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RESEARCH PAPER

Risk factors for congenital hydrocephalus: a nationwide, register-based, cohort study

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ABSTRACT

Objectives To investigate the associations between isolated congenital hydrocephalus (CHC) and maternal characteristics, maternal medical diseases, and medicine intake during pregnancy as well as birth characteristics of the child in a retrospective, register-based, nationwide cohort study. Furthermore, to identify the risk factors unique for isolated CHC as compared to syndromic CHC.

Methods We established a cohort of all children born in Denmark between 1978 and 2008. Information on CHC and maternal medical diseases were obtained from the National Patient Discharge Register, maternal intake of medicine during pregnancy from the National Prescription Drug Register, and birth characteristics of the child from the Danish National Birth Register. Rate ratios (RR) of isolated and syndromic CHC with 95% CI were estimated using log-linear Poisson regression.

Results In a cohort of 1 928 666 live-born children, we observed 1193 cases of isolated CHC (0.062/1000) born children. First-borns had an increased risk of isolated CHC compared to later-borns (1.32 95% CI 1.17 to 1.49) (0.72/1000 born children). First trimester exposure to maternal use of antidepressants was associated with a significantly increased risk of isolated CHC compared to unexposed children (RR 2.52, 95% CI 1.47 to 4.29) (1.5/1000 born children). Risk factors also found for syndromic CHC were: Male gender, multiples and maternal diabetes.

Conclusions The higher risk for isolated CHC in first-born children as well as behavioural aspects and comorbidities associated with maternal use of antidepressants, should be the targets for future research. Potential biological pathways by which antidepressants may cause hydrocephalus remain to be elucidated.

INTRODUCTION

Congenital hydrocephalus (CHC) is a condition defined by a pathological accumulation of cerebrospinal fluid in the ventricular system due to impaired balance between formation and absorption of cerebrospinal fluid. CHC often requires surgical intervention and life-long treatment with multidisciplinary involvement. Despite being one of the most frequent congenital malformations of the central nervous system, very little is known about its aetiology.

Genetic as well as environmental risk factors are thought to be of importance. A number of pregnancy-related potential risk factors have been suggested and include maternal intake of contraceptive medicine, alcohol consumption during pregnancy, certain infections and pregestational diabetes.[1–5] However, these findings have been inconsistent or contradictive in previous case-control studies and small cohort studies. We therefore established a nationwide cohort study to investigate potential maternal and pregnancy-related risk factors using the unique Danish registers.

The specific aims of this study were to investigate the associations between isolated CHC (eg, children diagnosed with CHC as the only congenital malformation) and maternal characteristics, maternal medical diseases, and medicine intake during pregnancy as well as birth characteristics of the child. Furthermore, to identify the risk factors unique for isolated CHC by comparison with the corresponding risks for syndromic CHC (eg, children with other congenital malformations).

METHODS

Establishment of the study cohort

Using information from the Civil Registration System, we established a cohort comprising all persons born in Denmark from 1978. All residents living in Denmark since 1968 have been assigned a personal identification number (PIN) in the Civil Registration System.[6] This register contains information on gender, parents, date and place of birth, and continuously updated information on date of death and emigration. The individuals included in the cohort were identified by the PIN, which further allowed linkage across the various Danish population-based health registers.

Identification of CHC cases

The etiologic subgroup of primary interest was isolated hydrocephalus cases defined as congenital cases without a known, likely causative aetiology or syndrome diagnosis (ie, isolated CHC).

By using the PIN, information on isolated CHC was obtained by linkage to the Danish National Patient Register (DNPR), a mandatorily reportable nationwide register of all hospital discharge diagnoses of inpatients and operations performed since 1978. From 1995 all outpatients were registered as well. Specifically, the following diagnostic codes according to the International classification of disease (ICD), eighth revision (ICD-8) up to 1993, and tenth revision (ICD-10) from 1994–2008, were used to extract the hydrocephalus cases from the DNPR: ICD8 74200, 74201, 74208, 74209, 34793–5; and ICD-10 Q03x, G910-G912, G918-G919. These diagnoses are specified in the online supplementary eAppendix. Individuals with

a diagnosis of causative CHC (ie, caused by underlying tumour, infection, traumatic or perinatal intracranial haemorrhage, etc) were excluded from the cohort. Individuals with a diagnosis of spina bifida were excluded as well. Only individuals diagnosed with CHC within the first year of life were included.

In order to detect risk factors unique for isolated CHC, we performed similar analyses of the associations between the identified risk factors and syndromic CHC. Syndromic CHC was defined as CHC cases having other malformations inside or outside the CNS and/or known chromosome anomalies (ie, including Arnold Chiari or Dandy Walker syndrome), retrieved by the following diagnostic codes: ICD-8 740, 741x, 743x-75x, ICD-10 Q00-02, Q04-07, Q10-Q99. Patients, who initially were given a hydrocephalus diagnosis without known underlying aetiology but later were diagnosed with a chromosome anomaly, would be regarded as cases of syndromic CHC.

