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Seasonal variation of birth defects in Norway

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ABSTRACT

Background: Seasonal variation in the occurrence of birth defects provides indirect evidence of the causal role of environmental factors, because genetic factors do not exhibit seasonality.
Aim: This study was undertaken to assess the seasonal variation of birth defects in Norway.
Methods: We conducted a nationwide cross-sectional study of 326,560 births in years 1993–1998, using information from the Medical Birth Registry in Norway. We applied the Lorenz curve and associated Gini index and its 95th percentiles from 10,000 Monte Carlo simulations to identify specific birth defects and birth defect groups with statistically significant seasonal variation. For identified outcomes we applied logistic regression analysis to quantify deviations of risk in high and low peak months.
Results: The Gini index indicated statistically significant seasonal variation ($\alpha = 0.05$) for any birth defect, 0.040 (95th percentile = 0.024), respiratory defects, 0.140 (95th percentile = 0.141), and for Down syndrome, 0.148 (95th percentile = 0.126). Based on logistic regression adjusting for maternal age, parity, centrality, population density, and industrial profile, highest risk for respiratory defect was among infants born in March (adjusted odds ratio [OR] 1.82, 95% confidence interval [CI] 1.33–2.50), and for Down syndrome in February (adjusted OR 1.64, 95% CI 1.21–2.22) compared to risks of infants born in other months.
Conclusion: Findings suggest that environmental factors with seasonal variation play a role in the etiology of respiratory defects and Down syndrome.

1. Introduction

Accumulating evidence indicates both genetic and environmental factors playing roles in etiology of birth defects [1]. It is very likely that multilevel interaction exists between genetic and environmental factors [2]. Seasonal variation in the occurrence of birth defects yields indirect evidence of a causal role of environmental factors such as prenatal exposure to disinfection by-products, which has been reported to exhibit seasonality [3].

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A series of epidemiologic studies have assessed seasonal variation of birth defects [4–30]. Seasonal variation in occurrence of neural tube defects has received the most attention, but studies conducted in diverse regions provide conflicting results. Studies in the United Kingdom [8], Newfoundland [9], and South Africa [14] reported significant seasonal variation in occurrence of neural tube defects; research in Canada [6], Utah [7], South America [11], Italy [12], Japan [20], and Northern Germany [21] found none. Others report seasonal variation in occurrence of oesophagial atresia [12], diaphragmatic hernia [12], cleft lip [22,27,28], anomaly of pulmonary valule [29], ventricular septal defects [25,30], and Down syndrome [17].

We previously reported relations between exposure to disinfection by-products and risk of birth defects, in particular neural tube, cardiac, respiratory system, and urinary tract defects [31,32]. Among specific birth defects, only risk of ventricular septal defect was significantly elevated with an exposure response pattern [32]. Elaboration of seasonal variation of these and other birth defects would provide additional insight into the role of environmental factors. We thus evaluated seasonal variation in occurrence of birth defects in Norway, using population-based information on all births registered by the nationwide Medical Birth Registry for the years 1993–1998.

2. Methods

2.1. Study population

The source population comprised all 361,767 newborns registered by the Norwegian Birth Registry from 1993 to 1998. We excluded 35,207 (9.7%) due to incomplete information on gestational age. The study population included 326,560 (90.3%) term births, with study protocol approved by the Institutional Review Board of Bloomberg School of Public Health at Johns Hopkins University, in compliance with principles outlined in the Helsinki Declaration.

2.2. Birth defects

We focused on the most common specific birth defects and five groups of defects: neural tube, cardiac, respiratory, oral cleft, and urinary tract defects. These were used in the previous study of Norwegian births [14].

All births after the 16th week of gestational age are compulsorily reported to the Medical Birth Registry. During the child's 1st week of life, a physician (usually a pediatrician) makes diagnoses of birth defects, which are recorded in the registry. Hence, birth defects diagnosed later in life are excluded from the registry. According to the International Classification of Diseases, Eighth Revision (ICD-8), up to three birth defects are coded for each child.

