Allergy prevalence, height of children and village size in rural Bavaria

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Abstract

Background: A lower allergy rate in coal heated homes has been described in the Alpine foothills and subsequently attributed to LPS exposure. As also vitamin D prophylaxis may be less frequently used in smaller villages of this rural environment we tested if village size is a risk factor for allergy. In addition the association with body height is examined as a possible further side effect of vitamin D exposure.
Methods: An epidemiological study in 1989/90 of 1,685 fourth-grade children was reanalyzed. Parents answered a questionnaire while children completed a skin prick test and height measurements. Home addresses were geocoded to village boundaries.
Results: Allergic rhinitis (OR 2,8; 0,8-9,1) and sensitization to airborne grass (OR 3,3; 1,2-9,3) was more frequently found in villages of >3000 inhabitants than in villages with <1000 inhabitants. In addition children were 2,2 cm taller (p=0,05 for linear increase) but there was no direct association of allergy and body height.
Conclusions: The dual effect of village size on allergy prevalence and body height could point towards a common causal factor although not operating in the same individuals. Differences in vitamin D supplementation is a possible explanation for the differences of allergy rates observed in Upper Bavaria 1989.

Background

Allergy prevalence has been on the rise worldwide and nearly hundred years after coining "Allergie" in the "Münchner Medizinische Wochenschrift" (Pirquet 1906) the causal risk factor is still unknown.

At the end of the 1980ies, air pollution related effects have been thought to be responsible for the allergy epidemic. It turned out, however, that traffic related combustion was not the main culprit in Munich City, as found by the inner city distribution of pollutants (Wjst, Reitmeir et al. 1993). In a parallel study in the South of Munich on the Alpine foothills, a protective effect of coal heating was accidentially found (P. Reitmeir, pers.comm. 1991) and published later (von Mutius, Illi et al. 1996). This effect received little attention as the public interest focused on West- and East German difference at that time. Only until the end of the 1990ies the coal heating effect provoked a long series of studies in the farming environment (Kilpelainen, Terho et al. 2002),(Von Ehrenstein, Von Mutius et al. 2000),(Riedler, Braun-Fahrlander et al. 2001) that lead to the hypothesis that atopy develops where the natural high endotoxin level on farms decreases (Braun-Fahrlander, Riedler et al. 2002).

An alternative hypothesis stems from the observation that vitamin D, used in the newborn period to prevent rickets (Wjst and Dold 1999) has also potent hormone effects by its main metabolites. The endocrine action is only the "tip of the iceberg" (Feldman D 1997) where most vitamin D effects are on the immune system. Vitamin D suppresses dendritic cell function resulting in the inability to mount a sufficient Th1 response. More recently, animal studies (Matheu, Back et al. 2003) and genetic studies (Poon, Laprise et al. 2004), (Raby, Lazarus et al. 2004) as well as epidemiological studies (Milner, Stein

et al. 2004), (Hyppönen, Sovio et al. 2005 in press) support this perspective. The Finish study (Hyppönen, Sovio et al. 2005 in press) even reported a much lower compliance of vitamin D supplementation in farmers.

We were therefore interested in a reanalysis of our earlier study in rural Bavaria. Vitamin D supplementation is very common in Germany with supplementation (Wjst 2004). As there is no untreated control group in the general population, the only possibility is the analysis of parameters of an altered compliance that could have influenced vitamin D supplementation.

Rural village size may partially fulfill this requirement as home childbirth is more common while at the same time early medical intervention seems to be more restricted at remote locations. As an independent outcome current body height of children (which was recorded for adjusting pulmonary function parameters) may be also included. Body height has been described as a possible further side effect of vitamin D treatment (Brooke, Butters et al. 1981),(Sankaran, Papageorgiou et al. 1996),(Du, Zhu et al. 2004),(Burne, McGrath et al. 2005). Interestingly, the secular height increase has been speculated to be in parallel to the allergy pandemic (Beasley, Leadbitter et al. 1999).

