Infections in Child Day Care Centers and Later Development of Asthma, Allergic Rhinitis, and Atopic Dermatitis

Prospective Follow-up Survey 12 Years After Controlled Randomized Hygiene Intervention

Teija Dunder, MD; Terhi Tapiainen, MD, PhD; Tytti Pokka, BSc; Matti Uhari, MD, PhD

Objective: To evaluate the effect of successful prevention of common infections in child day care centers on the later development of allergic diseases.

Design: Prospective follow-up survey with a questionnaire administered 12 years after a controlled randomized hygiene intervention.

Setting: Twenty municipal child day care centers in Oulu, Finland.

Participants: A questionnaire was sent to 1354 prior participants (98%) in the intervention trial. The response rate was 68% (928 of 1354 participants).


Main Outcome Measures: The number of respondents who had a diagnosis of asthma, allergic rhinitis, and/or atopic dermatitis made by a physician, and the number of those who reported symptoms of atopic diseases.

Results: Asthma was diagnosed by a physician in 48 of the 481 respondents (10%) from the intervention child day care centers, with markedly fewer infections, and in 46 of the 447 controls (10%) (relative risk, 1.0; 95% confidence interval, 0.7-1.4). Similarly, no differences were found in the numbers of children who had a diagnosis of other atopic diseases or who had reported such symptoms.

Conclusion: The prevention of common respiratory tract and enteric infections during early childhood does not change later allergic morbidity.

Arch Pediatr Adolesc Med. 2007;161(10):972-977

In 1989 Strachan1 introduced the hygiene hypothesis, which postulates that the inverse association between the number of siblings in the family and hay fever at ages 11 and 23 years noted in a British cohort was due to the protective effect of specific environmental factors such as infections in infancy. Since then, numerous observational surveys have been published, only some of them supporting this inverse association between infections and allergic disorders.2-8 Even though the association has not been found in all surveys, reports with a positive finding have gained almost universal acceptance.9

At the same time these clinical observations were made, it was found that a dominance of helper T type 2 (Th2) subsets of CD4 T lymphocytes promotes allergic disorders6,10 and that infections can shift this Th2 dominance to Th1 dominance.11 In experimental models, microbial compounds were found to modify allergic inflammation and it was concluded that the shift toward Th1 dominance could prevent the development of allergic disorders.12 Along with these developments in the theoretical immunological background, interest in the hygiene hypothesis increased markedly. Our immunological knowledge has widened rapidly in recent years, however. It has been learned, for example, that CD8 T lymphocytes have subpopulations (cytotoxic T type 1 cells [Tc1] and cytotoxic T type 2 cells [Tc2]) that inhibit either Th1 (by Tc2) or Th2 (by Tc1) cells, making the immunological explanation behind the hygiene hypothesis much more complex.13,14 Furthermore, it has been learned that the specific Th1 and Th2 polarization caused by infection is a diverse phenomenon regulated by the signaling Toll-like receptors and varies with the type of microbe.15,16

Observational surveys serve as a source of hypotheses that should then be tested.
in controlled randomized intervention trials to properly control for confounding factors. Nevertheless, there are many hypotheses in clinical medicine that cannot be tested in this way, such as effects of smoking and breastfeeding. Similarly, it is not feasible to induce infections in a randomized manner to evaluate the development of allergic disorders. It is possible, however, to evaluate the prevention of infections in a randomized controlled trial. We conducted a randomized hygiene intervention trial lasting 15 months from March 1, 1991, to May 31, 1992, at child day care centers (CDCCs), where we succeeded in reducing infections. The number of days with rhinitis was reduced by 17%, cough by 11%, and diarrhea by 18%. Still more importantly, there were 27% fewer episodes of acute otitis media and the number of days receiving antimicrobials was 24% fewer among those who attended the intervention CDCCs.

We hypothesized that if the hygiene hypothesis applies to either common viral or bacterial respiratory tract and enteric infections in childhood, there should be more atopic diseases among those who had attended the intervention CDCCs in our earlier trial than among those who had attended the control CDCCs. Thus, we conducted a follow-up survey 12 years after the randomized hygiene intervention to compare the development of atopic dermatitis, allergic rhinitis, and asthma between these 2 groups of adolescents.

