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ORIGINAL ARTICLE

Complexities of sibling analysis when exposures and outcomes change with time and birth order

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In this study, we demonstrate the complexities of performing a sibling analysis with a re-examination of associations between cell phone exposures and behavioral problems observed previously in the Danish National Birth Cohort. Children (52,680; including 5441 siblings) followed up to age 7 were included. We examined differences in exposures and behavioral problems between siblings and non-siblings and by birth order and birth year. We estimated associations between cell phone exposures and behavioral problems while accounting for the random family effect among siblings. The association of behavioral problems with both prenatal and postnatal exposure differed between siblings (odds ratio (OR): 1.07; 95% confidence interval (CI): 0.69–1.66) and non-siblings (OR: 1.54; 95% CI: 1.36–1.74) and within siblings by birth order; the association was strongest for first-born siblings (OR: 1.72; 95% CI: 0.86–3.42) and negative for later-born siblings (OR: 0.63; 95% CI: 0.31–1.25), which may be because of increases in cell phone use with later birth year. Sibling analysis can be a powerful tool for (partially) accounting for confounding by invariant unmeasured within-family factors, but it cannot account for uncontrolled confounding by varying family-level factors, such as those that vary with time and birth order.

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Keywords: sibling analysis; cellular phone; child; behavior; confounding

INTRODUCTION

A number of epidemiological studies have shown associations between cell phone exposures and behavioral and cognitive changes in children. Findings have included poorer accuracy of working memory and associative learning, shorter reaction times for simple learning tasks, and longer completion times for Stroop color-word naming tasks in children reporting more cell phone voice calls.[1] Associations between radiofrequency exposure and behavioral problems among adolescents and conduct problems among children were reported in one study.[2] Another more recent study indicated a positive association between cell phone voice calls and attention-deficit hyperactivity symptoms among children with high blood lead levels; however, reverse causation could have produced these results.[3] Conversely, another investigation did not detect an association between prenatal cell phone use and behavioral problems in children, albeit this study was based on a small sample size, particularly a small number of exposed cases.[4]

Two analyses conducted among children in the Danish National Birth Cohort (DNBC) by Divan et al.[5,6] in 2008 and 2010 reported associations between prenatal and postnatal cell phone exposures and behavioral problems at age 7. Overall behavioral problems and specific behavioral outcomes were assessed using the Strengths and Difficulties Questionnaire (SDQ).[7] The original analysis included 13,159 children, and reported odds ratios (ORs) for higher overall behavioral problems scores of 1.80 (95% confidence interval (CI): 1.45–2.23) in children with both prenatal and postnatal exposure to cell phones.[5] They also reported associations among children with prenatal-only or postnatal-only exposure, with ORs for higher overall behavioral problems scores of 1.54 (95% CI: 1.32–1.81) and 1.18 (95% CI: 1.01–1.38), respectively. To demonstrate that associations between cell phone exposure and behavioral problems were not limited to early adopters of technology and persisted in the new sample after adjustment for several additional potential confounders, the authors replicated their findings in a separate group of 28,745 children from the same cohort.[6] Although the authors did not find evidence of confounding by measured factors, the possibility that confounding by unmeasured social, environmental, and hereditary factors may explain the observed associations could not be ruled out. An analysis that compares siblings in the DNBC may help to resolve some of the problems of unmeasured confounding. Compared with studies among unrelated individuals, studies among siblings can offer partial control of some unmeasured genetic, social, and lifestyle confounders that are shared within families.[8–10] However, sibling analysis can also be complicated by uncontrolled confounders that vary between siblings, making the results difficult to interpret.

For example, trends of increasing cell phone use and changes in cell phone technology over time could have contributed to the results observed by Divan et al.[5,6] The DNBC enrolled pregnant women during a time when cell phones were rapidly gaining popularity and many women were just beginning to use them. Children born earlier in the cohort are, therefore, less likely to have been exposed prenatally than those born later. We also expect those born later to have been more likely to use a cell phone at age 7. Conversely, exposure per use may have decreased over

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time because of changes in technology. All of these factors could have resulted in important differences between siblings in terms of their exposure that make a sibling analysis far from straightforward.

