Cesarean Section and Chronic Immune Disorders

Astrid Sevelsted, MSc[a], Jakob Stokholm, MD, PhD[a,b], Klaus Bønnelykke, MD, PhD[a], Hans Bisgaard, MD, DMSc[a]

abstract

OBJECTIVES: Immune diseases such as asthma, allergy, inflammatory bowel disease, and type 1 diabetes have shown a parallel increase in prevalence during recent decades in westernized countries. The rate of cesarean delivery has also increased in this period and has been associated with the development of some of these diseases.

METHODS: Mature children born by cesarean delivery were analyzed for risk of hospital contact for chronic immune diseases recorded in the Danish national registries in the 35-year period 1977–2012. Two million term children participated in the primary analysis. We studied childhood diseases with a suspected relation to a deviant immune-maturation and a debut at young age. The effect of cesarean delivery on childhood disease incidences were estimated by means of confounder-adjusted incidence rate ratios with 95% confidence intervals obtained in Poisson regression analyses.

RESULTS: Children delivered by cesarean delivery had significantly increased risk of asthma, systemic connective tissue disorders, juvenile arthritis, inflammatory bowel disease, immune deficiencies, and leukemia. No associations were found between cesarean delivery and type 1 diabetes, psoriasis, or celiac disease.

CONCLUSIONS: Cesarean delivery exemplifies a shared environmental risk factor in early life associating with several chronic immune diseases. Understanding commonalities in the underlying mechanisms behind chronic diseases may give novel insight into their origin and allow prevention.

WHAT'S KNOWN ON THIS SUBJECT: Cesarean delivery has previously been associated with increased risk of specific immune diseases in children. The mechanism remains unknown.

WHAT THIS STUDY ADDS: In 1 large population-based cohort, we demonstrate cesarean delivery as a shared risk factor for several immune-related diseases. Such common risk factor suggests early life commonality in the origins of these chronic immune disorders.

[a]*Copenhagen Prospective Studies on Asthma in Childhood, Faculty of Health and Medical Sciences, University of Copenhagen & Danish Pediatric Asthma Center, Gentofte Hospital, University of Copenhagen, Copenhagen, Denmark; and* [b]*Department of Pediatrics, Naestved Hospital, Naestved, Denmark*

Dr Bisgaard, the guarantor of the study, has been responsible for the integrity of the work as a whole, from conception and design to conduct of the study and acquisition of data, analysis, and interpretation of data and writing of the manuscript; Ms Sevelsted was responsible for acquisition, analysis, and interpretation of data and critically reviewed the manuscript; Drs Stokholm and Bønnelykke contributed to data interpretation and critically reviewed the manuscript; and all authors approved the final manuscript as submitted.

The funding agencies have no role in design and conduct of the study; collection, management, and interpretation of the data; or preparation, review, approval of the manuscript, or decision to publish. The corresponding author is the proprietary owner of and had full access to all the data, and had final responsibility for the decision to submit for publication.

www.pediatrics.org/cgi/doi/10.1542/peds.2014-0596

DOI: 10.1542/peds.2014-0596

Accepted for publication Oct 21, 2014

Address correspondence to Hans Bisgaard, MD, DMSci, Copenhagen Prospective Studies on Asthma in Childhood, Health Sciences, University of Copenhagen & The Danish Pediatric Asthma Center, Copenhagen University Hospital, Gentofte, Ledreborg Allé 34, 2820 Gentofte, Copenhagen, Denmark. E-mail: bisgaard@copsac.com

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

Chronic diseases such as asthma, allergy, inflammatory bowel disease, and type 1 diabetes have shown a parallel increase in prevalence during the last decades in westernized countries.[1] Evidence suggests that early life events may be programming these diseases, as demonstrated by changes in disease prevalence in populations immigrating to westernized countries[1] and by identification of perinatal risk factors.[2] This suggests that the parallel increase in prevalence of immune diseases may be due to shared environmental risk factors and disease mechanisms in early life.