STATISTICAL ANALYSIS

The differences between those who responded and those who did not respond to the questionnaire were tested with either χ² test (number of nonsmoking and smoking mothers and fathers and number of mothers and fathers with basic or higher education) or t test. We used t test for parametric variables (mean age of attendance in CDCC, mean duration of exclusive breastfeeding, mean number of episodes of acute otitis media, and mean number of days receiving antimicrobials). Univariate analysis of variance was used to test interaction in parametric variables of background data (mean age of attendance in CDCC at the beginning of the intervention, mean duration of exclusive breastfeeding, mean number of episodes of acute otitis media, and mean number of days receiving antimicrobials) between subjects assigned to the intervention and control CDCCs and whether they replied to the questionnaire in 2003. In this analysis, the differences between the proportions of nonsmoking and smoking mothers as well as nonsmoking and smoking fathers were tested with the standard normal deviate test. The differences between proportions of mothers and fathers with basic or upper secondary degree education and mothers and fathers with higher education were tested likewise (Table 1).

The primary outcome measure was the number of respondents who had a diagnosis of asthma, allergic rhinitis, and/or atopic dermatitis made by a physician, backed up by a corresponding analysis of self-reported symptoms. Separate analyses were performed to compare the ages of the children at the time of diagnosis (asthma, allergic rhinitis, and/or atopic dermatitis) between the intervention and control CDCC participants. The possible increases in the risks of developing atopic dermatitis, allergic rhinitis, and asthma were evaluated according to diagnoses made by a physician or to corresponding self-reported symptoms after the hygiene intervention by calculating relative risks with 95% confidence intervals between the hygiene intervention and control groups. Ages at the time of diagnosis of asthma, allergic rhinitis, or atopic dermatitis were compared between the intervention and control participants with cumulative hazard curves and log-rank test. The data were analyzed using SPSS for Windows, version 12.0 (SPSS, Inc, Chicago, Illinois).

Those who replied to the questionnaire differed from those who did not reply in having a higher average level of parental education, less parental smoking, more episodes of acute otitis media, and more days receiving antimicrobial agents when they were younger than 2 years. Most importantly, however, the intervention respondents and nonrespondents and control respondents and nonrespondents did not differ in their background demographic data (Table 1). Thus, the subjects who responded were representative of their initial group.

METHODS

STUDY DESIGN

Altogether, 1376 children had participated in the hygiene intervention trial in 1991 and had been in the follow-up for at least 2 months. Details of the infection prevention program and its implementation have been published. In brief, the hygiene intervention was conducted in 10 CDCCs, while 10 other randomly allocated centers matched with them for size and geographical location served as controls. The basic background data of the study population were collected in both 1991 and 2003. The intervention included several steps, of which the most important was the improvement of hand hygiene by the use of an alcohol-based hand rub. In 2003, we conducted a follow-up survey 12 years after the randomized hygiene intervention to compare the development of atopic dermatitis, allergic rhinitis, and asthma between these 2 groups of adolescents.

©2007 American Medical Association. All rights reserved.

Figure 1. Study profile. CDCC indicates child day care center.

1376 Children took part in randomized infection prevention program in 1991 and 1992

Children in the intervention CDCCs had 15% fewer days with symptoms of infections and 24% fewer prescriptions for antibiotics than those in the control CDCCs

A follow-up questionnaire was sent to 1354 adolescents in 2003

6 Had moved abroad
4 Had died
12 Had unknown address

426 Did not reply
227 In intervention CDCCs
199 In control CDCCs

Comparison of background data

928 Replied

Table 1

Comparison

Study profile. CDCC indicates child day care center.
Asthma was diagnosed by a physician in 48 of the 481 respondents (10%) from the intervention CDCCs, with markedly fewer infections, and 46 of the 447 controls (10%), with no reduction in the infections (relative risk, 1.0; 95% confidence interval, 0.7-1.4). Similarly, there were no differences in the numbers who had developed allergic rhinitis or atopic dermatitis as diagnosed by a physician or who had reported asthma, allergic rhinitis, or atopic dermatitis symptoms (Table 2). There were no significant differences in the background data between the respondents who had been randomly assigned to the intervention and control CDCCs with regard to their family history of atopic diseases, duration of breastfeeding, or numbers of siblings (Table 3).
COMMENT

These results indicate that the successful prevention of respiratory tract and enteric infections during early childhood does not increase later allergic morbidity. No differences were found here in the development or clinical course of asthma, allergic rhinitis, or atopic dermatitis in adolescence between those who had fewer infections and those who had experienced markedly more infections.

