Applying the CAMP trial asthma remission prediction model to the Dutch asthma remission studies

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TABLE I. Preterm birth and risk of food allergy

Preterm birth (<37 wk of gestation)	Adjusted HR; 95% CI*
<28 wk	**0.14; 0.04-0.56**
28-29 wk	0.82; 0.38-1.75
30-31 wk	**0.68; 0.50-0.93**
32-33 wk	**0.63; 0.52-0.76**
34 wk	0.85; 0.73-1.00
35 wk	0.96; 0.85-1.07
36 wk	1.00; 0.92-1.09

Statistically significant findings are presented in boldface.
*Adjustment for sex, maternal age at delivery, country of birth, parity, body mass index, early pregnancy smoking, maternal asthma/pulmonary disease, cesarean delivery, and birth weight.

most apparent in very preterm infants delivered vaginally. The somewhat higher relative risk of food allergy in very preterm infants with cesarean delivery indicates a positive impact of this latter exposure on the risk of childhood food allergy,[3] most likely through a delayed and altered gut microbiota composition,[4] in line with the hygiene hypothesis.[5]

Regarding the second point made by Winslow, we attempted stratification of very preterm and moderately preterm born infants by age in gestational weeks completed at birth. This analysis showed that risk estimates for food allergy decreased by earlier preterm gestational ages. In particular, the HR for food allergy in infants born at less than 28 gestational weeks was 0.14 (95% CI, 0.04-0.56), strengthening the theory of a protective role of very preterm birth on the development of food allergy.[6] Low-risk estimates remained until the end of the 33rd week of gestation (the only exception was observed in infants born at 28-29 weeks; HR, 0.82; 95% CI, 0.38-1.75), whereupon the HRs were no longer statistically significant (Table I). Indeed, in some of the subgroup analyses, statistical significance was not attained likely because of inadequate power (considering that the overall risk estimate was 0.74 for very preterm birth and 0.96 for moderately preterm, large numbers of participants are required to uncover minor excess risks).

It is well known that food allergy starts early in life. Recent studies have provided strong evidence that an opportunity window occurs during the first year of life within which to induce immunologic tolerance.[7] The inverse association between very preterm birth and food allergy identified in our cohort is consistent with both the "hygiene"[5] and the "dual-allergen exposure"[7] hypotheses, suggesting that earlier exposure to pathogens and early ingestion of food proteins, respectively, might lead to clinical immune tolerance to food allergens in very preterm born infants. Future research should not only aim to identify perinatal exposures that predispose to food allergy but also immunologic mechanisms and early-life environmental factors that might protect from atopic disease and potentially promote a tolerogenic response.

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Applying the CAMP trial asthma remission prediction model to the Dutch asthma remission studies

To the Editor:

A small subset of patients with asthma can go into spontaneous remission later in life.[1,2] Predicting this clinical trajectory would be of great interest, because these asthma remission subjects are not burdened by symptoms anymore and no longer require any medication. Wang et al[3] created a prediction model that could predict asthma remission outcome. They showed that the combination of normal FEV_1/forced vital capacity (FVC) ratio, less severe bronchial hyperresponsiveness, and blood eosinophil counts of less than 500 cells/μL at age 8 years yields more than 80% probability to achieve asthma remission by adulthood.

We were interested in the generalizability of predicting remission in childhood and applied this prediction model on our Dutch asthma remission cohorts. Children included in these cohorts described by Vonk et al (cohort 1, n = 94) and Carpaij et al (cohort 2, n = 157) had doctor-diagnosed asthma and were bronchial hyperresponsive (ie, substance provocative concentration causing a 20% drop in FEV_1 [PC_{20}] ≤16 mg/mL histamine).[1,2] Similar to the definition used by the Childhood Asthma Management Program (CAMP), we defined asthma remission at follow-up as no wheeze or asthma attacks in the last year, having an FEV_1/inspiratory vital capacity (IVC) ratio of greater than or equal to 80%, and no use of asthma-related medication. We used a different measure for airway obstruction, that is, FEV_1/IVC, because no data on FVC were available. Subjects with missing data were excluded. Normally and nonnormally distributed variables were compared with *t* test and Mann-Whitney *U* test, respectively. We constructed 6 groups on the basis of baseline criteria provided in Wang et al and calculated the prevalence of subjects in remission for each group.

