Antimicrobials in early life

The 9th Finnish Gut Day

2016 01 21

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In Collaboration with Aalto University, Dept of Building Technology

Aalto University

A six-fold gradient in the incidence of type 1 diabetes at the eastern border of Finland

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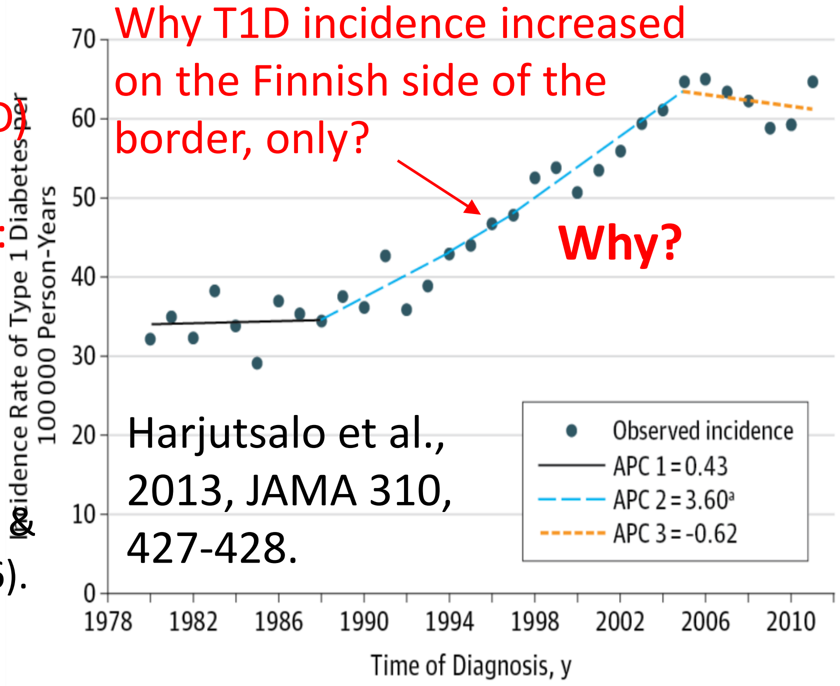
Figure 1. Age-adjusted mean annual incidence of type 1 diabetes in 0–14 year-old children in Russian Karelia and in Finland during the years 1990–99. Black triangles=Russian Karelia; black squares=Finland; vertical bars=95% confidence intervals.

Finland has world-record in diagnosed diabetes type 1 (T1D) among children less than 15 years of age: incidence climbed from 12 to 65 new cases /per 100 000 person-years from 1950's to 2006. (Knip & Siljander, Nat Rev. 2016).



Autoimmune diseases are **illnesses caused by dysfunction of the immune cells, responsible for microbial defences of our body** :
Diabetes type 1 (destruction of pancreatic beta-cells)
Hypothyreoiditis (thyroidal dysfunction)
Asthma (dysfunction of bronchia)
Allergy, atopy (dysfunction of innate immunity system of the skin)
Inflammatory bowel diseases (IBD, ulcerative colitis, Crohn's disease)
Alzheimer syndrome (neuronal dysfuntion)

WHY do Karelian children on the Finnish side of the Finnish-Russian border have SIX-FOLD higher incidence of Thyroid Autoimmunity than on the Russian side?

Serological Evidence of Thyroid Autoimmunity among Schoolchildren in Two Different Socioeconomic Environments

Anita Kondrashova, Hanna Viskari, Anna-Maija Haapala, Tapio Seiskari, Petri Kulmala, Jorma Ilonen, Mikael Knip, and Heikki Hyöty

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Patients or Other Participants: A total of 532 schoolchildren from Russian Karelia and 532 schoolchildren in Finland matched for age, gender, and season of the blood sampling were included.

Interventions: There were no interventions.

Main Outcome Measures: The prevalence of thyroid peroxidase antibodies (TPOAb), thyroglobulin antibodies (TGAb) and HLA-DQ alleles was measured.

Results: The prevalence of TPOAb was significantly lower in Russian Karelian than in Finnish children (0.4 *vs.* 2.6%, $P = 0.006$). A similar difference was observed for TGAb (0.6 *vs.* 3.4%, $P = 0.002$). Finnish girls tested positive for both TPOAb (4.3 *vs.* 0.4%, $P = 0.01$) and TGAb (5.3 *vs.* 0.9%, $P = 0.01$) more frequently than Finnish boys. Seven of the 23 tested subjects with signs of thyroid autoimmunity (30%) had increased serum TSH concentrations as a sign of subclinical hypothyroidism. The frequency of HLA genotypes did not differ between the two countries or between autoantibody-positive and -negative subjects.

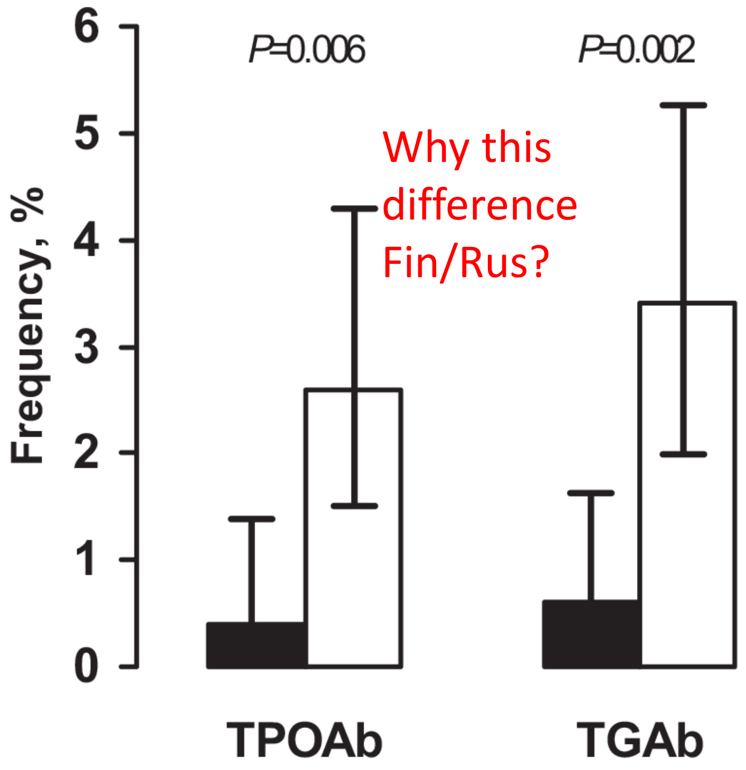

FIG. 1. Frequency of TPOAb and TGAb in schoolchildren in Russian Karelia (*black bars*) and in Finland (*white bars*). The error bars represent the 95% CI.

