Association between infant swimming and rhinovirus induced wheezing

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Short title: Infant swimming and rhinovirus-induced wheezing

Abstract

Aim: Infant swimming has been considered as a risk factor for wheezing, but the role that respiratory viruses play is unclear. We explored the effects of infant swimming on the risk of all wheezing illnesses and wheezing associated with rhinoviruses.

Methods: We followed up a birth cohort of 1,827 children until 17-months-of-age, collecting data on infant swimming, other risk factors and physician diagnosed bronchiolitis or recurrent wheezing. Viral diagnostics were performed in a subset of children with all respiratory tract infections.

Results: Data on infant swimming were obtained for 1,038 children, with viral follow up for 635 children. At least one wheezing illness was documented in 45/469 (9.6%) swimming children versus 39/569 (6.9%) non-swimming children ($p = 0.11$) and rhinoviruses were associated with wheezing in 11/296 (3.7%) swimming children versus 4/339 (1.2%) non-swimming children ($p = 0.04$). In adjusted logistic regression analyses, swimming had an odds ratio of 1.71 ($p = 0.05$) for bronchiolitis and 3.57 ($p = 0.06$) for rhinovirus associated wheezing. An association between infant swimming and rhinovirus associated wheezing was detected for children with atopic eczema ($p = 0.006$).

Conclusion: There may be a link between infant swimming and rhinovirus induced wheezing illnesses in atopic infants.

Keywords: bronchiolitis, respiratory syncytial virus, respiratory tract infection, rhinovirus, wheeze

Key Notes

- Infant swimming has been considered as a risk factor for wheezing, but the role that respiratory viruses play is unclear.
- We followed up a birth cohort of 1,827 children until 17-months-of-age, collecting data on infant swimming for 1,038 children, plus other risk factors and physician diagnosed bronchiolitis or recurrent wheezing.
- Our findings suggest that there may be a link between infant swimming and rhinovirus induced wheezing illnesses in atopic infants.

Introduction

Taking babies swimming has become a popular practice for families in many countries. However, authors of the so-called 'chlorine hypothesis' suggest that swimming in chlorinated pools at a young age could increase the risk of wheeze or asthma in childhood (1, 2). It is assumed that substances such as trichloramine (NCl_3), which is an irritant and volatile by-product of chlorination, might have a detrimental influence on lung epithelium integrity. Trichloramine arises from the interaction of chlorine with organic matter, such as sweat and urine, brought into the pool by bathers. Using different pneumoproteins as markers, Bernard et al found that children's regular pool attendance was associated with a dose-dependent increase in lung epithelium permeability and an increased risk of developing asthma, particularly in combination with other risk factors such as atopy or parental smoking (1-5). Increased risk of bronchiolitis has also been reported (6).

Bronchiolitis, which is defined as the first wheezing illness under the age of one or two years, depending on the study, is most frequently caused by the respiratory syncytial virus (RSV). However, the human rhinovirus (HRV) also causes bronchiolitis, particularly in children older than six months (7-10). HRV is often detected in association with recurrent wheezing episodes, and infants with atopy and underlying airway eosinophilic inflammation are at risk of developing wheeze during rhinovirus infections (9). Bronchiolitis and recurrent wheezing are associated with an increased risk of developing asthma and the risk of asthma is higher after HRV bronchiolitis than after RSV bronchiolitis (11, 12).

Few prospective cohort studies have been undertaken to examine the effects of swimming in chlorinated pools during infancy. In the Norwegian Mother and Child Cohort Study, children with atopic mothers who attended baby swimming

sessions had an increased risk of wheeze (13). In another cohort study conducted in Germany, higher incidences of respiratory infections were reported among infants who practiced baby swimming, with no increased risk concerning asthma or other atopic illnesses (14). No conclusive evidence between the association of childhood swimming pool use and prevalence of asthma was found in a meta-analysis (15). There is a need for longitudinal studies that take into consideration the viral causes of wheezing associated with baby swimming.