2.3. Covariates

We used routine birth registry data to construct covariates: maternal age (younger than 20 years; 20–34 years; age 35 years or older), and parity (0; 1; 2; and $\geq$3 previous deliveries). We received municipal-level data from the Norwegian Social Science Data services, to construct three municipal level indicators of socioeconomic status: centrality, population density, and industrial profile. Centrality means urbanity and geographical placement in relation to a regional center. In the current analyses, we divided data into three levels, low (municipalities with urban centers up to 15,000 residents), medium (urban areas up to 50,000 residents), and high (includes a regional center). Population density is the proportion of urban population in a municipality. We categorized the data as: (1) <20%; (2) 20–39.9%; (3) 40–59.9%; (4) 60–79.9%; and (5) 80% or more. Industrial profile indicates relative distribution of trade in a municipality, given by three levels: mainly agriculture/fisheries (low), mainly industry (medium), and mainly services (high).

2.4. Statistical methods

We applied the Lorenz curve and associated Gini index described by Lee [33] to assess seasonal variation of birth defects. This method is more sensitive to minute temporal changes, its power relatively higher than that of other commonly used seasonality tests, such as χ^2 goodness-of-fit, Edwards, Roger, and Kuiper. Analyses proceeded in three phases: (1) construction of the Lorenz curve, (2) calculation of the Gini index, and (3) iteration of phases one and two using smoothing techniques.

The main parameter in analyses was the monthly birth defect ratio (R_i), calculated for each of 12 months by dividing number of cases (C_i) occurring in a given month i during 6 years by number of days (D_i) in the corresponding month in the same time period (Table 1). First, we ranked the months according to the monthly birth defect ratio from lowest to highest. We constructed the Lorenz curve by plotting cumulative percentage of cases in rank order (y-axis) against cumulative percentage of days (x-axis). The area between a diagonal line and curve (A_s) quantifies seasonality; i.e., deviation from homogeneous monthly birth defect ratio (Fig. 1).

The Gini index was defined as two times A_s, varying from 0 representing no seasonal variation, to 1 with maximal seasonal variation. We used 10,000 Monte Carlo simulations for each sample size to derive approximate Gini index distribution describing chance variation of the Gini index and to define statistical significance of observed seasonal variation. We used the 95th percentile Gini index value to assess statistical significance at the $\alpha = 0.05$ level.

Monthly birth defect ratios are subject to substantial chance variation due to the relatively small numbers of cases. We used a smoothing technique to reduce chance variation. We first calculated the 3-month moving average R_i for each month, with two weighting schemes (1/3, 1/3, 1/3 and 1/4, 2/4, 1/4), then used the smoothed R_i to derive expected cases for each month. Gini indices were defined for both weighting schemes, as described previously (Gini-1 and Gini-2).

When seasonal variation was identifed by Gini indices, we used the prevalence odds ratio to quantify timing of the peak and amplitude in seasonal variation. We compared the risk of birth defects in each month to the rest of the months, applying logistic regression to estimated odds ratios adjusted for possible confounding factors such as maternal age, parity, centrality, population density, and industrial profile of the municipality where the mother lived during pregnancy.

Table 1 – Monthly ratio of respiratory defects and corresponding 3-month moving average in Norway 1993–1998.

Month	No. of cases (C_i)	Number of days (D_i)	Monthly birth defect ratio (R_i)	Three-month moving average			
				with weights: 1/3,1/3,1/3		with weights: 1/4, 2/4, 1/4	
				Monthly birth defect ratio (R_{i1})	No. of cases (C_{i1})	Monthly birth defect ratio (R_{i2})	No. of cases (C_{i2})
Jan	28	186	0.15054	0.14806	27.54	0.14868	27.65
Feb	26	169	0.15385	0.18390	31.08	0.17639	29.81
Mar	46	186	0.24731	0.17261	32.11	0.19128	35.58
Apr	21	180	0.11667	0.16613	29.90	0.15376	27.68
May	25	186	0.13441	0.13184	24.52	0.13248	24.64
Jun	26	180	0.14444	0.13596	24.47	0.13808	24.85
Jul	24	186	0.12903	0.14134	26.29	0.13826	25.72
Aug	28	186	0.15054	0.13208	24.57	0.13669	25.43
Sep	21	180	0.11667	0.13029	23.45	0.12688	22.84
Oct	23	186	0.12366	0.10048	18.69	0.10627	19.77
Nov	11	180	0.06111	0.10818	19.47	0.09642	17.35
Dec	26	186	0.13978	0.11714	21.79	0.12280	22.84
Total	305	2191			303.9		304.2

