SHORT RESEARCH ARTICLE

Hygienic habits are a risk factor for adult-onset asthma

[version 1; peer review: 2 not approved]

Anna G Polunina

Municipal Ambulatory Medical Service N124, Moscow Health Care Department, Moscow, 119526, Russian Federation

V1 First published: 06 Mar 2013, 2:80
<https://doi.org/10.12688/f1000research.2-80.v1>
Latest published: 06 Mar 2013, 2:80
<https://doi.org/10.12688/f1000research.2-80.v1>

Abstract

Multiple etiologies have been shown to contribute to asthma development, with excessive hygiene and microbial deprivation being one of the strongest risk factors for asthma onset in pediatric populations. The present study evaluated the contribution of hygienic habits in the development of adult-onset asthma. Twenty three adult-onset asthma patients (age of onset ranged from 21 to 71 years old) and 36 controls were asked to respond to a questionnaire concerning their frequency of shower taking and hand washing. Nine of the 23 (39.1%) asthmatic patients reported taking showers twice per day, compared to 2 controls (5.6%; $\chi^2 = 15.4$, $p=0.017$). In addition, sixteen (69.6%) of the asthmatic patients reported very frequent hand washing (≥ 7 times per day), whereas only 6 (16.7%) controls reported less frequent (2 – 6 times per day) hand washing habits. These data confirm that excessive hygienic habits are associated with the development of adult-onset asthma.

Keywords

bronchial asthma, hand washing, hygienic hypothesis, shower taking

Open Peer Review

Approval Status **XX**

	1	2
version 1 06 Mar 2013	X view	X view
1. Dina Czeresnia , Fundação Oswaldo Cruz, Rio de Janeiro, Brazil		
2. Paul Licciardi , Murdoch Children Research Institute, Melbourne, Australia		
Any reports and responses or comments on the article can be found at the end of the article.		

Corresponding author: Anna G Polunina (anpolunina@mail.ru)

Competing interests: No competing interests were disclosed.

Grant information: The author(s) declared that no grants were involved in supporting this work.

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How to cite this article: Polunina AG. Hygienic habits are a risk factor for adult-onset asthma [version 1; peer review: 2 not approved] F1000Research 2013, 2:80 <https://doi.org/10.12688/f1000research.2-80.v1>

First published: 06 Mar 2013, 2:80 <https://doi.org/10.12688/f1000research.2-80.v1>

Introduction

Asthma is an important cause of quality of life impairment^{1,2}, complications in long-term corticosteroid therapy^{3,4}, increased health care utilization⁵ and mortality¹. For instance, a recent study by Jia and colleagues¹ demonstrated that the loss of the quality-adjusted life expectancy was 7.0 years for people with asthma compared to those without asthma. The prevalence of asthma has considerably increased during the twentieth century in both Western and Eastern Europe. For instance, in the UK, the rate of children consulting for asthma showed an eightfold increase from 1955/6 to 1991/2, and the rate of adults showed a three to fourfold increase⁶. Although from the mid-1990s the incidence of asthma stabilized or even somewhat decreased in Western societies⁶, this has not been true in Russia's case. The Ministry of Healthcare of the Russian Federation reported an increase of asthma prevalence from 0.62% to 0.82% during the period from 2000 to 2008⁷.

Multiple factors have been shown to be associated with an increased risk of asthma. Allergy in parents and genetic factors^{8–10}, bronchitis or pneumonia in infancy⁸, viral infections¹¹, air pollution¹², insufficient aerobic exercise¹³, obesity¹⁴, and special dietary patterns¹⁵ have all been associated with an increased asthma risk. At the same time, growing up or living in rural settings has been consistently shown to be associated with a reduced risk of asthma and allergies^{9,16,17}. A study of 13,889 Belarusian children confirmed earlier findings in Western populations of the protective effects of rural settings, pet ownership and the presence of siblings on the risk of asthma development¹⁸. The latter findings underlie the hygiene hypothesis, which postulates that infections and unhygienic contact may confer protection against the development of allergic illnesses^{16,17}.