Incidence Trends of Pediatric Inflammatory Bowel Disease in Finland, 1987–2003, a Nationwide Study

Pieta Lehtinen, MD,† Merja Ashorn, MD, PhD,*‡ Sari Iltanen, MD, PhD,* Raimo Jauhola, MD,§ Pekka Jauhonen, MD,‖ Kaija-Leena Kolho, MD, PhD,¶ and Anssi Auvinen, MD, PhD****

Inflamm Bowel Dis Vol 17, 1778-1783 (2011)

Why has the total incidence of inflammatory bowel disease (IBD) increased three-fold in Finnish children in less than 20 years? IBD is a serious, usually life-long, debilitating illness . Is IBD caused by our ”better” socio-economic conditions?

Finns started in 1980’s increasingly to use ready-made foods, especially for babies and children’s meals at day-care and school: microbe-free, with preservatives or vacuum to prevent microbial growth.

Has this change upset the immunological balance between our body and the microbes in our gut?

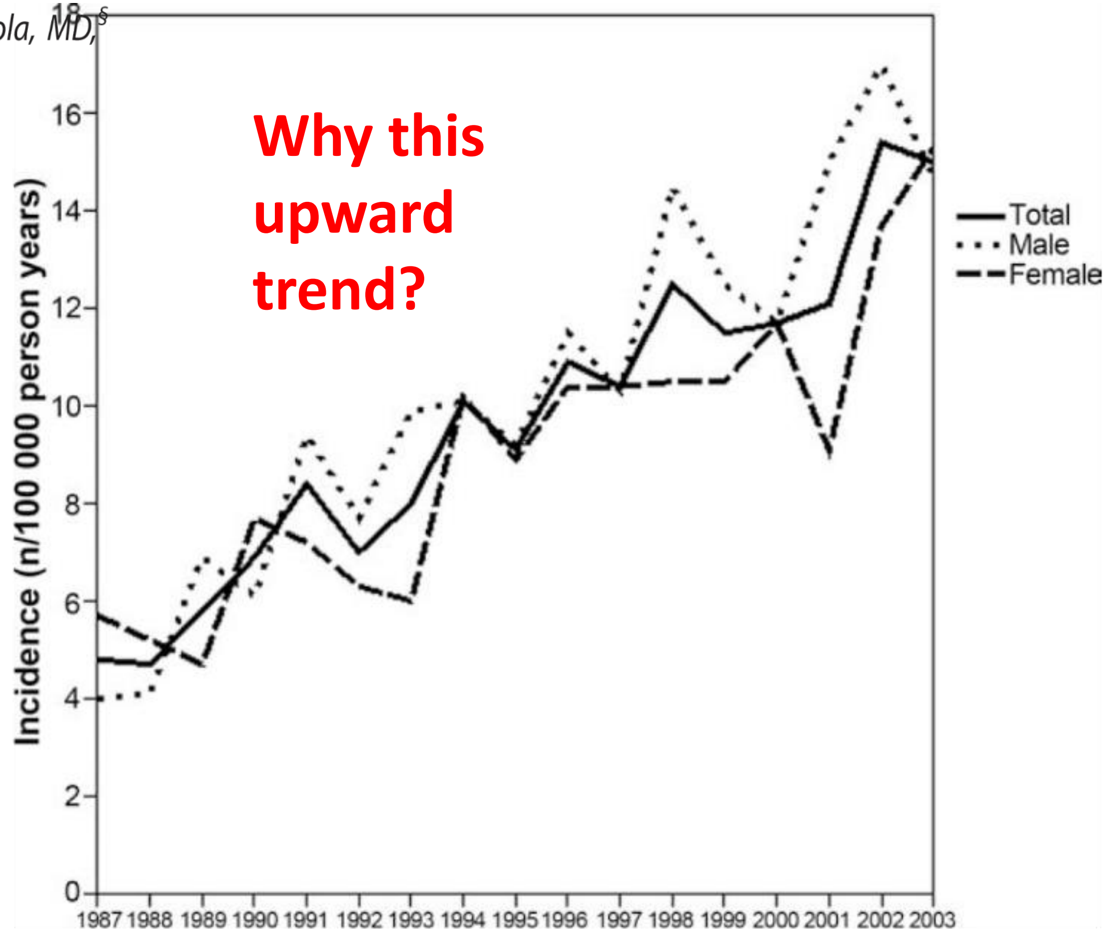

FIGURE 1. The total incidence rates of pediatric IBD in Finland, 1987–2003. The incidence rates of boys and girls are marked separately.

