAMA study, CAPPS, and the PREVASC study, respectively. Effect modification was tested for significance by including an interaction term of intervention by genotype into a full regression model. The characteristics of the study populations are shown in Table I.

Endotoxin levels in the children's mattresses, which were measured in the PIAMA study at 3 months of age, were lower with active than placebo covers only when expressed per square meter (median, 758 vs 929 EU/m²). In the subsets of children with genotypes available, we found no significant main effects of the

TABLE I. Characteristics of the study populations in the first year of life

	PIAMA study			CAPPS		PREVASC study	
	Active IMC	Placebo IMC	NHS high risk	Active MFI	Control group	Active MFI	Control group
No. included	217	169	218	140	132	110	113
Sex (% boys)	47.0	56.2	52.8	55.7	50.8	51.8	46.9
Mother allergic (%)	100	100	100	61.4	60.6	63.9	64.0
Father allergic (%)	38.4	32.5	28.9	48.9	50.8	58.3	55.9
Maternal education (% high)	39.8	43.2	42.9	59.3	68.2	44.0	41.6
Mother smoking during pregnancy (%)	10.0	9.5	17.6*	5.7	7.6	7.7	10.0
Duration of breast-feeding (%)							
Never	15.3	13.1	14.2	5.7	9.9	18.1	24.8
<12 wk†	32.9	30.4	28.9	11.4	13.6	28.6	19.3
≥ 12 wk	51.9	56.5	56.9	82.9	76.5	53.3	56.0
Smoke exposure in the house (%)	19.0	18.3	18.3	21.4	22.1	17.2	21.4
Cat at home (%)	30.9	22.6	22.9	20.0	21.2	9.5	11.9
Dog at home (%)	15.7	10.1	17.0	30.0	25.0	21.9	19.3
Other children <12 y at home (%)							
0	52.1	53.0	50.7	9.6	7.6	40.0	38.1
1	34.6	31.5	35.0	60.8	64.7	42.7	38.9
≥ 2	13.4	15.5	14.3	29.6	27.7	17.3	23.0
Day care at age 1 y (%)	22.7	28.4	23.3	5.7	11.3	34.6	30.9
Genotype rs2569190 (%)							
CC	30.9	24.9	26.6	20.0	22.7	30.9	32.7
CT	51.6	56.2	47.7	53.6	40.9*	44.5	49.6
TT	17.5	18.9	25.7	26.4	36.4	24.5	17.7
Median endotoxin (EU/mg)							
Child's mattress age 3 mo	14.2	15.1	NA	NA	NA	NA	NA
Living room floor age 3 mo	23.5	15.0	NA	NA	NA	NA	NA
At 5 sites age 7 y	NA	NA	NA	86.8	71.3	NA	NA

MFI, Multifaceted intervention; NA, not available; NHS, natural history study.

*Significant difference ($P < .05$).

†For CAPPS, the cut point is 16 wk.

TABLE II. Distribution of asthma and allergy outcomes in the intervention, placebo, and control groups for the PIAMA study, CAPPs, and the PREVASC study stratified by *CD14*/rs2569190 genotype

	CT or CC			TT		
	Active IMC group	Placebo IMC group	NHS high-risk group	Active IMC group	Placebo IMC group	NHS high-risk group
PIAMA cohort, age 8 y						
Atopy	24.1 (32/133)	27.8 (27/97)	22.8 (29/127)	42.9* (12/28)	11.1 (3/27)	27.5 (11/40)
Total IgE (IU/mL)	63.0 (136)	81.7 (103)	54.6 (117)	145.1* (34)	42.2 (25)	71.6 (38)
Asthma symptoms last 12 mo	19.3 (31/161)	16.5 (21/127)	19.4 (31/160)	30.6 (11/36)	17.9 (5/28)	21.6 (11/51)
Diagnosed asthma last 12 mo	5.4 (8/148)	5.0 (6/121)	3.8 (6/158)	11.4† (4/35)	7.4 (2/27)	0 (0/49)
	CT or CC			TT		
	Active MFI group	Control group		Active MFI group	Control group	
CAPPS cohort, age 7 y						
Atopy	50.5* (55/109)	31.3 (31/99)		44.4 (12/27)		51.7 (15/29)
Total IgE (IU/mL)	22.2 (98)	17.1 (90)		22.9 (25)		26.0 (24)
Asthma symptoms last 12 mo	NA	NA		NA		NA
Diagnosed asthma last 12 mo	16.1 (18/112)	23.5 (24/102)		10.7 (3/28)		26.7 (8/30)
	CT or CC			TT		
	Active MFI group	Control group		Active MFI group	Control group	
PREVASC cohort, age 6 y						
Atopy	NA	NA		NA		NA
Total IgE (IU/mL)	24.7 (87)	17.3 (78)		33.4 (24)		19.0 (18)
Asthma symptoms last 12 mo	25.0 (19/76)	19.5 (17/87)		13.0 (3/23)		26.7 (4/11)
Diagnosed asthma last 12 mo	22.2 (18/81)	14.1 (13/92)		12.5 (3/24)		22.2 (4/15)

Data are presented as percentages (numbers affected/total numbers) or geometric means (total numbers).

Boldface values are significant: * $P < .05$ compared with placebo or control group and † $P < .05$ compared with natural history study high-risk group.

