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Caesarean section increases the risk of hospital care in childhood for asthma and gastroenteritis

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Summary

Objective To investigate if caesarean section (CS) increases the risk for childhood asthma and gastroenteritis with reference made to children born with vaginal delivery (VD).

Methods Retrospective study of data from linked Swedish medical service registers – Medical Birth Registry (MBR) and Hospital Discharge Registry (HDR). Data were obtained from women without any background/perinatal morbidity noted, and from children without any neonatal complications. Children that had reached at least 1 year of age and were found in the HDR were considered as cases, whereas children not found in the HDR or hospitalized for other causes than asthma or gastroenteritis were defined as controls. Odds ratios (OR) stratified for year of birth, maternal age, parity and smoking in early pregnancy were calculated. Investigations were made comparing the risk for in hospital treatment for asthma or gastroenteritis in CS children and in VD siblings of CS children. The overall inpatient morbidity in CS and VD children were also investigated.

Results The OR for asthma in CS children was 1.31 [95% confidence interval (CI) 1.23–1.40]. The same OR, 1.31, was found for gastroenteritis (95% CI 1.24–1.38). The OR for CS children having experienced both asthma and gastroenteritis was further increased (1.74, 95% CI 1.36–2.23). The risk for asthma in VD siblings of CS children was not significantly increased, whereas VD siblings experienced a slightly increased risk for gastroenteritis. CS children had an increased overall in hospital morbidity when compared to VD children.

Conclusion There is a significant increase of the risk for developing symptoms of asthma and/or gastroenteritis that motivates admission for hospital care in CS children older than 1 year. It is speculated that a disturbed intestinal colonization pattern in CS children may be a common pathogenic factor.

Keywords asthma, caesarean section, childhood, gastroenteritis

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Introduction

Delivery with caesarean section (CS) disturbs the normal establishment of the intestinal flora of the baby, as compared with the pattern seen after vaginal delivery (VD). After CS there is a delay in the colonization with anaerobic Gram-negative bacteria, lactobacilli and bifidobacteria [1–3], and new data suggest that the abnormal colonization may persist for several months or be permanent [4].

In the developed world there has been a strong increase in the prevalence of allergic diseases over the last decades and focus has been put on increased hygiene and decreased number of infectious episodes as contributive factors [5–8]. The relative lack of challenge to the immune system may cause an imbalance of T helper type 1/2 (Th1/Th2) cell responses that hinder the development of tolerance to allergenic substances [9]. The clinical outcome of these contributive factors could be the observed association between obstetrical complications, CS and subsequent asthma in the offspring [10–12]. Furthermore, the normal intestinal microflora exerts a resistance to colonization by pathogenic microbes [13], indicating that any impairment of the indigenous intestinal ecosystem could also make the host more vulnerable to gastrointestinal infections. In parallel with the increase of allergic disease, there has been a considerable increment in the frequency of CS, recently reported to amount to more than 20% of all deliveries in several countries [14]. These circumstances, stating both a chronological and biologically plausible relationship, provide a rationale for hypothesizing an association of CS with an increased risk for asthma and gastrointestinal infections in the child.

The aim of the present study was to investigate if analysis of data from Swedish medical service registers could support this hypothesis. Primarily, we chose to study if CS children were at increased risk for being treated as inpatients, with the specific diagnoses of asthma or gastroenteritis. In order to detect putative confounders, thorough investigations were made comparing the risk for asthma/gastroenteritis in VD siblings of children born with CS and comparing the overall inpatient morbidity in CS and VD children.

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Materials and methods

Infants born in 1984–96 were identified from the Medical Birth Register (MBR) [15]. The MBR is kept by the National Board of Health and Welfare and contains medical information on nearly all deliveries in Sweden (coverage about 99%). Standardized record forms are used at all antenatal clinics, all delivery units and at all paediatric examinations of newborn infants in the maternity ward. Copies of these forms are sent to the National Board of Health and Welfare where they are computerized.

The Swedish Hospital Discharge Registry (HDR) contains information on diagnoses (before 1987 ICD8, 1987–1996 ICD9, 1997 and onwards ICD10) and operation codes of all inpatients admitted to any Swedish hospital. The HDR 1985–1997 was linked with the MBR 1984–1996, and infants who were at least 1 year of age at the hospitalization and were given a diagnosis of asthma (493, J45), or gastroenteritis UNS (009, A09) were regarded as cases. Infants who were not identified from the HDR were included in control group A (infants never hospitalized), whereas infants who were hospitalized after 1 year of age and never had been diagnosed with asthma or gastroenteritis were included in control group B. All analyses were based on infants, regardless of numbers of hospitalizations.

