Title: Register-based research in children

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Publication base

1. Hospitalization for respiratory syncytial virus infection and invasive pneumococcal disease in Danish children aged <2 years: a population-based cohort study. Stensballe LG, Hjuler T, Andersen A, Kaltoft M, Ravn H, Aaby P, Simoes EA. Clin Infect Dis. 2008 Apr 15;46(8):1165-71.
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hospitalization for infection until 15 months of age in Denmark. A randomized clinical multicenter trial. J Pediatric Infect Dis Soc. 2018 Apr 7. doi: 10.1093/jpids/piy029

Paper number 1 was included in the PhD-thesis by Thomas Hjuler “Population-based Studies of Invasive Pneumococcal Disease in Denmark. Childhood Risk Factors and Familial Aggregation”, University of Copenhagen, 2007.

Table of Contents

List of abbreviations and acronyms in alphabetical order

ATC	Anatomical Therapeutic Classification
BCG	Bacille Calmette Guerin
CI	Confidence Interval
CONSORT	Consolidated Standards of Reporting Trials
COPSAC	Copenhagen Prospective Study on Asthma in Childhood
CPR	Central Person Registration
CRS	Civil Registration System
DNBC	Danish National Birth Cohort
DNPR	Danish National Patient Register
DNHSR	Danish National Health Service Register
DNBR	Danish National Birth Register
ICD10	International Classification of Disease, version 10
IPD	Invasive Pneumococcal Disease
MMR	Measles-Mumps-Rubella
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RECORD-PE	Reporting of studies Conducted using Observational Routinely collected health Data for Pharmacoepidemiology
RMPS	Danish National Registry of Medicinal Product Statistics
RSV	Respiratory Syncytial Virus
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
WHO	World Health Organization

List of links to registers and databases in alphabetical order

Clinical quality databases	https://sundhedsdatastyrelsen.dk/da/registre-og-services/om-de-kliniske-kvalitetsdatabaser
DNBC Steering Committee	https://www.ssi.dk/Forskning/Forskningsomraader/Epidemiologi/BSMB
Microbiological diagnostics, MiBa	https://miba.ssi.dk
National health data in Denmark	https://sundhedsdatastyrelsen.dk
National health data in Finland	https://rekisteritutkimusen.wordpress.com/registers/register-controllers
National health data in Norway	https://www.fhi.no/en/more/access-to-data/about-the-national-health-registries2
National health data in Sweden	https://www.registerforskning.se/en
Statistics Denmark	http://www.dst.dk
The Danish Twin Register	http://www.dtr.sdu.dk

Dansk resumé

Baggrund

Forskning i børns sundhed har høj socioøkonomisk prioritet men er udfordrende af etiske grunde og fordi der er færre børn end voksne. Siden 2006 har EU fokuseret på forskning blandt børn og udvikling af medicin til børn. CPR-nummersystemer i Danmark og andre nordiske lande giver sammen med de unikke nationale social- og sundhedsregistre mulighed for store befolkningsbaserede kohortestudier, hvor den samlede børnebefolkning medvirker.

Børn er særlig følsomme overfor helbredspåvirkninger pga. deres endnu ikke færdigudviklede immunforsvar, og deres hastige fysiske og psykiske udvikling. Børn metaboliserer medicin anderledes og reagerer anderledes på helbredspåvirkninger end voksne. Børn har forventelig lang levetid til at udvikle og leve med bivirkninger og langtidskonsekvenser af medicin og behandling. Der er følgelig til børn brug for evidensbaserede, gode og effektive behandlinger med få bivirkninger.

Metode

Dette review præsenterer og diskuterer hvordan register-baseret forskning kan bidrage til forskning blandt børn:

- Tvillingestudier kan bruges til at undersøge brudfladen mellem miljø og genetik
- Befolkningsbaseret forskning nedsætter risikoen for selektionsbias og kan give studiestyrke til undersøgelse af sjældent forekommende påvirkninger og udfald blandt børn
- Replikationsstudier sikrer kvalitet og reelt klinisk potentiale af forskningsresultater
- Registerbaserede langtidsopfølgninger, herunder i klinisk randomiserede afprøvninger, giver mulighed for omkostningseffektive, pragmatiske undersøgelser og mindre bias
- Registerbaserede farmakoepidemiologiske undersøgelser giver mulighed for med høj studiestyrke og lang tidshorisont at følge behandlingseffekter og udvikling af bivirkninger blandt børn

Implikationer

Registerbaseret forskning blandt børn er non-invasiv, omkostningseffektiv, og sikker. Registerbaseret forskning kan generere vigtig viden om børns helbred, forbrug af sundhedsydelser og kort- og langtidskonsekvenser af sygdom, medicinforbrug og vaccination.

Summary in English

Background

Health research in children has high socioeconomic priority but may be challenging due to ethical and sample size reasons. Since 2006, the European Union have focused on addressing the low level of research and development into medicines for children. In the Nordic countries the use of the unique individual identification number provided at birth in combination with the long history of high-quality national health registers provide possibilities of large-scale national population-based studies, embracing whole populations without selection as the study cohort.

The paediatric population is characterised by its vulnerability due to a not fully developed immune system, and the ongoing development throughout childhood and adolescence. Children metabolise and react differently than the adult population to health interventions and drug exposure. Although sample size is sometimes a limitation, children have long life expectancy to live with long-term consequences and develop adverse events. Evidence-based and successful health intervention with low adverse event profile is highly warranted from an ethical and socio-economic point of view.

Methods

The present review aims to present and discuss study types and designs which are useful in paediatric register-based research:

- Twin studies can be used to detect how an association may be influenced by genetic and non-genetic confounding factors
- Population-based research diminishes bias and increases power to study rare exposures or outcomes
- Replication studies secures robustness and true clinical potential of research results
- Register-based follow-up in trial populations offers low-bias long-term results in pragmatic study designs
- Register-based pharmaco-epidemiologic studies inclusive vaccine-studies have potential for high-power adjusted long-term safety studies

Implications

Register-based paediatric research can in a safe and cost-effective manner serve to fill the knowledge gap regarding children's health, health service utilisation patterns and long-term consequences of disease, drug use and vaccination.

Introduction

While a child grows up, its early development, diseases, exposures, and interventions tend to have lifelong impact on this individual's health and survival. Well known examples of important childhood interventions effective to improve health and survival are vaccination coverage (1;2) and socio-economy (3-5). If improved, both are known to potentially cause long-term individual health benefits, despite being different by nature. In contrast immaturity (6) or severe chronic disease in childhood may cause long-term health challenges (7).

It is too simplistic to consider infants, children, and adolescents as small size adults. The growth and rapid cognitive, somatic, and psychomotor development are unique features to the first stages of life. Children react differently to exposures than adults, exemplified by differences in distribution, bioavailability, and metabolism of medications between children and adults (8).

Further, the paediatric population is characterised by its vulnerability, by a not fully mature, plastic and rapidly developing immune system (9;10), by the ongoing development, and in ethical and legal aspects. Children benefit from prolonged life expectancy but will simultaneously have to endure potential long-term sequelae and adverse events from early interventions. Evidence-based and successful paediatric health interventions with a low rate of adverse events are highly warranted from an ethical and socio-economic point of view.

Resulting in the highest level of evidence (11;12), clinical trials are essential in promoting more effective and less toxic treatments (13-16), but may be costly, time consuming, and compromise the safety of the participants. Until the last decades, recruiting infants and children into trials has been challenged by ethical considerations from health care professionals, families, and authorities. In 2007, the European Union (17) and World Health Organizations addressed (18) the low level of research and development into medicines for children by implementing a law on the development of innovative medicines for children. This has resulted in a 50% increase in clinical trials among European children 2007-2017 (17).

Still, more can be done to increase the quantity and quality in paediatric research as the base for efficient and effective health intervention. Other methodologies than clinical trials may be valid in research: The observational studies where the investigator does not intervene but simply observes and assesses the strength of the association between exposure and outcome (19;20). To use data,

which is already available is cost-effective and even more of an obligation when it comes to the most vulnerable parts of our population, the children. In the Nordic countries, register-data have been collected for decades and is readily available for research. A register-based study may be a cost-effective first step in the process of identifying what associations worthwhile to pursue in more resource intensive study designs, be used for replication studies, long-term follow up after health interventions, or designed to in fact answer relevant research questions specifically pertinent to children.

The present review aims to inspire researchers to embark on register-based research by presenting the public registers mostly used in Denmark, and discuss the study types and designs, which are useful in quantitative observational research. The most common strengths and limitations of observational studies are presented, exemplified, and discussed. Although the focus is on the paediatric population, the presentation is relevant for research in all age groups. Within study types, the focus will be on population-based twin studies, and national population-based cohort studies used for replication studies, register-based follow-up in trial populations, and pharmaco-epidemiological studies. Based on the author's own research experience, study examples are provided throughout.

The basics

Observational research investigates the association between an exposure/treatment and a subsequent outcome (also called the event) in a population defined by inclusion and exclusion criteria. Most often, the group of individuals with the exposure is compared with the group of individuals without exposure, or the group of individuals with exposure I/treatment I is compared with the group of individuals with exposure II/treatment II. Exposure/treatment must be clearly defined, which may pose as a challenge to register-based research, where the underlying data are basically collected for administrative purposes and therefore may not perfectly suit the research process.

The statistical analysis is based on estimation or hypothesis testing and compares measures, or time to event between groups.

A good understanding and experience with the topic of research is essential before take-off. The research group should from the beginning involve all relevant experts, for example clinicians, epidemiologists, and biostatisticians in an initial group discussion specifying the research question, the hypothesis, the study design, the population, the potential statistical analysis etc. This approach may seem time consuming but save time and resources on the long run and moreover prevents serious and potentially irreparable mistakes.

National health registers in Denmark

The national health registers are cornerstones in register-based research (Table 1). Data have been collected routinely for administrative purposes for decades and have proven to be invaluable in research. Usually, data are made available for research by electronical access to a pseudonymised data copy via a safe and password protected data portal at the Danish Health Data Authority (https://sundhedsdatastyrelsen.dk), or at Statistics Denmark (below).

The Civil Registration System (CRS) of Denmark

Since 1968, each person residing in Denmark is given a unique identification number, the central person registration (CPR) number, which serves as a key reference to the individual in all public registers (21;22). The CPR number is used to link individual data from the registers.

The Danish National Patient Register (DNPR)

The register contains data on all hospital contacts since 1976. The data available today includes inpatient hospitalisation, emergency room visits, outpatient hospital visits, admission, and discharge dates, all surgical procedures, and all diagnosis codes (23). The diagnoses are based on international classification of disease, version 10 (ICD-10 codes).

The Danish National Birth Register (DNBR)

The register contains information on all births in Denmark since 1973 (24;25), including the pregnancy, type of birth, complications, gestational age, and anthropometrics. DNBR has been part of DNPR since 1997.