The rate of cesarean delivery has also increased in recent decades.[3] Even though the World Health Organization recommends cesarean delivery as indicated choice of delivery mode in less than 15% of births,[4] many developed countries have a much higher prevalence, pointing toward a less strict medical indication for the procedure.[5,6] Cesarean delivery has been linked to the development of asthma and allergic rhinitis,[7–10] as well as other immune disorders[11–16] in the offspring.

We hypothesized cesarean delivery as an example of a shared environmental risk factor for immune-associated diseases. We analyzed children born by cesarean delivery for risk of hospital contact for diseases suspected to be related to a deviant immune maturation and with a debut at young age, including asthma, systemic connective tissue disorders, juvenile arthritis, inflammatory bowel disease, type 1 diabetes, immune deficiencies, psoriasis, celiac disease, and leukemia in the Danish national registries in the 35-year period 1977–2012.

METHODS

The study was based on data from national registries and was approved by the Danish Data Protection Agency (J.no. 2012-41-0388). Subjects were not contacted as a part of the study; hence the ethics committee did not require written informed consent.

Study Cohort

The Danish Civil Registration System (CRS) has registered every person with a citizenship in Denmark since 1968. This provides a unique 10-digit number, encoding date of birth and gender, which is assigned at birth and is used as the identifying number in all Danish registries. Further, the register contains date of emigration.[17]

The Danish Medical Birth Registry has existed since 1973 and contains data on birth weight, parity, mode of delivery, and maternal smoking during pregnancy. The Danish Register of Causes of Death was computerized in 1970 and contains data on date of death.

The Danish National Patient Registry was established in 1977 and contains data on all primary and secondary diagnosis on all in-patient discharges since 1977, and on outpatient admissions since 1994. The diagnoses are based on the *International Classification of Diseases, 8th Revision* (ICD-8 until 1994; *International Classification of Diseases, 10th Revision* [ICD-10] thereafter).[18]

We identified a cohort of all live born children in Denmark in the period January 1, 1973, through January 1, 2012, and used their unique CRS number to link information on gender, parity, birth weight, mode of delivery, and maternal CRS from the Danish Medical Birth Registry; information on date of death from the National Death Registry, information on date of first hospital in- or outpatient admission for any of the predefined diseases (primary or secondary diagnosis) from the Danish National Patient Registry and information on date of migration from the Danish CRS.

Maternal Disease

We obtained information from the Danish National Patient Registry on mother's hospital admission for the specified diseases to adjust the analyses for maternal disease. Only children whose mothers were born after 1952 were included in the analyses.

Exclusion Criteria

Premature children (defined as birth weight below 2500 g) and children missing information on birth weight were excluded from all analyses.

Case Definitions

Cases were identified by the ICD-8 and ICD-10 diagnoses. Nine groups of diseases were investigated. Asthma (ICD-10 J45.x; J46.x), systemic connective tissue disorders (ICD-10 M3x.x), juvenile arthritis (ICD-10 M05.x; M08.x; M09.x; M13.x), inflammatory bowel diseases (ICD-10 K50.x; K51.x), diabetes type 1 (ICD-10 E10.x; E13.x; E14.x), immune deficiencies (ICD-10 D80.x–D89.x), psoriasis (ICD-10 L40.x), celiac disease (ICD-10 K90.0), and leukemia (ICD-10 C91.x–C96.x). Negative control: fractured forearm or elbow (ICD-10 S52.x). A list of the corresponding ICD-8 diagnosis codes is provided in Supplemental Table 2.

Confounders

Confounders were chosen a priori as gender, parity (first child, second child, third child, or more), birth weight ($\geq$2.5 to $<$3.0 kg; $\geq$3.0 to $<$3.5 kg; $\geq$3.5 to 4.0 kg; 4.0 kg or more), attained age (1-year groups), calendar time (3-year groups), season of birth (December to February; March to May; June to August; September to November), maternal age ($\leq$25; 26–30; 31–35; $\geq$36 years), and maternal illness (maternal diagnosis of the disease in question, see above).