It is also important to consider changes in reported behavioral problems among children in relation to the birth order. Maternal perceptions of child behavior are expected to change with increased parenting experience.[11–13] Parents may have a more accepting attitude toward their second or third child's behavior compared with their first child. Mothers may have reported behavioral problems in their children differentially based on the child's birth order, thus affecting the observed associations between cell phone exposures and behavioral problems. Another possibility is that parenting styles may change with increased parenting experience and parental age, potentially resulting in fewer behavioral problems in higher-birth-order children.

We hypothesize that differences in exposures and outcomes because of factors that differ between siblings can complicate a sibling analysis. Our objective is to discuss the complexities of conducting a sibling analysis using the data on cell phone exposures and behavioral problems in the DNBC as an example. To do so, we investigated time trends in cell phone exposure and potential changes in the reporting of behavioral problems by birth order among siblings and non-siblings in the DNBC. We also performed an analysis of the associations between cell phone exposures and behavioral problems among siblings to illustrate the possibility of additional uncontrolled confounding from factors that vary between siblings.

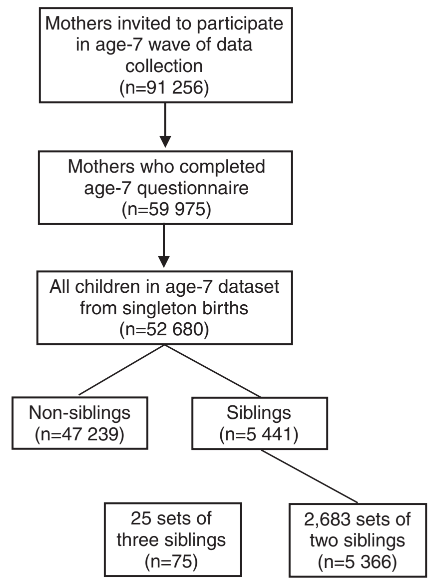

Figure 1. Participation and structure of the age-7 sample of the DNBC.

METHODS

The DNBC enrolled 91,661 pregnant women in Denmark between 1996 and 2002. The women and their children born into the cohort between 1997 and 2003 have been followed since enrollment. For each pregnancy, the DNBC collected information on various lifestyle and environmental exposures from interviews with the mothers at gestational weeks 12 and 30 and again when the children were 6 and 18 months of age.[14] Mothers were eligible to participate in the cohort more than once as they could re-enroll each time they became pregnant during the enrollment period, and thus contribute siblings to the cohort. Of the 91,661 women originally enrolled, 405 requested to discontinue participation in the study or their child passed away before age 7.

When the children reached 7 years of age, 91,256 mothers were invited to complete a questionnaire that focused on the child's environmental exposures (including cell phone exposures), lifestyle, and health problems.[15] Letters were sent to participants' homes instructing them about how to access the web-based version of the questionnaire. Reminders were mailed to women that did not respond within 4 weeks. Paper questionnaires were sent to women who had not responded 4 weeks after the reminders were sent. The format and questions of the web-based and paper questionnaires were identical.[5]

A total of 59,975 completed and submitted the age-7 questionnaire (66% participation rate). Children from multiple births (twins, triplets, and so on) were not included in this analysis, and data from the most recently completed questionnaires (after April 2010) were not available. This analysis is based on data from 52,680 children from singleton births included in the age-7 questionnaire. The data set consists of children included in the previous studies by Divan et al.,[5,6] plus 11,139 for whom data were coded after completion of the previous analyses. About 10% ($n = 5441$) of these children had at least one sibling from a singleton birth also included in this data set. Figure 1 illustrates the structure of the analytical sample in terms of the main subgroups of interest.

Two or more children in our data set with the same biological mother will be referred to as "siblings" participating in the DNBC. The group of all siblings in our data set will be referred to as the "sibling subset". All other children included in the age-7 wave will be referred to as "non-siblings". It is noteworthy that non-siblings in this study are not necessarily only-children, as they may have siblings that are not included in the DNBC. "Birth order" and "pregnancy order" refer to a child's birth order according to mothers' reported number of previous births, which could predate the inception of the DNBC.

Cell phone exposure was assessed by mothers' reports in the age-7 questionnaire. Previous waves of data collection did not assess cell phone exposure. Mothers reported whether or not they used a cell phone during pregnancy and whether or not the child uses a cell phone at age 7. Data from these questions were used to categorize children as having no exposure, prenatal-only, postnatal-only, or both prenatal and postnatal exposure (0 = no exposure, 1 = prenatal exposure only, 2 = postnatal exposure only, 3 = both prenatal and postnatal exposure).

