Medical Faculty of Martin Luther University Halle-Wittenberg

How often are children affected by acute respiratory infections?

Frequency and symptom burden of acute respiratory infections in the first two years of life by using symptom diaries in the LöwenKIDS study

Dissertation

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Abstract

Background: Acute respiratory infections (ARIs) represent the most common illnesses in the first two years of life worldwide. Most ARIs are usually not severe, but they contribute to numerous physician consultations, antibiotic prescriptions, and socio-economic burden. Initial findings also show possible associations between ARIs and chronic diseases, like Asthma. The reported frequencies of ARI in infancy vary widely and have been insufficiently studied in Germany so far. In particular, birth cohort studies with the use of symptom diaries represent an effective design and tool to assess the frequency and full burden of disease.
The goal of this work is to give an overview of birth cohort studies recording ARIs by using symptom diaries, starting at birth, and to determine the frequency of ARI and possible factors associated with the frequent occurrence of ARI in the first two years of life.

Methods: A systematic scoping review (ScR) using four electronic databases (PubMed, Embase, CINAHL, and Web of Science) was conducted at the beginning to give an overview. To present the burden of ARI, data from the LöwenKIDS birth cohort study collected collaboratively by the LöwenKIDS team including the author of this work was analyzed. The ongoing LöwenKIDS study recruited 782 newborns from November 2014 to February 2018 in five study regions in Germany. Analyses were limited to 288 participants with nearly complete diary entries before the covid pandemic. Descriptive analysis was based on longitudinal as well as cross-sectional data. Associated factors were identified using Poisson regression.

Results: The ScR showed that only 22 birth cohort studies worldwide used symptom diaries to identify respiratory infections starting from birth. The LöwenKIDS-cohort represents the youngest cohort and, together with the COPSAC cohort, one of the few that collected symptom diary data over six years. The analysis of respiratory infections demonstrated that on average 13.7 ARIs (SD: 5.2, median: 14.0, IQR: 10-17) were reported in the first two years of life, with a mean duration of eleven days per episode (SD: 5.8, median: 9.7, IQR: 7-14). ARIs occurred more frequently in the winter than in the summer, increased over the first year of life, remained stable through about the second year of life, and slowly declined towards the end. Attending daycare and having siblings was associated with an increased frequency of ARIs in the first two years of life, while exclusive breastfeeding for less than four months was associated with fewer ARIs compared to exclusive breastfeeding for a longer period.

Conclusion: This thesis gives an overview of birth cohort studies using symptom diaries and provides detailed insight into the symptom burden of ARI in children in Germany during the first two years of life.

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Referat

Hintergrund: Akute respiratorische Infektionen (ARIs) stellen weltweit die häufigsten Erkrankungen in den ersten zwei Lebensjahren dar. ARIs sind meist nicht schwerwiegend, führen dennoch zu zahlreichen Arztbesuchen, Antibiotikaverschreibungen und sozioökonomischen Belastungen. Die berichteten ARI Häufigkeiten variieren stark und sind bisher unzureichend in Deutschland untersucht. Geburtskohortenstudien mit Symptomtagebuch-Ansatz stellen ein wirksames Instrument dar, um die gesamte Krankheitslast zu erfassen.

Ziel dieser Arbeit ist es, einen Überblick über bestehende Geburtskohortenstudien zu geben, in denen ARIs mit Hilfe von Symptomtagebüchern erfasst wurden, und die Häufigkeit von ARIs sowie mögliche assoziierte Faktoren für das häufige Auftreten von ARIs in den ersten zwei Lebensjahren zu bestimmen.

Methoden: Zu Beginn wurde ein systematischer Scoping Review (ScR) unter Verwendung von vier elektronischen Datenbanken (PubMed, Embase, CINAHL und Web of Science) durchgeführt. Zur Darstellung der Krankheitslast durch ARI wurden Daten aus der LöwenKIDS-Geburtskohorte herangezogen. Die LöwenKIDS-Studie rekrutierte von 2014 bis 2018 782 Neugeborene in fünf Studienregionen in Deutschland. Die Analysen beschränkten sich auf 288 TeilnehmerInnen mit nahezu vollständigen Tagebucheinträgen vor der COVID-19-Pandemie. Die deskriptive Analyse basierte sowohl auf Längsschnitt- als auch auf Querschnittsdaten. Assoziierte Faktoren wurden mittels Poisson-Regression identifiziert.

Ergebnisse: Der ScR zeigte, dass weltweit nur 22 Geburtskohortenstudien Symptomtagebücher zur Erfassung von ARI ab der Geburt verwendeten. Die LöwenKIDS-Kohorte stellte dabei die jüngste Kohorte dar. Die Analyse der ARIs ergab, dass in den ersten zwei Lebensjahren durchschnittlich 13,7 ARIs (SD: 5,2, Median: 14,0, IQR: 10-17) detektiert werden konnten, mit einer durchschnittlichen Dauer von 11 Tagen pro Infektion (SD: 5,8, Median: 9,7, IQR: 7-14). ARIs traten häufiger im Winter als im Sommer auf und das mittlere Alter für die erste ARI-Episode betrug 91 Tage (IQR: 57–128, Mean: 107, SD: 84.5). Der Besuch einer Kindertagesstätte und das Vorhandensein von Geschwistern wurde mit einer erhöhten Häufigkeit von ARIs in den ersten zwei Lebensjahren in Verbindung gebracht, während ausschließliches Stillen über einen Zeitraum von weniger als vier Monaten mit weniger ARIs verbunden war, als ausschließliches Stillen über einen längeren Zeitraum.

Schlussfolgerungen: Diese Dissertation gibt einen ersten Überblick über Geburtskohortenstudien mit Symptomtagebuch-Ansatz und bietet einen detaillierten Einblick in die Symptomlast von ARIs bei Kindern in Deutschland während der ersten zwei Lebensjahre.

Langer, Susan: Wie häufig sind Kinder von akuten respiratorischen Infektionen betroffen? Häufigkeit und Symptomlast akuter respiratorischer Infektionen in den ersten zwei Lebensjahren, basierend auf Symptomtagebuchdaten der LöwenKIDS-Studie, Halle (Saale), Univ. Med. Fak., Diss., 79 Seiten, 2022

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List of abbreviations

ARE	acute respiratory episode(s)
ARI	acute respiratory infection(s)
ALRI	acute lower respiratory infection
AOM	acute otitis media
COPSAC	Copenhagen prospective studies on asthma in childhood
hMPV	human metapneumovirus
HRV	human rhinovirus
LRTI	lower respiratory tract infections
NHS	National Health Service
PIV	parainfluenza virus
RSV	respiratory syncytial virus
ScR	scoping review
URTI	upper respiratory tract infections
WHO	world health organization

1 Introduction and objectives

1.1 Disease burden of respiratory infections in early childhood

In general the immune system is constantly developing from birth to adulthood, especially during the neonatal period and the first years of life [1]. Before and immediately after birth, the infant´s immune system is supported by trans placental IgG antibodies from the mother. Thereafter, some immunity is transferred to the infant through the mothers' milk [2]. However, especially after birth, the immune system is challenged by exposure to various microorganisms. Infants come into contact with a variety of different pathogens throughout their lives, including pathogens that infect the respiratory tract to which they are particularly susceptible [3]. Because infants do not have the long-term protective immunity as adults, they are more susceptible to ubiquitous respiratory viruses such as influenza and respiratory syncytial virus (RSV) and suffer from recurrent respiratory infections [4].

1.1.1 Acute respiratory infections (ARI)

ARIs are considered among the most common childhood infections worldwide (WHO) in the first years of life and are the leading cause of death in children under five years, especially in developing countries, independent of pandemics [5-7].
According to the anatomical location, ARI can be categorized in upper respiratory tract infection (URTI) and lower respiratory tract infection (LRTI).

Upper respiratory tract infection (URTI) includes all conditions, upper respiratory tract affecting the larynx, pharynx, nose and ear and result in symptoms like the common cold with rhinorrhea, sore throat, sneezing, runny/ blocked nose, cough, hoarseness and sometimes fever. Accordingly, typical illnesses are rhinitis, sinusitis, otitis media, pharyngitis and laryngitis [8, 9]. Most ARIs are URTIs, which usually have shorter duration and milder course of infection than LRTIs [10, 11]. **Lower respiratory tract infection (LRTI)** accordingly includes all diseases of the lower respiratory tract, i.e. the trachea, the primary bronchi and the lungs. Typical diseases are bronchitis, bronchiolitis and pneumonia, which can be accompanied by symptoms such as tachypnea, wheezing, severe cough, fever and shortness of breath [8]. It occurs less frequently, but with considerably more severe symptoms than URTI [9].

1.1.1.1 Typical viruses and bacteria in ARI

Most commonly, ARIs are caused by viruses, like human rhinovirus (HRV), respiratory syncytial virus (RSV), influenza viruses, coronaviruses, parainfluenza viruses, adenoviruses, respiratory enteroviruses, human metapneumovirus hMPV, human bocavirus [12, 13]. HRV is observed as the most common causative agent of URTIs, which are usually mild in the form of a single infection [11, 14]. Severe courses may also occur in some cases, most of them are more likely to be due to coinfection of HRV and RSV[14]. Costa et al. also showed, however, that despite the predominance of symptoms of the upper respiratory tract (63.6%), more than one-third of HRV single infections also had symptoms of LRTIs, with many cases of bronchiolitis and wheezing bronchitis or bronchospasm [14]. The exact contribution of the presence of HRV varies widely between 10-80% of all URTIs in different settings [11, 13, 15-17]. In contrast to the most common agent of URTIs, respiratory syncytial virus (RSV) is the most commonly detected agent for LRTIs in children during the first two years of life [11, 18]. Almost all children undergo RSV infections in the first two years of life, while RSV is also the leading cause of hospitalization and death in children up to one year of age [14, 19]. A review by Li et al., combining data from 481 studies, estimated RSV-associated acute LRTIs in the first five years of life at 33 million worldwide in 2019 [20]. Among these, three to six million RSV-associated acute LRTIs were associated with hospitalization. A total of 101 400 RSV-associated deaths are estimated in the first five years of life. Approximately 6. 6 million RSV-associated acute LRTIs were shown in infants 0-6 months of age, and one to four million RSV-associated acute LRTIs were shown in hospitalizations. This included 45700 deaths attributable to RSV. Particularly in children aged 28 days to six months, three to six present of deaths can be attributed to RSV. More than 97% of RSV-associated deaths in all age groups occurred in low- and middle-income countries [20]. In addition to the aforementioned viruses, bacteria or even fungi can also lead to LRTIs. While bacteria pneumococcus is the most common pathogen in the occurrence of pneumonia, Haemophilus influenzae type b (Hib) is the second most common cause of bacterial pneumonia. Another agent for causing pneumonia is mycoplasma pneumoniae [21]. Pneumonia is an inflammation of the lung tissue and / or alveoli [5] and according to the WHO, approximately 740,180 children under the age of five died worldwide in 2019, accounting for about 14% of all deaths in children under the age of five years. Most deaths occur in South Asia and sub-Saharan Africa. Normally,

pneumonia can be treated with antibiotics, but only one third of children worldwide receive the antibiotic they need [5]. However, it is difficult to distinguish clinically between viral or bacterial pneumonia [22], mixed infections account for up to 30% of infections, which determine the patient's symptom burden [5, 23]. The risk of transmission is dependent on the specific virus [9].

1.1.1.2 Frequency of ARI

Different frequencies of development of ARI in the first two years of life are reported internationally [24-27]. The number of ARI depends on various factors, such as the selection of the survey method, the choice of the definition of ARI, the survey period, the selection of the study participants, the corresponding family history and the age of entry into a child care setting. Especially in Germany, the number of acute respiratory episodes (ARE) in early childhood has not been sufficiently studied. Many parents are concerned about the numerous infections in young children and suspect a weakened immune system, potentially leading to numerous unnecessary examinations, according to Grüber et al. [28]. In various studies internationally between three and nine ARI per year were found in early childhood for children up to two years of age [25, 26, 28-32]. Among all these studies, a German study showed the lowest reported number of ARI in the first year of life with 3.1 episodes, while von Linstow et al. from Denmark ranked the highest with 9.7 episodes in the first year of life [32]. In Germany, Grüber et al. were able to report reference values and thus the frequency of ARI for children born in 1990 based on questionnaires. Average numbers of ARI were recorded with 3.1 ARI in the first and 3.2 ARI in the second year of life. In preschool age (3-5 years), the frequency of infections decreased to 2.1 to 2.3 episodes per year and stabilized at one ARI per year in school age (6 -12 years) [28]. Similarly, in the Netherlands, De Hoog et al. show that the incidence of ARI peaked in the first two years of life and declined thereafter [33]. No frequency of ARI in children has been published in Germany since the study by Grüber et al. 2008 with data from 1990. ARI episodes were more common in the winter months showing a well-known seasonal variation of respiratory tract infections in the northern hemisphere [28, 32]. Individual information on the frequency of infections can indicate a particularly high susceptibility to infections and initiate further investigations.

1.1.1.3 ARI definition

As mentioned in 1.1.1.2, the frequency of ARI varies widely internationally and depends on several factors. Considering uniform study designs, such as prospective birth cohort studies with a uniform use of symptom diaries, which is a useful tool for assessing the comprehensive burden of disease caused by ARI in young children, one factor should still receive intensive consideration. The correct definition of ARI plays an important role. A research group led by Zoch et al. identified all definitions used to determine ARI in prospective symptom diary studies and compared them using their own data set [34]. They considered the definitions of Kusel et al. [30], Lambert et al. [35], von Linstow et al. [32], Samet et al. [29], Sarna et al. [25], and Douglas et al. [36]. They demonstrated that the use of different definitions of ARI episodes resulted in considerably differences in the number and duration of ARI episodes. In addition, they showed that the total number of ARI episodes and the total number of days with ARI varied by a factor of 1.69 and 1.53, respectively, between the lowest and highest number of duration used for ARI definition [34]. The analyses in the present work were based on the episode definition of Lambert et al., which was in the middle range of these variations and neither underestimated nor overestimated ARI episode frequency [24, 35]. We classified ARIs by distinguishing between A- and B-symptoms. An A-symptom was defined as fever, wheezing, wet cough, and doctor-diagnosed pneumonia or otitis media, whereby B-symptoms included dry cough, chills, sore throat, runny or blocked nose, increased need to sleep, loss of appetite, and increased attachment. We defined the beginning of an ARI episode as the occurrence of at least one A-symptom or a day with two B-symptoms. If there were no symptoms for three consecutive days, the episode ended and a new episode could begin. The occurrence of single/isolated B-symptoms were considered within an episode, but not as the start of an episode (P1).

1.1.1.4 Symptom burden and symptom duration

All children in all age groups experience ARI symptoms at some point and seek medical attention. In the prospective cohort study “Avon Longitudinal Study of Parents and Children (ALSPAC)” with 13,617 preschool children in the southwest of England, parents were regularly asked about their children's symptoms at six, 18, 30, 42, and 57 months of age. A total of 7865 (57.8%) parents responded to all five questionnaires [37]. A median of one or two different symptoms led to a consultation. The most common respiratory symptoms were cold and cough. For example, in the first six months of life, 88% of children showed typical cold symptoms, 65% cough, and 39% high temperature. Compared to the age of six to twelve months, 95% of the children showed cold symptoms, 84% cough and 68% high temperature in that time span. The latter proportions at six to twelve months of age remained relatively similar until the age of 54 months. Symptoms like wheezing, headache, rash and earache, affected at least 20% of children. Shortness of breath, ear discharge and respiratory failure were less common and affected no more than 10% of children in each age group [37].

In their prospective longitudinal study (n=263) in Australia, Kusel et al. observed symptom burden in children up to five years of age using a symptom diary and regular interviews with parents [30]. Similarly, cold symptoms, such as runny / stuffy nose were the most common symptom, lasting between four days and two weeks in approximately 69% of participants. More than 75% of ARI were associated with cough, which also lasted between four days and two weeks. One-third of ARIs were associated with fever above 38°C, which resolved between one and three days and were associated with rattling or wheezing. In 81% of these cases, symptoms resolved within seven days after onset [30]. Fifty-three percent of children in the first year of life experienced at least one LRTI, with most symptoms lasting one to two weeks and in some cases up to four weeks. In the first three years of life, a symptom duration of seven to 14 days could be measured. The duration of ARI also differed depending on age and whether there was a physician consultation. The children without consultation were less ill than the children with consultation. Children, who did not undergo medical consultation, experienced on average six days of symptoms, whereas children with consultation experienced on average nine days with symptoms. In children younger and older than three years, the average symptom duration was eleven and seven days, respectively. Similarly,

differences in symptom duration were evident between symptoms reported for URTI (twelve days) and symptoms for LRTI with eight days [30].

1.1.1.5 Physician consultation

Although most ARIs are not severe they still contribute to high numbers of outpatient visits [37]. Young children, in particular, often show symptoms and parents accordingly seek medical attention frequently, especially for respiratory problems [37]. Sands et al. showed in their study at a UK university hospital, that 44.4% of patients at a pediatric emergency department presented with respiratory symptoms and fever [38]. They also showed that of all children in this cohort aged zero to 15 years, 70% comprised the age zero to four years. In addition, Kusel et al. found that approximately 46% of ARI episodes were presented to a primary care physician. Of these, 23% were treated with antibiotics, and younger children with LRTI symptoms were more likely to see a primary care physician [30]. Hay et al. showed that parents with previous experience in their other children were less likely to see a doctor [37].

1.1.1.6 Hospitalization

A proportion of these physician consultations also resulted in hospitalizations. For example, one modeling study examined the global burden of hospitalizations for acute LRTI caused by RSV in young children in 58 countries in 2019. Results showed that the median RSV-associated ALRI hospitalization was 514 (339-866) hospitalizations per thousand children younger than five years. Large differences were found between countries. Nevertheless, a very high number of RSV-associated ALRI hospitalizations was observed in infants younger than one year in all countries (median 45%, IQR 32-56, of all hospitalizations for ALRI), especially in low-income countries (58% IQR 50-62) [39].

1.1.1.7 Prescription of antibiotics

Related to the frequency of respiratory infections in young children is the very frequent prescription of antibiotics. In a comparison of five European countries (2005-2008), Germany followed Italy in first place in the ranking, with an antibiotic prescription rate in children of 560.8 prescriptions per 1000 person-years. The Netherlands were ranked fifth, with a prescription frequency of 294.2 prescriptions per 1000 person-years [40]. Both nationally [41] and regionally [40], children with ARI are prescribed antibiotics too

frequently, although the infections are usually caused by viral pathogens [42]. The German Society for Pediatric Infectious Diseases (DGPI) also reported that generous and untargeted use occurs, especially for respiratory infections, and moreover half of the antibiotics administered are incorrectly dosed, resulting in the spread of antibiotic resistance [43]. In addition to possible adverse effects and risks, early application of antibiotics may be associated with an increased incidence of atopic dermatitis. Mubanga et al. showed this in their study, while Kusel et al. were unable to show these effects [44].

1.1.1.8 Absenteeism in education and work/ economic burden

When children fall ill with ARIs, they cannot attend daycare or school and also parents taking care of their sick children at home often cannot be present at work. Using two randomized controlled trials, Schot et al. found that ARI had major effects on the overall well-being of children who consulted a physician. More than 50% of children (n=149) did not attend daycare or school for several days after the doctor's consultation. Twenty-eight percent of mothers and 20% of fathers reported absence from work. Parent care was required in 48% of cases. A quarter of the parents reported that they had to make extra arrangements for the childcare [45].

The high incidence of ARIs represent a marked economic burden. In a model, Fendrick et al. estimated the cost of non-influenza ARI related to the entire U.S. population, at $40 billion annually. Direct medical costs are approximately 45% ($17 billion) of total costs, and indirect costs are approximately 55% ($22.5 billion) of total costs. Indirect costs include a significantly higher proportion of costs due to lost work time for the care of children than lost work time for an individual's own illness [46]. Specific to ARI in children, Hollinghorst et al. examined the costs associated with acute cough in otherwise healthy preschool children aged three to 59 months in an incidence- and prevalence-based cost-of-illness study from the perspective of the UK NHS (National Health Service) and parents and caregivers. They found that acute cough in children in this age range was associated with substantial costs for healthcare providers. Mean cost per episode to the NHS in September 2004 - May 2005 was: £27.43 (95% CI: £24.38 - £30.49), with a mean cost per episode to parents and carers of: £14.77 (£4.90 - £24.65). The annual cost to the NHS in the UK: was at least £31.5m (95% CI: £28.0m - £35.0m). The majority of these costs were incurred by physician consultations. For parents, there were some personal costs associated with travel and expenses for over-the-counter preparations, and there may be considerable loss of income [47].

1.1.2 Factors associated with frequency of ARI

There are several factors associated with the frequency of ARI in the first two years of life. Previous studies have found that, for example, increasing age (until the second year of life) [25, 28, 32], cold seasons [25, 28, 32], daycare attendance [25, 28, 32, 33, 48-50], presence of older siblings [28, 32, 48, 49], maternal smoking [48], maternal asthma [49] and male sex are associated with a higher incidence of ARI [49], whereas full breastfeeding is associated with a lower incidence of ARI [51-53]. For example, de Hoog et al. showed that children who go to daycare in the first year of life have considerably earlier URTI and acute otitis media (AOM) compared to children who were cared for at home. Overall, children who attend a daycare center between the ages of six and twelve months use more health resources overall than children not attending daycare. These children did show a higher incidence rate for URTI and AOM in the first year of life, but a lower incidence rate from four to six years of age [33].

1.1.3 Association to asthma bronchiale

The WHO states that events in early childhood, such as respiratory infections, which can affect the developing lung, increase the risk of asthma [54]. Similarly, other sources indicate that infections in the early childhood phase may influence the development of Asthma [55-57]. The exact mechanism is not yet known [58]. Toivonen et al. showed that children with asthma at the age of seven years have a 7.2-fold risk of having nine or more ARIs per year in the first two years of life, compared to children who did not develop asthma at the age of seven [26]. Similarly, children with asthma in the seventh year of life are more likely to have had more days with symptoms, especially wheezing, to have been hospitalized for severe wheezing, to have had pneumonia and a RSV infection than children without asthma. In contrast, children with asthma show a less frequent occurrence of ARI due to a rhinovirus infection [26]. In conclusion, an increased number of ARIs in the first 24 months of life was associated with an increased risk of asthma at age of seven years.

Children who developed asthma had more prolonged and severe ARIs in the first 24 months of life than other children. These findings of Toivonen et al. suggest that the susceptibility to ARIs and asthma may share common pathophysiological mechanisms, or recurrent ARIs in early childhood may predispose the child to the development of asthma [26]. A meta-analysis by Kenmoe et al. examined the relationship between infant

LRTI and the development of asthma. They showed, considering numerous confounding factors, that LRTI at age less than two years is associated with a markedly increased incidence of asthma up to age 20 years. This was independent of virus and LRTI type [59]. A recent meta-analysis from Europe, which combined original data from 38 birth cohort studies, similarly showed that respiratory infections in early childhood can influence the development of chronic obstructive pulmonary disease later in life, with the strongest effects seen in LRTIs [60].

1.2 Different methods to measure the burden of ARI

1.2.1 Different designs in data collection

Respiratory infections often heal spontaneously, and in less than 50% of cases a doctor's consultation is required, in even fewer cases hospitalization [30, 46]. Therefore, it is impossible to determine the true frequency and burden of ARI from physician reports or hospital-based studies [61, 62]. Individual information on the frequency of infections can indicate a particularly high susceptibility to infections and initiate further investigations. Previous observational studies have used different survey methods to determine the frequency of ARI episodes. These were mainly retrospective surveys with parent-based questionnaires or interviews [50, 63, 64], studies in which patients visit the clinic when symptoms occur and documentation is done there. Few studies used prospective symptom diaries which were kept by the parents with enormous efforts [36, 65, 66]. In rare cases a combined approach of symptom diaries kept by parents and interviews was chosen [67, 68]. Retrospective survey methods were most commonly used. However, such retrospective methods can lead to underreporting and recall problems [69] unless only a short period of time is considered [70]. Therefore, it is of high importance to assess the frequency of ARI using a real-time approach, such as daily entries in a symptom diary. Symptom diaries are tools that allow participants to record symptoms daily and systematically over a period of time [71]. Symptom diaries are an excellent tool to counteract under-reporting and to allow a detailed description of the burden of disease. Symptom diaries are a valuable tool in research projects, but they can also support diagnostic and therapeutic processes in clinical practice [69, 71, 72].

1.2.2 Birth cohort studies

For many specific etiologic questions, information on a mild course of infections is needed. However, this requires prospective data, and collecting this information is challenging. Therefore, accurate recording of ARI in early childhood requires carefully planned prospective birth cohort studies using symptom diaries. This permits the analysis of a prospective evolution of symptoms associated with specific pathogens (if bio samples allow identification of pathogens) and taking into account previous episodes of infection, age at infection, and time since the last episode. Symptom diaries have a long tradition in the evaluation of acute infections [29, 73, 74] but are also very challenging. Therefore, other approaches are more commonly used, but possible recall bias must be accepted [75]. In addition, retrospective assessment does not adequately examine the duration of symptoms or how symptoms change over time. In birth cohort studies, newborns or infants are recruited before, at, or shortly after birth and followed for many years to examine associations between early childhood exposures and outcomes later in life.

Many birth cohorts have focused on respiratory infectious diseases, and various aspects of these studies have been addressed in systematic reviews and scoping reviews [76-78]. However, none of these studies focused on the prospective recording of respiratory tract infections using symptom diaries in combination with bio samples. This information can be used to study patterns and severity of symptoms associated with pathogens and other factors such as susceptibility, immune system development, or development of chronic diseases in life.

1.2.2.1 LöwenKIDS birth cohort

The results of this thesis are based on data from the LöwenKIDS birth cohort, which was established by a large multicenter interdisciplinary study team that includes the author of this thesis. The LoewenKIDS study is an ongoing population-based observational birth cohort study, which recruited 782 newborns between November 2014 and February 2018 in five study regions in Germany (Clinicaltrials.Gov Identifier: NCT02654210). Participants were recruited antenatal and postpartum until the age of three months and are followed up until the age of 15 years (Figure 1). In 2020, all study participants were two years old or older, and analyses were based on pre-covid pandemic data.