In this study, we examined the hypothesis that infant swimming affects the overall risk of wheezing illnesses, and in particular HRV associated wheezing, possibly in combination with other factors.

Methods

Study population and conduct

We used the cohort of the observational Steps to the Healthy Development and Well-being of Children Study, which consists of 1,827 children from 1,797 families, including 923 who were followed for viral aetiology of all respiratory tract infections from birth up until the age of two years. In this study we collected data on wheezing illnesses until 17-months-of-age. Recruitment occurred in two stages from women with a live birth between 1 January 2008 and 31 March 2010 in the Southwest Finland Hospital District (n = 9,811). During the first stage, 1,387 families were recruited through community midwifery services during pregnancy and a further 410 families joined the study soon after the birth of their child (Figure 1) (16). The Ethics Committee of the Hospital District of Southwest Finland approved the study protocol. The parents of the participating children gave their written, informed consent.

Parents completed detailed questionnaires when their children were specific ages. Information on background covariates was collected at gestational week 20 and information on physician detected atopic eczema or wheeze at the age of 13 months (Figure 1). The latter questions were based on the International Study of Asthma and Allergies in Childhood (17). Personal study diaries contained direct physician reported information from physician visits that did not take place in our study clinic and they specifically stated whether wheezing was part of the presentation. Symptoms of respiratory tract infections were also recorded on a daily basis in the diaries and these provided us with information on symptoms, such as coughs, rhinorrhea, fever and wheeze, detected by parents. Fever was defined as a temperature above 38 °C. Families were invited to attend a study clinic for routine annual visits, starting from the age of 13 months. In practice, the first visit took place for all children between the ages of 13 and 17 months.

Data on baby swimming practices were obtained by sending out an additional internet questionnaire, which covered frequency, duration and the age when the infant started swimming. Some families could not be contacted by e-mail, so an equivalent questionnaire was posted to them. At this point the children were between the ages of 13 months and three years and five months.

We received 1,038 (57%) answers to the 1,827 infant swimming questionnaires and 635 of the children were included in the detailed follow up of infections and their aetiology (Figure 1). Participants in this group were advised to visit our study clinic with even minor respiratory infections, thereby enabling us to obtain direct clinical information using a structured case form that was completed by the responsible physician. During medical consultations for wheezing illnesses or other acute respiratory infections we obtained two nasal swabs, one from each nostril, for

respiratory virus analysis. Alternatively, parents had the option to collect nasal swabs at home and send them to the laboratory by mail.

Respiratory virus detection

The nasal swabs were suspended in phosphate buffered saline and nucleic acids were extracted from the specimens by NucliSense easyMag (BioMerieux, Boxtel, Netherlands) or MagnaPure 96 (Roche, Penzberg, Germany) automated extractor. Extracted ribonucleic acid was reverse transcribed and the complementary deoxyribonucleic acid amplified using real-time polymerase chain reaction (PCR) for HRV, enteroviruses and RSV as described earlier (18), with the modification that proprietary dual label probes were included into the PCR mix for differentiation of the virus-specific amplicons.

Outcomes

The primary outcomes of the study were bronchiolitis regardless of aetiology and HRV associated wheezing. Documentation of bronchiolitis or wheezing was based on clinical records obtained at visits to the study clinic or on physician reported symptoms and diagnosis recorded in the study diary during consultations elsewhere. Secondary outcomes were RSV positive bronchiolitis and the number of days per year with rhinorrhea, cough or fever recorded in the symptom diary.

Definition of bronchiolitis and wheezing

Bronchiolitis was defined as the first physician detected acute respiratory infection with expiratory wheeze or expiratory obstruction (prolonged expirium, increased respiratory effort/ use of accessory muscles, increased breath rate) not related to laryngitis or pneumonia. Recurrent wheezing episodes were diagnosed according to similar criteria.

Collectively, bronchiolitis and recurrent wheezing were referred to as wheezing illnesses. Diagnoses had to be based on clinical findings, not on the history alone, and all diagnoses were performed before the age of 17 months.