All cases and controls were divided into four groups: (i) vaginally (non-instrumentally) delivered, (ii) emergency caesarean section, (iii) elective caesarean section, (iv) delivered with the aid of forceps or vacuum extractor (VE). Only mothers for whom no information of asthma/chronic lung disease (or any other disease) was recorded at the first antenatal visit were included. In order to reduce confounding due to circumstances which could lead to decisions of instrumental delivery, all children who fulfilled any of the following criteria were excluded from the analyses: birth weight (< 2500 g or > 5000 g), multiple births, pre-term (< 37 completed weeks), infants small for gestational age (< -2SD below expected birth weight) [16], and infants with Apgar score at 5 min below nine. Infants with any diagnosis indicating complications during the perinatal period, infants with a diagnosis of any congenital malformation (either diagnosed at birth or later when treated as inpatient) and infants who died before 1 year of age were also excluded. The numbers of the source population, exclusions and study population are shown in Table 1.

In the analysis of asthma or gastroenteritis in VD siblings to CS children, all VD infants, born in 1984–1996, with at least one VD sibling (but no brother or sister delivered by CS) were included in the reference group; the exposed group consisted of VD infants, born in 1984–1996, with at least one brother or sister delivered by CS. The same exclusion criteria as mentioned above were used. The identification of siblings was possible by using the unique identification number of each woman.

Information on maternal educational level was included by linking the MBR with the Register of Education kept by Statistics Sweden. The latter register contains information on the educational level (nine years of compulsory school included) of each woman and the educational level on 1 January 1996 was linked from it. Thus, the educational level used in this study to estimate socioeconomic status does not necessarily refer to the actual educational length of each woman at the time she was giving birth. This makes it possible to estimate socioeconomic status also for young women. The MBR also contains prospectively collected information on smoking habits in early pregnancy. All odds ratios (OR) were calculated using Mantel–Haentzel's technique [17]. The varying observation time was throughout the analyses controlled for by stratification for year of birth. Stratification was also made for, gender, maternal age (five year classes), parity (1–4+) and educational level (unknown, < 10 years, 10–12 years, 13–14 years, and ≥ 15 years), gestational duration and county of delivery. The latter two variables did not alter the risk estimates, and therefore they were not considered as confounders in the final analyses. Also, 95% confidence intervals (CI) were estimated using Miettinen's method [18].

Tests of homogeneity of the OR across strata were based on weighted sums of the squared deviations of the stratum-specific log ORs from their weighted means. In order to detect putative linear trends in stratified ORs along an independent variable x,

Table 1. Number of the source population, exclusions, and study population by admission to hospital

	Admitted for asthma	Admitted for gastroenteritis	Never admitted as inpatients	Admitted for other reasons than asthma or gastroenteritis
Source population, total	22 606	32 914	893 525	316 918
Exclusions				
Apgar score < 9	1915	2286	46 944	21 723
Deaths (age 0–364 days)	0	0	1853	0
Multiple births	549	727	14 870	6158
Neonatal diagnoses*	5387	7238	130 153	76 130
Maternal diagnoses†	395	371	10 123	2209
Birth weight < 2500 g or > 5000 g	135	190	4475	1656
Gestational age < 37 or > 44 weeks	262	328	8172	3199
Infant gender unknown	0	2	69	13
Maternal smoking unknown	905	1395	38 732	13 320
Maternal age unknown	0	0	233	0
Study population	13 058	20 377	637 901	192 510

Admissions to hospital are only counted in infants more than 1 year of age. *Any diagnosis indicating complications during the perinatal period, or diagnosis of any congenital malformation (either diagnosed at birth or later when treated as inpatient). †Mothers for whom information of asthma/chronic lung disease or any other disease is reported.

weighted linear regression analyses of the log (OR) were carried out (Appendix A).

As a complement to the ORs from the Mantel–Haentzel analyses, Cox regression analyses (Gauss^{TM}, Aptech Systems Inc., Maple Valley, WA, USA, http://www.aptech.com) were performed to estimate proportional hazards. The results from the Cox regression analyses were obtained after adjustment for the same confounders as were stratified for the Mantel–-Haentzel analyses. Maternal age was entered as a continuous variable, whereas the other possible confounders were entered to the models as class-variables. Only the first hospitalization of each child was considered.