Behavioral problems in children were assessed as part of the age-7 questionnaire using the parent SDQ module. Mothers responded to 25 statements regarding the child's behavior on a three-point scale (1 = not true, 2 = partly true, and 3 = very true). A previously developed algorithm generated a "total behavioral difficulties" score using responses to 20 of the 25 items in the SDQ.[16] *A priori*-defined cutoff points for the score were used to classify each child as "normal" (score = 0–13), "borderline" (score = 14–16), or "abnormal" (score = 17–40) for overall behavioral problems.[7] These cutoff points were based on population-based norms and were included with the SDQ algorithm when this study was conducted. They were the same cutoff points as those used by Divan, et al.[5,6]

From prenatal and postnatal interviews, the DNBC has also collected information from mothers regarding parity, social-occupational factors, history of psychiatric illness, smoking, and breastfeeding. Additional data were obtained by linking each mother and child to Danish national social and medical registers. Children's birth data were obtained from the Danish Medical Birth Registry.[17]

Associations between cell phone exposures and behavioral problems were compared between different sibling categories by computing ORs and 95% CIs using cumulative logistic regression models stratified by siblings, non-siblings, siblings from first pregnancies, and siblings from second pregnancies. Statistical adjustments were made for mother's age at the birth of the child, history of psychiatric illness, social-occupational status, prenatal smoking, and breastfeeding, as well as child's sex and birth order, where appropriate.

An analysis of the association between cell phone exposure and behavioral problems was conducted among siblings, controlling for the random effect of family. Generalized linear mixed models with a (cumulative) logit link function were used to compute ORs and 95% CIs for the associations between prenatal and postnatal, prenatal-only, and postnatal-only exposures to cell phones and behavioral problems in children compared with children without exposure.[18] Varying-intercepts (that is, partially pooled family-specific intercepts for the outcome) in these mixed models accounted for sibling clustering within families. Fixed effects included mother's age at the birth of the child, history of psychiatric illness, social-occupational status, prenatal smoking, and breastfeeding, as well as child's sex and birth order.

Further comparisons were made to examine the distribution of exposure and behavioral problems by overall birth order and calendar year of birth. All statistical analyses were conducted in SAS version 9.2 (SAS Institute, Cary, NC, USA).

This study was approved by the DNBC, the Danish Data Protection Agency, regional science ethics committees in Denmark, and the Office of the Human Research Protection Program at the University of California, Los Angeles.

RESULTS

Siblings and non-siblings in our data set differed on a number of characteristics (Table 1). Mothers of siblings in the cohort were more likely to report breastfeeding their children and less likely to report a history of psychiatric illness or smoking during pregnancy compared with mothers of non-siblings. Mothers of siblings tended to be younger and be in a higher social-occupational category than mothers of non-siblings. The percentage of children exposed to cell phones prenatally or postnatally and the percentage with abnormal or borderline behavioral difficulty scores were lower among siblings than that in non-siblings. Consistent with secular trends in smoking and cell phone use, we found that mothers were less likely to smoke while pregnant with the second sibling than with the first sibling, and second siblings were more likely to have prenatal-only exposure or both prenatal and postnatal cell phone exposure.

When comparing the sibling subset to all non-siblings, associations between prenatal-only and both prenatal and postnatal cell phone exposure and behavioral problems were weaker among siblings than among non-siblings (Table 2). Associations among first-born siblings who were exposed to cell phones both prenatally and postnatally were similar to non-siblings (and to the results of the full cohort), with increased ORs for behavioral problems. The associations tended to be weaker for postnatal-only cell phone exposure, particularly among second-born siblings and second pregnancies, but no clear pattern in the associations emerged for postnatal-only cell phone exposure overall. The results for siblings did not change after accounting for within-family similarities using the random-intercept generalized linear mixed models described above.

Regardless of cell phone exposure, children from mothers' second and third pregnancies overall had lower odds of behavioral problems than first children with ORs of 0.93 (95% CI: 0.85–1.03) and 0.76 (95% CI: 0.65–0.89), respectively (Table 3). Similar trends were observed when comparing siblings and non-siblings from first, second, and third pregnancies in the DNBC (data not shown).