3. Results

3.1. *Any birth defect*

Among 326,560 births in the study population during 1993–1998, we identified 10,207 births (3.13%) with a birth defect of interest. Table 2 plots the number and prevalence (%) of birth defects, empirical Gini indices and 95th percentile Gini index values from Monte Carlo simulations. The Gini index for any birth defect was 0.039 (95th percentile = 0.024). The Gini index was larger than the 95th value from the Monte Carlo simulation indicating a significant seasonal variation, at the 0.05 level. To reduce sampling variation of R, we used the smoothing technique to Gini-1 and Gini-2. Values for Gini-1 and Gini-2 are also given in Table 2. In general, test statistics for Gini, Gini-1, and Gini-2 were similar. Based on the month of birth, Table 3 shows statistically significant increases in risk for any birth defect in February (adjusted odds ratio [OR] 1.13, 95% confidence interval [CI] 1.06–1.22) and October (adjusted OR 1.09, 95% CI 1.02-1.17). Fig. 2 graphs seasonal variation of birth defect by month of birth.

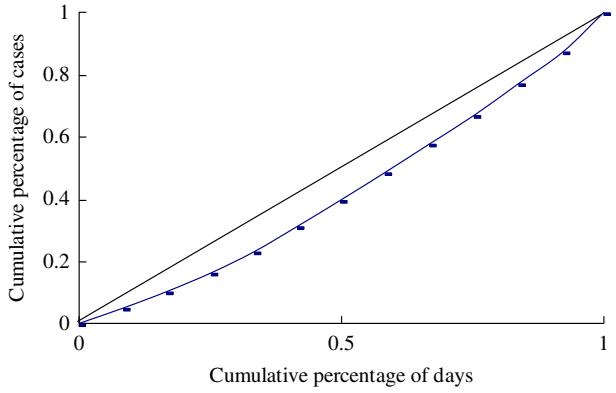

Fig. 1 – Lorenz curve of respiratory defects in Norway during 1993–1998.

3.2. *Neural tube defects*

We identified 250 births (0.08%) with neural tube defects: 87 (0.03%) anecephalus, 21 (0.01%) encephalocele, and 142 (0.04%) spina bifida cases. Gini index of neural tube defects (Table 2) was estimated as 0.112 (95th percentile = 0.156), lower than 95th percentile of 10,000 Monte Carlo simulations with sample size 246. Gini index for anencephalus was 0.144 (95th percentile = 0.261), for encephalus 0.316 (95th percentile = 0.507), and for spina bifida 0.110 (95th percentile = 0.205). Thus there was no significant seasonal variation of these defects (Table 2).

3.3. *Cardiac defects*

A total of 931 cardiac defects (0.29%) were identified; Table 2 shows no substantial seasonal variation (Gini = 0.056, 95th percentile = 0.081). Nor did seasonal variation appear in specific cardiac defects: transposition of great vessels (Gini = 0.232, 95th percentile = 0.318), left heart ventricular hyposplasia (Gini = 0.196, 95th percentile = 0.305), tetralogy of Fallot (Gini = 0.332, 95th percentile = 0.400), ventricular septal defet (Gini = 0.093, 95th percentile = 0.113), and atrial septal defect (Gini = 0.143, 95th percentile = 0.217).

3.4. *Respiratory defects*

In all, 305 infants (0.09%) were identified with respiratory defects. The Gini-2 index for respiratory defects was 0.101 (95th percentile = 0.088), showing that a null hypothesis of no seasonal variation was rejected at $\alpha = 0.05$. The test statistic for Gini-1 was 0.098 (95th percentile = 0.082), consistent with Gini-2, but for Gini borderline seasonal variation was shown (Gini = 0.140, 95th percentile = 0.141). Thus, respiratory defects exhibited significant seasonal variation, with the highest risk in March (adjusted OR 1.82, 95% CI 1.33–2.50) and lowest risk in November (adjusted OR 0.46, 95% CI 0.25–0.83), as shown in Fig. 3.