Results

Introductory analyses (Table 2) where made in order to detect risk factors for asthma or gastroenteritis, necessary to control for when evaluating CS as a risk factor for any of these conditions. Weak, but statistically significant, associations were found between low maternal age at delivery and childhood inpatient treatment with a diagnosis of asthma or gastroenteritis. However, for infants treated for asthma, the distribution of maternal age at delivery did not differ from the corresponding distribution among children who had been admitted to hospital for other reasons than asthma or gastroenteritis (control group B). First-born children seem to be at an increased risk of obtaining a diagnosis of gastroenteritis, but of a decreased risk of a diagnosis of asthma. A strong, statistically significant, association was found between maternal smoking in early pregnancy and childhood inpatient treatment for asthma, whereas no association was indicated between maternal smoking and childhood gastroenteritis. Compared with control group B, children admitted for gastroenteritis were less exposed to maternal smoking during pregnancy. Children of mothers with low educational level seem to be of a somewhat increased risk of childhood inpatient treatment for asthma as well as gastroenteritis, but the educational level of the mothers of

Table 2. Characteristics of children treated as inpatients with a diagnosis of asthma or gastroenteritis

	Asthma $n = 13\,058$			Gastroenteritis $n = 20\,377$			Controls	
							$n^A = 637\,901$	$n^B = 192\,510$
	%	OR^A	OR^B	%	OR^A	OR^B	%	%
Maternal age at delivery (years)								
< 20	3.2	1.3‡	1.0	3.3	1.3‡	1.0	2.3	3.3
20–24	23.9	1.1‡	1.0	25.5	1.1‡	1.0	20.9	25.0
25–29	37.7	Reference		37.5	Reference		38.0	37.7
30–34	24.5	0.9‡	1.0	23.9	0.9‡	1.0	26.9	23.8
35–39	9.2	0.9‡	1.0	9.0	1.0	1.1†	10.1	8.6
≥ 40	1.5	0.8*	0.9	1.6	1.0	1.1†	1.8	1.6
Maternal parity at delivery								
1	37.5	Reference		44.4	Reference		39.4	40.1
2	37.8	1.1	1.1†	34.7	0.9‡	0.8‡	37.4	36.8
3	17.4	1.1‡	1.1†	14.9	0.8‡	0.8‡	16.5	16.4
4+	7.4	1.2‡	1.1*	6.0	0.8‡	0.8‡	6.7	6.7
Maternal smoking in pregnancy								
1–9 cig./day	19.6	1.5‡	1.3‡	15.4	1.0	0.9‡	14.0	17.2
≥ 10 cig./day	13.3	1.7‡	1.4‡	9.1	1.0	0.9‡	8.2	10.7
Non-smoking	67.1	Reference		75.4	Reference		77.7	72.1
Maternal educational level								
Unknown	4.0	0.6‡	0.9	3.1	0.6‡	1.0	11.4	3.1
≤ 9 years	19.2	1.1†	1.0	17.4	1.1‡	1.0	14.2	17.9
10–12 years	53.3	Reference		54.1	Reference		48.4	53.9
13–14 years	15.0	1.0	1.0	15.8	1.0	1.0	15.4	15.7
≥ 15 years	8.6	0.9‡	1.0	9.6	0.9‡	1.0	10.5	9.3
Child's gender								
Male	63.3	1.9‡	1.4‡	50.4	1.1‡	0.8‡	47.6	54.9
Female	36.7	Reference		49.6	Reference		52.4	45.1

For each variable, the level with the largest number was selected as reference category. The results from comparisons with two different control groups are shown. The first control group (A) contains children, not treated as inpatients, whereas control group (B) consists of infants treated as inpatients for any other condition than asthma or gastroenteritis. Year of birth, maternal age, parity, smoking, maternal educational level, and infant gender were considered as potential confounders and were controlled for. *$P < 0.05$. †$P < 0.01$. ‡$P < 0.001$.

infants treated for asthma or gastroenteritis did not differ from the corresponding level among mothers of infants who were hospitalized for other reasons. Boys were more likely than girls to be hospitalized for asthma, but compared to children who were admitted as inpatients with other diagnoses than asthma or gastroenteritis, boys were less likely than girls to be hospitalized for gastroenteritis.