Risk factors

Infant swimming was defined as any swimming activity intended specifically for infants in an indoor facility. We included in the analyses swimming before the age of 17 months. In addition to infant swimming, the following covariates were included as potential risk factors: family income, maternal age, parental smoking, older siblings, sex, prematurity (gestational age <37 weeks), parental asthma and atopy in the child. Atopy was defined as parent-reported, physician-detected atopic eczema by the age of 13 months.

Statistical analysis

The effects of infant swimming and other potential risk factors on the risk of bronchiolitis were first estimated by using the Chi-square test (Fisher's exact test for low numbers of observations) and unadjusted binary logistic regression analysis. Then, adjusted binary logistic regression was performed with all above-mentioned risk factors except family income and maternal age, which were not found to have an effect and were not included in the final model. Adjusted odds ratios (aOR) with 95% confidence intervals (CI) were determined. In the next step, the effect of infant swimming on the risk of HRV associated wheezing was estimated by logistic regression with similar adjustments for covariates. Furthermore, the association between infant swimming and HRV-associated wheezing was analyzed by Chi-square or Fisher's exact tests in data stratified by reported atopy. The effect of infant swimming on parent reported

respiratory symptoms documented as the number of days per year with symptoms was analyzed by using the t-test. As there were no differences between the groups, no further analysis was performed. All statistical analyses were carried out using SAS version 9.1 (SAS, Cary, NC, USA).

Results

Characteristics and outcomes in swimming and non-swimming children

Of 1,038 children included in the study, 469 (45%) practiced infant swimming. Of these, 345 (81%) started swimming at the age five months or younger and 405 (86%) practiced swimming at least once every two weeks. Descriptive characteristics of the study population, distribution of potential risk factors for bronchiolitis, rates of bronchiolitis and respiratory tract symptoms in swimming and non-swimming groups are shown in Table 1. There was a difference in maternal age between the groups, but the proportion of very young mothers, less than 21-years-of-age, was only 0.4% for infants with reported swimming. As low monthly income was more frequent in the families of non-swimming children, it was not considered as a confounding factor between swimming and wheezing episodes.

The incidence of physician-diagnosed bronchiolitis before the age of 17 months was 8% of the whole study population. There was no significant difference in the overall incidence of bronchiolitis between the swimming and non-swimming children, but wheezing illnesses caused by HRV were more common in swimming children: 11/296 (3.7%) versus 4/339 (1.2%) ($p = 0.04$). Symptoms of respiratory tract infections (cough, rhinorrhea or fever) were equally common in swimming children and in those not swimming (Table 1).

Risk factors for bronchiolitis

In unadjusted analyses, the presence of atopic eczema in the child was associated with the risk of developing bronchiolitis (p = 0.001) (Table 2). Using adjusted logistic regression analysis, the association between practice of infant swimming and bronchiolitis was at the limit of statistical significance (aOR, 1.71; 95% CI, 0.99–2.95; p = 0.05). The presence of atopic eczema in the child was associated with bronchiolitis (aOR, 2.79; 95% CI, 1.56–4.95).

Risk factors for wheezing illness caused by HRV were calculated similarly by using adjusted logistic regression, excluding co-infections by HRV and RSV, but the low number of children with defined viral aetiology of wheezing episodes decreased the statistical power of this analysis. The highest odds ratios were detected for infant swimming (aOR, 3.57; 95% CI, 0.94–13.52; p = 0.06) and for atopic eczema in the child (aOR, 3.36; 95% CI, 1.02–11.05; p = 0.05).

Viral aetiology of wheezing illnesses in swimming and non-swimming children

In the above-described results, bronchiolitis in general and wheezing illnesses caused by a specific virus were analysed as dichotomous variables for each child. For comparison of the viral causes of wheezing illnesses in swimming and non-swimming children, we included all cases of wheezing episodes with a sample taken for PCR analysis. As some children experienced recurrent wheeze, there were 64 cases of wheezing illnesses with a specified viral aetiology in 47 children. The distribution of causative viruses in swimming and non-swimming children is shown in Figure 2. As the HRV associated wheezing illnesses were of particular interest, we compared the proportions of HRV positive and negative wheezing episodes in all swimming and non-swimming children, and in groups stratified by the presence of atopic eczema (Table 3). The proportion of

HRV associated wheezing episodes was significantly higher only in swimming children with atopy ($p = 0.006$).

