

Research letters

Frequency of atopy in the Arctic in 1987 and 1998

Tyra Grove Krause, Anders Koch, Jeppe Friberg, Lars K Poulsen, Bjarne Kristensen, Mads Melbye

Few studies have measured the frequency of atopy with objective measures, and most of these studies have been done in industrialised countries. We analysed serum samples from 859 15–80-year-old Greenlanders who had participated in population-based screening campaigns in 1987 and in 1998. We defined atopy as a positive result in an assay that tests for specific IgE against the eight most common inhalant allergens in one pool (grass, birch, mugwort, dog, cat, horse, *Cladosporium herbarum*, house dust mite). The frequency of atopy doubled between 1987 (39 [10%] of 392) and 1998 (87 [19%] of 467; risk ratio 1.88 [95% CI 1.31–2.68]). This increase was largest in 15–19-year olds, but also occurred in older people, suggesting that the risk factors responsible for the increase in atopy do not operate only in childhood.

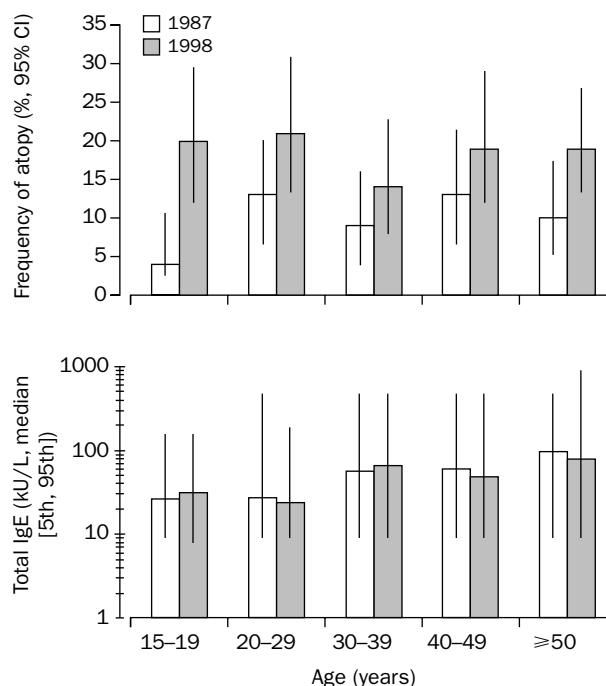
Lancet 2002; **360**: 691–92

Allergic diseases have been reported to be increasing in western countries; however, few studies have used objective measurements to document the increase.¹ A population-based blood-sample screening campaign was done in Greenland in 1987 and 1998. We analysed these data to find out whether the frequency of atopy increased in Greenland in the past decade in parallel with the increased westernisation of the country.

In 1987, a screening campaign for syphilis was done in most towns on the west coast of Greenland.² About 54% of the adult population aged 15–80 years took part in the programme; a random sample of 5658 serum samples was stored at –20°C. In November, 1998, all citizens older than 6 years and living in Sisimiut, the second largest town on the west coast of Greenland, were offered screening for HIV antibodies.³ 2842 individuals took part in the study, which included 50% of all adults. Serum samples were stored at –20°C. For both studies, information on age, sex, place of birth, and place of living at the time of blood sampling was obtained from the Danish Civil Registration System.

In our analysis, we included individuals older than 15 years, who were born, and at the time of blood sampling still living, within an area on the Greenlandic west coast stretching from Uumaanaaq just above the Disko Bay in the north to Maniitsoq just south of the Disko Bay area. 1502 participants from 1987 and 2206 from 1998 fulfilled these criteria. Participants in both studies were divided by 5-year age groups and by sex. A fixed number of samples were randomly chosen from each sex and age group from each study using SAS, version 8.2. An age and sex-stratified sample of 410 individuals from the 1987 study and 490 from the 1998 study was thus chosen. 41 samples contained too little serum, leaving 392 participants' samples from 1987 and 467 from 1998. The study was approved by the Danish Data Protection Agency and ethics approval was obtained from the Commission for Scientific Research in Greenland.