The magnitude of the reduction in infections and the duration of the intervention in our randomized hygiene intervention trial should have led to an increase in asthma rates if the hygiene hypothesis were to apply to common childhood infections. The mean annual number of acute respiratory tract illnesses in children aged 0 to 4 years has been found to be 4.9 in a 11-year community survey.20 Child day care increases the risk of common colds as compared with children cared for at home by approximately 70% in the 1-year age group and by 10% in the 3-year age group.21 Overall, the risk of acute otitis media in day care is 2.5 relative to home care.22 Our infection prevention program succeeded in reducing infectious morbidity significantly, even though it was not reduced to the home care level. For the intervention group as compared with the control group, the number of days spent with any infection symptom was 16% fewer, the diagnoses of otitis media were 27% fewer, and prescriptions for antimicrobials were 24% fewer.17 As our intervention lasted 15 months, we believe that this duration would have been long enough to show at least some effect on the occurrence of asthma, but this was not seen.

The response rate for the follow-up questionnaire was 68%, ie, about two-thirds of the former participants responded. We were able to evaluate possible differences between the respondents and nonrespondents using the background data collected 12 years earlier showing that the respondents had higher levels of parental education and more days receiving antimicrobial agents when they were younger than 2 years than the nonrespondents. Most importantly, however, the intervention and control respondents and nonrespondents did not differ in their background characteristics. Thus, it is unlikely that data from those not responding would have changed our results.

The association between asthma and respiratory tract infections is difficult to analyze because asthma itself may cause symptoms such as cough and rattly chest that resemble viral respiratory tract infections.23 On the other hand, the symptoms of rhinoviral infections, the most common cause of respiratory tract infection, are often markedly different among individuals with normal airway reactivity and those with hyperreactive airways.24-26 Therefore, the viral respiratory tract disease of an individual with asthma is more likely to be pro-

---

Table 3. Background Characteristics of Respondents to the Follow-up Questionnaire in 2003

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intervention Group (n=481)</th>
<th>Control Group (n=447)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>15.2 (1.9)</td>
<td>15.2 (1.9)</td>
</tr>
<tr>
<td>Duration of breastfeeding in infancy, mean (SD), mo</td>
<td>7.9 (5.0)</td>
<td>7.3 (4.4)</td>
</tr>
<tr>
<td>Children, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boys</td>
<td>239 (50)</td>
<td>221 (49)</td>
</tr>
<tr>
<td>Maternal smoking during pregnancy</td>
<td>56 (12)</td>
<td>63 (14)</td>
</tr>
<tr>
<td>First child in the family</td>
<td>215 (47)</td>
<td>210 (52)</td>
</tr>
<tr>
<td>0 Siblings</td>
<td>47 (12)</td>
<td>29 (8)</td>
</tr>
<tr>
<td>1 or 2 siblings</td>
<td>312 (78)</td>
<td>299 (80)</td>
</tr>
<tr>
<td>Pet(s) at home</td>
<td>253 (53)</td>
<td>217 (49)</td>
</tr>
<tr>
<td>Long-term disease</td>
<td>29 (6)</td>
<td>23 (5)</td>
</tr>
<tr>
<td>Continuous or intermittent medication</td>
<td>22 (5)</td>
<td>16 (4)</td>
</tr>
<tr>
<td>Mothers with given disease, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>52 (11)</td>
<td>50 (11)</td>
</tr>
<tr>
<td>Allergic rhinitis</td>
<td>115 (24)</td>
<td>116 (26)</td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td>77 (16)</td>
<td>84 (19)</td>
</tr>
<tr>
<td>Food allergy</td>
<td>83 (18)</td>
<td>71 (16)</td>
</tr>
<tr>
<td>Fathers with given disease, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>41 (9)</td>
<td>34 (8)</td>
</tr>
<tr>
<td>Allergic rhinitis</td>
<td>66 (15)</td>
<td>70 (17)</td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td>59 (14)</td>
<td>45 (12)</td>
</tr>
<tr>
<td>Food allergy</td>
<td>28 (6)</td>
<td>38 (10)</td>
</tr>
<tr>
<td>Children with siblings having given disease, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>57 (15)</td>
<td>43 (12)</td>
</tr>
<tr>
<td>Allergic rhinitis</td>
<td>109 (29)</td>
<td>111 (31)</td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td>116 (32)</td>
<td>113 (32)</td>
</tr>
<tr>
<td>Food allergy</td>
<td>101 (28)</td>
<td>91 (26)</td>
</tr>
</tbody>
</table>

