8 Papers

Paper I
Original Article

Allergic disease and Staphylococcus aureus carriage in adolescents in the Arctic region of Norway

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Keywords
allergic disease; allergic multimorbidity; allergic rhinitis; asthma; eczema; Staphylococcus aureus

Abstract

Background: Allergic diseases are common chronic diseases in children and adolescents, but limited epidemiological data are available during transition into adulthood. Nasal Staphylococcus aureus carriage has been linked to increased prevalence of allergic disease. The objective of this study was to define the prevalence of allergic diseases in adolescents above the Arctic Circle in Northern Norway and to study the associations of S. aureus carriage with allergic diseases.

Methods: A school-based cohort in late adolescence (18–19 years) was invited to participate in a cross-sectional study on lifestyle and health, and 868 attended (71.9%). Self-reported allergic disease and severity of eczema were assessed by Mechanisms of the Development of Allergy and Patient-Oriented Eczema Measure questionnaires. Participants were tested with spirometry and exhaled nitric oxide (FeNO) and swabbed for bacterial culture from nose and eczematous skin.

Results: We found asthma, eczema, allergic rhinitis (AR), and nasal S. aureus carriage among 11.9%, 10.4%, 26.0%, and 51.3% of the participants, respectively, and 10.2% had allergic multimorbidity. Lifetime prevalence for any allergic disease was 45.1%. Reduced lung function and increased FeNO were found in 11.6% and 22.1% in participants with asthma, respectively. Nasal S. aureus carriage was associated with eczema, severe asthma, and severe AR. FeNO > 25 ppb was associated with both asthma and nasal S. aureus carriage.

Conclusion: Asthma, eczema, and AR are common among adolescents above the Arctic Circle in Norway. Allergic disease is associated with S. aureus carriage, but its role in the pathogenesis and severity is not established.
asthma. In infants and preschool children, no clear association between *S. aureus* carriage and wheeze or airway inflammation has been shown so far (12). However, in older children and adolescents, *S. aureus* nasal carriage has been associated with increased risk of asthma and asthma exacerbations (13).

Few studies have examined the prevalence of allergic disease and their association with *S. aureus* carriage in late adolescence. The aims of our study were firstly to describe the prevalence of allergic disease among adolescents above the Arctic circle in Northern Norway and secondly to analyze associations between nasal *S. aureus* carriage and allergic diseases.

### Methods

#### Sample

The Tromsø Study Fit Futures (TFF) cohort was initiated in 2010–2011. All first-year high school students in both academic and vocational educational programs from all 8 high schools in the municipalities of Tromsø and Balsfjord were invited to participate (TFF1) and 92.8% attended (14). In this region, more than 90% of the population in the age group 16-19 years attend high school. In the second wave of the study (2012–2013), all third-year high school students, including all participants from TFF1, were invited for follow-up (TFF2). Among 1208 invited students, 868 (71.9%) participated in TFF2. Each participant completed a web-based general health and lifestyle questionnaire (http://www.questback.com) and underwent clinical examinations, 812 (93.5%) measured fractional exhaled nitric oxide (FeNO) with NIOX MINO® (Aerocrine AB, Solna, Sweden) with one measurement for each participant in the sitting position before performing spirometry (18).

#### Spirometry with reversibility test

Lung function was measured with the Easy On-PC Spirometry System (Medizintechnik AG, Zürich, Switzerland) in the sitting position. The best result of approved tests (minimum 2) was used in the analysis. Decision on approval was taken by trained assistants performing spirometry. Questionnaire data were blinded to the assistants. Reversibility was tested using 0.2 mg salbutamol inhalation aerosol (Airomir Autohaler®, Teva UK Limited, Eastbourne, UK). Post-reversibility spirometry was performed 15–25 min after the salbutamol inhalation. The Global Lungs Initiative (GLI 2012) equations were used as reference for spirometry (19). Spirometry data were anonymized at analysis.