Ascertainment of maternal characteristics

The Civil Registration System contains links between parents and their children. Therefore, it can be used to assess the reproductive history of an individual including information on the number of children, their dates of birth, and maternal age at the time of each child`s birth. Information on maternal medical diseases was obtained from the DNPR using the following diagnostic codes: Epilepsy (ICD-8 34509-11, 34518-19, 34529-31, 34538-39, 34599, ICD-10 G41x), pregestational diabetes (ICD-8 25008-9, ICD-10 E10-14), gestational diabetes (ICD-8 63474, ICD-10 O24x), maternal infections (ICD-8 00x, 10x, 11x, 12x, 13x, ICD-10 A00-B99), and pre-eclampsia (ICD-8 63700-4, 63709, 63719, ICD-10 O12-15).

Maternal thyroid conditions were identified using data on prescribed medications for thyroid conditions, as described below. By linkage to Statistics Denmark, information on maternal educational level could be determined (eg, the highest educational level registered prior to the birth of interest).

Ascertainment of perinatal characteristics of the children

The Danish National Medical Birth Registry (MBR) has existed in computerised form since 1973,[7] and contains information obtained by the midwives attending the delivery on prenatal and perinatal factors of all births in Denmark, including home births. Information on gender, birth weight, gestational age and many other birth characteristics were available from this registry. The variable birth weight by gestational age (WGA) was generated from the birth weight of each child in the cohort, and the centiles were estimated according to gestational age and gender in the total cohort. Multiples were identified as individuals having the same mother and being born on the same day (±1 day on either side of midnight). Detailed information on mode of delivery was available from 1977.

Ascertainment of the maternal use of medicine during pregnancy

The National Prescription Drug Register was established in 1995 and contains individual-level information on all prescriptions filled at any pharmacy in Denmark.[8] Each record contains the PIN, dispensing date, anatomic therapeutic chemical (ATC) code, number of packages, package size and number of defined daily doses (DDD) in the prescription. We extracted information on all prescriptions on the most commonly used types of orally administered medication during the first trimester of pregnancy, according to data from The National Prescription Drug Register on approximately 830 000 consecutive births between 1996 and 2008. We used the following ATC codes: Antibiotics (ATC code J01), antidepressants (N06A), antiepileptic medicine (N03A), anticonceptive medicine (G03A), corticosteroids (methylprednisolone (H02AB04) and prednisolone (H02AB06)), NSAID´s (M01A), proton-pump inhibitors (A02BC), medicine for thyroid conditions (H03A, H03B), antidiabetic medicine, overall (A10), insulin (A10A), blood glucose-lowering medicine, excluding insulin (A10B).

Statistical analyses

Each live-born individual was followed from 1 January 1978 to the first of the following events: (1) isolated CHC diagnosis; (2) syndromic CHC diagnosis; (3) death; (4) emigration; (5) designated 'missing person' in the CRS; (6) end of follow-up (31 December 2008); or (7) causative diagnosis.

The associations between the potential risk factors and the development of CHC were estimated by rate ratios (RR) using log-linear Poisson regression models. The SAS procedure GENMOD (SAS V.9.2; Cary North Carolina, USA) was used. In all analyses, we adjusted for a number of a priori defined confounders including year of birth (1978–1982, 1983–1987, 1988–1992, 1993–1997, 1998–2002, and 2003–2008), maternal age(≤20, 20–24, 25–34, 35–39, 40+ years), and parity (1, 2, 3, 4+ births).

The variables pre-eclampsia, maternal infections, maternal diabetes, all birth characteristics of the children and maternal use of medicine were further adjusted for child's gender and multiples. In an additional analysis, maternal use of antidepressants was adjusted for maternal education (categorised as in table 1) to take into account the previous observations of depression being associated to educational level.[9] Risk factors for isolated and syndromic CHC were compared using a competing risks approach.[10] All tests were twosided likelihood ratio tests.

Ethics

The study was approved by The Danish Data Protection Agency. According to the Danish law, ethical approval is not required for register-based studies in Denmark.

RESULTS

Of the 1 928 666 cohort members of live-born children in Denmark in 1978–2008, we identified 1193 cases of isolated CHC (0.62/1000 live-born children) and 985 cases of syndromic CHC (0.51/1000 live-born children).

The RRs for isolated CHC according to maternal characteristics, maternal medical diseases, maternal use of medicine during pregnancy, and birth characteristics of the child are shown in tables 1–3. In order to identify which risk factors were unique for isolated CHC, we compared the RRs for the variables showing significant associations with isolated CHC in tables 1–3 to the corresponding estimates for syndromic CHC. These results are presented in table 4.