ORIGINAL ARTICLE EPIDEMIOLOGY AND GENETICS

Allergy gap between Finnish and Russian Karelia on increase

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[1]Department of Chronic Disease Prevention, National Institute for Health and Welfare, Helsinki; [2]Skin and Allergy Hospital, Helsinki University Central Hospital, Helsinki; [3]National Institute for Health and Welfare, International Affairs Unit, Helsinki; [4]Department of Bacteriology and Immunology, University of Helsinki, Helsinki; [5]North Karelia Centre for Public Health, Joensuu; [6]National Institute for Health and Welfare, Division of Welfare and Health Promotion, Helsinki, Finland

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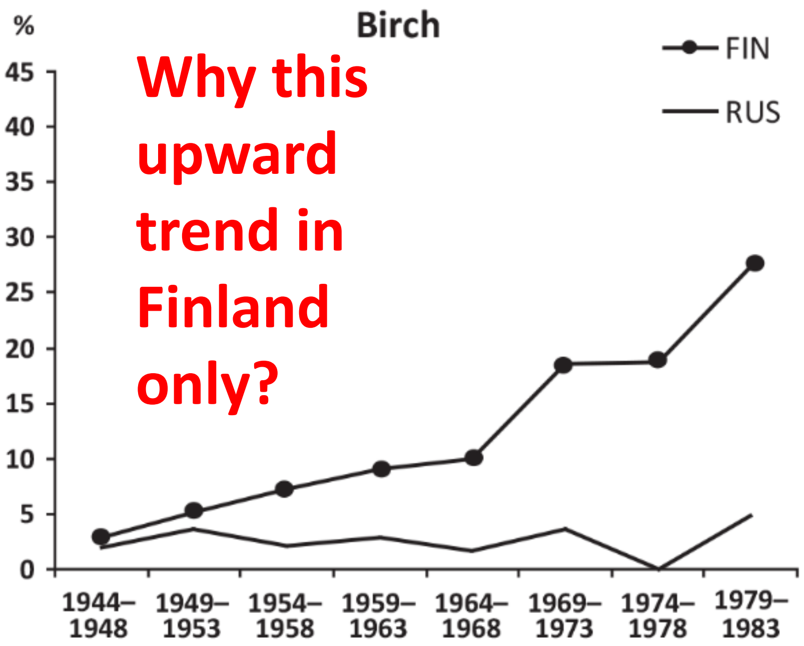
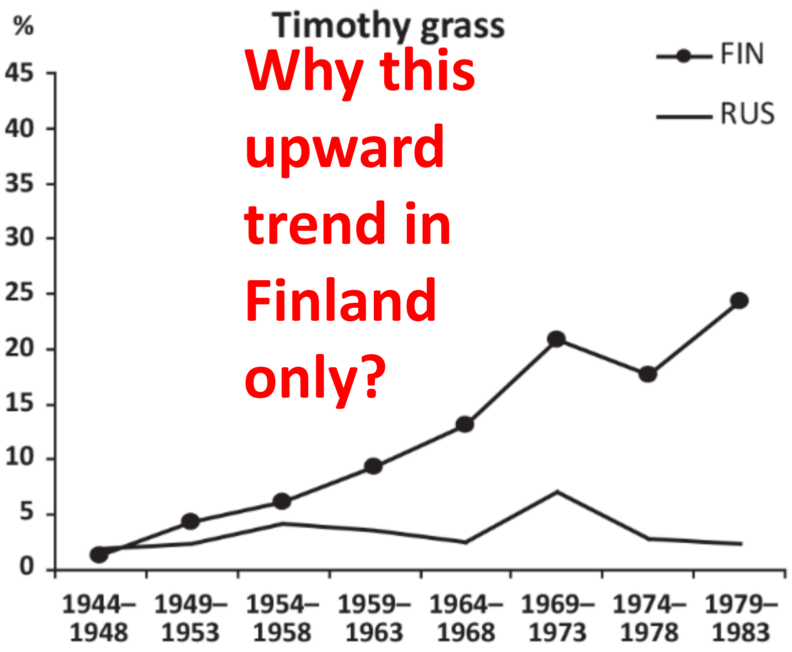
Birch pollen allergy and hey fever (timothy) increased in 1964 – 1984 up to 3-fold on the Finnish side of Karelia but not on the Russian side of the border.





Genetic ethnicity, climate, birch pollen and timothy hey have not changed since centuries! , but **socioeconomic conditions** after 1950's developed very differently.

Is our "higher" living standard sensitizing us to pollen and hey?

The microbial communities in Russian Karelian homes were very different from those in Finnish Karelian homes: DNA based analysis showed high prevalence of gram-positive bacteria, Firmicutes and Actinobacteria in Russian Karelian home dust, whereas gram-negatives, Proteobacteria and chloroplasts of plants formed the majority of prokaryotic DNA in Finnish Karelian home dust.

Environmental Microbiology (2008) **10**(12), 3317–3325 doi:10.1111/j.1462-2920.2008.01723.x

Predominance of Gram-positive bacteria in house dust in the low-allergy risk Russian Karelia

Jaakko Pakarinen,[1]* Anne Hyvärinen,[2] Mirja Salkinoja-Salonen,[1] Sirpa Laitinen,[3] Aino Nevalainen,[2] Mika J. Mäkelä,[4] Tari Haahtela[4] and Leena von Hertzen[4]

