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To Markus, Christopher and Viola

ABSTRACT

Linnea Schuez-Havupalo, MD

Psychosocial and environmental influences in early childhood and their relation to respiratory tract infections

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Respiratory tract infections (RTIs) are most common in under-school-aged children, and they have a range of effects on society. In this study we aimed to examine modifiable risk factors relating to the young child's immediate environments, namely the home, daycare, and free-time activities.

This is a prospective birth cohort study carried out in Southwest Finland. We followed 1570 children for RTIs from birth until the age of 3 years, and documented medical-, psychological-, environmental-, and social factors applying diaries and questionnaires. A subset of 982 children were included in a more intensive infection follow-up, which included nasal swabs for virus analysis and visits at the study clinic during acute RTIs.

We found maternal depressive symptoms during pregnancy to predict higher cumulative rates of acute otitis media by the age of 10 months in the infant, and maternal emotional loneliness to predict higher cumulative rates of physician visits within the same age frame. Acute otitis media, physician visits, and antibiotic consumption were marginally less frequent for infants of families with social loneliness in either or both parents.

Comparing monthly sick days (days with symptoms of a RTI), antibiotic medications, and parental absences from work for children 0-24 months of age, we detected a steep rise of these measures after the start of daycare, and a subsequent clear decline within our follow-up, which ended 9 months after the initiation of daycare. When comparing the same outcome measures at the ages of 30-35 months of age, there were no significant differences for sick days between children in home care and those in out-of-home daycare. However, antibiotic medications were significantly more common for children in daycare centres, as compared to those in home care.

When examining possible links between infant swimming activities and respiratory symptoms for children up to 17 months of age, no significant differences with respect to rates of RTIs could be observed. There was a statistically significant association between swimming and rhinovirus-associated wheeze for children with atopic eczema.

This study strengthens our understanding on modifiable risk factors for RTIs in young children and is of relevance with respect to preventative strategies.

Keywords: acute otitis media, child, daycare, infant swimming, parental depression, parental loneliness, respiratory tract infections, risk factors

TIIVISTELMÄ

LL Linnea Schuez-Havupalo

Psykososiaalisten ja ympäristötekijöiden vaikutukset hengitystieinfektioiden sairastamiseen varhaislapsuudessa.

Turun yliopisto, lääketieteellinen tiedekunta, kliininen laitos, lastentautioppi, Turun yliopiston tutkijakoulu, Turun kliininen tohtoriohjelma (TKT); Lasten ja nuorten klinikka, Turun yliopistollinen keskussairaala.

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Hengitystieinfektioita esiintyy eniten alle kouluikäisillä lapsilla ja ne vaikuttavat monella tavoin ympäröivään yhteiskuntaan. Tämän tutkimuksen tavoitteena oli tutkia hengitystieinfektioiden modifioitavia riskitekijöitä, jotka liittyvät pienen lapsen arkisiin ympäristöihin: kotiin, päivähoitoon ja vapaa-ajan harrastuksiin.

Tämä prospektiivinen syntymäkohorttitutkimus toteutettiin Varsinais-Suomen sairaanhoito-piirissä. Seurasimme 1570 lasta syntymästä 3 vuoden ikään hengitystieinfektioiden suhteen ja keräsimme tietoa terveyteen liittyvistä, psykologisista, sosiaalisista ja muista ympäristötekijöistä päiväkirjojen ja kyselykaavakkeiden avulla. Osa kohortista (982 lasta) osallistui tarkempaan infektioseurantaan, johon sisältyivät nenästä otetut näytteet virusmäärityksiä varten ja käynnit tutkimusvastaanotolla äkillisten hengitystieinfektioiden aikana.

Äidin raskaudenaikaiset masennusoireet ennustivat välikorvatulehdusten suurempaa kumulatiivista määrää 10 kuukauden ikään mennessä ja äidin emotionaalinen yksinäisyys ennusti lääkärikäyntien suurempaa määrää samassa iässä. Välikorvatulehdukset, lääkärikäynnit ja antibioottikuurien määrä olivat hieman vähäisempiä sellaisilla lapsilla, joiden perheissä esiintyi sosiaalista yksinäisyyttä toisella tai molemmilla vanhemmilla.

Alle 2-vuotiaiden lasten kuukausittaisten sairaspäivien määrä (päivät, jolloin lapsella oli hengitystieinfektion oireita), antibioottihoidot ja vanhempien poissaolot työstä lapsen sairauden vuoksi lisääntyivät voimakkaasti päivähoidon aloituksen jälkeen ja vähenivät sitten selvästi 9 kuukauden seurannan aikana. Kun vertasimme samoja vasteita 30-35 kuukauden iässä, hengitystieinfektiopäivien määrässä ei ollut merkitsevää eroa kotihoidossa ja kodin ulko-puolisessa päivähoidossa olevien lasten välillä. Antibioottikuureja oli kuitenkin merkitsevästi enemmän päiväkotihoidossa käyvillä lapsilla.

Tutkimme myös mahdollisia yhteyksiä vauvauinnin ja hengitystieinfektioiden välillä 17 kuukauden ikään saakka. Hengitystieinfektioiden määrässä ei ollut eroa vauvauintia harrastaneiden ja muiden lasten välillä. Lapsilla, joilla oli atooppinen ihottuma, havaitsimme yhteyden vauvauinnin ja rinoviruksen aiheuttaman hengityksen vinkumisen välillä.

Tutkimuksen tulokset lisäävät ymmärrystämme pienten lasten hengitystieinfektioiden modifioitavista riskitekijöistä ja antavat työkaluja ehkäisevien toimien kehittämiseen.

Avainsanat: hengitystieinfektiot, lapsi, päivähoito, riskitekijä, vanhempien masennus, vanhempien yksinäisyys, vauvauinti, välikorvatulehdus

TABLE OF CONTENTS

ABBREVIATIONS

AOM	acute otitis media
CI	confidence interval
DCC	daycare center
DNA	deoxyribonucleic acid
FDC	family daycare
RV	rhinovirus
RNA	ribonucleic acid
OR	odds ratio
PCR	polymerase chain reaction
RSV	respiratory syncytial virus
RT	reverse transcriptase
RTI	respiratory tract infection
SEM	structural equation model

DEFINITIONS

Acute otitis media: Acute infection of the middle ear with clinical signs and symptoms of middle ear inflammation (cf. page 16,17, 41).

Bronchiolitis: The first episode of wheeze or expiratory obstruction during a respiratory tract infection up to the age of 24 months (cf. page 17, 41).

Daycare centres: Large-group, centre-based childcare provided by several professional caregivers, either by the municipality or on a private basis (cf. page 40).

Daycare initiation: The date when a child started daycare in a daycare centre or in a family daycare setting (cf. page 40).

Depression: Depressive symptoms were assessed during pregnancy in both mothers and fathers using the Beck's Depression Inventory (BDI-II). In this work, we did not assess effects of clinical diagnoses of depression, but rather those of symptoms indicating some degree of deficient well-being relating to the spectrum of depressive disorders (cf. page 40).

Extrinsic risk factors: Extrinsic risk factors (environmental risk factors) are defined as factors relating to the environment of a child, which may increase rates of respiratory tract infections (cf. page 16).

Family daycare: Daycare provided by a trained caregiver in his or her own home, or, in some circumstances, in the children's homes. Group sizes were generally limited to no more than 5 children (cf. page 40).

Infant swimming: Any indoor swimming activity intended for babies or young children (cf. page 40).

Intrinsic risk factors: Intrinsic risk factors (host-related risk factors) are defined as inborn or inherited characteristics, which may increase rates of respiratory tract infections (cf. page 16).

Loneliness: Symptoms of loneliness were assessed during pregnancy in both mothers and fathers using the UCLA loneliness scale. Loneliness was categorised into social and emotional components. Social loneliness refers to an experienced deficit of social networks. Emotional loneliness touches on an all-encompassing sense of absent intimate attachments (cf. page 40).

Respiratory tract infection: Infection of the upper or lower respiratory tract including acute otitis media. In this context, this term refers to acute and often self-limiting infections of the patient.

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which are referred to in the text by the Roman numerals I-IV. Previously unpublished data are also included. When not published under open access licences, the original publications have been reproduced with the permission of the copyright holders.

I Schuez-Havupalo L, Lahti E, Junttila N, Toivonen L, Aromaa M, Rautava P, Peltola V, Räihä H. Parents' depression and loneliness during pregnancy and respiratory tract infections in the offspring: a prospective birth cohort study. Submitted.

II Schuez-Havupalo L, Toivonen L, Karppinen S, Kaljonen A, Peltola V. Daycare attendance and respiratory tract infections: a prospective birth cohort study. *BMJ Open* 2017;7e014635.

III Schuez-Havupalo L, Karppinen S, Teros-Jaakkola T, Toivonen L, Peltola V. Respiratory tract infections and daycare: Infection rates at 30 to 35 months of age in a prospectively followed birth cohort. Submitted.

IV Schuez-Havupalo L, Karppinen S, Toivonen L, Kaljonen A, Jartti T, Waris M, Peltola V. Association between infant swimming and rhinovirus-induced wheezing. *Acta Paediatrica* 2014; 103:1153-1158.

1 INTRODUCTION

Respiratory tract infections constitute the main burden of disease in early childhood, and they add significantly to the workload of primary medical, as well as pediatric services (see J. Nokso-Koivisto, et al. 2006). It has been estimated that every fourth respiratory infection leads to a physician visit, and during infancy this figure is increased to about half of all respiratory tract infections (A.S. Monto and B. M. Ullman. 1974).

This thesis examines risk factors associated with respiratory tract infections in children younger than 3 years of age. Since intrinsic factors relating to pathophysiological processes of the immune system are extensively being investigated, the focus of this work shall be on modifiable extrinsic risk factors lending themselves to investigation within the framework of a prospective observational birth cohort study carried out in Southwest Finland.

Life at home with the parents, in daycare, and in the context of free-time activities forms the main arena of young children's early years in our society. This study assesses aspects relating to each of those environments with the aim to facilitate preventative strategies in the future.

Even in a country like Finland, where special efforts are made to ensure social equality, children are born into a variety of different situations. The parental role is obvious, when it comes to infant well-being, but studies on parental psychological risk factors with regard to respiratory tract infections in early childhood are sparse. Furthermore, interpretations on causality are challenged by the fact that recurrent respiratory tract infections may adversely affect the psychological well-being of the entire family (K. Louhi-Pirkanniemi, et al. 2004a). Previous studies also tend to focus on the mother, thereby leaving out the paternal role altogether.

Next to spending time at home with their parents, children are increasingly cared for in a variety of daycare institutions after the elapse of parental leave. Daycare, as a risk factor for respiratory tract infections, has been broadly studied. However, questions remain with regard to the chronology of infection rates as a function of time in relation to daycare initiation. Some previous studies propose that increased incidences of infectious disease are limited to the period after starting daycare (M. Kamper-Jørgensen, et al. 2006), and in fact effects may be reversed after some time (S. Cote, et al. 2010). A chronologically limited effect of daycare on respiratory tract infections in young children would have wide-ranging implications for families, as well as medical providers.

It has become ever more popular for families with young children to participate in different free-time activities, one of which is infant swimming. According to several studies, chlorination-by-products in the air of swimming pools constitute a

risk factor for the development of wheezing illnesses in young children (C. Voisin, et al. 2010, A. Bernard, et al. 2007). Other studies have postulated increased infection risks associated with baby-swimming (W. Nystad, et al. 2003, Y. Schoefer, et al. 2008), but these claims have also been disputed (W. Nystad, et al. 2008). It is evident that conditions in swimming pools in Finland cannot be compared to those in Central-European countries, and thus national data, only, help to establish an understanding relating to the possible risks of infant swimming.

In the following work, the effects of parental psychological well-being, daycare, and infant swimming on respiratory tract infections in children under 3 years of age shall be examined.

2 REVIEW OF THE LITERATURE

2.1. Epidemiology of respiratory tract infections

Respiratory tract infections (RTIs) are the most common reason for medical consultations in children, with an average of around 5-6 episodes of infections per child per year (M.M. van der Zalm, et al. 2009, L. Toivonen, et al. 2016b, T. Chonmaitree, et al. 2008). Children under 2 years of age are particularly vulnerable to RTIs (A.S. Monto and B. M. Ullman. 1974), and in one study even over 75% of infants younger than 6 months had already developed an upper RTI, even though they still may have had maternal antibodies (T. Chonmaitree, et al. 2016). RTIs show distinct seasonality for both adults and children with incidences rising during autumn and winter in temperate climates of the northern hemisphere, and during the rainy season in the tropics (see T. Heikkinen and A. Järvinen, 2003). Reasons for this are not fully understood.

Rhinoviruses (RV) are the most common cause of RTIs, not only in young children (M.M. van der Zalm, et al. 2009, M.M. Kusel, et al. 2006), but in all age groups (see T. Heikkinen and A. Järvinen. 2003), and they therefore play a major role in the epidemiology of acute respiratory infections. They also constitute the largest group of viruses affecting the respiratory tract, and over 160 rhinovirus types are already known (see L. Royston and C. Tapparel. 2016). RV could be detected in 59% of acute RTIs in 0-2 year-old Finnish children (L. Toivonen, et al. 2016b), and up to 91% of children were shown to have antibodies against RV by the age of 2 years (S. Blomqvist, et al. 2002). RV are non-enveloped viruses with a single-stranded RNA genome, which form part of the Enterovirus genus in the *Picornaviridae* family (see L. Royston and C. Tapparel. 2016). Transmission usually occurs through direct or indirect contact, droplets, or aerosols. RV are able to survive on surfaces for hours to days (B. Winther, et al. 2011). Most sources report an incubation period of 2-4 days, although a systematic review found a median incubation time of 1.9 days based on experimental data (J. Lessler, et al. 2009). After artificial inoculation with RV to the nasal cavity or the nasopharynx, viral shedding reaches a peak on the second day, but ceases gradually after 2-3 weeks (B. Winther, et al. 1986). The seasonality of RV shows a peak during early autumn, and another one in the spring, but RV can be detected throughout the year, such that their relative occurrence in comparison to other viruses is most common during the summer (A.S. Monto. 2002). RV are known to primarily replicate in the nasopharyngeal epithelium, but to some extent also in the lower respiratory tract (J.E. Gern, et al. 1997).

Next to RV, a large variety of other viruses cause RTIs, although some are also associated with other additional clinical manifestations. In longitudinal studies of young children carried out in a community setting in the USA, the Netherlands,

Vietnam, and Finland adenovirus (up to 27%), enteroviruses (up to 14%), coronaviruses (up to 11%), parainfluenza viruses (up to 10%), bocavirus (up to 9%), respiratory syncytial virus (RSV) (up to 9%), influenza A and B viruses (up to 7%), and metapneumovirus (up to 1%) were detected in a considerable proportion of RTI episodes (T. Chonmaitree, et al. 2008, K.L. Anders, et al. 2015, M.M. van der Zalm, et al. 2009, L. Toivonen, et al. 2016b). Determined frequencies of these viruses are strongly dependent on methodological aspects, age, and season of year, such that conclusions from these figures are clearly limited. Table 1 shows the classification, structure, primary modes of transmission, seasonality, and incubation periods of the above mentioned viruses (see T. Heikkinen and A. Järvinen. 2003, see P.L. Mackie. 2003, see D. Musher. 2003, see H. Brodzinski and R. Ruddy. 2009, see T.P. Sloots, et al. 2008, J. Lessler, et al. 2009, M.T. Jepsen, et al. 2018, see J. Jacques, et al. 2008, see K. Hedman, et al. 2011).

Transmission of respiratory viruses occurs via a number of mechanisms, and varies between different virus types: Direct propulsion of larger-sized droplets, airborne aerosols, or contact with secretions, often by self-inoculation due to contaminated hands, may be implicated to varying degrees (see T. Heikkinen and A. Järvinen. 2003, see D. Musher. 2003). Furthermore, the number and virulence of transmitted organisms, the immune response of the host, and mechanisms relating to the pathogenesis of the specific virus determine, whether infection results, or whether clinical manifestations of disease develop. For reasons not fully understood, all infections do not lead to symptomatic disease.

Table 1. Common respiratory viruses and basic characteristics. (Seasonalities described with reference to Northern Europe).

	Family	Structure	Primary transmission	Seasonality	Incubation period
Adenoviruses (family)	*Adenoviridae*	double-stranded DNA (non-enveloped)	contact with secretions, droplets, airborne aerosols, faeco-oral route	Infections throughout the year without any clear seasonality	7-13 days
Respiratory syncytial virus (species)	*Paramyxoviridae*	single-stranded RNA (enveloped virus)	contact with secretions, large droplets	infections during the winter months with biannual peaks in infection rates in Scandinavian countries	4-5 days
Human Metapneumovirus (species)	*Paramyxoviridae*	single-stranded RNA (enveloped virus)	Lack of formal studies, contact with secretions and airborne aerosols probable	infections during the winter months	3-5 days
Parainfluenza viruses 1-3, 4a, 4b (species)	*Paramyxoviridae*	single-stranded RNA (enveloped virus)	contact with secretions, droplets, airborne aerosols	infections peak during the beginning of spring	2-6 days
Influenza viruses A, B, C (genus)	*Orthomyxoviridae*	single-stranded RNA (enveloped virus)	airborne aerosols	infections during the winther months	1-4 days
Human non-polio enteroviruses A, B, C, D (species)	*Picornaviridae*	single-stranded RNA (non-enveloped)	variable for different serotypes; contact with secretions, droplets, faeco-oral route, contaminated water	variable for different serotypes; infections throughout the year	1-15 days
Coronaviruses (family)	*Coronaviridae*	single-stranded RNA (enveloped virus)	Contact with secretions, droplets, rarely: faeco-oral route	infections throughout the year, epidemies in late winter	2-5 days (for human non-SARS)
Human bocavirus (species)	*Parvoviridae*	single-stranded DNA (non-enveloped)	Lack of formal studies	infections during winter and spring	Lack of formal studies

2.2. Effects of RTIs in young children on society

It has been estimated that non-influenza-related RTIs in the USA amount to total annual costs of 40 billion dollars, of which 22.5 billion account for indirect costs associated with productivity losses (A.M. Fendrick, et al. 2003). RTIs in young children are mainly associated with indirect costs (S.B. Lambert, et al. 2008). A survey-based study reported an average of 1.2 parental work hours lost for every RTI episode of an under 13-year-old child (T.J. Bramley, et al. 2002). In a Finnish study from the 1990s, it was estimated that costs from RTIs for under-school-aged children amounted to an average of 1000 euros per child per year in the population (T. Nurmi, et al. 1991).

It has been shown that parenting young children directly increases infection rates experienced by caregivers themselves, and that children in the family often transmit RV to their parents and siblings (V. Peltola, et al. 2008a). In an epidemiological study from the 1970s, RTI infection rates decreased after the age of 2 years, but clearly increased for subjects between the ages of 25-29 years (A.S. Monto and B. M. Ullman. 1974) suggesting transmission of infection from young children.

Complications of RTIs result in a range of effects. Viral bronchiolitis has been shown to be associated with an increased risk of asthma later in life (see E. Piippo-Savolainen and M. Korppi. 2008), although direct causalities are improbable. Acute otitis media (AOM) is a major indication for antibiotic use (U.M. Rautakorpi, et al. 2001), and thereby it acts as a mediator in the development of antibiotic resistance (see A. Vergison, et al. 2010, S.J. Holmes, et al. 1996). Excess use of antibiotics also leads to other issues by affecting the microbiome (L. Dethlefsen, et al. 2008). There is some evidence that important public health problems in developed countries, such as obesity, diabetes, and the metabolic syndrome, may be related to such changes (E. Munukka, et al. 2012, P.J. Turnbaugh, et al. 2009). This may also hold true for a range of other chronic conditions (L. Virta, et al. 2012, B. Cukrowska, et al. 2017, F. Lv, et al. 2017).

In addition to economic losses and indirect effects of RTI-related complications, respiratory infections cause different degrees of deterioration in quality of life and potential suffering or anxiety to children and families. On a global level, RTIs constitute an enormous public-health problem with an estimated 2.2 million deaths in the world each year in children under 1 year of age, which means an estimated annual loss of almost 200 million person-years (see J. Chretien, et al. 1984).

2.3. Description of topic

For the purpose of this thesis, risk factors related to RTIs are categorised into intrinsic and extrinsic risk factors.

INTRINSIC RISK FACTORS (host-related risk factors) are considered inborn or inherited characteristics. These include genetic traits, chronic diseases and conditions, age, and sex of the child.

EXTRINSIC RISK FACTORS (environmental risk factors) are considered factors relating to the environment of a child. Exposures to external agents and conditions, such as allergens, viruses, other microbes, dietary factors, chemicals and pollutants form part of this entity. In addition to these, relationships within the family and beyond form an integral part of the environment of a child, and thus psychological and social factors are also included in this category.

The following thesis will focus on some modifiable extrinsic risk factors, which lend themselves to investigation in a community-based approach within an observational birth cohort study carried out in Scandinavia. A larger range of risk factors will be reviewed from the literature. Vaccines, dietary factors, factors relating to the human microbiome, and those less relevant to life in Scandinavia, or other developed countries, will not be considered in the following work.

Due to the community-based approach of this study, upper RTIs are the mainstay of this thesis, but all forms of RTIs are included. Bronchiolitis will be considered separately for its associations with infant swimming, but this work will not include a detailed review on the vast topic of asthma development and allergic sensitization.

