BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-011972
Article Type:	Research
Date Submitted by the Author:	21-Mar-2016
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Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Emergency medicine, Epidemiology, Health services research, Paediatrics
Keywords:	cerebral palsy, traffic crash, preterm birth, prenatal care, road accident, Motor vehicle trauma

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Motor Vehicle Crashes During Pregnancy and Cerebral Palsy During Infancy

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Conflicts of Interest: The authors report no conflicts of interest.

Short Title: Crashes in pregnancy and cerebral palsy

Single Sentence:
Motor vehicle crashes during pregnancy were associated with an increased subsequent risk of cerebral palsy in children with preterm birth.

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words: 2,532 abstract: 261 Tables 5

Abstract

Objectives: To assess the incidence of cerebral palsy among children born to mothers who had their pregnancy complicated by a motor vehicle crash.

Design: Retrospective longitudinal cohort analysis of children born from April 1, 2002 to March 31, 2012 in Ontario, Canada.

Participants: Cases defined as pregnancies complicated by a motor vehicle crash and controls as remaining pregnancies with no crash.

Main Outcome: Subsequent diagnosis of cerebral palsy by age three years.

Results: A total of 1,325,660 newborns were analyzed, of whom 7,933 were involved in a motor vehicle crash during pregnancy. A total of 2,328 were subsequently diagnosed with cerebral palsy, equal to an absolute risk of 1.8 per 1,000 newborns. For the entire cohort, motor vehicle crashes correlated with a marginal 29% increased risk of subsequent cerebral palsy (95% confidence interval: -16 to +110, p = 0.274). The increased risk was only significant for those with preterm birth who showed an 89% increased risk of subsequent cerebral palsy associated with a motor vehicle crash (95% confidence interval: +7 to +266, p = 0.037). No significant increase was apparent for those with a term delivery (95% confidence interval: -62 to +79, p = 0.510). Propensity score matched analysis of preterm births yielded a 138% increased relative risk of cerebral palsy associated with a motor vehicle crash (95% confidence interval +27 to +349, p = 0.007), equal to an absolute increase of about 10.9 additional cases per 1,000 newborns.

Conclusion: Motor vehicle crashes during pregnancy may be associated with an increased risk of cerebral palsy among the subgroup of cases with preterm birth. The increase highlights a specific role for traffic safety advice in prenatal care.

Key Words: cerebral palsy, traffic crash, preterm birth, prenatal care, road accident

Article Summary

Strengths and Limitations

- Motor vehicle crashes in pregnancy were identified in a large comprehensive population cohort of women who subsequently gave birth
- Long-term outcomes among children were tracked longitudinally for years to examine a subsequent diagnosis of cerebral palsy after preterm birth
- The non-randomized design means an association of motor vehicle crashes in pregnancy with an increased relative risk cerebral palsy may not be causal
- The absolute risk of cerebral palsy following a motor vehicle crash among children with preterm birth is not large
- The absolute risk of cerebral palsy following a motor vehicle crash among children without preterm birth is small and easily attributed to chance

Background

Cerebral palsy is a leading cause of disability during childhood, with about 25 children diagnosed with cerebral palsy each day in the United States.[1] The severity spectrum spans from individuals living independently in the community to those needing comprehensive care in an institution. The average lifetime cost of cerebral palsy amounts to about $1 million in the United States.[2] Several causes of cerebral palsy have been identified including prematurity [3 4 5 6 7 8 9 10], abnormal genetics [11 12], multiple pregnancy [13], maternal infections [14 15 16], and birth asphyxia [17 18]. However, many cases of cerebral palsy are unexplained and considered due to an unidentified injury to the young developing brain[19 20 21].

Motor vehicle crashes are a common cause of maternal trauma [22 23 24 25], complicating over 2,000 per 100,000 pregnancies.[26 27 28] The consequences include maternal death (1 per 100,000 pregnancies) and fetal death (4 per 100,000 pregnancies).[29] The non-fatal short-term consequences of a motor vehicle crash include placental abruption, premature rupture of membranes, uterine disruption, or early delivery.[30 31 32 33 34] Fetal injury following a motor vehicle crash can occur without direct uterine injury, may have a delayed presentation, and correlates imperfectly with the severity of maternal injury.[35] Hence, maternal trauma from a motor vehicle crash might cause injury to a young developing brain.