All variables that were evaluated as putative risk factors for asthma and/or gastroenteritis are known to be associated with route of delivery. Thus, the results shown in Table 2 indicate that the listed variables must be regarded as possible confounders in the investigation of the influence of route of delivery on the incidence of asthma and/or gastroenteritis.

Table 3 shows the number of children who were treated in hospital with a diagnosis of asthma and/or gastroenteritis and children not treated as inpatients, with route of delivery indicated. Using infants who were never admitted as in patients as control group, rather strong, statistically significant, associations were detected between CS and treatment as inpatient in childhood with a diagnosis of asthma or gastroenteritis. These associations remained statistically significant but were less pronounced when infants who were treated for other reasons than asthma or gastroenteritis were used as controls (control group B). The OR associated with elective CS were somewhat stronger than that for acute CS (P-value for homogeneity = 0.06). With gastroenteritis, the ORs associated with elective or acute CS were of similar magnitude. No significant heterogeneity over strata was detected. Stratification for gestational duration, county or delivery unit did not substantially change the risk estimates. A weak, but statistically significant, association was detected between delivery with the aid of VE/forceps and asthma or gastroenteritis, respectively. Cases were also analysed with regard to in-hospital treatment for asthma and gastroenteritis during the study period. OR for CS children having experienced both diagnoses was further increased in comparison with OR for either of the diagnoses.

Cox regression analyses were performed as a complement to the Mantel–Haentzel analyses. Compared to children who were never hospitalized (control group A), the adjusted, proportional hazards for CS were 1.35 (95% CI 1.27–1.44), and 1.31 (95% CI 1.24–1.37) among infants hospitalized for asthma or gastroenteritis, respectively. When compared to children hospitalized for other reasons (control group B), the corresponding estimates were 1.15 (95% CI 1.08–1.23) and 1.11 (95% CI 1.06–1.17), respectively. The point-estimates from the Cox analyses were found to be almost identical to the Mantel–Haentzel estimates.

VD siblings to CS children were not more likely than infants whose mothers had at least two VDs but hitherto never experienced a CS, to be treated as inpatient with a diagnosis of asthma (Table 4). The OR for gastroenteritis was somewhat elevated for VD siblings to CS children, at least when infants who were never hospitalized were used as controls. A weak but statistically significant association was found between VD infants with sibling(s) delivered by CS and any treatment as in patient.

Table 3. Number of children treated as inpatients with a diagnosis of asthma or gastroenteritis and OR for each certain route of delivery as specified

	n	OR^A	95% CI	OR^B	95% CI
Asthma 493, J45					
Caesarean section, total	1120	1.31	1.23–1.40	1.14	1.07–1.22
Acute	654	1.26	1.16–1.37	1.08	0.99–1.18
Elective	466	1.38	1.26–1.52	1.23	1.11–1.36
Instrumental deliveries (VE or forceps)	632	1.10	1.01–1.19	1.07	0.98–1.16
Non-instrumental vaginal deliveries	11 306	Reference		Reference	
Gastroenteritis UNS 009, A09					
Caesarean section, total	1739	1.31	1.24–1.38	1.13	1.07–1.19
Acute	1085	1.31	1.23–1.40	1.13	1.06–1.21
Elective	654	1.30	1.20–1.41	1.13	1.04–1.24
Instrumental deliveries (VE or forceps)	1033	1.07	1.00–1.14	1.02	0.95–1.09
Non-instrumental vaginal deliveries	17 605	Reference		Reference	
Asthma and Gastroenteritis					
Caesarean section, total	72	1.74	1.36–2.23	1.50	1.17–1.94
Acute	44	1.78	1.31–2.42	1.48	1.07–2.03
Elective	28	1.64	1.11–2.43	1.54	1.03–2.30
Instrumental deliveries (VE or forceps)	26	0.92	0.61–1.38	0.89	0.59–1.34
Non-instrumental vaginal deliveries	515	Reference		Reference	
Controls				Control Group A	Control Group B
Caesarean section, total				43 749	14 694
Acute				26 020	9285
Elective				17 729	5409
Instrumental deliveries (VE or forceps)				29 958	9088
Non-instrumental vaginal deliveries				564 194	168 728

The ORs (with 95% CI) were obtained after stratification for year of birth of the child, gender, maternal age and parity at delivery, maternal smoking in early pregnancy, and maternal educational level. Two different control groups were used. The OR^As were obtained using infants not admitted to hospital as control group whereas the OR^Bs were obtained using infants admitted for other reasons than asthma or gastroenteritis as control group. Control Group A: children not treated as inpatients. Control Group B: children treated for reasons other than Asthma or Gastroenteritis.