The Danish National Health Service Register (DNHSR)

In Denmark, the socialised healthcare system implies that a wide range of health services provided by general practitioners, specialists, and dentists (until patient age 18 years) are free of charge. Since 1990, the health professionals report their services to the Danish National Health Service

Register to receive reimbursement (26). For example, data on visits at the general practitioner, specialists, and immunisations are available in DNHSR.

The Danish National Registry of Medicinal Product Statistics (RMPS)

The database contains information on the total sale of medicinal products in Denmark since 1994. Prescribed medications are registered by CPR number. In 1996 all new-borns began to receive their CPR-number immediately after birth; hence the information on prescriptions among infants is accurate from this timepoint onwards. The medicinal products are classified according to the World Health Organization (WHO) Anatomical Therapeutic Classification System (ATC) coding system (27-29). Medication administration in hospitals is not registered by CPR-numbers, and this information is not available for analyses on an individual level.

Statistics Denmark

Statistics Denmark (http://www.dst.dk) was established in 1850. The institution collects detailed socioeconomic information on all Danish inhabitants regarding education, occupation, economics, etc. Statistics Denmark holds a copy of the national health registers; and makes the data available for research.

The Danish Twin Register

The Danish Twin Register (http://www.dtr.sdu.dk) consists of Danish twins born from 1870 to 2004 (30;31). From 1968 there is complete ascertainment of all live-born twins. Zygosity has been determined from four questions on similarity and mistaken identity in a mailed questionnaire. This method correctly assigns zygosity in more than 96% of the cases (32).

The Danish Cancer Registry

The Danish Cancer Registry records incident cancers in Denmark using ICD-10 and ICD-0–3 morphology codes (33).

The Danish National Register of Causes of Death

Since 1875, the National Board of Health has maintained a register of deaths among Danish inhabitants dying in Denmark, and since 1970 the records have been computerised. From 1994, the classification of cause of death was based on ICD-10 codes (34).

Table 1. List of Danish data collections of relevance to paediatric register-based research

Name	Established
The Civil Registration System	1968
The Danish National Patient Register	1976
The Danish National Birth Register	1973
The Danish National Registry of Medicinal Product Statistics	1994
Statistics Denmark	1850
The Danish Twin Register	1870
The Danish Cancer Registry	1943 (mandatory since 1987)
The Danish National Register of Causes of Death	1970

National health data in the Nordic countries

Sweden (https://www.registerforskning.se/en/), Norway (https://www.fhi.no/en/more/access-to-data/about-the-national-health-registries2/), Finland (https://rekisteritutkimusen.wordpress.com/registers/register-controllers/) and Iceland (35) have similar national health registers. The inclusion of data from other Nordic countries can increase the data pool, and thus the study power in studies of rare exposures or outcomes.

Clinical quality databases

Besides the public registers, there is a wide range of clinical databases available for register-based research: https://sundhedsdatastyrelsen.dk/da/registre-og-services/om-de-kliniske-kvalitetsdatabaser. Finally, of special interest to paediatricians the following three data collections are relevant to mention: The Danish national prospective cohort of approximately 250 infants born 1994-1995 with gestational age < 28 weeks and birthweight < 1000 grams (Ekstrem Tidlig Født Og Lavvægtig, The ETFOL study)(36-39); the Neobase data collection established in 1996 and used in various neonatal intensive care units throughout the country for variable time periods (40-42); and the database containing information on all samples collected in Danish hospitals for microbiological diagnostics, MiBa (https://miba.ssi.dk) (43).

The use in the Nordic countries of the unique individual identification number provided at birth in combination with the long history of high-quality national health registers provide possibilities of large-scale national population-based studies, where whole populations without selection present the study cohort. The populations' acceptance of being registered leading to data completeness very close to 100% along with long-term follow-up provides a unique data source for research.

Common limitations of observational studies

Essential to all scientific studies is of course the thorough project planning and protocol writing, which the validity of the results is based upon (44).

Essentially, associations and predictions are easily identified in observational research, but may not have anything to do with causality. Therefore, observational studies are primarily hypothesis generating, while trials are needed to prove causation. Rigorous study design and a pre-planned stringent statistical analysis plan including adjustment for all relevant confounders improve the likeliness of the results of observational studies being replicable.

Bias

The risk of bias is a constant source for consideration in research, and especially in observational studies. Bias is an unidentified, systematic difference between the exposed individuals/ cases/ intervention group and the comparison group, resulting in an erroneous estimation of the effect of the exposure and the outcome. Bias can occur in the planning, data collection, analysis, and publication phases of research, and can severely compromise results, interpretation, and implication. Bias has also been defined as “a combination of various design, data, analysis, and presentation factors that tend to produce research findings when they should not be produced” (45). Table 2 presents the different types of bias and potential implications.

Table 2. Bias[1] in quantitative health research

Type	Description	Consequence	Example	References[2]
Selection bias (incl. survival bias (called prevalence/incidence bias or Neyman bias in case-control studies), admission rate (Berkson) bias, non-respondent bias, membership bias, volunteer bias, healthy participant/vaccinée bias, attrition bias)	Non-comparable criteria are used to enrol participants/define case persons, but the difference is interpreted as being related to the exposure	The sample is not representative of the population intended to be analysed. The comparison groups are not comparable but selected by exposure, this leading to inflation/deflation in the estimation of associations	Prevalence/incidence (Neyman) bias, where a late look at those exposed will miss fatal and short/mild/silent episodes (e.g. in clinical coronary heart disease), and episodes where the evidence of exposure disappears with disease onset (e.g. hypercholesterolemia)	(46-50)
Observation/interviewer bias (incl. unmasking bias, detection signal bias, diagnostic suspicion bias, exposure suspicion bias, publication bias)	The investigator elicits or interprets data in a non-comparable way for exposed/non-exposed (cases/controls)	The investigator who knows the disease status of the participants, and/or is aware of the hypothesis, may probe differently for information on exposures among cases and controls, leading to inflation/deflation in the estimation of associations	Information about smoking may be collected and recorded more thoroughly and thus differently in lung cancer patients compared to other participants	(47;51-56)
Information bias (incl. recall bias, family information bias)	Exposed participants recall and report events differently from non-exposed	Exposed individuals or individuals with an adverse outcome recall and report their experiences differently from individuals who are not affected	Individuals who have experienced adverse outcomes tend to identify causes and thus remember and report differently from other individuals; this leading to over-reporting of exposures Opposite, unhealthy or socially un-acceptable behaviour like smoking and drinking may be under-reported (or missing)	(47;57-59)

[1] A systematic error in the design, recruitment, data collection, or analysis that results in a mistaken estimation of the effect of the exposure and the outcome

[2]References from both the paediatric and adult population

In register-based research using national health and socioeconomic registers, the whole population is available for follow-up. This diminishes the risk of selection bias and optimises study power. It should be noted, however, that – if not including the total population even when a study is meant to be population-based - the sample of individuals included may somehow be different from the underlying population. The Danish National Birth Cohort (DNBC) (60), a prospective cohort of approximately 100,000 pregnant women and their children born 1997-2003, is by design population-based, however the cohort does not completely represent the underlying population. Mothers with low socioeconomic status were underrepresented compared to the background population (61). A healthy and wealthy participant bias was observed within the DNBC cohort during follow-up where maternal responders to the 14-year follow-up survey based on register data were healthier, had better socio-economic status, and were older compared to the non-responders compared by register-based data (62). The implication of these socioeconomic sample selection biases is that the results are not fully applicable to the underlying population.

Confounding

Confounding is defined by the association between exposure and outcome being distorted by the presence of another/other variable(s): factors which at the same time are predictors (markers) of the exposure and associated with the outcome, affecting the risk of developing or experiencing the outcome independently of the exposure. Thus, confounding occurs when there are differences between the exposed and unexposed groups concerning independent risk factors for the outcome of interest. Confounding can bias the association both away from the null and toward the null. Confounders must be distinguished from mediators, which are factors in the causal pathway between exposure and outcome (63).

In Denmark, a heated media debate regarding a potential association between human papilloma virus (HPV) vaccination in young females and severe adverse events resulted in a dramatic decrease in the HPV vaccination coverage from 2013 and the following years. A Danish study examined the role of confounding in the association between HPV vaccination and adverse events and found that the females reporting severe adverse events after HPV vaccination had a different and more intense pattern of health service utilisation already *before* the HPV vaccination (64). I.e. the association to severe adverse events after HPV vaccination was likely to be confounded by high pre-vaccination level of health service utilisation. The authors concluded that pre-vaccination

morbidity must be considered in the evaluation of vaccine safety signals (64). These findings were supported by other studies (65;66), and the HPV vaccine coverage in Denmark increased again.

Confounding can be reduced by careful selection and measurement of potential confounders (67), randomisation, restriction or matching in the study design (68), or in the analysis by stratification or multivariable regression (adjustment) of the analyses (68-72), however residual confounding may remain, or non-confounders may be inappropriately adjusted for (73-78).

Administrative data

Data in health and socioeconomic registers are collected primarily for administrative purposes, which potentially compromises the clinical relevance, sensitivity (79-81), specificity (81) and the possibility to adjust for all relevant confounders since the data may not be available in the registers (82;83).

Within pharmaco-epidemiology, it is a clear limitation that only prescribed medication is registered on an individual level in RMPS, while medication administered in hospitals is not (79;84). This severely limits the possibility to study the long-term effects of biologicals, important and expensive new medications, which are often administered or distributed in hospital. The administration of biologicals during hospitalisation may be captured by specific ICD10 treatment codes. However, that approach may still yield sensitivities below what is acceptable for good study designs (79). Fortunately, many patient groups exposed to biologicals are registered in clinical registers, making high quality data on exposure to biologicals available for research (85-87).

Strengths of register-based studies

Data

National, public health registers and registers on socio-economy provide rich, readily available and cost-effective sources of data for research. Register-based research offers unique possibilities within data completeness and duration of follow-up (22;88). All individuals of the total population are registered and followed life long, and the data collection has been on-going for decades (83). Register data are collected independently of the study team, decreasing the risk of influence by study personnel and participants (83). The data are under on-going validation by the authorities which use the data for administrative and reimbursement purposes, and by the researchers (89).

Researchers may improve data quality by identifying and reporting to the authorities potential missing values and errors (89). Further, the increasing awareness among clinicians about the importance of high quality data for register-based research motivate health personnel to improve coding and registration, and point out important data to be included in the collection, for example individual data on medication administered in hospitals (90).

Design

In observational studies, investigators observe natural associations between exposures and outcomes without acting upon study participants. The various designs of observational studies are presented in Table 3. Generally, to reduce bias, the individuals selected to be in the examination group and the individuals selected to be the comparison group must derive from the same source population. When the entire population is used as the sample, the risk of selection bias is diminished (83). In terms of bias, the precision of the effect estimates, and the potential of causal inference, the cohort study design is superior among observational studies (19;91).