Discussion

Our results clarify the relation between infant swimming and wheezing illnesses by demonstrating that swimming seems to be associated specifically with HRV bronchiolitis. Children with atopy were at risk of developing HRV associated wheeze if they attended infant swimming programs.

Allergic sensitization has been linked to wheezing associated with rhinoviruses, but not other viruses, and allergic inflammation and its effects on lung epithelium integrity have been proposed as pathophysiological mechanisms (19). Basal cells within the airway epithelium have an increased susceptibility to HRV infection, a finding that explains the importance of airway epithelium integrity (20). Decreased levels of the pneumoprotein CC16, which is also thought to protect from bronchiolitis, have been documented in connection with swimming pool attendance (4). It has also been hypothesised that swimming related disruption of lung epithelium integrity may lead to allergic sensitisation (3). These earlier findings are in a good accordance with our data showing that swimming infants with atopy are a high-risk group for HRV associated wheezing. However, the interactions between swimming, atopy, and wheezing illnesses may be more complex, since swimming has been suggested to increase also the risk of atopy (21).

Trichloramine has been suggested as a major culprit in terms of wheezing illnesses and their possible association with swimming. Trichloramine concentrations are determined by a number of factors including water-chlorination levels, water temperature, ventilation of the facility and organic contamination of water, which in

turn depends on the number of bathers and swimming hygiene measures. Other pathophysiological mechanisms involving chemical or infection related stressors may also play an important role in the association between swimming and HRV associated wheezing. As with other social activities, attendants in infant swimming programs may be assumed to be in close physical contact with each other and the transmission of respiratory viruses may be facilitated. However, in our study there was no difference in the total number of days with symptoms of respiratory infection between swimming and non-swimming children, which suggests that infant swimming programs are not important in the transmission of viruses.

In our cohort more affluent families and families with younger mothers were more likely to participate in infant swimming practices. Extremes of young maternal age and smaller proportions of maternal post-secondary education, which may be connected to family income, have elsewhere been described as risk factors for bronchiolitis (10). In this study, no confounding effects could be demonstrated for family income and maternal age. Otherwise, our cohort is thought to represent the Southwest Finnish population well, but the parental education and family income of participating families was higher than average (16). Questionnaire data were not received from all participants, which might cause selection bias. However, a comparison of background variables between responders and non-responders was performed for the data collected at 13-months-of-age and there were only minor differences between the groups (16). Day care was not regarded as a confounding factor since for most of the ages included in our follow-up period most children were cared for at home. Children usually start day care at around the age of one year in Finland.

Although our cohort was relatively large, this study had insufficient power to produce statistical significance for risk factors with moderately low odds ratios. Due

to missing data, the adjusted logistic regression analysis could only be carried out for 668 children. In our cohort the incidence of physician-diagnosed bronchiolitis was relatively low (8%) compared with incidences of 10 to 30% for the first year of life in other studies (6, 10).

We assessed our cohort longitudinally for wheezing illnesses and other respiratory tract infections up to the age of 17 months. There, we had a relatively short time of follow up. However, with the exception of a Norwegian study (13) we are not aware of any large prospective studies that have been carried out looking at similarly young populations. Schoefer et al carried out a prospective birth cohort study, but exposure data were obtained years later (14). We consider our comparatively large cohort in combination with detailed follow up one of the main strengths of our study. Identification of causative viruses for wheezing illnesses in association with infant swimming is unique to our study.

In conclusion, infant swimming may play some role as a risk factor for wheezing, although the overall effect on incidence of bronchiolitis was statistically insignificant in the present study. Interestingly, our results suggest HRV as a pathophysiological link between infant swimming and wheezing illnesses in atopic infants. These findings are, however, based on a small number of cases and have to be interpreted with caution.