In line with secular trends of cell phone use, there was a clear trend of increasing cell phone exposure among all children in the cohort with increasing year of birth (Figure 2). The majority of children (57%) born in 1997 or 1998 had no reported cell phone exposure, and those that were exposed were more likely to use a cell phone postnatally (7 years later) than to have only been exposed prenatally. Children born in 2003 were nearly four times as likely as those born in 1997 or 1998 to have both prenatal and postnatal exposure, and more than twice as likely to have been exposed prenatally only. This time trend of increasing exposure by year of birth also persists within strata of birth order (for example, first siblings only, second siblings only, and so on; data not shown).

Table 4 presents results comparing associations between cell phone exposures and behavioral problems among children from mothers' first pregnancies and second or later pregnancies by year of birth. No association between postnatal-only exposure and behavioral problems was detected among children born in later years (2001–2003), regardless of birth order. The pattern of associations between other cell phone exposure categories and behavioral problems are generally similar among children born in earlier years (1997–2000) compared with those born later (2001–2003).

DISCUSSION

Compared with studies among unrelated individuals, studies among siblings can offer some control of unmeasured genetic, social, and lifestyle confounders that are shared within families.[8–10] In this investigation, the strong associations observed previously by Divan et al.[5,6] were replicated for first-born and non-siblings but not observed among second-born siblings. Accounting for random family effects did not change the results. Although the positive associations we observed among first-born siblings were not statistically significant, we do not consider these null results. Rather than statistical significance alone, we also use consistency and pattern (especially magnitude and directionality of the point estimates) to guide our interpretation.

We found that the OR for the association between cell phone exposures and behavioral problems was larger among siblings from first pregnancies than siblings from second pregnancies within the DNBC catchment period, although not significantly. This difference in associations by birth order suggests that a comparison between siblings can be imbalanced, given the trend of increasing cell phone use with time. We also estimated associations between cell phone exposure and behavioral problems stratified by birth order for all children in the data set regardless of sibling status, but the results did not explain the differences between siblings. Our findings indicate that the siblings in our data set are different from the non-siblings and should be kept separate in the analyses, or analyses should be restricted to first-borns only.

Parents' perceptions of their children's behavior may differ from one child to the next with increased parenting experience and parity,[11–13] as well as changes in societal influences regarding child and parenting behaviors. Further, parental coping styles may change with increased parenting experience or with increased age of the parents. The results from this study support the hypothesis that differences in the association of interest between first-born and later-born siblings may be because of changes in parenting behaviors, parental age, or parent perceptions of behavioral problems with increased parity. Although we controlled for maternal age at the birth of the child in the analysis, this adjustment would not have accounted for the difference in the mother's age between two related siblings. Regardless of cell phone use, mothers were less likely to report behavioral problems for higher-birth-order children than that for first-born children, which may reflect greater parenting experience.

The differences in the association between cell phone exposure and behavioral problems between first-born and later-born siblings may have been due, in part, to changes in exposure with time. Over the past few decades, cell phone use has rapidly increased, with more users and heavier use, whereas the evolution of cell phone technology has lowered the rate of individual radiofrequency exposure per use.[19–21] Overall, there is a strong trend of increasing cell phone use with time, as reflected in the DNBC data set. Prenatal and postnatal cell phone exposures increased dramatically by year, reflecting an increase in use by mothers and children. This increase in cell phone use compensates somewhat for the possible reduction in exposure from newer phones. In fact, associations between prenatal-only and both prenatal and postnatal cell phone exposure and overall behavioral problems among first children with an early year of birth were similar to those for first children born later.

There are a number of other approaches to comparing siblings in epidemiological studies besides the method used in this investigation. One common approach is the discordant-pair method, in which an exposed child is matched to their

Table 1. Sample characteristics.