Register-based research offers unique possibilities within data combinations. Using the CPR as the unique individual identifier, data are precisely combined on an individual level, yielding a very wide scale of combinations of exposures, outcomes, and co-variables for confounder adjustment. Data regarding hospital contacts can be combined with data on prescribed medication (92), immunisations (93;94), visits, and treatments administered at the general practitioner or specialist (93;94), and with data regarding education (95), economics, and occupation (96).

Data representing a wide range of variables available on the total population opens for flexibility in analytical strategies. Complex associations, where the question is what came first, e.g. the association between RSV-infection, wheezing and asthma can be studied in both directions: with RSV-infection as the exposure and asthma as the outcome, and *vice* versa (97;98). As for all scientific research in order to yield valid and replicable results the analytical strategy has to be preplanned in a statistical analysis plan (44).

The use of register data opens for study designs where clinical data, or data collected within trials are combined with register data allowing for cost effective long-term follow-up (99;100) (detailed below in “Register-based follow-up in trial populations”). Epidemiologic population-based studies

offer pragmatic study designs in real-life settings and may be a valuable long-term reality check of effects of interventions.

Table 3. Observational study designs (19;50;101)					
Type	**Description**	**Risk measure**	**Strengths**	**Limitations**	**Study examples of paediatric relevance**
Ecological	Retrospective comparison of population clusters	Crude prevalence ratio	Timely Not very resource consuming Easy to assign exposure levels	Inaccurate Limited confounder control No establishment of temporal relationship between exposure and outcome	(102)
Cross-sectional	Prevalence study: participants are randomly selected based on exposure status/levels and the outcome is assessed at one single point in time	Odds ratio Prevalence odds ratio Prevalence ratio Prevalence difference	Timely Individualised data Multiple outcomes Multiple confounder control	One time point only Not good for rare/short lasting conditions No establishment of temporal relationship between exposure and outcome	(103)
Diagnostic accuracy study	Compare new diagnostic measure with current "gold standard" diagnostic procedure in a cross-section of both healthy and diseased participants	Sensitivity Specificity Positive predictive value Negative predictive value Positive likelihood ratio Negative likelihood ratio Diagnostic odds ratio	Supports the clinical decision-making process	Difficulties selection the "gold standard" comparator	(81)
Case-control	Selection of participants by their outcome status (outcome=cases, no outcome=controls) and retrospective quantification of	Odds ratio	Timely Advantageous for rare diseases Individualised data Can examine multiple exposures simultaneously	Cannot calculate prevalence One specific outcome only Limited number of cases Recall bias Selection of controls may introduce bias Outcome ascertained before the exposure	(104)

	exposure among cases *versus* controls		Multiple confounder control	No establishment of temporal relationship between exposure and outcome	
Nested case-control	A variation of a case–control study in which cases and controls are drawn from the population in a fully enumerated cohort (incidence density sampling)	Hazard ratio	Reductions in costs and efforts of data collection and analysis compared with the full cohort approach, with relatively minor loss in statistical efficiency. Advantageous for studies of biologic precursors of disease	The control population can often only be used for one specific outcome Non-trivial estimation of absolute risks or rates	(105)
Case-crossover	Retrospective study where the cases act as their own controls	Odds ratio	Timely Advantageous for acute outcomes with a defined exposure Reduces some bias	Selection of comparison time point difficult Challenging execution Recall bias Exposure and outcome ascertained at the same time No establishment of temporal relationship between exposure and outcome	(106)
Retrospective cohort	Identification of participants according to exposure status and reconstructing data that were created prior to the development of the outcome	Incidence rate ratio Attributable risk Relative risk Risk ratio Hazard ratio Odds ratio Prevalence odds ratio Prevalence ratio Prevalence difference	Timely Advantageous for rare exposures Can examine multiple outcomes simultaneously Establishment of temporal relationship between exposure and outcome Can suggest causation	The exposure is not randomly assigned Causal conclusion cannot be proven from an observational study Large sample size Limited control over the data collection	(107)
Prospective cohort	Identification of participants according to exposure status and	Incidence rate ratio Attributable risk Relative risk	Advantageous for rare exposures	The exposure is not randomly assigned Causal conclusion cannot be proven from an observational study	(92;97;98;108)

	following the cohort of participants forward over time	Risk ratio Hazard ratio Odds ratio Prevalence odds ratio Prevalence ratio Prevalence difference	Can examine multiple outcomes simultaneously Establishment of temporal relationship between exposure and outcome Best suited for suggesting causation Exposure is ascertained before outcome is ascertained	Long follow-up duration Large sample size Loss to follow-up which may lead to attrition bias	
Case-cohort	Cases are defined as those participants of the cohort who developed the disease of interest, but controls (the subcohort) are identified before the cases develop	Incidence rate ratio Attributable risk Relative risk Risk ratio Hazard ratio Odds ratio Prevalence odds ratio Prevalence ratio Prevalence difference	The main advantage of case-cohort design over nested case-control design is that the subcohort can be used for comparison with different case groups in a case-cohort study	The exposure is not randomly assigned Causal conclusion cannot be proven from an observational study Long follow-up duration Large sample size Loss to follow-up which may lead to attrition bias	(109)

Power

Power calculation is based on the scientific idea of hypothesis testing, where the alternative hypothesis of effect challenges the *status quo* (null effect) named the null hypothesis. Researchers evaluate if the null hypothesis can be rejected by their study findings. The purpose of sample size calculations is to ensure that a study will be of appropriate size to identify an important difference (effect) as statistically significant. Sample size calculations leads to estimation of the number of individuals required to achieve the desired statistical properties and must be increased by number of individuals anticipated to be lost for follow-up. Sample size is a function of three factors the researcher must decide on – the magnitude of the difference (effect size), significance level, and power:

1) The magnitude of the effect of interest to be detected in the treatment group in comparative studies, or the degree of marginal error of estimate in descriptive design. A larger sample size is needed to detect a small effect and large effect variation (standard error) requires an increase in sample size. For time-to-event analyses, the anticipated event rate in the control group must be known or assumed. To study rare events a large sample size is required.

2) The type I error, α, is the probability of making false-positive conclusions, in other words to reject the null-hypothesis when it is in fact true, and is most frequently set at significance level 0.05, equal to a less than 5% risk of making a false-positive conclusion. 1-α is the confidence level and to increase the study confidence level, the sample size must increase; the confidence interval being inversely associated with sample size.

3) The type II error, β, measures the probability of making false-negative conclusions, in other words to accept the null-hypothesis when it is in fact false. B is most frequently set at 20% equal to a less than 20% chance of making a false-negative conclusion. Type II errors occur when sample sizes are too small. The calculation of β is based on the definition of one explicit alternative hypothesis, typically regarding the anticipated effect on the primary study outcome. Power, 1-β, represents the probability of avoiding a false-negative conclusion. When β = 0.2, power = 0.8. Power is the likelihood of detecting with statistical significance a difference, assuming the difference exists. To increase study power, the sample size must increase (110-116).

Since sample size calculations are based on assumptions, there is no single correct sample size answer. However, sample size considerations are prerequisite for a scientific study to yield interpretable results and a conclusion (117). To include too few study participants obviously lead to both participants' and researchers´ waste of time and resources, because the study is inconclusive. Register-based research where the total populations or large population-based samples can be included offer optimal power to study rare events such as childhood cancers (118-151) or mortality (4;152-171). However, to include too many participants may be unethical, a waste of resources, and large sample sizes can magnify bias associated with error resulting from sampling or study design (172).

Register-based research potentially provides high study power and may allow for the examination of rare exposures and/or outcomes. In register-based research the costs (price of data and data management) usually depends more on number of registers and variables, and less on number of participants, so preferably the total population is included to diminish the risk of bias. It is noteworthy that as the sample size approaches ∞, the power approaches 1.0 for all magnitudes of differences meaning that any observed difference will be found statistically significant with a large enough sample size no matter how clinically irrelevant it may be.

Study types particularly pertinent to the paediatric population

Twin studies

The classical twin method quantifies how genetic versus environmental factors contribute to variation in phenotype, for example the presence of a disease (173). If brought up together, the two twins of a pair are assumed to share their early environment, so the difference lies in the number of genes shared. Monozygotic (MZ) twins share all their genes while dizygotic (DZ) twins share an average of only 50%. Consequently, phenotypic dissimilarities between MZ twins are assumed to be caused by non-shared environmental differences between the two twins of a pair (174), whereas dissimilarity between DZ twins is assumed to be due to both genetic and non-shared environmental differences. Therefore, if MZ twins are more similar for a phenotype than DZ twins, a genetic contribution to the phenotype is inferred (175).

The classical twin method can be extended to examine several traits simultaneously to estimate whether the same genetic and environmental factors influence different traits: using measured covariance between different traits, a larger covariance, or resemblance between two traits across MZ compared with DZ twins indicates that those two traits share genetic variance. A further extension of the twin method can be used to infer the direction of causation between two measured traits: the information from the cross-trait cross-twin correlations for a pair of measured traits can be used to resolve the direction of causation in cross sectional twin data, particularly if the measured traits have different modes of inheritance (175). Further, by comparing same-sex versus opposite-sex twin pairs, twin studies can be used to examine research questions related to sex (176).

Danish researchers have a longstanding tradition of twin studies based on the Danish Twin Register, however until now most studies have been carried out in the adult twin population. We used different designs of twin studies to study the association between respiratory syncytial virus (RSV) and subsequent asthma (97;174;175). In a prospective cohort study based on data from the Twin Registry, DNPR, RMPS, Statistics Denmark, and the RSV Database we examined the associations between RSV hospitalisation and asthma by using registry information on RSV hospitalisation and asthma among all N=18,614 Danish twins born 1994 to 2003. We examined the associations in both directions, with hospitalisation for RSV as exposure and asthma as outcome, and with asthma as exposure and hospitalisation for RSV as outcome. We found 4.6% of the twins have been hospitalised for RSV. Since nearly all hospitalisations for RSV took place before 2 years of age also among the twins, this exceeded the 2.8% observed in the background population below two years of age (177). Nearly 6% of the twins have been hospitalised with asthma, exceeding the 2.8% of Danish children < 5 years of age hospitalised with asthma 1994-2003 (author's unpublished data). We identified a bi-directional association between severe RSV infection and asthma: in accordance with the clinical observation of bronchial hyperresponsiveness during and after RSV infection, we found severe, hospitalisation-requiring RSV infection associated with increased risk of asthma the first year after the hospitalisation for RSV. The adjusted relative risk of asthma hospitalisation after hospitalisation for RSV was time-dependent, decreasing from a significantly increased relative risk of 6 the first 2 months after the RSV hospitalization, to a relative risk of 2 from 3 to 11 months after hospitalisation for RSV. When

studying the association between hospitalisation for RSV subsequent to asthma, we found asthma associated with a long-term, time-independent 3-fold risk of hospitalisation for RSV, suggesting a host factor being responsible for the severe response to RSV infection. Thus, severe RSV infection and asthma may share a common genetic predisposition (97;174;175). However, as illustrated by the difference in percentages of twins hospitalised for RSV or asthma compared with the background population, these findings among twins may not be generally applicable to the background child population.