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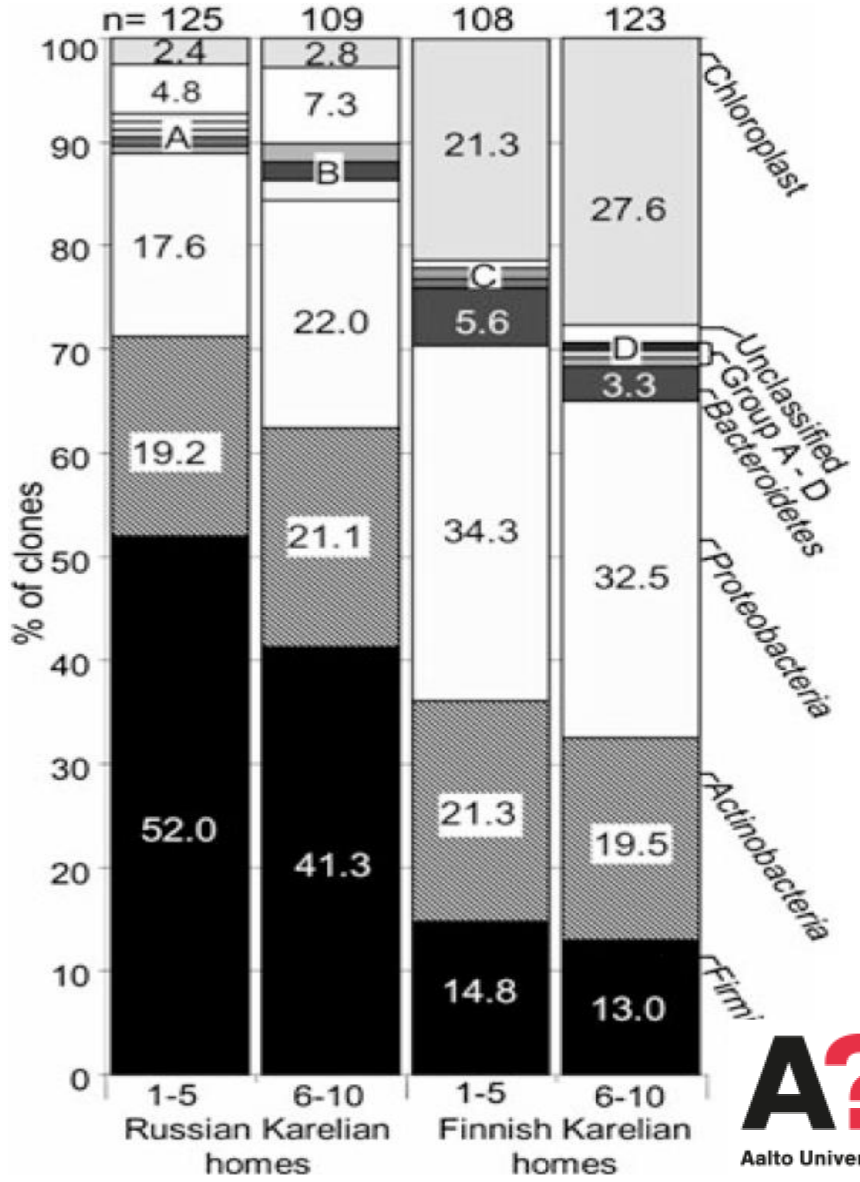
species and of chloroplast, indicating plant biomass, were more numerous in Finnish than in Russian Karelian dust. In conclusion, this study revealed major disparities between Finnish and Russian house dusts. The higher bacterial content and the predominance of Gram-positive bacteria in Russian dust may have implications for occurrence of atopy.

Introduction

Many studies have indicated association of raised risk for atopic diseases with Western lifestyle and urbanization (Viinanen *et al.*, 2005; von Hertzen and Haahtela, 2006;



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International Archives of Allergy and Immunology

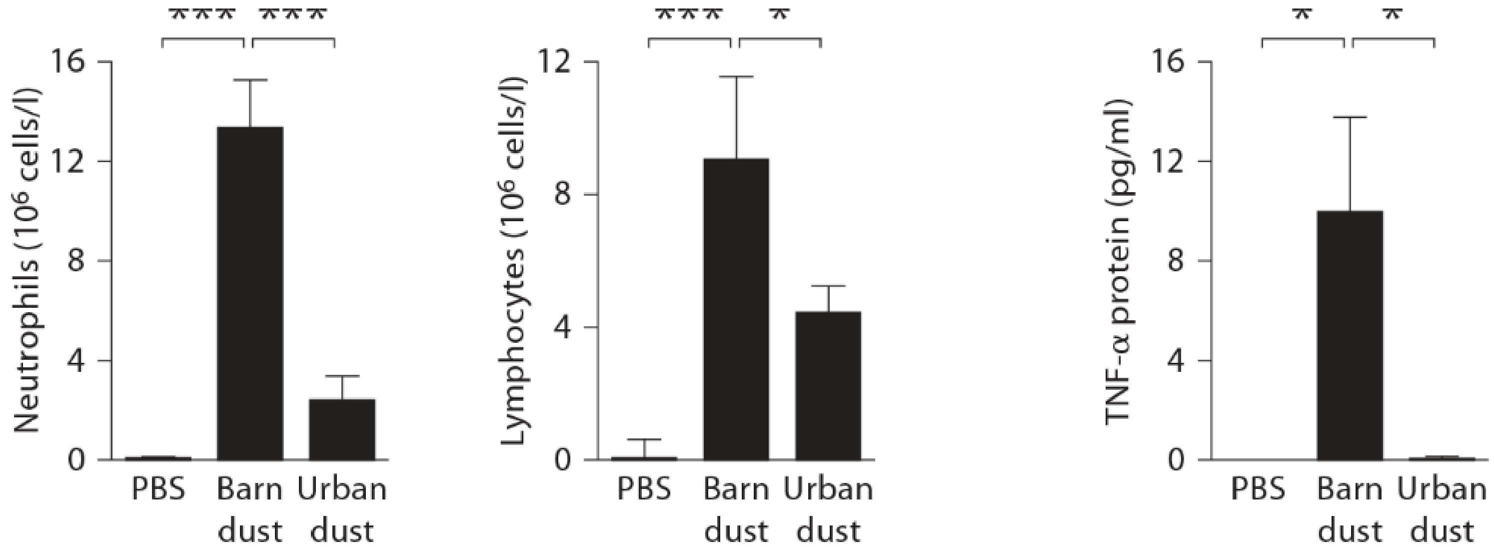
Int Arch Allergy Immunol 2009;149:81–90
DOI: 10.1159/000176310

Contrasting Immunological Effects of Two Disparate Dusts – Preliminary Observations

Harri Alenius[a] Jaakko Pakarinen[b] Ossian Saris[a, b] Maria A. Andersson[b] Marina Leino[a] Kristiina Sirola[a] Marja-Leena Majuri[a] Jari Niemelä[c] Sampsa Matikainen[a] Henrik Wolff[d] Leena von Hertzen[e] Mika Mäkelä[e] Tari Haahtela[e] Mirja Salkinoja-Salonen[b]

Aalto University

Comparison of immunological responses of human dendritic cells to Finnish urban home dust and rural environment dust of the 2000's: cells cells exposed to urban home dust expressed Th2- type of response (=directed towards allergy), elicited **no expression** of the cytokine Tnf-alfa. In contrast, the rural dust directed the dendritic cells to Th1 response (non-allergy) and elicited "normal" cytokine release.