2.4. Upper and lower RTIs and their clinical picture

Traditionally, RTIs have been classified into infections of the upper and lower respiratory tract with the larynx level serving as the anatomical dividing point. Since the respiratory tract constitutes one functional system, this classification is somewhat artificial. However, due to the wide approach of this thesis, the aim here is a broad terminological categorisation.

Upper RTIs

Upper RTIs in young children are generally characterised by varying degrees of rhinorrhoea, cough, hoarseness, sore throat, and commonly fever. General malaise, skin manifestations, and gastrointestinal complaints may sometimes accompany respiratory symptoms. Findings on clinical examination may include nasal discharge, pharyngitis, conjunctivitis, injection of the tympanic membrane, or

frank signs of AOM. The clinical course is generally self-limited lasting for a mean duration of 7-10 days (see T. Heikkinen and A. Järvinen 2003), but symptomatic relief may be achieved by antipyretic and analgetic medication. AOM is a common complication (T. Chonmaitree, et al. 2016) and a major indication for antibiotic use (U.M. Rautakorpi, et al. 2001). Acute bacterial sinusitis is a comparatively rare complication in young children, but has been reported to occur in 8% of upper RTIs in children under 4 years of age (T. Marom, et al. 2014). A barking cough, hoarseness, stridor, and inspiratory difficulty may be associated with laryngitis, which is often caused by parainfluenza virus (F.W. Denny, et al. 1983). Tonsillitis is an entity of its own. Adenovirus-related tonsillitis may cause the common upper RTI symptoms of rhinorrhoea and cough (O. Ruuskanen, et al. 1984), which are unusual for A-streptococcal tonsillitis.

Lower RTIs and wheezing illnesses

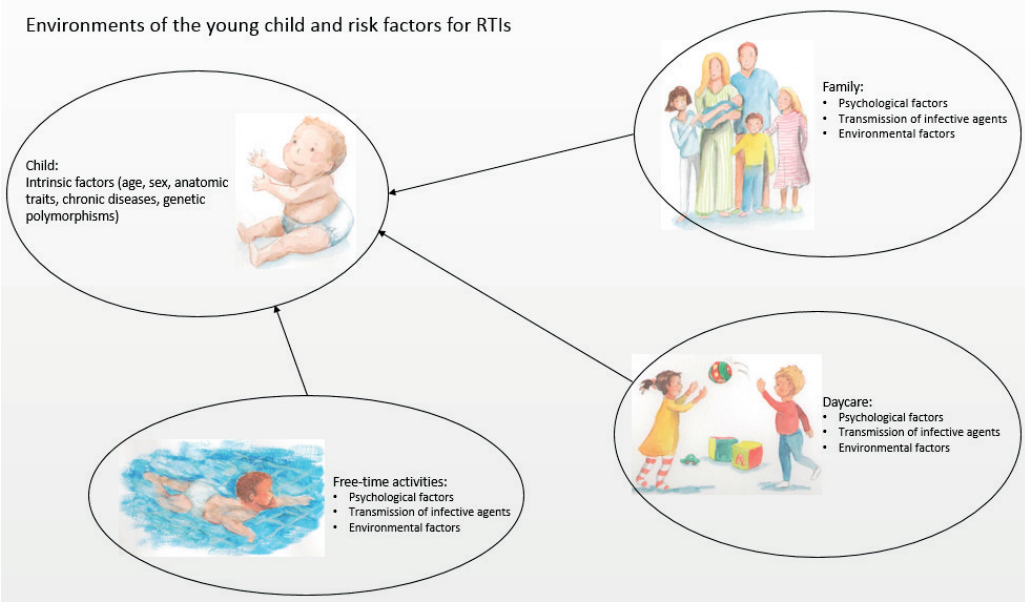
It is thought that about one third of viral RTIs in young children cause symptoms of the lower respiratory tract (see J.S. Tregoning and J. Schwarze. 2010). Clinical findings may include tachypnoea, changes in oxygen saturation, crackles, wheeze, reduced breath sounds, prolongation of the expirium, and other signs of increased respiratory effort.

In longitudinal studies, the prevalence of wheeze during RTIs for children under 3 years of age is about 12-32% (see E. Piippo-Savolainen and M. Korppi. 2008, L.M. Taussig, et al. 2003). The first episode of wheeze during a RTI is usually referred to as bronchiolitis (T. Jartti, et al. 2009) with a literature-source-depending age limit of up to 12 or 24 months of age. Bronchiolitis is characterised by inflammation, oedema, and necrosis of epithelial cells lining the bronchioles, which results in bronchospasm and increased mucus production (see American Academy of Pediatrics Subcommittee on Diagnosis and Management of Bronchiolitis. 2006). This, in turn, leads to small airway obstruction and thus a clinical picture characterised by obstruction during the expirium. In a study assessing wheeze and viral aetiology, RSV has been shown to be the predominant causal agent for children under 12 months of age, in comparison to the age group of over 12-months-old children who commonly display RV aetiologies (T. Jartti, et al. 2009). Overall, enterovirus and RV rates increase, and RSV and human metapneumovirus rates decrease with age (T. Jartti, et al. 2009).

Pneumonia is a comparatively rare illness with an estimated incidence of 36 cases per year per 1000 under 5-year-old children (T. Heiskanen-Kosma, et al. 1998).

2.5. Risk factors for RTIs

A



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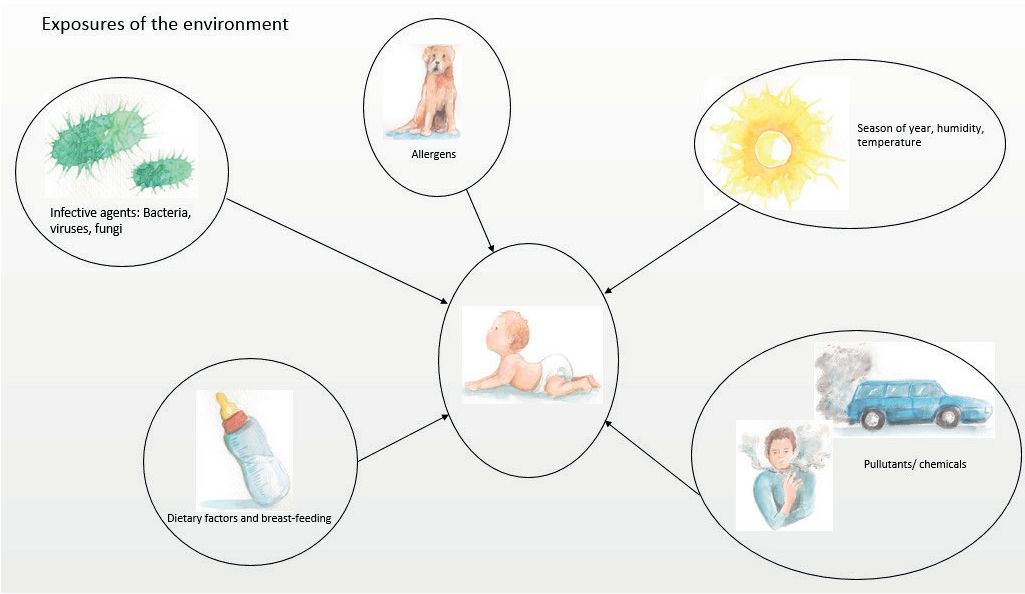

Figure 1: Environments of the young child and risk factors for RTIs (panel A) and specification of environmental exposures that have been studied as possible risk factors for RTIs (panel B).

Artwork: Rebecca Lujan.

Figure 1 shows extrinsic and intrinsic risk factors that have been studied concerning their associations with RTIs in young children. Few large longitudinal studies of RTIs and their risk factors in children under 3 years have been carried out. Risk factors reported include the presence of older siblings, male sex, low education of the mother, short duration or lack of breast feeding, and season of year (L. Toivonen, et al. 2016a, K.L. Anders, et al. 2015, O.P. Alho, et al. 1990, A.S. Monto and B. M. Ullman. 1974). Smaller studies with varying design from Germany and Iceland found age, sex, daycare, family history of frequent RTIs, asthma, allergies, humid conditions and mould in the home to be associated with RTIs (B. Benediktsdottir. 1993, R. Rylander and Y. Megevand. 2000). Higher maternal age was a protective factor in some studies (K.L. Anders, et al. 2015, R. Rylander and Y. Megevand. 2000). A recent birth cohort study conducted in the USA reported daycare attendance, the presence of older siblings in the family, and a short duration of breast feeding, or no breast feeding, as direct risk factors for RTIs in children under 6 months of age (T. Chonmaitree, et al. 2016).

Given the fact that RTIs are mainly self-limited, diverse with regard to symptoms and their intensity, and caused by a wide variety of viruses, direct community-based studies on risk factors in early childhood are sparse. Literature searches needed to cover a range of different diagnoses and viruses, and thereby necessitated a variety of independent key word combinations. AOM constituted an important key word, as it is a common complication of RTIs (T. Chonmaitree, et al. 2008) with about half of all children experiencing an episode of AOM during the first year of life (T. Chonmaitree, et al. 2016). However, it has to be borne in mind that risk factors for AOM cannot be equated with those for RTIs in general for a number of reasons: Some viruses, such as adenovirus and RSV, are thought to be associated with a particularly high proportion of AOM cases, and this has been especially shown for RSV (M. Uhari, et al. 1995). Furthermore, bacterial colonization interacts with respiratory viruses to increase AOM risks (T. Chonmaitree, et al. 2008, T. Chonmaitree, et al. 2016). Incidences of AOM also differ considerably on an international level and over time (see K.A. Daly, et al. 2010, T. Chonmaitree, et al. 2016, H. Alpert, et al. 2011), which may reflect true differences in risk factor and protective measure distributions (M.M. Rovers, et al. 2006), but it may also indicate differences in clinical diagnostic criteria (J.H. Wolleswinkel-van den Bosch, et al. 2010). Additionally, Eustachian tube dysfunction, which is related to otitis media, may also be caused by other factors than RTIs. Independent risk factors from RTIs, such as allergic rhinitis, have been described particularly for chronic otitis media with effusion (B.C. Pau and D. K. Ng. 2016, Y. Zhang, et al. 2014). Even though different types of otitis media are not always easily distinguished in clinical practice, literature searches were limited to diagnoses of AOM, and chronic otitis media with effusion, which is generally characterised by the absence of effusion-free intervals, was excluded. Risk factors predominantly related to local mechanisms and to dysfunction of the Eustachian

tube have been described also for AOM, and they will not be considered in the following work. They include feeding position, hypertrophy of the adenoids, anatomic abnormalities, and gastro-oesophageal reflux disease (see K.A. Daly, et al. 2010, R.C. O'Reilly, et al. 2008). The latter has also been implicated as a risk factor for lower RTIs and symptoms of cough and wheeze (M. Ghezzi, et al. 2011). Pacifier use constitutes another risk factor related to local mechanisms (M. Niemelä, et al. 1995, M. Uhari, et al. 1996, M. Niemelä, et al. 2000), but it carries relevance because of its potential confounding effects with parental psychological aspects.

The following risk factors for AOM were found: young age under 2 years, daycare, passive smoking, male sex, older siblings in the family, lack of breast feeding, or a short period of breast feeding, winter season, traffic-related pollutants, allergic diathesis, genetic susceptibility, low birthweight, prematurity, ethnic and socioeconomic factors (see K.A. Daly, et al. 2010, M. Uhari, et al. 1996, J.F. Lubianca Neto, et al. 2006, L. Vernacchio, et al. 2004, M.M. Rovers, et al. 2006). Highest prevalences of AOM have been reported in Inuits and Australian Aborigines (see K.A. Daly, et al. 2010).

Intrinsic risk factors

Age, sex, and prematurity

Numerous studies report higher incidences of RTIs in males than in females (K.L. Anders, et al. 2015), although associations are less clear for individuals over 3 years of age, and they may even be reversed in the older age-range (A.S. Monto and B. M. Ullman. 1974).

Young age is characterised by an immaturity of both the innate and adaptive immune system (see B. Adkins, et al. 2004), and susceptibility to infections as a function of age seems to be determined by declining maternally-derived immunoglobulin G during the first year of life on the one hand, and maturation of immunological processes on the other. Thus, infection rates tend to be comparatively high for children between 6 months and 2 years of age, but decline subsequently (A.S. Monto and B. M. Ullman. 1974) with incidences of around 2-4 RTIs per year for adults (see T. Heikkinen and A. Järvinen. 2003). Age-related environmental factors, such as initiation of daycare, are considered elsewhere. Neonates and premature infants mainly rely on the innate immune response (see T. Strunk, et al. 2011), and they are particularly vulnerable to both bacterial and viral infections. Active trans-placental transport of maternal immunoglobulin G mainly occurs during the latter half of the third trimester, which further contributes to infection susceptibility of the very premature.

Chronic conditions

Chronic conditions, which affect the immune system or the respiratory tract, or which are treated with immunosuppressive medications may act as risk factors for RTIs. An important example is asthma, which predisposes to lower RTIs and which will be discussed below. Malnutrition may occur for different reasons, but is of major importance on a global level. Anatomic abnormalities of the lungs or upper airways with surrounding structures, including the Eustachian tubes, may predispose to infection.

Allergies and atopic predisposition

There are a number of studies supporting associations between allergies or atopic disease and otitis media in childhood (Y. Zhang, et al. 2014, see K.A. Daly, et al. 2010, see A.R. Skoner, et al. 2009). It is evident that allergies, as well as RTIs, may lead to Eustachian tube dysfunction and thereby AOM. There is also evidence, that allergic adult patients have more frequent and prolonged RTIs in comparison to non-allergic adults (I. Cirillo, et al. 2007). Also in children, there are data to support allergies or atopic disease, or a family history of those conditions, as risk factors for RTIs (B. Benediktsdottir. 1993, R. Rylander and Y. Megevand. 2000, K. Hatakka, et al. 2010). Birth-cohort studies have found allergy-prone children attending child-care during the first year of life to be at an increased risk of RTIs, compared to children without a family history of allergic disease (J. Celedon, et al. 1999, L.P. Koopman, et al. 2001). Koopman et al. reported these associations for lower respiratory tract infections. Links between RV-induced wheezing during early childhood and asthma later in life are well-established, and studies have linked RV-associated wheeze during early life to allergic sensitization and atopic eczema (see T. Jartti and J. Gern. 2011). Underlying mechanisms are not fully understood, but direct causalities are unlikely. There is some evidence that interferon responses to RV in asthmatic patients are lower compared to those in non-asthmatic patients (P.A. Wark, et al. 2005, see T. Jartti and J. Gern. 2011). It has also been reported that interferon-gamma secretion during infancy is lower in infants with atopic features (see T. Jartti and J. Gern. 2011). A low interferon response has been associated with susceptibility to RV (see T. Jartti and J. Gern. 2011, D.A. Stern, et al. 2007). Furthermore, atopic inflammation is thought to increase the expression of the major receptor of RV, ICAM-1 (intracellular adhesion molecule 1) (A. Bianco, et al. 1998, see T. Jartti and J. Gern. 2011). Together, these findings imply that infants with atopic features are at an increased risk for more severe viral respiratory illnesses and wheeze upon infection with RV.

Genetic aspects

Several studies have reported on a substantial heritability with regard to otitis media, and a Norwegian study assessing a large population of twins found considerable heritability irrespective of sex (E. Kvestad, et al. 2004). Other twin

studies have been conducted with similar results (M.L. Casselbrant, et al. 2004). A number of Single Nucleotide Polymorphisms in cytokine genes and those of the innate immune response have been identified with regard to their associations with AOM and RTIs (see R. Mittal, et al. 2014, L. Toivonen, et al. 2016c). These include variants of genes for tumour necrosis factor (TNF) alpha, interferon (IFN) gamma, interleukins (IL), Mannose-binding lectins (MBL), and Toll-like receptors (TLR), amongst others (L. Toivonen, et al. 2016c, see R. Mittal, et al. 2014, C.M. Alper, et al. 2009, K. Revai, et al. 2009).

Extrinsic risk factors

Older siblings

A virus-transmitting source is a prerequisite for infection. It is thus no surprise that factors resulting in close contact between children, such as the presence of older siblings in the family, are often associated with increased rates of RTIs. Efficient transmission of RV from children to other family members has been demonstrated (Peltola et al. 2008). Close contact between children is also a characteristic of out-of-home daycare, and both of these risk factors display similarities in their effects on the growing child (E.S. Hurwitz, et al. 1991), which will be discussed elsewhere.

Season of year

The effect of season of year is not well understood, and dissimilar seasonalities between different viruses remain unexplained. During autumn and winter, crowding of people in indoor facilities may occur more frequently, in comparison to the summer season, and thus facilitate transmission of infection. There is no conclusive evidence on the effect of environmental exposures, such as cold temperatures and varying humidity, and, historically, studies have failed to demonstrate greater susceptibility to respiratory viruses in association with cold exposure after their artificial inoculation (R.C. Douglas, et al. 1967). Recent studies have shifted from assessing mere effects of temperature to taking also into account air humidity. Air humidity may not only determine the stability of a virus (F.L. Schaffer, et al. 1976), but it is also known to affect how long droplet nuclei remain airborne. At low humidities, evaporation is increased, which leads to a reduction in droplet size, and thereby easier suspension in air (see J. Shaman and M. Kohn. 2009). Associations between low temperatures, low humidity, and increased rates of RTIs have been shown by a number of ecological studies (N. Sundell, et al. 2016, T.M. Mäkinen, et al. 2009, K. Jaakkola, et al. 2014), partly carried out on conscripts in a sub-arctic climate (T.M. Mäkinen, et al. 2009, K. Jaakkola, et al. 2014), and partly specifically assessing influenza (K. Jaakkola, et al. 2014). Studies on conscripts in a northern environment offer exceptional

possibilities to assess cold exposure in vivo, but they do not take into account crowding, which may play a significant role in the military setting, and this thereby appears to be a major limitation.

A number of studies have assessed host responses in relation to environmental exposures. It has been postulated that cold-associated vasoconstriction in the nose and upper airway may negatively affect defence mechanisms and may thus convert an asymptomatic infection into a clinical RTI (see R. Eccles. 2002, see E.G. Mourtzoukou and M. E. Falagas. 2007). Additionally, mouse models have demonstrated that interferone responses to RV are more efficient at higher temperatures (37 degrees Celsius, as compared to 33 degrees Celsius) (E.F. Foxman, et al. 2015), which in part explains the nasal tropism of RV, but which may also indicate impairment of defence mechanisms with respect to weather-related cooling of the mucosa. In a guinea-pig model assessing influenza virus transmission, lower temperatures (5 degrees C) were associated with prolonged viral shedding and increased transmission efficiency (A.C. Lowen, et al. 2007).

In the tropics and subtropics, respiratory infections tend to increase during the rainy season. However, seasonal patterns are often less clear than in temperate regions. For instance, influenza viruses may be detected throughout a large proportion of the year in different tropical or sub-tropical locations. Evaporation of droplets is decreased in moist air, and thus airborne spread of viruses may play a less significant role in the tropics than in temperate climates (see S. Paynter. 2015). It follows that other modes of viral transmission, namely direct contact, may be more generally implicated. This hypothesis has also been supported by animal models (A.C. Lowen, et al. 2008). The effect of high temperatures and humidity on viral transmission will be discussed later.

Social status

Some studies have reported high social status to be inversely related to susceptibility to infections in both humans and monkeys (S. Cohen. 1999). There have also been links between a lower socioeconomic status and RTIs in children (K.L. Anders, et al. 2015). Crowding, multiple siblings, parental smoking, housing conditions, and nutritional factors may act as confounding factors in some populations. A systematic review has found a clear association between families' low socioeconomic status and rates of otitis media, but also racial disparities have been reported (D.F. Smith and E. F. Boss. 2010). Socioeconomic status and ethnic effects may partially confound each other, and exceptionally high infection rates are known for some indigenous populations (A. Banerji, et al. 2013, R.C. Holman, et al. 2011, see K.A. Daly, et al. 2010). Some studies found a higher socioeconomic status to be associated with increased RTI (A.S. Monto and B. M. Ullman. 1974) and AOM rates (J. Pukander, et al. 1982), and differences in utilization of health care services may serve as an explanation (A. Hjern, et al. 2000).

There is some evidence that low socioeconomic status in childhood may also have immunological effects on a longer-term basis. In one study, adults' higher susceptibility to infection after artificial nasal inoculation with respiratory viruses was reported to correlate with lower socioeconomic status in childhood, as measured by reported parental home-ownership during that time (S. Cohen, et al. 2004). Given the fact that it is impossible to control the vast array of confounders over such an extended period of time, causality cannot be derived from these types of studies, although personality characteristics, education, current home-ownership, and parental education were taken into account.

Parental smoking

Previous data suggest that, internationally, parental smoking may account for at least 1000 to 5000 excess RTI diagnoses and 500 to 2500 excess hospitalisations per 100000 young children, which may be directly attributable to passive smoke exposure in the family (see J.K. Peat, et al. 2001). A vast number of studies of varying design and several meta-analyses have been published assessing smoking and RTIs with consistent evidence of the detrimental effects associated with smoking to the developing lung and respiratory infectious outcomes. Effects of parental smoke exposure are particularly strong with regard to the development of bronchiolitis (L.L. Jones, et al. 2011), and an increase of hospitalisations due to bronchiolitis has been shown for children under 1 year of age (M. Lanari, et al. 2015). Studies have described effects of pre-natal exposure independently from those of postnatal exposure for both respiratory infectious symptoms (A.K. Johansson, et al. 2008), and AOM (S.E. Håberg, et al. 2010). Maternal smoking has been shown to exert particularly pronounced effects (D. Jurado, et al. 2005) in comparison to paternal smoking or other environmental exposures to tobacco smoke. Mechanisms behind the observed associations may include changes in airway wall thickness and resulting proneness to airway narrowing, damage to the lung epithelium and naso-pharyngeal mucosa, and modulation of the immune response.