Limitations

Twins differ from the singleton population in several aspects. Their average gestational age is shorter, the birth weights are lower, and the risk of congenital malformation and the neonatal morbidity and mortality are higher (178-180). Over 40% of twins are born preterm (before 37 weeks) and >50% weigh <2500 g at birth. Further, twins have a higher risk than singletons of congenital malformations (179;180). Thus, results from twin studies cannot readily be generalised to the non-twin population (97;181).

Strengths

Twin studies allow for observational investigation of genetic versus environmental influence on phenotype. Particularly, studies of twin pairs discordant for an exposure or a disease outcome can be used to detect how an association may be influenced by genetic and non-genetic confounding factors (174). Twin study designs can be used to minimise residual confounding (182).

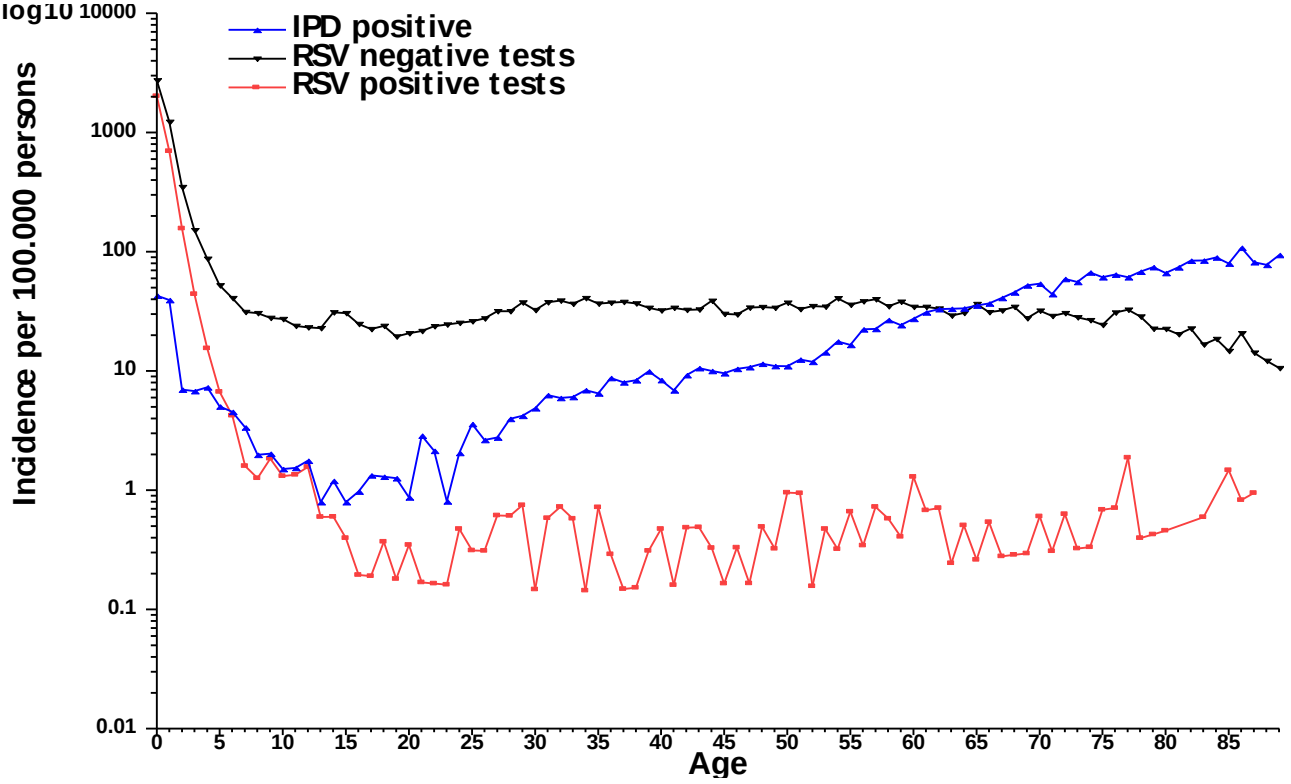
National population-based cohort studies

A national, population-based cohort study is defined by all individuals of a population in a country being available for inclusion without selection. It may be relevant to limit the inclusion to individuals with certain important characteristics, for example women only in a study of oral contraception and risk of breast cancer (183), or all individuals of a certain age group in paediatric studies.

We used the entire Danish population born January 1 1996 to 1 July 2003 to study the association between hospitalisation for RSV infection and the rare event invasive pneumococcal disease (IPD) (98) (Figure 1). To establish the cohort and obtain data on exposure, outcome and confounders,

data were obtained from two national public health registers: CRS and DNPR in combination with two clinical databases: The Danish *Pneumococcus* database (184;185) and the RSV database (186;187). In the >7 million person-years of follow-up, 61 individuals experienced both hospitalisation for RSV infection and IPD.

Figure 1. Incidence of RSV and IPD in Denmark during 1996-2003 by age



We examined the associations between RSV and IPD bi-directionally: We compared the rate of IPD among children hospitalised with RSV infection with the rate of IPD observed among the background population of children who were not hospitalised for RSV infection; and we compared the rate of hospitalisations for RSV infection among children with IPD with the rate of hospitalisations for RSV infection among children who did not have IPD. We included information on non-RSV respiratory hospitalisation to explore if potential associations were limited to infection with RSV or general for hospitalisation-requiring airway infections. Analyses were performed by age (<2 years vs. ≥ 2 years) since hospitalisation for RSV is frequent in early childhood, and by time since exposure (<30 days vs. ≥ 30 days) trying to distinguish between a direct potentially causal effect, and the effect of shared risk factors. We replicated the temporal correlation between RSV and IPD found in earlier studies (188-190) (r=0.55, p<0.01), however the temporal association

between IPD and non-RSV respiratory infection was found to be even stronger ((r=0.65, p<0.01), and the temporal correlation was not present in children below two years of age (r=0.08, p=0.41). We found no increased risk of hospitalisation for RSV after IPD, but a strong association between IPD and subsequent hospitalisation for non-RSV respiratory infection, both within and after 30 days after IPD, pointing towards residual confounding of shared risk factors, and maybe an increased level of attention and care after severe IPD. We found that recent severe RSV infection in fact increased the risk within 30 days of IPD in children below 2 years of age, the rate ratio (RR) adjusted for co-morbidity and the 95% confidence intervals (CI) being 7.1 (3.6-14.3). The association to IPD recently after non-RSV respiratory infection was also strong, adjusted RR 4.5 (CI 2.0-10.0). These findings may be explained by reduced epithelial barrier function (191) and increased invasiveness of colonising bacteria during and after acute severe viral airway infection (192).

In another study with cross national design, we used the entire populations of children born in Denmark from 1997 to 2011 (N=972,836) or born in Sweden from 2006 to 2010 (N=534,541) to establish up-to-date incidence rates of atopic dermatitis, asthma, and allergic rhinoconjunctivitis in the Danish and Swedish child populations (92). The incidence rates of atopic dermatitis, asthma, and allergic rhinoconjunctivitis in the Danish and Swedish child cohorts were ascertained through information on disease-specific dispensed prescribed medication, specific hospital contacts, or both. Incidence rates were calculated using 2006, the approximate mid-year of the study period, as reference year. The study revealed similar trends, with stable incidence rates of atopic dermatitis in both Danish and Swedish children, an increase and then stabilisation in asthma incidence rates in Denmark and an increase in Sweden, and a decrease in allergic rhinoconjunctivitis incidence rates. At age 5 years, one third of children in the total cohort were affected with at least one of the conditions of atopic dermatitis, asthma, or allergic rhinoconjunctivitis (92).

To carry out the atopic disease incidence study (92), we developed three algorithms, one for each of the three atopic diseases, to define children with atopic dermatitis, asthma, or allergic rhinoconjunctivitis based on register data on disease-specific medication, specific hospital contacts, or both. Each algorithm was generated in three steps: 1. selection of disease-specific

hospital diagnoses and disease-specific medications; 2. application of criteria of repetition of the disease-specific medications within 12 months because all 3 conditions are characterized by chronicity and recurrence; and 3. exclusion of other medical conditions known to lead to use of the medication types used as inclusion criteria in step 1. The three outcome diseases were defined separately, and therefore each child could be affected by more than one atopic disease. It is of note that the criteria of repetition of the disease-specific medications within 12 months means that one year of follow-up was required.

In a separate study in Denmark, we validated the algorithms versus gold standard deep telephone interviews with the caretaker about physician-diagnosed atopic dermatitis, wheezing, asthma, or allergic rhinoconjunctivitis in the child (81). Using random sampling from families participating in DNBC, we included a total of N=454 children with atopic dermatitis (N=205), asthma (N=202), or allergic rhinoconjunctivitis (N=198) according to the algorithm, and carried out interviews with the caretaker, including questions from validated surveys for ascertaining atopic dermatitis, asthma and allergic rhinoconjunctivitis. Confirmative answers to questions about physician diagnosed atopic dermatitis, asthma or allergic rhinoconjunctivitis were used as the gold standard for the comparison with the diagnoses generated by the algorithms, resulting in sensitivities and specificities and 95% confidence intervals. For atopic dermatitis, the sensitivity of the algorithm was 74.1% (66.9%-80.2%) and the specificity 73.0% (67.3%- 78.0%). For asthma, both the sensitivity of 84.1% (78.0%-88.8%) and the specificity of 81.6% (76.5%-85.8%) were high compared with physician-diagnosed asthmatic bronchitis. The sensitivity remained high when capturing physician-diagnosed asthma: 83.3% (74.3%-89.6%); however, the specificity declined to 66.0% (60.9%-70.8%). For allergic rhinoconjunctivitis, the sensitivity was 84.4% (78.0-89.2) and the specificity 81.6% (75.0-84.4). In conclusion, we found the algorithms to be valid and valuable tools to identify children with atopic dermatitis, wheezing, asthma or allergic rhinoconjunctivitis on a population level using register data (81). The methodology of using algorithms was commented upon in an editorial, where the authors concluded that our results reinforced the possibilities to study the causes and consequences of atopic and potentially other complex disease in population-based register linkages (193).

We replicated the methodology of algorithms based on register data to also identify children with the complex disease entity of hemodynamically significant congenital heart disease (194). We found that it was indeed possible to identify a subgroup of children with hemodynamically significant congenital heart disease using an epidemiological approach and an algorithm with high validity (194). Again, these results enable well-powered national cohort studies of children – and adults – with complex clinical conditions (193).

Finally, another relevant example is situations where for ethical reasons; children cannot be randomised to not receive immunisations which are already part of national child vaccination programmes. Thus, long term effects of child immunisation from national child vaccination programmes must be studied using observational study designs. It should be noted that such studies should be carefully analysed due to the risk of healthy vaccinée bias and confounding by indication (please see below), and even so the results must be interpreted with caution.