Adult-onset asthma and allergies appear to be highly prevalent in contemporary Russia. The official epidemiologic data do not show the real prevalence and incidence of asthma due to poor diagnostics at ambulatory centers and imperfect statistical service. However, even the official statistics showed an increase of adult-onset asthma incidence from 0.048% to 0.060% in 2008 compared to 2002⁷. In a recent Swedish study, the incidence rate of adult-onset asthma (defined as “physician-diagnosed” asthma with onset at or after 16 years of age) was 2.3%¹⁹. In the Russian Federation, the prevalence of adult-onset allergy and asthma appeared to increase after the boundaries of the country were opened in the 1990s, and many Russian citizens visited European countries and adopted European life-styles, including daily showers and frequent hand washing.

No previous studies on the effects of hygienic habits on the risk of adult-onset asthma could be identified. Here the results of a pilot investigation of hygienic habits in asthmatic patients are presented. The findings presented here were discovered as part of a larger investigation on the evaluation of neurological complications of chronic asthma medications with a special attention

to steroid myopathy²⁰. Therefore, only two short questions concerning hygienic habits were added to the study protocol. Nevertheless, the findings of excessive hand washing and shower taking in asthmatic patients were significant in comparison with controls, and, therefore suggest excessive hygiene as a risk factor in asthma development in adults.

Methods

The design of the present study was reviewed and approved by the administration of the Municipal Ambulatory Medical Service N124 of Moscow Health Care Department.

Patients

Patients with bronchial asthma attending the Municipal Ambulatory Medical Service N124 of the Moscow Health Care Department were invited to participate in the study. The inclusion criteria for patients with asthma were: 1) recent consultation in the Pulmonology department, which confirmed that the patient suffered bronchial asthma; 2) asthma onset over the age of 20. The exclusion criteria were: 1) age younger than 20 and older than 85 years; 2) serious concomitant diseases. The first control group included patients attending the medical service due to non-allergic diseases (i.e., arterial hypertension, diabetes mellitus, etc.) or subjects who visited the medical center for prophylactic examination. In addition, we included patients with autoimmune diseases (sarcoidosis, pulmonary fibrosis, etc.) who received steroids, as the primary aim of our main study was the evaluation of symptoms of steroid myopathy. Patients with autoimmune diseases constituted the second control group. An age of 75 years or over, emergency cases and severe conditions were exclusion criteria for patients of control groups.

It was explained to all patients that the examination did not concern the medical management of their disease and was conducted as a part of scientific research. The methods of the examination were explained to all patients, and 23 asthmatic patients, 24 controls and 12 patients with autoimmune diseases gave a verbal informed consent to participate in the study as is customary in Russia.

Hygienic questionnaire

We asked patients and healthy subjects to complete a two item questionnaire by choosing one of four possible responses. The first item contained the following question: ‘How often do you take shower or bath?’ The optional responses were: 1) twice per week or less; 2) 3–4 times per week; 3) once per day; 4) twice per day. The second item was: ‘How often do you wash hands?’ The optional responses were: 1) once per day or less; 2) 2–3 times per day; 3) 4–6 times per day; 4) 7 times and more per day. Responses demonstrating infrequent hygienic behaviors were evaluated as 1 point, and excessive hygienic behaviors (e.g., taking showers twice per day and hand washing over 7 times per day) were evaluated as 4 points, whilst intermediate habits ranged from 2 to 3 points.

Statistical analysis

All analyses were performed using SPSS software for windows (SPSS 17.0, Chicago, IL, USA).

Group characteristics were compared by ANOVA with a post hoc Bonferroni multiple comparisons correction. The distribution of hand washing and shower taking frequency in the three groups were compared by Pearson χ^2 - tests. Mann-Whitney tests were used for comparing mean scores on the hygienic habits questionnaire.

Results

Group characteristics

Patient characteristics and statistics are presented in Table 1. The mean age of asthma onset was 43.4 ± 12.8 years old in our patient group (range 21–71 years old). Patients of the first control group visited the medical service due to diabetes mellitus, arterial hypertension, myelopathy, gastritis, pancreatitis, dorsopathy and coronary disease. The autoimmune disease control group included patients with sarcoidosis, pulmonary fibrosis, chronic inflammatory demyelinating polyneuropathy and rheumatoid arthritis.