Air pollution

In a country like Finland, traffic-related and industrial air pollution may be of comparatively little importance, but exposures may particularly affect children living in city areas with close proximity to industrial plants. An 18-year time-series conducted in the United States has shown correlations between ambient air pollutant concentrations and visits at the emergency department for RTIs in children under 4 years of age, suggesting that traffic pollutants, ozone, and organic carbon fractions of certain size exacerbate RTIs in young children (L.A. Darrow, et al. 2014). Other studies have found an association between traffic-related air pollution and the incidence of otitis media (M. Brauer, et al. 2006), and industrial air pollution and incidence of chronic otitis media (I. Holtby, et al. 1997).

Breast feeding

Breast feeding has long been well-established as a protective factor against infection-related mortality in developing countries (see World Health Organization. 2000). For industrialised countries, there is also substantial evidence that exclusive breast feeding to an age of at least 4-6 months reduces rates of RTIs (L. Duijts, et al. 2010) and gastrointestinal infections. Protective agents in breast-milk with regard to RTIs include immunoglobulin A, oligosaccharides, and lactoferrin, of which immunoglobulin A and oligosaccharides interfere with the attachment of pathogens, and lactoferrin carries antimicrobial properties (see L.A. Hanson, et al. 2002, see R.M. Lawrence and C. A. Pane. 2007).

2.6. Parental psychological factors and RTIs

Data to support a link between psychological stress and proneness to infection have been available for a period of time (N.M. Graham, et al. 1986, S. Cohen, et al. 1991). Cohen et al. showed in a study based on 420 healthy adults that, after the administration of nasal drops containing one of five respiratory viruses, infection rates were clearly higher for individuals with high stress-levels (S. Cohen, et al. 1991). Consideration of confounders, such as quality of sleep, smoking, diet, and exercise did not alter associations, which showed a dose-response pattern. Links between psychological stress and RTIs have also been demonstrated in children (M. Mäntymaa, et al. 2003, J.M. Turner Cobb and A. Steptoe. 1998, P.D. Drummond and B. Hewson-Bower. 1997, N.M. Graham, et al. 1990). In a 15-week longitudinal follow-up of 116 children aged 5-16 years, hassle levels were increased during the weeks before the onset of RTIs. Furthermore, life events reflecting stress on the one hand, and social support on the other, interacted in predicting RTIs, such that social support protected against infections, but only at low levels of event-induced stress (J.M. Turner Cobb and A. Steptoe. 1998). Another study assessing a small sample of 45 children with recurrent RTIs aged 8 to 12 years in comparison to 45 healthy children of the same age and sex distribution reported an increase in a variety of psychological stress-measures in the children with recurrent infections, and there was also a lower ratio of secretory immunoglobulin A to albumin in the saliva of these children (P.D. Drummond and B. Hewson-Bower. 1997). Indirect indicators of stress in children, such as deficiencies in the mother-infant interaction or maternal stress, have also been linked to RTIs and other chronic or recurrent physical health problems (N.M. Graham, et al. 1990, M. Mäntymaa, et al. 2003).

With regard to our research question of the effect of maternal or paternal psychological symptoms during pregnancy on respiratory infectious outcomes in the offspring, MEDLINE was repeatedly searched via PubMed (from inception to 5 May 2018) using the MeSH terms ‘depression’, or ‘anxiety’, or ‘psychological

stress', or 'loneliness' in combination with 'infant', 'respiratory tract infections', and either 'mothers', or 'fathers'. The MeSH term of 'Postpartum depression' was seperately searched in combination with 'respiratory tract infections'. Only articles written in English were included. Studies primarily focusing on other entities, such as allergic sensitisation, or physical abuse on women were excluded. Due to the low yield of studies, a number of other more general searches were additionally applied also using citations from the already retrieved articles.

Some studies have examined maternal stress and anxiety during pregnancy and infection-related outcomes in the offspring (R. Beijers, et al. 2010, N.M. Nielsen, et al. 2011, M. Tegethoff, et al. 2011, R.E. Henriksen and F. Thuen. 2015). Beijers et al. assessed maternal antenatal stress and anxiety by self-report and cortisol measurements in a sample of 174 mothers who tended to be highly educated, and they found these factors to predict a significant proportion of variance in health-outcomes in the offspring during the first year of life with values of 9.3% for respiratory illnesses and 7.6% for antibiotic use (R. Beijers, et al. 2010). In a Danish nation-wide cohort, there was a link between maternal stressful life events during pregnancy, or up to three years before conception, and infection-related hospitalizations in the offspring (N.M. Nielsen, et al. 2011). A large Norwegian birth cohort study, based on 100 027 children, examined prenatal stressful life-events and marital quality, as reported by the mother, in connection with possible links to childhood infections during the first year of life, and found significant associations with regard to RTIs and other infections (R.E. Henriksen and F. Thuen. 2015).

One study has been published on maternal perinatal depression and lower respiratory and gastrointestinal infections (L. Ban, et al. 2010). In this study carried out in the UK, a large set of data from electronic primary care medical records was applied in order to conduct a cohort study of 107 587 mothers and their first-born singleton children born within a 16-year period and covering a child-specific follow-up until the age of 4 years. There was a 27% increased rate of lower RTIs for children of mothers with perinatal depression compared to those born to women with no such diagnosis. In spite of the study design using a large database of primary care data, this study had a drop-out rate of about 20%, which may have biased the results.

Next to stress, anxiety, and depression, other psychological factors may play a role. Parental loneliness has been shown to strongly correlate with parental anxiety, depression and low self-efficacy (N. Junttila, et al. 2015), all of which are thought to constitute important determinants with regard to psychological problems in the child (see T.L. Jones and R. J. Prinz. 2005, S.N. Biehle and K. D. Mickelson. 2011, J.J. Wernand, et al. 2014). On the contrary, social support networks and ties have been shown to exert a protective effect against RTIs (S. Cohen, et al. 1997, S. Cohen, et al. 2015). Screening for loneliness in a clinical setting may be less

subject to denial, in comparison to evaluations for depressive symptoms, and it may thus be a more sensitive indicator of deficient psychological well-being compared to depressive symptoms (J.T. Cacioppo, et al. 2010).

When considering the effect of parental psychological factors on the physical health of the child, it is evident that parental healthcare-seeking behaviour may play a major role as a confounding factor and thus has to be taken into account. Parental depression has been shown to be associated with increased health service utilization for children (M. Olfson, et al. 2003), and the former therefore serves as a poor indicator of respiratory infectious disease itself. It also has been shown that children with recurrent antibiotic therapy display increased frequencies of medical consultations already during the first 3 months of life, although infection rates tend to be comparatively low at this very early age (K. Louhi-Pirkanniemi, et al. 2004b). An older study showed a correlation between maternal high psychotropic medication use and high use of antibiotics in the corresponding children (J.G. Howie and A. R. Bigg. 1980).

The above described studies relate to psychological stress-, anxiety- and depression- related effects on the occurrence of RTIs in all age-groups and in childhood. The potential for reverse causation poses a problem in some studies assessing effects of postnatal psychological symptoms in parents on RTIs in the offspring. Therefore, the assessment of parental symptoms during pregnancy offers a unique possibility to study factors influencing early childhood in a hypothetical cause-effect time-sequence. To date, there is only a few studies assessing maternal stress during pregnancy and RTIs in the offspring, and one study examining maternal depression during pregnancy with regard to RTIs in the infant (L. Ban, et al. 2010). There is a significant body of evidence to support the importance of the paternal role with regard to the psychological development in the child (A.L. Kvalevaag, et al. 2013, P.G. Ramchandani, et al. 2008b), but studies on effects relating to RTIs are lacking. There are also no studies on potential associations between parental loneliness during pregnancy and RTIs in the offspring.

2.7. Daycare and RTIs

Along with other searches of the literature, MEDLINE was searched via Pubmed (from inception to 5 May 2018) using the MeSH terms ‘respiratory tract infections’ together with ‘child day care centres’. Inclusion criteria were: English language, age under 36 months for at least part of the study cohort, and systematic study design with a control group (involving comparison between children in daycare centres, children in home care, and optionally those in family daycare). Studies on daycare-associated risks of infectious respiratory outcomes are numerous, so the focus was on studies allowing for interpretations on the aspect of time as a variable

in relation to daycare initiation. Very small studies (involving a single daycare facility or those with less than 50 participants per group) were excluded.

Daycare is a known major risk factor for RTIs in children (A.B. Doyle. 1976, K. Strangert. 1976, D.W. Fleming, et al. 1987, E.R. Wald, et al. 1988), and early studies have reported a daycare attributable risk of 31% for rates of upper RTIs and 66% for rates of AOM diagnoses in the under 5-year-old (D.W. Fleming, et al. 1987). Also a meta-analysis reported clear associations between daycare and AOM (M.M. Rovers, et al. 1999). Out-of-home daycare is becoming an increasingly important prerequisite for the functioning of modern life in high-income countries where often both parents are working. However, this frequently means that already young children from the age of 1 year, or even younger, are cared for in a variety of different daycare facilities. When a law was passed in Finland to oblige the local authorities to provide daycare for all children under 3 years of age in the 1990s, numbers of adenoidectomies performed in this age-group increased by 30% with no other apparent reason (M. Niemelä, et al. 1998). As a mediator of infections, daycare may have wide-ranging societal effects with regard to spread of infections across different populations, associated costs, and emergence of antibiotic resistance. It has been shown that enrolment in a daycare facility during the age of 0 to 2 years doubled the risk of receiving an antibiotic prescription drug (N. Thrane, et al. 2001). In another study, the start of daycare attendance between 6 and 12 months of age was associated with higher numbers of antibiotic prescriptions during the first 6 years of life. (L. Rooshenas, et al. 2014). As previously discussed, the excess use of antibiotics contributes to the increasing emergence of antibiotic resistance (see S.J. Holmes, et al. 1996) and has also other effects. Furthermore, daycare-attributable infections carry financial losses. In the year 2000 it was estimated that infection control education programmes implemented in daycare settings might have saved 550 million dollars in the US annually (S.B. Duff, et al. 2000).

Frequencies of respiratory viruses occurring in daycare settings may differ from those detected in home-reared children, but due to the large number of confounding factors it is difficult to obtain conclusive evidence. Fairchok et al. identified adenovirus, RV, and RSV to cause the greatest impact in their cohort of daycare-attending children aged 0 to 30 months. Co-infections were common with more than one virus present in 27% of cases. (M.P. Fairchok, et al. 2010). Another study described human metapneumovirus and human coronaviruses to be most strongly linked to childcare attendance in Australian under 5-year-old children (S.B. Lambert, et al. 2007).

Factors reflecting contact rates, such as group size, or size and type of the daycare facility have consistently been identified as important risk factors (M.M. Rovers, et al. 1999, A. Hardy and M. Fowler. 1993, J. Marx, et al. 1995, P. Louhiala, et al. 1995, The National Institute of Child Health and Human Development Early Child

Care Research Network. 2001, S. Cote, et al. 2010, E.S. Hurwitz, et al. 1991), but very large groups of over 40 children do not necessarily further increase risks (J.P. Collet, et al. 1994). Effects relating to the time spent at daycare every week have been inconsistent in different studies (The National Institute of Child Health and Human Development Early Child Care Research Network. 2001), (A. Hardy and M. Fowler. 1993). Hygiene measures are important and have previously been demonstrated to reduce infections (A.E. Aiello and E. L. Larson. 2002). A number of studies have demonstrated the effectiveness of direct or indirect hygiene interventions with regard to RTIs in a daycare setting (M. Uhari and M. Möttönen. 1999, L. Roberts, et al. 2000, A. Pönkä, et al. 2004). These interventions have been reported to be most effective for those under 2-3 years of age (L. Roberts, et al. 2000, A. Pönkä, et al. 2004), which might be explained by the fact that those children require comparatively more assistance with at-risk activities, such as nose-blowing or other care relating to personal hygiene. Interventions applied in different studies included education of caregivers on transmission of infections, emphasis on hand-washing, use of disinfectants and paper-towels, cleaning or circulating of toys, avoidance of tooth-brushing at daycare, amongst others. Significant effects of hygiene interventions with regard to RTIs have not been demonstrated in all studies (K. Hedin, et al. 2006, T. Gudnason, et al. 2013, J.B. Kotch, et al. 1994, T.P. Zomer, et al. 2015), and this may be explained by a high standard of hygiene in daycare facilities of the control groups, insufficient adherence to interventions by caregivers in the intervention facilities, or partly ineffective or insufficient measures. Basic prevention-activities, such as handwashing, may not have any significant effect if not systematically adhered to (T. Jefferson, et al. 2009).

Children of young age have been shown to be particularly vulnerable to daycare-related effects regarding transmission of infections (E.S. Hurwitz, et al. 1991, P. Louhiala, et al. 1995, The National Institute of Child Health and Human Development Early Child Care Research Network. 2001, A. Zutavern, et al. 2007, M. Kamper-Jørgensen, et al. 2006, S. Cote, et al. 2010, N. Lu, et al. 2004, J. Celedon, et al. 1999, E.R. Wald, et al. 1991). In an American study assessing repeated diagnoses of AOM in 5818 children under 6 years of age, effects of daycare were strongest for those between 1 and 2 years (A. Hardy and M. Fowler. 1993). A Finnish study of 2558 children between the age of 1 and 7 years, reported significant excess risks of AOM and RTIs for 1 and 2 year-old children (P. Louhiala, et al. 1995). Another American study based on 1188 children aged up to 5 years demonstrated significantly increased risks of upper RTIs in association with daycare for children under 1.5 years of age, but not for those between 1.5 and 5 years of age (N. Lu, et al. 2004). A Canadian study of 185 children aged 0 to 2 years found no differences regarding RTIs between children under 3 months of age, who were ever versus never in care for over 1 day per week. For children

between 3 and 24 months of age, daycare constituted a significant risk factor with regard to RTIs (R.E. Dales, et al. 2004).

Hurwitz et al. conducted a cross-sectional study in the US based on 2137 children (E.S. Hurwitz, et al. 1991) aged 6 weeks to 59 months. They were the first to demonstrate a lower daycare-attributable risk of RTIs with increased time of exposure to daycare, and thus provided data to suggest that daycare-related infection risks were not exclusively linked to the absolute age of a child. They also showed that older siblings in the family constituted a competing RTI-risk to daycare for children aged 18 to 35 months, in that there was no statistically significant risk of RTIs associated with daycare for those with older siblings. Another study to take into account exposure-time was a register-based study assessing 138 821 hospitalizations of 0-5 year old children for RTIs in Denmark (M. Kamper-Jørgensen, et al. 2006). This study found incidences of RTI hospitalizations to decrease after attending daycare over 6 months, and after 1 year the incidence was comparable with children cared for at home.

A few longitudinal cohort studies have been published taking into account chronological aspects of daycare. A birth cohort study on respiratory and gastrointestinal infections in Germany included 3097 children who were followed-up until the age of 6 years (A. Zutavern, et al. 2007). This study reports that children in daycare during the first two years of life experienced more infections, but that relationships were reversed at the age of 3-4 years with respect to bronchitis, pneumonia, otitis media, and diarrhoea, but not for the common cold. A US study, based on over 1200 participants aged 0-3 years, reported that children in daycare during the first 2 years of life had higher rates of respiratory and gastrointestinal infections, as compared to those cared for at home (The National Institute of Child Health and Human Development Early Child Care Research Network. 2001). These relationships were not significant anymore by the age of 3 years. A Canadian birth cohort study with a follow-up of 8 years on 1238 children reported that children who started daycare before the age of 2.5 years experienced significantly more RTIs and diagnoses of AOM at that age period when compared to children cared for at home. However, they experienced similar rates of RTIs and diagnoses of AOM during the ages between 3.5 and 4.5 years, and lower rates during the elementary school years (S. Cote, et al. 2010). Those children commencing daycare between the ages of 3.5 and 4.5 years experienced higher rates of RTIs and AOM diagnoses during this period of time, but at other times rates of infections were similar to children in home care. A protective effect of early daycare with regard to RTIs during the early school years has also been described in the Tucson Respiratory study, where protective effects waned by the age of 13 years (T.M. Ball, et al. 2002).

There is a lack of longitudinal studies that would allow detailed chronological conclusions particularly around the time of daycare initiation. In the previous

longitudinal cohort studies, data were partly collected retrospectively, and the exact point of enrolment into daycare was often not available. Chronological data are particularly needed for children under 2 years of age who appear to be at an especially high risk for daycare-related RTIs: On the one hand, it has been suggested that commencing daycare early might constitute a prerequisite in order to experience protective effects against RTIs later on (S. Cote, et al. 2010). On the other hand, an early age of daycare initiation has been related to complications, such as an increased risk of recurrent AOM, an increased lifetime risk of asthma (P. Nafstad, et al. 1999), or an increased risk of invasive pneumococcal infections (A.K. Takala, et al. 1995). It is known that early diagnosis of AOM is a risk factor for subsequent episodes (D.W. Teele, et al. 1989). A Dutch birth cohort study on 2217 children followed up to the age of 6 years, found first year daycare attendance to result in higher six-year total rates of family-physician consultations and specialist referrals, as compared to children reared at home (M.L. de Hoog, et al. 2014). However, physician-detected episodes of upper RTIs and AOM were similar between the daycare and home care groups during the 6 year period. Apparent daycare related risks may partially be explained by attitudes on health conveyed by daycare, rather than a true disease burden (L. Rooshenas, et al. 2014).

A chronological assessment of RTIs as a function of time with regard to daycare initiation in the age-group of under 2-year-old children would allow a better estimate of risks relating to early enrolment in daycare.

2.8. Infant swimming and RTIs

Infant swimming has become an increasingly popular free-time activity for many families. However, there have been concerns about potential risks with regard to the development of RTIs, and specifically bronchiolitis and wheezing illnesses in children who swim. Indoor swimming facilities are routinely chlorinated in order to achieve better hygiene standards, but potentially harmful, volatile chlorination-by-products arise when chlorine reacts with organic matter brought into the pool by bathers. Both, poorly maintained pools with low chlorine and pools with higher chlorine concentrations constitute potential health hazards by insufficient hygiene on the one hand, and potentially toxic volatile compounds on the other. Furthermore, like in any other social activity, close contact between children implies the possibility of viral and other infectious agent transmission between peers. The warm and humid environment of swimming facilities constitutes a unique feature, which has not been examined per se. However, high humidity has been described as a factor that may affect respiratory viral transmission and data are partially obtained from studies in the tropics. These studies have to be interpreted with caution, as ecological study designs do not allow for a controlled environment, and environments are not commensurate. Humidity is interconnected

with air temperature, since saturation vapor pressure increases exponentially with temperature, i.e. relative humidity (the ratio of the measurable water vapor pressure of the air to the vapor pressure of saturated air) is determined by both the temperature and water vapor content of air. Traditionally, transmission of viruses has been connected to dry and cold air. However, in the tropics, RTI rates tend to increase during the rainy season, and, with regard to influenza viruses and RSV, infection peaks have been shown to occur with maximum humidity (J.D. Tamerius, et al. 2013, J. Tamerius, et al. 2017, S. Paynter. 2015). Furthermore, in an experimental study on influenza A virus, relative humidity levels above 90% were shown to increase viability of the virus on surfaces (W. Yang, et al. 2012). As discussed earlier, hot and moist conditions may shift the mode of transmission away from airborne particles to that of direct contact (A.C. Lowen, et al. 2008). Also irrespectively of temperature and air humidity, direct contact may be assumed to be of importance when sharing the same bathing water. A shift in transmission mode can be assumed to have ramifications on transmission occurrences of specific viruses.

Searches on this topic included that of MEDLINE via PubMed (from inception to 5 May 2018) using the MeSH terms ’infant’ and ‘swimming pool’ together with either ‘infection’ or ‘bronchiolitis’. Articles were limited to those written in English. Studies with low and irregular exposures to indoor swimming-pools were excluded.

Advocates of the so-called ‘chlorine-hypothesis’ have reported data that suggests associations between swimming and respiratory symptoms not limited to the young age range, or aetiologies involving infectious agents, but more wide-ranging ones with the potential of general public health effects, specifically relating to wheezing illnesses and asthma development. Most of the studies available to date originate from the same study group in Belgium, and other groups have pointed out that the current evidence is insufficient in order to draw conclusions with regard to public health measures. Data supporting an increase of airway symptoms in competitive swimmers have been published earlier (B. Levesque, et al. 2006). One study assessed respiratory symptoms in lifeguards of indoor swimming facilities with the result that irritant eye, nasal, and throat symptoms were common, but bronchial hyper-responsiveness was not shown in those guards (N. Massin, et al. 1998). Ecological studies are strongly limited by their inability to control for the vast array of confounding factors, but one such study has been carried out comparing prevalences of asthma, hay fever, rhinitis, and atopic eczema in children, as reported by the International Study of Asthma and Allergies in Childhood (ISAAC), and the number of indoor swimming facilities per inhabitant. Economic and lifestyle factors were taken into account. The study concluded that the prevalence of childhood asthma and the availability of swimming pools in Europe are connected (M. Nickmilder and A. Bernard. 2007). Meta-analyses on asthma and swimming could find no conclusive evidence (M. Goodman and S.