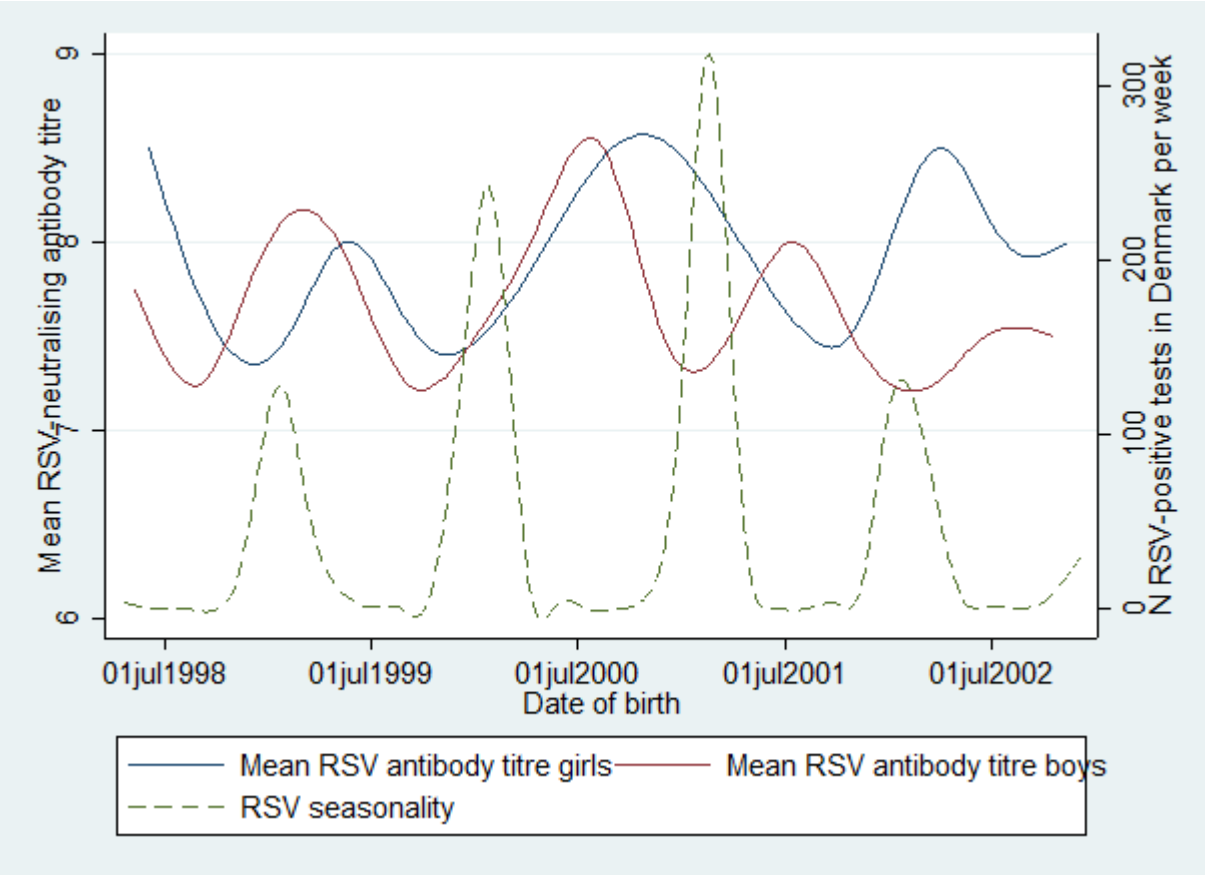
Collections of biological specimens in national cohorts

Collection of biological specimens such as blood samples is resource consuming and may cause ethical considerations, especially in children who cannot consent themselves at the time of specimen collection. In Denmark, however neonatal dried blood spots are routinely collected on standard Guthrie cards for the national new-born screening program for inborn errors of metabolism, hypothyroidism, and other diseases (195). Identifiable by CPR, since 1982 the Guthrie cards are stored at -20 °C in the Danish Neonatal Screening Biobank, providing a unique biospecimen repository to enable large cohort population-based research (196-207). Although the quality of dried blood spots put limitations to what these samples can be analysed for, the national collection of samples from neonates is unique in scale and data completeness.

Another large-scale biospecimen repository was established through the DNBC (60), which succeeded in collecting cord blood samples among more than 50% of the participants, approximately 50,000 individuals. The samples were separated in plasma and buffy coat and stored at -20°C and -80°C, respectively. Access to this unique collection can be applied for to the DNBC Steering Committee (https://www.ssi.dk/Forskning/Forskningsomraader/Epidemiologi/BSMB). We based studies on the association between level of maternal RSV neutralising antibodies and risk of hospitalisation

for RSV, or risk of recurrent wheezing on the DNBC collection of blood samples (208;209). Figure 2 below presents titres of maternally derived RSV-neutralising antibody from Danish infants born 1998-2003 by sex, and the incidence of RSV hospitalisation per 100,000 Danish infants younger than 6 months of age 1998-2003. Apparently, the kinetics of maternal antibodies differ between boys and girls. In future studies we plan to further evaluate RSV-epidemiology by sex.

Figure 2. Titres of maternally derived RSV-neutralising antibody in 457 cord blood samples from Danish infants born 1998-2003 and incidence of RSV hospitalisation per 100,000 Danish infants younger than 6 months of age 1998-2003



Note: The mean RSV antibody titer expressed to the log base 2 is presented by use of the cubic spline technique and based on 58 infants born in 1998, 92 infants in 1999, 112 infants in 2000, 110 infants in 2001, and 85 in 2002.

Limitations

The risk of bias and confounding must be considered in every observational study, although the risk of selection bias is minimised in study designs where all individuals in a population are included and followed. Although all individuals are included in the study cohort, bias can be

introduced in the analyses, for example in the selection of comparison groups. Confounders must be identified and adjusted for and still, residual confounding must be considered as an alternative explanation of significant associations observed (48).

For example, pharmacoepidemiological studies are prone to confounding by indication (elaborated upon below), and observational studies of vaccines are prone to confounding by indication and healthy vaccinée bias. Confounding by indication is of concern in observational studies where children who received live attenuated vaccines are compared with children who received subunit vaccines. The clinical indications for live vaccines *versus* subunit vaccines are different: live-attenuated vaccines are contraindicated in severely immunosuppressed individuals since the vaccine may replicate and infect the recipient. Individuals who also receive live vaccines are expected to be more immunocompetent than individuals who only receive subunit vaccines. A beneficial "effect" observed when comparing live-attenuated vaccine recipients with subunit vaccine recipients in an observational study design may be due to this inherent difference between the two comparison groups. Healthy vaccinée bias (also known as frailty bias or healthy user bias) occurs when individuals who are more susceptible to illness are vaccinated later or remain un-vaccinated. Healthy individuals are more likely to receive vaccines (210), so decreased risks of morbidity and mortality after vaccination may be explained by general better health and longer life expectancy in vaccine recipients. This bias is thoroughly studied and documented for influenza vaccine studies among adults where it is concluded that register-based cohort studies with un-specified outcomes, such as mortality or general measures of morbidity are not suited to measure influenza vaccine effectiveness (48). A study from the Netherlands found healthy vaccinée bias to explain what alternatively was interpreted as an observation of "beneficial non-specific effect" of the MMR-vaccine (211). Likewise, we have recently found residual confounding in a register-based study of childhood vaccines in Denmark (46).

Strengths

The opportunity of including information on all individuals from a population is unique and opens for research questions, which cannot be addressed in study designs due to problems with low study power for rare exposures or outcomes, or ethical considerations (83). A large amount of data are readily available on a national, or even cross-national base. These considerations are of particular importance in vulnerable patient groups such as children.

Replication studies

Replicability (defined by the chance that an independent experiment targeting the same scientific question will produce a result consistent with the original study) and reproducibility (defined by the ability to re-compute data analytic results given an observed data set and knowledge of the data analysis pipeline) are cornerstones in research (212-219). Only in case a scientific finding has been replicated, and the results from several studies have been meta- or mega-analysed (220) the finding can be considered robust and to have true clinical potential (221). Trials and meta-analyses of trials produce the highest level of evidence (222), but are resource consuming. And even results from trials have to be interpreted with caution, because of challenges with selective reporting of positive results (55), false-positive results due to multiple significance tests and unreported comparisons (223). Some exposures would be unethical to study in a clinical trial: harmful interventions, or to withhold the placebo group an intervention found to be beneficial, for example childhood vaccinations. In that case, replication in well-designed observational studies becomes even more important. Hence, there are numerous reasons to replicate findings in register-based study designs.

For example, we used the prospectively collected population-based data on 2,529 Danish infants from the DNBC born at 33 to 35 weeks of gestation and followed-up until 18 months after birth to replicate findings from prior studies on a predictive model of RSV hospitalisation among European children (224-228). Aiming to identify individuals at the highest risk to use the expensive passive prophylaxis against RSV, palivizumab, most rationally, the European Predictive Model identified seven variables describing the most important risk factors for RSV hospitalization in premature infants 33 to 35 weeks of gestational age. These variables were birth within 10 weeks of the start of the season, birth weight, breast-feeding 2 months, number of siblings ≥2 years of age, number of family members with atopy, male sex, and number of family members with wheeze. In the original study, information on these seven factors examined by discriminant function analysis resulted in a diagnostic accuracy of 71% when trying to identify premature infants hospitalized with RSV. In our replication among the Danish premature children, 139 (5.5%) were hospitalised for RSV, and the model had a diagnostic accuracy of 65.9% to distinguish between RSV-hospitalised versus non-RSV-hospitalised infants born at 33 to 35 weeks of gestation (229). Even

though 66% diagnostic accuracy was rather imprecise, it may still be better than national guidelines which have been found to be no better than chance to identify premature infants at increased risk of hospitalisation for RSV (226).

In another study, we tested the hypothesis that mother's use of antibiotics in pregnancy may influence asthma and eczema in early life in cohort study designs where all children were followed up until 5 years of age (108). First, we used data from the Copenhagen Prospective Study on Asthma in Childhood (COPSAC) cohort of children born of mothers with asthma (N = 411). In the COPSAC cohort, asthma and eczema were diagnosed by research unit physicians. Second, we replicated the analyses in children from the Danish National Birth Cohort (N = 30,675), where asthma outcomes were hospitalisation and use of inhaled corticosteroids, and eczema was defined by an algorithm developed from cases of clinically verified eczema. We found no associations between maternal use of antibiotics and eczema. In COPSAC, we found increased risk of asthma associated with maternal antibiotic use during third trimester, hazard ratio 1.98 (1.08-3.63). We replicated the finding in the unselected DNBC, the children's hazard ratio of asthma hospitalisation being 1.17 (1.00-1.36), and 1.18 (1.10-1.27) for use of inhaled corticosteroids if mothers used antibiotics any time during pregnancy. In a dose-response analysis, the risk of asthma increased significantly with increasing number of prescriptions. In a DNBC subgroup of children whose mothers used antibiotics for non-respiratory infections during pregnancy, the hazard ratio of hospitalisation for asthma was 1.32 (1.12-1.56), and 1.18 (1.10-1.27) for use of inhaled corticosteroids (108). Since this restricted analysis resulted in similar estimates and maternal asthma history did not modify the effect of use of antibiotics during pregnancy, it is unlikely that a shared genetic susceptibility to infections explains the associations. We concluded that the study supported hypotheses regarding pre- or perinatal bacterial ecology playing a role for the development of asthma.