Table 4. Number of vaginally delivered children treated as inpatients with a diagnosis of asthma or gastroenteritis by presence of CS sibling

	VD sibs to CS children (*n*)	VD sibs to VD children (*n*)	OR[A]	95% CI	OR[B]	95% CI
Asthma	239	7044	1.05	0.92–1.20	0.98	0.86–1.12
Gastroenteritis	387	10 909	1.12	1.01–1.25	1.05	0.94–1.17
Treated as inpatients, not for asthma or gastroenteritis (control group B)	3578	104 044	1.08	1.04–1.12	–	–
Children not treated as inpatients (control group A)	11 181	345 433	Reference			

The risk estimates for VD siblings to CS children to be treated for asthma or gastroenteritis, respectively, compared with the corresponding risk for VD siblings to VD children (without any brother or sister delivered by CS). ORs (with 95% CI) after stratification for year of birth of the child, and maternal age and parity at delivery. For all infants, the same exclusion criteria as described in Material and methods were used.

Table 5. Number of children treated as inpatients by route of delivery and diagnosis

Diagnosis (ICD 9; ICD 10)	Caesarean section	Vaginal delivery	OR	95% CI
Infectious diseases (001–139, A00–B99)	3678	39 225	1.25	1.20–1.29
Neoplasms (140–239, C00–D48)	233	2552	1.20	1.05–1.38
Endocrine, nutritional and metabolic diseases (240–279, E00–E90)	431	4616	1.23	1.11–1.36
Diseases of blood and blood-forming organs (280–289, D50–D89)	284	3204	1.18	1.04–1.33
Mental and behavioural disorders (290–319, F00–F99)	274	2689	1.36	1.20–1.55
Diseases of the nervous system, eye and adnexa, ear and mastoid process (320–389, G00–H99)	2216	23 879	1.26	1.21–1.32
Diseases of the circulatory system (390–459, I00–I99)	95	976	1.03	1.06–1.63
Diseases of the respiratory system (460–519, J00–J99)	6924	73 826	1.28	1.24–1.31
Diseases of the digestive system (520–579, K00–K93)	1673	19 051	1.17	1.11–1.23
Diseases of the genitourinary system (580–629, N00–N99)	834	9358	1.19	1.10–1.27
Diseases of the skin and subcutaneous tissue (680–709, L00–L99)	500	5886	1.14	1.04–1.25
Diseases of the musculoskeletal system (710–739, M00–M99)	454	5437	1.12	1.01–1.23
Symptoms and unspecified conditions not elsewhere classified (780–790, R00–R99)	3166	35 060	1.20	1.16–1.25
Injury, poisoning, external causes (800–999, S00–T99)	3779	46 486	1.11	1.08–1.15
Treated as inpatient with any of conditions above	16 994	191 671	1.19	1.17–1.22
Children not treated as inpatients	43 749	564 194	Reference	

OR for caesarean section for each diagnosis as specified. ORs with 95% CI after stratification for year of birth, maternal age and parity at delivery.

Despite the fact that only children without known neonatal complications were included, children delivered by CS were found to be of significantly higher risk to be treated in hospital, all diagnoses considered, in their childhood compared to non-instrumental vaginally delivered children (OR 1.19, 95% CI 1.17–1.22; Table 5). However, as shown in Table 3, compared to children treated in hospital with other diagnoses, children with a diagnosis of asthma or gastroenteritis were significantly more likely to have been delivered by CS.

Discussion

The present data show a 30% increase in the risk for developing symptoms of asthma or gastroenteritis that motivates admission for hospital care in CS children older than 1 year. The results support the hypothesis that CS is associated with an increased risk for subsequent allergic manifestations in the child and that an ecological disturbance of intestinal colonization could be a common contributive pathogenic factor.