Methods

This report shows the results of a cross sectional study carried out in 1989 and 1990 on a sample of fourth grade children in rural Bavaria. Villages were selected if less than 10,000 cars were crossing on their main road and then visited in nearly random order over the course of

the school year 1989/1990 where data from 63 schools are analyzed here. All the parents gave informed and written consent and the study was approved by the Ethics Committee of the "Bayerische Landesärztekammer".

From October 1989 to July 1990 a questionnaire consisting of 58 questions on the allergic and asthmatic symptoms of the child and its family was distributed where 1714 (87.5%) of the 1958 parents returned the questionnaire. Standardized questions were used to obtain histories of respiratory and allergic illness. Standing height was measured in socks but without shoes by using a graduated measuring rod usually by the same technician. Skin prick tests were performed with a multi-allergen test device pre-coated with 6 aeroallergens (Stallerkit, Stallergenes, France) and the reaction read after 15 to 20 minutes (for technical difficulties with this assay see (Heinrich and Wjst 1998))

Age of children was calculated as days since birth at the examination day. Home addresses of the children were matched in 2004 to village size by using data from http://de.wikipedia.org/wiki/Bayern. Home village size showed a range from 621 to 41,770 with a mean of 3,417 inhabitants. The following village size groups were defined: <1000 inhabitants (N=66), <2000 inhabitants (N=308), <3000 inhabitants (N=351) and >=3000 inhabitants (remaining N=466).

Allergic rhinitis was defined as a positive answer to one of the two diagnosis questions (F1 or F33) or with a positive response to both symptom questions (F31 and F32). A positive skin prick test was define by a response greater or equal than 2 mm against mixed grass pollen (variable STAL5).

Barcharts and boxplots were created for village size and height of the children. Contingency tables were analyzed using global χ^2 tests and generalised linear equations were fitted with a binomial link function for categorial and Gaussian link function for continuous measurements. Analyses were conducted for each single risk factors followed by the joint inclusion of known co-factors like history of allergic rhinitis in parents or sibs, age, sex, number of siblings. Statistical software R version 2.0.1 (http://www.r-project.org) was used for all analysis.

Results

The study population consisted of 1,685 4th grade children in an age range from 9 to 11 years (Figure 1). Children included in the current analysis had all German nationality. After restriction to mapped home address, 1,191 children living in 110 villages remained under analysis.

Village size on a continuous scale was associated with allergic rhinitis (P=0.0279) however not when tested for a linear trend of the four categories (P=0,3782, table 1). When comparing the highest versus the lowest category, larger villages showed an increased risk (OR 2.2 to 2.8). Also skin sensitization to grass pollen showed increased odds ratios with only the highest category being significant (OR 3.3, 95%-confidence limit 1.2-9.3, P=0.026, table 3).

Village size on a continuous scale was associated with standing height (P=0.05 for linear decrease, table 2). When compared to the lowest category larger village sizes showed an increased risk (OR 3.2 to 9.9) with only the two largest categories being significant (P=0.023 and P=0.010). The overall effect on standing height was similar in both

sexes, increasing steadily up to 2,2 cm between both extreme categories (figure 2). This association of village size and height remained significant also after adjustment for sex, history of allergic disease, heating and educational level of the father.

The lower height in children from fathers with high educational level (table 1) is probably an artefact as these children have been sent earlier to school earlier and are therefore younger. Adjustment for age/ education interaction resulted in a rather poorly fitted model. When comparing mean height in the group of exactly 10 year old children, however, children from parents with the highest education were also the tallest (143,2 cm), followed by children of parents with medium (143,0 cm) and low (142,9 cm) educational level. Residual confounding is also seen for the association with a history of atopic disease and lower height. Fathers with higher educational level report more frequently a history of allergic disease (30,4%) compared to those of low education (14,2%).