#### Assessment of *S. aureus* carriage – nose and skin

Using a NaCl-moistened sterile rayon-tipped swab, we swabbed both anterior nares (taking care to avoid skin contact) in 819 participants and eczematous skin areas in 46 participants with active eczema. The eczematous skin was rubbed with a NaCl-moistened compress prior to swabbing. *S. aureus* was identified using methods previously described with a few modifications; all swabs were submerged into Bacto® m Staphylococcus medium broth (Difco laboratories, Sparks, MD, USA) for enrichment and incubated for 18–24 h at 37°C before plating. The liquid culture was then plated on blood agar (Oxoid, Cambridge, UK) and *S. aureus* ID agar (SAID, bioMérieux, Marcy l’Etoile, France) and incubated for 18-24 hours at 37°C. The most dominating colony was selected and confirmed as *S. aureus* by the Staphaurex Plus (Remel, Lenexa, KS, USA) agglutination test. Only observations of bacterial growth on blood agar (Oxoid, Cambridge, UK) and *S. aureus* ID agar (SAID, bioMérieux, Marcy l’Etoile, France) plates were included. We defined a positive *S. aureus* culture result as *S. aureus* carriage. We did not perform quantitative analysis of bacterial load.

### Statistical methods

Statistical analyses were performed with IBM SPSS statistics, version 21 (North Castle, New York, USA). The characteristics of the study participants and prevalence of symptoms of allergic diseases were described with summary statistics. Pearson’s chi-square test and Student’s t-test were used in univariate comparisons of categorical and continuous variables, respectively. Mann–Whitney U-test was used for univariate comparisons of non-normally distributed continuous data. Multivariable

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logistic regression models were used to analyze associations between nasal *S. aureus* colonization and allergic diseases, including relevant co-variables (21, 22). The frequencies of the three major allergic diseases and their overlap were presented in Venn diagrams. For drawing of proportional Venn diagrams, Euler APE was used (http://www.eulerdiagrams.org/eulerAPE) (23). Statistical significance was assumed at a 5% level.

**Ethics**

Informed consent was signed by each participant in TFF2. The study was approved by the Regional Committee for Medical and Health Research Ethics.

**Results**

**General characteristics of study participants**

Among 868 participants, the mean age was 18.6 years and 26% were overweight (BMI ≥ 25 kg/m²) (Table 2). Men had more overweight, used more snuff tobacco, and had more screen-time than women.

**Prevalence rates for allergic diseases**

Table 3 shows the current (last 12 months) and lifetime prevalence for allergic diseases and multimorbidity. Women had higher current and lifetime prevalence for eczema and higher prevalence of current allergic multimorbidity. Fig. 1 shows the overlapping prevalence of asthma, AR, and eczema. Asthma (55%) and eczema (57%) were more common in conjunction with other allergic diseases than occurring as single entities. In contrast, AR (62%) more frequently occurred as a single entity.

**Asthma medication**

Among participants with asthma, over the last 12 months 86% were treated with short-acting β-2 agonists, 66% with inhaled corticosteroids (ICS) alone or in combination with long-acting β-2 agonists (LABA), 17% with LABA, and 15% with leukotriene receptor antagonists.

**Nasal *S. aureus* carriage and allergic disease**

Nasal *S. aureus* carriage was found in 51.3% of the participants with no gender difference. Nasal *S. aureus* carriage was associated with eczema, but not asthma and AR, in multivariable logistic regression models (Table 4). *S. aureus* carriage was associated with severe eczema, severe asthma, severe AR, or having one severe allergic disease (Table 4). When adjusting for the two other allergic diseases, the associations with nasal *S. aureus* carriage remained significant for severe asthma (OR = 2.88, 95% CI = 1.10–7.55), severe eczema (OR = 2.36,
95% CI = 1.20–4.63), and severe AR (OR = 1.73, 95% CI = 1.09–2.75). When adjusting for the two other severe allergic diseases, only the association between severe eczema and nasal S. aureus carriage remained significant (OR = 2.22, 95% CI = 1.02–4.84).