A possible link between obstetric complications, including CS, and subsequent symptoms of allergic disease in the offspring has been demonstrated by others [11, 12, 19, 20]. Maternal asthma increases the risk for asthma in the child [21, 22] and pregnant women with asthma are at an increased risk for obstetric complications and caesarean section [23, 24]. Because of these strong confounders, we primarily excluded all mothers with a history of asthma/lung disease (or any other disease) and all infants with any state of compromised health after delivery. With the availability of population-based data, the design of the present study still allows conclusions to be made from a very large cohort of mothers and infants of optimal health, reducing the role of genetic predisposition or perinatal morbidity that could coincide with an increased risk for developing asthma during childhood. The fact that VD siblings of CS children were not at increased risk for asthma strengthens the hypothesis by providing control for hereditary, socioeconomic and environmental factors.

There is clinical evidence that the characteristics of the gut flora differ between normal and allergic infants [25, 26], as well as experimental research showing the importance of the normal intestinal microflora for the development of oral tolerance [27, 28]. In addition, specific probiotic bacteria can directly enhance intestinal epithelial barrier function [29] and modulate

the expression of genes involved in different important intestinal functions such as nutrient absorption and epithelial maturation [30]. These results cohere with prophylactic and therapeutic clinical studies with per oral supplementation of probiotic bacteria that allay allergic symptoms in treated infants [31, 32]. There is also evidence that early antibiotic treatment, disturbing the ecological balance of the gut microflora, could predispose for allergic disease [33, 34]. Thus, there exist different pieces of suggestive evidence that converge in support of the association between allergic disease and abnormal intestinal microbial colonization.

Gastroenteritis was also increased in CS children, and gastroenteritis was significantly more common in CS children than in children hospitalized for other causes. A tentative explanation for the association between gastroenteritis and CS could be that the altered intestinal flora exerts an inferior colonization resistance to microbial pathogens [13]. Further indirect support in favour of the disturbed intestinal microflora as a risk factor for enteric infection is the fact that an adverse perinatal outcome, e.g., low birth weight – presumably associated with an increased frequency of CS and antibiotic treatment – increases the risk for subsequent hospitalization for gastroenteritis [35]. Infectious diarrhoea can also be mitigated by treatment with probiotic bacteria, an effect that may be exerted by immunological mechanisms [36]. The OR for gastroenteritis in VD siblings to CS children barely reached significance, whereas the OR for asthma in VD siblings did not. Increased exposure for contagious gastroenteritis can be expected to make also VD siblings of CS children increasingly affected. Hence, the strength of sibling morbidity for control of the effect of CS may be reduced for this disease.

The combined risk for CS children to experience in hospital episodes because of both asthma and gastroenteritis was further increased. If there is a common pathogenic factor to both conditions, such an increased risk could be anticipated. However, it is also conceivable that asthmatic children are frequently treated with antibiotics that may cause symptoms of diarrhoea during hospitalization.

Other causes of the observed associations must also be sought. There is some evidence that CS children are breast-fed to a lesser degree than are VD children [37]. Presumably, the decreased breastfeeding observed with CS mothers reflects a higher incidence of underlying maternal morbidity in this group as a whole. Considering that only mothers and infants without any denoted morbidity were included in the present study, it could be surmised that the prerequisites for intact breastfeeding were more favourable. Still, it is conceivable that a relatively shorter period of breastfeeding could confound our results and generate an increase in the incidence of allergic disease and gastroenteritis in the infants [38, 39]. Unfortunately, there are no register data available on feeding habits in the registers employed.

VD siblings to CS children showed an overall increased tendency to be hospitalized during childhood as compared to VD children without CS siblings. The mother who has had a CS may be more prone to demand or desire medical intervention not only for herself but also for her children. This fact could be a serious confounder when studying long-term morbidity in childhood in relation to mode of delivery. For many diagnostic groups, there was an increased risk for hospitalization in CS children (Table 5), a finding that to some extent supports the existence of such a confounder. On the other hand, the possibility that CS may increase the risk for various childhood conditions that motivate hospitalization could not be ruled out. Hence, in the study of asthma, gastroenteritis and CS, a bias towards unity could be expected if sick controls were used instead of healthy controls. On the other hand, by using healthy controls, the risk estimate may not only be a measurement of the risk increase for the specific condition, but can also inherit the overall risk increase for hospitalization in children born by CS. However, for the specific diagnoses of asthma and gastroenteritis, there was a significant association with CS when the comparison was made to either sick (for other reasons) or healthy controls. In VD siblings there was no significant association with asthma regardless of the control compared with, indicating that CS *per se* increases the risk for asthma.