Limitations

As in all research, poor study design, poor or no pre-planned statistical analysis plan, insufficient study power, and cherry picking of preferred results lead to invalid conclusions. In observational studies selection bias or confounding may explain all "effects" observed. Careful confounder control is essential to non-randomised studies. Even in studies attempting to have confounder control, the interpretation has to be cautious due to potential residual confounding (230).

In both study examples given above (108;229), participants were at least to some extent selected. Findings among 33-35 weeks of gestational age premature children may be applicable in general to other 33-35 weeks of gestational age premature children, but other factors such as socioeconomy may influence the generalisability.

Strengths

Carefully designed population-based observational studies are hypothesis generating and valuable in replicating, reproducing, and scrutinising associations between exposure and outcome, and in identifying mediators, confounding, and effect modification (108). Replicated hypothesis testing in combination with the potential of high statistical power in national study cohorts and rigorous study designs often lead to new ideas and insights (108;231;232).

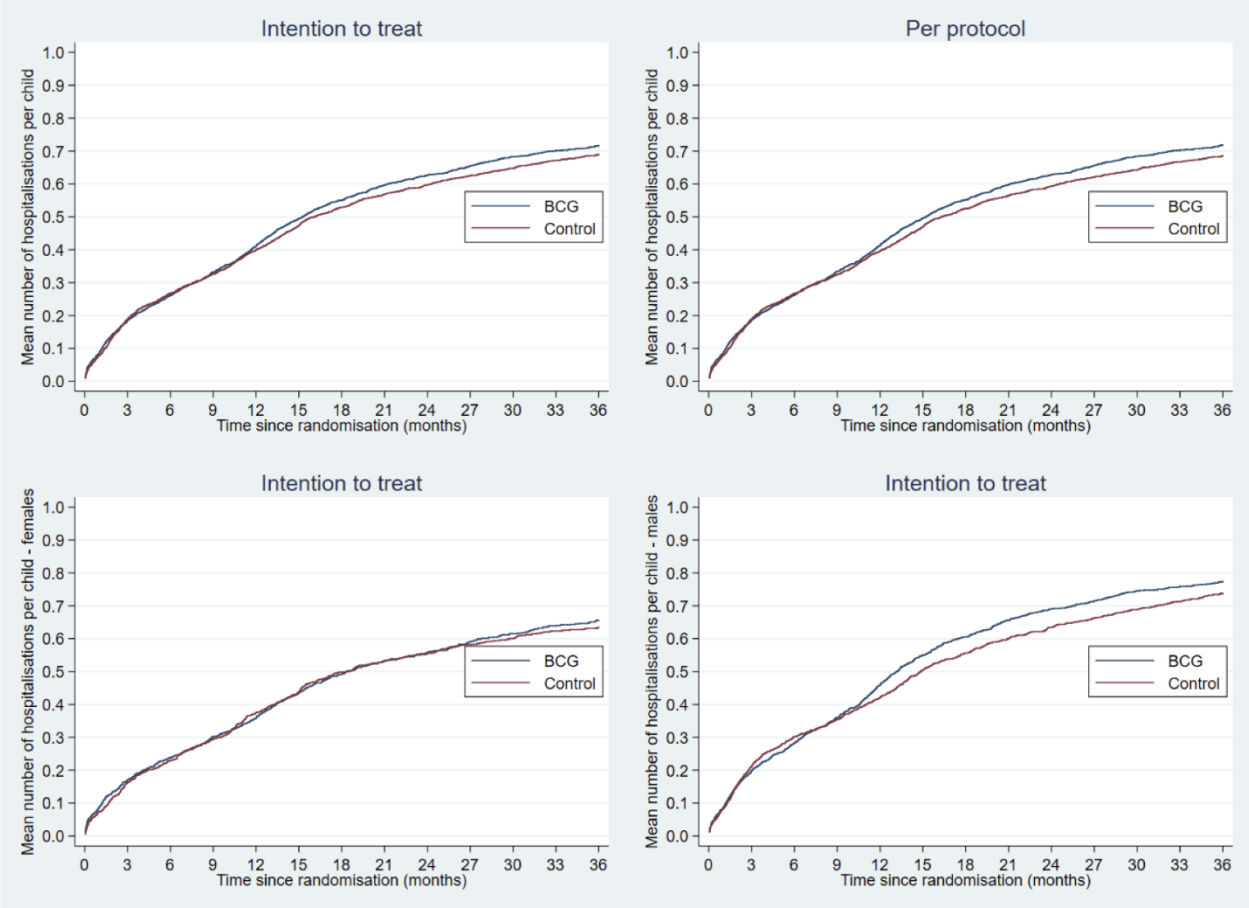
Register-based follow-up in trial populations

Besides being time- and resource consuming, trials may be carried out with such stringency that the results are not reproducible in a real-life setting. Efficacy trials must be followed by effectiveness trials (221;222). In many countries, an important challenge in effectiveness trials is, however, the lack of infrastructure to support pragmatic research, where the result of interventions is evaluated in usual practice settings and subjects (233). Again, register-based follow-up offers an advantageous solution to the challenge of effectiveness trials. When the initial randomisation, allocation and intervention/placebo has taken place, participants can be followed lifelong for relevant outcomes, which can be defined using register-data, as for example socioeconomic achievements, visits at the general practitioner or specialist, drug use, hospitalisation (99;100), and death. That approach allows for testing interventions in real-life settings with 100% follow-up.

In the Danish Calmette Study we studied the potential of beneficial non-specific effects of neonatal BCG-vaccine in a trial among 4262 Danish new-borns randomised to BCG within 7 days after birth or no intervention (control). The primary study outcome was all-cause hospitalisation defined as any hospitalisation for somatic disease (99). The follow-up data was collected independently of the study team since we used register-data including all ICD10 diagnosis codes from the DNPR on all hospital contacts in the study cohort to define the primary outcome. When

data are not collected by team members, the risk of observer bias is diminished. We found no non-specific beneficial effect of neonatal BCG. There was no difference in the risk of all cause hospitalisation up to 15 months of age; 2129 children randomised to BCG experienced 1047 hospitalisations with a mean of 0.49 hospitalisation per child compared with 1003 hospitalisations among 2133 control children (mean 0.47), resulting in a hazard ratio comparing BCG vs. no BCG in intention-to-treat analysis of 1.05 (0.93-1.18). Figure 3 presents the study cohort followed-up for all-cause hospitalisation until 3 years of age. Still, no effect was observed.

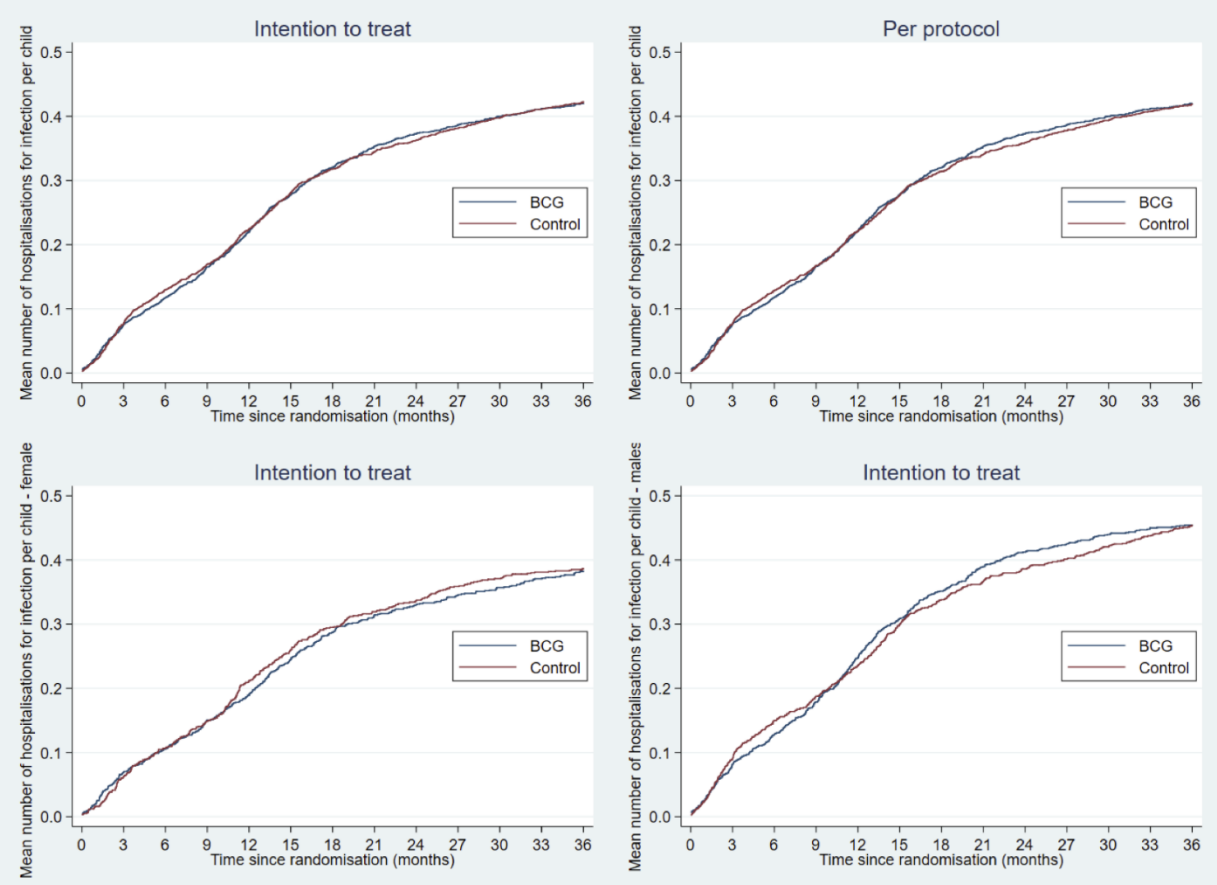
Figure 3. Mean number of all-cause hospitalisations by randomisation arm as a function of time since randomisation until 3 years of age among 4262 Danish children randomised to BCG at birth, or no intervention (Nelson-Aalen method). Presented by Intention-to-treat analysis, per-protocol analysis, intention-to-treat-analysis in girls, and intention-to-treat analysis in boys



In a secondary outcome study from the same trial, we selected all ICD10 diagnosis codes for infections to be able to study hospitalisation for infection (100). Again, we found no beneficial

effect of neonatal BCG. We observed 588 hospitalizations for infection (mean 0.28 hospitalisation for infection per child) among the 2129 children randomised to BCG compared to 595 (mean 0.28) among 2133 control children, the hazard ratio being 0.99 (0.85-1.15). Figure 4 presents the study cohort followed-up for hospitalisation for infection until 3 years of age.