a The respondents are grouped according to their assignment in the infection prevention trial.
b Data from the previous trial.
c Allergic diseases excluded.
d Medications for allergic diseases excluded.
longed or to be classified as a lower respiratory tract infection than an upper respiratory tract infection. This kind of misclassification bias is well demonstrated by Illi et al., who reported that the number of upper respiratory tract infections in infancy was associated with a decreased risk of asthma at age 7 years, whereas the number of lower respiratory tract infections was associated with an increased risk of asthma. Thus, when infections of the upper and lower respiratory tract are added together, the association with asthma disappears. A similar misclassification bias is a possible explanation for the finding of an association between antibiotic exposure and an increased risk of developing allergic disease, as the prolonged and more severe lower respiratory tract infections are more easily treated with antimicrobials. These differences in the clinical courses of viral respiratory tract infections in individuals with and without asthma can easily lead to different treatments and clinical diagnoses, resulting in misclassification biases in observational surveys aimed at evaluating the association of allergic diseases with infections.

Reporting bias is another effect that may confound observational surveys of infections and asthma. As children with airway hyperreactivity may have symptoms leading to visits to health care centers more often than healthy children with the same viral infections, their infectious episodes will be recalled and reported more exactly. Accordingly, Nystad et al.20 found recurrent infections to be mediators of a risk of asthma in early childhood. One cannot rule out the possibility of reporting bias in their survey, however.

In the observational study by Ball et al., attendance at day care during the first 6 months of life protected against the development of asthma, as did the presence of 1 or more older siblings at home. Attendance at day care during the first 6 months of life is rare in Finland because of the long maternity and paternity leave, and the youngest children attend day care at 9 to 12 months of age. Children have only a few infections while being cared for at home and start to have numerous infections immediately after beginning to attend a CDCC. In our study population, the mean age of those attending CDCCs was 3.3 years. In this age group, a reduction in the rates of common infections had no effect on atopic diseases 12 years later.

We have shown that a reduction in infections in children attending CDCCs can be achieved by simple infection prevention practices.23 This reduction in morbidity has a great impact on the quality of life in families with small children, and at the same time it reduces the economic burden. We can now say that it proved to be safe because it had no effect on later atopic morbidity.28 Our results are comparable to those of 2 recent cohort studies27,29 that show no inverse association between the number of infection episodes and the occurrence of atopic diseases later in childhood.

CONCLUSIONS

Our analysis of the association of asthma, allergic rhinitis, and atopic dermatitis with infections in the randomized study design enabled us to avoid both misclassification and reporting biases. In these analyses, changes in the occurrence of respiratory and gastrointestinal tract infections did not affect the development of allergic disorders. Our findings do not support the original hygiene hypothesis.

Accepted for Publication: April 29, 2007.
Correspondence: Teija Dunder, MD, Department of Pediatrics, University of Oulu, PO Box 5000, FIN-90014 Oulu, Finland (teija.dunder@oulu.fi).

Author Contributions: Study concept and design: Dunder, Tapiainen, and Uhari. Acquisition of data: Dunder, Tapiainen, and Uhari. Analysis and interpretation of data: Dunder, Tapiainen, Pokka, and Uhari. Drafting of the manuscript: Dunder, Pokka, and Uhari. Critical revision of the manuscript for important intellectual content: Dunder, Tapiainen, and Uhari. Statistical analysis: Dunder, Pokka, and Uhari. Obtained funding: Uhari. Administrative, technical, and material support: Dunder, Tapiainen, and Uhari. Study supervision: Uhari.

Financial Disclosure: None reported.

Funding/Support: This study was supported in part by a grant from the Päiviikki and Sakari Sohlberg Foundation and the Department of Paediatrics and Adolescence, Oulu University Hospital, Oulu, Finland.

REFERENCES


“When kids post personal info—from political opinions to tales of debauchery—on sites like MySpace, they’re creating a kind of shadow résumé that could follow them around for decades.”


©2007 American Medical Association. All rights reserved.