Statistical Methods

We investigated the effect of cesarean delivery versus vaginal birth in all children born 1973–2012. Children were followed for hospitalizations from January 1, 1977, where the registry started, or from date of birth if this occurred after January 1, 1977. Children were followed until January 1,

2012, or until age 16 years, migration, or death, whichever came first.

For each disease category, we accumulated person-time and -events (cases) stratified by cesarean delivery and chosen confounders.[19] Thereby we calculated the specific incidence rates (cases per person years).

The overall effects of cesarean delivery on the number of cases in each separate disease category in the complete time period and across the entire age span were estimated with log-linear Poisson regression models offset by the log of person time (years of observation), where any underlying age and calendar time variations for the various disease groups can be taken into account by adjusting for the attained age and calendar year as confounders (3-year intervals were chosen). Further, we add the chosen confounders to obtain the fully adjusted estimates for the effect of cesarean delivery. All confounders were included as categorical variables. The incidence rate ratio (IRR) with 95% confidence interval was calculated to show the effect of cesarean delivery. The population attributable risk fraction (PARF) was calculated from the adjusted IRR (aIRR) estimates as follows: PAR = Pe (RRe−1)/[1 + Pe (RRe−1)], where Pe is the prevalence of the exposure and RRe is the relative risk of disease because of that exposure. Potential changes in the effect were investigated as interaction terms between cesarean delivery and blocks of calendar years (eg, for changes in registration practice).

A significance level of 0.05 is used in all analyses. The data processing was computed with SAS version 9.3 for Windows (SAS Institute, Inc, Cary, NC).

RESULTS

Two and a half million children were born in Denmark in the period 1973–2012. Five percent had low birth weight (birth weight below 2500 g); 15% had missing data on birth weight or other confounders and were excluded from analysis, leaving 1.9 million (80%) children for the primary analysis. The study population was followed from 1977 to 2012 for a total of 23 million person years in the age range 0 to 15 years. Approximately 14% of the study population was delivered by cesarean delivery with a marked increase in the proportion of cesarean deliveries during the observation time (Fig 1). Disease prevalence is presented in Table 1.

The prevalence of several diseases among the mothers was significantly higher if they had ever delivered by cesarean delivery when compared with vaginal delivery. Especially mothers with type 1 diabetes (27%) had an increased risk of cesarean delivery compared with mothers without diabetes type 1 (14%; Supplemental Table 3).

Children delivered by cesarean section had significantly increased aIRR for asthma, systemic connective tissue disorders, juvenile arthritis, inflammatory bowel diseases, immune deficiencies, and leukemia (Table 1). Type 1 diabetes, psoriasis, and celiac disease were not associated with cesarean delivery. Arm fracture (included as "control condition") was not associated with cesarean delivery.

Limiting the children with asthma to those older than 5 years at first contact did not change the conclusion: aIRR 1.16 (1.13–1.19); $P < .0001$.

The effects of cesarean delivery were not impacted by the registry changes in terms of disease classification systems and outpatient registrations (no significant effect modification considering the number of interaction test; data not shown).

The PARF ranges up to 6% (Table 1).

