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Reference:

Eijsvoegel N. B., Hollegien M. I., Bok L. A., Derksen-Lubsen G., Dikken F. P. J., Leenders A. C. A. P., Pijning A., Post E. D. M., Wojciechowski Marek, Schmitz R.,-
Lower percentage of allergic sensitization in children with Down syndrome
Pediatric allergy and immunology - ISSN 0905-6157 - Hoboken, Wiley, 28:8(2017), p. 852-857
Full text (Publisher's DOI): <https://doi.org/10.1111/PAI.12796>
To cite this reference: <http://hdl.handle.net/10067/1485610151162165141>

PROFESSOR E DE VRIES (Orcid ID : 0000-0003-4311-3550)

Article type : Letter to the Editor

Corresponding author mail id: e.d.vries@jbz.nl

Lower percentage of allergic sensitization in children with Down syndrome

To the Editor:

Children with Down syndrome (DS) often suffer from respiratory symptoms like wheezing, cough and dyspnea, especially in their preschool years(1). Healthcare professionals (and parents) often associate these symptoms with allergy or asthma(1-3), and prescribe anti-allergic and anti-asthmatic medication, especially in young DS children(3).

Literature shows that allergic sensitization is present in around 27 to 40% of children in western countries(4-7). It is defined as the appearance of allergen-specific serum IgE (sIgE) antibodies after exposure to a certain allergen. The absence of allergic sensitization has a high negative predictive value (94.3%) for allergic asthma and/or rhinitis in non-DS individuals(5). The immune system in DS is different, it shows signs of deficiency as well as of dysregulation. This may lead to *less* (deficiency) as well as *more* (dysregulation) allergic sensitization. In several small studies using laboratory tests (RAST and/or specific IgE) and skin prick tests, this balance seems to tilt to less allergic sensitization in DS compared to the non-DS control groups(3, 6, 8, 9).

We conducted a multicenter cross-sectional cohort study in seven hospitals in 371 DS children (2-18yrs), after obtaining parental informed consent. A total of 358 parents completed a short questionnaire regarding allergy-related symptoms, suspicion (by parents) of allergy and/or asthma, and any special diets. Hospital medical records were reviewed (NE, MH) for 1) a diagnosis of asthma

/ viral induced wheezing / chronic nonspecific lung disease, hay fever, eczema, food allergy, recurrent
This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/pai.12796

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respiratory infections and/or surgery for cardiac abnormalities; 2) lung function tests for bronchial hyperreactivity and bronchoconstriction, skin prick tests for allergy, past blood tests for sIgE in serum, and/or an elimination/provocation test for any foods; 3) therapy with inhaled medication and/or an allergen-restricted diet (with the exception of a gluten-free diet). In 100 children stored serum was available [stored <1 year, at -20°C]; extra blood was obtained in 175 children during planned venipunctures for other reasons (4ml 2-16yrs, 7ml ≥16yrs). All blood samples were analyzed in the laboratory of the Jeroen Bosch Hospital. Allergic sensitization was evaluated using inhalation and food mix (Immulite-2000 XPi), detection limit 0.10kU/l; if either was positive, sIgE's were determined separately. 'Sensitized' was defined as ≥ 1 sIgE ≥ 0.35 kU/l. The laboratory classified the total IgE as normal if values were <50kU/l <10yrs and <90kU/l ≥ 10 yrs (detection limit 1.0kU/l). Results were compared with the cross-sectional KiGGS study(5) performed in 12,988 German children. The KiGGS cohort was used because it shows allergic sensitization in a large pediatric population, not bound to age limitations (which is the case for the KOALA and PIAMA studies(4, 7)). Furthermore, data found in this cohort is comparable with other limited studies performed in the Netherlands. We therefore considered it to be representative for the Dutch population. We divided the children in our study into the same age groups (3-6, 7-10, 11-13, 14-17yrs) for comparison. Statistical analysis was performed using SPSS (version 22.0). The association between age and sensitization was determined by logistic regression analysis. Possible effect modification was assessed to investigate whether the association between age and sensitization is different for children with and without DS; when the p-value of the interaction term was <0.1, stratified analyses were performed separately. $p < 0.05$ was considered statistically significant.