Table 2 – Seasonal variation of birth defects in Norway 1993-1998. Gini index magnitude indicates probability of observed seasonal variation; 95% percentiles represent limits of statistical significance on $\alpha = 0.05$.

Outcomes			Gini	Gini-1	Gini-2
Any birth defect					
N, Prevalence (%)	10,207	3.13			
Index value			0.040*	0.024*	0.027*
95th percentile			0.024	0.014	0.015
Neural tube defects					
N, Prevalence (%)	250	0.08			
Index value			0.112	0.034	0.039
95th percentile			0.156	0.093	0.099
Anencephalus					
N, Prevalence (%)	87	0.03			
Index value			0.144	0.057	0.067
95th percentile			0.261	0.155	0.164
Encephalocele					
N, Prevalence (%)	21	0.01			
Index value			0.316	0.183	0.192
95th percentile			0.507	0.310	0.329
Spina bifida					
N, Prevalence (%)	142	0.04			
Index value			0.110	0.043	0.050
95th percentile			0.205	0.121	0.129
Cardiac defects					
N, Prevalence (%)	931	0.29			
Index value			0.056	0.030	0.035
95th percentile			0.081	0.048	0.051
Transposition of great vessels					
N, Prevalence (%)	58	0.02			
Index value			0.232	0.110	0.123
95th percentile			0.318	0.189	0.201
Tetralogy of Fallot					
N, Prevalence (%)	36	0.01			
Index value			0.332	0.134	0.164
95th percentile			0.400	0.241	0.257
Ventricular septal defect					
N, Prevalence (%)	472	0.14			
Index value			0.093	0.038	0.041
95th percentile			0.113	0.066	0.071
Atrial septal defect					
N, Prevalence (%)	126	0.04			
Index value			0.143	0.067	0.078
95th percentile			0.217	0.128	0.137
Respiratory defects					
N, Prevalence (%)	305	0.09			
Index value			0.140	0.098*	0.101*
95th percentile			0.141	0.082	0.088
Oral cleft defects					
N, Prevalence (%)	631	0.19			
Index value			0.067	0.043	0.044
95th percentile			0.098	0.057	0.061
Cleft palate					
N, Prevalence (%)	183	0.06			
Index value			0.136	0.090	0.094
95th percentile			0.181	0.106	0.114
Cleft lip					
N, Prevalence (%)	133	0.04			
Index value			0.182	0.112	0.120
95th percentile			0.211	0.124	0.132
Cleft palate with cleft lip					
N, Prevalence (%)	315	0.10			
Index value			0.126	0.040	0.037
95th percentile			0.138	0.081	0.086
Urinary tract defects					
N, Prevalence (%)	399	0.12			
Index value			0.119	0.068	0.071
95th percentile			0.122	0.072	0.076
Renal agenesis					
N, Prevalence (%)	55	0.02			
Index value			0.227	0.105	0.123
95th percentile			0.326	0.196	0.208
Cystic kidney disease					
N, Prevalence (%)	72	0.02			
Index value			0.244	0.144	0.152
95th percentile			0.286	0.169	0.180
Obstructive defects of urinary tract					
N, Prevalence (%)	183	0.06			
Index value			0.153	0.086	0.092
95th percentile			0.181	0.107	0.114
Esophageal atresia					
N, Prevalence (%)	54	0.02			
Index value			0.267	0.128	0.140
95th percentile			0.327	0.194	0.207
Diaphragmtica hernia					
N, Prevalence (%)	82	0.03			
Index value			0.188	0.077	0.088
95th percentile			0.269	0.159	0.169
Down syndrome					
N, Prevalence (%)	381	0.12			
Index value			0.148**	0.094**	0.103**
95th percentile			0.126	0.074	0.079

*$p < 0.05$; **$p < 0.01$.