We did not have samples from Sisimiut from 1987. However, Sisimiut, where the screening campaign was



Frequency of atopy (top) and median total IgE in non-atopic people (bottom) by age group

done in 1998, and the towns we restricted the study to in 1987 are located within a well defined area on the west coast of Greenland where towns have similar sizes (1000–5000 inhabitants), climate, infrastructure, and living conditions. Thus, we think participants from 1987 and 1998 were comparable. Furthermore, since there was no overlap of participants between the two serum collections, analyses were based on two independent cross-sectional samples.

The serum samples were thawed out for the first time for our study. We analysed samples for total IgE (Unicap; Pharmacia, Copenhagen, Denmark) and for specific IgE against the most common inhalant allergens with the Phadiatop assay (Pharmacia, Copenhagen, Denmark), which tests for all allergens in one pool (grass, birch, mugwort, dog, cat, horse, *Cladosporium herbarum*, house dust mite). We classed individuals with a positive result in the Phadiatop test as atopic. Total IgE concentrations were not normally distributed after log transformation, therefore differences in concentrations were analysed with non-parametric tests and medians calculated.

Frequency of atopy was higher in all age groups in 1998 than in 1987, especially in teenagers (figure). Total IgE concentrations per age-group were similar in 1998 and in 1987 in non-atopic individuals (Wilcoxon's test, $p=0.90$; figure), as were total IgE concentrations in atopic

	1987		1998		Risk ratio* (95% CI)
	n	n atopic	n	n atopic	
Age group (years)					
15–19	69	3 (4%)	80	16 (20%)	4.91 (1.48–16.29)
20–29	79	10 (13%)	89	19 (21%)	1.73 (0.86–3.48)
30–39	75	7 (9%)	80	11 (14%)	1.49 (0.61–3.63)
40–49	78	10 (13%)	79	15 (19%)	1.48 (0.71–3.09)
≥50	91	9 (10%)	139	26 (19%)	1.89 (0.88–3.90)
All ages	392	39 (10%)	467	87 (19%)	1.88 (1.31–2.68)

*Adjusted for age and sex.

Prevalence of atopy in 1987 and 1998

individuals ($p=0.57$) (data not shown). The frequency of atopy was almost two-fold higher in 1998 than in 1987, and almost five-fold higher in 15–19-year olds after adjustment for sex and age (table).

Few studies have been designed to objectively assess trends in frequency of atopy. Our results show that in 11 years, the frequency of atopy increased by almost 90% in adult Greenlanders, which is equivalent to an 8% increase per year. Compared with 1987, the frequency of atopy was higher throughout all age groups in 1998. Since the age-dependent variation of atopy in adults was similar in 1987 and in 1998, it is unlikely that the increase resulted from a birth-cohort effect. Therefore, the potential risk factors that caused the increase in atopy operate in adulthood as well as in childhood.

Interpretation of our results is dependent on the stability of IgE in frozen samples. However, IgE does not degrade as a result of being frozen at -20°C for 8 years.^{4,5} Also, we noted no differences in concentrations of total IgE in atopic and non-atopic people between 1987 and 1998, which strongly suggests that no degradation of IgE had occurred. Since both screening programmes were for venereal diseases, and the participation rates were the same, we do not think that a selection bias with regard to presence or absence of allergic disease would have occurred.

We do not know what risk factors could have caused the increase in atopy, since Greenland has undergone major changes, including rapid urbanisation and a transition from a traditional hunting and fishing society to a modern society in which most people work in trade, administration, and services.

Contributors

T G Krause collected data, did statistical analyses, and wrote the first draft of the manuscript. A Koch contributed to data collection. J Friberg did the linkage with the Danish Civil Registration System. B Kristensen was responsible for laboratory analyses. L K Poulsen helped plan the study. M Melbye wrote the study protocol, was responsible for planning the study, and revised all drafts of the manuscript.

Conflict of interest statement

None declared.