Medical records were available for review in 363 DS children (43% male, mean age 9.8yrs, 30% <6yrs). In 19.6% (95%CI 15.8-23.9) symptoms of asthma, viral induced wheezing and/or chronic nonspecific lung disease were described (Table 1A). Bloemers et al. found a slightly higher percentage of 32% of recurrent wheeze, independent of a history of RS-virus infection(2). 95.6% (95%CI 93.0-97.3) of the patients in our cohort with these airway symptoms used inhalation

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medication at some point in time; this was discontinued later in 86.5% (95%CI 82.5-89.7) of them. Recurrent airway infections were reported in 42.7% (95%CI 37.7-47.8). sIgE had already been determined by the treating physician in 24.8% (95%CI 20.6-29.5); it was abnormal in only 6.6% (95%CI 2.8-14.5). This was much less frequent than reported by Weijerman et al. who found that sIgE was determined in 71% of their patients; no allergic sensitization was found in that cohort(3). In our cohort, parents reported they suspected allergy in 43.3% (95%CI 38.3-48.5) of the children with DS, and asthma in 12.3% (9.3-16.1). Weijerman et al. found comparable percentages (38.4% with symptoms of wheezing); only 3.1% of these patients were later diagnosed with asthma(3). In our cohort, upper airway problems occurred in 52.0% (46.8-57.1) of the children with DS and a special diet because of a suspected food allergy in 12.6% (9.5-16.4), according to the parents.

Laboratory testing showed 7.6% (95%CI 5.0-11.4) of the DS children were sensitized for ≥ 1 allergen, compared with 40.2% (95%CI 39.0-41.4) of the non-DS children in the KiGGS-study(5). This is in line with the results found in earlier, smaller studies using laboratory tests and skin prick tests (3, 6, 9, 10). An increased sIgE was mainly seen against grass pollen, tree pollen and house dust mite, in non-DS as well as DS children (Table 1B). When looking at the different age groups, the percentage of sensitized DS children differs significantly from those found in the different age groups of the KiGGS study(5). The included patients with DS were overall younger than the included patients in the KiGGS study. This could partly explain the difference found above. Logistic regression analysis showed a significant association between age and sensitization (OR 1.086; 95%CI 1.078-1.095). This association was not different for DS (our cohort) and non-DS (KiGGS) children (p-value of interaction term 0.917). The percentage of sensitized DS children remains lower than of non-DS children, also with increasing age.

Our study has some limitations. We focused mainly on lower airway symptoms, not on other allergy-associated problems such as urticaria, food allergy or hay fever. We only used medical data

from the involved hospitals. However, our survey of the hospital medical files showed that general practitioners did not have an important role in starting treatment for asthma or allergy in the DS children in our cohort. We did not assess the benefit some children may have had from these treatments. Most importantly, we determined the sensitization by the Immulite analysis, and Schmitz et al. used the ImmunoCAP, both contain the same allergens, but the ImmunoCAP also contains rice, carrot, horse dander, potatoes and apple allergens. Very few children were found to be allergic to the allergens mentioned above in the study by Schmitz et al. Therefore, we believe that not testing these specific allergens did not have much impact on the results we found in our cohort. Both techniques are considered to be reliable, and both are widely used(6).

In conclusion, our large multicenter cohort study confirms that allergic sensitization is much less prevalent in DS (7.6%) compared to non-DS (40.2%) children, whereas symptoms such as wheezing, cough and dyspnea are very common in DS. This has important implications for information intended for parents, as well as for diagnostic workup and treatment by professionals. Health professionals should seriously consider other causes of specific symptoms associated with allergies before starting a specific treatment. In this way, better tailored therapies as well as cost reductions may be achieved.

N.B. Eijvoogel, MD^A; M.I. Hollegien, MD^A; L.A. Bok, MD, PhD^B; G. Derksen – Lubsen, MD^C;
F.P.J. Dikken, MD^D; A.C.A.P. Leenders, PhD^E; A. Pijning, MD^F; E.D.M. Post, MD^G; M.
Wojciechowski, MD^H; R. Schmitz, PhD^I M. Hilbink, PhD^J; E. de Vries, MD, PhD^{J,K}.