DISCUSSION

Principal Findings of the Study

Cesarean delivery was a shared risk factor for several immune-related

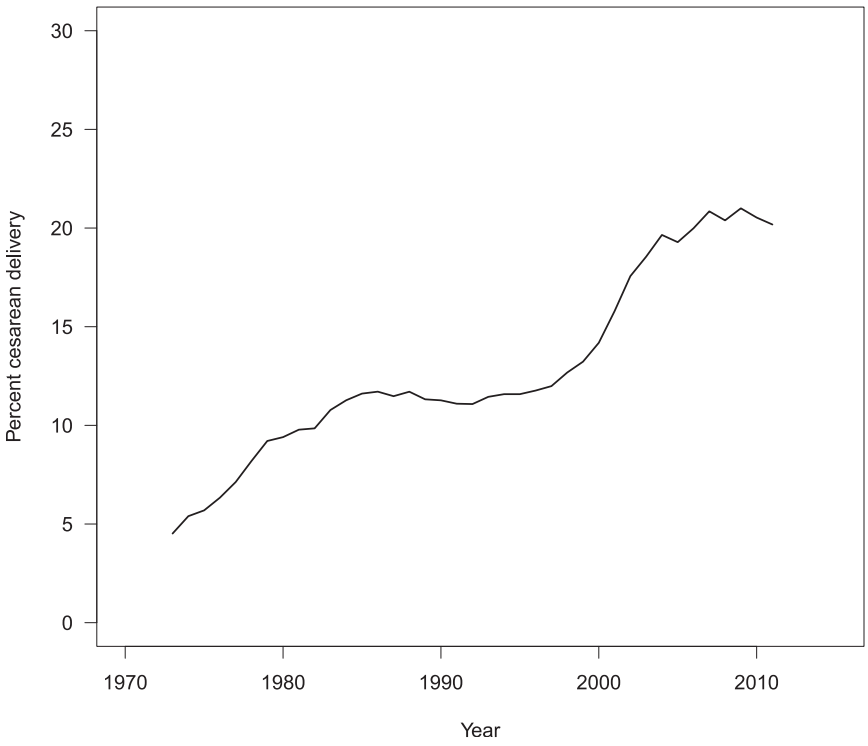

FIGURE 1
Yearly proportion of deliveries by cesarean delivery in relation to birth year. Number of cesarean deliveries has increased over the study period.

TABLE 1 IRRs by Cesarean Delivery in the 35-Year Period 1977–2011 Following 1.9 Million Term Children in the Age Span 0 to 15 Years

	Cases	aIRR (95% Confidence Interval); *P*	PARF (Cases)
Asthma[a]	103 822	1.23 (1.21–1.25); $P < .0001$	3.07 (3187)
Asthma >5 y[b]	48 858	1.16 (1.13–1.19); $P < .0001$	2.19 (1070)
Systemic connective tissue disorders	7498	1.11 (1.04–1.19); $P = .0021$	1.53 (115)
Juvenile arthritis	6946	1.10 (1.02–1.18); $P = .0117$	1.34 (93)
Diabetes type 1	6136	1.01 (0.93–1.10); $P = .82$	—[d]
Inflammatory bowel diseases	2697	1.20 (1.06–1.36); $P = .004$	2.70 (73)
Immune deficiencies	2589	1.46 (1.32–1.62); $P < .0001$	6.09 (158)
Celiac disease	1944	0.99 (0.87–1.14); $P = .89$	—[d]
Leukemia	1631	1.17 (1.00–1.36); $P = .048$	2.31 (38)
Psoriasis	1306	0.98 (0.81–1.18); $P = .81$	—[d]
Arm fracture[a,c]	77 490	0.99 (0.96–1.01); $P = .19$	—[d]

Cases are defined by first in- or outpatient admission to a hospital in Denmark. IRRs are adjusted for age, calendar year, birth weight, parity, gender, season of birth, maternal age, and maternal illness. The PARF is calculated based on an overall prevalence of 14% cesarean deliveries for diseases with significant association to cesarean delivery.

[a] Attained age and calendar year included in 1-y categories.

[b] Attained calendar year included in 3-y and age in 6-y categories.

[c] Not adjusted for maternal disease.

[d] PARF is not calculated for insignificant associations.

diseases including asthma, systemic connective tissue disorders, juvenile arthritis, inflammatory bowel diseases, immune deficiencies, and leukemia. There was no significant association with diabetes type 1, psoriasis, or celiac disease.

Strength and Weaknesses of the Study

Our study was hypothesis driven, searching for a shared risk factor between immune diseases with a debut in children. We did not search all other diagnoses systematically for similar associations because our aim was to exemplify such communality rather than explain individual disorders.