Abbreviations

aOR, adjusted odds ratio

CI, confidence interval

HRV, human rhinovirus

PCR, polymerase chain reaction

RSV, respiratory syncytial virus

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Table 1. Characteristics and outcomes in non-swimming and swimming children.

Variable	Non-swimming	Swimming	p value
Baseline variables			
Males	288/569 (51)	245/469 (52)	0.60
Atopic eczema in child	84/427 (20)	57/336 (17)	0.34
Parental asthma	72/466 (16)	71/405 (18)	0.41
Prematurity (<37 weeks' gestation)	28/569 (5)	20/469 (4)	0.62
Family income <2000 euro/ month	134/559 (24)	72/453 (16)	< 0.01
Maternal age at birth of child ≤30 years	251/568 (44)	250/469 (53)	< 0.01
Parental smoking[a]	121/492 (25)	85/428 (20)	0.86
Older siblings	313/569 (55)	176/ 468 (38)	< 0.01
Bronchiolitis	39/569 (7)	45/469 (10)	0.11
Outcomes within virologic follow-up cohort (n = 635)			
Bronchiolitis	20/339 (6)	27/296 (9)	0.12
HRV-associated wheezing	4/339 (1)	11/296 (4)	0.04
RSV-associated wheezing	12/339 (4)	10/296 (3)	0.91
HRV and RSV positive wheezing	2/339 (1)	0/296 (0)	ND
Enterovirus-associated wheezing	1/339 (0)	0/296 (0)	ND
Days with cough, rhinorrhea or fever / year	44 +/- 35	44 +/- 34	0.93

Data are presented as n/number in the group (%) or mean +/- SD. Lower numbers in the groups for some baseline variables are due to missing questionnaire data.

p values were obtained by Chi-square test or t-test as applicable.

[a]Parental smoking includes all cases with reported smoking of at least one parent either during pregnancy or after birth of the child.

HRV = human rhinovirus; ND = not determined; RSV = respiratory syncytial virus.

Table 2. Risk of bronchiolitis according to infant swimming and other variables.

Variable	Unadjusted analyses			Adjusted logistic regression (n = 668)		
	n	Bronchiolitis, n (%)	p value	aOR	95% CI	p value
Infant swimming	1038		0.11	1.71	0.99-2.95	0.05
Yes	469	45 (10)				
No	569	39 (7)				
Atopic eczema	763		0.001	2.79	1.56-4.95	< 0.001
Yes	141	23 (16)				
No	622	46 (7)				
Parental asthma	871		0.16	1.59	0.82-3.08	0.17
Yes	143	17 (12)				
No	728	60 (8)				
Parental smoking[a]	920		0.75	1.42	0.76-2.67	0.28
Yes	206	17 (8)				
No	714	64 (9)				
Siblings	1037		0.15	1.43	0.83-2.46	0.20
Yes	489	46 (9)				
No	548	38 (7)				
Family income	1012		0.16			
<2000 euro/ month	206	12 (6)				
>2000 euro/ month	806	71 (9)				
Maternal age at birth of child	1037		0.58			
≤30 years	501	43 (9)				
>30 years	536	41 (8)				

Differences in numbers of subjects are due to missing questionnaire data.

[a]Parental smoking includes all cases with reported smoking of at least one parent either during pregnancy or after birth of the child.

aOR = adjusted odds ratio; CI = confidence interval.

Table 3. Association of infant swimming with HRV positive wheezing in all children and in those with or without atopic eczema.

