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## APPLICATIONS OF DANISH REGISTERS IN RESEARCH

# Childcare and health: A review of using linked national registers

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### Abstract

**Introduction:** To present the work previously and presently being carried out based on the nationwide Childcare Database. **Research topics:** The Childcare Database comprises individually linked Danish register-based data on childcare attendance, childcare facility characteristics, child and family characteristics, and infectious disease hospitalisations. The database includes about 1 million children aged 0–5 years and has, since the creation, been linked with separate disease registers on atopic disease, pneumococcal disease, and childhood cancers. The present paper is a review of epidemiological studies based on the Childcare Database. Studies of childhood infections confirmed that childcare attendance dramatically increases the risk, but emphasised that the increased risk is often transient and confined to subsets of children. Studies of childhood cancers showed that early childhood infections are likely to reduce the risk of childhood leukaemia and that this risk reduction applies to all children. **Conclusion:** The Childcare Database is a unique data source for studying the association between childcare attendance and health outcomes. Further linkage with Danish registers is possible on an individual level. The studies based on the Childcare Database confirm and extend previous findings of an increased risk of infection associated with childcare attendance, as well as point towards a possible protective role of early infections in childhood cancer.

**Key Words:** Childcare, Denmark, epidemiology, health, hospitalisation, infectious disease, linkage, register

### Introduction

This review presents studies based on data from the Childcare Database, which contains nationwide Danish register-based individually linked information on childcare attendance, childcare facilities, child and family characteristics, and infectious disease hospitalisations [1]. So far, the Childcare Database has given rise to seven publications on acute respiratory infection [2,3], gastrointestinal infection [4], wheeze and atopic dermatitis [5], invasive pneumococcal disease [6], childhood acute lymphoblastic leukaemia [7], and childhood central nervous system cancers [8]. Whereas the research questions that originally prompted the establishment of the database have largely been addressed in these publications, collaborative projects assessing the impact of childcare on other outcomes such as

obesity, and educational achievement are currently ongoing. The scope of the present review article is to present the work previously and presently being carried out based on data from the Childcare Database, as well as to bring to notice the possibility for other researchers to use the Childcare Database in their future studies.

### Research topics

#### *Childcare Database*

The creation of, the information available in, and the potential of the Childcare Database has been described in detail in a previous study design article [1]. In brief, the database links municipal childcare attendance data, childcare facility data, child and family data, and infectious disease

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hospitalisation data. Childcare attendance data were obtained from three sources (KMD, GK-Consult, and IST), including data on attendance to crèche (age 6 months to 6 years, mean of ~40 children), daycare homes (age 6 months to 3 years, max. 5 children), age-integrated facilities (age 6 months to 6 years, mean of ~70 children), and kindergartens (age 3 to 6 years, mean of ~55 children). Childcare facility data from Statistics Denmark regarding the number of teachers and children in each facility was linked to childcare attendance data based on a unique childcare facility code. Hereafter data were linked to child and family characteristics such as age, sex, siblings, parents, date of birth and death, and migration were obtained from the Danish Civil Registration System, described elsewhere in the present supplement [9]. Finally, information on infectious disease hospitalisations was obtained from the Danish National Patient Register, also by linkage on the unique personal identification number (CPR-number). The database includes data from the 266 of the 271 Danish municipalities existing at the time of creation of the database, which electronically registered childcare attendance. It includes Danish children aged 0 to 5 years during the period from 1989 to 2004 with increasing coverage over time, stabilising around 90% of the Danish population of 0–5-year-olds in the late 1990s. As of 17 November 2004 when data was last collected, a total of 1,110,973 unique children were included in the Childcare Database at

some point in time. Figure 1 illustrates the data sources used in the creation of the Childcare Database. For specific projects, the Childcare Database has subsequently been linked with data from the Danish National Birth Cohort, the Danish Streptococcus Database, the Nordic Society of Paediatric Haematology and Oncology (NOPHO) database, and the Danish Cancer Registry. An overview of completed and ongoing studies based on the Childcare Database is presented in Table I.

Data regarding childcare attendance has routinely been collected in a uniform way from 1989 to 2004 to organise the payment and distribution of places in childcare facilities in Denmark, which is why the quality of data is thought to be high. Data from five Danish municipalities was not included in the database. Three of these were not able to deliver data electronically and two could only provide data that were not compatible with the remaining data. According to Danish standards two of these municipalities were big, two were middle-sized, and one was small. This may induce a slight underrepresentation of children from big municipalities. In the Childcare Database, private and unregistered childcare facilities are not included. This may cause children who are taken care of in a private or an unregistered childcare facility to be misclassified as being in homecare. The problem with private and unregistered childcare facilities is thought to be small since most Danish municipalities guarantee a place in