The study base covers 35 years of diagnoses from national registries. The registry on hospitalization covers all admissions and outpatient hospital contacts nationwide.

A priori children with a birth weight below 2500 g were excluded, and all analyses were adjusted for age, calendar year, gender, parity, birth weight, and maternal heredity. By analyzing only children above 2500 g, we hope to get a more comparable group of children, with only the delivery method to differ between them and not an underlying pathology leading to preterm birth.

Particularly, we adjusted for maternal disease of these immune-related diseases, some of which are associated with cesarean delivery (Supplemental Table 3) and could thereby confound an association. After adjustment, the results for type 1 diabetes was no longer statistically significant, but otherwise maternal disease did not materially alter the results.

We included a "negative control" in terms of an analysis of association between cesarean delivery and hospital contact for arm fracture. This demonstrates that the associations seen for other diseases are not caused by a methodological problem of "overregistration" of disease in the children delivered by cesarean delivery.

It may be a limitation to our study that we excluded mild diseases managed in the primary health care sector only. Yet this ascertainment bias is unlikely to influence the conclusion of a common risk factor for the severe chronic diseases.

Diagnostic classification was changed in 1994 from ICD-8 to ICD-10, and registration of outpatient hospitalizations was initiated. The categories used across these different classifications may not be completely congruent. However, the analyses are adjusted for calendar year as a categorical variable, which corrects the main association from time changing effects, and sensitivity analyses did not suggest any effect of this on the results.

Diagnosing asthma in a young child may be inaccurate. We therefore did a sensitivity test of children with a first hospital contact after age 5, where the diagnosis is more robust. The association remained significant.

Interpretation of the Study

Cesarean delivery was a shared risk factor for different immune-related diseases including asthma, systemic connective tissue disorders, juvenile arthritis, inflammatory bowel diseases, immune deficiencies, and leukemia. This suggests that critical events around time of birth initiate a disease trajectory. Such early events may cause an immune aberration leading to a variety of chronic immune diseases presenting later in life. By identifying commonalities between diseases, we may understand mechanisms of the shared "epidemic" seen for these diseases.

Previous studies have revealed individual disorders generally showing associations between cesarean delivery and asthma and allergy,[7–10] inflammatory bowel disease,[11] celiac disease,[12,13] type 1 diabetes,[14] and cancers[15,16] in the offspring. Another register-based study has associated cesarean delivery with a wide range of diagnoses.[20] Our study is the first to reveal cesarean delivery as a common risk factor across several specific immune-related disease categories in the same study and in a nationwide database of children. This reduces the risk of publication bias.

There is increasing evidence that immune-related diseases are programmed in early life as a result of complex gene environment interactions. The prevalence of immune-related diseases is higher in

westernized countries,[21] and immigrant studies reveal that the children of immigrants moving to more westernized countries will acquire the disease risk of westernized countries,[22] indicating the importance of early risk factors associated with western life style. Hygiene, in terms of disturbed early microbial exposure, is hypothesized to be responsible for the increasing prevalence of allergy-related diseases in westernized countries.[23] A similar etiology is suspected behind the increasing prevalence of childhood leukemia,[24] and a recent study revealed an association between allergy and later development of leukemia supporting a potential shared etiology in early life.[25] Reduced cytokine levels at birth have been associated with later development of allergy[26] and atopic predisposition,[27] and children who later developed childhood leukemia also had markedly reduced interleukin-10 levels at birth.[28]