The finding that vaginal delivery by vacuum extraction was associated with asthma in the child aligns with previous observations that obstetrical complications increased the risk for childhood asthma [10, 12]. In theory, this association could be due to confounding if the case group contained infants who suffered from neonatal unrecognized disorders that led to admission for hospital care later in life. An increased head circumference – not unlikely to be associated with increased use of vacuum extraction at delivery – of the newborn has also been associated with increased serum IgE and asthma [40–42] generating the hypothesis that during fetal life a 'programming' occurs that could influence future morbidity in the individual [43]. Associations between obstetrical complications and/or CS have been demonstrated for an array of subsequent conditions such as vascular abnormalities [44], diabetes [45] and behavioural/psychiatric diseases [46, 47]. In the present study we also found significant correlation to several diagnostic groups coinciding with CS. These results may provide additional background for the generation of new hypotheses and illustrate the complexity of possible relationships between obstetric complications, mode of delivery and subsequent morbidity in the child/adult. Our data also show that in families where one of the children has been born with CS, there is a slightly increased 'risk' for all the children in the family to be cared for as in patients. This fact could possibly reflect an increased propensity of these parents to seek medical advice for their children.

The validity of diagnoses is an inherent problem in retrospective register studies. In Sweden, hospital treatment of children for asthma and gastroenteritis occur exclusively in paediatric wards and diagnoses are attested by a senior doctor formally responsible for the care of the child. These routines ascertain a reasonable accuracy of the diagnoses given. In theory, losses to follow-up could also influence the results. Such losses could be due to death or emigration, both of which occur very rarely, and it is not plausible that these factors could influence the risk estimates studied.

Environmental factors that influence the prevalence of asthma include an urban/rural setting, with the rural environment being protective [48]. In the present study, we did not explicitly address this question, nor do we believe that it could be confounding, as stratification for county of birth did not affect the results of the introductory analyses.

Family size and socioeconomic background are linked to the incidence of allergic disease in the offspring. There is a strong inverse relationship between hayfever/eczema and the number of siblings in the family, but with asthma this relationship is not

unanimous [49]. In contrast to the study of Wickens et al. [50], our data show a slightly increased risk for childhood asthma as the parity of the mother increases, inferring that an early order of birth would rather be a protective factor for asthma, at least in CS children. Our study included only mothers without a recognized history of asthma/chronic lung disease. It is conceivable that maternal asthma, with relatively strong genetic penetration to the offspring [21, 22] and early debut in the child, influences family planning in favour of fewer children. If so, such families would have been excluded in the present investigation.

A late order of birth was associated with a decreased risk for gastroenteritis in CS children. Although a larger group of siblings would increase exposure to contagious agents, it may be assumed that parents of a large sibship would be more confident in coping with the problem of gastroenteritis without seeking medical advice. A lower parental socioeconomic background similarly exerts a protective role on hayfever/eczema in the children that is not consistently observed with asthma [49]. In the present study, the risk for both asthma and gastroenteritis was inversely related to maternal educational level. In coherence with other studies, our data show an increased incidence of asthma in boys and a correlation to maternal smoking during pregnancy [20, 51, 52]. Boys also more frequently suffered from gastroenteritis, but the latter diagnosis was not influenced by maternal smoking.

The present investigation thus supports the possibility that the increased frequency of CS may be a contributive factor to the increased prevalence of childhood asthma in Western societies. This association may give further arguments for obstetricians and midwives when advising pregnant women on the preferred route of delivery [53, 54].

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Appendix A

In order to detect putative linear trends in stratified ORs along an independent variable x, weighted linear regression analyses of the log (OR_i)s were carried out. Let $x_m = \Sigma\omega_i x_i / \Sigma\omega_i$, where $\omega_i = 1/V(\log(OR_i^*))$, be the weighted averages of the x_i : s, and y_m the corresponding weighted average of the $y_i = \log(OR_i^*)$s. To estimate the slope β in the regression equation $\log(OR_\chi) = y_m + \beta(x - x_m)$, let $S_{xy} = \Sigma\omega_i(x_i - x_m)(y_i - y_m)$. Then $\beta^* = S_{xy}/S_{xx}$ has 95% confidence limits $\beta^* \pm 1.96/\sqrt{S_{xx}}$.