Finally, there was no height difference between allergic and non-allergic children (data not shown).

Discussion

Increasing village size was associated with a higher prevalence of allergic rhinitis and sensitization. Many of these small communities were formed during the Bavarian land reform in 1978. Although the lowest category of village size will include more farming communities, farm exposure alone is unlikely to account for the lower allergy prevalence. In a study of European adults allergic rhinitis prevalence was both low when being born on a farm (18.4%) or in a small village

(20.8%) and increased only when being born in a large village (27,4%) or city (30.4%, Leynaert, pers. comm. 2004). Also a third study in Augsburg city and surroundings showed an association with village size (Heinrich, pers. comm. 2004).

The association of village size and height of the children comes rather unexpected. Although the effects are subtle, the observed height gain is equal to one additional year of lifetime. Height of children raised on farm is being expected to be at least the same than in peers where the nutritional status should not be different between small villages.

The dual effect of village size could point towards a common causal factor. If rural village size is interpreted as a proxy for medical compliance, a lower vitamin D prophylaxis rate could indeed be responsible for the low allergy rate in small villages. Village size is expected to influence compliance by distant travelling to hospital, pharmacy or physician as in an earlier study of the Alpine region more than half of all farms were located outside of villages (Waser, Schierl et al. 2004). Farming might also influence consuming more local food and less additives. The protective effect of farm milk could relate to the avoidance of otherwise fortified milk from supermarkets (e.g. on Crete (Barnes, Cullinan et al. 2001)) or to the higher calcium content of unprocessed food. Having many children will impose time restrictions to care for supplements while parents with lower education levels will avert the understanding of vitamin supplements.

Interestingly, there was no direct association of allergy and height that could explain the observed association with village size. With regard to the vitamin hypothesis, it is most likely that the endocrine effect on bone and growth acts on all exposed individuals (leading to an additive height shift) while the immunological effect acts only on a genetically sensitive subgroup. Without knowing the target height of the children, the additional height gain by vitamin D treatment is

difficult to identify.

Finally, it may be acknowledged, how difficult it is, finding a common risk factor. As Geoffrey Rose pointed out „...If everyone smoked 20 cigarettes a day, then clinical, case-control and cohort studies alike would lead us to conclude that lung cancer was a genetic disease... The hardest cause to identify is the one that is universally present, for then it has no influence on the distribution of disease..." (Rose 2001). A common exposure and even one with a long latency is extremely difficult to find. Even a prospective trial will be difficult to design due to the confounding by the ubiquitous supplements in baby food.

Authors Contributions

The author did the local study management and examined all children described in this paper. He developed the hypothesis presented here, conducted the statistical analysis, wrote the paper and approved the final version of the manuscript.

Competing Interests

The author declares that he does not have any competing interests with the contents of this manuscript.

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Tables and Figures

Table 1: Factors influencing allergic rhinitis in 1,643 fourth-grade school children with German nationality in Upper Bavaria examined in 1989/1990.

allergic rhinitis		N	OR crude	5%-CI	95%-CI	p-value	OR adjusted	5%-CI	95%-CI	p-value
home village size	<1000	57	1,00				1,00			
	<2000	261	2,16	0,63	7,3800	0,218	1,28	0,35	4,6700	0,708
	<3000	303	1,83	0,54	6,2400	0,333	1,10	0,31	3,9700	0,883
	3000+	408	2,75*	0,83	9,0900	0,098	1,52	0,43	5,3500	0,515
age	month		1,02	0,99	1,0600	0,194	1,03	0,99	1,0700	0,171
sex	male	694	1,00				1,00			
	female	706	**0,68**	0,48	0,9700	0,033	**0,61**	0,38	0,9600	0,034
history	no	1149	1,00				1,00			
	yes	251	**3,76**	2,61	5,4300	<0,001	**3,79**	2,36	6,1000	<0,001
coal/wood heating	no	798	1,00				1,00			
	yes	594	**0,53**	0,36	0,7700	0,001	0,66	0,39	1,1100	0,116
sibs	0	146	1,00				1,00			
	1	667	1,01	0,56	1,8200	0,980	0,73	0,33	1,6100	0,433
	2	375	0,90	0,48	1,7000	0,744	0,84	0,36	1,9500	0,685
	3+	205	1,05	0,52	2,1000	0,891	0,79	0,31	2,0200	0,628
education father	low	819	1,00				1,00			
	average	192	1,61	0,97	2,6600	0,066	1,13	0,61	2,1000	0,686
	high	225	**2,40**	1,56	3,6900	<0,001	**1,69**	0,99	2,8900	0,057