Hays. 2008, F. Valeriani, et al. 2017), apart from apparent associations between swimming and asthma in elite swimmers (M. Goodman and S. Hays. 2008). Overall, a problem consists in the fact that specific chlorination-by-product exposure has been measured in only few studies, and rather, swimming exposure has been used as a surrogate.

There are some studies evaluating risks of swimming-connected RTIs and wheezing illnesses in young children. A retrospective study of 430 kindergarten attenders with a mean age of 5.7 years showed an association between swimming pool use before the age of 2 years and an exposure-dependent risk of bronchiolitis (C. Voisin, et al. 2010). For those who developed bronchiolitis, there was also a higher risk of asthma and respiratory allergies later during childhood. In a cross-sectional Norwegian study on 2862 school-aged children, parents retrospectively reported on recurrent RTIs, otitis media, and infant-swimming practices during the first year of life. The prevalence of recurrent RTIs was significantly higher in children who had participated in swimming-programmes, compared to those who had not (W. Nystad, et al. 2003). Stratified analyses revealed parental atopy as a mediating factor, such that trends were only significant for children of atopic parents. Additionally, a longitudinal study was carried out by the same group using a Norwegian birth cohort of 30 870 children followed up until the age of 18 months. This study found an increase of wheeze for children of atopic mothers who participated in baby swimming activities (W. Nystad, et al. 2008). No associations were found between infant swimming and otitis media or lower respiratory tract infections. A German longitudinal birth cohort study of 2192 children followed for 6 years reported associations of infant swimming with infections (Y. Schoefer, et al. 2008). Gastrointestinal infections were more common in children who participated in infant-swimming, and similar results were shown for RTIs and AOM, although at the limit of statistical significance. This study could not confirm an increased incidence of atopic diseases later in life.

Measurements of lung-specific pneumoproteins have been carried out with the aim to assess lung epithelium integrity in relation to swimming (A. Bernard, et al. 2005), and a dose-dependent effect on epithelial permeability has been reported (A. Bernard, et al. 2003, A. Bernard, et al. 2007).

Longitudinal studies assessing potential links of infant-swimming with RTIs and wheezing illnesses are scarce. International variations in results may be expected due to lifestyle differences, but also local dissimilarities in chlorination practices, as well as other maintenance aspects of swimming pools that affect the development of volatile compounds in the air of those facilities.

3 AIMS OF THE STUDY

The aim of this thesis was to examine risk factors associated with respiratory tract infections in early childhood. This work focused on modifiable extrinsic risk factors, which lend themselves to further investigation within the framework of a prospective observational birth cohort study carried out in Southwest Finland: daycare, parental psychological factors, and infant swimming.

The specific objectives were:

1. To assess, whether deficiencies in parental psychological well-being during pregnancy affect infection rates of the infant during the first 10 months of age. (I)

2. To describe trends in respiratory infection rates associated with daycare initiation as a function of time in children under 24 months of age. (II)

3. To follow the previously examined cohort at a later time point for the ages of 30-35 months with regard to daycare in order to assess infection rates later on. (III)

4. To describe respiratory infectious symptoms, namely upper respiratory tract infections and wheezing illnesses, associated with baby swimming in infants up to 17 months of age. (IV)

4 MATERIALS AND METHODS

4.1. Study design

This work was carried out as part of the Steps (Steps to the Healthy Development and Well-being of Children) study, which constitutes a prospective birth cohort study with no interventions (see H. Lagström, et al. 2013). The study cohort consists of N = 1827 children, including 30 sets of twins, born between January 2008 and April 2010 in the Southwest Finland Hospital District. Recruitment of families occurred mainly during the first visit to community midwifery services, which took place between the 10^{th} and 15^{th} gestational week of pregnancy (1387 families), but 410 families were recruited on the labor wards of the Turku University Hospital or Salo Regional Hospital, thus joining the study shortly after the birth of their child. Registry data are available for the eligible cohort, which consists of N = 9811 mothers and N = 9936 children born during the study period in the Southwest Finland Hospital District. Families who did not speak the national languages Finnish or Swedish were excluded from the study. Recruitment to the study is shown in Fig. 2.

Families were followed for RTIs applying a daily symptom checklist from birth until the age of 2 years, and a weekly symptom diary during the third year of life. Additionally, data on physician visits and their outcomes, child development, free-time activities, and daycare were recorded in those diaries. Part of the cohort (982 children) were included in a more detailed infection follow-up. Participation in this group was offered to all study families with no exclusion criteria. Parents of children in this more detailed follow-up were asked to take nasal swabs from each nostril on day 1-3 of every RTI and send them for viral analysis by mail. Virological diagnosis was performed at the Department of Virology, University of Turku. Families participating in this group were entitled to visit our study clinic during acute RTIs. Equipment at the study clinic included tympanometry, as well as bedside laboratory tests (crp, leukocytes, rapid viral antigen test). Nasal swabs were also taken during clinic visits, if they had not already been taken at home. Continuity of care and research was granted, as physicians generally worked at the clinic on a daily basis and locum work was kept to a minimum. The study clinic was run by pediatricians and physicians in pediatric specialist training, and it was located in close proximity to the pediatric emergency department of the university hospital, where children were referred for further evaluation, if considered necessary. Hospital data were available for all study children.

All families in the study cohort received questionnaires on medical, psychological, family and other matters upon recruitment and when the child was 13, 18, and 24

months of age. Questionnaires were obtained from both the mother and the father, as applicable.

Mothers and fathers of families recruited during pregnancy completed questionnaires when first recruited (mothers only) during the first trimester and at gestational week 20. These contained information on family-related details, and the latter assessed information on parental depressive symptoms and loneliness (study I). Questions on daycare-arrangements were obtained from the questionnaires at the ages of 13, 18, and 24 months (study II and III). Questions on allergies and atopic conditions were assessed using previously evaluated forms of the International Study on Asthma and Allergies in Childhood (ISAAC) (The ISAAC Steering Committee. http://isaac.auckland.ac.nz/resources/tools.php). Questionnaire-based information on physician-detected atopic eczema and wheeze was collected when the child was 13 months of age (study IV). Data on infant swimming practices were collected by sending out an additional internet-based questionnaire, which assessed frequency, duration, and age at start of swimming. At this time children were between the ages of 13 and 41 months of age. Families who could not be contacted by e-mail received the questionnaire by mail. All families were invited for routine visits at our nurse-led study clinic when the child was 2, 13, 24, and 36 months of age. These routine visits were intended to provide an opportunity for discussion of any parental concerns, but also included measurement of growth and blood samples for serology, which were not applied in this study.

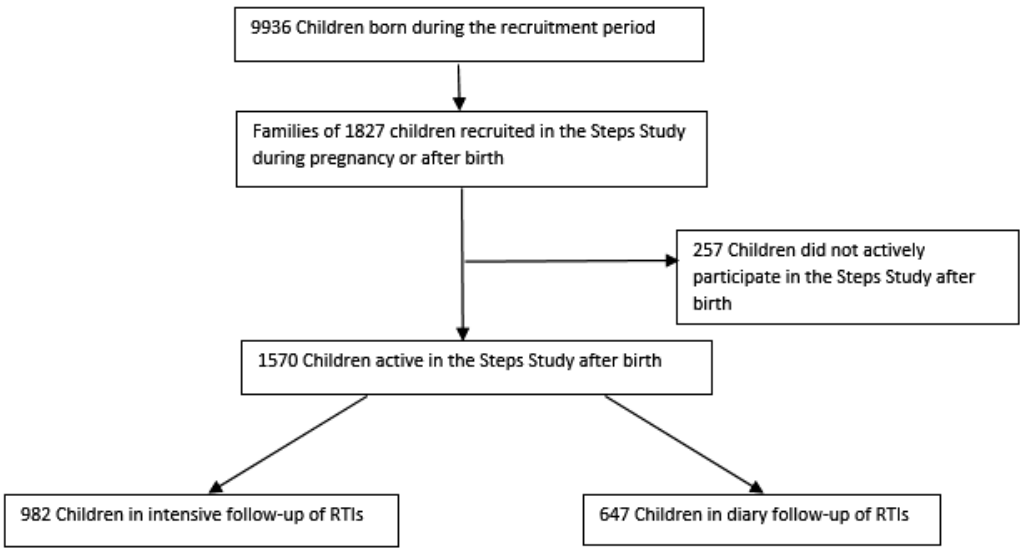

Figure 2: Recruitment to the Steps study.

Diagram modified from (L. Toivonen. 2016) with permission of the author.

4.2. Study cohort and dropouts

Different exclusion criteria and age frames were applied in relation to the varying research questions. They are described in the following:

Study I

In study I, families with twins and those recruited after pregnancy were excluded. Children were followed from birth to the age of 10 months. There were 924 children in this cohort after the exclusion criteria were applied, and 566 children were part of the intensive follow-up for RTIs. Recruitment to study I is shown in Fig. 3.

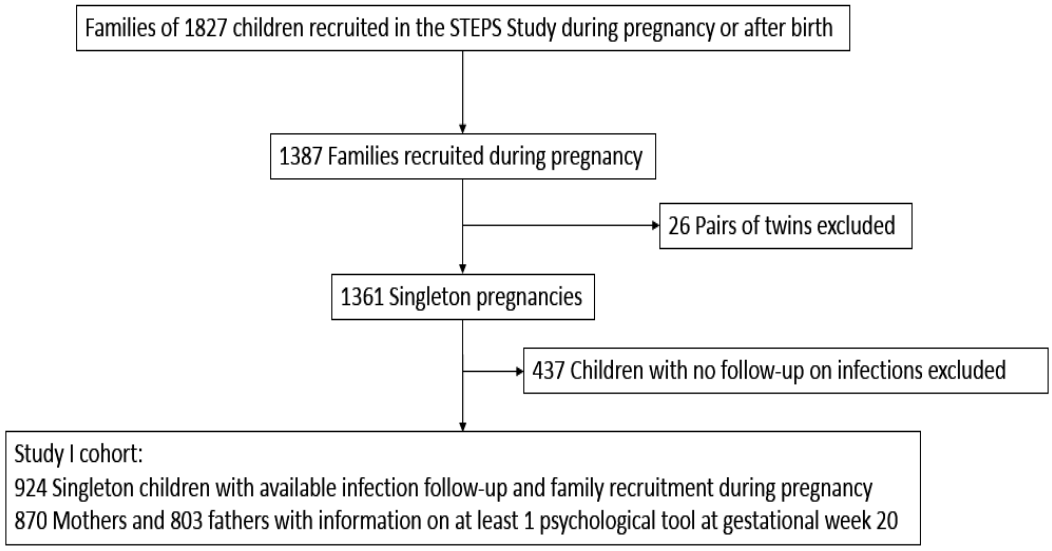

Figure 3: Cohort of study I

Diagram modified from (I).

Study II and III

The recruitment to study II is shown in Fig. 4. Children with discontinued follow-up before daycare initiation, insufficient information on daycare arrangements, or lack of information on home care were excluded from the study. Follow-up included an age frame of 0-23 months (II) with the modifications described in the statistics section. Children were stratified into groups of children in daycare centres (DCC), family daycare (FDC), or home care. In study III the same groups were

applied, but children with contradicting information on daycare arrangements at the age of 24 months compared to previous data were excluded from the analyses. We obtained data for 164 children in home care, 143 children in FDC, and 164 children in DCC (III). All children within the daycare groups of study III had been attending daycare for at least 6 months. Infection follow-up for study III included an age frame of 30-35 months.

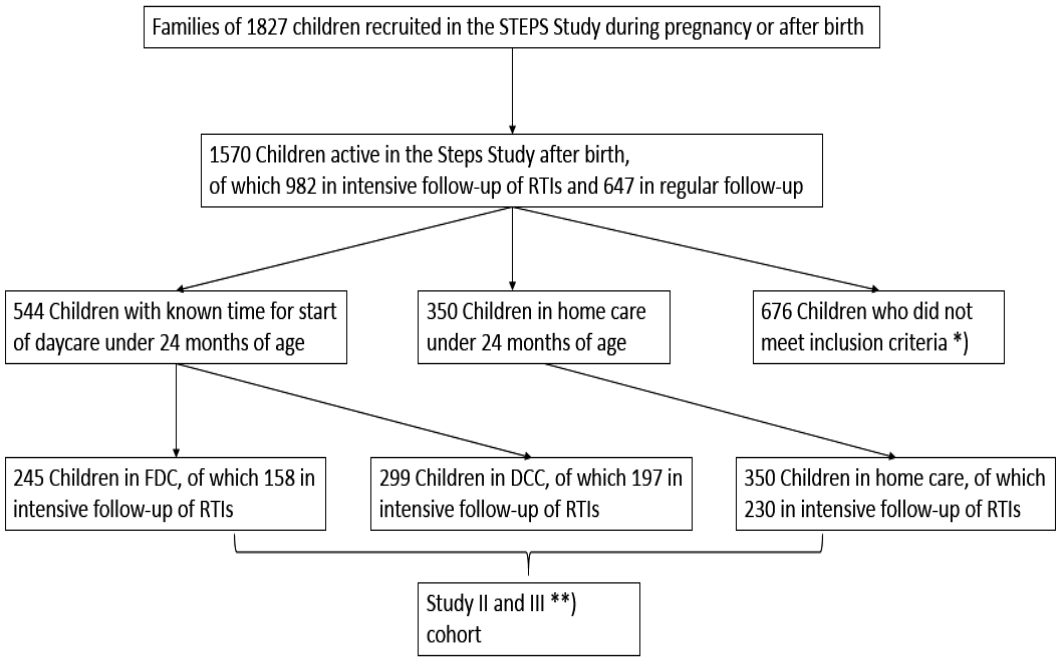

Figure 4: Cohort of studies II and III.

FDC, Family daycare. DCC, Daycare centres.

*) Children who dropped out before daycare initiation, children with unknown exact time for the start of daycare, or no explicit statement of home care.

**) For the cohort of study III the same daycare groups were used as in study II, but children with contradicting information on daycare arrangements at the age of 24 months compared to previous data were excluded. Data for study III were obtained from 164 children in home care, 143 children in FDC, and 164 children in DCC.

Diagram modified from (II)

Study IV

Study IV included families who responded to the separately posted questionnaire on infant swimming practices. For practical reasons, children were followed to the age of 17 months, which was when the last children attended the 1-year routine visit at the nurse-led clinic. Diary follow-up covered the period from birth to 1 year of age. The questionnaire on infant swimming practices was posted, when children were between the ages of 13 and 41 months, so it contained retrospective data. Recruitment to study IV is shown in Fig. 5.

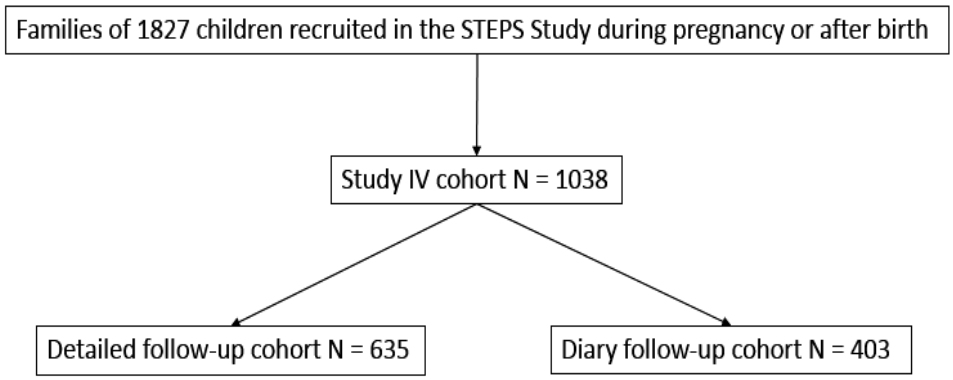

Figure 5: Cohort of study IV.

Diagram modified from (IV).

4.3. Virus PCR

Viral diagnostics were carried out at the department of virology, University of Turku by the group of docent Matti Waris. Nasal swabs were analyzed by reverse transcription-PCR. The nasal swab was suspended in phosphate buffered saline, and nucleic acids were extracted from the specimens by NucliSense easyMag (BioMerieux, Boxtel, Netherlands) or MagnaPure96 (Roche, Penzberg, Germany) automated extractor. The extracted RNA was then reverse transcribed and the cDNA amplified applying real-time PCR for HRV, enterovirus, and RSV, as described in earlier work (V. Peltola, et al. 2008b), with the modification that proprietary dual label probes were included into the PCR mix for differentiation of the virus-specific amplicons.

4.4. Variables

Psychological measures (I)

All psychological measures were obtained by questionnaires completed by both mothers and fathers at gestational week 20.

Parents' depressive symptoms were assessed using the Beck's Depression Inventory (BDI-II) (see A.T. Beck, et al. 1996). The Finnish version of the BDI-II includes 21 items with four choices (e.g. 0 = I don't feel disappointed in myself/ 1 = I am disappointed in myself/ 2 = I am disgusted with myself/ 3 = I hate myself).

Fathers' and mothers' social and emotional loneliness were evaluated using the Finnish version of the UCLA loneliness scale (N. Junttila, et al. 2013, see D. Russell, et al. 1980), which assesses factors of social and emotional loneliness rated on a 4-point scale (1 = never; 2 = rarely; 3 = sometimes; 4 = often). Loneliness is subjective anxiety relating to a discrepancy between one's perceived and desired relationships (N. Junttila, et al. 2013). Social loneliness refers to the subjective experience of a lack of social networks, and emotional loneliness describes the perceived absence of a close, intimate attachment to another person (see R. Weiss. 1973, N. Junttila, et al. 2013).

Family daycare (FDC) (II and III)

We defined family daycare as daycare provided by a trained caregiver in his or her own home, or sometimes in the children's homes, if families had arranged a rotational system. Local regulations limited FDC group sizes to no more than 5 children. However, on some occasions carers worked together forming a common nursery. These groups tended to be relatively small, and were therefore included in the FDC category. FDC was provided either by the municipality or on a private basis.

Daycare centres (DCC) (II and III)

Daycare centres were defined by larger-group, centre-based care provided by several professional caregivers, either by the municipality or on a private basis.

Home care (II and III)

Children cared for at home by parents or relatives.

Infant swimming (IV)

Infant swimming was defined as any indoor swimming activity intended for babies or young children.

4.5. Outcomes

Acute otitis media (I)

AOM was defined as acute infection of the middle ear with clinical signs and symptoms of middle ear inflammation. Diagnoses of AOM were documented by physicians in our research clinic and elsewhere. Physicians at the research clinic adhered to the AOM definition of the American Academy of Paediatrics and the American Academy of Family Physicians (see American Academy of Pediatrics Subcommittee on Management of Acute Otitis Media. 2004). In case of repeated diagnoses of AOM, an interval of 14 days was required before a new diagnosis was accepted.

Antibiotic treatments (I)

Number of antibiotic medications for RTIs prescribed in the research clinic or elsewhere from birth until the age of 10 months of age.

Physician visits (I)

Number of physician visits due to RTIs either in the study clinic or elsewhere from birth until 10 months of age.

Sick days/ weeks (II, III, IV)

Sick days were defined as days with symptoms of rhinorrhoea, cough, wheeze, or fever, detected by parents and recorded in the symptom diaries. Fever was defined as a temperature above 38 degrees Celsius. In study III, the above mentioned symptoms were indicated by parents in diaries on a weekly level. Symptoms did not necessarily have to last throughout the entire indicated week, but could cover only part of the time.

Antibiotic treatment days/ weeks (II and III)

Days with antibiotic medications as indicated in the symptom diaries by the parents. Antibiotic medications for any reason were included, but AOM was the main indication. In study III, antibiotic medications were indicated for any given week.

Parental absences from work (II and III)

Days with any parental absence from work due to the study child's illness. For children in home care, the stay-at-home parent could not be absent from work.

Bronchiolitis and wheezing (IV)

Bronchiolitis was defined as the first physician-detected RTI with expiratory wheeze or expiratory obstruction, if this was not related to a diagnosis of laryngitis or pneumonia. Expiratory obstruction was detected, if there were clinical findings

of a prolonged expirium, or use of accessory muscles, with or without an increased breath rate. Collectively, bronchiolitis and recurrent wheeze were referred to as wheezing illnesses. All diagnoses of bronchiolitis were made before the age of 17 months.

4.6. Confounders

Sex of the child (I, II, IV)

We assessed the background variable of male versus female children.

Parental age (I and IV for mothers)

Age of the mother or father at the birth of the child in years.

Siblings (I, II, IV)

Older siblings in the family, as indicated in the questionnaire completed upon recruitment.

Preterm birth (I, II, IV)

Birth under 37 weeks of gestational age.

Parental post-secondary education (I and II for mothers)

Post-secondary education was categorized into 8 ascending groups and 1 additional group 'other'. Mothers or fathers belonging to the higher 4 groups, which were equivalent to university/ college education, were classified as having higher post-secondary education.

Parental chronic illnesses (I)

Any known chronic illness in the mother or father marked in the baseline questionnaire obtained during pregnancy. Psychiatric diagnoses were included in this variable.

Breast feeding (I)

Exclusive or partial breast feeding until the age of 6 months.

Season of year at start of daycare (II)

Start of daycare during fall-winter (October to March) versus spring-summer (April to September).