The birth setting around cesarean delivery is different from vaginal birth with respect to several factors including anesthetic agents and antibiotics during birth, physiologic effects on the newborn, and the hospital environment after birth.[29] It may be speculated that the effect from cesarean delivery is mediated by changes in the microbiome of the newborn. The normal delivery canal exposes the child to a composite microbiome different from the one encountered during a cesarean delivery in an operation theater resulting in differences in microbiome of the newborn.[30,31] Furthermore, it has become standard procedure to give prophylactic antibiotics to all women delivering by cesarean delivery to reduce postpartum infections in the mother,[32] which is also likely to affect the microbiome of the newborn child. There are several indications that the diversity and composition of the human microbiome is associated with a variety of diseases such as asthma,[33] allergy,[34] inflammatory bowel diseases,[35] and type 1 diabetes[36] and type 2.[37] However, cesarean delivery entails several other components, which may potentially affect the early environment of the newborn. Biomarkers in the blood in children born by cesarean delivery differ from children born vaginally including lower number of leukocytes, neutrophils, monocytes, and natural killer cells in cord blood,[38,39] and likewise differences in leukocyte composition during the first year of life.[40] Also, stress hormone induction in the fetus is dependent on mode of delivery with a lower production in children born by cesarean delivery,[41] which may affect the immune maturation. Furthermore, pregnancy factors leading to cesarean delivery may already in utero affect the fetus and trigger the progression toward disease.

Because this is an observational study, we cannot rule out that the true casual factor underlying these associations could be a confounding factor related to cesarean delivery. Potential confounders not accounted for in the current study are lifestyle factors associated with maternal request for cesarean delivery or factors increasing the risk of cesarean delivery. Nevertheless, identification of cesarean delivery, or an associated factor, as a potential shared environmental risk factor behind several immune-related diseases is still important. It may give us lead to understand the mechanism and increasing prevalence of these diseases and eventually point to prevention. It is of interest that not all immune-related diseases were affected equally by delivery method, which might suggest different disease pathways. Opposite to some other studies, we did not find association to type 1 diabetes after adjustment for maternal disease. We demonstrated a high prevalence of cesarean delivery among women with type 1 diabetes, which may confound unadjusted results.

Our findings also support the hypotheses that perinatal life is important for later development of chronic diseases, which encourages a research strategy focusing on early life in the origins of chronic diseases.

Furthermore, research targeting the more common immune-related diseases like asthma and allergy may be a relevant approach for understanding the etiology of rare diseases where prospective studies are not feasible. Future research focusing on commonalities in mechanisms behind different disease entities may provide new mechanistic insights and understanding of lifestyle related changes in disease patterns of chronic immune-diseases.

CONCLUSIONS

Cesarean delivery is associated with increased risk of several chronic immune diseases suggesting a shared environmental risk factor in early life. Understanding the underlying disease mechanism may be a key to understanding the origin and increased prevalence of these diseases and promise a perspective for prevention.

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Copenhagen Prospective Studies on Asthma in Childhood (COPSAC) is funded by private and public research funds. COPSAC receives no funding from commercial companies. The Danish Council for Strategic Research, The Lundbeck Foundation, The Pharmacy Foundation of 1991, The Augustinus Foundation, and the Danish Medical Research Council and National Finance Act provided the core support for the COPSAC research.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