	Non-siblings only[a] (n = 47,239)		Siblings only[b] (n = 5,441)		P-value from χ^2-test for trend	First-born siblings[c] (n = 2,101)		Second-born siblings[d] (n = 2,481)		P-value from χ^2-test for trend
	n	%	n	%		n	%	n	%	
Sex of child										
Boy	24,184	51.2	2804	51.5	0.64	1070	50.9	1273	51.3	0.80
Girl	23,055	48.8	2637	48.5		1031	49.1	1208	48.7	
Child was breastfed										
Yes	28,926	61.2	3692	67.9	< 0.01	1355	64.5	1717	69.2	0.16
No	9997	21.2	1086	20.0		442	21.0	504	20.3	
Missing	8316	17.6	663	12.1		304	14.5	260	10.5	
Mother smoked while pregnant										
Yes	11,606	24.6	908	16.7	< 0.01	438	20.8	356	14.3	< 0.01
No	32,141	68.0	4151	76.3		1604	76.3	2000	80.6	
Missing	3492	7.4	382	7.0		59	2.8	125	5.0	
Mother has psychiatric history										
Yes	6694	14.2	649	11.9	< 0.01	249	11.9	297	12.0	0.90
No	39,119	82.8	4683	86.1		1809	86.1	2134	86.0	
Missing	1426	3.0	109	2.0		43	2.0	50	2.0	
Mother's age at birth of child										
> 35 years	6332	13.4	556	10.2		90	4.3	264	10.6	
31–35 years	16,859	35.7	1920	35.3		475	22.6	1029	41.5	
26–30 years	19,001	40.2	2497	45.9		1199	57.1	1084	43.7	
≤ 25 years	5047	10.7	468	8.6		337	16.0	104	4.2	
Mean (SD)	30.6 (4.3)		30.4 (3.8)		< 0.01[e]	28.7 (3.5)		31.0 (3.5)		< 0.01[e]
Socioeconomic status										
High	30,982	65.6	3848	70.7	< 0.01	1547	73.6	1857	74.8	0.53
Medium	12,571	26.6	1244	22.9		505	24.0	561	22.6	
Low	1532	3.2	147	2.7		46	2.2	57	2.3	
Missing	2154	4.6	202	3.7		3	0.1	6	0.2	
Child's cell phone exposure										
Both prenatal and postnatal	8903	18.8	878	16.1	< 0.01	217	10.3	519	20.9	< 0.01
Postnatal only	7396	15.7	817	15.0		340	16.2	351	14.1	
Prenatal only	9620	20.4	1070	19.7		352	16.8	546	22.0	
None	19,051	40.3	2456	45.1		1115	53.1	953	38.4	
Unknown	2269	4.8	220	4.0		77	3.7	112	4.5	
Overall behavioral difficulties										
Abnormal	1504	3.2	111	2.0	< 0.01	42	2.0	44	1.8	0.52
Borderline	1577	3.3	158	2.9		69	3.3	69	2.8	
Normal	43,955	93.0	5165	94.9		1989	94.7	2364	95.3	
Missing	203	0.4	7	0.1		1	< 0.1	4	0.1	

[a]All singleton-birth children who were included in the age-7 data set and do not have any singleton-birth siblings (child from the same mother) also in the age-7 data set.
[b]All singleton-birth children who were included in the age-7 data set and have at least one singleton-birth sibling (child from the same mother) also in the age-7 data set.
[c]Singleton-birth children from a mother's first pregnancy overall among children who were included in the age-7 data set and have at least one singleton-birth sibling (child from the same mother) also in the age-7 data set.
[d]Singleton-birth children from a mother's second pregnancy overall among children who were included in the age-7 data set and have at least one singleton-birth sibling (child from the same mother) also in the age-7 data set.
[e]*P*-value from two-sample *t*-test.

unexposed sibling. As this study examined four exposure categories rather than the usual two seen in published discordant-pair analyses, our sample did not have enough discordant sibling pairs in each category to perform a discordant-pair analysis. Many prior investigations of siblings have used generalized estimating equations (GEE) to separate within-family and between-family effects. This type of analysis is designed for use with continuous exposure variables, and is not appropriate for our categorical outcome data without making suspect assumptions. The random-intercept generalized linear mixed models with logit link (such as that implemented in the GLIMMIX procedure in SAS) that we used are appropriate for our objectives and clustered sibling data available from the DNBC. This approach is analogous to the GEE method but offers more flexibility in fitting non-marginal (that is, population averaged) models with ordinal or multinomial outcomes and categorical exposures.

Table 2. ORs for the associations between prenatal and postnatal cell phone exposures and overall behavioral difficulties by sibling status.