Several mechanisms could contribute to a possible association between a motor vehicle crash during pregnancy and subsequent cerebral palsy during infancy. The most direct mechanism is acute trauma leading to preterm birth.[36] Less direct mechanisms might include fetal cerebral hypoxia caused by maternal hypotension.[37 38 39] Other possibilities include a stress response involving the maternal autonomic vascular or metabolic systems that compromises uterine perfusion.[40 41] A further mechanism relates to chronic placental insufficiency from clot formation or traumatic shear stresses.[42] These mechanisms, however, are speculative and no population-based study has tested whether cerebral palsy during infancy might be linked to a motor vehicle crash during pregnancy.

Methods

Study Setting

We conducted a retrospective longitudinal population-based cohort study using datasets from the Institutes for Clinical Evaluative Sciences (ICES).[43] These datasets integrate information from medical encounters by patients throughout the Ontario healthcare system and covered by the universal health insurance plan.[44 45] This plan provided all-inclusive access to care with no cost to patients for emergency and prenatal treatments, thereby providing comprehensive longitudinal patient data for analysis. Patients were not involved in setting the research agenda and this study was approved by the ethics board of Sunnybrook Health Sciences Centre including a waiver for consent and permissions for database linkages.

Pregnancy Identification

We identified women (age 14 to 50 years) who gave birth between April 1, 2002 to March 31, 2012 by screening physician codes for a newborn delivery (codes P006, P018, P020) using the MOM-BABY database at ICES.[46] Abortions were excluded and repeat pregnancies were counted as separate events.[47] One woman, therefore, was counted for each birth and twins were counted as separate observations. Each pregnancy was categorized as complicated or not complicated by a motor vehicle crash, defined as a traffic event sending the woman to an emergency department.[48] Motor vehicle crashes included events as drivers, passengers, or other road users and excluded events related to aircraft or watercraft.

Newborn Identification

Children were identified using the MOM-BABY database at ICES that linked maternal and birth records with 98% accuracy.[49 50 51] The database has been used extensively.[52 53 54 55 56] We excluded individuals with faulty medical records, living outside Ontario, or high-order multiple births; otherwise, the sampling was comprehensive and complete. Limitations of the database include the lack of direct information on sibling relationships, paternal connections, and home environment.

The database also lacks information about multiple lifestyle behaviors including smoking, alcohol, substance abuse, domestic violence, dietary intake, toxin exposure, marital status, and other social determinants of health.

Identification of Crashes

We identified motor vehicle crashes using validated diagnostic codes from all emergency departments throughout Ontario (International Statistical Classification of Diseases version 10 codes V00 -V69).[57 58] Additional crash characteristics included day, season, clock-time (morning, afternoon, night), position (driver, passenger, other), enrolment interval, ambulance involvement, and triage severity. For each case we also tracked backward from the date of delivery and distinguished each month of pregnancy separately taking into account gestational age in weeks. Hence, infants born prematurely were assigned a beginning of pregnancy calculated from the delivery date and gestational age. Each trimester was defined as consecutive 13 weeks intervals starting at the beginning of pregnancy.

Identification of Cerebral Palsy

Newborns were followed for three years to determine survival and subsequent diagnosis since most cerebral palsy is diagnosed by age three.[59 60] Diagnostic codes were used to search for a physician diagnosis of cerebral palsy (International Statistical Classification of Diseases version 9 code 343, version 10 code G80).[61] We further distinguished cerebral palsy cases as explained or unexplained according to known antecedent; namely, congenital abnormalities, maternal infection, birth asphyxia, illicit drug use, and bleeding complication [62 63 64 65 66 67 68 69 70 71 72 73] (ICD version 10 codes Q00 to Q99; P02 to P04; P10-P15; P20-P21; P36 to P39). We did not define prematurity as a direct explanation because it might be an intermediate mechanism (explored in secondary outcomes).