The asthma and both control groups did not show significant differences in age, education, height or weight. The asthma patients (mean age = 56 ± 13 years) were older in comparison with the autoimmune disease group (44 ± 15 years). In addition, the asthma patients were significantly shorter (mean height = 168 ± 10 cm) in comparison with the patients with autoimmune disease (177 ± 7 cm). Although, there was a larger proportion of females in the asthma group, this was not significant.

Distribution of hygienic habits in asthma and control groups

Asthma patients significantly differed in hygienic habits from both control groups (Table 2). At the same time no differences in hygienic habits between the two control groups were found.

Nine of the 23 asthmatic patients reported taking showers twice per day, whereas only two patients with the autoimmune disease, and none in the non-autoimmune controls reported taking showers twice per day. Although 4 patients with asthma reported rare shower taking (twice per week or less), the same four patients reported excessive hand washing (7 or more times per day). When both control groups were combined together, asthma patients showed significantly higher shower taking scores (2.87 ± 1.14) in comparison with controls (2.11 ± 0.95 ; $z = -2.59$, $p = 0.01$).

Sixteen (69.6%) asthmatic patients reported very frequent hand washing (7 or more times per day), whereas only 2 of the 24 (8.3%) patients without allergic or immune diseases and 2 of 12 (16.7%) patients with autoimmune diseases reported very frequent hand washing habits. When the two control groups were combined together, asthmatic patients showed significantly higher hand washing scores (3.61 ± 0.72) in comparison with controls (2.69 ± 0.75 ; $z = -4.64$, $p < 0.001$).

When only males or only females were included in the analysis, the distribution of shower taking frequency did not reach significance. However, the distribution of hand washing frequency was still significantly higher in asthmatic patients in comparison with the combined control group in males [$\chi^2 = 13.0$, $p = 0.005$] and females [$\chi^2 = 8.7$, $p = 0.013$].

Table 1 Group characteristics*.

Characteristics	Asthma patients (n=23)	Controls (n=24)	Autoimmune disease control group (n=12)	Statistics
Males / Females	12/11	17/7	10/2	NS
Diagnosis (n)	Asthma(23)	DM(8), AH(5), Pro(3), My(2), Ga(3), Pa(1), Do(1), CD(1)	Sarcoidosis(7), PulmFibr(3), CIDP(1), RA(1)	–
Age (years)	56.0 ± 13.0	50.8 ± 14.2	43.9 ± 15.3	$F = 2.98$, $p = 0.059$ Asthma > ADG
Education (years)	14.7 ± 2.4	14.6 ± 3.0	13.8 ± 2.4	NS
Height (sm)	167.6 ± 10.3	173.4 ± 10.0	177.1 ± 6.7	$F = 5.01$, $p = 0.010$ Asthma < ADG
Weight (kg)	76.7 ± 19.5	82.2 ± 16.0	88.0 ± 18.7	NS
Age of asthma onset (years)	43.4 ± 12.8	–	–	–

*Means and standard deviations are presented where appropriate.

Abbreviations: ADG, autoimmune disease group; AH, arterial hypertension; CD, coronary disease; CIDP, chronic inflammatory demyelinating disease; DM, diabetes mellitus; Do, dorsopathy; Ga, gastritis; My, myelopathy; NS, not significant; Pa, pancreatitis; Pro, prophylactical examination; PulmFibr, pulmonary fibrosis; RA, rheumatoid arthritis.

Table 2 Distribution of responses of asthma patients and controls to the hygienic questionnaire.