The overall aim of the birth cohort LöwenKIDS is to record all respiratory and gastrointestinal infections in infancy in order to investigate the impact of infection patterns, timing and sequence, as well as other risk factors, on the development of asthma and atopic diseases from a life course perspective. A detailed description of the study design, recruitment methods, and data collection can be found elsewhere (P3).

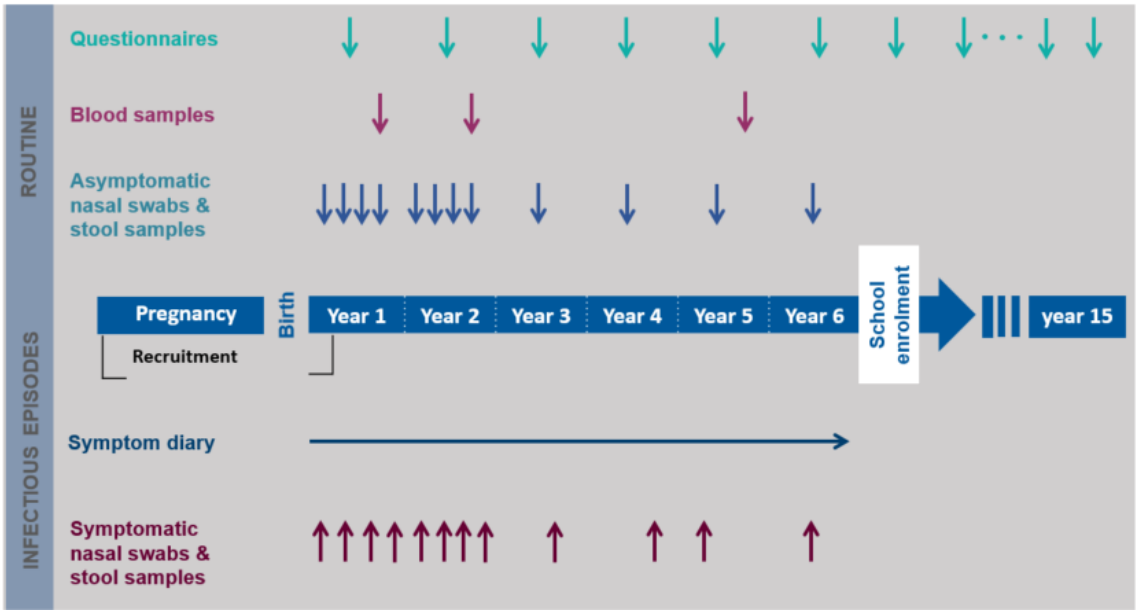

Figure 1 Data collection in the LöwenKIDS cohort during the entire study period.

1.3 Research question

In summary, ARIs represent the most common childhood illnesses worldwide, although the reported frequency varies widely. In Germany, the frequency of ARI was last reported for children born in 1990. Here, only three episodes per year were retrospectively recorded for children in the first year of life. Despite the fact that most ARIs are not severe, they still lead to a high number of physician consultations, hospitalizations, antibiotic prescriptions, socioeconomic burden, and absence from work and care. In addition, there are numerous associations with occurrence of asthma in later life. The study of symptoms of respiratory infections in the home setting requires specific prospective cohort studies that use diaries. Symptom diaries are an effective tool to address potential underreporting, particularly of milder infections, and thus provide an opportunity to highlight and assess the entire history of ARIs. To date, little is known about which and how many studies use (used) a prospective approach with symptom diaries to detect ARI and how often children are affected by ARI.

1. The present thesis gives an overview of research on ARI using a scoping review. Special attention was given to prospective birth cohort studies that identify ARIs using a symptom diary approach and are able to consider the whole history of infection from birth. Especially, we aimed to compile, map, and compare the existing birth cohort studies collecting symptom diary information on respiratory infections in childhood starting at birth to promote potential research collaborations and exploit synergies. We considered the different methods, the collection of bio samples and environmental exposures in order to identify studies suitable for providing a holistic understanding of the association of ARI as exposure with potential long-term sequelae in a life course perspective. The scoping review aims to inspire scientists and clinicians to collaborate with birth cohort studies to potentially identify and understand the pattern, timing, and sequence of respiratory tract infections and their association with immune system development and other exposures in a life course perspective.
2. In order to investigate a complete history of especially respiratory infections, the birth cohort LöwenKIDS was established. Based on this prospective population-based longitudinal study, symptom diary data and cross-sectional data permitted a first analysis of frequency and symptom burden as well as of factors associated with ARI in the first two years of life.

2 Discussion

The overall goal of this work was to identify the disease burden due to ARIs and to give an overview of birth cohorts by using a symptom diary, starting from birth to detect ARI in children. We identified 22 birth cohort studies that collected respiratory symptom data from birth by using a symptom diary. The number of participants was highly heterogeneous, ranging from 129 to 8677 newborns, similarly the duration of symptom diary use, which included a duration of five or six years in only four studies. In contrast, 16 studies collected symptom diary data only up to the second year of life. More than 70% of the studies completed recruitment 10 years ago, and four of the studies completed recruitment before 1992. The youngest and also one of the studies that used a symptom diary to collect ARI for the longest period of time is the LöwenKIDS study, followed in duration of follow-up by the Danish Copenhagen prospective studies on asthma in childhood (COPSAC) cohort, which also used the symptom diary for six years at birth. Nearly all studies collected bio samples and information on associated factors. Initial analyses of the LöwenKIDS birth cohort showed that children experienced on average 13.7 ARI episodes during the first two years of life (first year 6.0 ARIs, second year 7.7 ARIs) with a mean duration of eleven days. ARIs increased until approximately 14 months of age and stabilized thereafter. They occurred more frequently in the winter months than in the summer months. The most common symptoms in the first two years of life were found to be mainly runny / stuffy nose and cough. Attending daycare and having siblings in the same household was associated with an increased risk of a greater frequency of ARIs in the first two years of life, while exclusive short-term breastfeeding (less than four months) was associated with fewer ARIs compared with exclusive breastfeeding for four to six months.

The individual results have already been discussed in the publications (P1, P2), thus in the following discussion the broader context is considered and the results are discussed comprehensively.

2.1 How many infections are normal?

In general, the occurrence of numerous ARIs in the first two years of life is often described as normal. The definition of the terminology *"normal"* which accompanies numerous descriptions is of particular importance. Grüber et al. established reference values for Germany about 30 years ago, using data from the MAS-90 birth cohort study. In addition to the average ARI frequencies, they stated in 2008 that in infants of up to eleven ARI in the first two years can be considered "normal" and that an immune deficiency does not have to be suspected, thus reassuring parents and avoiding over diagnosis [28].

The term “normal” can assume different meanings: On the one hand, "normal" can be perceived as something "natural", "usual", "typical" or "harmless", on the other hand as a dichotomous comparison (normal vs. abnormal). Normal is also known to be used to separate health from disease. According to Marktl, "normal" can also be understood as "typical" when a generally accepted practice is the reference or ultimately as "average" when describing what is most representative in a group [79]. In numerous international birth cohort studies, the average number of ARI varies from 3.1 to 9.7 episodes in the first year of life [28, 32]. In our LöwenKIDS cohort, we identified an average of six ARIs in the first year of life, eight ARIs in the second year of life, and about fourteen ARIs in the first two years of life. The cumulative distribution of ARI frequency shows that about 25% of children had less than ten ARI episodes and 25% even more than 17 ARI episodes in the first two years of life (P1). So we use average values as a basis for our assessment, which we then interpret colloquially as normal? So, does that mean that everything that occurs frequently is to be assessed colloquially as healthy? Thereby, we still know far too little especially in the field of infection epidemiology with regard to ARI. We know from this and numerous other studies e.g. how many ARIs a child experiences on average in the first years of life [24, 26, 30], how long these infections persist, at which time infections occur most frequently and when they occur for the first time in life [61], which symptoms are predominant at which time, which pathogens occur most frequently in which ARIs [80] and which associations exist with factors that increase the occurrence of these infections [25, 30, 61, 80, 81]. We also know that the immune system must first develop, particularly during the neonatal period and in the first years of life, in order to respond to the exposure to pathogens [1, 2].

However, it is not yet sufficiently known whether these many ARI in the early childhood, which are considered colloquially as "normal", have a possible positive effect on children, as postulated by the hygiene hypothesis, e.g. with regard to allergies [82], or whether a later negative effect, e.g., the development of chronic diseases in later life due to infections in early childhood, is predominant [60].

The hygiene hypothesis aims to explain why allergy and asthma prevalence has increased in recent decades in more western industrialized countries, especially in urban regions. In doing so, it invokes that exposures to certain microorganisms in early childhood protect against allergies. The hypothesis originated from the observation of Stachan, who as early as 1989 tried to find an explanation for the enormous increase in asthma and atopic diseases, with increasing hygienic conditions. He found that contact with an increasing number of older siblings in the household was inversely related to the development of hay fever [83]. He hypothesized that decreasing family size and improved hygienic conditions over time reduced certain cross infections of young families [83]. This hypothesis stimulated many researchers to study these topics and represented a central cornerstone in asthma and allergy research [82]. According to von Mutius, this hypothesis has been confirmed in numerous populations and is considered today to be one of the most solid epidemiological findings related to allergies [82]. A very interesting aspect is, that with increase of older siblings in the household the probability of developing hay fever for smaller siblings decreases. In relation to our results and question, we can show in parallel that the presence of siblings in the same household is associated with a higher incidence of ARI in children in the first two years of life (P1).

Despite extensive research in the field, scientists, especially around the team of Mutius et al., struggled to identify and mechanistically understand the relevant components to develop prevention strategies in the field of asthma and allergies [82]. The main directions that have emerged have focused, on the one hand, on infections with different pathogens, on the importance of environmental exposure to microbial compounds and, on the other hand, on their effects on the immune system [84]. The consideration of infections and their impact on asthma is still ongoing. A causal relationship between infections and asthma has not yet been demonstrated. However, two meta-analyses from 2022, among numerous other studies [26, 56, 85, 86], show associations between LRTIs and a later onset of asthma. In addition to Kenmoe et al. (see 1.1.3), a recent and very impressive study by Van Meel et al. showed associations between LRTIs and asthma. The special

characteristic of this work was the combination of results from 38 birth cohort studies with analysis of data from over 150000 children. The results show that children with early LRTIs had lower lung function scores at school age than children with URTIs in the early childhood phase. As mentioned earlier, the risk of children to develop asthma was increased if they had early LRTIs in infancy [60]. These associations seem to be strengthened over time. In contrast, the team around von Mutius was able to show, when looking at mild URTIs, that repeated mild viral infections excluding LRTIs in early life can reduce the risk of developing asthma by school age [87].

2.2 Birth cohorts and collaboration

Exposures during the prenatal and postnatal periods have implications for children's health and may also have implications for later morbidity. Symptom diaries are an effective tool to address potential underreporting, particularly of milder infections, and thus provide an opportunity to highlight and assess the entire history of ARIs. Birth cohort studies with prospective approaches are needed to examine these associations [88].

In these scoping review (P2), we identified 22 birth cohort studies using a symptom diary to collect symptoms of respiratory infections beginning within the first four months after birth. The number of detected birth cohort studies using diaries is small compared to the overall number of birth cohort studies that were established on bronchial asthma, allergies, and respiratory infections. It is particularly notable that there are many birth cohorts but few with a valuable symptom diary approach directly from birth or shortly after birth. Similarly, it is striking that each study collects vast amounts of data on its own, cleans them, and in the end can only include a certain proportion of participants for analysis.

The LöwenKIDs study represents one of the youngest birth cohorts in the ScR and at the same time with the Danish COPSAC study [89, 90], also one of the rare ones that collects and collected, respectively, valuable symptom diary data on ARIs - from birth onwards- over a long period of six years. Two other studies, the Australian Perth Cohort [11] and the Finnish STEP- Study [91] can draw on five years of symptom diary data on ARIs. All other birth cohorts identified only collected symptom diary data for the first three years or less. In addition, most of these studies, e.g. the STEP study with 1827 participants, the PASTURE study with 1133, the LöwenKIDS study with 782 participants, the Perth cohort with 263 participants, and the COPSAC cohort with 441 participants, partially

have high numbers of participants at baseline (P2). However, all the researchers around these birth cohorts know the problem of participant recruitment and the consequently even greater challenge of being able to retain these participants over a long period of time. Another challenge is the completeness of the data, especially with symptom diaries requiring daily entries. Based on the drop-out rates of the studies in the ScR (P2), the difficulty in retaining participants in the study is recognizable. The identified drop-out rates in the first year of life ranged from around 10% in the Perth cohort [30] and the Copenhagen cohort [80] to 47% in the Adelaide cohort [36]. In contrast, the STEPS study [92] reported a drop-out rate of 6% at 13 months. The LoewenKIDS- cohort showed 12% at two years, 32.5% in the Vigall cohort [93], and 58% in the Adelaide cohort [36].

In 2004, Kongevinas et al. described the importance of joint collaborations. He identified three main reasons for the urgency of cohort collaboration and shared data use. These reasons include increasing statistical power, efficient design because a large multinational study population allows selective sampling by exposure or outcome, and reproducibility of results [88]. In the field of asthma and allergy research alone, there are over 130 birth cohorts that have been established over the last approximately 40 years [88]. These cohorts contain an impressive amount of data that are isolated and housed in independent databases in a wide variety of institutions in different countries.

To overcome this problem, some European Union research initiatives have formed, such as The Global Allergy and Asthma European Network (GA2LEN) or The Mechanisms of the Development of Allergy (MeDALL), and have sought to identify, compare, and evaluate data from existing European birth cohorts [94, 95].

For this purpose systematic reviews were conducted and the relevant birth cohort studies in Europe were identified and the data were pooled in a database- as part of the GA2LEN-initiative [96]. Major challenges existed in harmonizing data already collected in different ways. To partially prevent this for future surveys, the MeDALL initiative has even developed its own harmonized MeDALL-Core Questionnaire on asthma symptomatology (MeDALL-CQ), which is freely available in nine different languages and has already been used by numerous birth cohort studies [97].

This may allow for more comparable data and insights across different cohorts and countries in Europe in the future [97]. The success of such collaborations is documented by the above-mentioned initiatives and resulting publications [98, 99]. Kogevinas, who

in 2004 proposed more collaboration among birth cohorts, participated in the previously mentioned work of Van Meel et al. [60]. In this meta-analysis with original data, which was achieved by merging 38 birth cohort studies, data from 150000 children could be analyzed. It showed associations between infections in infancy, especially URTIs, and the later occurrence of asthma [60].

The author of this thesis chose a similar approach as Keil et al. [96] and compiled an extensive research on the methods of birth cohort studies - however on the topic of ARI and with a focus on symptom diary data - in the form of a ScR (P2) in order to stimulate potential international research collaborations and to exploit synergies.

The above-mentioned initiatives have tended to involve the pooling of birth cohort studies with a focus on questionnaires. No initiatives focusing on valuable diary data and ARI in infancy exist to date. A pooling of studies with the same study design and similar questions to make research in this area more efficient would certainly support birth cohort studies with a focus on the collection of the entire infection history and thus the use of a symptom diary. Such data could be combined with data from analysis of bio samples and exposures. As a further possible foresight, the approach described by Zoch et al. of transferring different definitions to a uniform one, e.g. by the Delphi-method [34], could be pursued with such a cooperation. It would also be conceivable to develop a uniform approach to recording symptoms, for example by means of a uniform symptom diary in several languages, as was done with the MeDALL-CQ [97].

2.3 Strengths and limitations

The strengths of this study were the prospective birth cohort study design and the presence of detailed diary data on respiratory symptoms in the first two years of life. Symptom diaries, with their prospective approach, provide more valid data compared with retrospective data, i.e., higher reporting and incidence rates, thereby mitigating recall bias [69, 72, 73]. However, this design also presents numerous difficulties, starting with challenging and particularly time-consuming data collection, which can be very stressful for participants and affect compliance [100, 101] and even leads to tiredness [102]. This may explain the drop-out rate of 12% at two years in our study. It is also likely that the chosen study design with a symptom diary approach discouraged study candidates from participation in the first place. Comparison of ARI episodes can be very difficult if different recording methods (retrospective or by physician consultations) were used regardless of the different exposures to which the children were exposed. However, comparison is also difficult when the same recording method but different definitions are used to identify an ARI episode based on symptoms [34].

The scoping review is, to our knowledge, the first comprehensive attempt to summarize, map, and compare birth cohort studies with symptom diaries in which a symptom diary for respiratory symptoms was maintained from birth. The strength of our review is the comprehensive search of the literature. Our rather specific search strategy in four databases was comprehensively extended by a very extensive search in registries and networks and in the reference lists of identified publications from all four databases. We hypothesize that this expanded search strategy minimized the likelihood of having missed a birth cohort study with the use of symptom diaries from birth onward. Finally, to ensure the accuracy of the extracted data, we contacted one or two authors of all included birth cohorts and had them confirm or supplement the extracted information. Accordingly, our study also had some limitations. There is always the possibility that a cohort study could not be detected by our criteria, for reasons such as the lack of a standardized wording for diaries, the lack of a registration requirement, the fact that not all birth cohort studies have a cohort profile, or the lack of publication to date. We hope that these problems could be minimized by a broad additional search.

2.4 Conclusion

This thesis provides up-to-date and detailed findings on the occurrence of respiratory diseases and their symptom burden in the first two years of life - pre-pandemic - of children living in Germany, who are / were participants in the established LöwenKIDS birth cohort. Effects of increasing age, seasonality, daycare attendance, breastfeeding and the presence of siblings could be shown. Thus, this thesis provides pediatricians and researchers with information on the range of infection frequency in generally healthy children. This can be considered as a guide to the occurrence of ARIs in the 21st century. The results show a previously undescribed high frequency and burden of acute respiratory illness in German children in the first two years of life, which consequently may also place a great burden on parents and should therefore receive more public attention at this stage.

In addition, this thesis provides methodological insights into the assessment of ARIs by means of symptom diaries. Thereby, a comprehensive overview of all birth cohort studies, which are suitable to present a holistic understanding of the relationship of ARI as exposure to possible long-term consequences in a life course perspective, could be given. In detail, 22 birth cohort studies that used symptom diaries, starting from birth to identify ARIs were found. Symptom diaries are a particularly powerful tool for prospective data collection, but long-term use is very difficult, so they are unlikely to be widely used. Our review shows that it can be done and has been done in several studies. Many questions related to the role of infections in immune development require information on symptom development and infection history over time. When combined with the collection and analysis of bio samples, this detailed information is very valuable. This review helps form collaborations among researchers to study the pattern, timing, and sequence of respiratory infections and their association with the developing immune system and other exposures in a life course perspective.

In conclusion this thesis aims to stimulate collaborations related to diary data and ARI, among others, in asthma research, as is already being performed via numerous initiatives on similar topics. Thereby, a collaboration for a standardization of ARI definitions up to a standardization of a symptom diary could take place, which could lead to an international standardization of data collection.

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4 Theses

(1) Acute respiratory infections (ARI) occur very commonly in the first two years of life and, despite their usually mild course, are associated with a high disease burden and later onset of chronic diseases such as bronchial asthma.

(2) Birth cohorts with a symptom diary approach from birth represent an effective design to capture the complete disease burden of ARI.

(3) Despite a large number of existing birth cohort studies, there are 22 cohorts that collect(ed) ARI data starting from birth and using a symptom diary. Only four birth cohorts include both bio samples and a symptom diary over a five- or six-year period.

(4) The LöwenKIDS study of the Institute of Medical Epidemiology, Martin Luther University Halle-Wittenberg, is currently the most recent study using a symptom diary approach and one of the few studies collecting symptom diary data from birth to the age of six years.

(5) ARI occurred more frequently in the winter months than in the summer months. Frequency of ARI increased with age in the first year of life and decreased slightly toward the end of the second year of life.

(6) An average of 13.7 ARIs (first year of life, 6.0 ARIs; second year, 7.7 ARIs) occurred during the first two years of life, with an average duration of eleven days (SD: 5.8, median 9.7, IQR: 7-14). The median age at first ARI episode was 91 days (IQR: 57-128, mean: 107, SD: 84.5).

(7) The presented frequencies of ARI of the LöwenKIDS study differ considerably from the most recently published and most comparable study in Germany, MAS-90 (Grüber et al. 2008), which refers to data from 1990 and shows a considerably lower average frequency in the first year of life of 3.1 ARI.

(8) Symptoms of respiratory infections occurred most frequently between 13 and 18 months of age. Runny or blocked nose and cough represented the most common symptoms in the first two years of life.

(9) Children who attended a daycare center during the first two years of life showed a 1.27-fold risk [95% CI 1.14; 1.42] of developing ARIs in the first two years of life compared to children who did not attend daycare. Similarly, children who lived with more than one sibling during the first two years of life showed a 2.7-fold risk [95% CI 0.76; 4.76] of developing ARIs during the first two years of life compared with children without siblings in the same household.

5 Publications

List of included publications

1. Symptom Burden and Factors Associated with Acute Respiratory Infections in the First Two Years of Life - Results from the LoewenKIDS Cohort (P1)

Langer S, Horn J, Gottschick C, Klee B, Purschke O, Caputo M, Dorendorf E, Meyer-Schlinkmann KM, Raupach-Rosin H, Karch A, Rübsamen N, Aydogdu M, Buhles M, Dressler F, Eberl W, Koch FEV, Frambach T, Franz H, Guthmann F, Guzman CA, Haase R, Hansen G, Heselich V, Hübner J, Koch HG, Oberhoff C, Riese P, Schild R, Seeger S, Tchirikov M, Trittel S, von Kaisenberg C, Mikolajczyk R. Symptom Burden and Factors Associated with Acute Respiratory Infections in the First Two Years of Life-Results from the LoewenKIDS Cohort. Microorganisms. 2022 Jan 5;10(1):111. doi: 10.3390/microorganisms10010111. PMID: 35056559; PMCID: PMC8781593.

2. Birth cohort studies using symptom diaries for assessing respiratory diseases – a scoping review (P2)

Langer S, Klee B, Gottschick C, Mikolajczyk R (2022) Birth cohort studies using symptom diaries for assessing respiratory diseases–a scoping review. PLoS ONE 17(2): e0263559. doi.org/10.1371/journal.pone.0263559

3. Cohort profile: The LoewenKIDS Study-life-course perspective on infections, the microbiome and the development of the immune system in early childhood (P3)

Gottschick C, Raupach-Rosin H, **Langer S,** Hassan L, Horn J, Dorendorf E, Caputo M, Bittner M, Beier L, Rübsamen N, Schlinkmann K, Zoch B, Guzman CA, Hansen G, Heselich V, Holzapfel E, Hübner J, Pietschmann T, Pieper DH, Pletz M, Riese P, Schmidt-Pokrzywniak A, Hartwig S, von Kaisenberg C, Aydogdu M, Buhles M, Dressler F, Eberl W, Haase R, Edler von Koch F, Feidicker S, Frambach T, Franz HGB, Guthmann F, Koch HG, Seeger S, Oberhoff C, Pauker W, Petry KU, Schild RL, Tchirikov M, Röhrig E, Karch A, Mikolajczyk R. Cohort Profile: The LoewenKIDS Study - life-course perspective on infections, the microbiome and the development of the immune system in early childhood. Int J Epidemiol. 2019 Aug 1;48(4):1042-1043h. doi: 10.1093/ije/dyz001. Erratum in: Int J Epidemiol. 2019

Personal contribution to publications relevant to the thesis

P1: Langer S., Horn J., Klee B. et al. 2022

Data collection, development of the research question, parts of data cleaning and data preparation, setting definitions, planning and execution of statistical analysis, reporting of results, interpretation of results, writing of the manuscript, revision of the manuscript.

P2: Langer S., Klee B., Gottschick, C. et al. 2022

Conception, development of search string, literature search, data screening, data extraction, presentation of results, writing of manuscript, revision of manuscript.

P3: Gottschick C*, Raupach-Rosin H*, Langer S, et al. 2019

Transfer of the study from the Braunschweig study center to Halle, transitional study coordination 2017-2018, recruitment of participants, participant management, data collection, contribution to the manuscript, revision of the manuscript.

Publication 1 (P1)

Langer S, Horn J, Gottschick C, Klee B, Purschke O, Caputo M, Dorendorf E, Meyer-Schlinkmann KM, Raupach-Rosin H, Karch A, Rübsamen N, Aydogdu M, Buhles M, Dressler F, Eberl W, Koch FEV, Frambach T, Franz H, Guthmann F, Guzman CA, Haase R, Hansen G, Heselich V, Hübner J, Koch HG, Oberhoff C, Riese P, Schild R, Seeger S, Tchirikov M, Trittel S, von Kaisenberg C, Mikolajczyk R. **Symptom Burden and Factors Associated with Acute Respiratory Infections in the First Two Years of Life-Results from the LoewenKIDS Cohort**. Microorganisms. 2022 Jan 5;10(1):111. doi: 10.3390/microorganisms10010111. PMID: 35056559; PMCID: PMC8781593. **[103]**

microorganisms

MDPI

Article

Symptom Burden and Factors Associated with Acute Respiratory Infections in the First Two Years of Life—Results from the LoewenKIDS Cohort

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Abstract: Acute respiratory infections (ARIs) are the most common childhood illnesses worldwide whereby the reported frequency varies widely, often depending on type of assessment. Symptom diaries are a powerful tool to counteract possible under-reporting, particularly of milder infections, and thus offer the possibility to assess the full burden of ARIs. The following analyses are based on symptom diaries from participants of the German birth cohort study LoewenKIDS. Primary analyses included frequencies of ARIs and specific symptoms. Factors, which might be associated with an increased number of ARIs, were identified using the Poisson regression. A subsample of two hundred eighty-eight participants were included. On average, 13.7 ARIs (SD: 5.2 median: 14.0 IQR: 10–17) were reported in the first two years of life with an average duration of 11 days per episode (SD: 5.8, median: 9.7, IQR: 7–14). The median age for the first ARI episode was 91 days (IQR: 57–128, mean: 107, SD: 84.5). Childcare attendance and having siblings were associated with an increased frequency of ARIs, while exclusive breastfeeding for the first three months was associated with less ARIs, compared to exclusive breastfeeding for a longer period. This study provides detailed insight into the symptom burden of ARIs in German infants.