* P=0,3782 for trend

Table 2: Factors influencing standing height in 1,643 fourth-grade school children with German nationality in Upper Bavaria examined in 1989/1990.

standing height (cm)		N	OR crude	5%-CI	95%-CI	p-value	OR adjusted	5%-CI	95%-CI	p-value
home village size	<1000	63	1,00				1,00			
	<2000	296	3,21	0,58	17,87	0,183	2,07	0,33	13,09	0,441
	<3000	327	**7,24**	1,32	39,73	0,023	4,08	0,67	25,02	0,129
	3000+	444	**8,95***	1,69	47,38	0,010	4,48	0,74	27,09	0,103
age	month		**1,37**	1,29	1,46	<0,001	**1,33**	1,23	1,43	<0,001
sex	male	719	1,00				1,00			
	female	758	**0,22**	0,11	0,42	<0,001	**0,26**	0,12	0,56	0,001
history	no	1203	1,00				1,00			
	yes	274	0,47	0,20	1,08	0,076	0,48	0,18	1,32	0,157
coal/wood heating	no	846	1,00				1,00			
	yes	623	0,82	0,42	1,60	0,567	1,02	0,44	2,35	0,970
sibs	0	154	1,00				1,00			
	1	698	0,42	0,14	1,28	0,128	0,60	0,14	2,60	0,499
	2	395	0,46	0,14	1,52	0,204	0,72	0,16	3,33	0,675
	3+	223	0,37	0,10	1,40	0,145	0,31	0,06	1,68	0,176
education father	low	866	1,00				1,00			
	average	212	0,74	0,28	1,97	0,551	0,95	0,33	2,77	0,926
	high	234	0,59	0,23	1,51	0,274	0,64	0,23	1,80	0,394

*** P=0,050 for trend**

Table 3: Factors influencing skin prick test of mixed grass pollen in 1,643 fourth-grade school children with German nationality in Upper Bavaria examined in 1989/1990.

SPT grass		N	OR crude	5%-CI	95%-CI	p-value	OR adjusted	5%-CI	95%-CI	p-value
home village size	<1000	61	1,00				1,00			
	<2000	287	2,31	0,79	6,7100	0,125	1,53	0,51	4,5900	0,451
	<3000	311	2,04	0,70	5,9400	0,190	1,43	0,48	4,2700	0,520
	3000+	424	**3,26***	1,15	9,2600	0,026	2,16	0,74	6,3100	0,158
age	month		1,03	1,00	1,0600	0,066	1,02	0,99	1,0500	0,277
sex	male	679	1,00				1,00			
	female	723	1,16	0,86	1,5600	0,334	0,89	0,62	1,2900	0,553
history	no	1136	1,00				1,00			
	yes	267	**1,60**	1,13	2,2700	0,008	**1,67**	1,09	2,5600	0,019
coal/wood heating	no	803	1,00				1,00			
	yes	594	**0,55**	0,40	0,7500	<0,001	0,70	0,46	1,0700	0,097
sibs	0	139	1,00				1,00			
	1	657	1,11	0,66	1,8600	0,703	1,17	0,58	2,3500	0,666
	2	389	1,00	0,58	1,7400	0,998	1,18	0,57	2,4500	0,662
	3+	211	0,59	0,30	1,1500	0,120	0,72	0,30	1,7200	0,462
education father	low	825	1,00				1,00			
	average	201	**1,51**	1,00	2,2800	0,048	1,17	0,71	1,9000	0,541
	high	218	1,33	0,88	2,0000	0,177	1,16	0,72	1,8700	0,536

*** P=0,0569 for trend**

Figure 1: Study area with school locations.