Question 1: How often do you take shower or bath?				
	Twice per week or less (1 point)	3–4 times per week (2 points)	Once per day (3 points)	Twice per day (4 points)
Asthma patients (n=23)	4	4	6	9
Controls (n=24)	9	5	10	0
Autoimmune disease control group (n=12)	3	5	2	2
Question 2: How often do you wash hands?				
	Once per day or less (1 point)	2–3 times per day (2 points)	4–6 times per day (3 points)	≥ 7 times per day (4 points)
Asthma patients	1	0	6	16
Controls	0	11	9	4
Autoimmune disease group (n=12)	0	6	4	2

Excessive hygiene and adult-onset asthma in Russia data

2 Data Files

<http://dx.doi.org/10.6084/m9.figshare.641445>**Discussion**

These results support the hypothesis that excessive hygiene may underlie the high prevalence of allergic diseases in the contemporary world. Here it was found that excessive hygiene is significantly associated with adult-onset bronchial asthma. Interestingly, it was found that excessively frequent hand washing was more strongly related to bronchial asthma in comparison with shower taking. In contrast, non-allergic autoimmune diseases did not show associations with hygienic habits in this pilot study.

Investigations of the effects of infectious diseases on the risk of allergy development show an inverse and frequency dependent relationship: the more infections subjects have encountered as assessed by positive serology, the lower the observed prevalence of atopy, allergic rhinitis and asthma¹⁷. Many epidemiologic studies suggest that 'microbial deprivation' considerably contributes to the etiology of allergy and asthma²¹.

A range of recent pediatric studies demonstrated that intestinal microbiota imbalances in infants are associated with the development of asthma and allergies in children over the age of three^{22,23}. Higher counts of *Lactobacilli*, *Bifidobacteria* and *Enterococci* in stool samples were characteristic for non-allergic

children, whereas an increased number of *Clostridia* were typical for children who developed allergies²². Collectively, these studies demonstrated the importance of gut microbial community as a correlate of the development of atopy²³. Many studies have demonstrated the effectiveness of probiotic treatment for reducing atopic eczema in children, though studies of probiotic effects on asthma symptoms are limited²⁴. In addition, a regular intake of probiotics was consistently shown to reduce respiratory symptoms of the common cold in both schoolchildren²⁵ and adult²⁶ cohorts.

Overall, the negative effects of excessive hygiene in this patient cohort may be explained by an insufficient microbial load (brought about through excessive hygienic habits) and, therefore, abnormal functioning of the immune system in asthmatic patients. Insufficient immune system stimulation in infants has consistently been recognized as an important contributor to allergy development in previous studies^{22–24}. These results provide evidence that excessive hygiene, perhaps mediated through microbial deprivation, is associated with adult-onset asthma as well.

Competing interests

No competing interests were disclosed.

Grant information

The author declares that no grants were involved in supporting this work.