	Wheezing illnesses with specified aetiology				
	No. of children	No. of cases	HRV positive, n (%)	HRV negative, n (%)	p value
All children (n = 635)					
Swimming	27	37	14 (38)	23 (62)	0.06
Non-swimming	20	25	4 (16)	21 (84)	
With atopic eczema (n = 98)					
Swimming	5	8	6 (75)	2 (25)	0.006
Non-swimming	7	11	1 (9)	10 (91)	
Without atopic eczema (n = 406)					
Swimming	17	23	6 (26)	17 (74)	0.99
Non-swimming	10	11	2 (18)	9 (82)	

HRV and RSV co-infections (n = 2) were excluded from the analysis.

p values were obtained by Chi-square or Fisher's test as applicable.

HRV = human rhinovirus

Figure legends

Figure 1. A flow chart of study cohort.

Figure 2. Viral aetiology of bronchiolitis in children who swam and in those who did not swim.

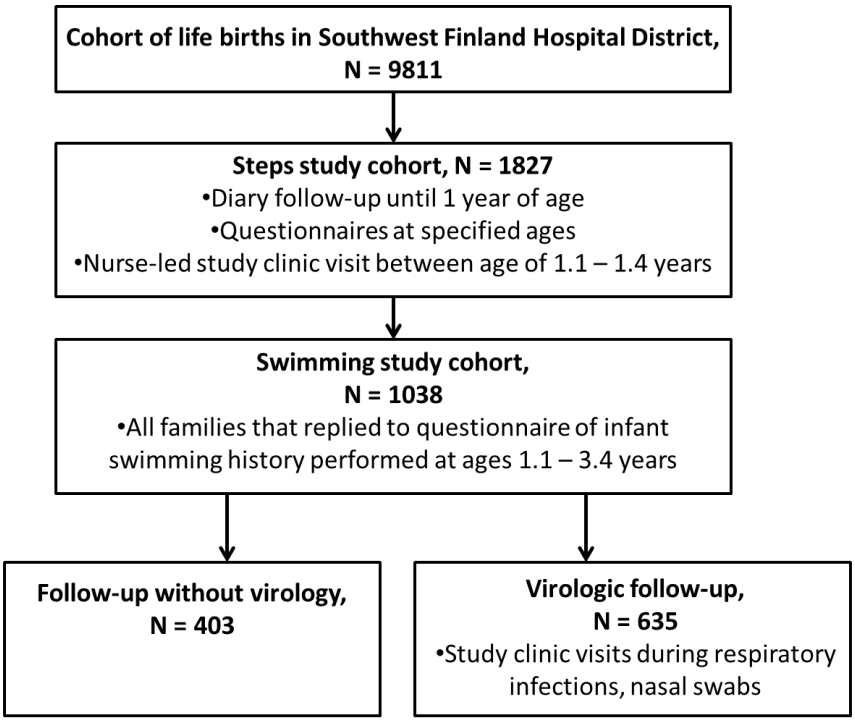
Cohort of life births in Southwest Finland Hospital District, N = 9811
Steps study cohort, N = 1827
•Diary follow-up until 1 year of age
•Questionnaires at specified ages
•Nurse-led study clinic visit between age of 1.1 – 1.4 years
Swimming study cohort, N = 1038
•All families that replied to questionnaire of infant swimming history performed at ages 1.1 – 3.4 years
Follow-up without virology, N = 403
Virologic follow-up, N = 635
•Study clinic visits during respiratory infections, nasal swabs

Figure 1.

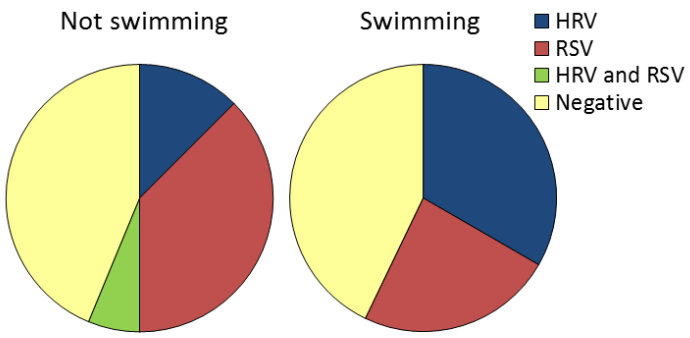

Figure 2.