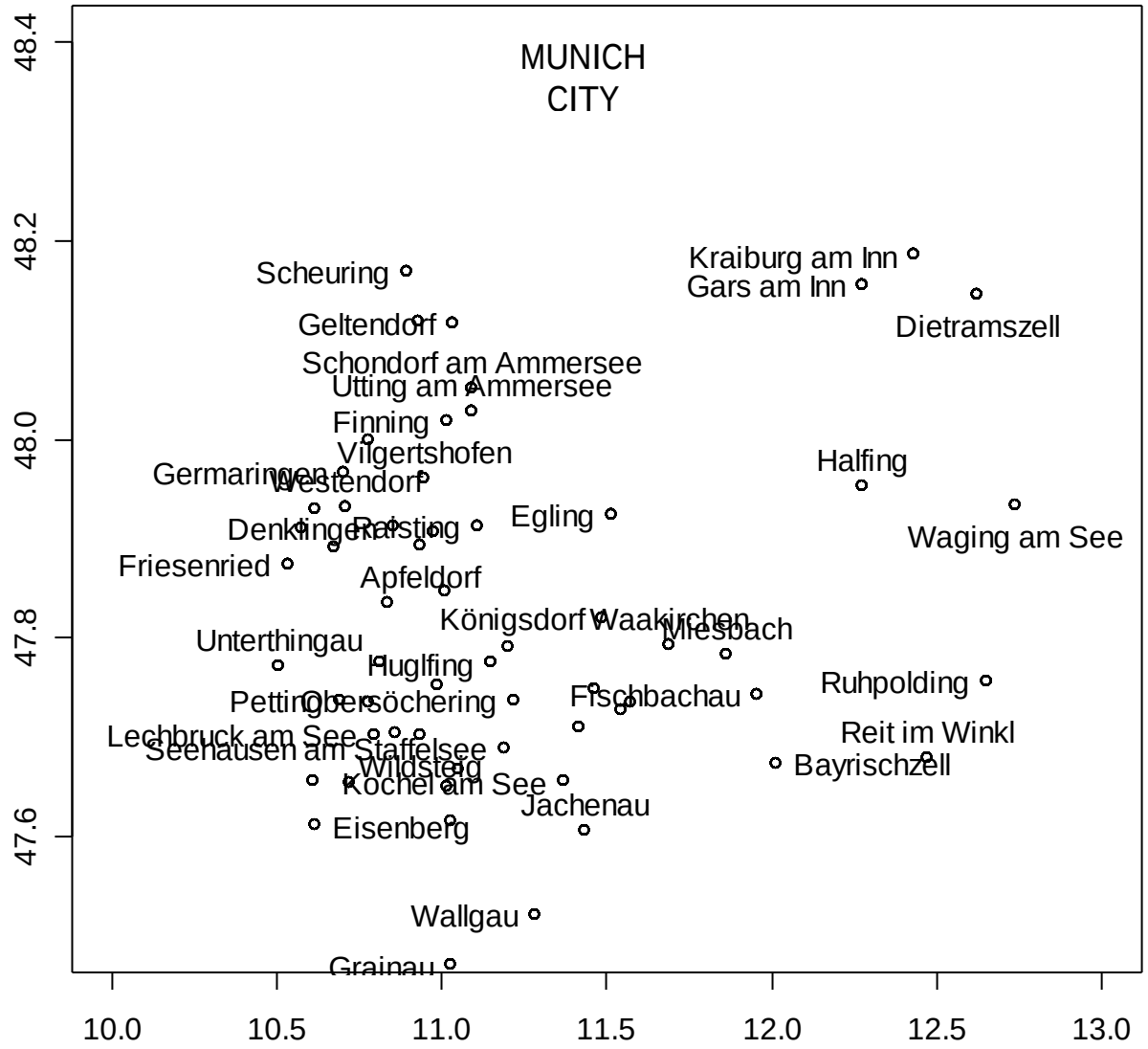