MFI, Multifaceted intervention; NA, not available; NHS, natural history study.

intervention on asthma or allergy outcomes in the PIAMA study at age 8 years or the PREVASC study at age 6 years. In the white subset ($n = 272$) of CAPPs used in the genetic analysis, the protective effect of the intervention on asthma became borderline significant (odds ratio [OR], 0.55; 95% CI, 0.30-1.02; $P = .06$), and there was a significant increase in the risk for atopy in the intervention group (OR, 1.73; 95% CI, 1.06-2.83; $P = .03$).

In both the PIAMA study and CAPPs, significant adverse effects of the intervention on atopy were found; however, these effects existed in subgroups with opposite genotypes. We found that PIAMA children with the TT genotype had significantly higher mean total IgE levels and a higher prevalence of atopy in the active IMC group (145 IU/mL and 43%, respectively) than in the placebo IMC group (42 IU/mL and 11%, respectively; Table II). An effect in the same direction was found in PREVASC children with the TT genotype, with IgE levels being 33 IU/mL in the active MFI group versus 19 IU/mL in the control group ($P = .10$). In CAPPs a significantly higher prevalence of atopy existed in the active MFI group compared with that seen in control subjects in the CC/CT genotype group (51% vs 31%, Table II).

Although the prevalence of diagnosed asthma at age 8 years was significantly higher in the active IMC group than in the natural history study high-risk control group in PIAMA children with the TT genotype (11% vs 0%, Table II), we found no convincing evidence for an effect on asthma development.

The rs2569190 genotype significantly modified the effect of the active intervention on atopy to inhalant allergens in both the PIAMA study and CAPPs when tested as an interaction term in regression analyses. The OR of having atopy in the active intervention group compared with the control group was 2.40 (95% CI, 1.34-4.31; $P = .03$ adjusted for recruitment center) in children from CAPPs with a CC or CT genotype. In the PIAMA study children with the TT genotype had a significant OR for

atopy in the active intervention group compared with the placebo group (OR, 5.59; 95% CI, 1.21-25.83; $P = .03$ adjusted for potential confounders). A significant effect modification was observed in the PIAMA study for total IgE levels as well. In the PREVASC study there was a tendency toward a similar effect.

We can only speculate about an explanation for our observation that the effects of intervention were modified by the same genetic locus but with opposite genotypes. The effect of decreasing the amount of microbial exposure on the development of atopy might depend on the *CD14* genotype on the one hand and the background level of microbial exposure on the other hand. Differences in lifestyle and environments between the Dutch PIAMA study and the Canadian CAPPs might have resulted in differences in microbial exposures. There were certainly differences in exposures (dog allergens and incidence of asthma and atopy) between the 2 Canadian recruitment sites (Winnipeg and Vancouver), which necessitated the inclusion of a center variable in the analyses. Unfortunately, we were unable to directly compare absolute endotoxin levels in the PIAMA study and CAPPs because the methods of measurements were substantially different.

Nevertheless, we found some indications that the levels of microbial exposure were relatively low in the PIAMA study. First, the levels of endotoxin measured on the living room floor and in infants' mattresses in the PIAMA study at age 3 months were substantially lower than the mean of measurements at 5 different sites at age 7 years in CAPPs (Table I).⁹ Additionally, children in the CAPPs cohort were more likely to have an older sibling younger than 12 years in the home, which is generally considered an important source of microbial exposure. Furthermore, interventions in CAPPs and the PIAMA study were not identical, although both included the use of mattress covers.

We conclude that our results suggest that intervention measures aimed at preventing the development of atopy by reducing the

amount of exposure to inhalant allergens in high-risk children might have opposite effects in subgroups of children with specific *CD14* genotypes, possibly because of the simultaneous reduction of exposure to microbial products. We did not find substantial effects on asthma development.

Marjan Kerkhof, MD, PhD^{a,*}

Denise Daley, PhD^{b,*}

Dirkje S. Postma, MD, PhD^c

Julie E. Park, MMath^b

Maira Chan Yeung, MD^d

Alet H. Wijga, PhD^e

Ulrike Gehring, PhD^f

Johan C. de Jongste, MD, PhD^g

Henriëtte A. Smit, PhD^h

Bert Brunekreef, PhD^{f,h}

Onno C. P. van Schayck, MD, PhDⁱ

Allan Becker, MD^{j,k}

Gerard H. Koppelman, MD, PhDⁱ

From the Departments of ^aEpidemiology, ^cPulmonology, and ⁱPediatric Pulmonology and Pediatric Allergology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; ^bthe Department of Medicine, St Paul's Hospital, University of British Columbia, Vancouver, British Columbia, Canada; ^dthe Occupational and Environmental Lung Disease Unit, University of British Columbia, Vancouver, British Columbia, Canada; ^ethe National Institute for Public Health and the Environment, Bilthoven, The Netherlands; ^fthe Institute for Risk Assessment Sciences, University of Utrecht, Utrecht, The Netherlands; ^gthe Department of Pediatrics, Erasmus MC–Sophia Children's Hospital, Rotterdam, The Netherlands; ^hthe Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands; ⁱthe Care and Public Health Research Institute (Caphri), Maastricht University, The Netherlands; and the Departments of ^jPediatrics and Child Health and ^kCommunity Health Sciences, Faculty of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada. E-mail: denise.daley@hli.ubc.ca.

*These authors contributed equally to this work.

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