	Prenatal exposure only	*Postnatal exposure only*	*Both prenatal and postnatal exposure*
All children (n = *52,680)*			
OR (95% CI)	1.51 (1.37–1.66)	1.18 (1.05–1.32)	1.91 (1.74–2.09)
$OR_{adj}^{a,b}$ (95% CI)	1.28 (1.13–1.44)	1.13 (0.99–1.29)	1.51 (1.34–1.69)
Non-siblings only[c] (n = *47,239)*			
OR (95% CI)	1.53 (1.38–1.69)	1.15 (1.02–1.30)	1.95 (1.77–2.15)
$OR_{adj}^{a,b}$ (95% CI)	1.28 (1.13–1.45)	1.12 (0.97–1.29)	1.54 (1.36–1.74)
Siblings only[d] (n = *5441)*			
OR (95% CI)	1.29 (0.93–1.79)	1.41 (0.99–2.00)	1.34 (0.94–1.90)
$OR_{adj}^{a,b}$ (95% CI)	1.19 (0.80–1.75)	1.17 (0.76–1.80)	1.07 (0.69–1.66)
First-born siblings[e] (n = *2101)*			
OR (95% CI)	1.33 (0.78–2.27)	1.60 (0.96–2.67)	1.89 (1.07–3.35)
OR_{adj}^{a} (95% CI)	1.14 (0.61–2.16)	1.50 (0.83–2.72)	1.72 (0.86–3.42)
Second-born siblings[f] (n = *2481)*			
OR (95% CI)	1.64 (1.02–2.65)	0.96 (0.50–1.82)	1.10 (0.64–1.88)
OR_{adj}^{a} (95% CI)	1.28 (0.74–2.22)	0.86 (0.43–1.75)	0.63 (0.31–1.25)
First pregnancies overall[g] (n = *23,655)*			
OR (95% CI)	1.48 (1.29–1.70)	1.19 (1.01–1.40)	1.91 (1.63–2.17)
OR_{adj}^{a} (95% CI)	1.19 (1.01–1.41)	1.11 (0.91–1.34)	1.46 (1.24–1.72)
Second pregnancies overall[h] (n = *18,762)*			
OR (95% CI)	1.47 (1.25–1.73)	1.05 (0.87–1.26)	1.62 (1.37–1.91)
OR_{adj}^{a} (95% CI)	1.26 (1.03–1.53)	1.09 (0.88–1.35)	1.33 (1.09–1.62)
Siblings only[d]*, controlling for family effects*[i] (n = *5441)*			
OR (95% CI)	1.28 (0.87–1.89)	1.48 (0.98–2.24)	1.34 (0.88–2.03)
OR_{adj}^{a} (95% CI)	1.18 (0.77–1.82)	1.19 (0.74–1.90)	1.07 (0.66–1.73)
$OR_{adj}^{a,b}$ (95% CI)	1.19 (0.77–1.82)	1.18 (0.74–1.89)	1.08 (0.66–1.74)

Abbreviations: CI, confidence interval; OR, odds ratio.
Reference category is no exposure.
[a]Adjusted for child's sex, mother's age at birth of child, mother's smoking during pregnancy, mother's history of psychiatric problems, social-occupational status, and breastfeeding.
[b]Adjusted for birth order.
[c]All singleton-birth children who were included in the age-7 cohort data set and do not have any singleton-birth siblings (child from the same mother) also in the age-7 cohort sample. Note: non-siblings are not necessarily only-children as they may have siblings that are not included in the DNBC.
[d]All singleton-birth children who were included in the age-7 data set and have at least one singleton-birth sibling (child from the same mother) also in the age-7 cohort sample.
[e]Singleton-birth children in the sibling subset from a mother's first pregnancy overall.
[f]Singleton-birth children in the sibling subset from a mother's second pregnancy overall.
[g]Singleton-birth children from a mother's first pregnancy.
[h]Singleton-birth children in the sibling subset from a mother's second pregnancy overall.
[i]Models included partially pooled family-specific intercepts for the outcome to account for sibling clustering within families.

Table 3. ORs for the association between behavioral problems and birth order.