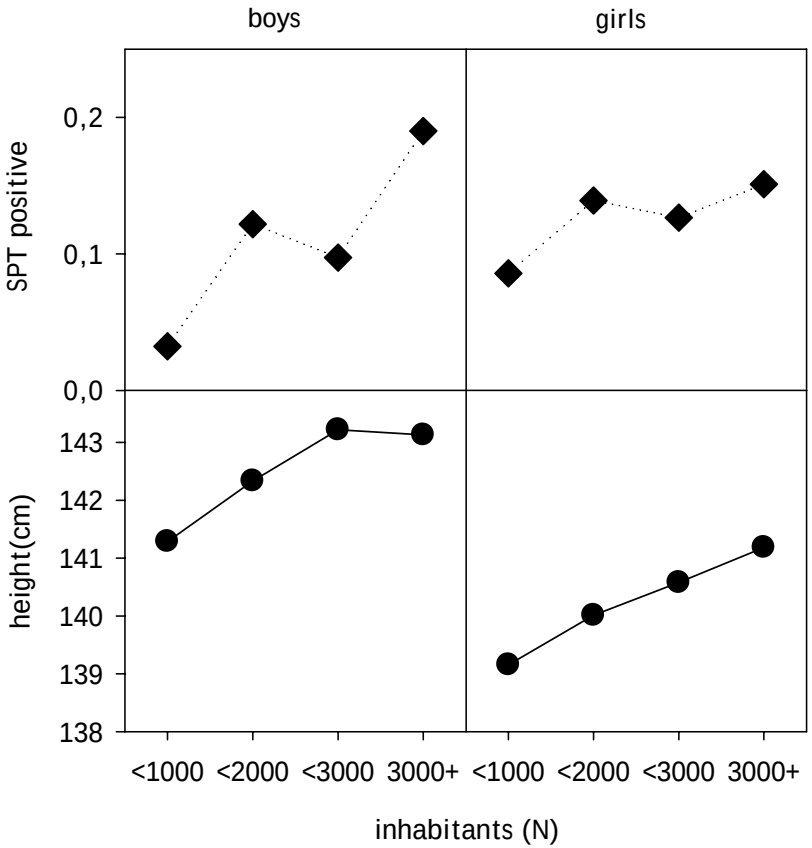