Acknowledgments

The study was supported by a grant from the Danish Medical Research Council (9700560) and the Committee for North Atlantic Research (9803022/2023–00–0008). The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

- Wieringa MH, Vermeire PA, Brunekreef B, Weyler JJ. Increased occurrence of asthma and allergy: critical appraisal of studies using allergic sensitization, bronchial hyper-responsiveness and lung function measurements. *Clin Exp Allergy* 2001; **31**: 1553–63.
- Misfeldt J, Jorgensen BB, Larsen SO. A serological mass examination for syphilis in Greenland in 1987. *Arctic Med Res* 1988; **47**: 173–78.
- Olsen OR, Koch A, Krause TG, Barselajsen G, Christiansen CB, Melbye M. Population screening for HIV in Sisimiut, Greenland. *Ugeskr Laeger* 2000; **162**: 4652–55.
- Paganelli R, Ansotegui IJ, Sastre J, et al. Specific IgE antibodies in the diagnosis of atopic disease: clinical evaluation of a new in vitro test system, UniCAP, in six European allergy clinics. *Allergy* 1998; **53**: 763–68.

- Linneberg A, Nielsen NH, Madsen F, Frolund L, Dirksen A, Jorgensen T. Increasing prevalence of specific IgE to aeroallergens in an adult population: two cross-sectional surveys 8 years apart: the Copenhagen Allergy Study. *J Allergy Clin Immunol* 2000; **106**: 247–52.

Department of Epidemiology Research, Danish Epidemiology Science Centre, Statens Serum Institut, Copenhagen, Denmark (T G Krause MD, A Koch PhD, J Friberg MD, Prof M Melbye DMSc); **Allergy Unit, National University Hospital, Copenhagen** (L K Poulsen DMSc); and **Pharmacia, Copenhagen** (B Kristensen)

Correspondence to: Dr Tyra Krause, Department of Epidemiology Research, Statens Serum Institut, Artillerivej 5, 2300 Copenhagen S, Denmark (e-mail: tgv@ssi.dk)

Association between activating mutations of calcium-sensing receptor and Bartter's syndrome

Sumiyo Watanabe, Seiji Fukumoto, Hangil Chang, Yasuhiro Takeuchi, Yukihiro Hasegawa, Ryo Okazaki, Noriko Chikatsu, Toshiro Fujita

Bartter's syndrome is a heterogeneous disorder characterised by deficient renal reabsorption of sodium and chloride, and hypokalaemic metabolic alkalosis with hyper-reninaemia and hyperaldosteronaemia. Mutations in several ion transporters and channels have been associated with the pathogenesis of Bartter's syndrome. We describe two hypocalcaemic patients with deficient parathyroid hormone secretion who also showed characteristics of Bartter's syndrome. We found activating mutations of the gene for the calcium-sensing receptor (CASR) in both patients. Activation of this calcium-sensing receptor inhibits the activity of a renal outer-membranous potassium channel that is mutated in type 2 Bartter's syndrome. We therefore suggest that some activating mutations of CASR could provide new mechanisms for the development of Bartter's syndrome.

Lancet 2002; **360**: 692–94

Bartter's syndrome is a heterogeneous disorder characterised by deficient renal reabsorption of sodium and chloride, and hypokalaemic metabolic alkalosis with hyper-reninaemia and hyperaldosteronaemia. Mutations in several genes have been associated with the disorder. Recessive inactivating mutations of the gene encoding the sodium-potassium-chloride cotransporter (*NKCC2*) cause type 1 Bartter's syndrome, and the gene for the renal outer-membranous potassium channel (*ROMK*) is mutated in type 2 Bartter's syndrome. Type 3 Bartter's syndrome results from deficient function of the chloride channel *CLCKB*, and type 4 Bartter's syndrome is caused by inactivating mutations of *BSND*, the gene for the β -subunit of *CLCKB*.¹ Gitelman's syndrome is a hypocalciuric variant of Bartter's syndrome caused by inactivating mutations in the gene for the sodium-chloride cotransporter of the distal convoluted tubule (*NCCT*).

The calcium-sensing receptor (CASR) is a G-protein-coupled receptor essential for regulating secretion of parathyroid hormone.² In addition to the parathyroid, CASR is expressed in several other tissues, including the kidney. Activation of CASR by high concentrations of extracellular calcium ions inhibits the activity of ROMK in rats.² Because potassium secretion by ROMK is essential for maintenance of positive luminal potential in the thick ascending limb of Henle that drives paracellular