	First pregnancy (n = *23,655)*		*Second pregnancy* (n = *18,762)*		*Third pregnancy* (n = *6631)*	
	n	%	n	%	n	%
Abnormal	793	3.4	526	2.8	167	2.5
Borderline	897	3.8	590	3.1	139	2.1
Normal	21 880	92.5	17 566	93.6	6 300	95.0
Missing	85	0.4	80	0.4	25	0.4
OR (95% CI)	1.00		0.82 (0.76–0.89)		0.63 (0.56–0.72)	
OR_{adj}^{a} (95% CI)	1.00		0.93 (0.85–1.03)		0.76 (0.65–0.89)	

Abbreviations: CI, confidence interval; OR, odds ratio.
Reference category is first pregnancy.
[a]Adjusted for child's sex, mother's age at birth of child, mother's history of psychiatric problems, mother's smoking during pregnancy, social-occupational status, and breastfeeding.

Although sibling analysis can be a powerful tool for (partially) accounting for confounding because of unmeasured but stable within-family factors, all sibling analyses face an important limitation in that they cannot account for uncontrolled confounding by unmeasured time-varying (or sibling-varying) within-family factors. When performing sibling studies, researchers should carefully consider factors that may affect the exposure and outcome differently between siblings. As demonstrated in this investigation, societal factors, time trends, birth order, and parental perceptions and behaviors can have an impact on

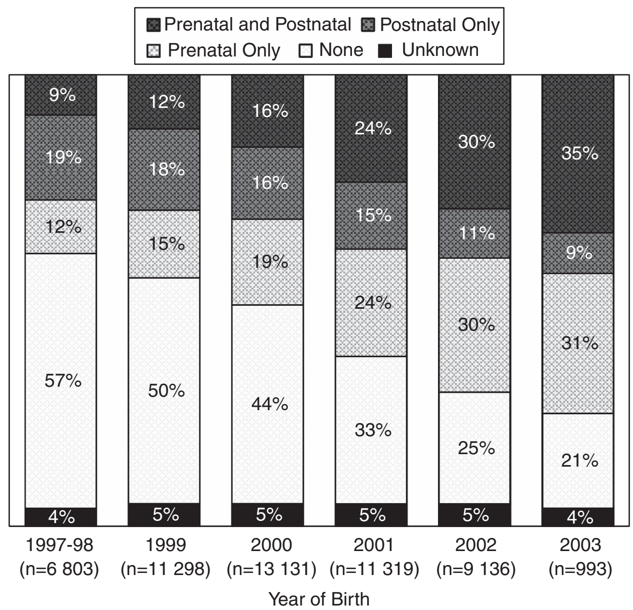

Figure 2. Exposure type by year of birth among all children in the age-7 sample of the DNBC ($n = 52,680$).

associations of interest at the level of an individual child or family. These factors can easily be overlooked, even in a sibling analysis, and may be difficult or impossible to measure and control and may invalidate the results of a sibling analysis regardless of the type of analytic method used. Under these conditions, a sibling design may well perform worse than a non-sibling design and produce misleading results.

Exposure misclassification in this study cannot be ruled out, but we do not expect it to have produced these results. Although assessment of cell phone use during pregnancy was retrospective, pregnancy leaves a strong impression on women's memories, and women therefore tend to remember their behaviors during this unique time with high accuracy.[22,23] Assessment of the child's exposure was very general (whether the child uses a cell phone more or less than 1 h per week or not at all); mothers should have been able to answer the question quite accurately.

It is possible that children (and, perhaps, mothers) who are heavier cell phone users may have been less likely to participate in the age-7 data collection wave and are underrepresented in our data. A study in the DNBC found that mothers lost-to-follow-up were more likely to be in the low social-occupational status category than women who continued participation.[24] Several studies have reported that cell phone use among children and adolescents is inversely associated with social-occupational status.[25–29] As social-occupational status may be related to child behavior, this loss-to-follow-up could have biased some of our

Table 4. ORs for the association between cell phone exposure and behavioral problems by birth order (first pregnancies overall compared with second or higher-order pregnancies overall) by late or early year of birth.