The Finnish urban home dust consisted almost exclusively of human commensal bacteria and **no microbes** of the natural outdoor environment.

Outdoor microbes are needed to direct the human innate immunity cells towards healthy defence response.

EU-HITEA study : dust collected from Finnish schools was inactive in provoking cytokine release, whereas Dutch and Spanish school dusts were highly reactive. (Huttunen et al., Indoor Air, 2015)

Microbial content of drinking water in Finnish and Russian Karelia – implications for atopy prevalence

Allergy (2007), 62, 288-292

Background and aim: The influence of microbial quality of drinking water from different sources on the occurrence of atopy has been poorly examined. This study was undertaken to clarify the association between the overall microbial content in drinking water and the occurrence of atopy among schoolchildren from two neighbouring areas with profound differences in living conditions and lifestyles.

Methods: Drinking water samples were obtained from kitchens of nine schools in North Karelia, Finland and of nine schools from Pitkäranta, the Republic of Karelia, Russia. The pupils of these schools were participants of the Karelian Allergy Study. Occurrence of atopy, determined by skin prick test positivity (one or more) to 14 common airborne and food allergens, was measured in all 563 children, aged 7–16 years, from these 18 schools. Water samples were analysed using standard methods for drinking water analyses including viable counts for *Escherichia coli*, intestinal enterococci, coliform bacteria and heterotrophic bacteria. In addition, total cell counts including both viable and nonviable bacteria, algae and protozoans were assessed using epifluorescence microscope with 4′-6-diamidino-2-phenylindole (DAPI) staining.

L. von Hertzen[1], T. Laatikainen[2], T. Pitkänen[3], T. Vlasoff[4], M. J. Mäkelä[1], E. Vartiainen[2], T. Haahtela[1]

[1]Skin and Allergy Hospital, Helsinki University Central Hospital, Helsinki, Finland; [2]Department of Health Promotion and Chronic Disease Prevention, National Public Health Institute, Helsinki, Finland; [3]Department of Environmental Health, National Public Health Institute, Kuopio, Finland; [4]The North Karelian Center for Public Health, Joensuu, Finland

Is the morbidity in autoimmune disease like atopy connected to **deficiency of microbial exposure** in early life?

Conclusion: High overall content of micro-organisms in drinking water may be associated with reduced risk of atopy, independently from other determinants.

Accepted for publicatio

ORIGINAL ARTICLE

Dampness, bacterial and fungal components in dust in primary schools and respiratory health in schoolchildren across Europe

José Jacobs,[1] Alicia Borràs-Santos,[2,3,4] Esmeralda Krop,[1] Martin Täubel,[5] Hanna Leppänen,[5] Ulla Haverinen-Shaughnessy,[5] Juha Pekkanen,[5,6] Anne Hyvärinen,[5] Gert Doekes,[1] Jan-Paul Zock,[2,3,4] Dick Heederik[1]

ABSTRACT

Background Respiratory health effects of damp housing are well recognised, but less is known about the effect of dampness and water damage in schools. The HITEA study previously reported a higher prevalence of respiratory symptoms in pupils from moisture damaged schools, but the role of specific microbial exposures remained unclear.

Objectives To study associations between school dampness, levels of fungal and bacterial markers, respiratory symptoms and lung function in children.

Methods Primary schools in Spain, the Netherlands and Finland were selected on the basis of the observed presence (n=15) or absence (n=10) of moisture, dampness and/or mould. Settled dust was repeatedly sampled in 232 classrooms and levels of 14 different microbial markers and groups of microbes were determined. Parental reports of respiratory symptoms were available from 3843 children aged 6–12 years, of whom 2736 provided acceptable forced spirometry testing. Country-specific associations between exposure and respiratory health were evaluated by multilevel mixed-effects logistic and linear regression models and combined using random-effects meta-analysis.

Results The prevalence of respiratory symptoms was higher in moisture damaged schools, being more pronounced in Finnish pupils. Effects on lung function were not apparent. Levels of microbial markers were

What this paper adds

- Several studies found consistent evidence for an association between dampness and mould observations in buildings and adverse effects on respiratory health in domestic and occupational settings; little is known about health effects related to exposure in school buildings.
- We studied associations between school dampness, microbial exposure and respiratory health in children.
- Associations were found between school dampness and respiratory symptoms, but not with lung function. These associations were not explained by levels of a range of (molecular) microbial markers.
- Our results indicate that associations between moisture, microbial exposure and health may vary between countries, meaning that future studies on microbial exposure across different regions and countries should also take into account differences in culture, climate and building use.

EU-HITEA project: largest research effort ever executed in Europe, focused on ill health connected to school buildings. What was learned?

RESULT:

The classroom dusts in Finnish schools were almost empty of :

- **glucans and endotoxin,**
- **total and taxon specific DNAs (cell eqv./day) of fungi and bacteria**

(lower by factor 10x to 50x or more) compared to those from the Spanish and Dutch school dusts.