REFERENCES

1. Bach J-F. The effect of infections on susceptibility to autoimmune and allergic diseases. *N Engl J Med*. 2002; 347(12):911–920
2. Barker DJP. Human growth and chronic disease: a memorial to Jim Tanner. *Ann Hum Biol*. 2012;39(5):335–341
3. MacDorman MF, Menacker F, Declercq E. Cesarean birth in the United States: epidemiology, trends, and outcomes. *Clin Perinatol*. 2008;35(2):293–307, v
4. World Health Organization. Appropriate technology for birth. *Lancet*. 1985; 2(8452):436–437
5. Althabe F, Sosa C, Belizán JM, Gibbons L, Jacquerioz F, Bergel E. Cesarean section rates and maternal and neonatal mortality in low-, medium-, and high-income countries: an ecological study. *Birth*. 2006;33(4):270–277
6. Cho CE, Norman M. Cesarean section and development of the immune system in the offspring. *Am J Obstet Gynecol*. 2013; 208(4):249–254
7. Thavagnanam S, Fleming J, Bromley A, Shields MD, Cardwell CR. A meta-analysis of the association between Caesarean section and childhood asthma. *Clin Exp Allergy*. 2008;38(4):629–633
8. Renz-Polster H, David MR, Buist AS, et al. Caesarean section delivery and the risk of allergic disorders in childhood. *Clin Exp Allergy*. 2005;35(11):1466–1472
9. Roduit C, Scholtens S, de Jongste JC, et al. Asthma at 8 years of age in children born by caesarean section. *Thorax*. 2009;64(2):107–113
10. Pistiner M, Gold DR, Abdulkerim H, Hoffman E, Celedón JC. Birth by cesarean section, allergic rhinitis, and allergic sensitization among children with a parental history of atopy. *J Allergy Clin Immunol*. 2008;122(2):274–279
11. Bager P, Simonsen J, Nielsen NM, Frisch M. Cesarean section and offspring's risk of inflammatory bowel disease: a national cohort study. *Inflamm Bowel Dis*. 2012;18(5):857–862
12. Mårild K, Stephansson O, Montgomery S, Murray JA, Ludvigsson JF. Pregnancy outcome and risk of celiac disease in offspring: a nationwide case-control study. *Gastroenterology*. 2012;142(1):39–45.e3
13. Decker E, Engelmann G, Findeisen A, et al. Cesarean delivery is associated with celiac disease but not inflammatory bowel disease in children. *Pediatrics*. 2010;125(6). www.pediatrics.org/cgi/content/full/125/6/e1433
14. Cardwell CR, Stene LC, Joner G, et al. Caesarean section is associated with an increased risk of childhood-onset type 1 diabetes mellitus: a meta-analysis of observational studies. *Diabetologia*. 2008;51(5):726–735
15. Cnattingius S, Zack M, Ekbom A, Gunnarskog J, Linet M, Adami HO. Prenatal and neonatal risk factors for childhood myeloid leukemia. *Cancer Epidemiol Biomarkers Prev*. 1995;4(5): 441–445
16. McLaughlin CC, Baptiste MS, Schymura MJ, Zdeb MS, Nasca PC. Perinatal risk factors for neuroblastoma. *Cancer Causes Control*. 2009;20(3):289–301
17. Pedersen CB, Gøtzsche H, Møller JO, Mortensen PB. The Danish Civil Registration System. A cohort of eight million persons. *Dan Med Bull*. 2006; 53(4):441–449
18. Andersen TF, Madsen M, Jørgensen J, Mellemkjoer L, Olsen JH. The Danish National Hospital Register. A valuable source of data for modern health sciences. *Dan Med Bull*. 1999;46(3): 263–268
19. Rostgaard K. Methods for stratification of person-time and events - a prerequisite for Poisson regression and SIR estimation. *Epidemiol Perspect Innov*. 2008;5:7
20. Håkansson S, Källén K. Caesarean section increases the risk of hospital care in childhood for asthma and gastroenteritis. *Clin Exp Allergy*. 2003; 33(6):757–764
21. Beasley R; The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. *Lancet*. 1998; 351(9111):1225–1232
22. Bodansky HJ, Staines A, Stephenson C, Haigh D, Cartwright R. Evidence for an environmental effect in the aetiology of insulin dependent diabetes in a transmigratory population. *BMJ*. 1992; 304(6833):1020–1022
23. Strachan DP. Family size, infection and atopy: the first decade of the "hygiene hypothesis". *Thorax*. 2000;55(suppl 1): S2–S10
24. Wiemels J. Perspectives on the causes of childhood leukemia. *Chem Biol Interact*. 2012;196(3):59–67
25. MacArthur AC, McBride ML, Spinelli JJ, Tamaro S, Gallagher RP, Theriault GP. Risk of childhood leukemia associated with vaccination, infection, and medication use in childhood: the Cross-Canada Childhood Leukemia Study. *Am J Epidemiol*. 2008;167(5):598–606
26. Prescott SL, Macaubas C, Smallacombe T, Holt BJ, Sly PD, Holt PG. Development of allergen-specific T-cell memory in atopic and normal children. *Lancet*. 1999; 353(9148):196–200
27. Følsgaard NV, Chawes BL, Rasmussen MA, et al. Neonatal cytokine profile in the airway mucosal lining fluid is skewed by maternal atopy. *Am J Respir Crit Care Med*. 2012;185(3):275–280
28. Chang JS, Zhou M, Buffler PA, Chokkalingam AP, Metayer C, Wiemels JL. Profound deficit of IL10 at birth in children who develop childhood acute lymphoblastic leukemia. *Cancer Epidemiol Biomarkers Prev*. 2011;20(8): 1736–1740
29. Hyde MJ, Mostyn A, Modi N, Kemp PR. The health implications of birth by Caesarean section. *Biol Rev Camb Philos Soc*. 2012;87(1):229–243
30. Dominguez-Bello MG, Costello EK, Contreras M, et al. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. *Proc Natl Acad Sci USA*. 2010;107(26):11971–11975
31. Adlerberth I, Lindberg E, Aberg N, et al. Reduced enterobacterial and increased staphylococcal colonization of the infantile bowel: an effect of hygienic lifestyle? *Pediatr Res*. 2006;59(1):96–101
32. Smaill FM, Gyte GM. Antibiotic prophylaxis versus no prophylaxis for preventing infection after cesarean section. 2014. *Cochrane Database Syst Rev*. (10);CD007482
33. Bisgaard H, Hermansen MN, Buchvald F, et al. Childhood asthma after bacterial colonization of the airway in neonates. *N Engl J Med*. 2007;357(15):1487–1495