Keywords: birth cohort; respiratory infection; newborn; children; symptom diary; longitudinal observation; infectious diseases; symptom burden; LoewenKIDS

1. Introduction

Acute respiratory infections (ARIs) continue to be the most common health problem during childhood worldwide. Although most ARIs are not severe [1], they contribute to a high number of outpatient visits [2], antibiotic prescriptions, hospitalizations [2,3], as well as to socioeconomic burden [4,5] and absenteeism in education and work [6]. In addition, infections with respiratory viruses (e.g., human rhinovirus, enterovirus, and adenovirus) in early childhood can influence the development of chronic and immune-mediated diseases such as asthma, type II diabetes, and obesity later in life [7,8]. Respiratory infections often heal spontaneously, and, in more than 50% of the cases, there is no doctor's consultation required, and, in even less cases, hospitalization is involved [4,5]. Therefore, it is impossible to determine the true frequency and burden of ARIs based on medical reports or hospital-based studies [9,10]. Individual information on frequency of infections can indicate particularly high susceptibility to infections, and initiate further assessment. For this purpose, contemporary norms are necessary.

Previous observational studies [11–14] used different assessment methods to determine the frequency of ARI episodes, often including a retrospective assessment. However, retrospective methods may result in under-reporting and recall problems [14], if not only a short time period is considered [15]. It is therefore highly relevant to assess the frequency of ARIs with a real-time approach, such as daily entries into a symptom diary. Symptom diaries are an excellent method to counteract under-recording and allow a detailed description of the burden of disease. Different studies found between three to seven ARIs per year in early childhood (children up to two years old) [16–19]. In Germany, frequencies of ARIs were last reported for children born in 1990 [1]. Here, only three episodes per year were recorded for children in the first year of life. Since then, no publication was published in Germany which estimated the frequencies of ARIs in children.

There are several factors which might influence the frequency of ARIs in the first two years of life. Previous studies already found out, that older age (compared to the first six months), cold seasons, childcare attendance [18,19], having older siblings, maternal smoking [20], and male sex [21] are associated with a higher number of ARIs, while full breastfeeding [22] is associated with a lower frequency of ARIs. With societal changes, the role of these factors might be changing.

Therefore, we investigated the frequency, the full burden of symptoms, as well as factors associated with ARIs in the first two years of life based on symptom diary data of the German population based on the prospective birth cohort study LoewenKIDS.

2. Materials and Methods

2.1. Study Population

A detailed description of the study design, methods of recruitment, and data collection is provided elsewhere [14]. Briefly, the LoewenKIDS-study is an ongoing population-based observational birth cohort study, which recruited 782 newborns between November 2014 and February 2018 in five study regions in Germany (Clinicaltrials.Gov Identifier: NCT02654210 (Accessed on: 1 January 2021)). Participants were recruited antenatal and postpartum until the age of three months and are followed up until the age of 15 years. In 2020, all study participants were two years old or older.

2.2. Data Collection/Symptom Diary

Parents were invited to keep a daily symptom diary in the first six years of life of their child. They recorded all the child's symptoms, symptom-free days, doctor consultations, diagnoses, medication, and absence from work or childcare on a daily basis. Participants could choose between a paper-based diary, an online version, or an app. Changes between the different modes were allowed. Symptoms such as fever, wheezing, chills, sore throat, runny/congested nose, increased need to sleep, and increased attachment were included in the symptom diary, as well as severity of the aforementioned symptoms. The symptom diary was developed on the basis of the symptom diary used by the birth cohort ORChID [15] and adapted after a feasibility study [16].

2.3. Questionnaires

Parents filled in questionnaires at the birth of their child and at the age of six months, one year, and then annually until the age of 15 years. Questionnaires contain information on social and health characteristics, pregnancy, and birth, as well as on selected diseases and environmental factors.

2.4. Classification/Definition of ARI Episode

We adapted the ARI definition proposed by Lambert et al. [23–25]. We classified ARIs by distinguishing between A- and B-symptoms. An A-symptom was defined as fever, wheezing, wet cough, and doctor diagnosed pneumonia or otitis media, whereby B-symptoms included dry cough, chills, sore throat, runny or blocked nose, increased need to sleep, loss of appetite, and increased attachment. We defined the beginning of an ARI episode as the occurrence of at least one A-symptom or a day with two B-symptoms. If there were no symptoms for three consecutive days, the episode ended and a new episode could begin. The occurrence of single/isolated B-symptoms were considered within an episode but not as the start of an episode.

2.5. Data Processing and Statistical Analyses

Data analysis was performed using R, v. 4.0.5 for Windows. Descriptive analysis included calculating frequencies and duration of ARI episodes by age, sex, and seasonality. Classification into A- and B-symptoms, as well the generation of acute respiratory episodes and the calculation of outcome variables were carried in the R-package lkstaR [26]. Summary statistics are presented as mean (standard deviation, SD) or median (interquartile range, IQR) for continuous variables and frequency (percentage) for categorical variables. We compared different strata according to the number of ARIs using *t*-Test.

ARI frequencies and associations between participant characteristics were estimated using the Poisson regression. Multivariable analysis included duration of exclusive breastfeeding, time of entry in daycare attendance, type of delivery, birth term, sex, and having older siblings. Multivariable models included all the above-mentioned associated factors. Effect estimates and their corresponding 95% confidence intervals (95% CI) are presented. This analysis is based on data collected from 2014 to February 2020.

2.6. Ethical Approval

The parents of all children participating in the study provided informed written consent. The respective Ethics Committees of the Martin-Luther-University Halle-Wittenberg, Medizinische Hochschule Hannover and Ludwig-Maximilians-Universität Munich, Germany approved the research protocol.

3. Results

3.1. Characteristics of Participants

Out of the 782 enrolled children in the LoewenKIDS study, the parents of 732 (93.6%) participants submitted daily symptom diaries. The parents of 433 (55.4%) participants provided entries for 80% of days, however, in order not to miss any potential infection events, we restricted the sample for this analysis to 288 participants (37%), who completed symptom diary on 98% of the days during the first two years of life. The present sample of 288 participants does not differ much in terms of sociodemographic factors from the 732 participants in the overall sample. Characteristics of the study population show that 85% were born at term, 70% spontaneously, 48% were male, 30% had one or more siblings, 85% attended daycare, and 65% were exclusively breastfed for at least four until six months (Table 1).

Table 1. Characteristics of 288 LoewenKIDS study participants analyzed in this study. Mean number of ARI episodes and 95% confidence intervals (mean difference) are shown.

Children	Frequency (%) or Mean (±SD)	No. of ARIs * in the First Two Years, Mean	95%CI $ Difference to Reference Group
Sex (*N* = 288)			
Male	139 (48)	13.7	0.2 (−1.00; 1.43)
Female	149 (52)	13.5	Reference
Birth term (*N* = 288) §			
Full-term birth ~	266 (92.4)	13.7	Reference
Early-term birth ~	22 (7.6)	12.4	−1.3 (−3.18; 0.54)
Birth weight (g) § (*N* = 286) §	3400 (±488)		
<2500	13 (4.5)	13.1	Reference
>2500–4000	252 (88.2)	13.6	0.5 (−1.91; 2.97)
>4000	21 (7.3)	14.1	1.0 (−2.40; 4.53)
Birth mode (*N* = 287) §			
Vaginal birth	221 (77.0)	13.7	Reference
C-section	66 (23.0)	13.1	−0.6 (−1.96; 0.84)
Number of older siblings (*N* = 286) §			
0	195 (68.2)	13.1	Reference
1	73 (25.5)	14.5	1.4 (0.01; 2.81)
2 or more	18 (6.3)	15.8	2.7 (0.76; 4.76)
Duration of exclusive breastfeeding (*N* = 267) §#			
1 to 3 months $	25 (9.4)	10.8	−3.2 (−5.08; −1.22)
4 to 6 months	165 (61.8)	14.0	Reference
7 to 13 months	62 (23.2)	14.0	0.0 (−1.52; 1.58)
No breastfeeding +	15 (5.6)	12.5	−1.5 (−4.11; 1.13)

Table 1. *Cont.*

Children	Frequency (%) or Mean (±SD)	No. of ARIs * in the First Two Years, Mean	95%CI $ Difference to Reference Group
Entry in childcare attendance (*N* = 288) §			
>0 to 12 months	98 (34.0)	13.8	2.4 (0.44; 4.42)
13 to 26 months	145 (50.4)	14.1	2.7(0.81; 4.66)
No childcare	45 (15.6)	11.4	Reference
Domestic pets (*N* = 288)			
Yes	80 (27.8)	13.0	−0.8 (−2.16; 0.41)
No	208 (72.2)	13.8	Reference
Parents			
Age mothers at birth in years (*N* = 287)	32.9 (±4.0)	-	-
Age fathers at birth in years (*N* = 285)	35.6 (±5.4)	-	-
Highest academic degree of mothers (*N* = 286) §			
Apprenticeship	77 (27.0)	12.4	−1.5 (−3.02; 0.05)
Bachelor's degree	16 (6.0)	14.0	0.1 (−2.77; 3.02)
Master's degree	131 (46.0)	13.9	Reference
PhD/ equivalent	57 (20.0)	14.3	0.4 (−1.06; 1.93)
Other	5 (2.0)	14.8	0.9 (−5.42; 7.27)
Highest academic degree of fathers (*N* = 281) §			
Apprenticeship	86 (31.0)	12.7	0.7 (−2.09; 0.70)
Bachelor's degree	9 (3.0)	16.7	3.3 (−0.06; 6.68)
Master's degree	145 (52.0)	13.4	Reference
PhD/ equivalent	37 (13.0)	15.3	1.0 (−0.12; 3.94)
Other	4 (1.0)	18.0	4.6 (−7.40; 16.68)
Monthly household net income in Euro (*N* = 287) §			
<3000	43 (15.0)	13.4	−1.1 (−3.05; 0.86)
3000 to 3999	72 (25.0)	14.5	Reference
4000 to 5000	60 (21.0)	13.1	−1.4 (−3.15; 0.33)
>5000	68 (24.0)	14.1	0.4 (−2.14; 1.31)
Did not provide any information	42 (15.0)	11.8	−2.7 (−4.76; 0.74)
At least one parent with asthma (*N* = 278)	85(30.6)	13.5	0.1 (−1.49; 1.27)
Smoking (*N* = 279) §,&			
Maternal smoking	3 (1)	9.6	-
Paternal smoking	29 (10)	13.2	-

Abbreviations: * ARI means acute respiratory infection; § participants who filled in the questionnaire, difference to 288 are missing; + 3 of 36 participants did breastfeed but not exclusively; ⁻ early-term birth (<38 + 4 week), full-term birth (38 + 4–41 + 3 week); # breast milk exclusively, no other nutritional products; & sample too small, difference between groups not tested. $ CI: confidence interval.

3.2. Symptom Burden

In total, 206,001 child-days with diary entries were available for analysis of the included participants. Observed symptoms included cough, wheeze, sore throat, chills, fever, attachment, high need for sleep, loss of appetite, and runny or blocked nose. One or more of these symptoms were reported on 44,441 days (21.6%), corresponding to a mean of 154.3 (IQR: 76.2–216) days with ARI symptom per child (Figure 1A). Symptoms occurred in the first six months of life on average for 19.4 days, at 7–12 months for 41.8 days, at 13–18 months for 49.5 days, and at 19–24 months for 43.4 days (Figure 1B, Table 2).

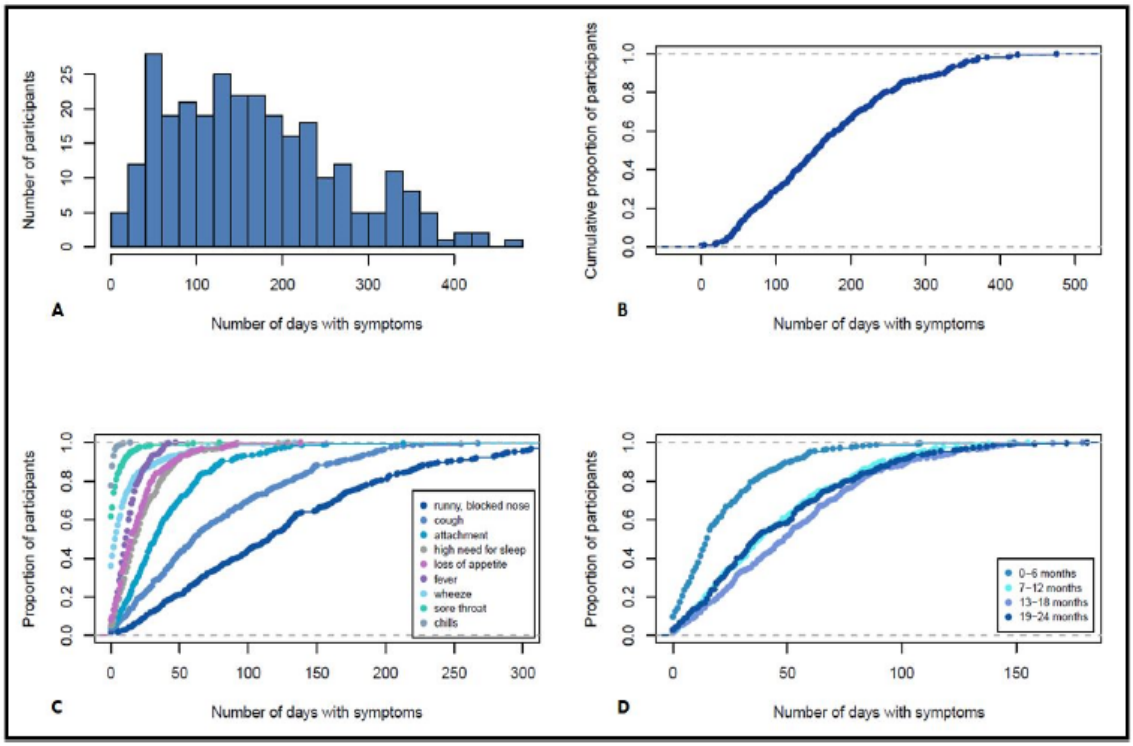

Figure 1. (**A**) Histogram of all days with symptoms within the first two years of life. (**B**) Cumulative distribution of days with symptoms within the first two years of life. (**C**) Cumulative distribution of days with specific symptoms in the first two years of life. (**D**) Cumulative distribution of days with any symptoms in the first two years of life in six months age strata.

Table 2. Days with symptoms in the first two years of life by six-month lifespans per child and days with specific symptoms.

	0–6 Months	7–12 Months	13–18 Months	19–24 Months	Overall	Cough	Runny Nose	Wheeze	Fever	Attachment	High Need for Sleep
Min	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
1st Quantile	4.0	14.8	20.8	16.0	76.3	29.8	57.8	0.0	6.0	16.0	9.0
Median	13	33.0	41.5	33.0	132.5	60.5	115.5	3.50	11.0	33.0	18.0
Mean	19.4	41.8	49.5	43.4	154.3	76.8	125.8	11.7	13.3	41.2	23.1
3rd Quantile	27.3	60.0	71.0	62.0	216.0	115.0	176.0	13.0	18.0	57.3	34.0
Max	149	157	179	183	477.0	363.0	399.0	134.0	47.0	326.0	129.0

Figure 1C shows the cumulative distribution of days with specific symptoms in the first two years of life in percentiles. The most common symptoms were runny or blocked nose with an average of 125 days (median: 115.5, IQR: 58–176) and cough in various forms with 76.8 days (median: 60.5; IQR: 30–115). In contrast, rare symptoms such as chills occurred on average 0.5 days (median: 0, IQR: 0), sore throat 3.2 days (median: 0; IQR: 0–3), and wheezing 11.7 days (median: 3.5; IQR: 0–13) on average (Table 2, Figure 1C).

3.3. Frequency of Acute Respiratory Infections (ARI) Episodes

In the next step, we aggregated the reported symptoms to ARI episodes based on the applied definition. Among the 288 children, a total of 3911 ARIs were reported in the first two years of life (Figure 2A). On average, 13.7 ARI episodes (IQR: 10–17, SD: 5.2, 10th percentile: 7 ARIs, 90th percentile: 20 ARI)) were reported in the first two years of life (Figure 2A). The cumulative distribution of ARI frequency shows that about 25% of children have less than 10 ARI episodes and 25% show more than 17 ARI episodes in the first two years of life independent of sex (Figure 2B). The median age at first ARI episode was 91 days (IQR: 57–128, mean: 107, SD: 84.5) after birth. The mean duration of ARIs was 11 days (SD: 5.8, median 9.7, IQR: 7–14). The proportion of children with ARIs at a given day increased markedly with age (Figure 2C). The frequency of ARI episodes in the first year was slightly lower with a mean of 6.0 ARI episodes compared to the second year with a mean of 7.7 ARI episodes (Table 3).

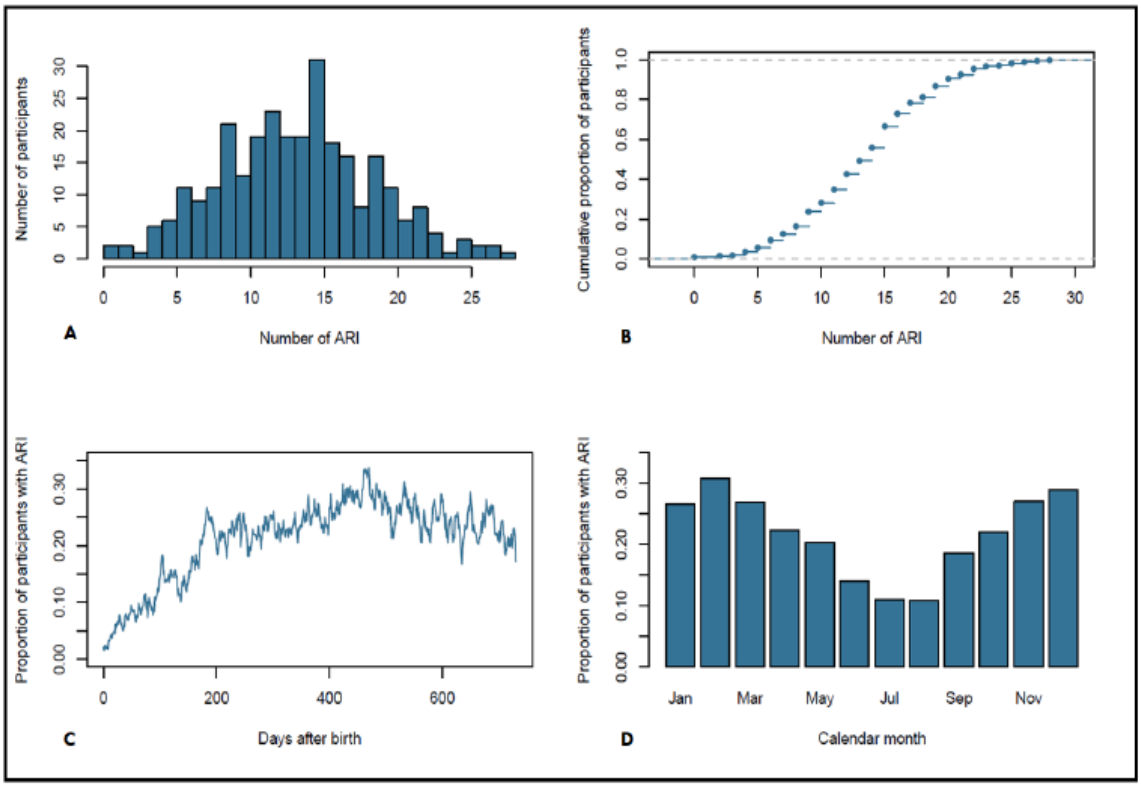

Figure 2. (**A**) ARI episodes of all children in the first two years of life. (**B**) Cumulative distribution of ARI episodes. (**C**) Proportion of children with ARIs in the first two years of life per day (in days after birth). (**D**) Proportion of children with ARIs by month (season).

Table 3. Number of acute respiratory infections (ARIs) in 288 children in the first two years of life in different age groups.

	0–6 Months	7–12 Months	13–18 Months	19–24 Months	0–12 Months	13–24 Months	0–24 Months
Min	0.0	0.0	0.0	0.0	0.0	1.0	2.0
1st Quantile	1.0	2.0	3.0	2.0	4.0	5.0	10.0
Median	2.0	4.0	4.0	3.0	6.0	8.0	14.0
Mean	2.4	3.6	4.0	3.7	6.0	7.7	13.7
3rd Quantile	3.0	5.0	5.0	5.0	8.0	10.0	17.0
Max	9.0	9.0	9.0	11.0	15.0	19.0	28.0

ARI episodes were more common in the winter months showing a well-known seasonal variation of respiratory tract infections in the northern hemisphere (Figure 2D).

3.4. Factors Associated with Acute Respiratory Infections (ARI)

The frequency of ARIs strongly depends on age and seasonality (Figure 2C,D). With increasing age, participants show a marked increase in ARI frequency in the first six months of age (Figure 2C). Furthermore, an increased ARI frequency was observed in winter months compared to the summer months (Figure 2D). In addition, the results from the multivariable analysis in Table 4 show that factors associated with a substantially increased risk of ARIs in the first two years of life are any childcare attendance and having any number of older siblings. However, neither the time point of first childcare attendance nor the exact number of siblings seem to be important for the cumulative number of infection episodes at the age of two. In contrast, the analysis shows that short-term exclusive breastfeeding (less than four months) is associated with a lower risk of ARIs 0.78 [95% CI 0.69; 0.89] within the first two years compared to exclusive breastfeeding for four to six months (Table 4). Children with a longer exclusive breastfeeding of more than six months had the same risk as those with the reference group of four to six months of exclusive breastfeeding. We did not observe any association between birth mode, birth term, or sex of the child.

Table 4. Multiple Poisson regression analysis of frequency of acute respiratory infections (ARIs) in 288 children during their first two years of life.

Variable	Crude RR [+]	95% CI	adj. RR [*]	95% CI
Duration of exclusive breastfeeding [#]				
No breastfeeding	0.89	(0.77; 1.04)	0.90	(0.77; 1.05)
1 to 3 months	0.77	(0.68; 0.88)	0.78	(0.69; 0.89)
4 to 6 months	1.00	Reference	1.00	Reference
7 to 13 months	1.00	(0.93; 1.08)	1.00	(0.92; 1.08)
Birth mode				
Vaginal birth	1.00	Reference	1.00	Reference
C-section	0.96	(0.89; 1.03)	0.99	(0.92; 1.08)
Birth term				
Full-term birth [~]	1.00	Reference	1.00	Reference
Early-term birth [~]	1.11	(0.98; 1.25)	1.10	(0.97; 1.25)
Number of older siblings				
0	1.00	Reference	1.00	Reference
1	1.11	(1.03; 1.20)	1.08	(1.00; 1.16)
2 or more	1.21	(1.07; 1.37)	1.17	(1.03; 1.33)
Entry in daycare				
No daycare in the first two years	1.00	Reference	1.00	Reference
0 to12 months	1.21	(1.01;1.34)	1.27	(1.13; 1.42)
13 to 26 months	1.24	(1.13; 1.37)	1.27	(1.14; 1.42)
Sex				
Male	1.00	Reference	1.00	Reference
Female	1.02	(0.95; 1.08)	1.01	(0.94; 1.07)

[#] Reference group is a duration of breastfeeding 4 to 6 months breast milk exclusively, no other nutritional products; [~] early term birth (<38 + 4 week), full-term birth (>38 + 3 week); [+] RR from univariable regression; CI: confidence interval; [*] RR from multivariable regression are adjusted for factors in Table 4.

4. Discussion

In the LoewenKIDS birth cohort study, we found that children show an average of 13.7 ARI episodes (first year 6.0 ARIs, second year 7.7 ARIs) with a median duration of 11 days in the first two years of life. ARIs increase with age and occur more frequently during the winter months compared to the summer months. Within the 13- to 18-months lifespan, children in our cohort showed the highest frequency of ARIs, days with symptoms, and occurrence of specific symptoms, such as runny nose or cough during the first two years of life. Attendance at daycare and the presence of siblings in the same household

were associated with an increased risk for a higher frequency of ARIs, while exclusive short-term breastfeeding (less than four months) was associated with less ARIs compared to exclusive breastfeeding for four to six months.

The use of symptom diaries to study ARIs is rarely reported. The frequency varies widely between studies, ranging from three to seven ARIs per year in early childhood. Our results are similar to birth cohort studies in Australia [16,18], Scandinavia [27,28], and Canada [29]. However, some studies report lower frequencies such as the Perth study with 4.0 ARIs [17]/4.2 ARIs [5], the Dutch Whistler study with 4.2 [19], or the German Mas-90 Study [1] with the lowest of 3.1 ARIs in the first year of life. It should be noted that all studies took place at different times and under different conditions.

To our knowledge, there is only one study about the frequency of ARIs in early childhood in Germany using symptom diaries, which was published 30 years ago [1]. The Mas-90 study examined children born in 1990 and found an ARI frequency of 3.1 in the first year of life and 3.2 in the second year, which are considerably lower than our results. This is probably because symptoms were recorded only in a kind of symptom diary, rather retrospectively (personal consultation), and additionally, half of the participants with incomplete data were included in the analysis [1]. Therefore, underestimation may be possible. In addition, the number of daycare places for children under three years has increased considerably in Germany since 1990 [30]. It is well known that children attending daycare centers have a higher risk of ARIs [13,18–20,31,32], which is in line with the findings of this study. Children in our cohort who entered daycare at the age of 13–26 months show a 1.26-fold risk of developing ARIs (RR: 1.26; CI [1.15; 1.39]) compared with children who did not attend daycare until the age of two years. A cohort study from Pittsburgh [33] as early as 1990 showed that the risk of infection increases with the number of contacts in different care settings. They showed that children in childcare with a group size of at least seven children as well as children with a care time of at least 20 h per week contracted considerably more infections than children who were in home care or in group care with three to six children. Similarly, children having siblings are more likely to have an increased number of infections, which was shown in our cohort as well as in other studies before [1,16,17,20,34]. We could not find any relationship when considering sex, birth mode, or birth term, and we were unable to measure an association between smoking exposure and ARI frequencies because an insufficient number of parents in our cohort reported smoking.