Figure 4. Mean number of hospitalisations for infection by randomisation arm as a function of time since randomisation until 3 years of age among 4262 Danish children randomised to BCG at birth, or no intervention (Nelson-Aalen method). Presented by Intention-to-treat analysis, per-protocol analysis, intention-to-treat-analysis in girls, and intention-to-treat analysis in boys



In the Danish Calmette Study, we studied several other outcomes without finding significant effect on prespecified primary or secondary outcomes (99;234-251). Because of the size and design of the study, we could conclude, that there was no indication in Denmark to re-introduce routine neonatal BCG for the sake of non-specific beneficial effects.

Limitations

The data available in national health registers may not always be ideal for the definition of study outcomes and co-variables. In that case, and for replication reasons, the trial teams may decide to collect supplemental data, which can be linked to the register-based data collection using the CPR-number as unique individual identifier as we did in the Danish Calmette Study (239).

In trials with long-term follow-up after the allocation code has been un-blinded, researchers may be prone to observer bias.

Strengths

The 100% follow-up, the potential of pragmatic study designs, and the collection of data outside the study team are advantages of register-based follow-up in trial populations.

Pharmaco-epidemiology

After the thalidomide disaster (252), a drug-licensing system, the Medicines Act, was introduced in 1968 to ensure safe and effective medicines (253). However, much medication used routinely by paediatricians has not been formally evaluated through trials in children. The introduction of a steadily increasing number of biological medicines adds to the need of prospective long-term follow-up studies to ensure safety and efficiency of drug use, as also required by the European Medicines Agency and the United States Food and Drug Administration (254;255). Population-based national register information on prescribed medication at an individual level offers unique possibilities to examine short and long-term consequences of exposure to medication in pragmatic study designs with optimal study power and diminished risk of bias.

Using the entire Danish and Swedish child populations in cross-national population-based cohort studies including data from 769,523 Danish children born 1999 to 2010 and 581,742 Swedish children born 1 July 2005 to 2010, we made pharmacoepidemiologic studies on the associations between the rare exposure of biological medication, palivizumab, as passive prophylaxis against severe infection with RSV, palivizumab, and the outcomes allergic disease (256), or autoimmune disease (257). For atopic disease, we found exposure to palivizumab to neither increase the risk of atopic disease nor protect against asthma (256). The risk of autoimmune disease was not increased after palivizumab exposure (257). Given the small number of incident cases

of autoimmune disease observed the latter study was insufficiently powered, and the finding should be interpreted cautiously.

Table 4 presents pharmacoepidemiologic register-based studies in Danish children. For an overview, figure 5 presents the number of studies per year. Evidently, the number of studies increases over the years.

Table 4. Pharmacoepidemiological studies including Danish children

Publi-cation year	Title	Design	Number of participants	Study period	Conclusion	Reference
2018	Use of proton pump inhibitors among Danish children: A 16-year register-based nationwide study	Cohort study	78489	2000-2015	The use of PPIs among Danish children has increased substantially during the last 15 years. In general, treatment with PPIs among children was of short duration. Attention should be paid to indications and rationality behind initiation of therapy	(258)
2018	Vitamin D Status and Seasonal Variation among Danish Children and Adults: A Descriptive Study	Cohort study	3092 persons aged 2 to 69 years	2012-2014	We found substantial seasonal variation in the 25(OH)D concentrations. Most participants were vitamin D-sufficient in autumn, but many experienced vitamin D insufficiency during the spring, emphasizing the need for individual, bi-seasonal measurements when assessing status	(259)
2018	In utero beta-2-adrenergic agonists exposure and risk of epilepsy: A Danish nationwide population-based cohort study	Cohort study	686,800	1998-2008	In utero exposure to β2AAs, particularly in the first or second trimesters, may be associated with an increased risk of epilepsy. It may partly be due to the indication of β2AAs use, but a direct effect of β2AAs cannot be ruled out.	(260)
2018	UGT polymorphisms and lamotrigine clearance during pregnancy	Retrospective case series	40 pregnancies	2008-2014	Genetic polymorphism in UGT1A4 and UGT2B7 may play a modest role in LTG clearance changes during pregnancy	(261)

2018	Use of paracetamol, ibuprofen or aspirin in pregnancy and risk of cerebral palsy in the child	Cohort study	185,617 mother-child pairs from the Danish National Birth Cohort and the Norwegian Mother and Child Cohort Study	1996-2008	We observed an increased risk of spastic CP in children prenatally exposed to paracetamol and aspirin	(262)
2017	A multinational comparison of antipsychotic drug (AP) use in children and adolescents, 2005-2012	Multi country repeated cross-sectional	All inhabitants <20 years of age	2005-2012	AP use prevalence increased in all youth cohorts from European countries and decreased in the US cohort	(263)
2017	Prenatal exposure to β2-adrenoreceptor agonists and the risk of autism spectrum disorders in offspring	Cohort study	All live singleton births	1997-2008	Children born to women who used β2AA during pregnancy have an increased risk of ASDs in later life, which is more likely due to underlying maternal diseases rather than the exposure to β2AA itself	(264)
2017	Trends in ADHD medication use in children and adolescents in five western countries, 2005-2012	Multi country repeated cross-sectional	All inhabitants <20 years of age	2005-2012	Although there was a substantially greater use of ADHD medications in the US cohort, there was a relatively greater increase in ADHD medication use in youth in the four European countries	(265)
2017	Palivizumab Exposure and the Risk of Atopic Dermatitis, Asthma and Allergic Rhinoconjunctivitis: A Cross-National, Population-Based Cohort Study	Cohort study	769,523 Danish children 581,742 Swedish children	1999-2010	Exposure to palivizumab neither increased the risk of atopic disease nor protected against asthma	(256)
2017	Psychopharmacological drug utilization patterns in pregnant women with bipolar disorder - A nationwide register-based study	Cohort study	Danish women aged 15-55 with of bipolar disorder, who gave birth to their first and	1997-2012	A decrease was observed in the proportion of women redeeming prescriptions on psychopharmacological drugs during pregnancy	(266)

			singleton child (336 pregnant case women)			
2016	Prenatal exposure to antidepressants and risk of epilepsy in childhood	Cohort study	734,237	1997-2008	Antidepressant use during pregnancy was associated with a higher risk of epilepsy among children whose mothers had also a registry-based hospital diagnosis of depression during pregnancy	(267)
2016	Palivizumab Exposure and the Risk of Autoimmune Disease: A Cross-National Cohort Study	Cohort study	769,523	1999-2010	The risk of autoimmune disease was not increased after palivizumab exposure	(257)
2016	Birth outcomes after exposure to mebendazole and pyrvinium during pregnancy - A Danish nationwide cohort study	Cohort study	713,667 births	1997-2007	We found no association between exposure to mebendazole and major congenital malformations (OR = 0.7 (CI 95% 0.5-1.1)) or other negative birth outcomes and we found no association between exposure to pyrvinium and major congenital malformations (OR = 0.8 (CI 95% 0.4-1.5)) or other negative birth outcomes	(268)
2016	Low Risk of Birth Defects for Infants Whose Mothers Are Treated With Anti-Tumor Necrosis Factor Agents During Pregnancy	Cohort study	1,272,424 live-born Danish and Swedish infants	2004-2012	Women who received anti-TNF agents during pregnancy had a slightly (but not significantly) higher risk of having children with birth defects	(269)
2015	Inflammation and depression: combined use of selective serotonin reuptake inhibitors and NSAIDs or paracetamol and psychiatric outcomes	Cohort study	25% random sample of the Danish population	1997-2006	Concomitant use of SSRIs and NSAIDs occurred frequently, and effectiveness and safety outcomes varied across individual NSAIDs	(270)
2015	Exposure to systemic antibacterial medications	Cohort study	817,244 Danish children	1995-2009	The results of this study indicate that most antibacterial drugs used during	(130)

	during pregnancy and risk of childhood cancer		629,994 Swedish children		pregnancy were not related to childhood cancer risk in the offspring	
2015	Incidence rates of atopic dermatitis, asthma, and allergic rhinoconjunctivitis in Danish and Swedish children	Cohort study	972,836 Danish children and 534,541 Swedish children	1997-2011	The study revealed similar trends, with stable incidence rates of atopic dermatitis in both Danish and Swedish children, an increase and then stabilization in asthma incidence rates in Denmark and an increase in Sweden, and a decrease in allergic rhinoconjunctivitis incidence rates	(92)
2015	Time trends of period prevalence rates of patients with inhaled long-acting beta-2-agonists-containing prescriptions: a European comparative database study	Cohort study	The Danish population (and other European populations)	2002-2009	We found highest rates of LABA-containing prescriptions in elderly patients and distinct differences in the increased utilisation of LABA-containing prescriptions within the study period throughout the five European countries	(271)
2015	Children with hemodynamically significant congenital heart disease (CHD) can be identified through population-based registers	Cohort study	All children born July 1, 2005– December 31, 2010 in Sweden	2005-2010	It was possible to identify a subgroup of children with hemodynamically significant CHD using an epidemiological approach and an algorithm with high validity	(194)
2014	HIV infection and its association with an excess risk of clinical fractures: a nationwide case-control study	Case-control	124,655 fracture cases 373,962 controls matched on age and gender	2000	HIV infection is associated with an almost 3-fold increase in fracture risk compared with that of age- and gender-matched uninfected patients	(272)
2014	Ethnic and migrant differences in the use of anti-asthmatic medication for children: the effect of place of residence	Cohort study	Child population in the Capital Region from 0 to 17 years in 2008 (n = 342,403)	2008	Ethnic differences in the use of anti-asthmatic medication were documented, and they cannot be explained by socioeconomic characteristics of place of residence	(273)
2014	ADHD, stimulant treatment in childhood and subsequent substance abuse in adulthood -	Case-cohort study	208 children with ADHD compared with the	Exposure to stimulants 1969-1981	The relative risk (RR) of SUD and alcohol abuse for cases with ADHD, compared to the background	(274)

	a naturalistic long-term follow-up study		background population		population was 7.7 (4.3-13.9) and 5.2 (2.9-9.4), respectively	
2014	Trimethoprim use before pregnancy and risk of congenital malformation: re-analysed using a case-crossover design and a case-time-control design	Case-cross over Case-time-control	685,600	1996-2008	This study corroborates that trimethoprim is a potential teratogen when used 3 months before pregnancy and demonstrates the value of case-only approaches for studying, for example, adverse effects of antibiotics in reproductive epidemiology	(275)
2014	Association between Attention-Deficit Hyperactivity Disorder in childhood and schizophrenia later in adulthood	Case-cohort	208 children with ADHD compared with the background population	Exposure to stimulants 1969-1981	This prospective follow-up study found children with ADHD to be at higher risk of later schizophrenia than controls	(276)
2013	An inventory of European data sources for the long-term safety evaluation of methylphenidate	Methodology study	-	-	-	(277)
2008	Driving forces behind increasing cardiovascular drug utilization: a dynamic pharmacoepidemiological model	Cohort study	All Danish residents January 1996	1996-2006	Age-related increases in treatment intensity and prevalence, rather than population ageing, drove the increasing treatment intensity with cardiovascular drugs	(278)
2004	Drug use among fathers around time of conception: two register-based surveys from Denmark and The Netherlands	Cohort study	56,735 Danish fathers 5859 Dutch fathers	1991-2000	A large proportion of fathers used drugs around the time of conception	(279)
2003	Rising prevalence of diabetes: evidence from a Danish pharmaco-epidemiological database	Cohort study	470,000 people living in the county of Fyn, Denmark	1992-1999	Although prevalence increased (odds ratio: female, 1.026 [95% CI 1.020-1.032]; male, 1.041 [1.036-1.047]), mortality in those treated declined (rate ratio: female, 0.976 [95%CI 0.952-1.001]; male, 0.966 [0.943-0.990])	(280)