From the ^ADepartment of Pediatrics, Jeroen Bosch Hospital, 's-Hertogenbosch; ^BDepartment
of Pediatrics, Máxima Medical Centre, Veldhoven; ^CDepartment of Pediatrics, Juliana
Children's Hospital/Haga Hospital, The Hague; ^DDepartment of Pediatrics, Gelre Hospital,

Zutphen; ^EDept. Of Medical Microbiology, Jeroen Bosch Hospital, 's-Hertogenbosch; ^FDepartment of Pediatrics Slingeland Hospital, Doetinchem; ^GDepartment of Pediatrics, St. Antonius Hospital, Nieuwegein, the Netherlands. ^HUniversity of Antwerp, Antwerp University Hospital, Department of Pediatrics, Antwerp, Belgium. ^IRobert Koch Institute, Dept. Epidemiology and Health Monitoring, Berlin, Germany. ^JJeroen Bosch Academy, Jeroen Bosch Hospital, 's-Hertogenbosch; ^KDepartment Tranzo, Tilburg University, Tilburg, the Netherlands.

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Figure 1: Allergic sensitization in our cohort of DS children and in non-DS children from the reference population (percentages). There was no age group of 0-2 in the KiGGS study, therefore this age group is not displayed in the figure. In our research no children with DS aged 0-2 showed allergic sensitization. *Non-DS patients were aged 14-17 years (KiGGS research). DS children in dark grey, non-DS children in light grey (KiGGS). The confidence intervals of the DS and non-DS children do not overlap; therefore the differences are statistically significant.

Table 1. The Down syndrome patients

A. medical records	Age 0-2 (n=16)	Age 3-6 (n=104)		Age 7-10 (n=92)		Age >10 (n=151)		Total (n=363)	
Male (n (%))	4 (25)	43 (41)		38 (41)		72 (48)		157 (43)	
Specific symptoms (%; 95%CI)									
Asthma/VIW/CNLD*	18.8 (6.6-43.0)	8.7 (4.6-15.6)		23.9 (16.4-33.6)		24.5 (18.3-31.9)		19.6 (15.8-23.9)	
Hay fever	0	4.8 (2.1-10.8)		5.4 (2.3-12.1)		8.6 (5.1-14.2)		6.3 (4.3-9.3)	
Eczema	0	2.9 (1.0-8.1)		7.6 (3.7-14.9)		8.6 (5.1-14.2)		6.3 (4.3-9.3)	
Food allergy	0	0		4.3 (1.7-10.7)		6.6 (3.6-11.8)		3.9 (2.3-6.4)	
Heart abnormality	0	30.8 (22.7-40.2)		27.2 (19.1-37.0)		24.5 (19.3-31.9)		27.0 (22.7-31.8)	
Recurrent airway infections	25.0 (10.2-49.5)	35.6 (27.0-45.1)		50.0 (40.0-60.0)		43.7 (36.1-51.7)		42.7 (37.7-47.8)	
Inhaled drugs (%; 95%CI)									
Never	68.8 (44.4-85.8)	63.5 (53.9-72.1)		57.6 (47.4-67.2)		66.9 (59.0-73.9)		63.6 (58.6-68.4)	
Past	31.3 (14.2-55.6)	26.0 (18.5-35.1)		38.0 (28.8-48.3)		31.8 (24.9-39.6)		31.7 (27.1-36.6)	
Present	0	10.6 (6.0-18.0)		4.3 (1.7-10.7)		1.3 (0.4-4.7)		4.7 (2.9-7.4)	
Allergen restricted diet (%; 95%CI)									
Never	100	99.9 (94.8-99.8)		93.5 (86.5-97.0)		93.4 (88.2-96.4)		95.3 (92.6-97.1)	
Past	0	1.0 (0.2-5.2)		5.4 (2.3-12.1)		4.0 (1.8-8.0)		3.3 (1.9-5.7)	
Present	0	0		1.1 (0.2-5.9)		2.6 (1.0-6.6)		1.4 (0.6-3.2)	
Diagnosis (%; 95%CI)									
Lung function tests	0	0		0		0.7 (0.1-3.7)		0.3 (0.0-1.5)	
Skin prick test	0	1.0 (0.2-5.2)		0		0.7 (0.1-3.7)		0.6 (0.2-2.0)	
sIgE blood test	0	9.6 (5.3-16.8)		29.3 (21.0-39.3)		35.1 (27.9-43.0)		24.8 (20.6-29.5)	
Elimination/ provocation test	0	0		4.3 (1.7-10.7)		0		1.1 (0.4-2.8)	
B. Allergic sensitization	Age 0-2 (n=8)	Age 3-6 (n=81)	Age 3-6 (n=2953)	Age 7-10 (n=65)	Age 7-10 (n=3667)	Age > 10 (n=121)	Age >10 (n=6368)	Total (n=275)	Total (n=12988)