S. aureus carriage on eczematous skin and POEM score

On the day of visit, 63 of 825 participants (7.6%) had active eczema; 42 women (63.7%) and 21 men. The distribution of POEM scores is shown in Fig. 2. Eczema severity was moderate, severe, or very severe in 60.4% of the participants with eczema on the day of visit. S. aureus carriage was found in 23 of 46 (50%) samples from eczematous skin of whom 21 (91.3%) also had nasal carriage. Fig. 3 shows that participants with eczematous S. aureus skin carriage had higher POEM score (mean 14.1, SD 6.9) compared with participants without S. aureus skin carriage (mean 8.5, SD 4.8) (p = 0.003).

Spirometry, FeNO, and association with nasal S. aureus carriage

FEV₁/FVC below lower level of normal (LLN) was more frequent in asthmatic (11/95; 11.6%) vs. non-asthmatic participants (37/688; 5.4%) (p = 0.021). Mean improvement in FEV₁ after inhalation of salbutamol was 4.5% and 2.9% (p = 0.017) for asthmatic and non-asthmatic participants, respectively. Only 5 of 95 (5.3%) asthmatic participants had more than 12% improvement in FEV₁ after inhalation of salbutamol. Twenty-one of 95 (22.1%) asthmatic participants and 70 of 694 (10.1%) non-asthmatic participants had FeNO more than 25 ppb (p = 0.002). Participants with asthma had higher mean levels of FeNO (21.5 ppb, SD 16.4) compared with non-asthmatic participants (16.4 ppb, SD 13.3) (p = 0.005).

FeNO > 25 ppb was associated with both asthma (OR = 2.48, 95% CI = 1.41–4.35) and nasal S. aureus carriage

Table 2 Characteristics of the study participants. The Tromsø Study Fit Futures 2

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total</th>
<th>Women</th>
<th>Men</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>868 (100%)</td>
<td>480 (55.3%)</td>
<td>388 (44.7%)</td>
<td>0.464</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>18.6 (1.5)</td>
<td>18.6 (1.1)</td>
<td>18.5 (1.8)</td>
<td>0.025</td>
</tr>
<tr>
<td>BMI ≥ 25 kg/m²</td>
<td>26.3%</td>
<td>22.7%</td>
<td>29.8%</td>
<td>0.121</td>
</tr>
<tr>
<td>Daily Smoker</td>
<td>4.6%</td>
<td>3.6%</td>
<td>5.6%</td>
<td>0.182</td>
</tr>
<tr>
<td>Smoking sometimes</td>
<td>20.4%</td>
<td>18.2%</td>
<td>22.6%</td>
<td>0.121</td>
</tr>
<tr>
<td>Daily use of snuff tobacco</td>
<td>30.0%</td>
<td>26.6%</td>
<td>33.3%</td>
<td>0.034</td>
</tr>
<tr>
<td>Sometimes use of snuff tobacco</td>
<td>9.5%</td>
<td>10.8%</td>
<td>8.1%</td>
<td>0.197</td>
</tr>
<tr>
<td>Physical activity outside school hours</td>
<td>62.3%</td>
<td>61.1%</td>
<td>63.6%</td>
<td>0.475</td>
</tr>
<tr>
<td>≥4 h screen-time on week days</td>
<td>39.0%</td>
<td>30.2%</td>
<td>47.8%</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

*Pearson’s chi-square test and Student’s t-test were used in univariate comparisons of categorical and continuous variables, respectively. BMI: body mass index. n = 868, n may vary (between 850 and 888) due to missing values. Total prevalence is adjusted for gender difference in participation rate.