Maternal characteristics and the risks of isolated CHC

First-born children had an increased rate ratio of 1.32 (95% CI 1.17 to 1.49) compared to later-born children (table 1). Accordingly, children born as a second (RR 0.75, 95% CI 0.66 to 0.86), or third child (RR 0.76, 95% CI 0.62 to 0.91) had significantly reduced risks for isolated CHC compared to first-born children. By contrast, no association between maternal parity and syndromic CHC was found. The RRs for isolated CHC according to parity were significantly different from the corresponding RRs for syndromic CHC (p=0.004) (table 4) hence,

Table 1 Rate ratios (RR) of isolated congenital hydrocephalus (CHC) according to maternal characteristics, pre-existing and pregnancy-related morbidities among Danish children born 1978–2008

	Isolated CHC				
	Children	Cases	RR	95% CI	p Value*
Maternal age (years)†					
≤20	50 731	53	1.35	1.01 to 1.79	0.19
20–24	370 798	251	0.95	0.81 to 1.10	
25–34	1 276 810	774	1	(Ref.)	
35–39	196 583	100	0.91	0.73 to 1.13	
40+	30 367	15	0.83	0.48 to 1.41	
Maternal parity†					
1	858 781	621	1	(Ref.)	0.0001
2	714 669	383	0.75	0.66 to 0.86	
3	261 791	137	0.72	0.62 to 0.91	
4+	90 113	51	0.83	0.62 to 1.12	
Maternal epilepsy†‡					
Yes	5421	4	1.20	0.45 to 3.21	
No	1 920 063	1189	1	(Ref.)	
Maternal diabetes†					
Yes	39 896	45	1.79	1.33 to 2.42	
No	1 885 588	1148	1	(Ref)	
Maternal pre-eclampsia§					
Yes	24 112	34	2.11	1.50 to 2.97	
No	1 901 372	1159	1	(Ref.)	
Maternal infections during pregnancy treated in hospital†					
Yes	8467	5	0.99	0.41 to 2.38	
No	1 917 017	1188	1	(Ref.)	
Maternal education prior to pregnancy†¶					
Compulsory school	183 533	103	1	(Ref.)	0.13
Secondary school	114 816	51	0.73	0.52 to 1.04	
Vocational or short tertiary school	297 985	183	1.05	0.81 to 1.37	
Medium or long education	222 950	123	0.93	0.70 to 1.25	
Missing**	15 984	11	1.26	0.67 to 2.35	

*Test for homogeneity.
†Adjusted for year of birth, maternal age and parity.
‡Diagnosed within 5 years prior to birth.
§Adjusted for year of birth, maternal age and parity, child's gender and multiples.
¶Information on maternal education was available from 1995 and onward.
**Individuals with missing information were not included in the tests.

first-born children had an increased risk for isolated CHC but, interestingly, not for syndromic CHC.

Compared with unexposed, children exposed to maternal diabetes during fetal life (pregestational or gestational diabetes) were at significantly increased risk for isolated CHC (RR 1.79, 95% CI 1.33 to 2.42) but also syndromic CHC (RR 1.56, 95% CI 1.10 to 2.20). Children born from mothers with pre-eclampsia compared with mothers without pre-eclampsia, seemed also to be at increased risk for isolated CHC (RR 2.11, 95% CI 1.50 to 2.97). However, the RR showed not to be significantly different (p=0.12) from the non-significant corresponding RR for syndromic CHC (0.87, 95% CI 0.28 to 2.71) as shown in table 4.

Birth characteristics of the child

The birth characteristics of children born with isolated hydrocephalus are presented in table 2. The birth characteristics that were significantly associated with isolated CHC are compared with the corresponding birth characteristics of children born with syndromic CHC in table 4.

The risks for isolated as well as syndromic CHC were higher for children of male gender (RR 1.85, 95% CI 1.64 to 2.09 and RR 1.66, 95% CI 1.46 to 1.89, respectively) and for multiples (RR 2.84, 95% CI 2.29 to 3.51 and RR 2.93, 95% CI 2.33 to 3.69, respectively) (table 4). Strong associations were found between the risk of isolated CHC and being born preterm (gestational age (GA) 28–31 weeks) and extremely preterm (GA<28 weeks) as compared to children being born at term. A similar association was found between GA and syndromic CHC, however, the association was significantly stronger for syndromic CHC than for isolated CHC (p=0.002) (table 4). Birth weight for gestational age (WGA), either below the 10 percentile or beyond the 90 percentile, was also significantly associated with isolated CHC as compared to children born within the 10–89 percentile. As presented in table 4, a similar pattern was observed for syndromic CHC, however, the association for syndromic CHC was somewhat stronger.