Our cohort showed that short-term exclusive breastfeeding (less than four months) without other nutritional support is associated with a lower risk for ARIs, 0.78 (95% CI 0.69; 0.89), within the first two years compared to exclusive breastfeeding for four to six months. Children with longer exclusive breastfeeding more than six months had the same risk as those with the reference group four to six months of exclusive breastfeeding. There are some studies which showed an association between breastfeeding and a lower risk of ARIs compared to no breastfeeding in early life [20,22,35,36]. However, the results are inconsistent. Cushing et al. showed a protective effect only for lower respiratory infections and no association with upper respiratory infections [22]. Frank et al. showed a protective effect between exclusive breastfeeding in the age period of three to six months compared with no breastfeeding only for ear infections and ARIs with fever and no association for ARIs in general [36]. In contrast, Wright et al. [35] also showed a protective effect of breastfeeding and a reduction in upper respiratory tract infections (URTIs), but only in the first four months of life, and Vissing et al. also showed inconclusive results [20]. On the other hand, there are studies with no evidence for a positive association [37] or even with negative effects for long breastfeeding [1,16,36]. The authors [1,16] assume that the negative effects are due to possible selection effects by, for example, over-reporting of episodes in participating families with higher social status, longer breastfeeding and less smoking.

A birth cohort study from Copenhagen [27] indicated that children in the first year of life had a runny nose an average of 16% of days, 7.9% cough, 4.9% attachment, and 1.5% wheezing. These findings are in line with our results. In comparison to the study from

Copenhagen, in our cohort there were slightly more days with runny or blocked nose (17% vs. 16% of days) and a little more cough (10% vs. 7.9% of days). In the younger age strata, we detected only a few days with sore throat and chills. Children at this age cannot yet report sore throat, and the occurrence of chills is certainly also very rare, so we did not expect high frequencies in these age strata in our cohort either.

In 2018, Sarna et al. estimated the average age of the first infection in life at a median of 2.9 months [9]. This is consistent with our estimate of a median of 91 days after birth.

There are many different ARI definitions that have been used in recent research to analyze recorded symptoms [5,16,18,25,27,38], so there is a legitimate question of whether our definition leads to more overestimation or even to underestimation of ARI episodes based on the choice of definition. We adapted the ARI definition proposed by Lambert et al. [25], which in direct comparison of different definitions provided middle estimates in a past study [24].

5. Strengths and Limitations

The strengths of this study were the prospective birth cohort study design and the presence of detailed diary data of respiratory symptoms in the first two years of life. Compared with retrospective data, symptom diaries provide more valid data, i.e., higher reporting and incidence rates, thereby mitigating recall bias [39–41]. However, the data collection is very time-consuming and challenging. Parents in our cohort were required to keep entries for each day, even if the child was asymptomatic.

It is well known that comparison of ARI episodes is very difficult when different recording methods (retrospective or by physician consultations) have been used. In addition, the studies were conducted in different regions with different environmental factors. However, it must also be said that a comparison is also difficult even with the same recording method if different definitions are used for the identification of an ARI episode based on the symptoms. This is shown by Zoch et al. [24] for six definitions for the identification of an ARI in a single dataset.

Completing a daily symptom diary can be a burden for participants and can affect compliance [42,43] and also leads to tiredness [44]. This is likely the reason why in our study only a subsample of participants submitted complete diaries. We also observed some dropout (11% dropped out of the study in the first two years and even some more stopped recording symptoms). In addition, the symptom diary as a study component likely kept many people from participation.

6. Conclusions

This study provides up-to-date, detailed data on the incidence of respiratory diseases in the first two years of life of German children and shows the effects of increasing age, seasonality, daycare attendance, breastfeeding, and the presence of siblings. This study provides pediatricians and researchers with information on the range of infection frequency in generally healthy children. It can be considered as a guideline for the normal occurrence of ARIs in the 21st century. These results show a previously undescribed high frequency and high burden of acute respiratory disease in German children in the first two years of life, which consequently can also represent a great burden for parents and should therefore receive more public attention in this phase.

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administration, E.D., C.G. and R.M. All authors have read and agreed to the published version of the manuscript.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the participants to publish this paper.

Data Availability Statement: Most of the quantitative results are provided in the tables. Distributions and individual level data in anonymized form can be obtained upon request and from the R-package lkstaR [26].

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PLOS ONE

RESEARCH ARTICLE

Birth cohort studies using symptom diaries for assessing respiratory diseases–a scoping review

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Data Availability Statement: All relevant data are within the article, Table 2, and Table 3. This Scoping Review is based on purely descriptive data contained in these tables. The graphs are also based on the data in the tables. No other data are available. No mean values, standard deviations were reported, and no analysis in figures was carried out, only a purely qualitative evaluation with a few counts in the tables for the graph. All extracted information from each publication of the Scoping Review is reported in Table 2 and Table 3. There is no additional raw data.

Abstract

Background

Respiratory infections are the most frequent health problem in childhood leading to morbidity and socioeconomic burden. Studying symptoms of respiratory infections in home based settings requires dedicated prospective cohort studies using diaries. However, no information is available on which birth cohort studies using symptom diary data. A review of birth cohort studies with available symptom diary data, follow-up data, and bio samples is needed to support research collaborations and create potential synergies.

Methods

We conducted a scoping review of birth cohort studies using diaries for the collection of respiratory symptoms. The scoping review was conducted in accordance with the PRISMA Extension. We searched the electronic databases PubMed, Embase, Web of science and CINAHL (last search November 2020) resulting in 5872 records (based on title and abstract screening) eligible for further screening.

Results

We examined 735 records as full text articles and finally included 57 according to predefined inclusion criteria. We identified 22 birth cohort studies that collect(ed) data on respiratory symptoms using a symptom diary starting at birth. Numbers of participants ranged from 129 to 8677. Eight studies collected symptom diary information only for the first year of life, nine for the first two years or less and six between three and six years. Most of the cohorts collected biosamples (n = 18) and information on environmental exposures (n = 19).

Conclusion

Information on respiratory symptoms with daily resolution was collected in several birth cohorts, often including related biosamples, and these data and samples can be used to study full spectrum of infections, particularly including those which did not require medical treatment.

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Abbreviations: ARI, Acute respiratory infection; ScR, Scoping Review; AUS, Australia; CAN, Canada; SWE, Sweden; CHE, Switzerland; FRA, France; AUT, Austria; EUR, Europe; USA, United States of America; DK, Denmark; NLD, Netherlands; FIN, Finland; NIC, Nicaragua; AUS, Australia; TWN, Taiwan; DEU, Germany; RUS, Russia; EST, Estonia.

Introduction

Acute respiratory infections (ARI) are the most common health problems in early childhood [1], and the most common causes of death in children under the age of 5 years worldwide [2]. Although most of ARI are not severe [1], they are frequent and cause a high number of doctor visits [3, 4], hospitalizations, antibiotic prescriptions [3, 5], a high socioeconomic burden [6, 7], and absenteeism in education and work [8]. Infections with respiratory viruses (e.g. human rhinovirus, enterovirus and adenovirus) in early childhood may influence the development of chronic and immune-mediated diseases such as asthma, type II diabetes and obesity later in life [9, 10], however, it is not clear how. Research in this area therefore remains very important. About half of ARI in infancy do not lead to consultation of a physician, which leads to a significant underestimation of the true incidence [7, 11–14].

For many specific etiologic questions, it is necessary to have information on a light course of infections. However, this requires prospective data, and collecting this information provides a large challenge. Therefore, the accurate recording of ARI during early childhood needs thoroughly planned prospective birth cohort studies using symptom diaries. Symptom diaries are tools for participants to record symptoms daily in a systematic manner over a defined period [15]. This allows analyses of a prospective evolution of symptoms linked to specific pathogens (if biosamples allow identification of pathogens) and accounting for previous infection episodes, age at infection and time since the last episode. Symptom diaries have a long tradition in evaluating acute infections [13, 16], but are also very demanding. Therefore, other approaches such as retrospective questionnaires, reports from clinical visits or retrospective interviews are more often used [17–23], but have to accept the possibility of recall bias [24]. Additionally, retrospective assessment does not allow studying the duration of symptoms or the change of symptoms over time adequately.

In birth cohort studies, newborns or infants are recruited before, at, or shortly after birth and observed over many years to examine associations between early life exposures and outcomes later in life [25]. Many birth cohorts have been focusing on respiratory infectious diseases and various aspects of these studies were covered in systematic and scoping reviews [26–32].

However, none of them focused on the prospective recording of respiratory infections using symptom diaries and the combination with biosamples. This information can be used to study patterns and severity of symptoms associated with pathogens and other factors such as susceptibility, immune system development or the development of chronic diseases later in life.

In this scoping review, we aimed to compile, map, and compare the existing birth cohort studies collecting symptom diary information on respiratory infections in childhood starting at birth to promote potential research collaborations and exploit synergies. We considered respiratory infections, the collection of biosamples and environmental exposures in order to identify studies suitable for providing a holistic understanding of the association of ARI as exposure with potential long-term sequelae in a life course perspective.

Material and methods

Inclusion and exclusion criteria

This scoping review was performed using PRISMA Extension [33]. We included (1) prospective observational birth cohort studies that (2) examined healthy newborns and (3) used a symptom diary related to respiratory infections. We defined a birth cohort study as a study that recruits children prospectively prior to birth or up to the age of four months.

We excluded all other study designs such as randomized controlled trials, case control studies, cross sectional, qualitative studies and publications in languages other than English. In addition, we excluded studies that focused only on children with chronic lung disease, studies that included children only when a specific symptom or virus was identified, studies that recruited children older than 4 months, or studies that focused only on preterm infants. There were no requirements for the duration of the symptom diary or a time limit for the date of publication.

Search strategy

In a first step, we searched four electronic databases (last search 11.2020): MEDLINE; EMBASE; CINAHL; Web of Science. The search strategy was developed to include several terms referring to respiratory infections in children, symptom diary, and study design. In Table 1, we present the search strategy that was used for MEDLINE and was applied with minor changes to the other databases.

Cohort identification took place between January 2019 and November 2020.

One researcher (SL) screened titles and abstracts of identified studies with respect to the inclusion and exclusion criteria. In a second step, two authors (SL and BK) conducted a backward search whereby bibliographies of the included studies were screened to identify any studies that might have been missed in the first screening. Subsequently, titles, abstracts and full text articles of additionally identified references were screened according to the inclusion and exclusion criteria. The results of both screeners were compared and discrepancies were discussed. In a third step, we scanned other sources such as registers of birth cohort studies (BirthCohorts.net (https://www.birthcohorts.net/) (11.2020), Asthma Birth Cohorts Database (https://asthmabirthcohorts.niaid.nih.gov/) and performed a grey-literature search and reviewed other reviews of birth cohorts (last search 11.2020). The final search results were exported into EndNote and duplicates were removed. Two authors (SL and BK) extracted data from all included birth cohorts independently, based on predefined criteria, compared the results, and discussed disparities. Data of interest included: cohort name, country in which the study took place, number of participants, enrollment period, follow-up times without symptom diary, symptom diary duration (from birth), at what age questionnaires were answered, if and at what time communication was via email, telephone and if interviews were conducted, if

Table 1. Search strategy for PubMed.

(Child [TIAB] OR Children [TIAB] OR Childhood [TIAB] OR newborn [TIAB] OR infant [TIAB] OR newborn [MH] OR infant [MH] OR child [MH])
AND
("birth-cohort" [TIAB] OR birth* [TIAB] OR "Prospective-study" [TIAB] OR "longitudinal study" [TIAB] OR "follow-up study"[TIAB] OR cohort* [TIAB] OR "Birth cohort study" [TIAB]OR "cohort studies"[MH])
AND
("respiratory-tract-infection" [TIAB] OR"Infectious diseases" [TIAB] OR "Infection diseases" [TIAB] OR "communicable diseases" [TIAB] OR "respiratory infections" [TIAB] OR "virology" [TIAB] OR "immunology" [TIAB] OR "virus disease" [TIAB] OR "viral disease" [TIAB] OR "infectious" [TIAB] OR "bacterial infection" [TIAB] OR "infections" [TIAB] "respiratory tract infections"[MH]"communicable diseases"[MH] OR "virology"[MH] OR "allergy and immunology"[MH] OR" virus diseases"[MH] OR "bacterial infections"[MH] OR "infection"[MH])
AND
("Daily-diary-study" [TIAB] OR Diary [TIAB] OR "daily-diary" [TIAB] OR "daily-diaries" [TIAB] OR "daily-observation" [TIAB] OR "daily- records" [TIAB] OR "self-reported-Questionnaire"[TIAB] OR "Symptom records"[TIAB] OR "Symptom questionnaire"[TIAB]OR "Symptom diary" [TIAB] OR "Symptom diaries" [TIAB])

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and when home visits, examinations in the clinic or in general took place. In addition, we extracted data on what biosamples were collected and at what time. In addition, it was of interest which risk factors for respiratory infections were of interest in each study. In only three of the cohorts a cohort profile was available. Thus, information on the study design was often taken from several publications focusing on different aspects of the same cohort study. It was often not possible to extract complete data from these specialized publications. Therefore, the last step was to validate and complement the extracted results by contacting the authors of the most recent publications of the respective birth cohorts via email and asking them to confirm or complete the available information (February-November 2020). Reminders were sent 3–5 weeks later. Investigators of 14 out of 22 studies (63.6%) responded to our inquiries.

Results

Search results

We identified 5960 records by database search and by backward reference, register and review search (Fig 1).

After removing duplicates, 5872 records were included in the screening of abstracts and titles of which 735 were found eligible for full-text analysis based on our inclusion criteria. Of these, a final number of 57 full-text articles met the inclusion criteria. Based on the articles, we identified 22 birth cohort studies that collect data or have already completed data collection on respiratory symptoms using a symptom diary (Table 2).

Characteristics of included cohorts

The majority of included birth cohorts were conducted in Europe (n = 12), four were conducted in Australia, four in the United States of America and one each in Canada, Nicaragua and in Taiwan. Three of those were conducted in several countries, such as the TEDDY Study, which was conducted in the United States and Europe.

The number of participants ranged from 126 in the VIGALL- Study [34] to 8677 in the Teddy-Study [35] (Fig 2A). The most recent study is the LoewenKIDS study from Germany

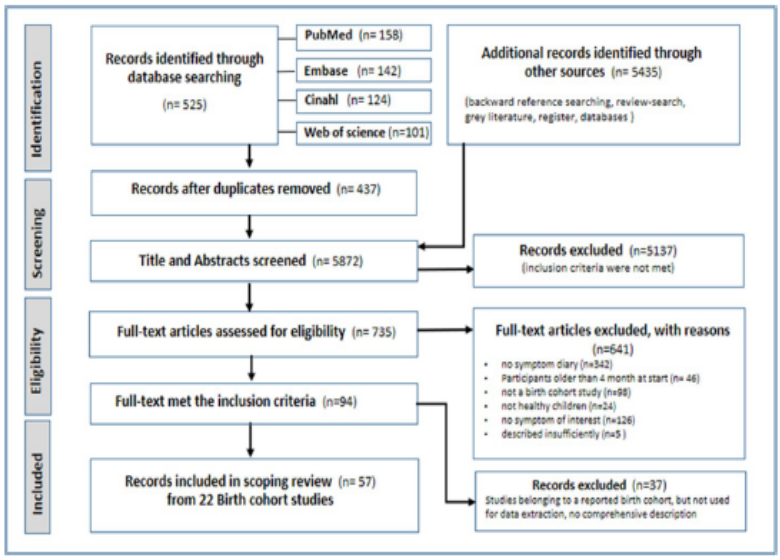

Fig 1. PRISMA-flow diagram.

https://doi.org/10.1371/journal.pone.0263559.g001

Table 2. Study characteristics sorted by descending enrollment period of birth cohort studies with approximately N = 26000 participants.

	REF	COUN-TRY	PARTICIPANTS (newborns)	ENROLLMENT PERIOD	SYMPTOM DIARY DURATION (from birth)	FOLLOW UP (FU) (without symptom diary)	QUESTIONNAIRE	CALLS/ INTERVIEW/ EMAIL	HOME-VISITS	CLINICAL VISITS/ EXAMINATIONS
PittsburghCohort (*)†	[42]	USA	n = 244	07/1985-04/1886	until 3 yrs	every 2 wks	-	every 2 wks	-	-
Adelaide-Cohort (*)†	[38]	South AUS	n = 1981	05/1987 04/1988	until 2 yrs	after birth, once every 3 m until 24 m	9 and 18 m	after delivery and discharge, then every 3 m until 2 yrs	-	-
New Mexico-Cohort(*)†	[11, 16, 36]	USA	n = 1205 χ [17]	01/ 1988 06/1990 χ	until 18 m	every 2 wks calls/ Interview	-	every 2 wks, up to age 18 m	at enrolment	-
Raine Study *	[43–46]	West AUS	n = 2868 χ [46]	05/1989-11/1991 χ (53)	first y of life	18, 34 wks gestation, birth, 1,2,3,5,8,10,14, 17,18,20,22,27 yrs	at age of 1, 2, 3, 4, 5, 8, 10, 14,17, 20 and 22, 27 yrs	telephone FU/ interviews Φ	-	at age of 1, 2, 3, 5, 8, 10, 14, 17, 18, 20, 22 yrs
Perth-Cohort (*)†	[5, 47]	AUS	n = 263	07/1996-06/1998	until 5 yrs	birth, 6 wks, 6, 12 m of age, then yl	not described in detail	telephone calls until resolution of the child's symptoms	home visit for respiratory symptoms	at 6 wks, 6 and 12 m of age, and then yl
VIGALL (*)	[34]	NLD	n = 126	08/1996-11/1998	wkly symptom card until 2 yrs	birth, 3m, 6m, 12m, 18m, 24m	birth, 3, 12, 24 m	-	during signs of URI	6 m, 12 m, 18 m, 24 m
PEIC (*)‡	[41, 48]	CAN	n = 332	06/1997 1999	until 2 yrs	twice mtly until 2 yrs	-	phoned twice mtly	-	-
Allergy-flora (*)	[49, 50]	SWE	n = 187	1998 2003	first y of life	6, 12 m until 18 m Contact to parents at wk 1, 2, 4 and 8 until 2005	-	at enrolment, then 6 and 12 m	-	at 18 m of age and if allergic symptoms occur
COPSAC 2000 (*)	[51, 52]	DK	n = 411	08/1998 12/2001	until 6 yrs Φ	2, 4 wks Φ, every 6 m until the age of 7 yrs, then at the age of 9, 12, 18 yrs	-	at enrolment, 1, 6, 12 m	-	at the age of 2 wks, every 6 m until the age of 7; if symptoms occur
WHIST-LER *	[53–57]	NLD	n = 2133 [58]	12/2001-01/2013	first y of life	at birth, mtly during the first 12 m, 5, 8 yrs	birth, mtly during first y, then yl	as reminder	to collect dust	2^{nd} or 3^{rd} wk of life /FU 5 and 8 yrs
PASTURE (*)	[58–60]	AUT DEU FIN FRA CHE	n = 1133	08/2002 03/2005	2 m until 1 y	before birth 2, 12, 18, 24, 36, 48, 60, 72 m, at the age of 6 yrs, 10,5 yrs (until 2015)	before birth, 2, 12, 18, 24 m, and then yl until age of 6, 10,5 yrs	before birth, 2, 12, 18, 24 m, and then yl until age of 6 yrs	age of 2 m	age of 1y
Kopen-hagen-Cohort(*)†	[37, 61, 62]	DK	n = 242 χ	05/2004 05/2005	first y of life	mtly until 1 y (1 May 2006)	-	at the first home visit, repeated every second m	mtly	mtly home visits

(*Continued*)

Table 2. (Continued)

	REF	COUN-TRY	PARTICIPANTS (newborns)	ENROLLMENT PERIOD	SYMPTOM DIARY DURATION (from birth)	FOLLOW UP (FU) (without symptom diary)	QUESTIONNAIRE	CALLS/ INTERVIEW/ EMAIL	HOME-VISITS	CLINICAL VISITS/ EXAMINATIONS
TEDDY Study *	[35, 63, 64]	USA/EUR	n = 8677	12/2004-02/2010	3 m until 2 yrs, then appropriate book	every 3 m until 4 yrs, then yl until the age of 15 yrs	3, 9 m, up-dated after 2 yrs, then every 4 y	during visits biannually at 4 yrs of age	-	every 3 m until the age of 4yrs, then biannual, subgroup every 3 m
Madigan Childcare Study (*) ‡	[65–67]	USA	n = 225 ¥	02/2006-04/2008 10/2008-06/2009	STA was completed by the child's parent for 10 days following illness onset for 2 y	interviews until 40 m of age χ	-	at enrolment and if symptoms occurred	at illness onset	a study physician documented visit/ nurse contact in childcare site
Utrecht-Cohort (*)†	[68–71]	NLD	n = 291 χ (39)	03/2006-02/ 2010χ	first y of life	1 and 12 m	at 1m and 1 y of age	around birth, 3 wks after delivery	first respi-ratory infection	to withdraw blood at first m
STEPS *	[72–75]	FIN	n = 1827	01/2008-04/2010	first two yrs of life daily, then wkly until 5 yrs of age	before and after birth, 13, 18, 24 m. until the age of 2 yrs	before birth, birth, 13, 18, 24 m, then yl	no	no	if symptoms occur/ age of 2, 13, and 24 m.
COPSAC 2010 *	[76]	DK	n = 700	2008/2010	until 3 yrs Φ	24, 36 wks gestation,1 wk, 1, 3, 6 m, then every 6 m until 36 m, then yl until 6 yrs, then at the age of 8, 10 yrs	online survey from 2016 onwards Φ	at regular intervals between visits	-	week 24 of gestation, 1, 3, 6 m, then every 6 m until 36 m, then yl until 7yrs; if symptoms occur
DIABIMMUNE	[77–80]	FIN EST RUS	n = 563	09/2008–10/2013	3m until 3 yrs	3, 6, 12, 18, 24, 36 m	3, 6, 12, 18, 24, 36 m	-	-	3, 6, 12, 18, 24, 36-m
OrChid (*)	[12, 81–83]	AUS	n = 158	09/2010-10/2014	until 2 yrs	every 3 m until 2nd birthday	no	telephone-interview 3-mtly	no	after delivery
NPICS (*)	[39, 84]	NIC	n = 518 n = 1705 ¥	2011–2013	until 2 yrs (subgroup)	until 2 yrs, wkly in diary subgroup	at enrollment, then yl.	yl calls and email as reminder	for part who did not attend FU	yl/ first signs of influenza-like illness
PATCH (*)	[85, 86]	TWN	n = 387	01/2012-11/2014	first y of life	1, 2, 4, 6, 12 m	at each planned visit	calls, interviews, emails	-	regular visits at clinic and examinations, if symptoms occur
Loewen KIDS *	[87]	DEU	n = 782	11/2014-02/2018	until 6 yrs	at birth, 3,6,12,18, 24 m, then yl until age of 15 y	at birth, 6 m, age 1 till 15 yl.	email as reminder	no	to withdraw blood

(*Continued*)

Table 2. (Continued)

	REF	COUN-TRY	PARTICIPANTS (newborns)	ENROLLMENT PERIOD	SYMPTOM DIARY DURATION (from birth)	FOLLOW UP (FU) (without symptom diary)	QUESTIONNAIRE	CALLS/ INTERVIEW/ EMAIL	HOME-VISITS	CLINICAL VISITS/ EXAMINATIONS
wk wkly m mtly y yl part	week weekly months monthly year yearly participant		¥ (*) * - ϰ †	over all sample size complete active data not reported varies according to publication if no study name was known the location of the primary centre is given	‡ ‡ Madigan Childcare-Study ‡PEIC URI Φ -	abbreviated cohort name Madigan Army Medical Centre-Childcare Study Prince Eduard Island Cohort upper respiratory infection validated through study stuff- different to data in publication Data not reported				

https://doi.org/10.1371/journal.pone.0263559.t002

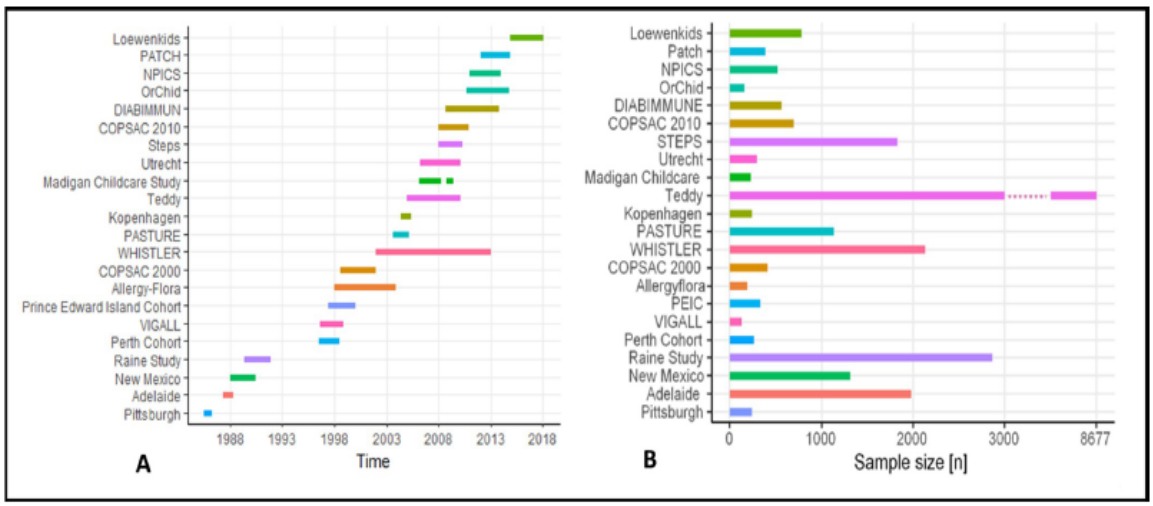

Fig 2. A. Time of enrollment B. Number of participants in considered studies.