3.5. *Oral cleft defects*

Overall, 631 births (0.19%) with oral cleft defects were identified, including 183 cleft palate (0.06%) and 133 cleft lip cases (0.04%), and 315 cases (0.10%) with both cleft palate and cleft lip. The Gini index of oral cleft defects (Table 2) was estimated as 0.067 (95th percentile = 0.098), for cleft palate, 0.136 (95th percentile = 0.181), for cleft lip, 0.182 (95th percentile = 0.211), and for cleft palate with cleft lip, 0.126 (95th percentile = 0.138). There was no significant seasonal pattern.

3.6. *Urinary tract defects*

We found 399 urinary tract defects (0.12%) in the study population, with no significant seasonal variation (Gini = 0.119, 95th percentile = 0.122) (Table 2). Consistently, the effect on specific urinary tract defects, renal agenesis (Gini = 0.227, 95th percentile = 0.326), cystic kidney disease (Gini = 0.244, 95th percentile = 0.286), and obstructive defects of the urinary tract (Gini = 0.153, 95th percentile = 0.181) was lower in estimation of Lorenz curve and associated Gini index compared with 95th percentile of 10,000 Monte Carlo simulations with each sample size of 55, 72, and 183, respectively.

3.7. *Down syndrome*

A total of 381 newborns (0.12%) were identified with Down syndrome; Gini index (Gini = 0.148; 95th percentile = 0.126) showed the null hypothesis of no seasonal variation rejected at $\alpha = 0.05$. Test statistics for Gini-1 (Gini-1 = 0.094; 95th percentile = 0.074), and Gini-2 (Gini-2 = 0.103; 95th

Table 3 – Prevalence odds ratio of birth defects by month of birth in Norway, 1993–1998.

Birth defects	N	P (%)	cOR (95% CI)	aOR (95% CI)
Any birth defect	10,207	3.13		
January	883	3.27	1.05 (0.98-1.13)	1.05 (0.98-1.12)
February	898	3.48	1.13 (1.05-1.21)	1.13 (1.06-1.22)
March	926	3.18	1.02 (0.95-1.09)	1.02 (0.95-1.09)
April	833	2.85	0.90 (0.84-0.97)	0.90 (0.83-0.96)
May	917	3.18	1.02 (0.95-1.09)	1.02 (0.95-1.10)
June	830	2.98	0.95 (0.88-1.02)	0.95 (0.88-1.02)
July	848	2.97	0.94 (0.88-1.01)	0.94 (0.88-1.01)
August	826	3.02	0.96 (0.90-1.03)	0.96 (0.90-1.04)
September	842	3.09	0.99 (0.92-1.06)	0.98 (0.91-1.06)
October	899	3.41	1.10 (1.03-1.18)	1.09 (1.02-1.17)
November	793	3.24	1.04 (0.97-1.12)	1.04 (0.97-1.12)
December	712	2.90	0.92 (0.85-0.99)	0.92 (0.85-1.00)
Respiratory defects	305	0.09		
January	28	0.10	1.12 (0.76-1.65)	1.12 (0.76-1.66)
February	26	0.10	1.09 (0.73-1.62)	1.09 (0.73-1.64)
March	46	0.16	1.81 (1.32-2.48)	1.82 (1.33-2.50)
April	21	0.07	0.75 (0.48-1.17)	0.76 (0.49-1.18)
May	25	0.09	0.92 (0.61-1.39)	0.92 (0.61-1.39)
June	26	0.09	1.00 (0.67-1.49)	1.00 (1.67-1.49)
July	24	0.08	0.89 (0.59-1.35)	0.89 (0.59-1.35)
August	28	0.10	1.11 (0.75-1.63)	1.10 (0.75-1.63)
September	21	0.08	0.81 (0.52-1.27)	0.81 (0.52-1.26)
October	23	0.09	0.93 (0.61-1.42)	0.92 (0.60-1.41)
November	11	0.04	0.46 (0.25-0.84)	0.46 (0.25-0.83)
December	26	0.11	1.15 (0.77-1.71)	1.14 (0.77-1.71)
Down syndrome	381	0.12		
January	35	0.13	1.12 (0.79-1.59)	1.08 (0.76-1.53)
February	48	0.19	1.68 (1.24-2.28)	1.64 (1.21-2.22)
March	39	0.13	1.16 (0.83-1.62)	1.15 (0.83-1.61)
April	32	0.11	0.93 (0.65-1.34)	0.93 (0.65-1.33)
May	35	0.12	1.04 (0.74-1.48)	1.03 (0.73-1.46)
June	31	0.11	0.95 (0.66-1.37)	0.76 (0.66-1.38)
July	34	0.12	1.02 (0.72-1.45)	1.04 (0.73-1.48)
August	19	0.07	0.57 (0.36-0.91)	0.58 (0.37-0.92)
September	20	0.07	0.61 (0.39-0.95)	0.59 (0.37-0.94)
October	39	0.15	1.30 (0.93-1.81)	1.29 (0.92-1.81)
November	26	0.11	0.90 (0.61-1.35)	0.93 (0.62-1.38)
December	23	0.09	0.79 (0.52-1.21)	0.83 (0.54-1.26)