In situations where a case of hydrocephalus is established prenatally, the typical mode of delivery is elective caesarean section (CS). In accordance with this practice, an association was found between elective CS and isolated CHC. It appeared that all three types of non-elective CS were associated with isolated CHC as well. Similarly, we observed high RRs between CS and syndromic CHC.

Table 2 Rate ratios (RR) of isolated congenital hydrocephalus (CHC), according to birth characteristics of the child among Danish children born 1978–2008

	Isolated CHC				
	Children	Cases	RR*	95% CI	p Value†
Child's gender					
Male	988 233	788	1.85	1.64 to 2.09	
Female	937 251	405	1	(Ref.)	
Multiples					
Yes	60 304	94	2.84	2.29 to 3.51	
No	1 865 180	1099	1	(Ref.)	
Gestational age (weeks)					
<28	4424	29	24.7	16.8 to 36.2	<0.0001
28–31	11 618	74	13.6	10.6 to 17.4	
32–36	84 426	178	4.07	3.43 to 4.82	
37–41	1 562 531	777	1	(Ref.)	
≥42	198 090	84	0.86	0.69 to 1.08	
Missing‡	64 395	51	1.18	0.88 to 1.58	
Weight for gestational age (percentiles)					
<2.5	44 588	79	2.78	2.19 to 3.53	<0.0001
2.5–4	42 515	37	1.45	1.04 to 2.02	
5–9	85 574	84	1.71	1.36 to 2.15	
10–14	87 498	57	1.03	0.78 to 1.36	
15–19	101 783	70	1.22	0.95 to 1.56	
20–79	1 110 815	586	1	(Ref.)	
80–84	99 255	55	1.12	0.85 to 1.47	
85–89	85 850	38	0.91	0.65 to 1.26	
90–94	99 976	67	1.40	1.09 to 1.81	
95–97.5	46 466	27	1.23	0.84 to 1.81	
>97.5	48 828	35	1.56	1.10 to 2.19	
Missing‡	72 336	58	1.21	0.92 to 1.60	
Mode of delivery, differentiated§					
Caesarean section (CS), acute	24 089	46	4.30	3.11 to 5.95	<0.0001
CS, planned	53 634	58	2.65	1.98 to 3.56	
CS during birth, not acute	8349	16	4.06	2.42 to 6.79	
CS during birth, acute	60 486	60	2.15	1.61 to 2.88	
Vaginal delivery	638 413	249	1	(Ref.)	

*Adjusted for year of birth, maternal age, parity, child's gender and multiple births.
†Test for homogeneity.
‡Individuals with missing information were not included in the tests.
§Information on mode of delivery was available from 1997 and onward.

Maternal use of medicine during pregnancy and isolated CHC

The risks for isolated CHC in children exposed to maternal use of medicine during the first trimester of pregnancy and isolated CHC are shown in table 3. Children exposed to maternal use of antidepressants during the first trimester had a significantly increased risk of isolated CHC (RR 2.52, 95% CI 1.47 to 4.29) compared to non-exposed children. This association remained statistically significant after additional adjustment for maternal education (RR 2.51, 95% CI 1.44 to 4.38). No association was found between maternal use of antidepressants and syndromic CHC. The antidepressants used by the mothers of isolated CHC cases were of the type selective serotonin reuptake inhibitors (SSRI) in 13 out of 14 cases. The risk (RR) of isolated CHC after maternal exposure specifically to SSRIs compared to the risk in unexposed children was 2.7, 95% CI 1.5 to 4.6.

The RR of isolated CHC in children born from mothers who used proton-pump inhibitors during their first trimester of the pregnancy was 2.35, 95% CI 1.26 to 4.41 compared to unexposed children (table 3). A similar risk increase was not found for syndromic CHC. However, in a comparative analysis these two risk estimates were not significantly different (p=0.06) and, therefore, the association was not regarded unique for isolated CHC.

DISCUSSION

We investigated potential risk factors for isolated CHC in an unselected, population-based cohort of almost two million children. The results revealed significantly increased risks for first-born compared to later-born children. A significantly increased risk was also observed for children exposed to maternal use of antidepressants during the first trimester of pregnancy as compared to non-exposed children.

Other risk factors that were identified in this study were not unique for isolated CHC, but also found for children diagnosed with syndromic CHC. Thus, significantly increased risks were found for isolated and syndromic CHC in children of male gender, multiples, and children exposed to maternal diabetes.