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which recruited participants between 2014 and 2016, while the oldest study is a cohort study from Pittsburgh, which enrolled subjects from July 1985 to April 1986 (Fig 2B).

Recruitment period had a median of 30 months and ranged between 9 and 133 months. Five studies are still collecting data at the time of writing, while 17 studies are completed.

Symptom diary and follow up

In most cases, symptom diary entries were only noted when study participants showed symptoms, in others, participants were asked to enter all days including those without symptoms. The response rate of symptom diary data was reported rarely. Six years was the longest period for which symptom recording by diary was planned, while the shortest was ten months (Table 2). Seven studies collected data by symptom diary only for the first year of life or less, seven studies for the first two years, three for three years or less, two for six years, and the other studies for five years, 21 months and 18 months.

Besides using symptom diaries, thirteen studies used questionnaires to conduct the follow-up of their participants. The mode of follow-up by questionnaires ranged between monthly assessments to a follow-up interval of 17 years, but the majority of birth cohorts sent out questionnaires very frequently in the first two years after birth. In addition to questionnaires, telephone calls, interviews, email contact, home visits, and clinical examinations were used to contact the participants and collect data. Most studies used phone calls and interviews to conduct follow-ups. Nine studies carried out home visits in order to collect data, to remind participants, or to conduct routine visits during the first respiratory infection or in cases where subjects could not come to the study center. Clinical visits or medical examinations took place in 18 studies, which were usually part of a fixed follow-up-appointment. A smaller proportion of these studies encouraged their participants to visit a health center when symptoms of respiratory infections occurred.

Almost all studies analyzed individual symptoms, such as dry or wet cough, wheezing, runny or stuffy nose, sore throat, fever, chills, loss of appetite and attachment. From these symptoms, most studies derived acute respiratory infections (ARI) as outcome variables. Lower and upper respiratory tract infection (LRTI, URTI) were reported in thirteen of the

studies listed. Some studies considered only individual diseases such as pneumonia, acute otitis media, or rhinitis.

We also considered the drop-out rates of the identified studies. However, not all studies reported a clear rate and those that did are very heterogeneous and not very comparable.

After six months, the New Mexico cohort recorded a drop-out rate of 12.5% [36]. The identified drop-out rates in the first year of life ranged from 10.3% in the Perth Cohort [6] and the Copenhagen Cohort [37] to 47% in the Adelaide Cohort [38]. The NPICS Cohort study was also in the lower third with 14.8% within at the first year [39]. In contrast, the STEPS study [40] reported a drop-out rate of 6% after 13 months. Three of the identified studies reported a drop-out rate of 12% after 2 years in the LoewenKIDS cohort (personal request), 32.5% in the Vigall cohort [34] and 58% in the Adelaide cohort. The PEIC cohort [41] reported a drop-out rate of 20.5% after three years. The data of all other studies considered here could not be clearly and comparably identified.

Biosamples

Eighteen studies collected biosamples from participants during follow up periods.

Blood samples. The collection of blood from children was part of the protocol in thirteen studies (Table 3). Eight of these studies took additional blood samples, including umbilical cord blood (n = 8) and maternal blood (n = 7). One study collected umbilical cord blood samples only.

Nasal swabs. A total of fifteen studies collected nasal swabs in different frequencies. In eight of fifteen studies, nasal swabs were taken when the child was free of respiratory infection symptoms and every time symptoms occurred, whereas in three of the fifteen studies, only asymptomatic swabs were taken.

Stool samples. Nine studies collected stool samples when children were free of gastrointestinal symptoms. Of these, one study additionally collected stool samples in symptomatic subjects.

Other biomaterials. In eight studies, genetic swabs (n = 6), urine samples (n = 4), placental sample (n = 1), toe nail clipping (n = 1), hair sample (n = 2), dried blood (n = 1), skin sample (n = 1), semen (n = 1), and samples of breastmilk (n = 4) were collected.

Exposures and potential risk factors for respiratory infections

In most studies, known exposures and risk factors such as environmental exposures in households and outside of households, information on social contacts, socioeconomic factors, birth mode, breastfeeding, presence of siblings, animal contact, daycare-attendance, vaccination, nutrition, stress, and information about the family history were part of the collected data (Table 4). Seven studies assessed all mentioned risk factors.

Discussion

In this scoping review, we identified 22 birth cohort studies using a symptom diary to collect symptoms of respiratory infections beginning within the first four months after birth. These studies varied in terms of number of participants, duration of data collection, follow-up times, as well as in respiratory outcomes, collected biosamples and assessed environmental exposures.

The number of detected birth cohort studies employing diaries is small compared to the overall number of birth cohort studies that were established on bronchial asthma, allergies, and respiratory infections over the past 35 years. Some excluded studies used symptom diaries after the first year of life and the majority of the excluded studies used other approaches like

Table 3. Biological samples collected in the birth cohorts studies.

COHORT -NAME	CHILD BLOOD	ASYMPTOMATIC NASAL SWAB	SYMPTOMATIC NASAL SWAB	ASYMPTOMATIC STOOL SAMPLE	MATERNAL BLOOD	CORD BLOOD	OTHER SAMPLES
Raine	age of 5, 8, 14, 17, 18, 20, 22 yrs	-	-	-	18 wks, 34 wks before birth	yes	placental-, semen-, urine-, saliva sample
VIGALL-Study	-	-	if symptoms occur	-	-	-	-
Perth-Cohort	5 yrs	one in winter and a second in summer	onset of respiratory symptoms	-	-	-	-
Allergyflora	age of 18 m	-	-	wk 1, 2, 4, and at 6, 8, 12, 18 m, part born after 07/2000 additionally at age of 36 m	-	-	-
COPSAC 2000	6 m, 18 m, 1, 4, 6 yrs	during infancy	1m, 1y and if symptoms occur until 3 yrs	1w, 1, 12, 18 yrs	ad-hoc but at least 2 yrs after birth	yes	hair-, urine-, breast-milk-, saliva-sample
COPSAC 2010	6, 18 m, 6,8,10 yrs	1 w, 1 m, 3 m	if symptoms occur	1w, 1m, yl until 6 yrs, then at the age of 8, 10 yrs	24th wk of pregnancy	yes	hair-, urine-, breast-milk-, saliva-, skin-, dried blood sample
PASTURE	1, 4, 6, 10,5 y	-	-	-	at birth, at age of 1 year	yes	breast milk (2 m)
Kopenhagen	age 5 days, 12 m	at every home visit (mtly)	-	-	at enrolment	-	-
Madigan Childcare Study	-	a sample at time of enrolment	at symptom onset and wkly thereafter until asymptomatic	study 2008–2009 wkly asymptomatic and symptomatic samples	-	-	-
TEDDY Study	every 3 m until to the end	at 9 m of age and at each visit thereafter	-	mtly until 48 m of age, then every three m until 10 yrs, then every six m until 08/2018.	gestation/ at birth	yes	toe nail clipping, urine, saliva sample
Utrecht-Cohort	age of 1 m	-	at every respiratory episode	-	-	-	-
STEPS	1, 2 and 3 yrs	2, 13 and 24 m	during respiratory infection	at the age of one year	yes	yes	breastmilk
WHISTLER	-	the start of every m (subgroup)	second day of a wheezing episode (only subgroup)	-	-	-	buccal sample at birth
DIABIMMUNE	3, 6, 12, 18, 24, 36m	during each visit of study clinic	-	every m starting at age of 1 m	-	yes	-
NPICS	yl for children > 6 m	-	during visits at health centre with symptoms	-	-	-	-
OrChid	-	at birth and wkly	-	at birth and once a week	-	yes	
PATCH	-	1, 2, 4, 6, 12 m	during acute wheezy episodes	-	-	-	-
LoewenKIDS	age of 1 y and 2 yrs in subcohort	once per year (age 0–6 yrs; complete cohort) four times per year (age 0–2; subcohort)	if respiratory symptoms occur	once per year (age 0–6 years; complete cohort) four times per year (age 0–2; subcohort) additionally symptomatic sample if symptoms occur	-	yes	buccal sample at the age of 1 y
wk	-	**Week**	**yrs**	**years**	**data not reported**		
wks		**wks**	**y**	**year**			
wkly		**weekly**	**yl**	**yearly**			
m		**months**	**Mtly part**	**Monthly participant**			

https://doi.org/10.1371/journal.pone.0263559.t003

Table 4. Recorded variables for exposures/ risk factors for respiratory infections.

COHORT NAME	RISK FACTORS												
	ENVIRONMENTAL	HOUSEHOLD EXP.	SOCIAL RELATION SHIP	SOCIOOECONOMIC STATUS	BIRTH MODE	BREAST FEEDING	SIBLINGS	ANIMAL CONTACT	DAY CARE ATTENDANCE	VACCINATION	NUTRITION	STRESS	FAMILY HISTORY
Pittsburgh	-	-	-	+	-	-	+	-	+	-	-	-	+
Adelaide-Cohort	+	-	+	-	+	+	+	-	+	-	-	-	+
Raine Study	+	+	+	+	+	+	+	+	+	+	+	+	+
New Mexico	+	+	+	+	+	+	+	-	+	-	-	-	+
VIGALL	-	+	+	+	+	+	+	+	+	-	+	-	+
Perth-Cohort	+	+	+	-	-	+	+	+	+	-	-	-	+
PEIC	+	+	+	+	-	+	-	+	+	-	-	-	+
Allergyflora	+	+	+	+	+	+	+	+	+	-	+	-	+
COPSAC 2000	+	+	+	+	+	+	+	+	+	+	+	+	+
COPSAC 2010	+	+	+	+	+	+	+	+	+	+	+	+	+
PASTURE	+	+	+	+	+	+	+	+	+	+	+	-	+
Kopenhagen-Cohort	+	+	+	+	+	+	+	+	+	+	+	-	+
Madigan Childcare Study	+	-	+	+	+	-	+	+	+	-	-	-	+
TEDDY	+	+	+	+	+	+	+	+	+	+	+	+	+
Utrecht-Cohort	-	+	+	+	+	+	+	+	+	-	+	-	+
STEPS	+	+	+	+	+	+	+	+	+	+	+	+	+
WHISTLER	+	+	+	+	+	+	+	+	+	-	+	-	+
DIABIMMUNE	+	+	-	-	+	+	+	+	+	+	+	-	+
NPICS	+	+	+	+	+	+	+	+	+	+	+	+	+
OrChid	+	+	+	+	+	+	+	+	+	+	+	-	+
PATCH	+	+	+	+	+	+	+	+	+	+	+	-	+
LoewenKIDS	+	+	+	+	+	+	+	+	+	+	+	+	+

+ yes

- data not recorded

https://doi.org/10.1371/journal.pone.0263559.t004

retrospective questionnaires, interviews and clinical visits to estimate the burden of respiratory diseases [17–23].

While episodes of respiratory infections can be recalled fairly well over a period of two months [88–90], it is unlikely that daily symptom evolution can be accurately recalled without prospective daily collection. Therefore, it is unlikely that the sequence of symptoms, especially if they were frequent and less severe, can be recalled with any degree of accuracy using retrospective records, thereby introducing recall bias into these studies [91]. Preventing this is particularly important for transient symptoms of childhood infections, especially when we are interested in the prospective evolution of symptoms. This includes duration, intensity, and whether only one or multiple symptoms occurred [52]. Therefore, symptom diaries have been used for many decades. They produce more valid data, i.e. higher reporting and incidence rates thereby mitigating recall bias [13, 91, 92].

Causes of low symptom diary use in birth cohort studies

An overall aim of this review was to map birth cohorts that use(d) symptom diaries to identify respiratory diseases. Of the numerous birth cohort studies identified, relatively few really used a symptom diary to identify respiratory illness. Substantial administrative study efforts, the effort involved in data analysis, but also possible upcoming problems due to drop-out rates, could be possible barriers from the researchers' point of view. In addition, filling out a daily symptom diary is a considerable burden for participants. Some studies show that, although the respondents themselves report good compliance, data collection protocols are often not followed, and a large number of missing records might occur [93, 94]. On the other hand, one reason for the rather infrequent use may be the risk of "hoarding", which is known as a problem where participants enter data into their diary retrospectively [93]. Unfortunately, hoarding is almost impossible to detect unless the time of data entry is recorded electronically. Weariness can also lead to a decline in diary completion rates over time [95]. It is therefore important to have a well-staffed and well-trained study team that can maintain good contact with the study participants to avoid missing data and drop-out.

This review shows that especially immediately after birth, when infants show a high susceptibility to respiratory illness, few studies use symptom diaries to record respiratory symptoms [96]. Because the immune system undergoes crucial developmental maturation during this time, detailed recording of all potential exposures, including infections, is crucial in understanding the development of the immune system and other outcomes. Most of the studies identified here were conducted in Europe, North America, and Australia, which may limit the generalizability of results and thus require more birth cohorts from other regions of the world.

Some studies retrieved either ARI, URTI or LRTI as respiratory outcomes from the symptom diary data, yet there is no consensus how to use the collected data in harmonized manner. This also makes it difficult to compare respiratory outcomes in this ScR. Additionally, most studies collected a broad range of environmental exposures, but only a few collected a broad range of biosamples. Nevertheless, biosamples are important because, they complement associations and research questions. For example, nasal swabs can be used to identify pathogens responsible for the development of ARI and to study them in relation to a specific combination of symptoms. Analysis of other biosamples, such as blood samples, can help to understand the immune system's response to the development of ARI.

Strengths and limitations

To our knowledge, this scoping review is the first comprehensive attempt to summarize, map and compare birth cohort studies with symptom diary information for respiratory symptoms

beginning from birth. The strength of our review is the comprehensive search of the literature. Our rather specific search strategy was comprehensively extended by a systematic search in four databases, an additional extensive search in registers and a very elaborate search in reference lists of the identified publications from all four databases. We assume that due to this extended search strategy the probability of having overlooked a birth cohort study with the use of symptom diaries from birth is low.

We also conducted additional searches of the gray literature to avoid omitting cohorts that had recently started. Finally, to ensure the accuracy of the extracted data, we contacted one or two authors of all included birth cohorts to confirm the extracted information or clarify, if questions remained open. Our study also had several limitations. It is possible that we failed to identify some cohort studies applying symptom diaries due to no uniform wording for symptom diaries. Not all birth cohort studies offer detailed cohort profiles, and information had to be collected in different publications. In addition, it may be possible that a birth cohort study could not be identified because it is neither registered in one of the web-based registers nor published in a way that met our search criteria. We hope that the broad search allowed to minimize these problems.

Conclusions

We have been able to provide a comprehensive review with all birth cohort studies that are suitable for providing a holistic understanding of the association of ARI as exposure with potential long-term sequelae in a life course perspective. We found 22 birth cohort studies that use(d) symptom diaries for respiratory infections. While, symptom diaries provide a powerful tool for prospective data collection, their long-term application is very challenging, so this is why it is not often applied. Our review shows that is possible and was done in several studies. Many questions related to the role on infections in the development of the immune system require information on symptom evolution and infection history over time. When combined with biosamples, this detailed information is very valuable. This overview helps to establish collaborations between researches in order to investigate the pattern, timing and sequence of respiratory infections and their association with the developing immune system and other exposures in a life-course perspective.

Supporting information

S1 Checklist. Preferred reporting items for systematic reviews and meta-analyses extension for scoping reviews (PRISMA-ScR) checklist.
(DOCX)

Author Contributions

Conceptualization: Cornelia Gottschick, Rafael Mikolajczyk.

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Formal analysis: Susan Langer.

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Methodology: Susan Langer.

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Supervision: Cornelia Gottschick, Rafael Mikolajczyk.

Validation: Susan Langer, Bianca Klee, Cornelia Gottschick.

Writing – original draft: Susan Langer.

Writing – review & editing: Bianca Klee, Cornelia Gottschick, Rafael Mikolajczyk.

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Publication 3 (P3)

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Cohort Profile

Cohort Profile

Cohort Profile: The LoewenKIDS Study – life-course perspective on infections, the microbiome and the development of the immune system in early childhood

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Why was the cohort set up?

The immune system of newborn children undergoes intensive development during the first years of life.[1] However, both, adaptive and innate immunity do not reach full capacity until teenage years.[2,3] The immune system is thus shaped by different external factors until adolescence.[4] A malfunctioning immune system not only leads to higher susceptibility to infections but can also cause atopic diseases like asthma and allergies.[5] According to the 'hygiene hypothesis' it was shown that children raised on farms or children in contact with dogs have a lower risk of developing asthma or allergies due to their environmental (e.g. microbial) exposures.[4,6] Furthermore, infections with different respiratory viruses (e.g. rhinovirus, enterovirus and adenovirus) in infancy influence the development of chronic and immune-mediated diseases like asthma, type 1 diabetes and obesity in later life.[7–9] Although many birth cohort studies have addressed asthma and allergies, only two studies, the INSPIRE study in the USA and the ORChID study in Australia, have focussed on infections and the development of atopic diseases.[10–12] However, INSPIRE lacks comprehensive data on infections during childhood and ORChID has a small sample size and collected data on infections only for 2 years. In order to prospectively assess the complete infection history during the first 6 years of life, we have initiated the German multicentre LoewenKIDS birth cohort study in 2015. The aim of this study is to combine the complete infection history with information on the development of the nasal and gut microbiome and the immune system, as well as the genetic background and information on the children's environment (nutrition, pets, siblings, day-care attendance, medication etc.). These data will help us to understand the association between infections, vaccinations, the microbiome, and genetics on the one side and immune-mediated diseases like atopic dermatitis, allergic asthma, and allergies on the other side. Before initiating the cohort, we conducted a pilot study to assess willingness to participate and a feasibility study testing different study components.[13,14] This study is funded by institutional resources of the Helmholtz Centre for Infection Research and the Martin-Luther-University Halle-Wittenberg.

Overall goals

The overall goal of our birth cohort is to record a complete history of respiratory and gastrointestinal infections in infancy in order to investigate the effect of pattern, timing and sequence of infections and other risk factors influencing the immune response on the development of asthma and atopic diseases from a life-course perspective. We further aim to study effects of timing and sequence of infections on the progression severity of subsequent infections, and how those affect the immune response to vaccinations and their waning.

Collaboration goals

We intend that several collaborations will allow us to address our study aims, but we also welcome further propositions. With a wide range of different biological samples and information on many aspects of children's daily life, we are able to address a broad range of research questions.

Who is in the cohort?

All newborn babies in five study regions in Germany [Braunschweig, Hannover, Bremen, Munich, Halle (Saale)] were eligible for enrollment in the study up to 3 months post-partum. Participants were recruited at antenatal preparation courses, information evenings in hospitals and in private practices, where approximately 35 000 families

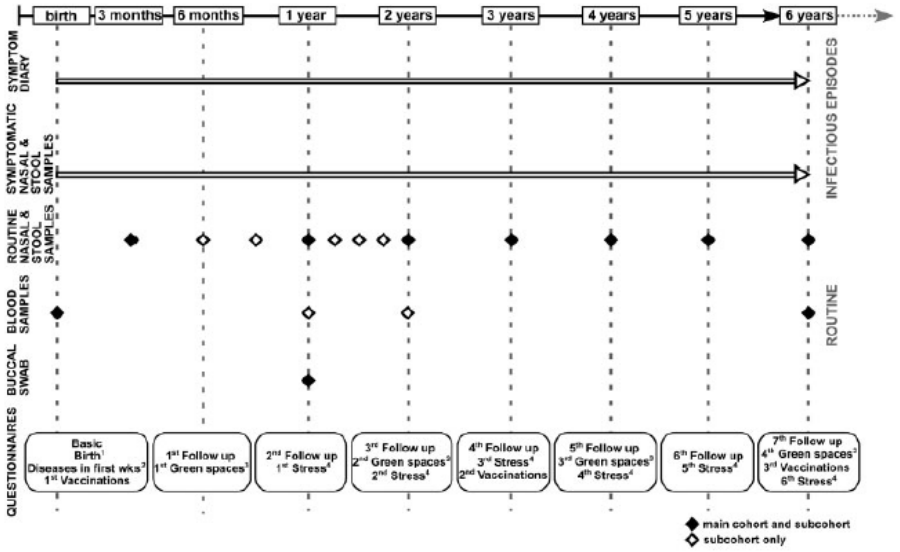

Figure 1. Study structure and materials over the whole study period of 6 years according to infectious episodes and tasks performed routinely in health. The timing of symptom diary, biological samples and questionnaires is shown separated for main cohort and subcohort and the subcohort only (depicted as full and empty diamonds, respectively). [1]'Birth' questionnaires collect data on all birth aspects, [2]'Diseases in the first weeks' questionnaires are completed by participants who have entered the study after their date of birth and could not fill in the symptom diary from the beginning, [3]'Green spaces' questionnaires collect data on the living environment, [4]'Stress' questionnaires address parental stress.

wks, weeks.

were reached. Overall, 782 newborns were enrolled, and of these 336 (43%) in Braunschweig, 174 (22%) in Hannover, 97 (12%) in Bremen, 91 (12%) in Munich and 76 (10%) in Halle (Saale) resulting in a response proportion of 2%. In total, 422 (54%) children were included before and 360 (46%) children after birth. The first enrolled child was born in November 2014 and the last in February 2018. The sex ratio of the participating children is 1:1. There are 27 sibling pairs within the cohort, including eleven pairs of twins. In total, 285 children (36%) were enrolled in a nested subcohort with more frequent collection of asymptomatic samples and additional blood sampling at the ages of 1 and 2 years (Figure 1).

How often have they been followed up?

During the first 6 years, all parents are asked to fill in a symptom diary every day, take nasal or stool samples whenever their child shows predefined respiratory or gastrointestinal symptoms, and collect asymptomatic nasal and stool samples in asymptomatic children once a year (main cohort) or four times a year in the first 2 years and once a year in years 3–6 (subcohort). All participants are planned to provide blood samples at the age of 6 years and participants of the subcohort provide blood samples at ages 1 and 2 years in addition. All blood samples are taken by a physician. Parents fill in follow-up questionnaires at the age of 6 months, 1 year, and then annually until the age of 6 years. After the follow-up period of 6 years, participants will receive yearly questionnaires until the age of 15 with the option to further extend that period.

What has been measured?

In the LoewenKIDS study, data are collected in symptom diaries, questionnaires and through biological samples (Figure 1).

Symptom diary

Acute respiratory and gastrointestinal diseases are assessed in a daily symptom diary through ticking corresponding boxes. Symptoms include the precise temperature of fever, wheezing, runny/congested nose, chills, sore throat, loss of appetite, increased need to sleep, increased attachment, vomiting and diarrhoea. Here, parents also rate the symptom severity, and provide data on doctor visits, work absenteeism and medication on a daily basis. In case of shorter or longer symptomless time periods, crossing out the whole period simplifies the use of the symptom diary making it more feasible in everyday life. The symptom diary was developed based on the symptom diary used by the Australian birth cohort ORChID and adapted according to the results of our feasibility study.[12,13] Participants can choose between a paper-based diary, an online version or an app. Changes between the different modes are allowed.

Table 1. Content of the questionnaires in the LoewenKIDS study

Topic	Pregnancy	Birth	6 months	1 year	2 years	3 years	4 years	5 years	6 years
Acute infections		Continuously in the daily symptom diary →							
Demographics	x					x			
Medication during pregnancy	x								
Selected diseases[a] in mother's family history	x								
Selected diseases[a] in father's family history	x								
Infection frequency mother	x	x							
Infection frequency father	x								
Smoking of parents	x		x						x
Opinion on child's vaccination	x								
Influenza vaccination mother		x							
Delivery		x							
Size and weight		x			x	x	x	x	x
Breastfeeding		x	x	x	x				
Vaccinations		x			x				x
Alcohol consumption during pregnancy			x						
Child's development			x	x	x	x	x	x	x
General health			x	x	x	x	x	x	x
Diseases			x	x	x	x	x	x	x
Sleeping			x	x	x	x	x	x	x
Dietary habits			x			x	x	x	x
Domestic pets			x	x	x	x	x	x	x
Siblings			x	x	x	x	x	x	x
Access to green areas			x		x		x		x
Day-care attendance				x	x	x	x	x	x
Stress of parents				x	x	x	x	x	x
Atopic dermatitis					x	x	x		
Allergy						x	x	x	x
Asthma bronchiale							x	x	x
Social and emotional quality of life							x	x	x
Leisure and physical activities								x	x

[a]Selected diseases are neurodermatitis, asthma, diabetes mellitus type I, diabetes mellitus type II, rheumatoid arthritis, lupus erythematosus, as well as hay fever, and allegies against house dust mites and pet hair, and lactose, gluten and fructose intolerance.

With increasing immunocompetence of our participants, we expect a drop in days with symptoms, decreasing the parent's workload over time.

So far, 754 (96%) of our children have turned 1 year old. Therefore, we have analysed the completeness of our symptom diary data in the first year of life based on the data we have to date. Of all 754 participants, at least 503 (67%) have filled out all quarter-yearly provided symptom diaries and another 62 (8%) have filled out at least three quarters of the symptom diaries in the first year of life. These proportions were similar in the subcohort and main cohort.

Questionnaires

Paper-based or online questionnaires collect data on the parents and child throughout the study (Table 1).