2002	Antibiotic prescribing in general practice: striking differences between Italy (Ravenna) and Denmark (Funen)	Cohort study	471,732 Danish inhabitants 350,434 Italian inhabitants	1999	These data show remarkable differences in antibiotic prescribing between Italy and Denmark, and suggest possible overuse and misuse of antibiotics in Italy	(281)
2001	Drug prescribing among Danish children: a population-based study	Cohort study	104,897 children 0-19 year born 1980 and onwards	1998	There is the same skewness of drug consumption among Danish children as among Danish adults, but the types of medication differ	(282)
1999	A one-year population-based study of drug prescriptions for Danish children	Cohort study	95,134 children 0-15 years	1997	The level of exposure to prescribed drugs was considerable at all ages and was highest in early childhood	(283)

1. PubMed search 05-02-2019. The search term "pharmacoepidemiology Danish child" yielded n=34 papers. The search term ""pharmacoepidemiology Danish infant" yielded 18 papers; n=4 of which was not already part of the first search, and n=1 paper from 2019 (excluded). Among the 38 (34+4) studies, n= 5 studies were not about pharmacoepidemiology (5 genetics association studies) (excluded), and n=1 study was about assisted reproduction (excluded). A total of 32 studies including children and other age groups than children were included. One study published both in a Danish and an international medical journal is mentioned only once, leaving 31 papers listed in Table 3.

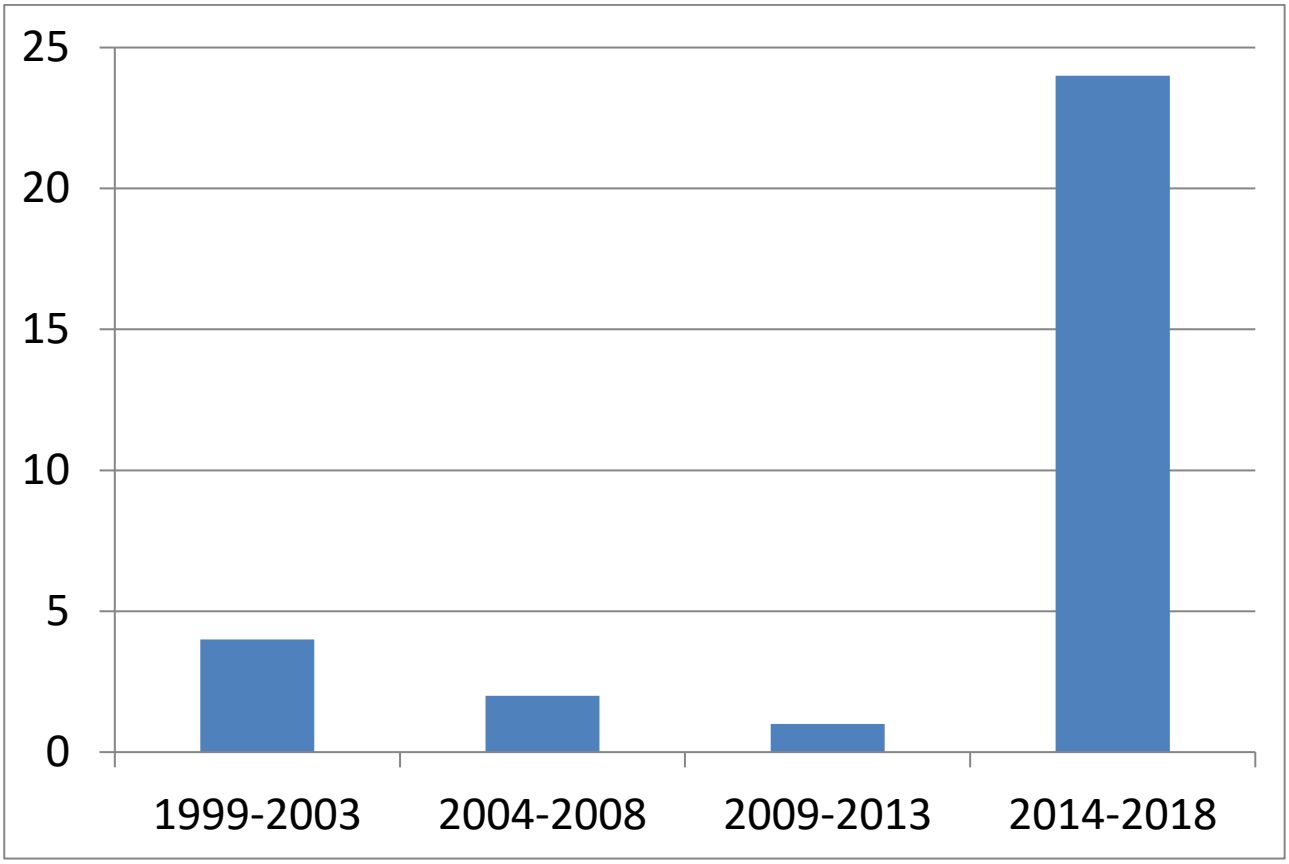


Figure 5. Pharmacoepidemiological studies including Danish children in 5 years intervals since 1999

Strengths

The potential of national and cross-national population-based pharmacoepidemiologic studies with long term follow-up is unique to the Nordic countries. Such studies combine precise information on exposure to a drug with the potential of 100% follow-up for multiple relevant health outcomes and potential side effects in pragmatic real-life study designs with large sample size and consequently high study power inclusive to adjust for confounding and decreased risk of selection bias. The extent of label vs. off-label use can be quantified, making studies, which may be considered ethically challenging in randomised clinical trial designs, feasible, simply because some drugs are used already off-label in populations of children or pregnant women.

Limitations

Confounding by indication (or contraindication) potentially occurs in observational pharmacoepidemiologic studies, including vaccine research. As drugs are indicated, or contraindicated by some medical reason, individuals who are prescribed a medication may be inherently different from those who do not take the drug. Even if the study population consists of subjects with the same disease, there may be an individual difference in the severity and need for medication.

For example, in the study we made on the association between palivizumab and atopic dermatitis, asthma and allergic rhinoconjunctivitis (256). When studying the association between palivizumab and asthma, it was important to consider confounding by indication, since palivizumab is indicated for frail infants at high risk of severe airway infection, hyperreactive airways and asthma. We did in fact observe an increased risk of asthma after palivizumab exposure. However, in further analyses using a propensity score to balance confounding factors no increased risk of asthma was observed indicating that the observed increased risk of asthma was caused by confounding by indication.

An improved design of pharmacoepidemiological studies has been developed to cope with the challenges of confounding by indication: the active comparator, new user design (284), which seeks to emulate the design of a randomised controlled trial.

As also mentioned above, in vaccine studies healthy and wealthy vaccinée bias may be of concern (46;48;211;285-296).

It is a limitation that medication administered at hospitals is not registered at an individual level in Denmark. Only prescribed medication is registered (79;84). Whether the patient takes the medication is unknown.

Discussion

Overall

Register-based research in children is a valuable research tool, which make use of readily available data to generate hypotheses, replicate findings, carry out longitudinal studies, and study pharmacoepidemiology in a real-life pragmatic study setting. The risks of bias and confounding are

well known and can be handled by rigorous design and analyses, and cautious interpretation of the study results. When studies are national, i.e. include all individuals of the population with close to 100% follow-up, the risk of bias is diminished while the study power is optimised. Since data are already available, the register-based based research approach is timely, economic, and ethic.

Ethical considerations

The data in national health registers are collected for administrative purposes. Individuals included in register-based research need not to invest time or take any research related risks.

According to the Danish Data Protection Act (297), register-based research must be notified to and permitted by the institutional representative of the Data Protection Board and can be carried out without further ethical clearance. Informed consent is not required.

The data collection in our registers depends on the trust of the population. Collecting, protecting and using register data are the responsibility of the authorities and the researchers (298). Data are typically accessed, managed and analysed pseudonymised via a safe and password protected data portal. This approach serves to protect against leaks of person-identifiable information.

Scientific inference

The inability to replicate findings in medical research have been subject to discussion both in the scientific and lay press. Ongoingly, the scientific society works on improving research quality, using peer review (299), recommendations and checklists like Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement for observational studies (300-303;303-305), Consolidated Standards of Reporting Trials (CONSORT) for trials (15;306-309), and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement for reviews and meta-analyses (310;311). REporting of studies Conducted using Observational Routinely collected health Data (RECORD) (305;312) represent a guideline for the reporting of observational studies based on routinely collected health register-data. In 2018, a statement regarding the reporting of studies conducted using observational routinely collected health data for pharmacoepidemiology (RECORD-PE) was published (313). The guidelines serve as best practice guidelines representing a minimum standard of items that should be reported in academic manuscripts.

Although there are signs of improvement (314;315), the low replicability lead to questionable recommendations, suboptimal clinical outcomes and biased decisions. Missing focus on rigorous experimental design, low statistical power and overconfidence in favourable p-values are possible explanations of the low replicability (212); all of which probably could be addressed by focus and education in good conduct of research (316). Moreover, the importance of researchers cognitive biases are underappreciated for their influence on scientific results (317). Of overall importance is it that the main role of a scientific experiment is to criticise theories, not to confirm them (13;318).

Perspectives

Register-based research using national health registers allows a wide variety of studies in the paediatric population.

The strength of national register-based research lies in the potential of large sample size, long-term follow-up, and the diminished risk of selection bias in studies where very close to all individuals from a population can be followed-up. Likewise, recall bias is not relevant in register-based studies. Data are readily available, so time and resources used by researchers on register-based studies are limited. Children and families do not need to be disturbed to participate in register-based studies.

The limitations lie in the potential of various biases inherent to observational studies, and the fact that register data are collected for administrative purposes limits the information available.

Register-based research is valuable for research regarding children's health, health service utilisation patterns and long-term consequences of disease, drug use, and vaccination.

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