ORIGINAL ARTICLE

Dampness and mould in schools and respiratory symptoms in children: the HITEA study

Alicia Borràs-Santos,[1,2,3,4] José H Jacobs,[5] Martin Täubel,[6] Ulla Haverinen-Shaughnessy,[6] Esmeralda JM Krop,[5] Kati Huttunen,[7] Maija-Riitta Hirvonen,[6,7] Juha Pekkanen,[6] Dick JJ Heederik,[5] Jan-Paul Zock,[1,2,3] Anne Hyvärinen[6]

OccupEnviron. Med 2013, 70, 681-687

ABSTRACT

Background The adverse respiratory health effects of dampness and mould in the home have been extensively reported, but few studies have evaluated the health effects of such exposures in schools.

Objectives To assess the associations between dampness and mould in school buildings and respiratory symptoms among 6–12-year-old pupils in three European countries with different climates.

Methods Based on information from self-reports and observations, we selected 29 primary schools with and 27 without moisture damage in Spain, the Netherlands and Finland. Information on respiratory symptoms and potential determinants was obtained using a parent-administered questionnaire among 6–12-year-old pupils. Country specific associations between moisture damage and respiratory symptoms were evaluated using multivariable multilevel mixed effects logistic regression analysis.

Results Data from 9271 children were obtained. Nocturnal dry cough was consistently associated with moisture damage at school in each of the three countries: OR 1.15; 95% CI 1.00 to 1.30 with p for heterogeneity 0.54. Finnish children attending a moisture damaged school more often had wheeze (OR 1.36; CI 1.04 to 1.78), nasal symptoms (OR 1.34; CI 1.05 to 1.71) and respiratory-related school absence (OR 1.50; CI 1.10 to 2.03). No associations with these symptoms were found in the Netherlands or Spain (p for heterogeneity <0.05).

Conclusions Moisture damage in schools may have adverse respiratory health effects in pupils. Finnish school children seem to be at higher risk, possibly due to quantitative and/or qualitative differences in exposure.

What this paper adds

- Exposure to dampness and mould in the home has been associated with adverse respiratory health effects.
- Dampness and mould in schools may also have adverse respiratory health effects in children, particularly in Northern Europe.
- Geographical differences in these effects may be related to qualitative and/or quantitative microbial exposure differences due to variations in climate and in building characteristics.
- Avoidance or remediation of damp and mould problems in school buildings may benefit pupils' respiratory health.

Institute of Medicine (USA), the prevalence of home dampness varies from 10% to 50% in affluent countries and is similar in developing countries.[1 2] A recent European review has shown a prevalence of home dampness of 12%.[3]

Several epidemiological studies conducted among adults and children have found an association between indicators of indoor dampness and health outcomes such as respiratory symptoms, respiratory infections and exacerbation of asthma.[1 4–7] Dampness and moisture in buildings can lead to microbial growth and harmful emissions into indoor air, but the causal mechanisms and aetiological agents are still largely unknown.[5 8 9]

Children are considered more susceptible to indoor air pollutants because their lungs and

HITEA results (contd.) : health of school children (n = 9271) in the damaged ("homekoulut") and non-damaged schools in Spain, Netherlands and Finland.

Citations from HITEA publications:

Finnish children attending a moisture damaged school more often had wheeze, nasal symptoms and respiratory –school absence .....

No associations with these symptoms were found in the Netherlands or Spain....

Finnish children seem to be at higher risk.....

Why....are our children more sensitive than those in other EU-countries?

Conclusions from EU-HITEA (many publications):

1. Indoor microbiota (bacteria, molds) in Finnish schools dust (whether damaged or reference) was extremely low as compared to Spain and the Netherlands

3. Finnish school dust was inert to murine macrophages. School dust from Spain and Netherlands was immunologically highly responsive

*4. The amount of dust in Finnish schools was **very low**.*

5. Finnish children (6 to 10 years) had more asthma and nasal (”no cold”) symptoms than the children of Dutch and Spanish schools.

QUESTION: could the low microbial content and high prevalence of building related illness be linked by a common cause?

Where is the MURDERER? Who/what killed the microbes in Finnish Karelia, not in Russian Karelia?

Why are Finnish school dusts void of microbes – fungi and bacteria? – whereas the microbes were plentifully present in Dutch and Spanish school dusts? Jacobs et al., Occup Environ Med 2014, 71: 704-712 DOI: 10.1136/oemed-2014-102246

….is the MICROBE ”MURDERER” in the BOTTLE?

Aalto University

Antimicrobial biocides are contained in most cleaning formulations used in Finland at home, schools, day care centres.

Baby products contain (2016) as antimicrobials **phenoxyethanol** , **sodium benzoate, potassium sorbate** and members of the **isothiazolin**-group compounds: wet wipes, creams intended for daily whole-body treatment, shampoos, ……

Dishwashing and handwashing liquids sold for use for the family incl. the baby, frequently contain **Isothiazolin**-biocides.

Triclosan, an extremely effective, highly mitochondriotoxic disinfecting biocide, in wide use since 1980, **high concentration in toothpastes**, with instruction of the dentist ”to leave the toothpaste in-mouth overnight, EVEN babies, to ”disinfect mouth”. Triclosan usage is now fading for commercial reasons (likely to become banned in EU within foreseeable period). *Ajao et al., 2015, Toxicology Reports dx,doi.org/10.10.1016*

KOOSTUMUS:

¤ Kationiaktiivista guanidiini kopolymeeriä (PHMB)

¤ UV –puhdistettu vesi

Box above: …copy pasted from a brochure of a PHMB-product marketed in Finland, as ”safe for indoor use”. (19.9.2012)