Identification of Additional Predictors

The demographic registry was used to obtain maternal data on age, socioeconomic status, and home location (urban, rural).[74] Prenatal care, pregnancy duration, mode of delivery, multiple gestations and length of hospital stay were determined based on linked identifiers.[75 76 77 78] Primiparity and multiparity was based on birth records from the previous 20 years. Neonatal variables included prematurity (binary), sex (binary), birth-weight (normal, very-low, low, overweight), day of delivery (weekend vs weekday), and enrolment interval (first five years, second five years).[79 80 81 82 83 84] The databases did not contain driving history, roadway infractions, chosen destinations, license status, travel diaries, vehicle distances, injury severity, and impact velocity.

Statistical Analysis

The primary study outcome was the risk of a subsequent diagnosis of cerebral palsy by age three. The main analysis used proportional hazards analysis to compare children born after a pregnancy that was complicated by a motor vehicle crash to children born after a pregnancy that was not complicated by a motor vehicle crash (interval deaths censored for the primary analysis and considered in secondary analysis). Stratified analyses were used to assess differences according to individual characteristics with special attention to those with preterm birth. Secondary tests also used propensity matched analysis to reevaluate the risk of cerebral palsy after adjusting for differences in baseline characteristics of preterm births. All p-values were two-tailed and calculated with 95% confidence intervals.

Results

Maternal Characteristics

A total of 884,897 women gave birth to 1,325,660 newborn children, of whom 7,933 newborns (1-in-170) had the pregnancy complicated by a motor vehicle crash. As expected, motor vehicle crashes involved women across a wide spectrum of age, socio-economic status, and pregnancy experience (Table 1). The mean maternal age was marginally lower for those pregnancies complicated by a motor vehicle crash compared to those pregnancies not complicated by a motor vehicle crash. Otherwise, the distribution of socioeconomic status, home location, prenatal care visits, parity, pregnancy duration, mode of delivery, and hospital length of stay were similar for the two groups.

*** Table 1 About Here ***

Subsequent Child Outcomes

A total of 2,328 children were diagnosed with cerebral palsy by age 3 years (1,325,660 identified newborns, 5,425 interval deaths). The median age at cerebral palsy diagnosis was 586 days and median age at death was 7 days. The most common identified reasons linked to cerebral palsy were perinatal disorders and congenital abnormalities, collectively accounting for 1,225 children. The remaining 1,103 children (47%) were classified as having unexplained cerebral palsy. The median age for diagnosing unexplained cerebral palsy was 610 days. The overall rate of cerebral palsy per 1,000 pregnancies was about the same in the first five years of the study and the second five years of the study (1.82 vs 1.70, respectively).

Motor Vehicle Crashes and Cerebral Palsy Risk

A total of 18 children diagnosed with cerebral palsy were born following 7,933 pregnancies complicated by a motor vehicle crash. In contrast, 2,310 children with cerebral palsy were born following 1,317,727 pregnancies with no motor vehicle crash. The difference in risk equaled a marginally increased incidence of cerebral palsy associated with motor vehicle crashes per 1,000 pregnancies (2.27 vs 1.75, p = 0.274), equal to a 29% relative increase in risk (95% confidence interval -16 to +110). The absolute difference amounted to 685 fewer cases of cerebral palsy among those who did not have a crash during pregnancy. The increased risk was most apparent before age 2 years (Appendix).

Patient Characteristics

The increased risk of cerebral palsy associated with a motor vehicle crash was evident for subgroups with different characteristics (Table 2). The highest observed relative risks were among pregnancies followed by a preterm delivery that showed a 89% relative increase in risk (95% confidence interval +7 to +266, p = 0.037). No increase was apparent for pregnancies followed by a term delivery (95% confidence interval: -62 to +79, p = 0.510). All confidence intervals were wide, almost all upper bounds overlapped a 100% relative increase in risk, and no subgroup showed a statistically significant contrary pattern.