Family income (II and IV)

Family net income under 2000 euros per month versus over 2000 euros per month.

Asthma in the parents (II, IV)

Known asthma in either the mother or father. These data were obtained during pregnancy or upon recruitment.

Cat or dog at home (II)

Presence of a pet cat or dog at home.

Atopy (IV)

Atopy was defined as physician-detected, parent reported atopic eczema by the age of 13 months.

Parental smoking (IV)

Known smoking in the mother, father or both during pregnancy or after the birth of the child.

4.7. Statistical analyses

Study I

Structural equation modelling (SEM) constitutes a second generation multivariate technique allowing for simultaneous processing of several dependent variables, which thereby provides a dynamic estimate of covariances and correlations between them. The analyses were conducted by SEM using Mplus 7.3 (see L.K. Muthen and B. O. Muthen. 2013). The fit of the models was evaluated by a chi-square, the root mean square error of approximation (RMSEA), a comparative fit index (CFI), the Tucker-Lewis Index (TLI) (see L.R. Tucker and C. Lewis. 1973), and the standardized root mean square residual (SRMR) (see J.H. Steiger. 1990, L. Hu and P. M. Bentler. 1999). The overall fit of models was considered to be acceptable if the following components were fulfilled: chi-square P values over 0.05, or chi-square values of more than 3 times the degree of freedom (DF), CFI and TLI of 0.90 or higher, and RMSEA and SMSR values below 0.08.

The effects of parental psychological symptoms during pregnancy on respiratory infectious outcomes in the offspring were assessed using path modelling, a type of SEM. Similar analyses were carried out for the effects of confounding variables on the determined outcome measures. Effect sizes are reported by standardized regression coefficients. The hypothesized model is shown in Fig. 6.

When evaluating the differences between mothers' and fathers' background variables, Cohen's d, which is defined as the difference between two means divided by a standard deviation of the data, was applied.

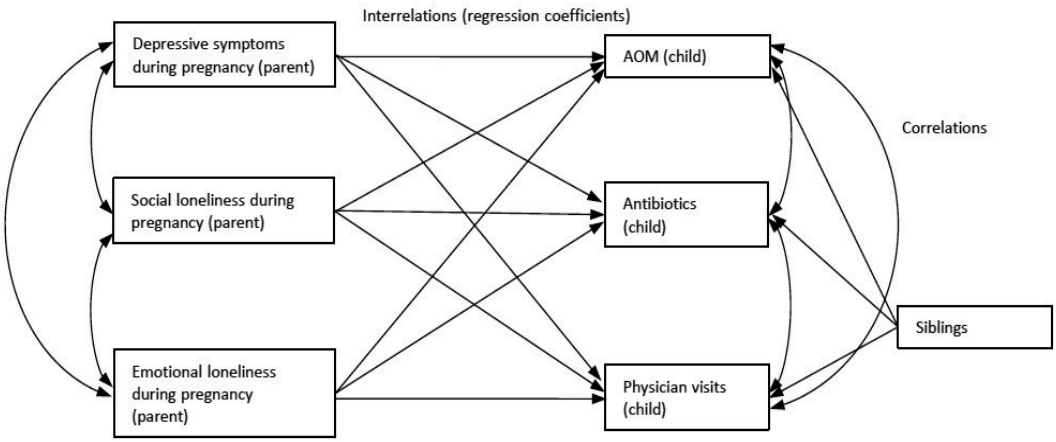

Figure 6: Hypothesized model relating to the effect of parental psychological symptoms during pregnancy on RTIs in the offspring.

Diagram reproduced from (I).

Study II

In the first step, outcome variables were formulated as days per month for every child and aligned in a time sequence in relation to the beginning of daycare. Chronological follow-up included a time of 6 months previous to and 9 months after daycare initiation. Not all above defined data related to the fixed time frame of 0-2 years, as children commenced daycare at different ages. Data from outside this age frame were excluded from the analysis using the SAS MIXED procedure. Data for the control group of children in home care were obtained at equivalent ages, which were calculated using the mean age of starting either family or centre-based daycare. According to this mean age, the age-range of follow-up for the control group was 9 to 24 months (6 months prior to and 9 months after the mean start of daycare at 15 months of age).

In case of discontinuation of daycare during follow-up, data were selectively excluded by the SAS MIXED procedure.

Preliminary testing was carried out by independent sample t-tests and variance analyses. After that, data were analysed by repeated measures variance analysis comparing all three groups - FDC, DCC and the control group – with regard to the effect of type of daycare and time, as well as their interaction. In a second step, chronological thresholds of significance were obtained by comparing all P values for the difference of least square means between all pairs of analysed months. The shortest time for any given trend with $P < 0.05$ was determined. Although the distributions of monthly outcome measures (sick days, days with antibiotic medication, and parental absences from work) were skewed in our analyses (coefficient of skewness up to 2.4 and kurtosis 7.6), the pairwise difference variables followed approximately a normal distribution.

In a third step, repeated measures variance analysis was repeated as in the previous model, but taking into account individual confounding factors.

Analyses were carried out using SAS version 9.4 (SAS, Cary, NC, USA).

Study III

In study III, the above mentioned outcome measures were compared between the DCC, FDC and home care groups using variance analyses. For situations with deficient homogeneity of variance between groups, analyses were confirmed by non-parametric tests (Kruskall Wallis and Mann-Whitney U tests); this was the case for the analyses of antibiotic medications and parental absences from work.

Study IV

In the first step, unadjusted binary logistic regression analyses, the chi-square test, and the Fisher's exact test (for low numbers of observations) were used in order to estimate effects of infant swimming and the above mentioned confounding factors on the risk of bronchiolitis. In the second step, adjusted binary logistic regression was carried out with all variables, except maternal age and family income, which did not have any significant effects and were therefore omitted in the final model. Results are presented as adjusted odds ratios (aOR) with 95% confidence intervals (CI). In the third step, logistic regression was performed in order to estimate the effect of infant swimming on the risk of RV-associated wheezing, and similar adjustments were made for confounding factors. We also examined the association between infant swimming and RV-associated wheeze in data stratified by reported atopy applying the chi-square or Fisher's exact tests. Effects of infant swimming on sick days were analysed using the t-test. No further analyses were performed, as there were no significant differences. Analyses were carried out using SAS version 9.1 (SAS, Cary, NC, USA).

In all analyses, P values of less than 0.05 were regarded as statistically significant.

4.8. Ethics

The Ethics Committee of the Hospital District of Southwest Finland and the Ministry of Social Affairs and Health approved the STEPS Study protocol (19.2.2008, 15.4.2008, 19.4.2011; STM 1575/2008, STM 1838/2009). Written, informed consent was obtained from the parents of all participating children, and parents were also informed of their right to withdraw from the study at any point. The scientific data were handled according to the standards of the Office of the Data Protection Ombudsman, and they are stored securely at the Faculty of Medicine, University of Turku.

5 RESULTS

5.1. Baseline characteristics

Baseline characteristics of children in the Steps cohort and the sub-cohorts of intensive- and regular follow-up have been described elsewhere (L. Toivonen. 2016). In comparison to the entire eligible cohort of children born during the recruitment period in the Hospital District of Southwest Finland, mothers of children participating in the study were more likely married (59.2% vs. 53.5%; $p < 0.0001$) and lived more often in an urban environment (city of Turku: 42.7% vs. 36.6%; $p < 0.0001$). They also were, on average, 7 months older, more highly educated, and the participating child tended to be their first (54.3% vs. 43.4%) ($p < 0.0001$ for maternal age and previous sibling status; $p = 0.0003$ for maternal occupation) (H. Lagström, et al. 2013).

5.2. The effect of parental psychological factors on RTIs in infants

In baseline comparisons between mothers and fathers, mothers were younger and displayed more depressive symptoms at gestational week 20. However, fathers showed more emotional loneliness, as evaluated at the same time point. There were no significant differences regarding social loneliness (table 2).

In comparisons with background variables, the presence of older siblings had an effect on all three outcome measures (table 3): cumulative numbers of AOM (standardized regression coefficient 0.260), antibiotic medications (standardized regression coefficient 0.281), and physician visits (standardized regression coefficient 0.191). This variable was therefore controlled in the final models.

Path modeling was applied to estimate effects of the previously defined parental psychological symptoms on the infant's risk of AOM, antibiotic medications, and physician visits until the age of 10 months. Results are shown in Fig. 7 for mothers and Fig. 8 for fathers. The goodness of fit indices estimated at least acceptable fit for both models (for mothers: chi-square, 23.158 with DF, 3; CFI = 0.974; TLI = 0.869; RMSEA = 0.085; SRMR = 0.039; for fathers: chi-square, 3.906 with DF, 3 and chi-square P value, 0.27; CFI = 0.999; TLI = 0.994; RMSEA = 0.018; SRMR = 0.018). The extremely good fit for fathers supported the hypothesized model, in spite of less favourable fit indices for mothers.

Mothers' depressive symptoms during pregnancy predicted higher cumulative numbers of AOM in their child during our follow-up time ($P = 0.03$) (Fig. 7), and their symptoms of emotional loneliness predicted more physician visits in the child during the same age frame ($P = 0.006$). There were no statistically significant

effects of these psychological measures in fathers on the rates of AOM, antibiotic medications, and physician visits in the child (Fig. 8). For both parents, the effect of social loneliness predicted a slight reduction of outcome measures in the child: AOM: P = 0.003, antibiotic medications: P = 0.04, physician visits: P = 0.001 for mothers, and AOM: P = 0.01, antibiotic medications: P = 0.009, and physician visits: P = 0.02 for fathers.

When considering background variables (table 3), older fathers exerted a small protective effect with respect to cumulative numbers of antibiotic medications (standardized regression coefficient -0.103) and physician visits (standardized regression coefficient -0.130). Children from more highly educated mothers had slightly higher numbers of AOM (standardized regression coefficient 0.092).

Table 2. Differences between Mothers and Fathers and Reliability Coefficients

			Differences between mothers (M) and fathers (F)	
	Min. / max.	Mean (sd)	p-value	Cohen´s d
Mothers (at gestational week 20)				
Age, years	17 / 43	30.67 (4.32)		
Depressive symptoms, score	0 / 49	8.76 (6.01)		
Social loneliness, score	6 / 21	9.63 (2.67)		
Emotional loneliness, score	6 / 21	8.78 (2.30)		
Fathers (at mother's gestational week 20)				
Age, years	18 / 56	32.67 (5.29)	<0.001	.414 M < F
Depressive symptoms, score	0 / 30	3.66 (4.66)	<0.001	.948 M > F
Social loneliness, score	6 / 20	9.60 (2.67)	0.68	ND
Emotional loneliness, score	6 / 21	9.47 (2.58)	<0.001	.282 M < F
Children				
Acute otitis media, No. / 0-10 months of age	0 / 6	0.56 (0.96)		
Antibiotics, No. / 0-10 months of age	0 / 9	0.74 (1.25)		
Physician visits for RTI, No. / 0-10 months of age	0 / 14	1.74 (2.17)		

F, Fathers; M, mothers; ND, not defined; SD, standard deviation

Table 3. Associations of Background variables with Outcome Measures

		Standardized Regression Coefficient (P)		
	N (%)/ group total	AOM	Antibiotics	Physician visits
Child's gender (boys)	461 (50)/ 924	0.056 (0.10)	0.034 (0.34)	0.056 (0.11)
Older siblings	448 (48)/ 924	**0.260 (<0.001)**	**0.281 (<0.001)**	**0.191 (<0.001)**
Born preterm (< 37 th gestational week)	34 (4)/ 913	-0.003 (0.91)	-0.009 (0.74)	-0.012 (0.66)
Breastfeeding (until 6 months of age)	503 (61)/ 831	0.005 (0.88)	0.007 (0.84)	0.001 (0.99)
Chronic illness/ father	367 (42)/ 873	-0.059 (0.09)	-0.059 (0.09)	-0.029 (0.43)
Chronic illness/ mother	456 (51)/ 895	0.025 (0.49)	0.056 (0.11)	0.039 (0.29)
Fathers' age	-/ 924	-0.071 (0.09)	**-0.103 (0.01)**	**-0.130 (0.003)**
Mothers' age	-/ 924	0.022 (0.62)	0.023 (0.59)	0.024 (0.59)
Mothers' education, lower (lower 4 groups)	336 (37)/ 912	**-0.092 (0.01)**	-0.040 (0.29)	-0.039 (0.31)
Fathers' education, lower (lower 4 groups)	477 (54)/ 887	0.007 (0.84)	0.018 (0.60)	0.016 (0.70)

Statistically significant values are bolded. Children's outcome measures were documented during 0-10 months of age. The variables of parental age and post-secondary education (8 groups) were analyzed as continuous variables. N = 749.

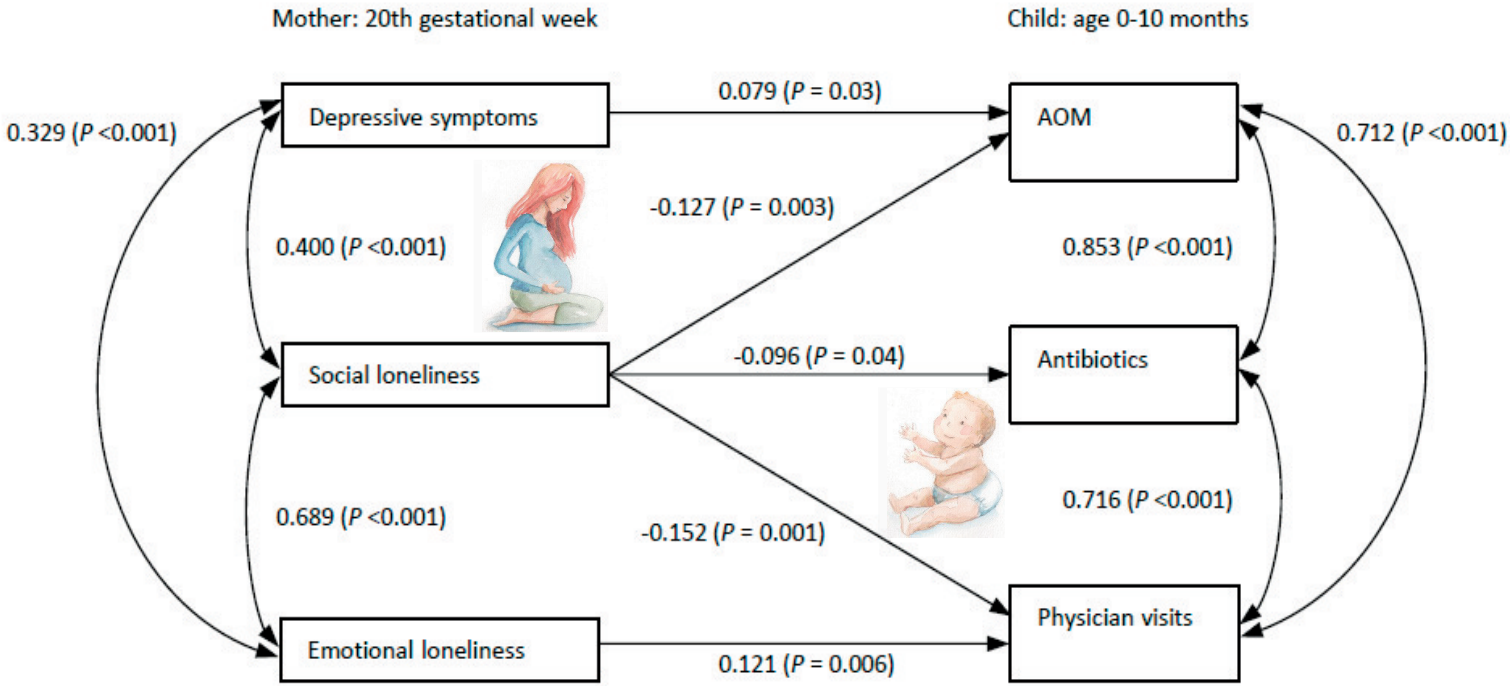

Figure 7: Mothers' loneliness and depressive symptoms during pregnancy predicting acute otits media, antibiotics, and physician visits in the offspring. Standardized regression coefficients and P-values after controlling the effect of siblings. The standardized regression coefficients for the effect of siblings were 0.235 for acute otitis media, 0.252 for antibiotics, and 0.162 for physician visits.

Artwork: Rebecca Lujan

Diagram modified from (I).

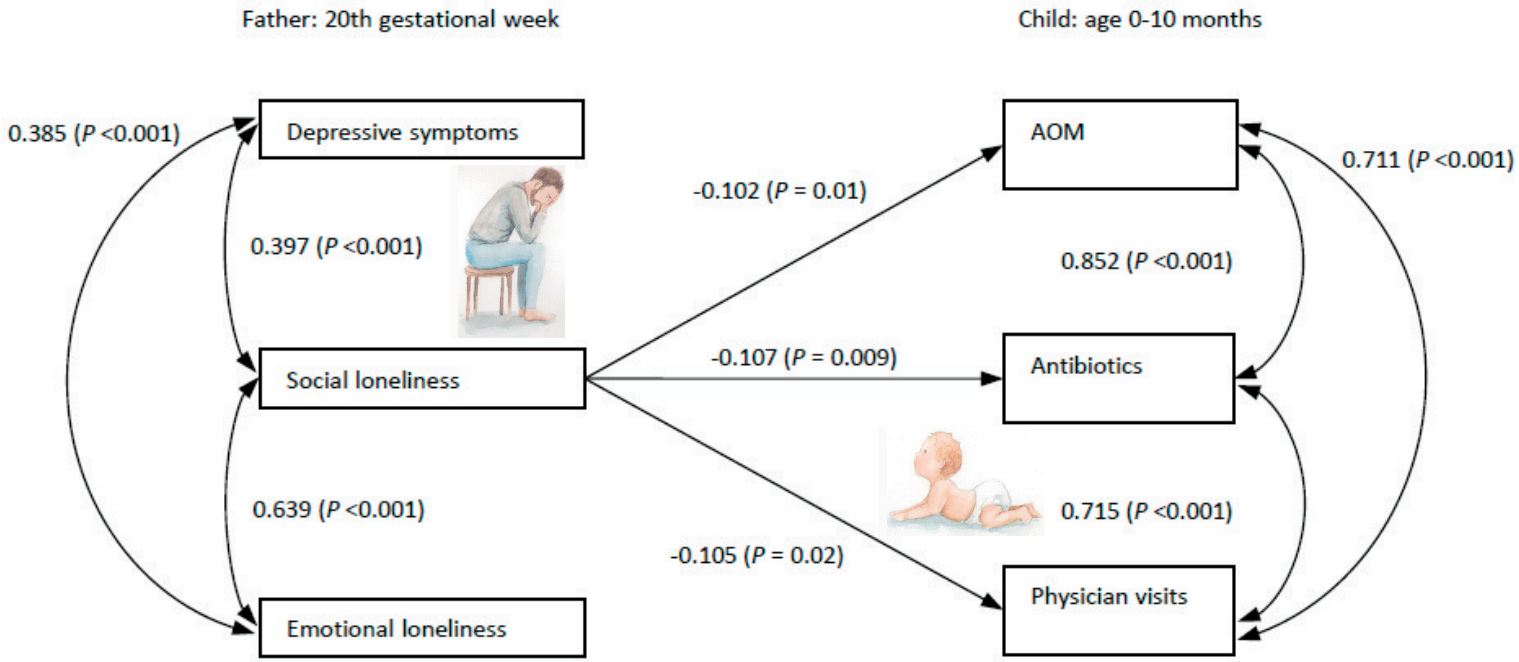

Figure 8: Fathers' loneliness and depressive symptoms during pregnancy predicting acute otitis media, antibiotics, and physician visits in the offspring. Standardized regression coefficients and P-values after controlling the effect of siblings. The standardized regression coefficients for the effect of siblings were 0.243 for acute otitis media, 0.258 for antibiotics, and 0.172 for physician visits.

Artwork: Rebecca Lujan

Diagram modified from (I).