Figure 2: Standing height and allergic rhinitis prevalence by village size in 1,643 fourth-grade school children with German nationality in Upper Bavaria 1989/1990.



References

Barnes, M., P. Cullinan, et al. (2001). "Crete: does farming explain urban and rural differences in atopy?" Clin Exp Allergy **31**(12): 1822-8.

Beasley, R., P. Leadbitter, et al. (1999). "Is enhanced fetal growth a risk factor for the development of atopy or asthma?" Int Arch Allergy Immunol **118**(2-4): 408-10.

Braun-Fahrlander, C., J. Riedler, et al. (2002). "Environmental exposure to endotoxin and its relation to asthma in school-age children." N Engl J Med **347**(12): 869-77.

Brooke, O. G., F. Butters, et al. (1981). "Intrauterine vitamin D nutrition and postnatal growth in Asian infants." Br Med J (Clin Res Ed) **283**(6298): 1024.

Burne, T. H., J. J. McGrath, et al. (2005). "Behavioural characterization of Vitamin D receptor knockout mice." Behav Brain Res **157**(2): 299-308.

Du, X., K. Zhu, et al. (2004). "School-milk intervention trial enhances growth and bone mineral accretion in Chinese girls aged 10-12 years in Beijing." Br J Nutr **92**(1): 159-68.

Feldman D, W. P. J., Glorieux F (eds) (1997). Vitamin D.

Gerhold, K., K. Bluemchen, et al. (2003). "Exposure to endotoxin and allergen in early life and its effect on allergen sensitization in mice." J Allergy Clin Immunol **112**(2): 389-96.

Heinrich, J., U. Gehring, et al. (2001). "Pets and vermin are associated with high endotoxin levels in house dust." Clin Exp Allergy **31**(12): 1839-45.

Heinrich, J. and M. Wjst (1998). "Increase of allergy in East Germany." Lancet **351**(9118): 1813; author reply 1814.

Hyppönen, E., U. Sovio, et al. (2005 in press). "Vitamin D supplementation in infancy and the risk of allergies in adulthood: a birth cohort study." Ann Am Acad Sci.

Kilpelainen, M., E. O. Terho, et al. (2002). "Childhood farm environment and asthma and sensitization in young adulthood." Allergy **57**(12): 1130-5.

Matheu, V., O. Back, et al. (2003). "Dual effects of vitamin D-induced alteration of TH1/TH2 cytokine expression: enhancing IgE production and decreasing airway eosinophilia in murine allergic airway disease." J Allergy Clin Immunol **112**(3): 585-92.

Milner, J. D., D. M. Stein, et al. (2004). "Early infant multivitamin supplementation is associated with increased risk for food allergy and asthma." Pediatrics **114**(1): 27-32.

Pirquet, v. (1906). "Allergie." Münchn Med Wschr **53**: 1457.

Poon, A. H., C. Laprise, et al. (2004). "Association of vitamin D receptor genetic variants with susceptibility to asthma and atopy." Am J Respir Crit Care Med **170**(9): 967-73.

Raby, B. A., R. Lazarus, et al. (2004). "Association of vitamin D receptor gene polymorphisms with childhood and adult asthma." Am J Respir Crit Care Med **170**(10): 1057-65.

Riedler, J., C. Braun-Fahrlander, et al. (2001). "Exposure to farming in early life and development of asthma and allergy: a cross-sectional survey." Lancet **358**(9288): 1129-33.

Rose, G. (2001). "Sick individuals and sick populations. 1985." Bull World Health Organ **79**(10): 990-6.

Sankaran, K., A. Papageorgiou, et al. (1996). "A randomized, controlled evaluation of two commercially available human breast milk fortifiers in healthy preterm neonates." J Am Diet Assoc **96**(11): 1145-9.

Von Ehrenstein, O. S., E. Von Mutius, et al. (2000). "Reduced risk of hay fever and asthma among children of farmers." Clin Exp Allergy **30**(2): 187-93.

von Mutius, E. (2004). "Influences in allergy: epidemiology and the environment." J Allergy Clin Immunol **113**(3): 373-9; quiz 380.

von Mutius, E., S. Illi, et al. (1996). "Relation of indoor heating with asthma, allergic sensitisation, and bronchial responsiveness: survey of children in south Bavaria." Bmj **312**(7044): 1448-50.

Waser, M., R. Schierl, et al. (2004). "Determinants of endotoxin levels in living environments of farmers' children and their peers from rural areas." Clin Exp Allergy **34**(3): 389-97.

Wjst, M. (2004). "The triple T allergy hypothesis." Clin Dev Immunol **11**(2): 175.

Wjst, M. and S. Dold (1999). "Genes, factor X, and allergens: what causes allergic diseases?" Allergy **54**(7): 757-9.

Wjst, M., P. Reitmeir, et al. (1993). "Road traffic and adverse effects on respiratory health in children." Bmj **307**(6904): 596-600.