The literature is very sparse regarding risk factors for CHC. Thus, a possible association between maternal parity and isolated CHC has not been investigated previously. Children who were not first-born had a significant 25 percentage lower risk of CHC compared to first-born children. One could speculate that

Table 3 Rate ratios (RR) of isolated congenital hydrocephalus (CHC), according to maternal intake of medicine during first trimester of the pregnancy among Danish children born 1995–2008

	Isolated CHC			
	Children	**Cases**	**RR***	**95% CI**
Antibiotics				
Yes	108 288	71	1.23	0.96 to 1.59
No	744 195	404	1	(Ref.)
Antidepressants				
Yes	9288	14	2.52	1.47 to 4.29
No	843 195	461	1	(Ref.)
Antiepileptic medicine				
Yes	2899	1	0.60	0.08 to 4.28
No	849 584	474	1	(Ref.)
Anticonceptive medicine				
Yes	10 092	6	1.07	0.48 to 2.39
No	842 391	469	1	(Ref.)
Corticosteroids				
Yes	2267	2	1.38	0.34 to 5.56
No	850 216	473	1	(Ref.)
NSAIDs				
Yes	16 552	12	1.31	0.74 to 2.33
No	835 931	463	1	(Ref.)
Proton-pump Inhibitors				
Yes	7762	10	2.35	1.26 to 4.41
No	844 721	465	1	(Ref.)
Medicine for thyroid conditions				
Yes	5521	4	1.25	0.47 to 3.34
No	846 962	471	1	(Ref.)
Antidiabetes medicine, overall				
Yes	4669	4	1.22	0.45 to 3.27
No	847 814	471	1	(Ref.)
Insulin				
Yes	2670	2	1.34	0.33 to 5.36
No	849 813	473	1	(Ref.)
Blood glucose-lowering medicine, excluding insulin				
Yes	2097	2	1.09	0.27 to 4.39
No	850 386	473	1	(Ref.)

*Adjusted for year of birth, maternal age, parity, child's gender and multiples.

mothers of children with CHC are less likely to have another child due to the disease burden explaining the higher rate in the first-born children compared to later-born children. However, this is unlikely for several reasons. By contrast with what would be expected under such an assumption, we did not observe the same association for syndromic CHC. Neither did we observe decreased risk for third-born children compared to second-born children, nor for 4 plus-born children compared to third-born children, as shown in tables 1 and 4. Additionally, the CHC prevalence is much too small to explain the observed 25% lower risk among second-born compared to first-born children. Hence, of the approximately 60 000 children born each year in Denmark, given the prevalence of 0.62/1000 live-born children, roughly 37 children will have isolated CHC. Assuming the worst case scenario that all 37 mothers stopped having children, the number of children born with isolated CHC would still be 37 ((60 000–37)×0.00062), as the recurrence rate among siblings is moderate (7.5).[11]

We speculate that the higher risk among first-born children could be explained by a potentially higher risk for clinically undetected intracranial haemorrhage increasing the risk for posthaemorrhagic CHC, due to lower mechanical compliance of the birth canal of the primiparous. In the literature, asymptomatic traumatic intracranial haemorrhage of the child has been reported in up to 51% of uncomplicated vaginal deliveries[12 13] which may support this explanation. This finding call for studies investigating whether factors related to difficult births (for instance, prolonged birth, severe ruptures of the vaginal skin) are associated to a higher risk of isolated CHC.

Another significant finding was the association between maternal use of antidepressants and isolated CHC, however, based on small case numbers (14 affected cases exposed to antidepressants, by which 13 were SSRIs) (tables 3 and 4). We specifically estimated the risk of isolated CHC after maternal use of SSRIs, and found a risk of 2.7, 95% CI 1.5 to 4.6 compared to unexposed children. The association between antidepressants and hydrocephalus has not been specifically investigated in previous studies where the focus has been on evaluating potential associations with major birth defects.[14–17] It must be underlined that we cannot know whether this association reflects a direct causal relationship. Hence, this finding may reflect comorbidities or behavioural aspects associated with the use of antidepressant which may also impact the risk of having a child with hydrocephalus. Such factors could possibly include poor maternal nutritional status, alcohol abuse, and lower compliance to routine check-ups during pregnancy, which include ultrasound screening for congenital malformations during the second trimester. The latter could potentially lead to a lower abortion rate of hydrocephalic children among depressed women. EUROCAT is a network of population-based registries for the epidemiological surveillance of congenital anomalies in 21 countries of Europe. From the EUROCAT studies, it is known that 48% of fetal hydrocephalus results in termination of pregnancy, and 5% results in fetal death.[18] In the current study, data were not available for the causes of abortions and stillbirths, neither were sufficient data on nutritional status of the mothers and their use of alcohol. Depression is a serious and potentially life-threatening condition, and the finding of this association should not be used to justify recommendations against the well-indicated use of antidepressants in pregnant women. We also found an increased risk for isolated CHC after first trimester exposure to proton-pump inhibitors (PPI) compared to unexposed children. However, this risk was accurately not significantly different from the corresponding non-significant risk for syndromic CHC (p=0.06) (table 4). Based on this finding, it appears unlikely that the use of PPIs influence the development of isolated CHC, although the rather small case numbers makes it difficult to interpret this finding. PPIs have been reported to be used during the first trimester in 0.6% of the pregnancies in Danish women resulting in a live birth.[19] Thus, we do not regard this finding robust enough to justify any changes in the current recommendations. However, the finding gave rise to the speculation that the association could reflect a potential association between nutritional problems and isolated CHC. As mentioned above, data on nutritional status for the cohort members were not available but could be an interesting factor to investigate in future risk factor studies.