Logistic regression analysis adjusted for maternal age, parity, centrality, population density, and industrial profile of municipality where the mother lived during pregnancy.
aOR = adjusted odds ratio; cOR = crude odds ratio.

percentile = 0.079) were consistent with Gini. Down syndrome occurred most often in February (adjusted OR 1.64, 95% CI 1.21–2.22), and least frequently in August (adjusted OR 0.58, 95% CI 0.37-0.92) and September (adjusted OR 0.59, 95% CI 0.37–0.94), as shown in Fig. 4.

4. Discussion

Based on Monte Carlo simulation, there was a statistically significant seasonal variation in the occurrence of any birth defect, respiratory defects, and Down syndrome. As a rule, birth defects occurred more often in February and October.

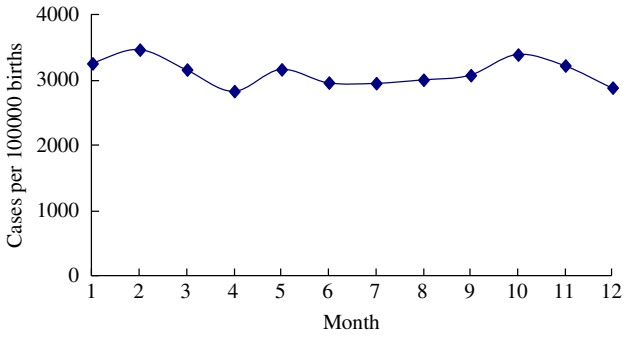

Fig. 2 – Seasonal variation of any birth defect in Norway, 1993–1998.

The highest occurrence of respiratory defects was in March, and Down syndrome in February. This seasonal variation of birth defects may imply an effect of environmental factors such as prenatal exposure to disinfection by-products [3] or viral infections [17,24,25], which are potential determinants of birth defects and known to exhibit seasonality. Taking into account length of gestation, the highest peak of conception of respiratory defects for all births over 28 weeks' gestation was in June and during the summer months. Interestingly, disinfection by-products might vary seasonally and increase with temperature [3]. The etiology of Down syndrome is still controversial and diffcult to understand. There are two possible explanations related to seasonal variation of Down syndrome. One can be expected as a consequence of seasonal variation in hormone production by the hypothalamus–pituitary–ovarian axis [19,34]; another is that the fetal brain is much more sensitive to viral infection during the first few months of gestation [17]. Further research should elaborate on whether a pregnant woman's exposure to disinfection by-products or virus infections is responsible for this seasonality.

4.1. *Validity of results*

The Medical Birth Registry supplied health information on large numbers of newborns, making it possible to assess seasonal variation of relatively rare birth defects. We excluded approximately one-tenth of these births due to insufficient gestational age data. This exclusion was not likely to introduce selection bias; characteristics of excluded individuals did

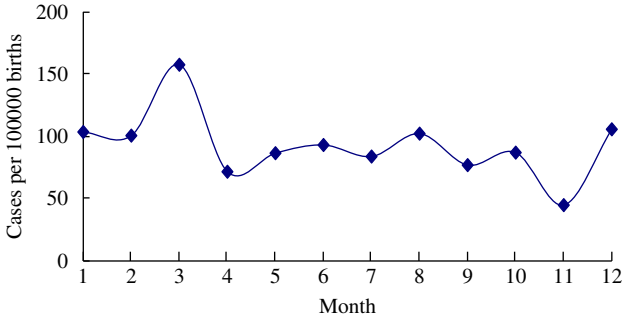

Fig. 3 – Seasonal variation of respiratory defects in Norway, 1993–1998.