TABLE I. Baseline clinical characteristics of 3 prospective childhood cohorts and application of the prediction model

Characteristic	Persistent asthma			Asthma remission		
	Cohort 1: Vonk et al[2] (n = 79)	Cohort 2: Carpaij et al[1] (n = 147)	CAMP: Wang et al[3] (n = 650)	Cohort 1: Vonk et al[2] (n = 15) (15%)	Cohort 2: Carpaij et al[1] (n = 10) (6.4%)	CAMP: Wang et al[3] (n = 229) (26.1%)
Enrollment year range	1966-1969	1972-1976	1993-1995	1966-1969	1972-1976	1993-1995
Age at baseline (y), mean ± SD	9.9 ± 2.0	9.7 ± 1.4	8.8 ± 2.1	9.6 ± 2.0	10.2 ± 1.2	8.6 ± 1.9
Mean follow-up (y)	16	15	12	16	15	12
Male sex, n (%)	58 (73.4)	105 (71.4)	407 (62.6)	9 (60.0)	7 (70.0)	115 (50.2)
FEV_1 % predicted, mean ± SD	82.1% ± 16.5%*	75.4% ± 14.3%*	92.2% ± 14.1%*	85.7% ± 17.2%*	82.0% ± 10.6%*	99.0% ± 12.7%*
FEV_1/VC ratio, mean ± SD†	75.0% ± 12.2%*	72.3% ± 7.9%*	77.9% ± 7.9%*	78.1% ± 12.0%*	79.7% ± 7.1%*	85.6% ± 6.3%*
PC_{20} threshold (mg/mL), median (IQR)†	2.0 (7.0)*	4.0 (6.0)*	0.9 (1.6)*	8.0 (30.0)*	8.0 (4.0)*	1.7 (3.6)*
Serum eosinophil count (cells/μL), median (IQR)	462.0 (495.0)*	385.0 (396.0)*	422.0 (493.5)*	220.0 (297.0)*	286.0 (236.5)*	320.5 (327.3)*

	Prediction model					
	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
	FEV_1/FVC% ≤ 75%	FEV_1/FVC% 75%-79%	FEV_1/FVC% 80%-84%	FEV_1/FVC% ≥ 85%; PC_{20} < 1 mg/mL	FEV_1/FVC% ≥ 85%; PC_{20} ≥ 1 mg/mL; blood eosinophils ≥500 cell/μL	FEV_1/FVC% ≥ 85%; PC_{20} ≥ 1 mg/mL; blood eosinophils <500 cell/μL
CAMP (n = 876) Predicted probability	9.5% (n = 199)	27.6% (n = 190)	53.8% (n = 228)	58.3% (n = 71)	65.4% (n = 49)	82.6% (n = 139)
Cohorts 1 + 2 (n = 251)	5.5% (n = 3 of 55)	5.6% (n = 7 of 126)	15.4% (n = 6 of 39)	0.0% (n = 0 of 1)	10.0% (n = 1 of 10)	40.0% (n = 8 of 20)

NA, Not applicable; *VC*, vital capacity.
*Either significant difference ($P < .05$) between asthma remission and persistent asthma within cohorts 1 + 2 or CAMP.
†FEV_1/IVC and PC_{20} histamine threshold on cohorts 1 and 2; FEV_1/FVC and PC_{20} methacholine threshold in CAMP.

After combining cohorts 1 and 2, the clinical and complete remission rate was 10.0% compared with 26.1% in CAMP (Table I). Like Wang et al, we observe an increase if the prevalence of remission as baseline FEV_1/IVC% is higher. In subjects with an FEV_1/IVC ratio of greater than or equal to 85%, PC_{20} value of greater than or equal to 1 mg/mL, and an eosinophil level of less than 500 cells/μL has additional value to predict asthma remission. In this group, the prevalence of remission was 40%, whereas those with greater than or equal to 500 eosinophils/μL had a 10% prevalence of remission. In accordance to the CAMP study, children in cohorts 1 + 2 had a significantly higher FEV_1, FEV_1/IVC%, and PC_{20} threshold and significantly lower serum eosinophils in the asthma remission group compared with the persistent asthma group. These are known clinical features associated with asthma remission.[4-6] The FEV_1/FVC% measured in CAMP was higher than in cohorts 1 + 2, resulting in a higher proportion of subjects subdivided in group 2. The definition for airway obstruction is not expected to be the cause, because the difference between FEV_1/FVC% and FEV_1/IVC% is marginal in children and young adults with mild to moderate asthma.[7]