Table 3 Prevalence of allergic diseases in the Tromsø study Fit Futures 2 compared with studies from Sweden (4), Germany (3), and United Kingdom (2)

<table>
<thead>
<tr>
<th>Allergic disease ever</th>
<th>Tromsø Study Fit Futures 2</th>
<th>Current allergic disease</th>
<th>Tromsø Study Fit Futures 2</th>
<th>BAMSE</th>
<th>MAS</th>
<th>IoW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td>18–19</td>
<td></td>
<td>18–19</td>
<td>16</td>
<td>20</td>
<td>18</td>
</tr>
<tr>
<td>Total*</td>
<td>868 (100%)</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Women</td>
<td>480 (55.3%)</td>
<td>55.3%</td>
<td>55.3%</td>
<td>55.3%</td>
<td>55.3%</td>
<td>55.3%</td>
</tr>
<tr>
<td>Men</td>
<td>388 (44.7%)</td>
<td>44.7%</td>
<td>44.7%</td>
<td>44.7%</td>
<td>44.7%</td>
<td>44.7%</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>0.464</td>
<td></td>
<td></td>
<td>0.007</td>
<td>0.007</td>
<td>0.007</td>
</tr>
<tr>
<td>Eczema</td>
<td>19.1%</td>
<td>24.6%</td>
<td>13.7%</td>
<td>0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>15.9%</td>
<td>16.3%</td>
<td>15.5%</td>
<td>0.776</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allergic rhinitis</td>
<td>28.9%</td>
<td>29.9%</td>
<td>28.7%</td>
<td>0.939</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any allergic disease</td>
<td>45.1%</td>
<td>48.0%</td>
<td>42.3%</td>
<td>0.062</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multimorbidity</td>
<td>15.7%</td>
<td>17.9%</td>
<td>13.4%</td>
<td>0.086</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In the Tromsø Study Fit Futures 2, the number of participants for the different allergic diseases varies due to missing values in the questionnaire (total n = 832–842, women n = 465–472, men n = 366–371). Current disease = 12-month prevalence. BAMSE = The German Multicentre Allergy Study (n = 942). IoW = The Isle of Wight birth cohort study (n = 1298). BAMSE = The Swedish birth cohort study on asthma and allergy (n = 2607). Outcome definitions are listed in Table 1.

*Total prevalence is adjusted for different participation rate among men and women.

**Pearson’s chi-square test for differences between genders.
(OR = 2.03, 95% CI = 1.26–3.24) in multivariable logistic regression models adjusted for the use of antibiotics last 3 months, sex, BMI, screen-time, physical activity, smoking, and the use of snuff tobacco. After stratification by carriage of S. aureus, the association between FeNO and asthma was strengthened among the carriers (OR = 3.00, 95% CI = 1.49–6.03), whereas no longer any association between FeNO and asthma was found in non-carriers (OR = 1.90, 95% CI = 0.65–5.23). FEV1/FVC below LLN was not associated with nasal S. aureus carriage (OR = 1.44, 95% CI = 0.79–2.63).

Figure 1 Area-proportional Venn diagrams showing overlapping prevalence rates for asthma, eczema, and allergic rhinitis. Total (n = 842), Women (n = 472) and Men (n = 371). The Tromsø Study Fit Futures 2.