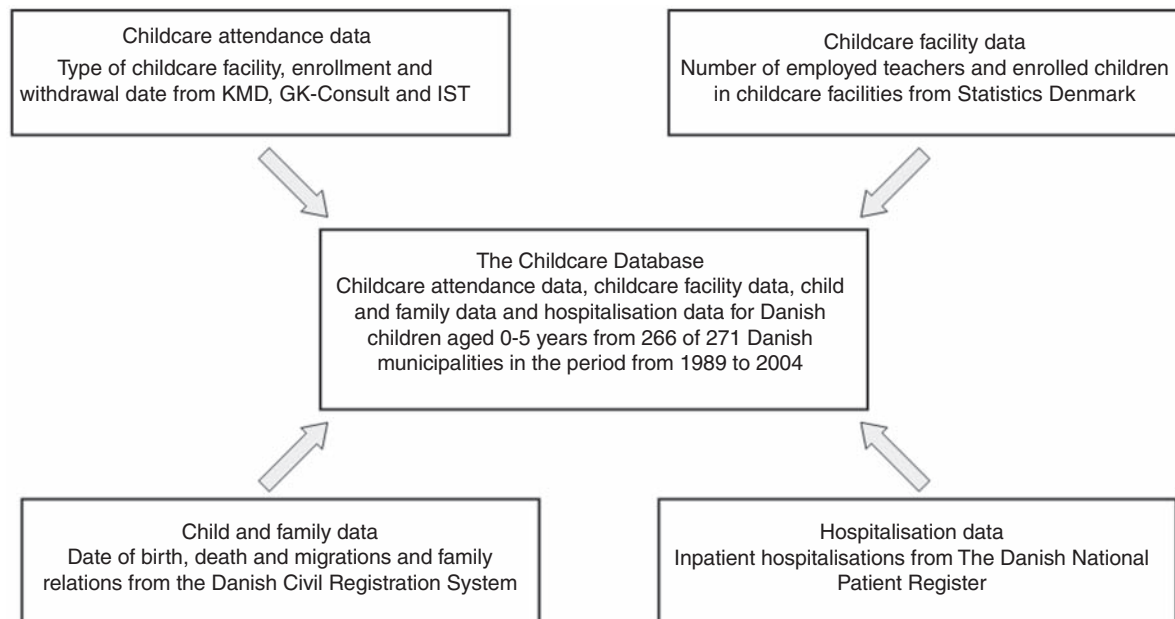


Figure 1. Data sources used in the creation of the Childcare Database.

a public childcare facility before, for example, 6 months of age. The validity and coverage of paediatric hospitalisations has previously been evaluated. Approximately 75% of diagnoses are correct and an additional 15% have a reasonable alternative in spite of a wrong diagnosis. Hospitalisations are coded based on the ICD-classification which was changed from the 8th to the 10th revision in Denmark in 1994.

#### *Childcare and infections*

Since the initial studies of the impact of childcare on childhood infectious disease in the 1930s by Lichtenstein [10] and Gyllenswård [11], the area has been immensely studied. Reasons for the huge scientific attention include that the vast majority of children are enrolled in childcare facilities in high-income settings [12] and that childcare attendance generally entails a short-term increased risk of acquiring childhood infections [13]. Moreover, because transmission of many infections in childcare facilities is easily reduced by good hygienic measures [14], the field holds a huge potential for prevention. Whereas numerous studies prior to the establishment of the Childcare Database had documented a general increased risk of childhood infections associated with childcare attendance, only few of these had the sufficient sample size to study the effect of childcare attendance on childhood infections in subgroups of children. Hence, little was known about which factors modified the increased risk of infectious disease associated with childcare attendance.

Initially, the Childcare Database was used to study as outcome hospitalisations registered in the Danish National Patient Register [15] due to the most frequent infections associated with childcare attendance, namely acute respiratory infections. By taking a special interest in the effect of time since enrolment into childcare, we were the first to describe in detail a markedly but transient increased risk of acute respiratory infection hospitalisation during the first

months of enrolment. This transient increased risk associated with childcare enrolment lasted for up to 1 year and was most distinct among children aged 0–2 years and children cohabitating with children younger than 5 years. Several other covariates such as gender, type of childcare facility, season, population density, and proxies of socioeconomic position did not modify the increased risk associated with childcare enrolment [2]. After having documented the significance of time since enrolment, the risk of acute respiratory infection hospitalisation among children exposed to other children hospitalised for acute respiratory infection in the childcare facility was studied. Although clustering of acute respiratory infection hospitalisation in childcare facilities occurred infrequently, an increased risk among children attending a facility where another child had been hospitalised for acute respiratory infection was found. This effect too was transient, lasting for approximately 1 month and being most pronounced among 0–2-year-olds and in facilities where the index acute respiratory infection case was a boy [3]. Based on a similar approach hospitalisations registered in the Danish National Patient Register due to gastrointestinal infection was subsequently studied. The results convincingly showed that childcare attendance was not a substantial risk factor for gastrointestinal infection hospitalisation in most Danish children. The effect of childcare attendance was not or only marginally modified by the previously mentioned covariates. However, late enrolment and the first short enrolment period were associated with a slightly increased risk of gastrointestinal infection hospitalisation [4]. In another study based on data from the Childcare Database and the Danish National Birth Cohort [16], the previously suggested hypothesis that maternal exposure to infections and microbes before or during pregnancy protected against atopic disease in the offspring was tested. No support for this hypothesis was found, as reflected by maternal employment in childcare facilities [5]. By combining data from the Childcare

Table I. Overview of completed and ongoing studies based on the Childcare Database.