In addition to factors that were specifically associated with isolated CHC, we identified a number of risk factors influencing isolated and syndromic CHC. We identified maternal diabetes as a risk factor for isolated and syndromic CHC which is supported by an American case-control study,[4] documenting a higher incidence of pregestational diabetes among mothers giving birth to CHC cases (6,0%), compared to controls (2.8%) (p=0.05). The same study reported a significantly higher incidence of maternal pregnancy-induced hypertension/ pre-eclampsia in CHC cases

Table 4 Rate ratios (RR) of isolated and syndromic CHC according to the maternal characteristics, the birth characteristics of the child, and the maternal use of medicine during pregnancy significantly associated with isolated CHC among Danish children born 1978–2008

	Isolated CHC			Syndromic CHC			Syndromic versus isolated CHC
	Cases	RR	95% CI	Cases	RR	95% CI	p Value*
Maternal characteristics							
Maternal parity†							
1	621	1	(Ref.)	439	1	(Ref.)	0.004
2	383	0.75	0.66 to 0.86	346	0.97	0.84 to 1.12	
3	137	0.72	0.62 to 0.91	126	0.96	0.78 to 1.18	
4+	51	0.83	0.62 to 1.12	73	1.59	1.23 to 2.07	
Maternal diabetes†							
Yes	45	1.79	1.33 to 2.42	33	1.56	1.10 to 2.20	0.52
No	1148	1	(Ref.)	952	1	(Ref.)	
Pre-eclampsia‡							
Yes	34	2.11	1.50 to 2.97	3	0.87	0.28 to 2.71	0.12
No	1.159	1	(Ref.)	982	1	(Ref.)	
Birth characteristics of the child							
Child's gender‡							
Male	788	1.85	1.64 to 2.09	627	1.66	1.46 to 1.89	0.22
Female	405	1	(Ref.)	358	1	(Ref.)	
Multiples‡							
Yes	94	2.84	2.29 to 3.51	79	2.93	2.33 to 3.69	0.94
No	1099	1	(Ref.)	906	1	(Ref.)	
Gestational age (weeks)‡							
<28	29	24.7	16.8 to 36.2	38	50.3	36.0 to 70.2	0.002
28–31	74	13.6	10.6 to 17.4	86	24.1	19.1 to 30.5	
32–36	178	4.07	3.43 to 4.82	193	6.60	5.57 to 7.82	
37–41	777	1	(Ref.)	553	1	(Ref.)	
≥42	84	0.86	0.69 to 1.08	76	1.18	0.93 to 1.49	
Missing§	51	1.18	0.88 to 1.58	36	1.26	0.89 to 1.77	
$P_{homogeneity}$		<0.0001			<0.0001		
Weight for gestational age (percentiles)‡							
<2.5	79	2.78	2.19 to 3.53	88	4.17	3.31 to 5.26	0.19
2.5–4	37	1.45	1.04 to 2.02	45	2.31	1.7 to 3.15	
5–9	84	1.71	1.36 to 2.15	66	1.76	1.36 to 2.28	
10–14	57	1.03	0.78 to 1.36	50	1.22	0.91 to 1.64	
15–19	70	1.22	0.95 to 1.56	42	0.95	0.69 to 1.30	
20–79	586	1	(Ref)	468	1	(Ref.)	
80–84	55	1.12	0.85 to 1.47	41	1.0	0.73 to 1.38	
85–89	38	0.91	0.65 to 1.26	33	0.94	0.66 to 1.34	
90–94	67	1.40	1.09 to 1.81	45	1.10	0.81 to 1.50	
95–97.5	27	1.23	0.84 to 1.81	23	1.21	0.8 to 1.84	
>97.5	35	1.56	1.10 to 2.19	30	1.51	1.04 to 2.19	
Missing§	58	1.21	0.92 to 1.60	54	1.55	1.16 to 2.07	
$P_{homogeneity}$		<0.0001			<0.0001		
Mode of delivery‡¶							
CS acute	46	4.30	3.11 to 5.95	43	5.76	4.08 to 8.12	0.76
CS, planned	58	2.65	1.98 to 3.56	53	3.32	2.42 to 4.55	
CS during birth, not acute	16	4.06	2.42 to 6.79	12	4.41	2.43 to 8.00	
CS during birth, acute	60	2.15	1.61 to 2.88	43	2.36	1.68 to 3.32	
Vaginal delivery	249	1	(Ref.)	174	1	(Ref.)	
$P_{homogeneity}$		<0.0001			<0.0001		
Maternal intake of medicine during pregnancy**‡							
Antidepressants, 1. trimester							
Yes	14	2.52	1.47 to 4.29	1	0.25	0.03 to 1.75	0.002
No	461	1	(Ref.)	364	1	(Ref.)	
Proton-pump inhibitors, 1. trimester							
Yes	10	2.35	1.26 to 4.41	4	1.19	0.44 to 3.18	0.06
No	465	1	(Ref.)	360	1	(Ref.)	