5.3. The effect of daycare on RTIs

Chronological aspects around daycare initiation until the age of 2 years

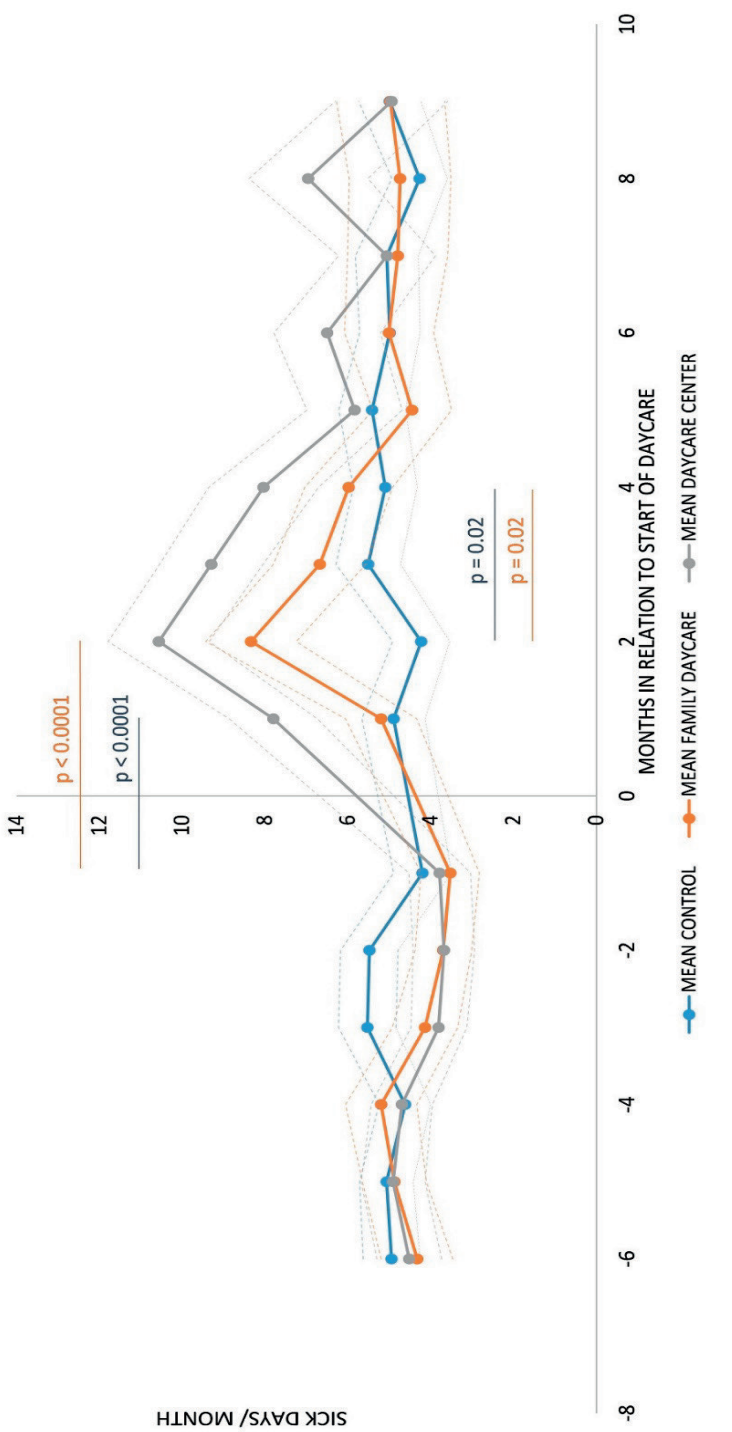

Figure 9: Means and 95% CIs (dashed lines) of sick days per month according to daycare groups in relation to start of daycare. Negative months denote the period prior to start of daycare. Horizontal lines indicate the shortest time for a significant rise (decline) from the last month prior to starting daycare (from the peak month).
Diagram reproduced from (II)

Within our cohort of 1570 children (cf. Fig. 2), the mean age at the start of daycare was 15 months (SD 4.1), with a mean age at daycare initiation of 1.24 years (SD 0.37) in FDC and 1.28 years (SD 0.35) in DCC. At the age of 13 months (with available information for 1264 children), 21.8% of children attended daycare (11.7% in DCC and 10.1% in FDC), and at the age of 24 months (with available information for 1079 children) 55.0% were in daycare (29.5% in DCC and 25.0% in FDC). Daycare exposure was high with 88.5% - 91.6% of children attending daycare over 5 hours per day at the ages of 13 and 24 months, respectively. The majority of children in FDC attended groups of less than 5 children (88.3% of children at 13 months of age and 82.7% at 24 months of age). In DCC, groups tended to range from 5-15 children (86.8% at 13 months and 87.8% at 24 months).

Sex was evenly distributed throughout the daycare groups (control, FDC and DCC), with 49.1% of boys in the control group, 50.6% in FDC and 54.1% in DCC. Prematurity, defined as a gestational age under 37 weeks, was evenly rare in all three groups (up to 5.0%, $p = 0.38$). In DCC and FDC, daycare initiation tended to occur a little more often in the spring-summer period with 61.8% of children starting daycare during the time from April to September (59.2% for FDC and 63.9% for DCC) (Table 5). Discontinuous daycare occurred in a small number of children (11 children in FDC and 13 children in DCC). Those children were not excluded from the analyses per se, but follow-up after discontinuation of daycare was.

In variance analyses not taking into account chronological aspects, children in DCC had only slightly more sick days per month (mean 5.54, SD 4.07), compared to the other two care groups (FDC: mean 4.85, SD 3.49; home care: mean 4.8, SD 3.39) ($p = 0.03$). There were no significant differences for days with antibiotic medications. There were also no significant differences between FDC and DCC with respect to days with parental absences from work. (Table 4). Children in home care could not be compared, since they tended to be cared for by a stay-at-home parent.

Table 4. Baseline comparisons of outcome measures according to daycare type.

	Type of daycare			
	Home care (n = 350)	Family daycare (n = 245)	Daycare centre (n = 299)	P
Sick days per month, mean (SD)	4.8 (3.39)	4.85 (3.49)	5.54 (4.07)	0.03 *
Days with antibiotic treatment per month, mean (SD)	0.74 (1.41)	0.82 (1.36)	0.93 (1.14)	0.21 *
Days with parental absences from work per month, mean (SD)	NA	0.31 (0.38)	0.36 (0.45)	0.17 **

NA, not applicable.
*) Unadjusted variance analysis
**) Independent sample t-test

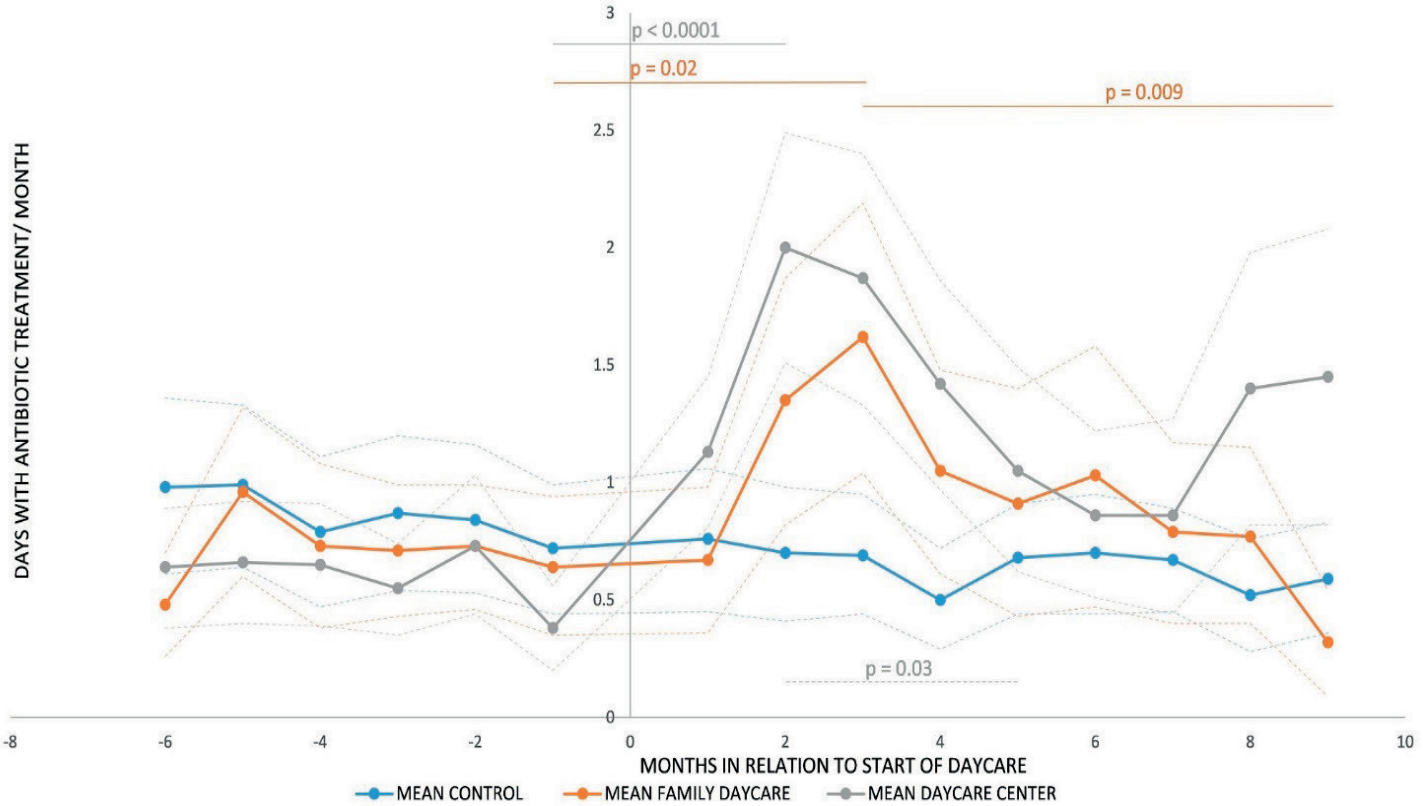

Figure 10: Means and 95% CIs (dashed lines) of days with antibiotic treatment per month according to daycare groups in relation to start of daycare. Negative months denote the period prior to start of daycare. Horizontal lines indicate the shortest time for a significant rise (decline) from the last month prior to starting daycare (from the peak month). Dashed lines: transiently below the significance level.
Diagram reproduced from (II).

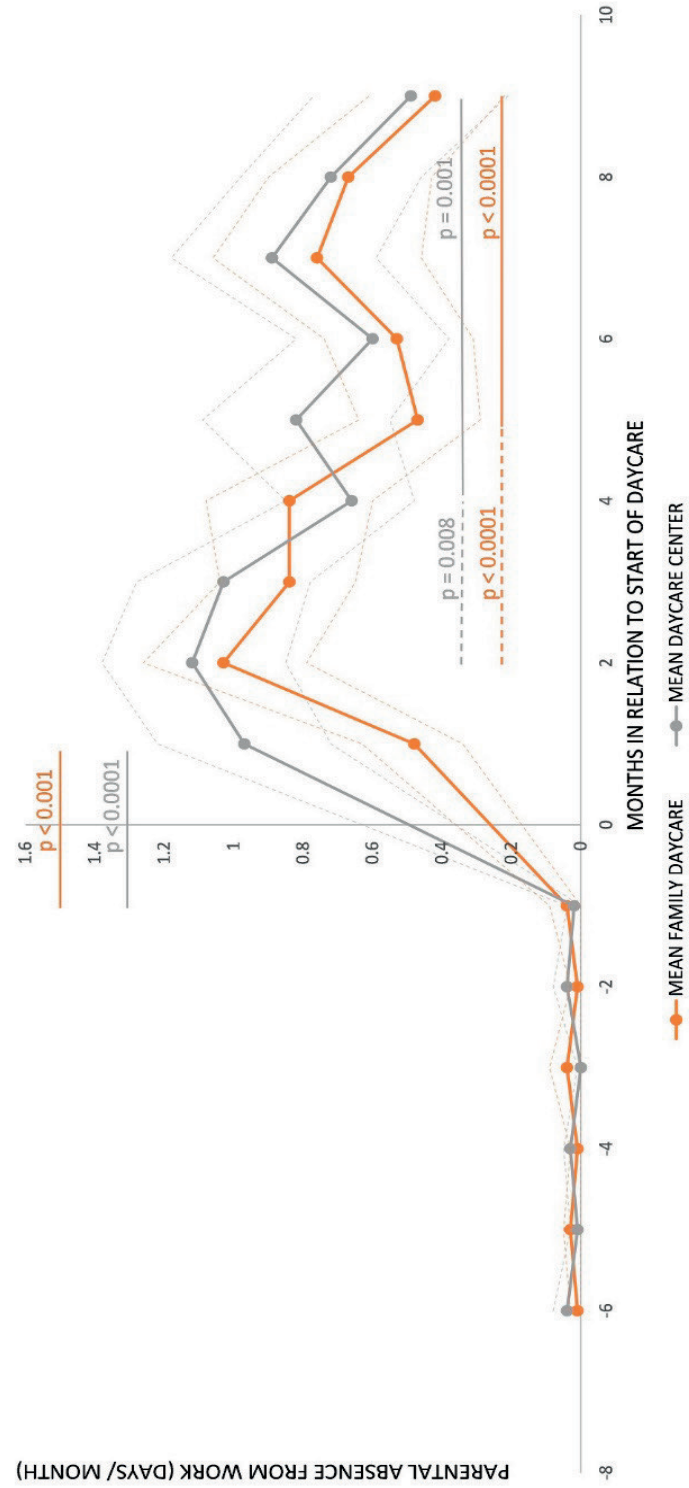

Figure 11: Means and 95% CIs (dashed lines) of days with parental absence from work per month according to daycare groups in relation to start of daycare. Negative months denote the period prior to start of daycare. Horizontal lines indicate the shortest time for a significant rise (decline) from the last month prior to starting daycare (from the peak month). Dashed lines: transiently below the significance level.
Diagram reproduced from (II).

Fig. 9 - 11 show the development of days with symptoms, antibiotic medication, and parental absences from work with respect to daycare initiation. The mean of sick days per month peaked at 2 months after the start of daycare in both daycare groups. For the FDC group, there was a maximum rise from 3.53 mean sick days (95% CI 2.83 to 4.24) during the month prior to daycare initiation to 8.34 mean sick days (95% CI 7.25 to 9.43) during the peak month, and for DCC from 3.79 mean sick days (95% CI 3.04 to 4.53) before to 10.57 (95% CI 9.35 to 11.79) mean sick days at 2 months after the start of daycare. For both of these groups, there was a clear subsequent decline of symptoms already within the follow-up period, such that this outcome measure was comparable to the home care group already at 5 months after the start of daycare. Similar, but less pronounced patterns were observed for use of antibiotics and parental absences from work. Pairwise comparisons between all individual months confirmed statistical significance of the above mentioned trends in the FDC and DCC groups, and the shortest time of a significant rise/ decline is indicated in Fig. 9 - 11. Pairwise comparisons showed no significant findings for the home care group.

In repeated measures variance analyses, all outcome measures displayed a significant overall effect for type of daycare and time, as well as their interaction (table 6), which portrayed the above described patterns of a rise and decline over time. In the home care group, no particular trends could be observed, but rather a random variation of symptoms over time. Without the aspect of time, sick days and use of antibiotics were higher in DCC compared to the home care group ($p<0.001$) and FDC group ($p < 0.001$ and $p = 0.04$, respectively). No significant differences could be found between the FDC and home care group.

Older siblings in the family, higher postsecondary education in the mother, and higher family income were all linked to an increase in the disease burden (table 5). Fig. 12 – 14 show the course of sick days in association with daycare initiation stratified according to these confounding factors. Daycare and siblings appeared to act as competing factors such, that the rise of sick days was less pronounced after the start of daycare for those with older siblings than for those without older siblings.

Repeated measures variance analyses were carried out stratified according to all possible confounding factors mentioned in the methods section. These still showed the before mentioned associations, with $p < 0.001$ for the effect of time and daycare type for all analyses regarding sick days, except for those with parental asthma (where $p = 0.004$ for daycare type).

Table 5. Effects of confounding factors on the rates of RTI symptoms (sick days) according to daycare type.

	Type of daycare							
	Home care		Family daycare		Daycare centre			
	n/N (%)	Sick days per month, mean (SD)	n/N (%)	Sick days per month, mean (SD)	n/N (%)	Sick days per month, mean (SD)	P*	P for interaction with mode of daycare
Older siblings							0.02	<0.001
Yes	162/ 350 (46.3)	5.55 (3.72)	99 /245 (40.4)	5.26 (3.33)	132/ 299 (44.1)	5.10 (3.72)		
No	188/ 350 (53.7)	4.16 (2.95)	146/ 245 (59.6)	4.58 (3.59)	167/ 299 (55.9)	5.88 (4.31)		
Higher post-secondary education in mother							0.009	0.27
Yes	211/ 341 (61.9)	5.12 (3.53)	161/ 239 (67.4)	5.12 (3.72)	203/ 293 (69.3)	5.66 (3.75)		
No	130/ 341 (38.1)	4.40 (3.17)	78 / 239 (32.6)	4.23 (2.97)	90/ 293 (30.7)	5.45 (4.79)		
Family net income under 2000 euros per month							0.005	0.37
Yes	83/ 343 (24.2)	4.15 (3.28)	33/ 239 (13.8)	3.43 (2.75)	56/ 294 (19.0)	5.29 (3.39)		
No	260/343 (75.8)	5.03 (3.43)	206/ 239 (86.1)	5.04 (3.57)	238/ 294 (81.0)	5.64 (4.23)		
Start of daycare during fall-winter (October-March)							0.39	0.61
Yes	NA	NA	100/ 245 (40.8)	4.90 (3.15)	108/ 299 (36.1)	5.69 (4.21)		
No	NA	NA	145/ 245 (59.2)	4.82 (3.73)	191/ 299 (63.9)	5.45 (4.0)		
Asthma in parents							0.95	0.72
Yes	35/ 340 (10.3)	4.65 (3.26)	26/ 234 (11.1)	5.54 (4.0)	30/ 287 (10.5)	5.83 (4.25)		
No	305/ 340 (89.7)	4.86 (3.43)	208/ 234 (88.9)	4.76 (3.45)	257/ 287 (89.5)	5.56 (4.08)		
Cat or dog at home							0.31	0.23
Yes	94/ 295 (31.9)	4.43 (3.07)	80/ 196 (40.8)	4.83 (3.07)	57/ 219 (26.0)	5.80 (4.28)		
No	201/ 295 (68.1)	5.14 (3.48)	116/ 196 (59.2)	4.92 (3.14)	162/ 219 (74.0)	5.68 (3.66)		

n/N, number of children per number of those with data available; NA, not applicable; RTI, respiratory tract infection.
*By univariate analysis, regardless of daycare type.

Table 6. P values* for the effects of daycare type and time on the rates of RTI symptoms (sick days), antibiotic treatments, and parental absence from work because of a child's illness

	Sick days per month, p	Days with antibiotic treatment per month, p	Parental absence from work, days per month, p
Time (month)	<0.001	0.004	0.003
Daycare type	<0.001	<0.001	0.02
Contrast: Home care - FDC groups	0.55	0.18	ND
Contrast: Home care - DCC groups	<0.001	<0.001	ND
Contrast: FDC - DCC groups	<0.001	0.04	ND
Interaction: time and daycare type	<0.001	<0.001	0.003
Time (month) for Home care group	0.005	0.64	ND
Time (month) for FDC group	<0.001	0.002	<0.001
Time (month) for DCC group	<0.001	<0.001	<0.001

ND, not determined; RTI, respiratory tract infection; FDC, family daycare; DCC, daycare centre.
*By repeated measures variance analysis.

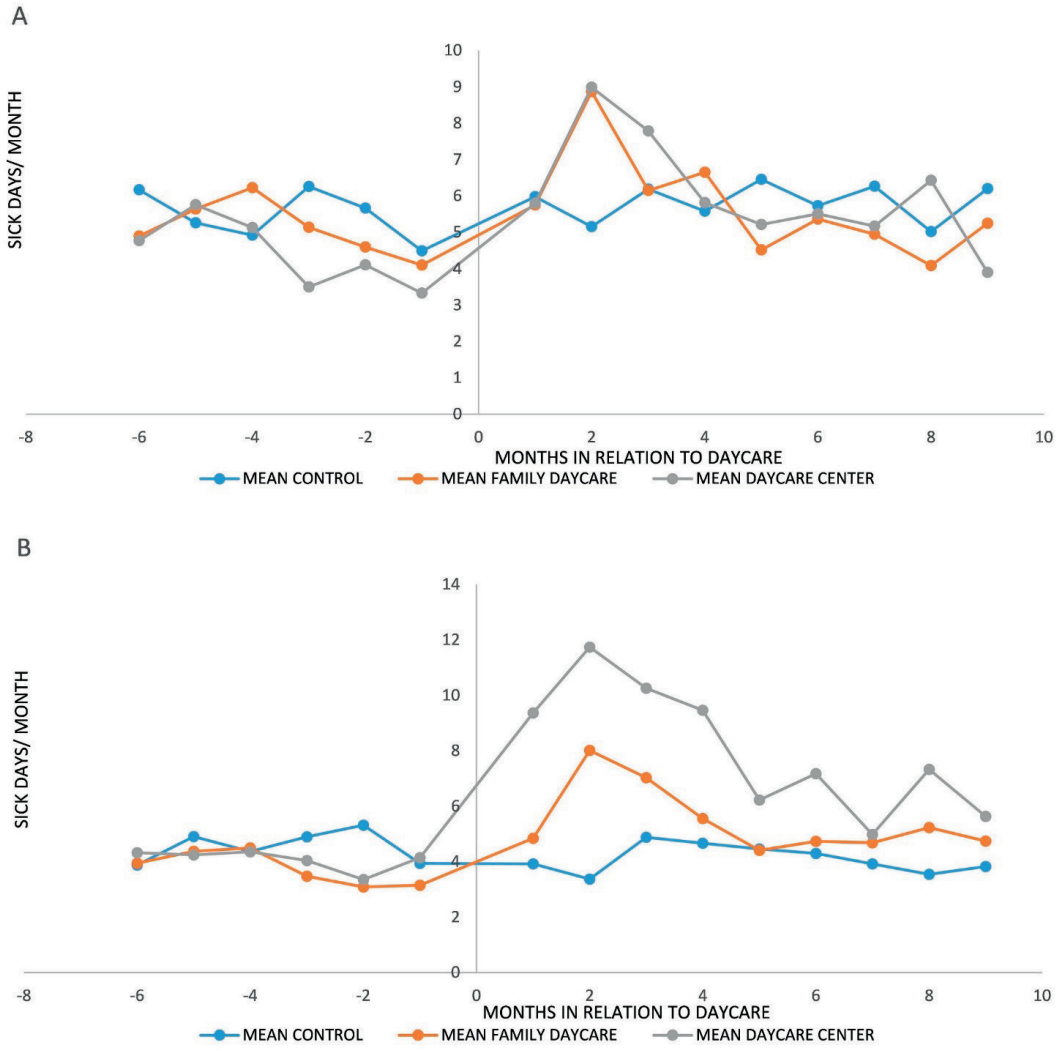

Figure 12: Chronological development of mean sick days per month according to daycare groups and stratified according to the significant confounder of older siblings. Developments are shown for children with older siblings (A) and for children without older siblings (B).