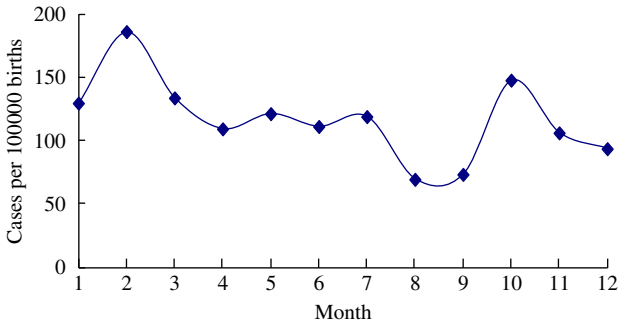

Fig. 4 – Seasonal variation of Down syndrome in Norway, 1993–1998.

not differ substantially from those included (data not shown). Because date of birth does not reflect the actual time period when the defect was induced and some defects also cause reduced length of gestation, we also estimated date of conception to evaluate the seasonal variation.

The issue of multiple comparisons should be considered when interpreting results of specific birth defects. In the current study of 32 comparisons (32 types of diagnostic defect and 1 seasonal pattern), two to three statistically significant associations at the 0.05 level would be found by chance alone [35,36]. Weak associations are more likely due to chance than strong associations. Thus, weak seasonal variation in occurrence of hydrocephalus could arise from multiple comparisons. Each reported association must be considered in light of previous epidemiologic and toxicologic evidence. This study had limited power to detect some of the rarer defects: e.g., only 21 of 326,560 newborns developed encephalocele.

Misclassification of birth defects is a potential source of random error, because diagnosis of birth defects is difficult due to the rarity of each condition. In general, these birth defects may be underreported, because we only included those diagnosed within the first week of life. However, we have no reason to believe that underreporting would be substantially related to month of birth. Therefore, in the presence of a true seasonal variation, underreporting would dilute the observed association rather than lead to erroneous inferences.

4.2. *Synthesis with previous knowledge*

Results indicate overall seasonal variation of birth defects in Norway, with peaks in February and October suggesting environmental factors playing a causal role. We evaluated consistency of seasonality over time by stratifying the study population into two strata according to year of birth and found no significant period effect. No previous study assessed the overall seasonal variation.

Newborns with neural tube defects was one group in Norway with risk related to exposure to disinfection by-products. Consistent with previous studies in Poland [5], Canada [6], Utah [7], South America [11], Italy [12], Japan [20], and northern Germany [21], we found no seasonal variation in the occurrence of neural tube defects in Norway. We noted seasonal variation in Down syndrome and respiratory tract defects. Stolwijk et al. reviewed 13 studies of Down syndrome published as of 1997 and concluded that there was no systematic seasonal pattern [19], pointing out that studies from the extreme end of the northern hemisphere suggested a seasonal pattern. Two such studies were from Sweden [37] and northern Finland [38]. Of the more recent studies, seasonal variation appeared in Hertfordshire, England [17] but not in a large population-based study of 7994 newborns with Down syndrome in England and Wales [23]. We did not identify previous observations of seasonal variation in respiratory defects. We found no seasonal variation in occurrence of several birth defects, which in previous studies have shown seasonality: esophageal atresia [12], diaphragmatic hernia [12], cleft lip [22,27,28], and ventricular septal defects [25,30].

5. Conclusion

In summary, this study indicates seasonal variation in occurrence of respiratory defects and Down syndrome in Norway. The peak occurrence of respiratory defects was in March and of Down syndrome in February. Further studies are needed to explain reasons for seasonal variation, which are likely to represent environmental causes of these birth defects.

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