References

- Jia H, Zack MM, Thompson WW: The effects of diabetes, hypertension, asthma, heart disease, and stroke on quality-adjusted life expectancy. *Value Health*. 2013; **16** (1): 140–7.
- Syk J, Alving K, Undén AL: Association between self-rated health and asthma: a population-based study. *Clin Respir J*. 2012; **6** (3): 150–8.
- Dahl R: Systemic side effects of inhaled corticosteroids in patients with asthma. *Respir Med*. 2006; **100** (8): 1307–17.
- Angeli A, Guglielmi G, Dovio A, *et al*: High prevalence of asymptomatic vertebral fractures in post-menopausal women receiving chronic glucocorticoid therapy: a cross-sectional outpatient study. *Bone*. 2006; **39** (2): 253–9.
- Chippes BE, Zeiger RS, Borish L, *et al*: TENOR Study Group. Key findings and clinical implications from The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study. *J Allergy Clin Immunol*. 2012; **130** (2): 332–42.
- Anderson HR, Gupta R, Strachan DP, *et al*: 50 years of asthma: UK trends from 1955 to 2004. *Thorax*. 2007; **62** (1): 85–90.
- Ovsyannikov NV, Lyapin VA: Bronchial asthma in a large industrial center of the Western Siberia. Omsk: Izdatelstvo, 2010.
- Glushkova AV, Grjibovski AM: Prevalence and correlates of asthma among children in central St. Petersburg, Russia: cross-sectional study. *Croat Med J*. 2008; **49** (6): 741–50.
- Wennergren G, Ekerljung L, Alm B, *et al*: Asthma in late adolescence—farm childhood is protective and the prevalence increase has levelled off. *Pediatr Allergy Immunol*. 2010; **21** (5): 806–13.
- Freidlin MB, Bragina Elu, Fedorova OS, *et al*: Genome-wide association study of allergic diseases in Russians of Western Siberia. *Mol Biol (Mosk)*. 2011; **45** (3): 464–72.
- Hanania NA, King MJ, Braman SS, *et al*: Asthma in the elderly: Current understanding and future research needs—a report of a National Institute on Aging (NIA) workshop. *J Allergy Clin Immunol*. 2011; **128** (3 Suppl): S4–24.
- Jacquemin B, Kauffmann F, Pin I, *et al*: Air pollution and asthma control in the Epidemiological study on the Genetics and Environment of Asthma. *J Epidemiol Community Health*. 2012; **66** (9): 796–802.
- Alexander CJ: Asthma: a disuse contracture. *Med Hypotheses*. 2005; **64** (6): 1102–1104.
- Kilic H, Oguzulgen IK, Bakir F, *et al*: Asthma in obese women: outcomes and factors involved. *J Investig Allergol Clin Immunol*. 2011; **21** (4): 290–6.
- Kim JH, Ellwood PE, Asher MI: Diet and asthma: looking back, moving forward. *Respir Res*. 2009; **10**: 49.
- Strachan DP: Family size, infection and atopy: the first decade of the “hygiene hypothesis”. *Thorax*. 2000; **55** (Suppl. 1): S2–10.
- von Mutius E: 99th Dahlem conference on infection, inflammation and chronic inflammatory disorders: farm lifestyles and the hygiene hypothesis. *Clin Exp Immunol*. 2010; **160** (1): 130–5.
- Kramer MS, Matush L, Bogdanovich N, *et al*: The low prevalence of allergic disease in Eastern Europe: are risk factors consistent with the hygiene hypothesis? *Clin Exp Allergy*. 2009; **39** (5): 708–16.
- Torén K, Ekerljung L, Kim JL, *et al*: Adult-onset asthma in west Sweden - Incidence, sex differences and impact of occupational exposures. *Respir Med*. 2011; **105** (11): 1622–8.
- Polunina AG, Isaev FV, Demianova MA: Steroid-induced myopathy. *Zh Nevrol Psikiatr Im S S Korsakova*. 2012; **112** (10–2): 60–64.
- Björkstén B: The hygiene hypothesis: do we still believe in it? *Nestle Nutr Workshop Ser Pediatr Program*. 2009; **64**: 11–8.
- Vael C, Vanheirstraeten L, Desager KN, *et al*: Denaturing gradient gel electrophoresis of neonatal intestinal microbiota in relation to the development of asthma. *BMC Microbiol*. 2011; **11**: 68.
- Yoo J, Tcheurekdjian H, Lynch SV, *et al*: Microbial manipulation of immune function for asthma prevention. *Proc Am Thorac Soc*. 2007; **4**: 277–282.
- Toh ZQ, Anzela A, Tanq ML, *et al*: Probiotic therapy as a novel approach for allergic disease. *Front Pharmacol*. 2012; **3**: 171.
- Rerksuppaphol S, Rerksuppaphol L: Randomized controlled trial of probiotics to reduce common cold in schoolchildren. *Pediatr Int*. 2012; **54** (5): 682–7.
- West NP, Pyne DB, Cripps AW, *et al*: Lactobacillus fermentum (PCC®) supplementation and gastrointestinal and respiratory-tract illness symptoms: a randomised control trial in athletes. *Nutr J*. 2011; **10**: 30.

Open Peer Review

Current Peer Review Status:

Version 1

Reviewer Report 27 March 2013

<https://doi.org/10.5256/f1000research.313.r870>

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Paul Licciardi

Allergy and Immune Disorders Group, Murdoch Children Research Institute, Melbourne, Australia

The manuscript by Polunina assesses the negative association of hand washing and shower taking with the development of asthma in adults. The premise for this work is based on the hygiene hypothesis where reduced microbial exposures in early life can lead to the development of allergic diseases.