Diagram reproduced from (II).

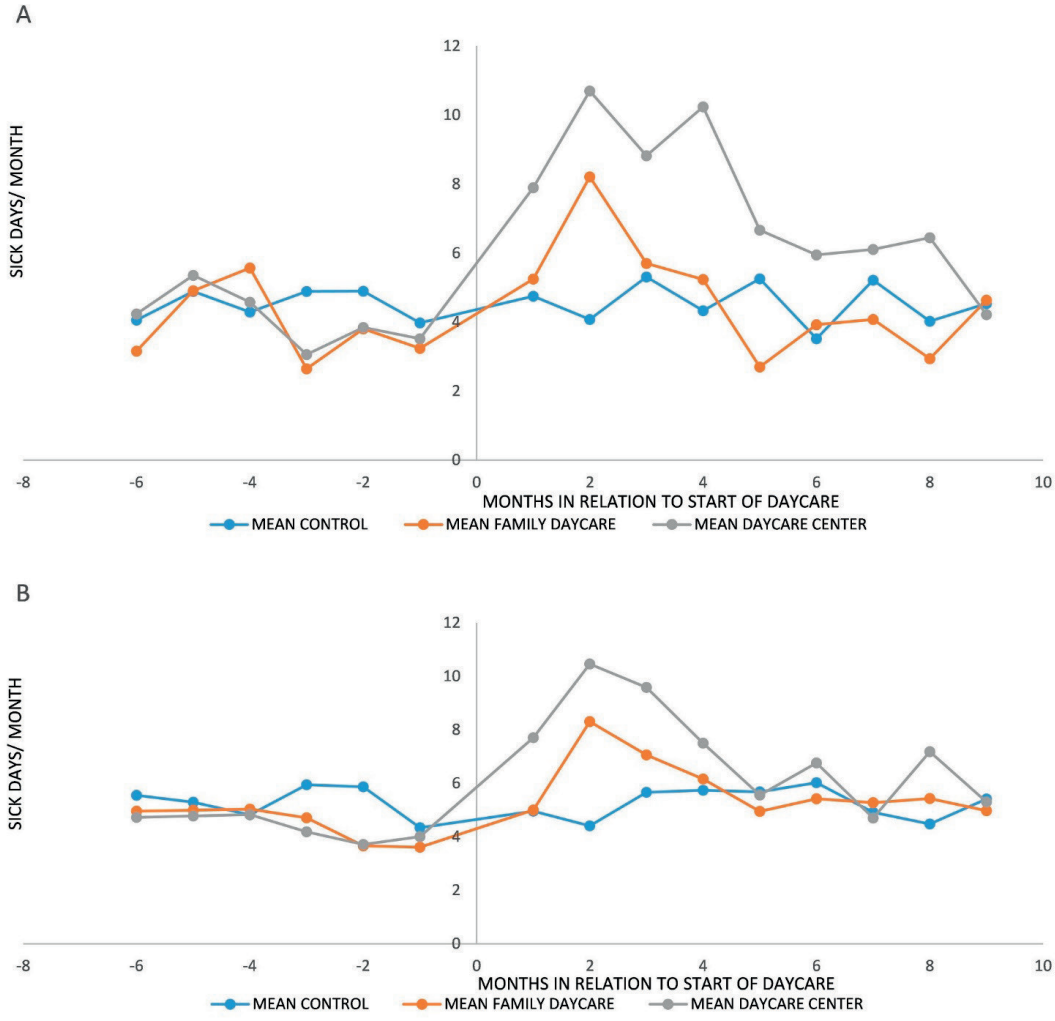

Figure 13: Chronological development of mean sick days per month according to daycare groups and stratified according to the significant confounder of maternal post-secondary education. Developments are shown for children of mothers with lower (A) and higher (B) post-secondary education.

Diagram reproduced from (II).

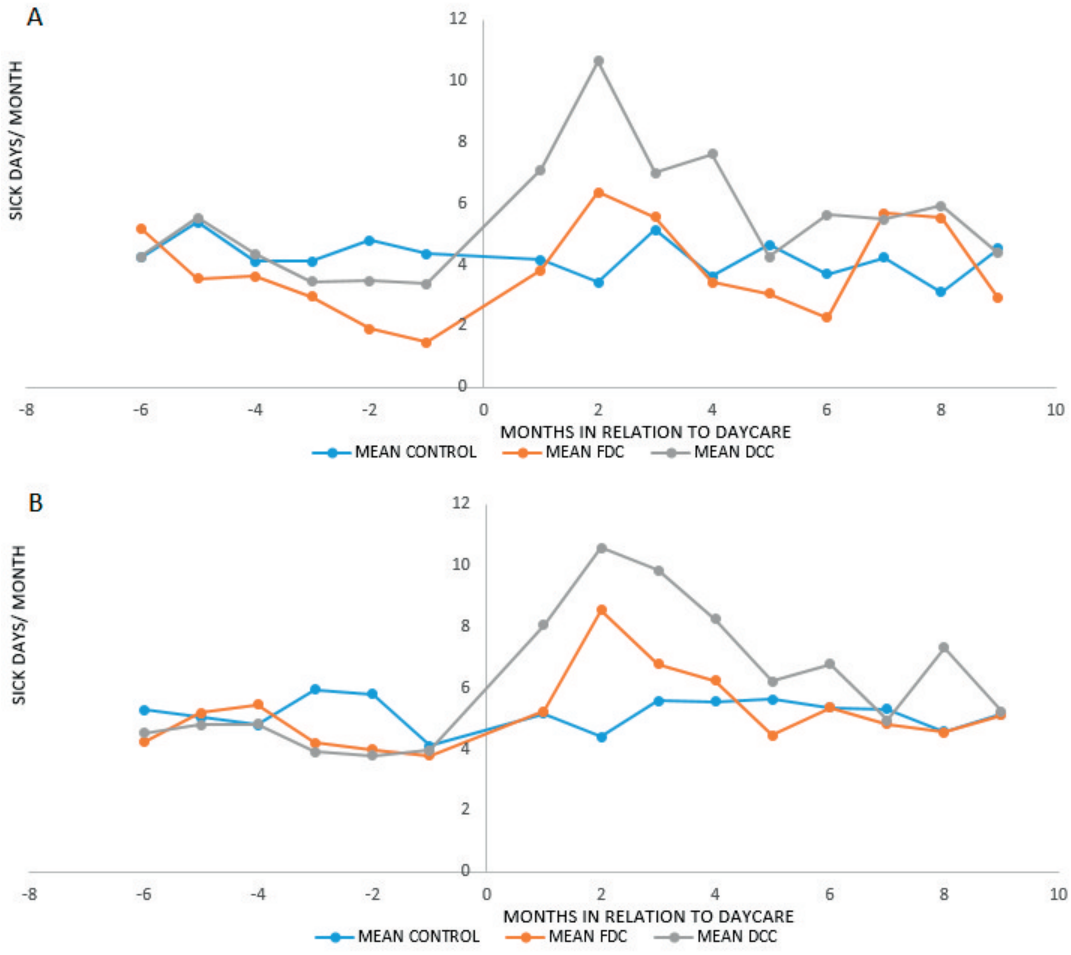

Figure 14: Chronological development of mean sick days per month according to daycare groups and stratified according to the significant confounder of family income. Developments are shown for children of mothers with lower (A) and higher (B) family income.

Chronological aspects for children in daycare age 2.5-3 years

When analysing the previously defined groups of children in home care, FDC and DCC at a later point in time such, that the elapsed time after daycare initiation was at least 6 months, we could not detect any significant difference with regard to sick days between the groups. For children in home care, there was a mean of 4.16 symptom-weeks during the 6 months of later follow-up, for children in FDC the mean was 4.04, and for children in DCC 4.53 (Table 7). However, for antibiotic use there was an association with daycare attendance, with a mean of 0.39 weeks with antibiotic medication for children in home care versus a mean of 0.7 weeks for children in DCC during the 6 months follow-up ($p = 0.003$). Parental absences from work could not be compared between the home care- and other groups, since children at home tended to have a parent who – by definition – could not be absent from work. Comparing the FDC and DCC groups, there were no significant differences for this outcome measure.

Table 7: Distribution of cumulative outcome measures over groups for the ages of 30-35 months.

Outcome measure	Group	N	Mean	SD	P-Value	P-Value between groups
RTI symptoms (weeks/ 6 months)	HC	164	4.16	3.5	0.48*)	NA
	FDC	143	4.04	3.53		
	DCC	164	4.53	4.08		
Antibiotic treatments (weeks/ 6 months)	HC	164	0.39	0.96	0.009**)	***) HC vs. FDC: 0.23
	FDC	143	0.41	0.75		FDC vs. DCC: 0.08
	DCC	164	0.70	1.52		HC vs. DCC: 0.003
Parental absences from work (days/ 6 months)	HC	164	0.06	0.34	0.26****)	
	FDC	143	1.31	2.17		
	DCC	164	1.80	3.01		

HC: Home Care. FDC: Family Daycare. DCC: Daycare Center. NA: Non-applicable.
*P-Values as determined by variance analysis
**P-Values as determined by nonparametric tests/ Kruskall Wallis.
*** P-Values as determined by nonparametric tests/ Mann-Whitney U-test
**** P-value as obtained by comparison between the FDC and DCC groups/ Kruskall Wallis

5.4. The effect of infant swimming on RTIs and wheezing illnesses

Risk factors for bronchiolitis

Within the cohort of 1038 children with information on swimming practices, 469 (45%) participated in swimming activities. The vast majority (405 children, 86%) practised swimming regularly at least every 2 weeks, and most (345 children, 81%) started swimming as a young infant of 5 months or younger. Table 8 shows the distribution of descriptive characteristics, risk factors for bronchiolitis, rates of bronchiolitis, and respiratory symptoms between the groups of swimming and non-swimming children. The variables of maternal age, older siblings, and family income showed some differences in distribution across the groups, such that more affluent families with younger first-time mothers were more prone to attend swimming practices. However, the proportion of very young mothers (<21 years of age) was only 0.4% for swimming infants.

Table 8. Characteristics and outcomes in non-swimming and swimming children.

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

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

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

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

RV = rhinovirus; ND = not determined; RSV = respiratory syncytial virus.

In the entire swimming cohort, the incidence of medically-diagnosed bronchiolitis before the age of 17 months was 8% (84/1038 children), and among those in intensive follow-up of infections 11% (71/ 635 children) ($p<0.001$; comparison to group with regular follow-up). In the entire Steps-cohort, incidence was 7% (92/1303 children with information on infections).

There was no difference between respiratory infectious symptoms or the incidence of bronchiolitis between swimming and non-swimming children, but RV-related wheezing illnesses were more frequent in swimming children ($p = 0.04$) (Table 8).

Table 9. Risk of bronchiolitis according to infant swimming and other variables.

Variable	Unadjusted analyses			Adjusted logistic regression (n = 668)		
	n	Bronchiolitis, n (%)	p value	aOR	95% CI	p value
Infant swimming	1038		0.11	1.71	0.99-2.95	0.05
Yes	469	45 (10)				
No	569	39 (7)				
Atopic eczema	763		0.001	2.79	1.56-4.95	< 0.001
Yes	141	23 (16)				
No	622	46 (7)				
Parental asthma	871		0.16	1.59	0.82-3.08	0.17
Yes	143	17 (12)				
No	728	60 (8)				
Parental smoking[a]	920		0.75	1.42	0.76-2.67	0.28
Yes	206	17 (8)				
No	714	64 (9)				
Siblings	1037		0.15	1.43	0.83-2.46	0.20
Yes	489	46 (9)				
No	548	38 (7)				
Family income	1012					
<2000 euro/ month	206	12(6)	0,16			
>2000 euro/ month	806	71(9)				
Maternal age at birth of child	1037		0,58			
≤30 years	501	43(9)				
>30 years	536	41(8)				

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

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

aOR = adjusted odds ratio; CI = confidence interval.

Atopic eczema in the child was associated with the risk of developing bronchiolitis in both unadjusted analyses (p = 0.001) and adjusted logistic regression analyses (aOR, 2.79; 95% CI, 1.56 – 4.95) (table 9). An association between infant swimming and bronchiolitis was observed at the limit of statistical significance using adjusted logistic regression analysis (aOR, 1.71; 95% CI, 0.99 – 2.95; p = 0.05).

Adjusted logistic regression analyses assessing risk factors for RV-related wheezing illnesses (RV and RSV co-infections excluded) were limited in power due to the small number of children with available viral diagnostics. The highest odds ratios were observed for atopic eczema in the child (aOR, 3.36; 95% CI, 1.02-11.05; p = 0.05) and infant swimming (aOR, 3.57; 95% CI, 0.94-13.52; p = 0.06).

Table 10. Association of infant swimming with RV positive wheezing in all children and in those with or without atopic eczema.

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

RV and RSV co-infections (n = 2) were excluded from the analysis.
P values were obtained by Chi-square or Fisher's test as applicable.
RV = rhinovirus

Viral aetiology of wheezing illnesses

All cases of wheezing episodes with an available sample for PCR analysis are shown in table 10. Samples were available in 47 children, but some children experienced recurrent wheeze, such that 64 cases of wheezing illnesses were included. The most common viruses were RV (18 cases excluding RV-RSV co-infections) and RSV (22 cases excluding RV-RSV co-infections). Their distribution across swimming and non-swimming cases are shown in Fig. 15. As RV-associated wheezing illnesses were of particular interest in this study, cases were divided into RV-positive and RV-negative groups, and stratified with regard to their swimming status and the presence of atopic eczema in the child. There was a significantly higher proportion in RV-related wheezing only in swimming children who also suffered from atopic eczema (p = 0.006) (table 10).

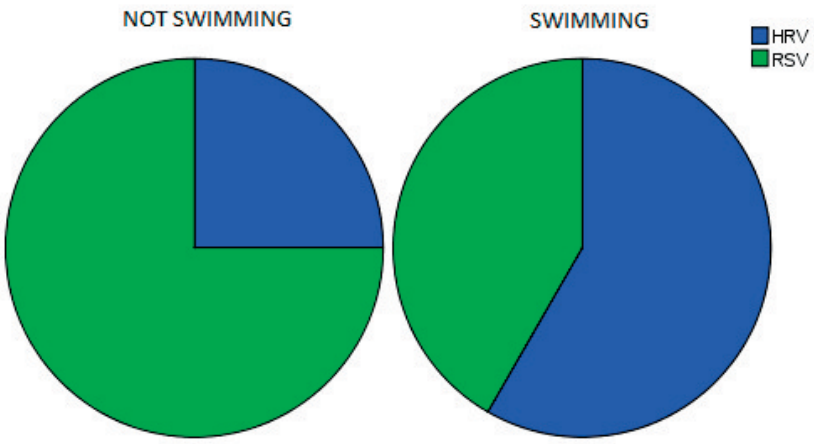

Figure 15: Ratio of RV versus RSV etiology in cases of swimming versus non-swimming children

HRV= Human Rhinovirus

RSV = Respiratory Syncytial Virus

6 DISCUSSION

6.1. Exposures during early life examined in this study

In this prospective cohort study we examined, whether different exposures in the main arenas of infants' lives may be related to RTIs in those young children.

Relationships with the parents and in the home appear to constitute the most immediate environment the infant encounters. Psychological disturbances within this environment may be more subtle than those encompassed by psychiatric diagnoses, and the primary aim in this study was therefore to describe effects of parental psychological symptoms, rather than those of clinical diagnoses. Already Hippocrates postulated that maternal stress during pregnancy could have negative effects on the progeny (see A.C. Huizink, et al. 2004). Parental depression, anxiety, stress, and marital dissatisfaction have thereafter been studied in this context with respect to infant RTIs (L. Ban, et al. 2010, R. Beijers, et al. 2010, N.M. Nielsen, et al. 2011, M. Tegethoff, et al. 2011, R.E. Henriksen and F. Thuen. 2015). In this work, we assessed the effects of parental depression as a conventional clinical measure, and also included psychological evaluation for social and emotional loneliness in our methods. Previous research on loneliness has indicated serious concomitants affecting psychological well-being, such as anxiety, social phobia, marital dissatisfaction, depression, and in some cases suicidal thoughts (see L.M. Heinrich and E. Gullone. 2006, N. Junttila, et al. 2015). It has also been shown that loneliness in both mothers and fathers tends to remain highly stable from pregnancy into the early childhood of the offspring (N. Junttila, et al. 2015). Our psychological measures are based on validated conventional, as well as validated novel methods, and aim to detect mild to severe psychological symptomatology in parents with the attempt to portray a relatively holistic picture of psychological risk in families, which might act as a negative early-life exposure.

Other than the home, daycare is an important sphere of life to the majority of young children in developed countries. Initiation of daycare often results in novel environments with new exposures of potential allergens, viruses, and other microbes. Additionally, it may be a stressful time to children and parents, as it often entails the first experience of a transient separation from the parents and family, as well as close contacts to potentially large numbers of unknown peers and carers. Transmission of pathogens occurs readily between daycare children, whose basic hygiene skills are only developing, and who are in close contact with each other. Factors associated with the spread of infection in a daycare population are complex, as they relate to the vast range of infecting agents themselves, the proportion of infected and susceptible children, contact rates, incubation times, duration of infectiousness, and routes of transmission. There is no conclusive evidence on the distribution of respiratory viruses in a daycare setting in

comparison to that within the population of children in home care. As discussed earlier, group sizes have been a consistently identified factor with regard to transmission of pathogens in daycare facilities (M.M. Rovers, et al. 1999, J. Marx, et al. 1995, S. Cote, et al. 2010), and they thus serve as a critical mediator of exposures.

Even young children spend an increasing extent of their time in free-time activities, which may involve a variety of exposures. Here, we evaluate the effects of infant swimming. There may be a range of stressors involved in this activity, such as exposure to pathogens in the bathing water or via close contact with peers and adults. Lately, concerns about volatile chlorination by-products in the air of indoor swimming-facilities have emerged (A. Bernard, et al. 2003, A. Bernard, et al. 2005, A. Bernard, et al. 2006). Swimming-pools are commonly disinfected by chlorination, which results in the release of hypochlorous acid. Hypochlorous acid, in turn, reacts with nitrogen compounds from sweat, saliva, urine etc. to form the highly irritant chloramines along with other products. Trichloramine (NCl_3) is a volatile chloramine that after formation is immediately released into the air, and is thus inhaled. Concentrations of trichloramine in the air of indoor swimming facilities in Europe have been reported to range from 300 to 800 ug/m3 (see A. Bernard, et al. 2007), and they are affected by a range of aspects, such as water temperature, water-chlorination levels, and effectiveness of ventilation. Most notably, the amount of organic matter brought into the pool by bathers determines trichloramine levels, and therefore hygiene standards are major determinants of measurable concentrations. Taking these factors into account, it is theoretically conceivable that infant swimming practices may be associated with particularly high exposures of this volatile product. In addition to inhaling trichloramine and other compounds, infants and young children may also breathe in small amounts of chlorinated water or hypochlorous-acid-laden aerosols. There are no studies evaluating direct chloramine exposure for infants during infant-swimming programmes. However, a Canadian study evaluating chloramine exposure and its relationship with respiratory symptoms in competitive swimmers found a correlation between respiratory complaints and exposure levels, with highest exposures in younger swimmers (B. Levesque, et al. 2006). Interpreting these results, it has to be noted that exposure measurements were not individualized, but swimming-pool specific, and confounders affecting measured concentrations were not taken into account.

In the following I will discuss the above mentioned exposures with respect to our study results.

6.2. Home: psychological well-being of parents

Our study showed an association between mothers' depressive symptoms during pregnancy and an increased frequency of AOM diagnoses in the infant. There was no corresponding increase in physician visits, suggesting true infection-proneness in infants rather than a mere difference in healthcare-seeking behaviour. Maternal emotional loneliness was associated with increased physician visits on the one hand. On the other hand, social loneliness in both mothers and fathers resulted in slightly decreased numbers of AOM diagnoses, antibiotic medications, and physician visits. It may be hypothesized that emotionally lonely mothers may have been in pursuit of external support and guidance, while social loneliness in parents resulted in more avoidant-type behaviour with regard to social situations, such as medical consultations, or it may have protected children from the transmission of pathogens due to a lack of social contacts. Previous studies have shown an effect on healthcare-seeking behaviour by loneliness in the adult population (J.S. Geller. 2004, A. Ellaway, et al. 1999, J. Geller, et al. 1999, N. Newall, et al. 2015). Studies assessing parental satisfaction with social support networks and use of healthcare services are rare, and they have reported conflicting results (A.W. Riley, et al. 1993, S.M. Horwitz, et al. 1985).