*Test for homogeneous RRs for isolated and syndromic CHC.
†Adjusted for year of birth, maternal age and parity.
‡Adjusted for year of birth, maternal age and parity, multiples and gender of the child.
§Individuals with missing information were not included in the tests.
¶Information on mode of delivery was available from 1997 and forward.
**Information on maternal intake of medicine was available from 1995 and onward.

(15.3%) compared to controls (5.5%) (p<0.0001).[4] Although we found a significant association between pre-eclampsia and isolated CHC in our initial analysis (RR 2.11, 95% CI 1.50 to 2.97) (table 1), such association seems questionable since it appeared not to be significantly different (p=0.16) from the non-significant association between pre-eclampsia and syndromic CHC (RR 0.87, 95% CI 0.28 to 2.71) (table 4).

Our finding of an increased risk for isolated and syndromic CHC in infants of male gender is also in line with the literature. For both subgroups X-linked genetic factors could play a role in the male predominance. Preterm delivery is often associated with congenital malformations, and the strong association observed in the present study with isolated, and syndromic CHC most likely reflects a general failure to thrive of a fetus with congenital malformation. The association may also be the result of intraventricular haemorrhage, which is known to occur particularly among preterm children due to their immature vessels in the matrix layer of the ependymal lining of the ventricular system. Thus, less severe haemorrhage may be subclinical and, therefore, not necessarily registered as a diagnosis. Our observation of a strong association with CS most likely is explained by reverse causality (eg, children are born by CS because of enlarged heads), but it could, in theory, also reflect an increased risk for mechanical birth complications due to enlarged heads and/or greater risk of fetal distress during labour because of increased or labile intracranial pressure. Since the observed associations between CS and CHC are rather strong, these data support careful consideration of the recommended mode of delivery of children with macrocephaly taking into account the size of the pelvic output.

Our study had several strengths. The Danish Civil Registration System allowed for nearly complete follow-up of our cohort, which minimised selection bias. Since discharge diagnoses in the healthcare system are mandatorily reportable in Denmark, and healthcare is free and easily accessible, the registration of CHC is considered virtually complete in the National Patient Register.[20] This is particularly true for a serious condition often leading to surgery.

A potential limitation of the study is the limited numbers of cases exposed to some of the types of medicine used during pregnancy. Therefore, the findings regarding lack of associations between isolated CHC and proton-pump inhibitors, maternal use of antiepileptic medicine, anticonceptive medicine, corticosteroids, antidiabetic medicine, and medicine for thyroid conditions, must be interpreted with some caution. We were able to adjust for many potential confounders, however, one might speculate that maternal alcohol use during pregnancy could confound the observed association with maternal use of antidepressants, but against this, a similar association was not observed for syndromic CHC. Finally, the study was based on live births only and, therefore, not considers cases among terminated pregnancies.

CONCLUSION

This large cohort study based on an entire, unselected population found that being first-born and being exposed to maternal use of antidepressants were associated with a significantly increased risk of isolated CHC. Hence, for first-born children, the rate ratio (RR) was 1.32, 95% CI 1.17 to 1.49, corresponding to 0.72/1000 born children, whereas the RR related to first trimester exposure of antidepressants was 2.52, 95% CI 1.47 to 4.29, which corresponds to 1.5/1000 born children. It remains to be shown what the mechanism is for the higher risk of isolated CHC in first-born children. However, this finding should be the target for further research since a potential modification of this single risk factor would have a significant impact on the incidence of CHC. Some focus should also be given to the underlying cause(s) of the observed association between isolated CHC and maternal use of antidepressants. Behavioural aspects associated with the use of antidepressants with a potential impact on the subsequent risk of having a child with isolated CHC should be a target for further research.