Taking this into account, we show that the model proposed by Wang et al can correctly predict future development of asthma remission in up to 40% of cases. Although usable, more research is needed to disentangle the pathophysiology of asthma remission, which is a highly relevant yet poorly understood outcome of childhood asthma.

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Reply

To the Editor:

In our article on childhood asthma remission from the Childhood Asthma Management Program (CAMP) cohort,[1] we identified predictors of both asthma remission and persistence into adulthood. The predicted probability of asthma remission was the highest (82.6%) in subjects with a baseline FEV_1 to forced vital capacity (FEV_1/FVC) ratio of greater than or equal to 85%, provocative concentration causing a 20% fall in FEV_1 (PC_{20}) of greater than or equal to 1 mg/mL, and serum eosinophil count of less than 500 cells/μL. A key question left unanswered in our study was whether our results were generalizable to more severe asthma, given that CAMP included only those with mild-to-moderate persistent childhood asthma.

Carpaij et al evaluated our prognostic model in a combined cohort of 251 children with asthma from The Netherlands.[2-4] Notably, the baseline characteristics describe children with significantly lower lung function (FEV_1 as a percent of predicted was in the mid 70% to low 80% range, whereas those in CAMP were in the low 90% range), suggesting a greater level of severity at baseline for the combined Dutch cohort. Further supporting this increased level of baseline severity is the report that their combined cohort demonstrated an overall remission rate of only 10.0% versus 26.1% in CAMP. Despite this, the Dutch children with asthma who met our prognostic remission criteria had a 40.0% (8 of 20) probability of asthma remission, greater than 5-fold higher than did those without the criteria (7.4%; 17 of 231). Overall, this validates our prediction model for remission across a range of childhood asthma severity. Conversely, we also identified a subgroup of children much more likely to have persistence of asthma into adulthood. Children with a baseline FEV_1/FVC ratio of less than 80% had a less than 10% probability of asthma remission. Similarly, Carpaij et al found the probability of remission to be 5.6% (10 of 181) in this subgroup of those with asthma. We wonder if treatments to improve baseline FEV_1/FVC in pediatric asthmatic patients would increase their probability of outgrowing the disease.

Clinical measurements are surrogate measures for biologic processes that in turn are influenced by genetics, epigenetics, and the environment. Therefore, to truly understand the biology and the factors influencing asthma remission, further studies in these fields are required. Indeed, the Dutch group has described genetic variants associated with remission across multiple cohorts, while we have previously noted microRNAs predictive of resolution of airways hyperresponsiveness in CAMP.[5,6] We anticipate that by combining clinical and multiomic data using systems biology, we will be able to further elucidate the mechanisms governing asthma remission and persistence. This will enable us to create personalized and more accurate prediction models for asthma remission and may eventually lead to novel therapeutic approaches for the secondary prevention of asthma.

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Amoxicillin sensitization rate in patients with eruptions after *Helicobacter pylori* eradication therapy

To the Editor:

I read with interest the recent article by Ito et al.[1] The authors reported that only 2 of 15 patients with skin eruptions after eradication therapy for *Helicobacter pylori* using amoxicillin, clarithromycin, and a proton pump inhibitor had positive results on repeated drug lymphocyte transformation tests (LTTs), and in another patient $CD4^+$ T cells expressed CD154 in response to the drugs. They elegantly demonstrated that a significant proportion of the patients with negative drug-specific responses (9/12) exhibited *H pylori*–specific immune responses.[1]

Table I summarizes 11 patients with skin eruptions after *H pylori* eradication therapy in our hospital during the last 3 years. Similar with the previous studies,[1,2] in most patients generalized maculopapular rash developed after completing the 7-day eradication therapy (Table I). In our patients, however, all but 1 exhibited positive LTT responses to amoxicillin (Table I).