Biological samples

We collect a vast amount of biological samples (Figure 1, Table 2). Our sample sizes will continuously increase as our participants get older and the number of biological samples is thus subject to change. Except for blood samples, all biological samples are self-collected by the parents. In the main cohort, routine nasal swabs and stool samples of the symptomless child are taken once a year for microbiome analyses. In the nested subcohort, routine samples are taken every 3 months in the first 2 years of life and yearly at ages 3–6 years. The collection of nasal swabs and stool samples during acute disease is triggered by signs of acute respiratory disease and signs of acute gastroenteritis, respectively. In detail, for respiratory symptoms, a swab is taken when the child shows one of the following symptoms: fever, wheezing, productive cough, or otitis media or

Table 2. Overview of the available biological samples

Sample type[a]	Main cohort ($n = 497$)		Subcohort ($n = 285$)		Total
	Age (years)	n	Age (years)	n	n
Nasal swab					
Symptomatic	0–3	2698	0–3	2090	4788
Asymptomatic, once per year	0–3	892	2 –3	116	1008
Asymptomatic, four times per year	–	–	0–2	1533	1533
Stool samples					
Symptomatic	0–3	639	0–3	609	1248
Asymptomatic, once per year	0–3	949	2 –3	117	1066
Asymptomatic, four times per year	–	–	0–2	1653	1653
Blood samples					
Umbilical cord blood samples	0	17	0	3	20
Whole blood	–	–	1	150	150
Whole blood	–	–	2	60	60
Genetic swabs					
	1	147	1	140	287

[a]Current sampling status as of 10/2018.

pneumonia diagnosed by a physician, or two of the following symptoms: rhinitis, dry cough, sore throat, rigors, lack of appetite, increased need of sleep, or increased attachment according to a definition by Lambert *et al.*[12] Swabs are taken using the Copan Liquid Amies Elution Swab (ESwab, Hain Lifescience) and transported via regular mail (typically 2–3 days) and stored at –80°C. For gastrointestinal symptoms, a sample is taken if diarrhoea occurs four or more times within 24 hours and/or vomiting occurs at least once within 24 hours. Stool samples are transported via mail and stored at –80°C in RNASepar Solution (Biosepar). For both, nose swabs and stool samples, we successfully tested the stability for up to 2 weeks at room temperature before starting collection. Four aliquots each containing at least 200 µl of the sample-storage solution mixture are available for nasal swabs and stool samples. Regarding completeness of biological samples, we have analysed the data of all 754 children (96%) who have turned 1 year old to date. In the main cohort, nasal swabs are 87% and stool samples 88% complete. In the subcohort, 67% and 75% have returned at least three of the four required nasal swabs and stool samples, respectively. Umbilical cord blood is taken whenever possible depending on the hospital chosen for birth. However, only 20 participants (3%) have provided samples, limiting the scope of research questions possible to address. Blood samples are taken by a physician within the subcohort at the age of 1 and 2 years and in all children at the age of 6 years (planned). We collect at least two aliquots each of 200 µl of serum and 500 µl of plasma and at least $3x10^6$ peripheral blood mononuclear cells. Blood samples are stored at –80°C or in liquid nitrogen. Of 285 eligible participants in the subcohort, 150 (53%) have provided a blood sample after the first year of life. We expect blood samples in about 70% of these participants after the second year of life, resulting in around 106 complete blood sample sets from the first and second birthday (calculation based on the samples we have collected after the second year so far). Buccal swabs for genetic analyses are planned to be taken from all children (dry sterile swabs, Nuova Aptaca). We ask the parents to provide these samples when the child is 1 year old. Buccal samples are transported via regular mail and stored at –80°C. So far, 53% of the already contacted participants of the subcohort and 44% of the main cohort have provided buccal swabs. However, not all participants have been contacted yet, explaining the relatively low number in Table 2.

Planned use of collected data

Effects of certain infections on the immune system and the microbiome and vice versa are of special interest to us. Here, we aim to use symptomatic nasal swabs and stool samples to identify causal pathogens of respiratory and gastrointestinal symptoms. For pathogen identification, we plan to implement a wide assay including 39 respiratory and 36 gastrointestinal pathogens (Allplex™ Respiratory Panel Assays and Allplex™ Gastrointestinal Panel Assays, Seegene). Our focus is on viruses and we expect prevalence of human respiratory virus and respiratory syncytial virus as well as rotavirus, norovirus and adenovirus.[13] Nevertheless, research on other causative agents of respiratory and gastrointestinal infections is planned or may evolve in future collaborations. Furthermore, all nasal

swabs and stool samples will be analysed regarding changes of microbial community composition over time and with respect to influencing factors like infections, vaccinations, antibiotic intake and breastfeeding/nutrition over time. Analyses based on 16S rRNA gene region sequencing are part of the analysis plan. This can be further extended to metagenome or metatranscriptome analyses for specific questions in subsets of eligible samples. Identification of the virome and mycobiome will give insights into a holistic understanding of the overall microbial development within the first years of life. Blood samples will be used to determine cytokine and serological patterns as well as cellular immunoprofiles after infections and vaccination, but may also be analysed with regard to certain microbiota enterotypes or extrinsic factors like breastfeeding/nutrition. Buccal swabs will be used to determine the genetic background, i.e. single nucleotide polymorphisms, with regard to infection susceptibility, asthma predisposition or responsiveness to vaccinations. In the long-term, all of these data can be connected, and once asthma and atopic diseases become prevalent in the LoewenKIDS cohort, they will be linked to the development of atopic diseases and allergies. However, it is important to emphasize that we rely on laboratories of collaboration partners regarding analyses of all biological samples. Since our youngest participant is born in February 2018, we are still gathering data and samples and have not begun with the analysis of biological samples yet. We have several aliquots of each sample and are thus relatively flexible and open to providing our biological samples for different approaches and research questions.

What has it found? Key findings and publications

As the study is still ongoing, only limited findings are described here. Characteristics of parents and children of the main cohort and subcohort showed no differences, thus results are combined and reported in detail in Tables 3 and 4.

The mean age of mothers and fathers at birth was 33 years [standard deviation (SD) ± 4 years] and 35 years (SD ± 5 years), respectively (Table 3). The average age of German mothers at birth is 30 years (not available for fathers).[15] Our mothers are thus older than average. Concerning the parents' education, 15% and 16% of the mothers and fathers completed an apprenticeship (German 'Lehre'), 45% and 46% held a master's degree or diploma and 16% and 12% a PhD (Table 3). In contrast, 45% of the German general population between 30 and 40 years of age completed an apprenticeship, 22% a master's degree or diploma and only 2% hold a PhD.[29] Our study is thus characterized by a highly educated study population, explaining the age of mothers at birth being above average. Furthermore, LoewenKIDS participants may have been intrigued to take part in our study because of their own background in academia. Of our study participants, 39% had a monthly household net income lower than 4000 Euro, 21% between 4000 and 5000 Euro and 25% above 5000 Euro (15% missing or unknown). With the average monthly net houshold income being 4761 Euro in Germany, the household income of our cohort is approximately average despite a high education level.[16]

Most prevalent diseases in the family histories of participating parents were allergies, with 69% affected by hay fever, 48% affected by house dust mite allergy and 46% affected by pet hair allergy. Lactose intolerance was the most common food intolerance with 23% of families affected. In the German general population, 15% are affected by hay fever and less by house dust mite and pet hair allergy, thus families of our cohort may be especially affected by allergies.[17] Furthermore, neurodermatitis, asthma and diabetes type II were highly prevalent in the family histories of our study participants (42%, 32% and 21%, respectively). In the German general population over all age groups, the prevalences of neurodermatitis, asthma and diabetes (type I and II) are 4%, 9% and 7%, respectively.[17,19] The high prevalence observed in our study may partly be due to biased sampling and an increased willingness to participate in parents with a history of these illnesses. However, it may also partly be due to the fact that we have asked for the complete family history, meaning diseases in parents, aunts and uncles, and grandparents of the participants.

In the cohort, 66% of the births were spontaneous, 27% had planned or unplanned C-sections (9% and 18%, respectively) and 7% were forceps- or vacuum-assisted deliveries, which is in line with data from the German general population (Table 4). Considering gestational age at birth and the <10th percentile and >90th percentile for weight according to Fenton and Kim,[20] 601 (84%) of the newborns had average weight, 39 (6%) were large for gestational age and 58 (8%) were small for gestational age, Table 4. Considering gestational age at birth and the same percentiles for length, 529 (74%) of the newborns were of average length, 140 (19%) above and 26 (4%) below averange length.

What are the main strengths and weaknesses?

LoewenKIDS is the first study to prospectively explore the sequence and cumulative load of infections in early childhood.

Table 3. Data on participating parents from the basic questionnaire

Parents	Total ($n = 740$)	Main cohort ($n = 467$)	Subcohort ($n = 273$)	*P*-value	Reference values[a]	Reference
Age mothers in years (mean ± SD)	33 ± 4	33 ± 4	33 ± 4	0.496	30	[15]
Age fathers in years (mean ± SD)	35 ± 5	35 ± 5	35 ± 5	0.971	n.a.	
Academic degree mothers						
Others	168 (23%)	106 (22%)	62 (23%)	0.810	31%	[29]b
Apprenticeship	110 (15%)	67 (14%)	43 (16%)			
Master's degree	335 (45%)	209 (45%)	126 (46%)		45%	
PhD	122 (16%)	83 (18%)	39 (14%)		22%	
Missing	5 (1%)	3 (1%)	2 (1%)		2%	
Academic degree fathers						
Others	176 (24%)	106 (23%)	70 (25%)	0.430	30%	[16]b
Apprenticeship	119 (16%)	84 (18%)	35 (13%)		48%	
Master's degree	341 (46%)	211 (45%)	130 (48%)			
PhD	89 (12%)	57 (12%)	32 (12%)		20%	
Missing	15 (2%)	10 (2%)	5 (2%)		2%	
Monthly household net income in Euro						
Unknown/ n.a.	104 (14%)	77 (16%)	27 (10%)	0.055	4761[c]	[16]
<3000	127 (17%)	88 (19%)	39 (14%)			
3000–3999	166 (22%)	102 (22%)	64 (24%)			
4000–5000	154 (21%)	91 (20%)	36 (23%)			
>5000	183 (25%)	106 (22%)	77 (28%)			
Missing	6 (1%)	4 (1%)	2 (1%)			
First pregnancy						
Yes	467 (63%)	298 (64%)	169 (62%)	0.675	-	-
No	273 (37%)	170 (36%)	103 (38%)			
Siblings						
Yes	253 (34%)	159 (34%)	94 (35%)	0.779	-	-
No	481 (65%)	306 (65%)	175 (64%)			
Missing	6 (1%)	3 (1%)	6 (1%)			
Pets in the household[d]						
None	465 (63%)	297 (64%)	168 (62%)	0.645	43%	[18]
Cats	116 (16%)	68 (15%)	48 (18%)	0.261	12%	
Dogs	75 (10%)	52 (11%)	23 (9%)	0.249	12%	
Others	98 (13%)	61 (13%)	37 (14%)	0.826	10%	
Selected diseases in family history[d]						
Asthma	239 (32%)	139 (30%)	100 (37%)	0.048	9%	[19,21,22]
Diabetes type I	42 (6%)	30 (6%)	12 (4%)	0.257	7%[e]	
Diabetes type II	155 (21%)	98 (21%)	57 (21%)	0.996		
Rheumatoid arthritis	124 (17%)	70 (15%)	54 (20%)	0.086	<1%	
Lupus erythematosus	11 (2%)	5 (1%)	6 (2%)	0.218	<1%	
Neurodermatitis	309 (42%)	186 (40%)	123 (45%)	0.145	4%	
Allergies in family history[d]						
Hay fever	507 (69%)	313 (67%)	194 (71%)	0.210	15%	[19,23]
House dust mite	354 (48%)	219 (47%)	135 (50%)	0.456	15%[f]	
Pet hair	343 (46%)	208 (44%)	135 (50%)	0.172	9%[f]	
Food intolerances in family history[d]						
Lactose	169 (23%)	105 (22%)	64 (24%)	0.733	15%	[24,25]
Fructose	44 (6%)	28 (6%)	16 (6%)	0.956	n.a.	
Gluten (coeliac disease)	38 (5%)	20 (4%)	18 (7%)	0.164	<1%	

[a]Reference values from the German general population.
[b]Only age groups 30–40 were considered based on the age of our study population at childbirth.
[c]Mean value.
[d]Multiple entries were possible.
[e]Diabetes mellitus type I and II combined.
[f]Allergy sensitization only.
Differences between main cohort and subcohort were assessed using either the Chi^2 test or the Student's *t*-test. Of all 782 participants, a total of 740 basic questionnaires were available.
SD, standard deviation; n.a., not available.

Table 4. Data on participating children from the birth questionnaire

Children	Total ($n = 715$)	Main cohort ($n = 452$)	Subcohort ($n = 263$)	*P*-value	Reference values[a]	Reference
Sex						
Female	351 (49%)	223 (49%)	128 (49%)	0.975	49%	[26]
Male	356 (50%)	224 (50%)	132 (50%)		51%	
Missing	8 (1%)	5 (1%)	3 (1%)			
Birth weight (median; IQR)						
Female	3325 g; 3027–3610 g	3330 g; 3070–3600 g	3325 g; 2995–3645 g	0.387	3390 g	[27]
Male	3500 g; 3230–3800 g	3490 g; 3210–3795 g	3535 g; 3240–3800 g	0.735	3530 g	
Birth length (median; IQR)						
Female	51 cm; 50–52 cm	51 cm; 50–52 cm	51 cm; 50–52 cm	0.653	51 cm	[27]
Male	52 cm; 50–53 cm	52 cm; 50–53 cm	52 cm; 51–53 cm	0.865	52 cm	
Weight depending on gestational age[b]						
<10th percentile	58 (8%)	33 (7%)	25 (9%)	0.572	n.a.	n.a.
10th – 90th percentile	602 (84%)	383 (85%)	219 (83%)			
>90th percentile	39 (6%)	27 (6%)	12 (5%)			
Missing	16 (2%)	9 (2%)	7 (3%)			
Length depending on gestational age[b]						
<10th percentile	26 (4%)	16 (3%)	10 (4%)	0.663	n.a.	n.a.
10th – 90th percentile	530 (74%)	333 (74%)	197 (75%)			
>90th percentile	140 (19%)	93 (21%)	47 (18%)			
Missing	18 (3%)	10 (2%)	9 (3%)			
Mode of birth						
Spontaneous	473 (66%)	305 (68%)	168 (64%)	0.749	61%	[28]
Forceps/suction	50 (7%)	29 (6%)	21 (8%)		7%	
C-section (planned+unplanned)	187 (27%)	114 (26%)	73 (28%)		32%	
Missing	3 (0%)	2 (0%)	1 (0%)			
Birth institution						
Hospital, inpatient	649 (91%)	403 (89%)	246 (94%)	0.235	n.a.	n.a.
Hospital, outpatient	42 (6%)	30 (7%)	12 (4%)			
Birthing centre	13 (2%)	10 (2%)	3 (1%)			
At home	11 (1%)	9 (2%)	2 (1%)			
Hospital admisssion in first 2 weeks						
Yes	77 (11%)	46 (10%)	31 (12%)	0.736	n.a.	n.a.
No	636 (89%)	405 (90%)	231 (88%)			
Missing	2 (0%)	1 (0%)	1 (0%)			

[a]Reference values from the German general population.
[b]Percentile placement derived from the Fenton 2013 Preterm Growth Chart.[20]
Differences between main cohort and subcohort were assessed using the Chi^2 test or the Wilcoxon test. Of all 782 participants, a total of 715 birth questionnaires were available.
IQR, interquartile range; n.a, not available.

Within this study, nasal and stool samples for microbiome and other omics analyses, blood samples for immune system analyses as well as buccal samples for genetic analyses are collected, providing an extensive view of biological processes during the first 6 years of life. Symptom diaries and multiple questionnaires covering a broad range of factors of the infantile development complete this holistic approach. The life-course perspective of this study enables a follow-up beyond the intensively monitored first 6 years of life that can provide valuable information on long-term effects. Similar to our study, the ORChiD study collected data from 154 children for 2 years in Brisbane, Australia. We designed the LoewenKIDS symptom

Profile in a nutshell

- LoewenKIDS is a birth cohort study prospectively assessing infectious diseases, the development of the microbiome and immune system as well as effects on the development of immune-mediated diseases like atopic dermatitis, allergic asthma and allergies during childhood and later life.
- Children within the cohort were born from November 2014 to February 2018 and recruited in multiple centres throughout Germany [Braunschweig, Bremen, Halle (Saale), Hannover, Munich].
- At baseline, the study included 782 new-born children, 285 thereof in an intensified nested subcohort.
- Children are followed up until the age of 6 years with the option of further study participation.
- Data are collected via symptom diaries, questionnaires and biological samples (nasal swabs, stool samples, buccal swabs, blood samples).
- Collaborations are intended. Data are held by the LoewenKIDS research team and access can be applied for.

diary to be similar to the one used in the ORChiD study and it will be interesting to compare or even combine our results with those obtained in Brisbane. In addition, we are looking forward to other suggestions for collaboration.

Due to the intensive study requirements we will be able to receive full datasets of only a fraction of participants for which we can combine all measured elements. Nevertheless, a higher number of complete data is available for several possible sub-analyses. As for biological samples, we were not able to collect samples more frequently. Therefore, highly dynamic events and variations in the microbiome will not be possible to assess. Basic characteristics of our study population are similar to the German general population except the mother's age at birth, a higher education level and more allergic diseases in the family histories of mothers and fathers. However, our cohort holds enough participants with lower education levels and without diseases in the family histories for us to be able to assess possible effects derived from these selection biases.

Can I get hold of the data? Where can I find out more?

The data are stored at the LoewenKIDS management centre. The reseach team is looking forward to potential collaborations, exchange of ideas, and suggestions. Access to the data can be obtained using the contact form on the website www.loewenkids-study.de and an application template. We are interested in collaborations based on specific expertise, particularly extending our own possibilities. The use of the data and samples must be approved and prioritized by our scientific steering committee.

Chief investigator: Prof. Dr med. Rafael Mikolajczyk.

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Conflict of interest: None declared.

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Complete list of own publications

1. **Langer, S.;** Klee, B.; Gottschick, C.; Mikolajczyk, R. Birth cohort studies using symptom diaries for assessing respiratory diseases-a scoping review. PloS one 2022, 17, e0263559, doi:10.1371/journal.pone.0263559.

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Appendix

LöwenKIDS study documents

All study documents that were particularly important for the analysis are listed here

Appendix 1 Contact form for parents

Appendix 2 Excerpt from a symptom diary

Appendix 3 Excerpts from different LöwenKIDS questionnaires that were importantly relevant for the analysis

Appendix 1 Contact form for parents

Exemplar Studienzentrale

UKH Universitätsklinikum Halle (Saale)

Imebi Institut für Medizinische Epidemiologie, Biometrie und Informatik

HELMHOLTZ ZENTRUM FÜR INFEKTIONSFORSCHUNG

Bitte ergänzen Sie folgende Daten, damit wir Ihnen weitere Mitteilungen bzw. die entsprechenden Studienmaterialien zukommen lassen können.

Herzlichen Dank!

Kontaktdaten

Name, Vorname: .....

Straße u. Hausnummer: .....

Postleitzahl, Ort: .....

Festnetz: .....

Handy: .....

E-Mail-Adresse .....@.....

Außerhalb normaler Versandaktionen würden wir gern im Bedarfsfall (Erinnerungen, Informationen, ...) per E-Mail mit Ihnen Kontakt aufnehmen.

Sind Sie damit einverstanden? ☐ ja ☐ nein

Symptomtagebuch (bitte wählen Sie nur eine der Möglichkeiten aus)

Ich bevorzuge die Dokumentation der Erkrankungen meines Kindes in folgender Form:

☐ Symptomtagebuch in Papierform

☐ Symptomtagebuch als Onlineversion und/oder App (App nur bei Android möglich)

(nur möglich bei Angabe einer E-Mail-Adresse)

Fragebögen (bitte wählen Sie nur eine der Möglichkeiten aus)

Ich bevorzuge die Beantwortung der Fragebögen in folgender Form:

☐ in Papierform ☐ als Onlineversion (nur möglich bei Angabe einer E-Mail-Adresse)

Geburtstermin

☐ voraussichtl. Geburtstermin (Geburt steht noch bevor) ☐ tatsächlicher Geburtstermin

|__|__| / |__|__| / |__|__|__|__| (Tag / Monat / Jahr)

Wenn Sie planen, in einer Klinik zu entbinden, welche wird dies voraussichtlich sein?.....

Wo sind Sie auf die LöwenKIDS-Studie erstmalig aufmerksam geworden?

☐ Hebammenpraxis ☐ Frauenarztpraxis ☐ Kinderarztpraxis ☐ Infoabend/Kreißsaalführung

☐ Wochenstation ☐ Kurs (z.B. Geburtsvorbereitung, Rückbildung) ☐ Kita

☐ Anmeldung zur Geburt ☐ Website ☐ Medien (Zeitung, ...) ☐ Anderes: .....

Hat Ihnen jemand die Studie persönlich vorgestellt?

Wenn ja, wer hat Ihnen die Studie persönlich vorgestellt?

☐ Hebamme ☐ Arzt/Ärztin ☐ LöwenKIDS-Team ☐ Andere: .....

Appendix 2 Excerpt of a symptom diary

0713389641

MARTIN-LUTHER-UNIVERSITÄT HALLE-WITTENBERG
Medizinische Fakultät
Institut für Medizinische Epidemiologie, Biometrie und Informatik (IMEBI)
Direktor: Prof. Dr. med. Reinhard Schneider

HELMHOLTZ ZENTRUM FÜR INFEKTIONSFORSCHUNG

LöwenKIDS Science

LöwenKIDS-Tagebuch für das

Liebe Eltern,

lesen Sie bitte zu Beginn der Studie und auch immer wieder zwischendurch die Hinweise sorgfältig durch. Bitte füllen Sie das Tagebuch gewissenhaft und wenn möglich **täglich** aus. Auch wenn keine Symptome aufgetreten sind, ist dies zu vermerken.

Dieses Heft enthält die Tage für ein Kalendervierteljahr. Das betreffende Kalendervierteljahr finden Sie vorne auf dem Deckblatt. Auf einer Seite ist jeweils eine Woche abgebildet. **Bitte tragen Sie die Kalenderwoche selbständig auf jedem Blatt oben links in der Ecke ein. Auf dem Deckblatt finden Sie einen Kalender mit den Kalenderwochen für das betreffende Kalendervierteljahr.**

In der oberen Tabelle sind aufgetretene Symptome (Krankheitsanzeichen) und Auswirkungen der Erkrankung einzutragen. In der unteren linken Tabelle können Sie eintragen, welche Medikamente Sie Ihrem Kind an welchen Tagen gegeben haben. Im Feld unten rechts ist Platz für sonstige Informationen, die Sie uns mitteilen möchten. Auf den nächsten Seiten finden Sie eine detaillierte Übersicht zu den Eintragungen in den einzelnen Spalten, sowie Beispiele für mögliche Eintragungen. Untenstehend finden Sie kurze Beschreibungen für einige Symptome.

Etwa einen Monat vor Ablauf des Kalendervierteljahres erhalten Sie ein neues LöwenKIDS-Tagebuch für das folgende Kalendervierteljahr zugesandt. Das ausgefüllte Heft schicken Sie bitte in dem beiliegenden frankierten und adressierten Rückumschlag an das Studienteam an der Martin-Luther-Universität in Halle (Saale).

Bei Fragen können Sie das Studienteam telefonisch oder per E-Mail wie folgt erreichen: **Tel.: 0345/557-5757**
E-Mail: loewenkids@uk-halle.de

Beschreibungen einiger Symptome:

„keuchen/pfeifend atmen":	ein ziehendes, pfeifendes oder rasselndes Geräusch beim Einatmen
„trockener Husten":	lauter, trockener Husten ohne Auswurf, klingt oft hart und bellend, wird oft auch als Reizhusten bezeichnet
„Husten mit Auswurf (Schleim):	Husten bei dem schleimig-eitriger, meist grün-gelber Auswurf produziert wird, klingt oft locker
„Schüttelfrost":	Zittern, Schütteln, Zähneklappern
„breiiger/flüssiger Stuhlgang":	ungewöhnlich wässriger Stuhl, meist übelriechend

Falls Sie unsicher sind, welche Art von Husten bei Ihrem Kind aufgetreten ist, füllen Sie bitte die Spalte „Weiß nicht" bei Husten aus.

0280389640

Kalenderwoche:			Symptome														Sind wegen der eingetragenen Symptome einer Erkältung oder Magen-Darm-Erkrankung folgende Dinge eingetreten?					Sonstiges		
			Fieber		Erkältung							Allgemeine Krankheits-anzeichen			Magen-Darm-Erkrankung									
						Husten																		
Tag	weiß nicht	keine Symptome	Temperatur in °C oder Kreuz, wenn nur gefühlt Fieber	Art der Messung After = A Ohr = O Stirn = S Achselhöhle = AH Mund = M	Keuchen/pfeifend atmen	trocken	mit Auswurf (Schleim)	weiß nicht	laufende oder verstopfte Nase	Schüttelfrost	Halsschmerzen	Appetitlosigkeit	erhöhtes Schlafbedürfnis	erhöhte Anhänglichkeit	Erbrechen	breiiger/flüssiger Stuhlgang	Fehltag Kind Kita/Tagesmutter	Betreuung (Mutter = M, Vater = V)	Fehltag Elternteil von der Arbeit wegen	Arztbesuch	Diagnose des Arztes Erkältung/ grippaler Infekt = ER Bronchitis = BR (Pseudo-)Krupp = (P)K Grippe/Influenza= GR Lungenentzündung = LE Magen-Darm-Infekt = MDI Erkältung mit MD-Symptomen= EMD Sonstiges bitte frei eintragen	Krankenhausaufenthalt	Arztbesuch aus anderem Grund	Grund des Arztbesuchs bzw. Diagnose des Arztes Impfung = I U-Untersuchung = U Mittelohrentzündung = ME Bindehautentzündung = BE Windpocken = WP Hand-Fuß-Mund-Krankheit = HFM Sonstiges bitte frei eintragen	Gabe von Medikamenten (Kreuz falls ja, Details unten)
					Ausprägung: leicht = 1, mittel = 2, stark = 3										Häufigkeit		Bitte ankreuzen oder eintragen falls zutreffend							
Mo	☐	☐															☐			☐		☐	☐	☐
Di	☐	☐															☐			☐		☐	☐	☐
Mi	☐	☐															☐			☐		☐	☐	☐
Do	☐	☐															☐			☐		☐	☐	☐
Fr	☐	☐															☐			☐		☐	☐	☐
Sa	☐	☐															☐			☐		☐	☐	☐
So	☐	☐															☐			☐		☐	☐	☐

Medikamente

Name des Medikamentes	Mo	Di	Mi	Do	Fr	Sa	So
	☐	☐	☐	☐	☐	☐	☐
	☐	☐	☐	☐	☐	☐	☐
	☐	☐	☐	☐	☐	☐	☐
	☐	☐	☐	☐	☐	☐	☐
	☐	☐	☐	☐	☐	☐	☐

Sonstige Angaben (Hinweise und Notizen)

Appendix 3 Excerpts from different LöwenKIDS questionnaires that were importantly relevant for the analysis

HELMHOLTZ ZENTRUM FÜR INFEKTIONSFORSCHUNG

Fragebogen LöwenKIDS-Studie
-Basisfragebogen-

Liebe Eltern,
wir freuen uns über Ihre Teilnahme an der LöwenKIDS-Studie. Der nachfolgende Fragebogen wendet sich hauptsächlich an die Mutter des Kindes, er beinhaltet aber auch Fragen an den Vater.
In diesem Fragebogen geht es um den Verlauf Ihrer Schwangerschaft. Außerdem erfragen wir, wie häufig Sie in der Schwangerschaft an Infektionen erkrankt waren und bitten um einige allgemeine Informationen.