Table 4 Associations between allergic disease and nasal S. aureus carriage

<table>
<thead>
<tr>
<th></th>
<th>Asthma</th>
<th>Severe Asthma</th>
<th>Eczema</th>
<th>Severe Eczema</th>
<th>Allergic rhinitis (AR)</th>
<th>Severe Allergic rhinitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Univariable</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasal S. aureus carriage</td>
<td>1.19</td>
<td>0.77–1.83</td>
<td>3.34</td>
<td>1.33–8.37</td>
<td>1.77</td>
<td>1.11–2.83</td>
</tr>
<tr>
<td><strong>Multivariable</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasal S. aureus carriage</td>
<td>1.17</td>
<td>0.75–1.82</td>
<td>3.47</td>
<td>1.37–8.82</td>
<td>1.79</td>
<td>1.11–2.91</td>
</tr>
<tr>
<td>Sex</td>
<td>1.38</td>
<td>0.87–2.19</td>
<td>1.45</td>
<td>0.61–3.44</td>
<td>2.66</td>
<td>1.57–4.51</td>
</tr>
<tr>
<td>BMI</td>
<td>1.29</td>
<td>0.79–2.10</td>
<td>1.41</td>
<td>0.59–3.36</td>
<td>1.41</td>
<td>0.84–2.37</td>
</tr>
<tr>
<td>Antibiotic use last 3 months</td>
<td>0.66</td>
<td>0.30–1.43</td>
<td>1.48</td>
<td>0.48–4.60</td>
<td>0.30</td>
<td>0.11–0.85</td>
</tr>
<tr>
<td>Screen-time on weekdays</td>
<td>1.01</td>
<td>0.64–1.61</td>
<td>1.11</td>
<td>0.48–2.57</td>
<td>1.04</td>
<td>0.63–1.71</td>
</tr>
<tr>
<td>Physical activity outside school time</td>
<td>1.39</td>
<td>0.86–2.23</td>
<td>0.85</td>
<td>0.37–1.93</td>
<td>1.18</td>
<td>0.72–1.93</td>
</tr>
<tr>
<td>Daily smoking</td>
<td>0.91</td>
<td>0.27–3.11</td>
<td>1.07</td>
<td>0.13–8.56</td>
<td>1.26</td>
<td>0.36–4.38</td>
</tr>
<tr>
<td>Daily use of snuff tobacco</td>
<td>1.06</td>
<td>0.65–1.72</td>
<td>0.47</td>
<td>0.17–1.30</td>
<td>1.27</td>
<td>0.77–2.10</td>
</tr>
</tbody>
</table>

Multivariable logistic regression model analyzed separately with asthma, severe asthma, eczema, severe eczema, AR, and severe AR as outcome and nasal S. aureus carriage as main predictor (yes vs. no), adjusted for sex (female vs. male), BMI (≥25 kg/m² vs. <25 kg/m²), use of antibiotics last 3 months (yes vs. no), screen-time on weekdays (≥4 h vs. <4 h), physical activity outside school time (yes vs. no), daily smoking (yes vs no), and daily use of snuff tobacco (yes vs no). OR = Odds ratio, 95% CI = 95% confidence interval. Outcome definitions are listed in Table 1.
In this large cohort of late adolescents, we found high prevalence of asthma (11.9%), eczema (10.4%), AR (26.0%), and allergic multimorbidity (10.2%). The lifetime prevalence for having any allergic disease was 45.1%. Compared with the Swedish BAMSE study (4), the British IOW study (2), and the German MAS study (3), the prevalence of allergic disease in our population is close to the findings in Sweden and Germany, except for asthma which is lower in Sweden. In the IoW study, there are higher prevalence for asthma, AR, and multimorbidity (2). Variations in prevalence rates may be due to regional differences, but may partially also be due to different outcome definitions. Operational definitions of asthma in recent epidemiological studies are inconsistent (24). We used the same outcome definition for asthma as in the MAS study (3). For eczema and AR, we used the same definitions as in the BAMSE study (4).

We found a female predominance of eczema and multimorbidity. It has been hypothesized that sex hormones play a role in the pathogenesis of allergic diseases (25, 26). Experimental evidence indicates that androgens appear to have immunosuppressive effects, while estrogens are proinflammatory and may increase the susceptibility to atopy. Influence of sex hormones may thus explain the gender difference in our results.