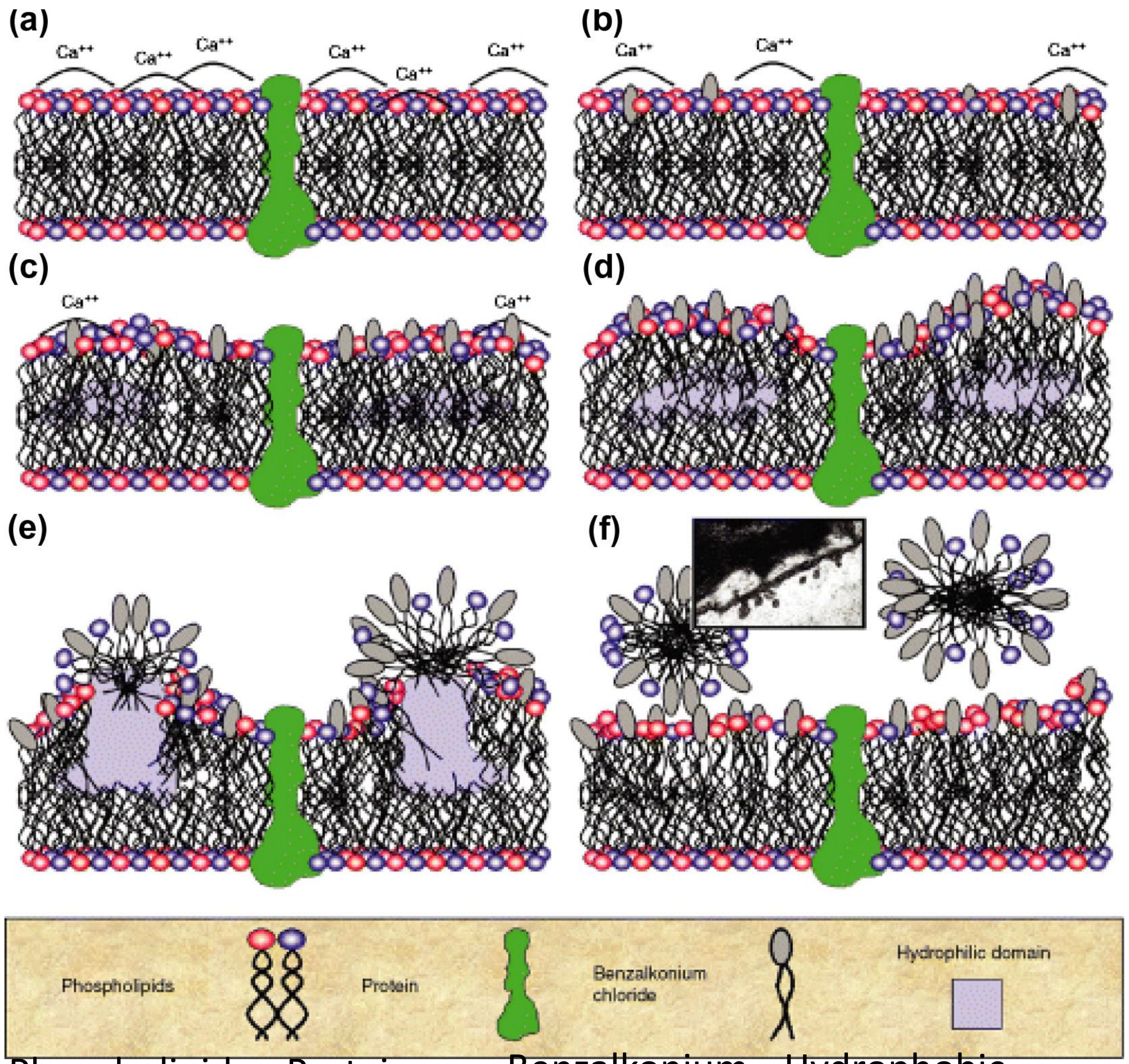
Polyguanidine biocides,are large scale used in Finland since early 1990's, for **anti-mold cleaning** and for ”prevention of mold and moisture damage ”. Marketing brochures these products advertise ”safety” by showing a baby sitting on polyguanide treated floor…. ..Also used as **textile fresheners**, for combatting odour, and ”remediating” indoor spaces with related health problem. This is common practice in Finland, in kindergartens, schools, residencial buildings.

Cationic surfactants (surface active agents) are synthetic chemicals that came in wide consumer use in Finland in 1980s.

Cationic surfactants are tertiary or quaternary alkyl-, aryl- or hybrid compounds. All are biocidal towards all kinds of living cells, most sensitive are bacteria and mammalian (incl. Human) cells. Therefore also called ”antibacterials”.

Cationic surfactants are contained in **MOST laundry liquids**, **ALL laundry softening agents** (used in rinsing water, and **remain in the textile)**

Wessels & Ingmer, 2013, Reg Toxicol Pharmacol 67, 456-467



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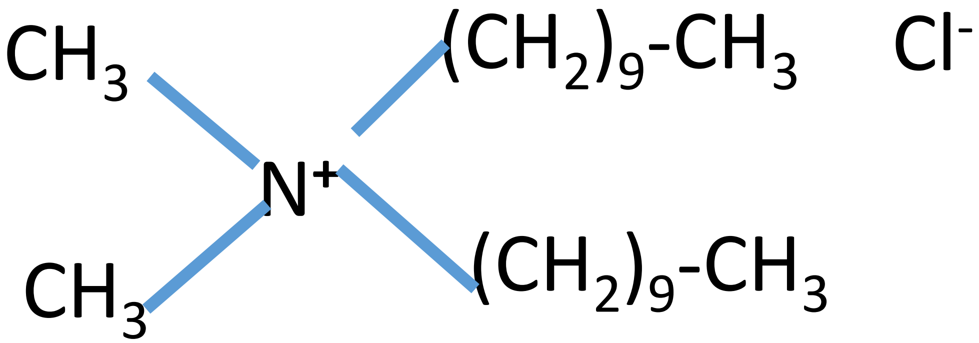
Didecyl-dimethyl-ammonium chloride, DDAC, is one of the cationic biocidal cleaning agents used in today's indoor space management in Finland. It is also suspected as causative agent of occupational asthma in the cleaning staff.

