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7 Article type : Letter to the Editor

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10 **Cleanliness, hygienic habits and aeroallergen sensitization: German Bitterfeld 3 study**

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36

37 **Conflict of interest**

38 None.

39

40 **Capsule summary:** Less frequent bathing and showering appears to be protective against
41 aeroallergen sensitization in children without current allergy from the German Bitterfeld 3 study.

42

43 **Key words:** allergic sensitization; bath; hand washing; epidemiology; children; shower.

44 ***To the Editor:***

45 According to the modern re-formulations of the hygiene hypothesis, loss of symbiotic relationships
46 with evolutionary relevant microorganisms prevents proper maturation of the immune system and is
47 therefore proposed to be the underlying cause for allergy epidemic in the western world. [1]
48 Biodiversity loss, diminished contact with environment and altered lifestyles all lead to reduced
49 microbiome diversity, which is related to allergic outcomes. [1] Large family size, presence of older
50 siblings, pet ownership and living on a farm have been demonstrated to reduce allergy risk,

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51 providing indirect support to the hygiene hypothesis. [2] However, almost no studies have investigated
52 whether increased cleanliness and improved hygienic habits are related to allergic sensitization and
53 manifestation. The results of our recent study in the German GINIplus and LISA cohorts have
54 demonstrated that children who bathed or showered not more often than once per week were less
55 likely to be sensitized to aeroallergens than their counterparts who bathed or showered every day. [3]
56 However, since the group of rare bathers/showerers constituted of less than 3% of the analytic
57 sample, this finding requires replication in an independent sample. Our current study aims to
58 investigate whether less frequent bathing and showering, as well as frequency of hand washing,
59 degree of cleanliness after playing outdoors and nails cleanliness usually – are associated with lower
60 risk of aeroallergen sensitization in children.

61 We used cross-sectional data on 11 to 15 years old children from the Bitterfeld 3 study residing in
62 the towns of Hettstedt, Zerbst and Bitterfeld in Sachsen-Anhalt, Germany between September 1998
63 and July 1999. [4] The Bitterfeld 3 study has been approved by the University of Rostock's Ethics
64 Committee, and informed consent was obtained from the parents of all participating children. For
65 the purpose of this study and in line with our previous analysis, [3] we limited our main analysis to
66 children without current allergies, that is, without current symptoms or treatment of asthma,
67 eczema in the last 12 months and symptoms of allergic rhinitis in the last 12 months. This was done
68 to reduce the potential impact of reverse causality, as children with current allergic diseases may
69 have different hygiene behaviour. As a sensitivity analysis, we further excluded children with ever
70 doctor diagnosed asthma, eczema or allergic rhinitis. We also present the results for allergic
71 sensitization and current allergy for the entire study population. Allergic sensitization was defined as
72 specific immunoglobulin E (IgE) ≥0.35 kU/L against birch pollen (t3), grass pollen (g6), mold
73 (cladosporium, m2), house dust mites (*Dermatophagoides pteronyssinus,* d1), or cat (e1), as
74 measured by the standardized radioallergosorbent test (RAST; Pharmacia, Freiburg, Germany). [5]
75 Individual associations with each of the hygiene- and cleanliness-related exposures were analyzed by
76 logistic regression models, adjusted for *a priori* selected covariates – area, sex, age, parental
77 education and parental atopy. To test whether associations differed across sexes, we stratified
78 models by this factor. Associations were assumed present at α-level <0.05.

79 Of 884 children from the analytic sample (Figure S1), 47% were females and 35% were sensitized
80 against at least one of the tested aeroallergens (Table 1). We observed that among 756 children
81 without current allergy, those who bathed or showered at most 1-2 times per week had 31% lower
82 odds of aeroallergen sensitization (Table 2) compared to those who bathed or showered more
83 frequently. This association was more pronounced in males than females, albeit it was borderline

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84 significant. For the rest of the exposure variables, odds ratios tended to be below one but none
85 reached formal statistical significance. In 685 children without ever allergies, odds ratios further
86 decreased and association with bathing/showering in males became statistically significant (Table
87 S1). In the entire study population, no associations were observed with aeroallergen sensitization.
88 Degree of cleanliness after playing outdoors was related to lower odds of current allergy in all
89 participants and in females (Table S2).

90 To our knowledge, this is the third epidemiological study to address the association between
91 hygiene habits, cleanliness and allergic sensitization. One previous study did not observe an
92 association between cleanliness score (which included frequency of hand washing and frequency of
93 taking bath and shower) assessed at 8 to 11 years, and atopic sensitization assessed at age of 5 years
94 by skin prick test. [6] We cannot directly compare our findings due to different age of children, as well
95 as different exposure and outcome assessment. Nevertheless, the observation from our current
96 study that less frequent bathing and showering is protective against aeroallergen sensitization is in
97 line with the results of our previous cross-sectional analysis in 15 years old children, [3] which speaks
98 against the chance finding.

99 Recent advances in microbiome and immunologic studies have demonstrated that skin barrier
100 epithelial cells are heavily involved in imposing important immune responses on the activation of
101 dendritic and T cells and innate immunity to allergens. Shampoos, soap and shower gels typically
102 contain antimicrobial agents, which have immune modulating properties. Several studies have
103 reported that urine concentrations of those agents like triclosan and parabens were associated with
104 allergic sensitization. [7-9] Thus, thorough hygiene could lead to development of atopy by reducing skin
105 epithelial barrier integrity. [2] Reverse causality is a likely reason why the association of
106 bathing/showering with aeroallergen sensitization or current allergy was not present in the entire
107 population.