Ausfüllhinweise zur Beantwortung der Fragebögen der LöwenKIDS-Studie

- Bitte lesen Sie die Fragen **aufmerksam** durch.
- Bitte schreiben Sie deutlich - am besten in **Druckbuchstaben**.
- Benutzen Sie zum Ausfüllen einen **blauen oder schwarzen Kugelschreiber**.
- Setzen Sie Ihre Kreuze direkt in die dafür vorgegebenen Kästchen.

  Bsp.: richtig: ☒ falsch: ☐×
- Bitte schreiben Sie Zahlen nur in die dafür vorgesehenen Kästchen (z. B. bei Datums- und Altersangaben).

  Bsp.: richtig: | 1 | 3 | falsch: | | 1 | 3
- Bitte kreuzen Sie immer nur eine Antwort an, außer bei Fragen mit dem ausdrücklichen Hinweis "Mehrfachantworten möglich". Wenn bei einer Frage ohne diesen Hinweis mehrere Antwortmöglichkeiten ausgewählt werden, kann leider keine Ihrer Antworten gewertet werden.
- Wenn Sie Aussagen bewerten sollen, kreuzen Sie bitte das Kästchen an, das am **ehesten** Ihrer Einschätzung entspricht.
- Bitte machen Sie **keine Randnotizen** oder Bemerkungen, außer in dafür vorgesehenen Feldern.
- Wenn Sie eine Antwort korrigieren möchten, streichen Sie bitte das falsch angekreuzte Kästchen erkennbar durch, kreuzen Sie die gewünschte Antwort an und kennzeichnen Sie diese zusätzlich mit einem Kreis.

Bsp.: ⊗ Ja ☐ Nein ☒ Weiß nicht

Vielen Dank für die Beachtung dieser Hinweise. Sie helfen uns damit, Ihre Daten fehlerfrei zu erfassen und auszuwerten!

Ausfülldatum: | | / | | / | | | | Tag/Monat/Jahr

Angaben zu Ihrer **Schwangerschaft**	
A1	Handelt es sich um Ihre erste Schwangerschaft? ☐ Ja ☐ Nein
A2	Bitte geben Sie Ihren errechneten Entbindungstermin an: |	/		/				 Tag Monat Jahr
A3	Hatten Sie (bisher) Komplikationen bzw. Gesundheitsprobleme in dieser Schwangerschaft? *An dieser Stelle interessieren uns Komplikationen bzw. Probleme wie z.B. Blutungen oder gesundheitliche Beschwerden, die Sie zu einem Arztbesuch veranlasst haben.* ☐ Ja ☐ Nein ⇨ ***weiter mit Frage A6***
A4	Bitte benennen Sie die Komplikationen/Gesundheitsprobleme: --- --- ---
A5	Waren ein oder mehrere Krankenhausaufenthalte aufgrund der Komplikationen/Gesundheitsprobleme notwendig? ☐ Ja ⇨ ***Wie lange dauerten diese insgesamt?*** Insgesamt			Tage ☐ Nein

Im nächsten Abschnitt geht es um Ihre **Erkrankungen** bzw. die Erkrankungen des Vaters des Kindes, die nicht mit der Schwangerschaft in Verbindung stehen. Da einige Erkrankungen gehäuft in Familien auftreten können, bitten wir Sie, die Informationen sowohl für **sich selbst als auch für Ihre Eltern und Geschwister** anzugeben. **Kreuzen Sie bitte auch ja an, wenn die Erkrankungen erfolgreich durch eine Therapie behandelt wurden oder nur kurzfristig auftraten.**

*An dieser Stelle bitten wir Sie um die Angaben der **leiblichen Eltern**.*

Sind Sie bzw. Ihre Eltern oder Geschwister an einer der nachfolgenden Erkrankungen erkrankt?		**Mutter des Kindes, ihre Eltern oder Geschwister**	**Vater des Kindes, seine Eltern oder Geschwister**
C1	Asthma	☐ Ja ☐ Nein ☐ Weiß nicht	☐ Ja ☐ Nein ☐ Weiß nicht
C2	Diabetes Typ 1	☐ Ja ☐ Nein ☐ Weiß nicht	☐ Ja ☐ Nein ☐ Weiß nicht
C3	Diabetes Typ 2	☐ Ja ☐ Nein ☐ Weiß nicht	☐ Ja ☐ Nein ☐ Weiß nicht
C4	Rheumatoide Arthritis	☐ Ja ☐ Nein ☐ Weiß nicht	☐ Ja ☐ Nein ☐ Weiß nicht
C5	Lupus erythematodes (Schmetterlingsflechte)	☐ Ja ☐ Nein ☐ Weiß nicht	☐ Ja ☐ Nein ☐ Weiß nicht
C6	Neurodermitis/Dermatitis/ Psoriasis	☐ Ja ☐ Nein ☐ Weiß nicht	☐ Ja ☐ Nein ☐ Weiß nicht

Allergien

Haben Sie bzw. Ihre Eltern oder Geschwister eine der nachfolgenden Allergien?		**Mutter des Kindes, ihre Eltern oder Geschwister**	**Vater des Kindes, seine Eltern oder Geschwister**
C7	Heuschnupfen	☐ Ja ☐ Nein ☐ Weiß nicht	☐ Ja ☐ Nein ☐ Weiß nicht
C8	Hausstaubmilbenallergie	☐ Ja ☐ Nein ☐ Weiß nicht	☐ Ja ☐ Nein ☐ Weiß nicht
C9	Tierhaarallergie	☐ Ja ☐ Nein ☐ Weiß nicht	☐ Ja ☐ Nein ☐ Weiß nicht

Lebensmittelunverträglichkeiten

Haben Sie bzw. Ihre Eltern oder Geschwister einer der nachfolgenden Lebensmittelunverträglichkeiten?		**Mutter des Kindes, ihre Eltern oder Geschwister**	**Vater des Kindes, seine Eltern oder Geschwister**
C10	Laktoseintoleranz	☐ Ja ☐ Nein ☐ Weiß nicht	☐ Ja ☐ Nein ☐ Weiß nicht
C11	Fructoseintoleranz	☐ Ja ☐ Nein ☐ Weiß nicht	☐ Ja ☐ Nein ☐ Weiß nicht
C12	Glutenintoleranz (Zöliakie)	☐ Ja ☐ Nein ☐ Weiß nicht	☐ Ja ☐ Nein ☐ Weiß nicht

Familiäres Umfeld Ihres Kindes

E1 Leben nach der Geburt beide (leiblichen) Eltern gemeinsam mit dem Kind in einem Haushalt?

☐ Ja

☐ Nein, das Kind lebt im Haushalt der Mutter

☐ Nein, das Kind lebt im Haushalt des Vaters

☐ Anderes: _____

E2 Wie viele Geschwister (auch Halbgeschwister) leben (zukünftig) mit dem Kind in einem Haushalt?

☐ Keine ⇨ ***weiter mit Frage E4***

☐ Anzahl: ☐☐

E3 Bitte machen Sie folgende Angaben zu den Geschwistern/ Halbgeschwistern, die mit dem Kind in einem Haushalt leben (werden) *(wenn es mehr als 4 Geschwister sind, dann nennen Sie bitte nur die vier jüngsten!)*:

	1. Geschwister-kind	2. Geschwister-kind	3. Geschwister-kind	4. Geschwister-kind
Geschlecht	☐ weiblich ☐ männlich	☐ weiblich ☐ männlich	☐ weiblich ☐ männlich	☐ weiblich ☐ männlich
Alter in Jahren	☐☐	☐☐	☐☐	☐☐

E4 Wie viele weitere Personen neben bereits genannten leben (zukünftig) mit dem Kind in einem Haushalt?

☐ Keine ⇨ ***weiter mit Frage E6***

☐ Anzahl: ☐☐

E5 Bitte benennen Sie weitere Haushaltsmitglieder.
Geben Sie hierzu die Beziehung zum Kind und das Alter in Jahren an (z.B.: Oma, 69 Jahre):

_____ , ☐☐ Jahre

_____ , ☐☐ Jahre

_____ , ☐☐ Jahre

_____ , ☐☐ Jahre

E6 Welche Haustiere leben in Ihrem Haushalt? *(Mehrfachantworten möglich)*

☐ Katze(n) Anzahl: ☐☐

☐ Hund(e) Anzahl: ☐☐

☐ Nagetiere (z. B. Hamster, Meerschweinchen, Ratte, Maus); Anzahl: ☐☐

☐ Hasen/Kaninchen Anzahl: ☐☐

☐ Reptilien Anzahl: ☐☐

☐ Vögel Anzahl: ☐☐

☐ Andere Tiere, und zwar _____

Anzahl: ☐☐

☐ Keine

Wenn Sie alleinerziehend sind und keine Aussagen zu einzelnen Fragen machen können, lassen Sie die Angaben zum anderen Elternteil des Kindes einfach frei.

G1 Welchen **höchsten** allgemeinbildenden Schulabschluss hat die **Mutter**/der **Vater** des Kindes? *Bitte kreuzen Sie Zutreffendes an!*	**Mutter**	**Vater**
Schüler/in, besucht eine allgemeinbildende Vollzeitschule	☐	☐
Von der Schule abgegangen ohne Hauptschulabschluss (Volksschulabschluss)	☐	☐
Hauptschulabschluss (Volksschulabschluss)	☐	☐
Realschulabschluss (Mittlere Reife)	☐	☐
Polytechnische Oberschule der DDR mit Abschluss der 8. oder 9. Klasse	☐	☐
Polytechnische Oberschule der DDR mit Abschluss der 10. Klasse	☐	☐
Fachhochschulreife, Abschluss einer Fachoberschule	☐	☐
Abitur/Allgemeine oder fachgebundene Hochschulreife (Gymnasium bzw. EOS, auch EOS mit Lehre)	☐	☐
Abitur über den zweiten Bildungsweg nachgeholt	☐	☐
Einen anderen Schulabschluss und zwar: Mutter: _____ Vater: _____	☐	☐
Weiß nicht	☐	☐

G2	Welchen **höchsten** Ausbildungsabschluss hat die **Mutter/der Vater** des Kindes? *Bitte kreuzen Sie Zutreffendes an!*	**Mutter**	**Vater**
	Noch in beruflicher Ausbildung (Berufsvorbereitungsjahr, Auszubildende/r, Praktikant/in, Student/in)	☐	☐
	Schüler/in und besuche eine berufsorientierte Aufbau-, Fachschule oder Ähnliches	☐	☐
	Keinen beruflichen Abschluss und nicht in beruflicher Ausbildung	☐	☐
	Beruflich-betriebliche Berufsausbildung (Lehre)	☐	☐
	Beruflich-schulische Ausbildung (Berufsfachschule, Handelsschule, Vorbereitungsdienst für den mittleren Dienst in der öffentlichen Verwaltung)	☐	☐
	Ausbildung an einer Fachschule der DDR	☐	☐
	Ausbildung an einer Fach-, Meister-, Technikerschule, Berufs- oder Fachakademie	☐	☐
	Bachelor an (Fach-)Hochschule abgeschlossen	☐	☐
	Fachhochschulabschluss (z. B. Diplom, Master)	☐	☐
	Universitätsabschluss, Abschluss an einer Pädagogischen Hochschule oder an einer Kunst- und Musikhochschule (z. B. Diplom, Magister, Staatsexamen, Master)	☐	☐
	Promotion	☐	☐
	einen anderen Abschluss und zwar: Mutter: _____ Vater: _____	☐	☐
	Weiß nicht	☐	☐

G3	Welche Erwerbssituation hatte die Mutter vor dem Mutterschutz/hat der Vater des Kindes? *(Nur eine Nennung möglich!)*	**Mutter**	**Vater**
	Vollzeiterwerbstätig (Arbeitszeit von 35 Stunden und mehr)	☐	☐
	Teilzeiterwerbstätig (Arbeitszeit von 15 bis 34 Stunden)	☐	☐
	Gelegentlich oder unregelmäßig beschäftigt	☐	☐
	Erziehungsurlaub älteres Kind, Elternzeit oder sonstige Beurlaubung	☐	☐
	Nicht erwerbstätig, und zwar ...	☐	☐
	... Schüler(in)/Student(in)	☐	☐
	... arbeitslos	☐	☐
	... Hausfrau/Hausmann	☐	☐
	... in einem freiwilligen ökologischen/sozialen/wissenschaftlichen Jahr	☐	☐
	... aus anderen Gründen nicht erwerbstätig		
	Weiß nicht	☐	☐

G4	Konnten Sie (die Mutter) im Falle einer Erwerbstätigkeit Ihre Tätigkeit bis zum Beginn des Mutterschutzes ausüben?
	☐ Ja ☐ Ja, mit Unterbrechung ☐ Nein

G5	Wie hoch ist das **durchschnittliche monatliche Nettoeinkommen** Ihres Haushalts insgesamt? *Unter dem durchschnittlichen monatlichen Nettoeinkommen Ihres Haushalts ist die Summe zu verstehen, die sich aus Lohn, Gehalt, Einkommen aus selbstständiger Tätigkeit (durchschnittliche Nettobezüge, das heißt abzüglich der Betriebsausgaben und der Steuern), Rente oder Pension ergibt. Rechnen Sie bitte auch die Einkünfte aus öffentlichen Beihilfen, Einkommen aus Vermietung und Verpachtung, Vermögen, Wohngeld, Kindergeld und sonstige Einkünfte hinzu und ziehen Sie dann Steuern und Sozialversicherungsbeiträge ab.*	
	Weniger als 1.250 Euro	☐
	1.250 bis unter 1.750 Euro	☐
	1.750 bis unter 2.250 Euro	☐
	2.250 bis unter 3.000 Euro	☐
	3.000 bis unter 4.000 Euro	☐
	4.000 bis unter 5.000 Euro	☐
	5.000 und mehr	☐
	Ich möchte darüber keine Auskunft geben.	☐
	Ich weiß nicht	☐

HELMHOLTZ ZENTRUM FÜR INFEKTIONSFORSCHUNG

Fragebogen LöwenKIDS-Studie -Geburt-

Ausfülldatum: ☐☐ / ☐☐ / ☐☐☐☐ Tag/Monat/Jahr

Angaben zu Ihrem Kind	
A1	Wann wurde Ihr Kind geboren? ☐☐ / ☐☐ / ☐☐☐☐ Tag Monat Jahr
A2	Bitte geben Sie das Geschlecht Ihres Kindes an ☐ Weiblich ☐ Männlich
A3	Bitte geben Sie die Größe Ihres Kindes bei Geburt an *(diese Information finden Sie im gelben U-Heft, bitte runden Sie auf ganze Zahlen auf)* ☐☐ cm
A4	Bitte geben Sie das Geburtsgewicht Ihres Kindes an *(bitte runden Sie auf ganze Zahlen auf)* ☐☐☐☐ g

Verlauf der Geburt Ihres Kindes	
B1	Fand die Geburt Ihres Kindes am errechneten Entbindungstermin statt? ☐ Ja ☐ Nein, ☐☐ Tage **oder** ☐☐ Wochen **früher** ☐ Nein, ☐☐ Tage **später**
B2	Wie haben Sie entbunden? ☐ Spontangeburt ☐ Zangen- oder Saugglockengeburt ☐ Im Vorfeld geplanter Kaiserschnitt ☐ Nicht geplanter Kaiserschnitt

B3	Hatten Sie einen Blasensprung **bevor** die Wehen eingesetzt haben? ☐ Ja ☐ Nein ⇨ ***weiter mit Frage B5*** ☐ Weiß nicht
B4	Wie viele Stunden vor dem Einsetzen der Wehen (geschätzt), kam es zu dem Blasensprung? ca. ☐☐ Stunden
B5	Wo haben Sie entbunden? ☐ Im Krankenhaus mit stationärem Aufenthalt: ⇨ Wir sind ☐☐ Tage im Krankenhaus geblieben ☐ Im Krankenhaus als ambulante Geburt: ⇨ Wir konnten das Krankenhaus nach ☐☐ Stunden verlassen und nach Hause gehen ☐ Im Geburtshaus ☐ Zu Hause ☐ An einem anderen Ort und zwar: _____
B6	Wurde Ihr Kind innerhalb der ersten zwei Wochen nach der Geburt aufgrund von Auffälligkeiten/Erkrankungen in einer Kinderklinik oder Spezialabteilung aufgenommen? ☐ Ja ⇨ ***Was war der Grund für die Aufnahme?*** _____ _____ ☐ Nein ⇨ ***weiter mit Frage C1***

Wir bitten Sie (die Mutter), uns zusammen mit dem Fragebogen Kopien Ihres Mutterpasses und Ihres eigenen Impfpasses zu schicken.
Die **Grippeschutzimpfung** wird häufig nicht im Impfpass eingetragen, deshalb fragen wir separat danach.

D1	Haben Sie sich in der Schwangerschaft gegen Grippe impfen lassen? ☐ Ja ⇨ In welcher Schwangerschaftswoche war das? ☐☐ .Woche ☐ Nein
D2	Ist Ihnen bekannt, dass die Grippeschutzimpfung für Schwangere ab dem 2. Trimester (bei gesundheitlicher Gefährdung ab dem 1. Trimester) von der Ständigen Impfkommission empfohlen wird? *(Mehrfachantworten möglich)* ☐ Ja, mein(e) Frauenarzt/ärztin hat mich darauf hingewiesen ☐ Ja, ich weiß es aus anderer Quelle ☐ Nein
D3	Hat Ihr Frauenarzt/Ihre Frauenärztin Ihnen zu der Impfung geraten? ☐ Ja ☐ Nein
D4	Haben Sie sich jemals gegen Grippe impfen lassen? ☐ Ja, regelmäßig (jährlich oder fast jährlich) ☐ Ja, unregelmäßig ⇨ ***Wann zuletzt?*** Jahr: ☐☐☐☐ oder: ☐ Weiß nicht ☐ Nein

Ausfülldatum: ___ / ___ / _____ Tag/Monat/Jahr

HELMHOLTZ ZENTRUM FÜR INFEKTIONSFORSCHUNG

MARTIN-LUTHER-UNIVERSITÄT HALLE-WITTENBERG
Medizinische Fakultät
Institut für Medizinische Epidemiologie, Biometrie und Informatik (IMEBI)
Direktor: Prof. Dr. med. Rafael Mikolajczyk

Fragebogen LöwenKIDS-Studie
- Erkrankungen in den ersten Lebenswochen -

Erkrankungen in den ersten Lebenswochen
Da Sie das Symptomtagebuch nicht ab dem ersten Lebenstag führen konnten, bitten wir Sie, eventuell schon aufgetretene Erkrankungen im folgenden Fragebogen zu notieren.
Bitte beachten Sie dabei nur die Wochen vor Beginn der Eintragungen in das LöwenKIDS Tagebuch.

1

Waren Sie mit Ihrem Kind in diesem Zeitraum bei einem Kinderarzt?

☐ Nein

☐ Ja ⇨ ***Was war der Grund des Arztbesuchs?*** *(Mehrfachantworten möglich)*

☐ U-Untersuchung

☐ Impfung

☐ Erkrankung des Kindes

⇩

Falls eine ärztliche Diagnose gestellt wurde, welche war das und wie alt war Ihr Kind zu diesem Zeitpunkt? *(Mehrfachnennungen möglich)*

Diagnose	Alter des Kindes in Wochen	Alter des Kindes in Wochen	Alter des Kindes in Wochen
_____	___	___	___
_____	___	___	___
_____	___	___	___
_____	___	___	___
_____	___	___	___

2

War Ihr Kind in diesem Zeitraum bereits in stationärer Behandlung? *(Krankenhausaufenthalte innerhalb der ersten zwei Wochen nach der Geburt werden im Fragebogen zur Geburt abgefragt. Bitte nennen Sie diese hier nicht erneut.)*

☐ Nein

☐ Ja ⇨ ***Welche ärztliche Diagnose wurde dabei gestellt und wie alt war Ihr Kind?*** *(Mehrfachnennungen möglich)*

Diagnose	Alter des Kindes in Wochen	Alter des Kindes in Wochen	Alter des Kindes in Wochen
_____	___	___	___
_____	___	___	___
_____	___	___	___
_____	___	___	___
_____	___	___	___

3

Hatte Ihr Kind bereits Atemwegserkrankungen, aufgrund derer Sie *keinen Arzt* aufgesucht haben?

*Eine Atemwegserkrankung liegt dann für uns vor, wenn: Ihr Kind entweder eins oder mehrere der unten stehenden Kategorie A-Symptome hatte **und/oder** bei Ihrem Kind zwei oder mehrere der unten stehenden Kategorie B-Symptome aufgetreten sind:*

Kategorie A-Symptome
- Fieber*
- keuchend/pfeifend atmen
- Husten mit Auswurf (Schleim)
- von einem Arzt diagnostizierte Mittelohr- oder Lungenentzündung

* Art der Messung	Temperatur
After	> 38°C
Mund	> 37,8°C
Achselhöhle	> 37,2°C
Ohr	Rektal-Modus > 38°C Mund-Modus > 37,5°C
Stirn	> 38°C

Kategorie B-Symptome
- Schnupfen (laufende oder verstopfte Nase)
- Husten (trocken, oder „weiß nicht")
- Halsschmerzen
- Schüttelfrost
- Appetitlosigkeit
- erhöhtes Schlafbedürfnis
- erhöhte Anhänglichkeit

☐ Nein

☐ Ja ⇨ ***Wie oft sind Atemwegserkrankungen bei Ihrem Kind aufgetreten?***

___ -mal

Wie alt (in Wochen) war Ihr Kind als die Erkrankungen auftraten?

1. Erkrankung: ___ Wochen

2. Erkrankung: ___ Wochen

3. Erkrankung: ___ Wochen

Ausfülldatum: ☐☐ / ☐☐ / ☐☐☐☐ Tag/Monat/Jahr

HELMHOLTZ ZENTRUM FÜR INFEKTIONSFORSCHUNG

Fragebogen LöwenKIDS-Studie
-1. Follow Up-

Gesundheit und Entwicklung Ihres Kindes	
A1	Wie würden Sie die allgemeine Gesundheit Ihres Kindes beschreiben? ☐ ausgezeichnet ☐ sehr gut ☐ gut ☐ ausreichend ☐ schlecht
A2	Wurde bei Ihrem Kind von einem Arzt/einer Ärztin ein gesundheitliches Problem festgestellt (z.B. im Rahmen einer U-Untersuchung)? ☐ Ja ⇨ ***Um welches Problem handelt es sich?*** --- --- ☐ Nein
A3	Wie viele Stunden schläft Ihr Kind zurzeit im Durchschnitt innerhalb von 24 Stunden? Bitte zählen Sie dabei die Stunden, die es **nachts und tagsüber** schläft, zusammen. **Mein Kind schläft durchschnittlich ☐☐ Stunden.**

Ernährung des Kindes	
C1	Wie lange haben Sie Ihr Kind ausschließlich, überwiegend bzw. insgesamt gestillt? ***Bitte geben Sie an, bis zu welchem Monat Sie ausschließlich, überwiegend bzw. insgesamt gestillt haben.*** ☐ Gar nicht ⇨ ***weiter mit Frage C2*** **Ausschließlich bis zu Lebensmonat:** ☐☐ oder ☐ Bis jetzt *... bedeutet an dieser Stelle, dass Ihr Kind nur Muttermilch (durch Stillen oder nach Abpumpen mit der Flasche) bekommen hat und Sie vollständig auf Beikost und/oder andere Getränke verzichtet haben. Wenige Ausnahmen, z. B. in der Eingewöhnungsphase, können Sie vernachlässigen.* ⇩ ***weiter mit Frage D1*** **Überwiegend bis zu Lebensmonat:** ☐☐ oder ☐ Bis jetzt *... bedeutet an dieser Stelle, dass Ihr Kind hauptsächlich Muttermilch (durch Stillen oder nach Abpumpen mit der Flasche) bekommen hat, Sie ihm aber auch Beikost und/oder andere Getränke gegeben haben.* **Insgesamt bis zu Lebensmonat:** ☐☐ oder ☐ Bis jetzt *...bedeutet an dieser Stelle, dass Ihr Kind noch mindestens 1-mal täglich Muttermilch (durch Stillen oder nach dem Abpumpen mit der Flasche) bekommen hat.*

C2	Falls Ihr Kind keine Muttermilch erhält oder zusätzlich zur Muttermilch weitere Nahrung/Getränke bekommt, was bekommt es? *(Mehrfachantworten möglich)* ☐ Pre-Nahrung/Anfangsmilch ☐ HA (hypoallergene) Anfangsmilch ☐ Folgemilch (2-Nahrung) ☐ HA (hypoallergene) Folgemilch (2-Nahrung) ☐ Frisch-Milch aus dem Supermarkt ☐ H-Milch ☐ Abgekochte Kuhmilch (frisch/roh vom Bauern) ☐ Nicht abgekochte Kuhmilch (frisch/roh vom Bauern) ☐ Sojamilch ☐ Wasser ☐ Saft ☐ Ungesüßten Tee ☐ Gesüßten Tee ☐ Zuckerlösung ☐ Obst- und Gemüsebrei ☐ Getreidebrei ☐ Brot/Brötchen ☐ Keine weitere Nahrung ☐ Andere und zwar: ---

C3 Enthält die Beikost/enthalten die Getränke Zusätze von Prä-/Probiotika?
(Präbiotika: Lebensmittelzusätze, die die Zusammensetzung der Darmflora beeinflussen;
Probiotika: probiotische Lebensmittel enthalten Mikroorganismen, die im Darm einer Fehlbesiedlung mit Keimen entgegenwirken sollen)

☐ Ja ☐ Nein ☐ Weiß nicht

Kontakte Ihres Kindes
Für die Entwicklung des Immunsystems und die Häufigkeit von Infekten kann es von Bedeutung sein, wie häufig Ihr **Kind Kontakt mit anderen Erwachsenen oder Kindern hat**. Im Folgenden fragen wir daher nach Kontakten Ihres Kindes.