	No exposure		*Prenatal exposure only*		*Postnatal exposure only*		*Prenatal and postnatal exposure*		*Unknown exposure*	
	n	%	n	%	n	%	n	%	n	%
1st pregnancy overall (born 1997–2000[a]) ($n = 13,358$)										
Abnormal	153	2.5	101	4.2	65	2.8	103	5.2	27	4.5
Borderline	187	3.1	97	4.1	102	4.5	110	5.5	19	3.2
Normal	5754	94.3	2178	91.6	2123	92.6	1773	89.2	492	82.1
Missing	6	0.1	3	0.1	3	0.1	1	0.1	61	10.2
OR (95% CI)		1.0	1.55 (1.29–1.85)		1.32 (1.09–1.61)		2.04 (1.70–2.44)			
OR[b] (95% CI)		1.0	1.20 (0.96–1.50)		1.26 (1.00–1.59)		1.56 (1.25–1.96)			
1st pregnancy overall (born 2001–2003[c]) ($n = 10,297$)										
Abnormal	54	2.1	102	3.5	26	2.1	143	4.6	19	4.2
Borderline	76	2.9	113	3.9	34	2.7	144	4.6	15	3.3
Normal	2438	94.8	2704	92.6	1189	95.0	2813	90.7	416	92.2
Missing	4	0.2	2	0.1	2	0.2	2	0.1	1	0.2
OR (95% CI)		1.0	1.50 (1.20–1.87)		0.95 (0.69–1.30)		1.92 (1.55–2.38)			
OR_{adj}[b] (95% CI)		1.0	1.17 (0.90–1.53)		0.82 (0.57–1.19)		1.38 (1.07–1.79)			
≥2nd pregnancy overall (born 1997–2000[a]) ($n = 16,701$)										
Abnormal	194	2.2	84	3.4	72	2.5	93	5.0	21	2.6
Borderline	196	2.3	91	3.7	92	3.1	75	4.0	25	3.1
Normal	8236	95.4	2274	92.7	2766	94.2	1697	90.9	681	84.3
Missing	10	0.1	5	0.2	5	0.2	3	0.2	81	10.0
OR (95% CI)		1.0	1.62 (1.35–1.95)		1.25 (1.03–1.51)		2.10 (1.74–2.54)			
OR_{adj}[b] (95% CI)		1.0	1.38 (1.10–1.73)		1.27 (1.02–1.58)		1.70 (1.35–2.15)			
≥2nd pregnancy overall (born 2001–2003[c]) ($n = 10,094$)										
Abnormal	64	1.9	83	3.4	30	2.2	87	3.7	14	2.6
Borderline	88	2.6	76	3.1	28	2.0	84	3.6	16	3.0
Normal	3194	95.4	2311	93.5	1337	95.8	2174	92.6	499	93.8
Missing	1	<0.1	1	<0.1	0	0.0	4	0.2	3	0.6
OR (95% CI)		1.0	1.45 (1.16–1.83)		0.92 (0.67–1.25)		1.66 (1.33–2.08)			
OR_{adj}[b] (95% CI)		1.0	1.32 (1.01–1.72)		0.90 (0.63–1.28)		1.40 (1.07–1.84)			

Abbreviations: CI, confidence interval; OR, odds ratio.
Reference category is no exposure.
[a]Postnatal exposure occurred approximately in 2004–2007.
[b]Adjusted for child's sex, mother's age at birth of child, mother's smoking during pregnancy, mother's history of psychiatric problems, social-occupational status, and breastfeeding.
[c]Postnatal exposure occurred approximately in 2008–2010.

results. Likewise, differences between siblings and non-siblings with regard to socio-occupational status and other factors, such as prevalence of breastfeeding and psychiatric history of the mother, may potentially be attributed to differences in participation between these two groups if participation was also related to these factors. However, when comparing siblings and accounting for shared family factors, we would not expect loss-to-follow-up bias in terms of social-occupational status or other characteristics shared between siblings to be a concern.

Despite the limitations of our sibling analysis, this study benefited from a large sample size with good exposure contrast and rich covariate data from a well-published prospective cohort. As women were pregnant during a time when cell phone use was still gaining popularity, our study sample included a large number of exposed and unexposed children. As enrollment occurred over a period of several years, we were able to observe changes in cell phone exposure with time and capture data for siblings from mothers who participated in the study multiple times.

On the face of it, controlling for family effects among siblings did not alter the results, indicating no confounding by factors that are shared within families. However, because of the differences between siblings and non-siblings and differences we observed by birth order, the sibling analysis does not appear to offer clear methodological or interpretational advantages in this complex case study.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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