Reference	Exposure and outcome	Conclusion
2	Childcare and acute respiratory infection	Transiently increased risk shortly after enrolment into childcare
3	Childcare and acute respiratory infection	Increased risk associated with clustering in childcare facilities
4	Childcare and gastrointestinal infection	Childcare is not a substantial risk factor
5	Maternal infection and offspring atopic disease	Maternal infections during pregnancy do not protect the offspring
6	Childcare and invasive pneumococcal disease	Increased risk associated with exposure to other young children
7	Childcare and childhood acute lymphoblastic leukaemia	Childcare attendance during the first 2 years of life reduces the risk
8	Childcare and childhood central nervous system cancers	No association with early childcare attendance
	Stressful life events and infectious disease	Project is ongoing
	Childcare and childhood obesity	Project is ongoing

Database with data from the Danish Streptococcus Database [17], perinatal and crowding-related risk factors for invasive pneumococcal disease was studied. It was found that during early childhood, exposure to other young children was clearly associated with invasive pneumococcal disease, but natural exposure appeared to occur rapidly and confer durable immunity [6]. Finally, the Childcare Database is currently being used for confounder control in an ongoing study of the possible association between stressful life events and subsequent risk of hospitalisation due infectious disease.

The studies of acute respiratory infection, wheeze and atopic dermatitis, and gastrointestinal infection were all designed as prospective cohort studies. Due to the time-to-event nature of the studies data were analysed using Poisson regression or Cox proportional hazards regression, depending on the sample size. The association between childcare attendance and the outcome was evaluated based on measures of relative risks and belonging 95% confidence intervals. Covariates were created as time dependent where relevant.

#### *Childcare and childhood cancer*

Until recent years, focus was put mainly on the effect of childcare attendance on infectious disease, whereas less attention was given to possible associations with childhood cancers. The idea that childcare attendance could have an impact on health later in life is not new, however. In 1953, Hesselvik [18] asked "to what extent is the later health of children [...] affected by day nursery infections?" Notions that childcare attendance might reduce the risk of childhood cancer was subsequently presented [19], but whether this reduced risk was dependent on characteristics of the childcare facility, the child and the child's family had not previously been studied.

The two-hit hypothesis, proposing that childhood acute lymphoblastic leukaemia is the result of a first hit (presence of pre-leukaemic cells) occurring prenatally, followed by a second hit (delayed or diminished exposure to infections) in early childhood was pursued. By linking the Childcare Database to the NOPHO database, it was found that children who ever attended childcare during their first 2 years of life had a reduced risk of childhood acute lymphoblastic leukaemia and that child and family characteristics seemed to play only a minor role in this association [7]. Based on a similar rationale, a collaborative study of the association between childcare attendance and childhood central nervous system cancers was conducted. In this study data from the Childcare Database was linked with the

Danish Cancer Registry. It was not possible to detect an altered risk of central nervous system cancers dependent on childcare exposure early in life [8].

The studies of childhood acute lymphoblastic leukaemia and central nervous system cancers, respectively, were designed as a matched case-control studies nested in cohort using the risk set sampling technique. Whether attendance to childcare was associated with the outcome was evaluated by odds ratios and accompanying 95% confidence intervals estimated using conditional logistic regression models.

#### **Conclusion**

Studies based on the individually linked population-based Childcare Database have confirmed and expanded previous findings on the association between childcare attendance and health. Having read the previously published study design article [1], researchers with an interest in the Childcare Database for reasons other than the link between childcare and infections have approached the research group. To follow up on previous findings of an elevated risk of obesity among American children who had been enrolled in early childcare [20], researchers from Harvard Medical School, USA, and Institute of Preventive Medicine, Denmark, invited us to engage in a confirmatory study based on Danish data. The project is ongoing and no results are currently available. Also, researchers from SFI - the Danish National Centre for Social Research, Denmark, have contacted us to embark on a research project studying the effect of childcare attendance on cognitive function. Finally, researchers from Statens Serum Institut, Denmark, have expressed their interest in studying the link between childcare attendance and development of asthma/allergy and appendicitis, respectively. The latter three projects have not yet been initiated. We believe that the approach by interested researchers illustrates the research potential of the Childcare Database.

As reflected in the title of the study design article "The Childcare Database: a valuable register linkage" [1], the research group believes that the creation of Childcare Database has substantially contributed to exploration of the effects of childcare attendance on health that has hitherto been poorly understood. Further, we have pleasantly experienced that the scope and application of the database is wider than what was originally intended. The strengths of the Childcare Database include linkage of nationwide individual data from various Danish registers, whereas the weakness of this approach is that it is

only possible to study severe outcomes, namely hospitalisations.

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