While the study is interesting and shows a decreased frequency of hand washing and shower taking in the control group(s) compared to the asthmatic group, there are still some major issues with the design of the study and interpretation of the data. Most significantly, the data described in this paper was collected at a single time point and so the author should be careful not to over-interpret the findings in relation to cause and effect since it cannot be established that the hygienic habits resulted in the asthma symptoms. It is also likely that individuals with asthma may have an increased likelihood of undertaking additional hygienic habits.

As the author notes, the hygiene hypothesis is complex and there are many different variables that can influence the development of allergic disease. Factors such as household size, vaccinations and diet can also have important contributions to this effect and should be taken into account in this cohort.

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Reviewer Report 22 March 2013

<https://doi.org/10.5256/f1000research.313.r858>

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Dina Czeresnia

Escola Nacional de Saúde Pública, Fundação Oswaldo Cruz, Rio de Janeiro, Brazil

The article aims to evaluate a causal association between hygiene habits (washing hands and taking showers) and the onset of asthma in adults.

In the introduction, the author justifies this option by using the hygienic hypothesis theory, which according to her 'postulates that infections and unhygienic contact may confer protection against the development of allergic diseases'. In my view this is a superficial proposal because the hygienic hypothesis theory, although so named, has a much wider scope than just considering hygiene habits as a risk factor to asthma.

The hygienic hypothesis theory is concerned with the maturation of the immune system after birth driven by exposure to commensal or pathogenic microbes. The origin of asthma and other allergies could be related to a failed or underdeveloped maturation of the immune system occurring mainly during the early infancy. This is not necessarily restricted to a relation with washing hands or taking showers frequently. What is the theory underlining the hypothesis on the relationship between hygiene habits and the onset of asthma in adults?

Furthermore, the research design is flawed. For instance, the questions about hygiene habits are investigated at the present time, and this disagrees with Hill's criteria about the temporal relationship between causes and effects.

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 23 Mar 2013

Anna Polunina, Municipal Ambulatory Medical Service N124, Moscow Health Care Department, Russian Federation

1) The hygienic hypothesis of allergies is yet the hypothesis but not the theory or completely clear scientific conception. Although, the association between the demographic characteristics of the populations and the prevalence of allergies, including asthma, is well established and reproduced in tens of contemporary studies, the immunological mechanisms underlying this association remain unclear.

Dina Czeresnia states that immunological system develops only in infancy, and therefore all effects of microbiological environment may be of importance only in that early period of life. I don't think that the human brain develops all through the life until the old age,

whereas immunity develops only in infancy.

Clearly, that many healthy and unhealthy immunological processes continue all through the life of the people. Therefore, changing of hygienic habits may influence immunity all through the life. For instance, my own allergy started when I was 21 years old, and I changed greatly my hygienic habits at that period due to my study in medical clinics and phobias of the infections in those clinic. I had no problems with allergy in my childhood, never.

2) I realize that the design of the study is far from the ideal, and the reported findings could be considered only as preliminary and pilot. However, if I could find in the available contemporary publications studies of the effects of the hygienic habits on allergy prevalence I would never spend my energy and time on making this study and article.

My interest to this problem relates to my observations as a practicing physician of tens of asthmatic patients with steroid myopathy, and many of them could not walk (I visited them at home). Steroid inhalers are considered to be safe, but they are not safe. Therefore, I consider asthma prevention as a very important and highly perspective field of the research.

Asthma prevention is possible, and control of hygienic habits is a very important issue. I think that the mechanism of negative effects of excessive shower taking and hand washing relates to excessive elimination of dust and microbes from the skin. OK, we can eliminate the dust and microbes from the skin, but we can't eliminate the latter from our bronches or mucosa of the respiratory tract. Therefore, the whole power of our immunity has nothing to do only to attack our bronches and other parts of respiratory tracts, and perhaps intestinum.

Contemporary people do not have helminths, but we still have 'antihelminth' immunity, i.e. eosinophiles and IgE. This immunity attacks dust on the skin and bronches, and mucosa of the respiratory tract. And when the dust is completely removed from the skin, bronchi is the only place of immunological attacks. Clearly, the future evidence-based studies are needed in this field.

Competing Interests: No competing interests were disclosed.

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