DDAC, is toxic to human, when inhaled as dust, sprays or aerosols. Many cleaning agents (sold at supermarkets, hardware stores) contain it.



DDAC is contained in many supermarket and hardware store products, here just one example:

3. KOOSTUMUS JA TIEDOT AINEOSISTA Delta Pronatura (Dr Beckmann)
3.1 Vaaraa aiheuttavat aineosat
3.1.1 CAS/Eynumero ja rekisteröintinumero
3.1.2 Aineosan nimi 3.1.3
Pitoisuus
3.1.4 Varoitusmerkki, R-lausekkeet ja muut tiedot aineosasta
67-63-0 / 200-661-7
7173-51-5 / 230-525-2
Propan-2-ol
Didecyldimethylammonium
chloride
2,5 - 10%
<2,5%
Xi, F, R11, R36, R67
C, Xn, R22, R34

Cationic surfactants and polyguanidines

Aalto University

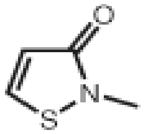
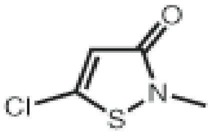
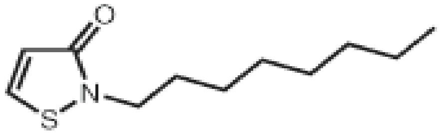
Cationic surfactants (surface active agents) are synthetic chemicals that came in wide consumer use in Finland, starting in 1980s.
Cationic surfactants are tertiary or quaternary alkyl-, aryl or hybrid compounds. **All of the are biocidal towards all kinds of living cells, most sensitive are bacteria and mammalian (incl. Human) cells.**

Polyguanidine biocides (PHMB), are cationic biocides, not surfactants. Sole of use of PHMB is biocide. NONBIODEGRADABLE.
Are used in Finland for

- skin disinfection (”käsi-desi”), as sprays for ”refreshing” textiles and other indoor property.
- Skin disinfection sprays by pedicyrists
- for ”prevention of mold and remediation of mold/ moisture damage ”. Also used as for combatting odour, and ”remediating” indoor spaces with indoor air related health problem.

This is common practice in Finland, in kindergartens, schools, residencial buildings

Schools & Day care centers and homes use cleaning agents that contain cationic tensides and ALSO antimicrobial isothiazolin-ons, some examples:

 MI	2-Methyl-4-isothiazolin-3-one CAS no. 2682-20-4 MW = 115.2 $\log P_{o/w}$ = - 0.11
 MCI	5-Chloro-2-methyl-4-isothiazolin-3-one CAS no. 26172-55-4 MW = 169.6 $\log P_{o/w}$ = 0.60
 OIT	2-n-Octyl-4-isothiazolin-3-one CAS no. 26530-20-1 MW = 213.3 $\log P_{o/w}$ = 3.6
 Dichloro-OIT	4,5-Dichloro-2-n-octyl-4-isothiazolin-3-one CAS no. 64359-81-5 MW = 282.2 $\log P_{o/w}$ = 4.9

2-Methyl-4-isothiazolin-oni (MIT), (”SAPU”, Berner OY, ”TahraSpurt”, Kiilto OY; KiiltoAlvari, Kiilto Biorine, Kiilto KISU

5-chloro-2-methyl-4-isothiazolin-3on (CMIT); 2-methyl-4-isothiazolin-oni (”SAPU”, Berner OY), Kiilto Biorine

2-n-Octyl-4-isotiazolin-3-on (OIT);

Benzyl-isothiazolin-on (TahraSpurt, Kiilto OY, KiiltoAlvari; Kiilto KISU

4,5-Dichloro-2-n-octyl-4-isothiazolin-3-on

These are **nonvolatile, water soluble , aerosolisable** . When aqueous cleaning formulation is spread on the floor, water evaporates and leaves the active substances as surface deposit on the floor or other ”cleaned” surfaces.

During daytime human mobility and mechanical ventilation cause turbulence that mobilises the chemicals into the air. If inhaled, users of the space become exposed to the biocidal chemicals.

The antimicrobial property is erraneously taken as an indicator of good hygiene.

Source: Contact Dermatitis, Vol 70, No 5, 270-275, 11 March 2014 DOI: 10.1111/cod.12184; http://onlinelibrary.wiley.com/doi/10.1111/cod.12184/full#cod12184-fig-0001

Bacteria and biocide-sensitive fungi have disappeared from Finnish Schools with indoor air connected health complaints!

Helsinki University team found that **bacteria had disappeared** from schools, where children and teachers experience building related ill health symptoms, and **the remaining few molds are BIOCIDE resistant** (90%):

FALL-OUT PLATE OBSEVATIONS

- Only few propagules grew per plate (Ø 9 cm)
- Over 90% of the colonies were resistant to boron chemicals (borate, borax) 5000 ppm; arsenic pentoxide (500 ppm); PHMB (500 ppm) or PHMG (500 ppm), cationic surfactants, isothiazolin-biocides
- Outdoor air contained molds are mainly sensitive to the above substances (= spiked fall-out plates grow less propagules or none).

Today's conclusion

1. **The microbial balance** between our children and their environment has **become destroyed** by the Finnish lifestyle.
2. Deprivation of microbial contact may hamper our children's innate immunity and immunological maturation, and appears to connect to dramatically increased pediatric autoimmune disease in the past 10 – 20 years.
3. Microbial deprivation was created a.o.t. by (*conclusions drawn by this presenter*):

- Prevention of entry of **outdoor microbes** into indoor space (mechanical ventilation with filters); no open windows
- Frequent usage of **antibacterial technochemical / hygiene products**
- **Preference of microbe-free food (e.g. those ready-to-eat foods that are stored at room temperature, heat treated or stabilized by antimicrobial preservatives)**
- **Processed juices instead of intact fruits**, post-pasteurized fermentation products….

We have done this ourselves, therefore, we are the ones to reverse this development.

Thank you for your attention!

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