108 Our findings should be interpreted keeping in mind several limitations. Bitterfeld 3 study was not
109 designed to answer the specific study question even though it collected hygiene-related data.
110 Despite of a relatively large sample size, we might have lacked statistical power to detect
111 associations with some exposure variables. Nevertheless, we dichotomized three exposure variables
112 that were originally four-categorical to obtain balanced/sufficient numbers in each newly created
113 category. Although current hygiene- and cleanliness-related habits may well reflect past behaviours,
114 [10] cross-sectional design of our study precludes us from any conclusions on directionality of
115 associations. Additionally, information on hygiene habits and cleanliness were collected by a

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116 questionnaire instead of examination, therefore misclassification and recall bias are likely. Finally, it
117 is difficult to directly compare current results to the results from our previous analysis [3] or to
118 generalize them to the entire German population. Due to more detailed categorization of possible
119 responses, rare bathers/showerers in the Bitterfeld 3 study amounted to almost one third of the
120 analytic sample compared to 3% in GINIplus/LISA. Additionally, Bitterfeld 3 data were collected 16-
121 12 years prior to the 15-year follow-up of the GINIplus and LISA (1998-1999 *vs* 2011-2014,
122 respectively).

123 In summary, less frequent bathing and showering appears to be protective against aeroallergen
124 sensitization in children without current allergy from this German study. More cleanliness was
125 related to current allergy.

126

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132

133 **Author contributions**

134 IM conducted the analyses, interpreted the data, drafted the initial manuscript, and revised the
135 manuscript. GB and MS contributed to the interpretation of the data and reviewed the manuscript.
136 JH contributed to the data collection, initiated and supervised the analysis. All authors approved the
137 final manuscript as submitted and agreed to be accountable for this work.

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Table 1. Description of the study population (n = 884)

Characteristic	**n (%)**
Area	
Zerbst	266 (30.1)
Bitterfeld	356 (40.3)
Hettstedt	262 (29.6)
Female sex	412 (46.6)
Age, years (median (minimum-maximum))	12 (11-15)
Parental school education	
≤8 years	45 (5.1)
10 years	441 (49.9)
≥12 years	398 (45.0)
Parental atopy[2]	286 (32.4)
Frequency of bathing/showering	
daily/3-6 times per week	635 (71.8)
1-2 times per week/more rarely	249 (28.2)
Frequency of hand washing after playing outdoors	
mostly	718 (81.2)
occasionally/seldom/never	161 (18.2)
missing	5 (0.6)
Degree of cleanliness after playing outdoors	
very clean/quite clean	306 (34.6)
quite dirty/very dirty	572 (64.7)
missing	6 (0.7)
Nails cleanliness usually	
clean	744 (84.2)
dirty	107 (12.1)
missing	33 (3.7)
Any aeroallergen sensitization[3]	234 (35.3)
against birch pollen	124 (14.0)
against grass pollen	197 (22.3)
against mold	44 (5.0)
against house dust mites	168 (19.0)
against cat	81 (9.2)

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SD – standard deviation.

[1]Definition based on highest parental level of education, classified according to the German education system.

[2]Defined as self-report of asthma, allergic rhinitis , eczema or other allergy by either of the parents.

[3]Defined as specific immunoglobulin E (IgE) ≥0.35 kU/L against birch pollen (t3), grass pollen (g6), mold (cladosporium, m2), house dust mites (*Dermatophagoides pteronyssinus*, d1), or cat (e1), as measured by the standardized RAST method (Pharmacia, Freiburg, Germany).

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Table 2. Association of hygienic variables with aeroallergen sensitization in children without current allergy (n = 756)[1], estimated by adjusted[2] logistic regression

Exposure	All			Females			Males		
	n/N	OR (95% CI)	p-value	n/N	OR (95% CI)	p-value	n/N	OR (95% CI)	p-value
Frequency of bathing/showering									
daily/3-6 times per week	543/756	1		231/352	1		312/404	1	
1-2 times per week/more rarely	213/756	**0.688 (0.475 – 0.999)**	**0.037**	121/352	0.813 (0.470 – 1.406)	0.459	92/404	*0.608 (0.363 – 1.018)*	*0.059*
Frequency of hand washing after playing outdoors									
mostly	612/753	1		276/350	1		336/391	1	
occasionally/seldom/never	141/753	0.977 (0.649 – 1.470)	0.910	74/350	0.885	0.705	54/391	1.062 (0.616 – 1.832)	0.829
Degree of cleanliness after playing outdoors									
very clean/quite clean	252/752	1		180/349	1		72/403	1	
quite dirty/very dirty	500/752	0.782 (0.541 – 1.132)	0.193	169/349	0.875	0.611	331/403	0.701 (0.412 – 1.194)	0.192
Nails cleanliness usually									
clean	637/731	1		320/340	1		317/391	1	
dirty	94/731	0.715 (0.435 – 1.175)	0.186	20/340	*0.169 (0.022 – 1.298)*	*0.087*	74/391	0.852 (0.498 – 1.459)	0.560

CI – confidence interval; n – number of participants in each category; N – number of participants with available exposure data; OR – odds ratio.

Significant associations ($p < 0.05$) are in boldface. Borderline significant associations ($p < 0.1$) are in cursive.

[1]Current allergy defined as current symptoms or treatment of asthma, eczema last 12 months or symptoms of allergic rhinitis last 12 months, or absence of such information.

[2]All models adjusted for area, sex, age, parental education and parental atopy.

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