This includes poor maternal nutrition, maternal use of alcohol, and low compliance with prenatal ultrasonography screening programmes. Potential biological pathways by which antidepressants may cause hydrocephalus remain to be elucidated.

Contributors TNM conceptualised and designed the study; she was responsible for data analysis and interpretation; she drafted and revised the manuscript and approved the final manuscript as submitted. M-LHR carried out the analyses, reviewed and revised the manuscript, and approved the final manuscript as submitted. JW coordinated and supervised the initial analyses, contributed significantly to interpretation of data, critically reviewed and revised the manuscript, and approved the final manuscript as submitted. MJ contributed to the analysis and interpretation of data, critically reviewed and revised the initial manuscript, and approved the final manuscript as submitted. MM had a supervising role in designing the study, data analysis, and the interpretation of data; he critically reviewed and revised the manuscript, and approved the final manuscript as submitted.

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REFERENCES

1 Aolad HM, Inouye M, Darmanto W, *et al*. Hydrocephalus in mice following X-irradiation at early gestational stage: possibly due to persistent deceleration of cell proliferation. *J Radiat Res (Tokyo)* 2000;41:213–26.
2 Rajab A, Vaishnav A, Freeman NV, *et al*. Neural tube defects and congenital hydrocephalus in the Sultanate of Oman. *J Trop Pediatr* 1998;44:300–3.
3 Stoll C, Alembik Y, Dott B, *et al*. An epidemiologic study of environmental and genetic factors in congenital hydrocephalus. *Eur J Epidemiol* 1992;8:797–803.
4 Van LM, Nguyen TV, Roberts A, *et al*. Risk factors of congenital hydrocephalus: a 10 year retrospective study. *J Neurol Neurosurg Psychiatry* 2009;80:213–7.
5 Zajicek M, Gindes L, Hoffmann C, *et al*. Prenatal diagnosis of obstructive hydrocephalus associated with parvovirus b19 infection. *Obstet Gynecol* 2010;116:521–2.
6 Pedersen CB, Gotzsche H, Moller JO, *et al*. The Danish Civil Registration System. A cohort of eight million persons. *Dan Med Bull* 2006;53:441–9.
7 Knudsen LB, Olsen J. The Danish Medical Birth Registry. *Dan Med Bull* 1998;45:320–3.
8 Gaist D, Sorensen HT, Hallas J. The Danish prescription registries. *Dan Med Bull* 1997;44:445–8.
9 Bjelland I, Krokstad S, Mykletun A, *et al*. Does a higher educational level protect against anxiety and depression? The HUNT study. *Soc Sci Med* 2008;66:1334–45.
10 Wohlfahrt J, Andersen PK, Melbye M. Multivariate competing risks. *Stat Med* 1999;18:1023–30.
11 Munch TN, Rostgaard K, Rasmussen ML, *et al*. Familial aggregation of congenital hydrocephalus in a nationwide cohort. *Brain* 2012;135:2409–15.
12 Looney CB, Smith JK, Merck LH, *et al*. Intracranial hemorrhage in asymptomatic neonates: prevalence on MR images and relationship to obstetric and neonatal risk factors. *Radiology* 2007;242:535–41.
13 Rooks VJ, Eaton JP, Ruess L, *et al*. Prevalence and evolution of intracranial hemorrhage in asymptomatic term infants. *AJNR Am J Neuroradiol* 2008;29:1082–9.
14 Alwan S, Reefhuis J, Rasmussen SA, *et al*. Use of selective serotonin-reuptake inhibitors in pregnancy and the risk of birth defects. *N Engl J Med* 2007;356:2684–92.
15 Pedersen LH, Henriksen TB, Vestergaard M, *et al*. Selective serotonin reuptake inhibitors in pregnancy and congenital malformations: population based cohort study. *BMJ* 2009;339:b3569.
16 Malm H, Artama M, Gissler M, *et al*. Selective serotonin reuptake inhibitors and risk for major congenital anomalies. *Obstet Gynecol* 2011;118:111–20.
17 Louik C, Lin AE, Werler MM, *et al*. First-trimester use of selective serotonin-reuptake inhibitors and the risk of birth defects. *N Engl J Med* 2007;356:2675–83.
18 Garne E, Loane M, Addor MC, *et al*. Congenital hydrocephalus--prevalence, prenatal diagnosis and outcome of pregnancy in four European regions. *Eur J Paediatr Neurol* 2010;14:150–5.
19 Pasternak B, Hviid A. Use of proton-pump inhibitors in early pregnancy and the risk of birth defects. *N Engl J Med* 2010;363:2114–23.
20 Andersen TF, Madsen M, Jorgensen J, *et al*. The Danish National Hospital Register. A valuable source of data for modern health sciences. *Dan Med Bull* 1999;46:263–8.

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Notes