There are several possible mechanisms implicated in the above findings. Differences in healthcare-seeking behaviour of the parents appear to be a major confounding factor not only with regard to loneliness, but also in relation to parental depression. Some studies have found an association between maternal depression and an increased use of acute healthcare for infants (H.A. Flynn, et al. 2004, C.S. Minkowitz, et al. 2005), and maternal prenatal loneliness has been linked to an increase in unscheduled hospital visits during pregnancy (J.S. Geller. 2004). Anxiety displayed by vulnerable mothers may also have some influence on clinical decisions, namely diagnostics in borderline cases and with respect to prescriptions for antibiotic therapies. Louhi-Pirkanniemi et. al. (K. Louhi-Pirkanniemi, et al. 2004b) support this hypothesis by their finding that frequent physician visits during the first 3 months of life were linked to recurrent antibiotic use later on. Since it is uncommon for recurrent RTIs to develop already under the age of 3 months, it may be assumed that families' behaviour explained part of this observation. Pacifier use as a risk factor for AOM is a potential confounding factor, which we were not able to control for in our study. An infant who is given a pacifier is more likely to self-soothe, and this may reduce stress and anxiety in parents. In line with this idea, one study showed that pacifiers helped to promote breast feeding among mothers at risk for post-partum depression (H.L. Sipsma, et al. 2017). It is conceivable that psychological symptoms in the mother or father may lead to increased use of pacifiers. Higher RTI rates in infants of mothers with psychological symptoms may also be due to deficiencies in maternal care of the

infant or unhealthy lifestyle factors (E. Fowles and L. Walker. 2009, A.H. Marques, et al. 2013).

Other mechanisms have been suggested. Maternal changes in cortisol physiology may lead to increased cortisol in the foetus (see A.C. Huizink, et al. 2004), and they may thereby exert programming effects on the hypothalamic-pituitary-adrenal axis of the infant (see B.R. Van den Bergh, et al. 2005, R. Beijers, et al. 2014) with associated influences on the developing immune system and immune programming (see E. Merlot, et al. 2008, E. Mattes, et al. 2009, T.G. O'Connor, et al. 2013, R.J. Wright, et al. 2010). Several studies describe stronger Th 2 immunity in the foetus or infant in association with maternal stress (R.J. Wright, et al. 2010, E. Mattes, et al. 2009), and there may be a relative suppression of Th1-mediated cellular immune responses (I.J. Elenkov and G. P. Chrousos. 1999, I.J. Elenkov. 2004, R.J. Wright, et al. 2010). Independently of the above described effects, stress towards the end of gestation has been associated with a disruption of trans-placental transfer of passive immunity to the foetus in animal models (see E. Merlot, et al. 2008). There is also some evidence that maternal stress during pregnancy may affect the intestinal microbiota of the infant (M.A. Zijlmans, et al. 2015) with possible subsequent immunomodulatory effects. Finally, genetic factors may affect susceptibility to infections in the infant, as well as the mother and related family members, with resulting psychological complaints before the detection of infectious outcomes in the index case.

It is apparent that psychopathology in the father during pregnancy does not exert direct pathophysiological effects on the infant. However, it may be assumed that the paternal role affects the psychological well-being of the growing child indirectly via maternal factors, as well as directly, if the father and child are in contact with each other. The importance of fathers to the psychological development of the child is becoming increasingly well-established (P.G. Ramchandani, et al. 2008b, P.G. Ramchandani, et al. 2008a, A.L. Kvalevaag, et al. 2013). There is also some evidence regarding the impact of the paternal role expressed by marital quality with regard to RTI rates in the first year of life (R.E. Henriksen and F. Thuen. 2015). In addition to affecting mothers' and children's psychological well-being with possible secondary effects, fathers may influence the healthcare-seeking behaviour of a family. In the study cited earlier by Louhi-Pirkanniemi et. al., frequent physician visits already during the first 3 months of life and paternal need for outside support were linked to recurrent use of antibiotics in the up to 18-months-old offspring (K. Louhi-Pirkanniemi, et al. 2004b) indicating a paternal role on family behaviour. Our finding of a protective effect relating to higher paternal age with regard to physician visits and numbers of antibiotic medications are in line with these earlier results, as older fathers may be able to provide stronger support to mothers.

6.3. Daycare

Our results demonstrate a strong effect of daycare initiation on rates of RTIs in children under 2 years of age, but this effect waned already during the short follow-up of 9 months after the first exposure to daycare. Strongest effects were observed for children within the DCC group, but also for those in FDC, we could observe a peak of infectious measures shortly after the beginning of daycare, and a decline thereafter. For sick days, levels were comparable to the baseline group at 5 months after daycare initiation, both for children in DCC and FDC. There was a less pronounced decline for the outcome measures of antibiotic treatments and parental absences from work. Usually, start of daycare in the child and re-start of employment in the previously stay-at-home parent accompanied each other, such that parental absences from work did not serve as a direct indicator of respiratory illness when comparing the phases pre- and post daycare initiation, or children in out-of-home versus home care. As described previously, the analyses were carried out by examining overall effects of time and mode of daycare, and subsequently further characterizing the observed pattern formed by their interaction. Children in home care served as a negative control group. Findings were conclusive apart from the fact that within our control group we obtained a significant effect for overall time (albeit much smaller than for the daycare groups) in our analysis for sick days. There was no specific trend over time, but rather a random variation between different months in the control group. The effect of epidemics and season of year was minimized by the way the control group was formed. However, since births were not distributed in an entirely linear fashion throughout the year, these effects are not completely excluded.

We considered different confounding factors, and demonstrated a clear confounding effect in relation to the presence of older siblings in the family. In their cross-sectional study characterizing effects of daycare in relation to rates of RTIs stratified according to age groups and overall exposure time, Hurwitz et al. described the factor of siblings as a competing risk to daycare attendance: in the 3 examined age groups of children 6 weeks through 17 months, 18 through 35 months, and 36 through 59 months, there was a statistically significant daycare-associated risk in relation to RTIs only for children in the youngest age group, or children in the middle group with no older siblings (E.S. Hurwitz, et al. 1991). In line with these findings, in our cohort the peak and decline in RTI rates after daycare initiation was clearly less pronounced in children with older siblings, both for the DCC and FDC groups.

In our follow-on study assessing the same groups of children at the ages between 30-35 months, we showed that even later on there were no differences in RTIs, as measured by symptom frequency, between children in daycare and home care. However, disproportionately, there was a statistically significant difference of antibiotic medications between children in home care and children in DCC.

Different explanations are possible: bacterial colonization in the nasopharynx of children attending daycare may differ from those in home care. For instance, colonisation with *Streptococcus pneumoniae* has been associated with bacterial complications during RTIs, such as AOM, sinusitis and pneumonia, on the one hand, and daycare attendance on the other (S. Petraitiene, et al. 2015). There are also psychosocial factors related to daycare attendance, which may increase the probability for a child to receive antibiotic treatments. For practical reasons, higher parental concerns, which have been demonstrated to increase antibiotic prescriptions (M. Andre, et al. 2007), may be connected to daycare attendance. It has also been shown that misconceptions with regard to antibiotic indications may be relatively widespread amongst daycare providers (J.F. Friedman, et al. 2004, L. Rooshenas, et al. 2014). Additionally, one British study reported that 41% of daycare providers who responded to a survey on infection exclusion practices were at times specifically advising parents on a perceived need for antibiotics, thus encouraging general practice consultations with the aim to seek antibiotic medication. Advice on the need for physician visits was given by 93% of daycare providers represented in the survey (L. Rooshenas, et al. 2014). Whilst daycare providers' advice to seek antibiotic prescriptions may pose a problem, it has also been shown that educational interventions may be effectively targeted via daycare settings: parents may not be reached directly, but daycare providers are in a unique position to educate families regarding guidance-based antibiotic policies (D.R. Croft, et al. 2007). Studies adjusting for background variables, symptom frequency, and parental attitudes have found similar use of antibiotic medications between children attending daycare and home care (K. Hedin, et al. 2007).

Our results confirm the transience of daycare-related effects on rates of RTIs and demonstrate the complex interplay of factors influencing the developing immune system: factors relating to transmission of pathogens by the frequency and quality of interactions with peers and adults on the one hand, and potential previous acquisition of immunity on the other. The age of the child, older siblings, and overall exposure time to daycare, or other activities with close contacts, appear to influence the latter. Maintaining good hygiene in a daycare setting poses particular challenges in the very young, while this age group displays an immature immunity, and appears to be particularly vulnerable to bacterial complications of RTIs, as earlier discussed. These observations need to be balanced with immunologically-mediated potential benefits later in life, such as reduced RTI risks at school age (S. Cote, et al. 2010, T.M. Ball, et al. 2002), a lower risk of childhood acute lymphoblastic leukaemia for children with exposure to common infections in early childhood (K. Urayama, et al. 2010), or a reduced risk of atopy and asthma at pre-school or school age for children who attend daycare at an early age (S. Illi, et al. 2001, M.M. Haby, et al. 2000), although results regarding the development of asthma later in life are conflicting (P. Nafstad, et al. 1999). In practice, knowledge about an approximate time frame regarding the transience of respiratory infectious

symptoms after daycare initiation for the majority of children may be of major help to families and clinicians when balancing risks and benefits.

6.4. Free-time activities: infant swimming

Our results did not show any difference between RTI rates in swimming and non-swimming children that might indicate transmission of pathogens through swimming practices. However, our findings demonstrated that children with atopy were at risk of developing RV-associated wheeze, if they participated in swimming programmes. Causalities that underlie this finding are not fully understood. It is possible that deficiencies in lung epithelium integrity may relate to RV-susceptibility in atopic individuals (T. Jartti, et al. 2010). This hypothesis is strengthened by the finding that basal cells within the airway epithelium are particularly susceptible to RV infection (B. Jakiela, et al. 2008). There is also evidence that swimming-related exposure to chlorination-by-products may affect lung epithelium integrity independently of atopic status. Different lung-specific proteins, collectively called pneumoproteins, have been measured to assess epithelium integrity in the given context. Clara cell protein (CC16) is secreted by Clara cells in the terminal bronchioles, and to a lesser extent in all other parts of the tracheobronchial tree (see F. Broeckaert, et al. 2000). It carries anti-inflammatory properties and seems to exert a protective role against oxidative stress (see F. Broeckaert, et al. 2000). Surfactant associated proteins A and B are secreted mainly by type 2 pneumocytes in the alveolar spaces (A. Bernard, et al. 2003), and are thus indicators of alveolar epithelium integrity. Some Belgian studies have shown changes in pneumoproteins, both Clara cell protein and surfactant associated proteins, in association with infant swimming and other swimming-pool attendance in children (A. Bernard, et al. 2007, A. Bernard, et al. 2003), and findings were partially found to be dose-dependent. An effect on the pulmonary epithelium seems thus plausible. It has also been postulated that atopic sensitization may occur secondary to swimming-related disruption of the respiratory epithelium (see A. Bernard. 2007). It is likely, that host and environmental factors interconnect in complex relations, and the lung may not be the only site for pathophysiological processes. One study reported increased rates of eczema for atopic children who attended infant swimming, which was hypothesized to result from breaches in the epidermal barrier (A. Chaumont, et al. 2012). Additional research is needed in order to establish a better picture of causalities.

Given the fact that a significant proportion of lung development takes place postnatally, environmental exposure to toxic agents may have particularly modifying effects during the first months of life (see J.N. Finkelstein and C. J.

Johnston. 2004), and infant swimming practices in indoor facilities may not be as harmless as previously believed.

6.5. Strengths and limitations

The main strength of this study is the prospectively conducted day-to-day follow-up of a larger-size cohort, which was based on systematically collected diaries and questionnaires posed at set ages. All symptom inquiries contained a control check-box for negative symptoms, thus allowing us to differentiate missing from negative data. Using information on symptoms in addition to other more objectively assessable measures enabled us to examine the true disease burden to children and families more comprehensively, in comparison to a merely diagnosis-, or treatment-based approach. Thus, we attempted to take into account aspects of families' experience of illness, in addition to strictly somatic outcomes. It is also of note that in study I, we particularly focused on psychological symptoms, rather than psychiatric diagnoses as risk factors for RTIs in the children. While self-report of symptoms widens the spectrum of available data, it is also associated with potential bias. In study I, the infection-related outcome measures were based on a synthesis of data obtained from physician visits in the study clinic or elsewhere. Study II and III concentrate on parent-reported outcome measures, which were partly symptom- and partly clinic- based. Parents also reported on other clearly defined outcomes (parental absences from work). In study IV, we used parent-reported symptoms, as well as data from physician visits on diagnoses of wheezing illnesses. Additionally, viral diagnostics were applied. Data were thus extracted from a wide range of sources. We were also able to compare data between the sub-cohort with direct intensive follow-up in our study clinic and that with regular follow-up, which gave us an estimate of some sources of bias. Compared to the rest of the cohort, wheezing illnesses were more common in the sub-cohort with intensive follow-up, and this held true also for the subset of children with information on swimming practices. Otherwise there were no significant differences with regard to diagnoses between the groups.

Although forms were easy to complete, the detailed follow-up for an extended time period involved some commitment from families and thereby a drop-out of subjects over time, which was accounted for by the exclusion of missing data. Missing data and drop-outs constitute the major limitation of this study, as they may result in a biased selection of available subjects with respect to the hypotheses already from the outset, but increasingly over time. However, it has to be noted that, with the exception of study III, drop-outs mainly occurred before the specific follow-up with regard to our research questions: In study I, observations were mainly limited by the availability of psychological tools relating to the parents. In study II, the limiting factor in terms of information were dates of enrolment into daycare and information of explicitly stated home care; the latter was gathered

around the time of daycare initiation. In study IV, only children of parents who responded to the separately posted questionnaire on infant-swimming practices could be included. The fact that families did not leave the study after the grouping variables were determined minimizes possibilities of bias relating to potential anticipation of our research questions by families. In order to assess missing data further with respect to potential bias, a comparison of background variables was performed for responders and non-responders at 13 months of age, and only minor differences were detected between the groups; a comparison between drop-outs and families with ongoing participation has also been carried out (H. Lagström, et al. 2013). In spite of the large size of the original cohort, there were insufficient numbers of specific virus findings in order to ascertain our hypothesis in study IV. In this study, there was also an uneven distribution of some family characteristics between the swimming and non-swimming groups. The fact that families with less pronounced risk factors (more affluent mothers without previous children) were more prone to participate in infant-swimming activities, may have further reduced the power in our observations.

Families' possibilities for active contributions in the study may be reflected by the fact that older siblings were less frequent and maternal occupational income was slightly higher in the study families compared to all eligible families (H. Lagström, et al. 2013). There was also a difference in maternal education in that it was slightly higher for study families. As discussed earlier, low social status has traditionally been linked to higher infection rates. However, utilization of health services may be lower in these disadvantaged families (A. Hjern, et al. 2000). A Swedish study reported also an association with lower out-of-home daycare attendance (A. Hjern, et al. 2000). The socio-economic characteristics of our cohort have to be borne in mind when drawing conclusions from our results that relate to other populations.

Prevalence of maternal smoking in Finland is relatively low at 15% during early pregnancy, and it tends to be associated with lower socioeconomic status (M. Ekblad, et al. 2014). In studies I and II we noted that, for the small number of children with smoking parents in our cohort, there were several indicators that diaries may not have been completed as carefully as in the remainder of the cohort, and the variable had to be excluded from the analyses. Previous research has shown that smoking parents may underutilize health care services with respect to RTI symptoms in their children (M.A.M. Jacobs-van der Bruggen, et al. 2007), and it is thus conceivable that the parental smoking status may also affect RTI symptom reporting. The sub-cohort with the more detailed infection follow-up was entitled to use our research clinic for RTIs in the study children free of charge, and these families may have been more motivated to document all experienced events. Inclusion in this group was offered to all study families.

As discussed previously, pacifier use is a known risk factor for AOM, and it also is possible that lonely parents, or parents with symptoms of depression, may display differences in pacifier use in comparison to parents without such

psychological risk factors. In our study, there were no data on pacifier use, so potential confounding effects could not be established for this variable.

For practical reasons, in study IV, direct exposure assessments of trichloramine and other chlorination-by-products were not possible, and swimming in indoor facilities was used as a surrogate exposure measure. This is a prevalent limitation also in the majority of other studies.

The recruitment period of around 2 years was relatively long, which meant that effects relating to the combination of young age and epidemics were evened out. However, in study II, we were able to observe variations of sick days in the control group, which did not show any specific trends, but were of statistical significance. We thus have to suspect some effects of epidemics, in spite of efforts to minimize these.

The time of follow-up varied for different parts of the study and no risk factor was assessed beyond the age of 3 years. The decision on dissimilar time periods of follow-up was considered inevitable due to different research questions and varying possibilities to control for confounders. Follow-up was relatively short, but it was sufficient to demonstrate the reported effects. The STEPS study is ongoing, and there is scope for further evaluations in the future.

6.6. Future perspective

Child development may be viewed as a longitudinal transactional process between different environmental and genetic factors on the child. Our study attempted to elucidate effects of the immediate environments on the young child with respect to rates of RTIs. Results from epidemiological studies are directly applicable to the index population only, although a careful interpretation of findings, with an attempt of taking into account the potentially highly complex interactions with background variables, may allow their wider application in preventative medicine. Certainly, there is scope for sizeable longitudinal studies testing our findings in other populations.

It is still unclear, why psychological stressors affect some children, but not others, and how cumulative psychological risks act on the child. There are a few studies on maternal prenatal depression, stress, and anxiety with regard to effects on RTIs of the infant later on. Paternal prenatal depression and parental loneliness have not been studied before, and there is only very limited knowledge with regard to the effects of maternal prenatal depression. As earlier discussed, parental loneliness may be an early indicator of parental psychological risk, and systematic screening for loneliness in parents may lend itself as a measure in preventative medicine in order to promote holistic well-being of families. More research is needed, before such measures can be implemented.

In this study, daycare-related follow-up was not assessed beyond the age of 3 years. However, earlier studies have indicated a reduction in rates of RTIs for children who commenced daycare early (S. Cote, et al. 2010). In the Tucson respiratory study, protective effects waned by the teenage years (T.M. Ball, et al. 2002). A longer follow-up of our cohort would be of interest in order to answer the question of potential protective effects of early daycare later on.

Previously, studies on infant swimming have been carried out mainly in Central Europe, where swimming conditions alter slightly from Scandinavia. Our study is the first one to assess infant swimming with respect to our research question in a Scandinavian setting. However, particularly for virus diagnostics, numbers of cases did not suffice in order to answer our questions comprehensively. There is scope for larger longitudinal studies on the matter. Furthermore, pathophysiological mechanisms relating to an association between infant swimming and RV-positive wheezing illnesses in atopic individuals are not fully understood and warrant more research in the future.

Rapid changes in developmentally relevant environmental factors can be observed over time, which means that findings from this study demand a dynamic interpretation and will have to be adjusted in the future.

7 SUMMARY AND CONCLUSION

Rates of RTIs in young children are affected by a range of environmental factors. In this study we examined aspects relating to the environments of the home, daycare and leisure-activities with their relation to RTIs by evaluating effects of deficiencies in psychological well-being for both mothers and fathers, chronological aspects of daycare, and exposures connected to infant swimming.

In our cohort there was an association between maternal depressive symptoms during pregnancy and a slight increase in diagnoses of AOM in infants. Maternal emotional loneliness increased physician visits, but maternal and paternal social loneliness slightly reduced AOM diagnoses, antibiotic medications, and physician visits. Our findings relating to the effects of loneliness may be explained by differences in healthcare-seeking behaviour in socially isolated families on the one hand, and emotional needs on the other. Social isolation may protect against transmission of pathogens via a reduction of contacts, or by avoidant-type behaviour reflected by less frequent physician visits. Emotional loneliness, in turn, may result in the attempt to seek for outside support through increased medical consultation rates. Even though further research in this area is needed, it appears that parental psychological factors during pregnancy may influence RTI rates during the first year of life in the offspring to some extent. These results strengthen our understanding on the importance of parental psychological factors with regard to the psychological and physical development of the growing child, and they should be taken into account with respect to preventative efforts and when treating young children with recurrent RTIs.

Our results relating to daycare illustrate a strong effect of daycare initiation on rates of RTIs. However, a sharp decline in symptom days to a level comparable to baseline could be observed already within our relatively short follow-up of 9 months post daycare initiation. There was a clear, but less pronounced decline also for the other outcome measures. We compared children cared for in daycare centres, in family daycare, and in home care, and found the strongest trends of a rise and subsequent decline in RTI-related outcomes after daycare initiation to be linked to care in daycare centres, followed by care in family daycare. For children in home care there were no specific patterns of RTI variability identified. When examining the study children later on at the ages of 30-35 months, we demonstrated similar RTI rates, as measured by sick days, between the children in out-of-home and home care, but there was a disproportionately higher consumption of antibiotics for children in daycare centers. Alterations in nasopharyngeal colonizations, or psychosocial factors may explain this difference. These studies confirm the transience of daycare-related RTIs in young children and illustrate chronological aspects in relation to daycare initiation on a month-to-month basis.

We examined infant swimming as an environmental risk factor with regard to its effects on RTIs and wheezing illnesses. No effects relating to RTI symptom days could be elicited, but there was an association between infant swimming and RV positive wheezing illnesses. Effects were particularly clear in children with an atopic predisposition.

Even after the advent of specific gene- and molecular-based treatment possibilities in many fields of medicine, RTIs remain a common problem particularly in the population of young children. Knowledge on aspects of the complex interplay between the environments of the home, daycare, and free-time activities with the developing immune system enables parents, health care professionals, and daycare providers to make informed choices with regard to preventative strategies.

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