34. Bisgaard H, Li N, Bonnelykke K, et al Reduced diversity of the intestinal microbiota during infancy is associated with increased risk of allergic disease at school age. *J Allergy Clin Immunol*. 2011; 128(3):646–652.e5

35. Cucchiara S, Stronati L, Aloi M. Interactions between intestinal microbiota and innate immune system in pediatric inflammatory bowel disease. *J Clin Gastroenterol*. 2012;46(suppl):S64–S66

36. Mathis D, Benoist C. The influence of the microbiota on type-1 diabetes: on the threshold of a leap forward in our understanding. *Immunol Rev*. 2012; 245(1):239–249

37. Vrieze A, Holleman F, Zoetendal EG, de Vos WM, Hoekstra JBL, Nieuwdorp M. The environment within: how gut microbiota may influence metabolism and body composition. *Diabetologia*. 2010;53(4): 606–613

38. Thilaganathan B, Meher-Homji N, Nicolaides KH. Labor: an immunologically beneficial process for the neonate. *Am J Obstet Gynecol*. 1994;171(5):1271–1272

39. Nikischin W, Peter M, Oldigs HD. The influence of mode of delivery on hematologic values in the umbilical vein. *Gynecol Obstet Invest*. 1997;43(2): 104–107

40. Huurre A, Kalliomäki M, Rautava S, Rinne M, Salminen S, Isolauri E. Mode of delivery - effects on gut microbiota and humoral immunity. *Neonatology*. 2008; 93(4):236–240

41. Gitau R, Menson E, Pickles V, Fisk NM, Glover V, MacLachlan N. Umbilical cortisol levels as an indicator of the fetal stress response to assisted vaginal delivery. *Eur J Obstet Gynecol Reprod Biol*. 2001;98(1):14–17

Cesarean Section and Chronic Immune Disorders

Astrid Sevelsted, Jakob Stokholm, Klaus Bønnelykke and Hans Bisgaard

Pediatrics 2015;135;e92
DOI: 10.1542/peds.2014-0596 originally published online December 1, 2014;

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Cesarean Section and Chronic Immune Disorders

Astrid Sevelsted, Jakob Stokholm, Klaus Bønnelykke and Hans Bisgaard

Pediatrics 2015;135;e92
DOI: 10.1542/peds.2014-0596 originally published online December 1, 2014;