D1 Wie oft hat Ihr Kind durchschnittlich **körperlichen Kontakt** (z. B. Spielen, Kuscheln, auf den Arm nehmen) **zu erwachsenen** Personen, die nicht im Haushalt wohnen?

	Nie	Un-regel-mäßig	1-mal pro Woche	Mehrmals pro Woche	Täglich
Verwandte	☐	☐	☐	☐	☐
Nachbarn	☐	☐	☐	☐	☐
Freunde	☐	☐	☐	☐	☐
Kita-Betreuer/innen	☐	☐	☐	☐	☐
Tagesmutter	☐	☐	☐	☐	☐
weitere Personen: _____	☐	☐	☐	☐	☐
_____	☐	☐	☐	☐	☐
_____	☐	☐	☐	☐	☐

D2 Wie oft besuchen Sie und Ihr Kind Treffen/Kurse (wie z. B. Krabbelgruppe, PEKIP, Babyschwimmen, …), an denen auch andere Eltern mit etwa gleichaltrigen Babys anwesend sind?

☐ Nie ☐ 1-mal pro Woche
☐ Seltener als 1-mal im Monat ☐ 2 bis 3-mal pro Woche
☐ 1 bis 3-mal pro Monat ☐ Mehr als 4-mal pro Woche

Rauchen

E1 **Rauchverhalten der Mutter**

Haben Sie jemals Zigaretten (auch E-Zigaretten), Zigarren, Zigarillos, Pfeife oder andere Tabakprodukte (wie z. B. Wasserpfeife) geraucht?
Wenn Sie bis auf ganz seltenes Probieren NICHT geraucht haben, antworten Sie bitte „Ich habe nie geraucht".

☐ Ja, ich rauche bis heute
☐ Ja, ich habe früher geraucht ⇨ ***weiter mit Frage E3***
☐ Nein, ich habe nie geraucht ⇨ ***weiter mit Frage E4***

E2 Wie viele Zigaretten rauchen Sie **derzeit** durchschnittlich?
Bitte geben Sie die Anzahl pro Tag oder, wenn Sie gelegentlich rauchen, pro Woche oder pro Monat an.

Anzahl Zigaretten: ☐☐☐ ☐ Angabe pro Tag **oder**
☐ Angabe pro Woche **oder**
☐ Angabe pro Monat

E3 Wie viele Zigaretten haben Sie durchschnittlich während der Schwangerschaft geraucht?
Bitte geben Sie die Anzahl pro Tag oder, wenn Sie gelegentlich geraucht haben, pro Woche oder pro Monat an. Wenn Sie in der Schwangerschaft nicht geraucht haben, geben Sie eine Null an.

Anzahl Zigaretten: ☐☐☐ ☐ Angabe pro Tag **oder**
☐ Angabe pro Woche **oder**
☐ Angabe pro Monat

E4 **Rauchverhalten des Vaters**

Haben Sie jemals Zigaretten (auch E-Zigarretten), Zigarren, Zigarillos, Pfeife oder andere Tabakprodukte (wie z. B. Wasserpfeife) geraucht?
Wenn Sie bis auf ganz seltenes Probieren NICHT geraucht haben, antworten Sie bitte „Ich habe nie geraucht".

☐ Ja, ich rauche bis heute
☐ Ja, ich habe früher geraucht
☐ Nein, ich habe nie geraucht

E5 **Rauchexposition des Kindes**

Wurde seit der Geburt Ihres Kindes in Ihrer Wohnung geraucht?

☐ Ja ☐ Nein

E6 War Ihr Kind seit seiner Geburt **außerhalb Ihrer Wohnung** Tabakrauch ausgesetzt?

☐ Täglich oder fast täglich ☐ Mindestens 1-mal pro Woche
☐ Gelegentlich ☐ Nie

F3 Wie häufig haben Sie vor und während der Schwangerschaft Alkohol getrunken?
Bitte machen Sie Angaben für alle vier Zeiträume!

	Vor der Schwanger-schaft	**1.Trimester** *(0.-12. Schwanger-schaftswoche)*	**2.Trimester** *(13.-24. Schwanger-schaftswoche)*	**3.Trimester** *(25.-40. Schwanger-schaftswoche)*
Nie	☐	☐	☐	☐
Seltener als 1-mal pro Monat	☐	☐	☐	☐
1 bis 3-mal pro Monat	☐	☐	☐	☐
1 bis 3-mal pro Woche	☐	☐	☐	☐
Häufiger als 3-mal pro Woche	☐	☐	☐	☐

Haushaltsmitglieder

G1 Hat sich die Zusammensetzung Ihres Haushaltes seit der Geburt Ihres Kindes verändert?

☐ Ja ⇨ ***Wie hat sich die Zusammensetzung Ihres Haushaltes verändert?***
(Bitte geben Sie an, welche Personen den Haushalt verlassen haben oder hinzugekommen sind und wie alt diese sind!)

Person (z.B. Oma)	Alter in Jahren	Hinzu-gekommen	Verlassen
_____	☐☐	☐	☐
_____	☐☐	☐	☐
_____	☐☐	☐	☐

☐ Nein

Haustiere

H1 Sind seit der Geburt Ihres Kindes neue Haustiere in Ihren Haushalt gekommen oder haben diesen verlassen?

☐ Ja ⇨ ***Bitte geben Sie an, welche Tiere, in welcher Anzahl seit der Geburt hinzugekommen sind oder nicht mehr in Ihrem Haushalt leben!***

Tier (z.B. Hund)	Anzahl	Hinzu-gekommen	Verlassen
_____	☐☐	☐	☐
_____	☐☐	☐	☐
_____	☐☐	☐	☐

☐ Nein

Impfungen

I1 Planen Sie, Ihr Kind gegen Masern/Mumps/Röteln/Varizellen impfen zu lassen?

☐ Ja, gegen alle

☐ Ja, aber nur gegen *(bitte kreuzen Sie die Erkrankungen an, gegen die Sie Ihr Kind impfen lassen wollen; Mehrfachnennungen möglich!)*

☐ Masern ☐ Röteln

☐ Mumps ☐ Varizellen

☐ Nein, gegen keine der Erkrankungen

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HELMHOLTZ ZENTRUM FÜR INFEKTIONSFORSCHUNG

LöwenKIDS Science

Fragebogen LöwenKIDS-Studie

1. Lebensjahr (2. Follow-Up)

Vielen Dank für die Beantwortung des Fragebogens!
Alles Gute wünscht Ihnen Ihr LöwenKIDS-Team.

Ausfülldatum: ☐☐ / ☐☐ / ☐☐☐☐ Tag/Monat/Jahr

Gesundheit und Entwicklung Ihres Kindes

A1 Wie würden Sie die allgemeine Gesundheit Ihres Kindes beschreiben?

☐ ausgezeichnet ☐ sehr gut ☐ gut ☐ ausreichend ☐ schlecht

A2 Wie viele Stunden schläft Ihr Kind zurzeit im Durchschnitt innerhalb von 24 Stunden? Bitte zählen Sie dabei die Stunden, die es **nachts und tagsüber** schläft, zusammen.

Mein Kind schläft durchschnittlich ☐☐ **Stunden.**

A3 Im Symptomtagebuch bitten wir Sie um die tägliche Eintragung der Infektionserkrankungen. Hier möchten wir nur ergänzend erfahren, ob Ihr Kind seit der Geburt ärztlich behandelt werden musste oder im Krankenhaus lag.

Musste Ihr Kind in den letzten sechs Monaten wegen einer Erkrankung ärztlich behandelt werden (es geht hier nicht um die Vorsorgeuntersuchungen/U-Untersuchungen)?

☐ Ja ⇨ ***Wenn eine ärztliche Diagnose gestellt wurde, welche war das?***

_____

_____

☐ Nein

A4 Musste Ihr Kind in den letzten sechs Monaten stationär im Krankenhaus behandelt werden?

☐ Ja ⇨ ***Aus welchem Grund?***

_____

_____

☐ Nein

Erkrankungen des Kindes
Hat **ein Arzt/eine Ärztin** bei Ihrem Kind seit der Geburt eine der folgenden Krankheiten festgestellt?

	Hat oder hatte Ihr Kind:	Ja	Nein
A5	Akute Bronchitis (Husten mit Fieber über einige Tage)	☐	☐
A6	Chronische Bronchitis (Husten länger als 3 Monate anhaltend)	☐	☐
A7	Lungenentzündung	☐	☐
A8	Pseudokrupp (Heiserkeit, bellender Husten bis zu Zeichen der beginnenden Erstickung; Besserung an der frischen Luft)	☐	☐
A9	Keuchhusten	☐	☐
A10	Mittelohrentzündung	☐	☐
A11	Dreitagefieber	☐	☐
A12	Fieberkrämpfe	☐	☐
A13	Hand-Mund-Fuß-Krankheit	☐	☐
A14	Windpocken	☐	☐
A15	Soor (Pilzinfektion) im Mund- oder Windelbereich	☐	☐

	Hat oder hatte Ihr Kind:	Ja	Nein
A16	Milchschorf, seborrhoisches Ekzem	☐	☐
A17	Nesselsucht (Urtikaria) oder Quincke-Ödem	☐	☐
A18	Atopisches oder allergisches Ekzem	☐	☐
A19	Nahrungsmittelallergie	☐	☐
A20	Heuschnupfen	☐	☐
A21	Andere Allergien **Welche?** ----------	☐	☐
A22	Nahrungsmittelunverträglichkeit **Welche?** ----------	☐	☐
A23	Andere Erkrankungen, und zwar: ----------		

Ernährung des Kindes

C1 Wie lange haben Sie Ihr Kind ausschließlich, überwiegend bzw. insgesamt gestillt?

Bitte geben Sie an, bis zu welchem Monat Sie ausschließlich, überwiegend bzw. insgesamt gestillt haben.

☐ Gar nicht ⇨ ***weiter mit Frage C2***

Ausschließlich bis zu Lebensmonat: ☐☐ oder ☐ Bis jetzt

... bedeutet an dieser Stelle, dass Ihr Kind nur Muttermilch (durch Stillen oder nach Abpumpen mit der Flasche) bekommen hat und Sie vollständig auf Beikost und/oder andere Getränke verzichtet haben. Wenige Ausnahmen, z. B. in der Eingewöhnungsphase, können Sie vernachlässigen.

⇩ ***weiter mit Frage D1***

Überwiegend bis zu Lebensmonat: ☐☐ oder ☐ Bis jetzt

... bedeutet an dieser Stelle, dass Ihr Kind hauptsächlich Muttermilch (durch Stillen oder nach Abpumpen mit der Flasche) bekommen hat, Sie ihm aber auch Beikost und/oder andere Getränke gegeben haben.

Insgesamt bis zu Lebensmonat: ☐☐ oder ☐ Bis jetzt

...bedeutet an dieser Stelle, dass Ihr Kind noch mindestens 1-mal täglich Muttermilch (durch Stillen oder nach dem Abpumpen mit der Flasche) bekommen hat.

Betreuung Ihres Kindes

D1 Hat Ihr Kind bislang eine oder mehrere Betreuungseinrichtungen, in der weitere Kinder anwesend waren, besucht?

☐ Ja

☐ Nein ⇨ ***Weiter mit Frage E1***

D2 Da die Kontakte mit gleichaltrigen Kindern eng mit der Infektionshäufigkeit und vielleicht auch mit der Entwicklung des Immunsystems zusammenhängt, möchten wir genau wissen, **in welchen Zeiträumen Ihr Kind außerhalb Ihres Haushaltes betreut** wird.

Bitte tragen Sie im Folgenden die außerhäuslichen **Betreuungszeiten** seit der Geburt ein.
Hat Ihr Kind die **Betreuung gewechselt**, bitten wir Sie, die Angaben dafür in der nächsten Tabelle zu vermerken. Fangen Sie hierbei bitte mit der ersten Betreuungsform Ihres Kindes an und fahren Sie mit den Folgentabellen fort.

Alter des Kindes: vom ☐☐ . bis zum ☐☐ . Lebensmonat

Betreuungsform für das angegebene Alter

☐ Tagesmutter ☐ Kinderkrippe 0 bis 3-Jährige ☐ Kinderkrippe 0 bis 6-Jährige

☐ Andere: ----------

Durchschnittlich Stundenzahl pro Woche in der Betreuung: ☐☐ h

Anzahl der Kinder in der Betreuungsgruppe: ☐☐

Alter der Kinder in der Betreuungsgruppe: von ☐☐ bis ☐☐ Monate

Anzahl der Betreuer in der Betreuungsgruppe: ☐☐

Alter des Kindes: vom ☐☐ . bis zum ☐☐ . Lebensmonat

Betreuungsform für das angegebene Alter

☐ Tagesmutter ☐ Kinderkrippe 0 bis 3-Jährige ☐ Kinderkrippe 0 bis 6-Jährige

☐ Andere: ----------

Durchschnittlich Stundenzahl pro Woche in der Betreuung: ☐☐ h

Anzahl der Kinder in der Betreuungsgruppe: ☐☐

Alter der Kinder in der Betreuungsgruppe: von ☐☐ bis ☐☐ Monate

Anzahl der Betreuer in der Betreuungsgruppe: ☐☐

Alter des Kindes: vom ☐☐ . bis zum ☐☐ . Lebensmonat

Betreuungsform für das angegebene Alter

☐ Tagesmutter ☐ Kinderkrippe 0 bis 3-Jährige ☐ Kinderkrippe 0 bis 6-Jährige

☐ Andere: ----------

Durchschnittlich Stundenzahl pro Woche in der Betreuung: ☐☐ h

Anzahl der Kinder in der Betreuungsgruppe: ☐☐

Alter der Kinder in der Betreuungsgruppe: von ☐☐ bis ☐☐ Monate

Anzahl der Betreuer in der Betreuungsgruppe: ☐☐

Kontakte Ihres Kindes

Für die Entwicklung des Immunsystems und die Häufigkeit von Infekten kann es von Bedeutung sein, wie häufig Ihr **Kind Kontakt mit anderen Erwachsenen oder Kindern hat**. Im Folgenden fragen wir daher nach Kontakten Ihres Kindes.

E1 Wie oft hat Ihr Kind durchschnittlich **körperlichen Kontakt** (z. B. Spielen, Kuscheln, auf den Arm nehmen) **zu erwachsenen** Personen, die nicht im Haushalt wohnen?

	Nie	Un-regel-mäßig	1-mal pro Woche	Mehrmals pro Woche	Täglich
Verwandte	☐	☐	☐	☐	☐
Nachbarn	☐	☐	☐	☐	☐
Freunde	☐	☐	☐	☐	☐
Kita-Betreuer/innen	☐	☐	☐	☐	☐
Tagesmutter	☐	☐	☐	☐	☐
weitere Personen: _____	☐	☐	☐	☐	☐
_____	☐	☐	☐	☐	☐
_____	☐	☐	☐	☐	☐

Haushaltsmitglieder

F1 Hat sich die Zusammensetzung Ihres Haushaltes seit der Geburt Ihres Kindes verändert?

☐ Ja ⇨ ***Wie hat sich die Zusammensetzung Ihres Haushaltes verändert?***

(Bitte geben Sie an, welche Personen den Haushalt verlassen haben oder hinzugekommen sind und wie alt diese sind!)

Person (z.B. Oma)	Alter in Jahren	Hinzu-gekommen	Verlassen
_____	☐☐	☐	☐
_____	☐☐	☐	☐
_____	☐☐	☐	☐

☐ Nein

Haustiere

G1 Sind seit der Geburts Ihres Kindes neue Haustiere in Ihren Haushalt hinzugekommen oder haben diesen verlassen?

☐ Ja ⇨ ***Bitte geben Sie an, welche Tiere, in welcher Anzahl seit der Geburt hinzugekommen sind oder nicht mehr in Ihrem Haushalt leben!***

Tier (z.B. Hund)	Anzahl	Hinzu-gekommen	Verlassen
_____	☐☐	☐	☐
_____	☐☐	☐	☐
_____	☐☐	☐	☐

☐ Nein

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LöwenKIDS Science

FRAGEBOGEN LÖWENKIDS-STUDIE

2. Lebensjahr (3. Follow-Up)

Ausfülldatum: ___ / ___ / ____ Tag/Monat/Jahr

Im ersten Teil des Fragebogens geht es um die **Gesundheit und Entwicklung** Ihres Kindes

A1	Wie würden Sie die Gesundheit Ihres Kindes im Allgemeinen beschreiben? ☐ Ausgezeichnet ☐ Sehr gut ☐ Gut ☐ Weniger gut ☐ Schlecht

	Welche Aussagen treffen für Ihr Kind zu bzw. nicht zu?	**Ja**	**Nein**
A2	Mein Kind kann über längere Zeit frei und sicher gehen	☐	☐
A3	Mein Kind kann rennen	☐	☐
A4	und weicht dabei Hindernissen aus	☐	☐
A5	Mein Kind kann im Stehen Gegenstände vom Boden aufheben	☐	☐
A6	ohne Festhalten an Möbeln oder Abstützen mit den Händen	☐	☐
A7	ohne Hinsetzen oder Hinknien	☐	☐
A8	Mein Kind spricht mindestens 10 richtige Worte außer Papa und Mama	☐	☐
A9	Mein Kind sagt: "Wau-Wau" zu einem Hund oder anderen Vierbeinern	☐	☐
A10	Mein Kind spricht 2-Wortsätze, z.B. „Mama da“	☐	☐
A11	Mein Kind kann 3 Bauklötzchen oder Becher aufeinander setzen	☐	☐
A12	Mein Kind räumt 10 Minuten lang konzentriert kleinere Gegenstände aus und ein und beschäftigt sich selbst damit.	☐	☐
A13	Mein Kind gibt Gegenstände auf Verlangen	☐	☐
A14	Mein Kind kann eingewickelte Bonbons oder andere kleine Gegenstände auspacken	☐	☐
A15	Mein Kind kritzelt mit dem Stift (wird in der Faust gehalten)	☐	☐
A16	Mein Kind zeigt im Bilderbuch auf bekannte Gegenstände	☐	☐
A17	und blättert die Seiten einzeln um (Pappbilderbuch)	☐	☐
A18	Mein Kind bleibt oder spielt etwa 15 min alleine, auch wenn die Mutter nicht in der Nähe ist	☐	☐
A19	Mein Kind freut sich über andere Kinder	☐	☐
A20	Mein Kind winkt zum Abschied	☐	☐

Erkrankungen des Kindes
Im Symptomtagebuch bitten wir Sie um die tägliche Eintragung der Infektionserkrankungen. Hier möchten wir nun ergänzend erfahren, ob Ihr Kind im 2. Lebensjahr ärztlich behandelt werden musste oder im Krankenhaus lag.

	Hat ein Art/Ärztin bei Ihrem Kind in den letzte 12 Monaten (also im 2. Lebensjahr) der folgenden Krankheiten festgestellt?	**Ja**	**Nein**	**Weiß nicht**
B1	Akute Bronchitis (Husten mit Fieber über einige Tage)	☐	☐	☐
B2	Chronische Bronchitis (Husten länger als 3 Monate anhaltend)	☐	☐	☐
B3	Lungenentzündung	☐	☐	☐
B4	Pseudokrupp (Heiserkeit, bellender Husten bis zu Zeichen der beginnenden Erstickung; Besserung an der frischen Luft)	☐	☐	☐
B5	Keuchhusten	☐	☐	☐
B6	Mittelohrentzündung	☐	☐	☐
B7	Dreitagefieber	☐	☐	☐
B8	Hand-Mund-Fuß-Krankheit	☐	☐	☐
B9	Windpocken	☐	☐	☐
B10	Soor im Mund- oder Windelbereich	☐	☐	☐
B11	Milchschorf, seborrhoisches Ekzem	☐	☐	☐
B12	Nesselsucht, Urtikaria oder Quincke-Ödem	☐	☐	☐
B13	Nahrungsmittelallergie	☐	☐	☐
B14	Heuschnupfen	☐	☐	☐
B15	Andere Allergie Welche? _____	☐	☐	☐
B16	Nahrungsmittelunverträglichkeit Welche? _____	☐	☐	☐
B17	☐ Andere Erkrankungen, und zwar _____ _____			
B18	Musste Ihr Kind in den letzten 12 Monaten (also im 2. Lebensjahr) stationär im Krankenhaus behandelt werden? ☐ Nein ☐ Ja Aus welchem Grund? _____ _____			

Im Folgenden geht es um Hautausschlag und Heuschnupfen bei Ihrem Kind

C1 Hatte Ihr Kind irgendwann einmal einen juckenden Hautausschlag, der stärker oder schwächer über mindestens 6 Monate auftrat?
☐ Ja ☐ Nein *--> falls nein, bitte weiter mit C7*

C2 Trat dieser Hautausschlag bei Ihrem Kind irgendwann einmal an einer der folgenden Körperstellen auf: Ellenbogen oder Kniekehlen, Hand- und Fußgelenken, im Gesicht, am Hals? ☐ Nein ☐ Ja

C3 In welchem Alter trat dieser juckende Hautausschlag zum ersten Mal auf?
☐ Im 1. Lebensjahr ☐ Im 2. Lebensjahr

C4 Wie oft ist Ihr Kind im Durchschnitt in den letzten 12 Monaten wegen dieses juckenden Hautausschlages nachts aufgewacht?
☐ Nie in den letzten 12 Monaten
☐ Weniger als eine Nacht pro Woche
☐ Eine Nacht und mehr pro Woche

C5 Waren Sie wegen des Hautausschlages jemals beim Kinderarzt/bei einer Kinderärztin? ☐ Nein ☐ Ja

C6 Hat Ihr Kind vom Kinderarzt/der Kinderärztin jemals Medikamente/Salben für den Hautausschlag verschrieben bekommen?
☐ Nein ☐ Ja, und zwar _____

C7 Hat der Kinderarzt/die Kinderärztin jemals eine Neurodermitis (Atopisches Ekzem, Endogenes Ekzem) diagnostiziert?
☐ Nein ☐ Ja Wenn ja, in welchem Lebensmonat hat der Kinderarzt/die Kinderärztin zum ersten Mal die Diagnose gestellt? Im _____ Lebensmonat

C8 Wurde bei Ihrem Kind von einem Arzt/einer Ärztin (z.B. im Rahmen einer U-Untersuchung) im zweiten Lebensjahr ein gesundheitliches Problem außer den schon oben genannten Erkrankungen festgestellt? (z.B. Schielen, Kurzsichtigkeit)
☐ Nein ☐ Ja Um welches Problem handelt es sich?
_____

Als nächstes möchten wir gerne erfahren, ob Sie Ihr Kind nach dem ersten Geburtstag weiter gestillt haben?

D1 Haben Sie Ihr Kind auch nach dem ersten Geburtstag noch gestillt?
☐ Nein
☐ Ja **Wenn ja**: Bis zum _____ Lebensmonat oder bis jetzt ☐

Angaben zur Betreuung Ihres Kindes

E1 Hat Ihr Kind im zweiten Lebensjahr eine Betreuungseinrichtung, in der weitere Kinder anwesend waren, besucht bzw. war Ihr Kind bei einer Tagesmutter in Betreuung?
☐ Nein
☐ Ja **Wenn ja**: Ab welchem Lebensmonat ist Ihr Kind in der Betreuung? Ab dem _____ Lebensmonat

Angaben zur Betreuung der Geschwisterkinder

F1 Bitte geben Sie an, ob ein oder mehrere Geschwisterkinder eine Betreuungseinrichtung besuchen.
☐ Unser Kind hat keine Geschwister
☐ Geschwister wird/werden zu Hause betreut
☐ Mindestens ein Geschwisterkind befindet sich in einer Betreuung außerhalb des Haushalts und zwar seit
☐ dem zweiten Lebensjahr des teilnehmenden Kindes.
☐ _____ / _____ (Monat/Jahr)

G6 Wenn Ihr Kind Erkältungssymptome (Husten, Schnupfen), aber kein Fieber hat, und ist zu einem Geburtstag eingeladen, lassen Sie es gehen?
☐ Eher ja ☐ Ja ☐ Eher nein ☐ Nein

G7 Wenn Ihr Kind Durchfall und/oder Erbrechen hat, und ist zu einem Geburtstag eingeladen, lassen Sie es gehen?
☐ Eher ja ☐ Ja ☐ Eher nein ☐ Nein

G8 Was schätzen Sie, wie häufig sich Ihr Kind an einem normalen Wochenendag (z.B. Sonntag) die Hände wäscht/wie häufig Sie mit Ihrem Kind die Hände waschen?
_____ Mal

Angaben zu den Haushaltsmitgliedern

H1 Hat sich die Zusammensetzung Ihres Haushaltes in den letzten 12 Monaten verändert?
☐ Nein
☐ Ja Wie hat sich die Zusammensetzung Ihres Haushaltes verändert? *(Bitte geben Sie an, welche Personen den Haushalt verlassen haben und wie alt diese waren **und** welche Personen hinzugekommen sind und wie alt diese sind!)*
_____
_____

Angaben zu Haustieren

I1 Bitte geben Sie an, ob innerhalb der letzten 12 Monate neue Haustiere in Ihrem Haushalt dazugekommen sind bzw. nicht mehr in Ihrem Haushalt leben?
☐ Nein
☐ Ja Bitte geben Sie an, welche Tiere, in welcher Anzahl in den letzten 12 Monaten hinzugekommen sind oder nicht mehr in Ihrem Haushalt leben!
_____
_____

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