Male (n (%))	3 (38)	37 (46)	1510 (51)	23 (35)	1898 (52)	58 (48)	3257 (51)	121 (44)	6665 (51)
Allergic sensitization** (% 95%CI)	0	4.9 (1.9-12.0)	29.3 (27.4-31.3)	7.7 (3.3-16.8)	39.1 (37.3-41.0)	9.9 (5.8-16.5)	45.6 (44.4-46.8)	7.6 (5.3-11.4)	40.2 (39.0-41.4)
Sensitization within inhalation panel (n (%))***	0					7 (5.8)		10 (3.6)	
- Grass pollen	0	1 (1.2)	343 (11.6)	2 (3.0)	840 (22.9)	4 (3.3)	1809 (28.4)	5 (1.8)	3000 (23.1)
- House dust mite	0	0	357 (12.1)	1 (1.5)	700 (19.1)	5 (4.1)	1817 (28.5)	7 (2.5)	2909 (22.4)
- Tree pollen/apple	0	1 (1.2)	195 (6.6)	0	506 (13.8)	4 (3.3)	1174 (18.4)	4 (1.5)	1883 (14.5)
- Dog dander	0	0	NA	0	NA	3 (2.5)	NA	4 (1.5)	NA
- Cat dander	NA0	1 (1.2)	NA	0	NA	NA0	NA	NA0	NA
- Animals		NA	168 (5.7)	NA0	422 (11.5)		1032 (16.2)		1637 (12.6)
- Fungalmix/ Weedmix		0	38 (1.3)		88 (2.4)		236 (3.7)		364 (2.8)
Sensitization within food panel (n (%))***									
- Peanut	0	0	NA	0	NA	2 (1.7)	NA	2 (0.7)	1377 (10.6)
- Wheat	0	0	NA	0	NA	1 (0.8)	NA	1 (0.4)	1285 (9.9)
- Soya	0	0	NA	0	NA	1 (0.8)	NA	1 (0.4)	818 (6.3)
- Cow milk	0	2 (2.5)	NA	4 (6.2)	NA	2 (1.7)	NA	8 (2.9)	740 (5.7)
- Egg	0	2 (2.5)	NA	2 (3.1)	NA	4 (3.3)	NA	8 (2.9)	649 (5.0)
- Cowmilk/Eggwhite	NA	NA	390 (13.2)	NA	330 (9.0)	NA	344 (5.4)	NA	1052 (8.1)
- Codfish	0	0	NT	0	NT	0	NT	0	NT

White column represents our cohort, the grey column represents the KiGGS study. * Asthma / viral induced wheezing / chronic nonspecific lung disease. NT = not tested ** defined as at least 1 allergen specific IgE ≥ 0.35 kU/L. *** The KiGGS study subdivided the different allergens into seven groups, for example Rice, Soya, Wheat and Peanut are shown together as “Food”. The data for different allergens separately are only available for the total population. If data is not available, this is indicated as NA (not available)

**** in children sensitized for allergens, the geometric mean was higher, namely 86.5 kU/l (95% CI 42.4-176.5).