More than half of late adolescents in our study had nasal S. aureus carriage. In contrast, only 1/4 of adults aged 30-69 years in a previous population-based study from the same region had nasal S. aureus carriage (20). The reason for strikingly higher nasal S. aureus carriage among adolescents is not clear. Nasal S. aureus carriage was associated with eczema, severe asthma, and severe AR, indicating that staphylococcal carriage may play a role in the pathogenesis of allergic diseases. Specific IgE to S. aureus superantigens in the nasal mucosa may induce immunomodulatory effects and a Th2-type eosinophilic inflammation in patients with AR (11, 27). In patients with asthma, superantigen-specific IgE is commonly detected, in particular frequent in patients with severe asthma (6, 28). When we adjusted each allergic disease for the other allergic diseases, only eczema was significantly associated with nasal S. aureus carriage, indicating that S. aureus carriage is more important for the severity of eczema than asthma and AR. However, asthma, eczema, and AR are closely related diseases that partially share the same genetic predisposition, etiology, and pathogenic mechanisms. As a consequence, adjusting for the other allergic diseases will underestimate the strength of the associations with nasal S. aureus carriage. Our epidemiological data do not prove causation, and the observed association could also be the result of reverse causation; inflammation due to allergic disease makes the mucosa more susceptible to S. aureus carriage. Many studies suggest that S. aureus carriage plays a role in the severity of established allergic diseases. This is supported by our findings, but pathophysiological mechanisms and putative therapeutic or...
prophylactic consequences need to be addressed in the future studies.

The role of *S. aureus* skin carriage as a factor contributing to the exacerbation of eczema is well established (8). The majority of participants with eczematous skin carriage were also colonized in the nose, pointing to the nose as the source of *S. aureus* in patients with eczema. However, even though the nose is the most consistent human niche for *S. aureus* carriage, we cannot rule out that *S. aureus* from the skin in some cases was the source of nasal carriage. The role of eczematous skin *S. aureus* carriage in eczema exacerbation was supported by increasing carriage rates with increasing eczema severity in our study. This has been shown in many studies (29, 30), but therapeutic strategies to restore permanent normal skin flora are lacking and may be complicated by high nasal carriage rate of *S. aureus* in patients with eczema and in the general population.

Spirometry showed signs of current obstruction in 11.6% of asthmatic participants, and only around 5% had more than 12% improvement in FEV₁ after inhalation of salbutamol. The poor sensitivity of spirometry to diagnose current asthma is also known from previous studies (31, 32). It may be due to both the intermittent course of asthma but also to good asthma control as nearly 2 of 3 of asthmatic participants were treated with ICS. In line with others (33), we also found that only 1 of 5 of asthmatic participants had increased levels of FeNO > 25 ppb. Furthermore, in a Norwegian study on adolescents with bronchiolitis in infancy, exhaled nitric oxide was related to atopy, but not to asthma (34). Some international guidelines recommend using FeNO in phenotyping airway inflammation and monitoring of severe asthma (33), while the recent international ERS/ATS guidelines on severe asthma suggest that clinicians should not use FeNO to guide therapy in adults or children (35). We found that FeNO > 25 ppb was associated with asthma only in participants with nasal *S. aureus* carriage. A possible explanation for this finding is nasal eosinophilic inflammation due to staphylococcal superantigens. As a consequence, nasal *S. aureus* carriage may contribute to the low specificity of FeNO in asthma diagnosis and disease monitoring.

The main strengths of our study are the school-based approach covering more than 90% of the late adolescents in this age group in the two municipalities, the large sample size with a high participation rate and the combination of both self-reported and objective health measurements. We believe our data represent good estimates of prevalence rates of allergic diseases in this population. However, the cross-sectional design is a limitation in evaluating the observed associations between allergic disease and *S. aureus* carriage. Furthermore, with only one nasal swab, we cannot distinguish between intermittent and persistent *S. aureus* carriage. Measurement of *S. aureus* enterotoxin IgE and Th2 markers was also not available, but could have added information to this study.

**Conclusion**

Asthma, eczema, and allergic rhinitis are common chronic diseases among adolescents in Northern Norway. Nearly half of the adolescent population has experienced one or more of these diseases by the age of 18–19, and multimorbidity of allergic disease exists in 10% of all adolescents. Allergic disease is associated with *S. aureus* carriage, but its role in the pathogenesis and severity is not established.

**Acknowledgments**

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**References**

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