*** Table 2 About Here ***

Additional Predictors in Cases with Preterm Birth

Several baseline characteristics were also associated with cerebral palsy following a preterm birth (Table 3). Older maternal age predicted lower risk (perhaps due to high risks in teenage mothers). Those born in more recent years had a lower risk (perhaps due to improved obstetrical and neonatal care). Prenatal care visits were associated with lower risk (perhaps due unmeasured health-oriented behavior). Conversely, past hospitalizations predicted higher risk (perhaps as a proxy for underlying patient illnesses). As expected, cerebral palsy was more frequent in boys. The absolute rate of cerebral palsy averaged about 9.7 per 1,000 pregnancies among all newborns with preterm birth.

*** Table 3 About Here ***

Propensity Matched Analysis in Preterm Birth

Propensity score matching yielded a cohort of 4,384 newborns with preterm birth of whom 548 had the pregnancy complicated by a motor vehicle crash and the remaining 3,836 had no motor vehicle crash (matching ratio 1-in-7 by design). As expected, the distribution of maternal characteristics was similar for the two groups (Table 4). A total of 38 children were subsequently diagnosed with cerebral palsy, equal to a 138% increased relative risk of cerebral palsy associated with a motor vehicle crash (95% confidence interval +27 to +349, p = 0.007). The absolute risk of cerebral palsy equaled about 10.9 additional cases per 1,000 pregnancies complicated by a motor vehicle crash (18.2 vs 7.3, p = 0.010).

*** Table 4 About Here ***

Crash Features

The increased overall risk of cerebral palsy associated with a motor vehicle crash was evident for crashes with different features (Table 5). The most frequent time for a crash was on a weekday and no large seasonal variation was apparent. The second trimester accounted for a disproportionate number of crashes and the afternoon hours accounted for more than half of the total crashes. All secondary estimates overlapped the primary analysis, most showed a nominal increase in relative risk, and most were not statistically significant in isolation. Afternoon crashes were a high outlier and associated with a 91% increased relative risk of cerebral palsy (95% confidence interval +19 to +225, p = 0.011).

*** Table 5 About Here ***

Discussion

We studied over a million newborn children and found that a motor vehicle crash during pregnancy was associated with an increased subsequent risk of cerebral palsy among cases with preterm birth. The baseline rate of cerebral palsy was similar to past reports and the most frequent predictor was preterm birth (observed in 1-in-15 newborns and 1-in-3 cases of cerebral palsy, equal to a five-fold increased cerebral palsy risk).[85 86] The relative risk of cerebral palsy associated with a motor vehicle crash was particularly large for those with preterm birth after adjusting for imbalances in measured baseline characteristics. The most vulnerable interval was afternoon traffic that explained more than half the crashes.

Our research supports past reports describing an increased risk of cerebral palsy following a motor vehicle crash. A case series of ten children with cerebral palsy following pregnancies complicated by motor vehicle crash found brain lesions on MRI consistent with cerebral-vascular damage from trauma.[87] Individual case reports have also described maternal injury causing fetal intracranial hemorrhage.[88 89 90 91 92] Direct injury to fetal brain tissue or diffuse axonal injury without brain deformation may be other possible mechanisms from blunt forces described in animal models.[93 94] In contrast, no study to our knowledge suggests that a motor vehicle crash in pregnancy might decrease the risk of cerebral palsy.

A different set of possible mechanisms relate to indirect injury to the fetus from placental compromise or preterm birth. Blunt trauma may cause the placenta to shear from the uterus resulting in placental blood flow insufficiency.[95] The extreme case is placental abruption; however, less severe trauma might result in small degrees of sheering and losses in perfusion that chronically deprive the fetus of nutrients needed for brain development.[96 97] A related speculative mechanism is transient placental under-perfusion due to maternal catecholamine surges from acute stress that shunt blood flow away from uterine arteries.[98 99] Regardless of potential mechanisms, our study also indicates the fetus is resilient because the vast majority of motor vehicle crashes during pregnancy do not result in cerebral palsy.

An important limitation of our research relates to random chance and statistical imprecision (since a high number of term births can mask a significant difference in the preterm group).[100] Collectively, the observed frequency of motor vehicle crashes exceeded 1 per 200 pregnant women and the sample size for the whole cohort amounted to about four million patient-years of follow-up. However, the estimated relative risks of cerebral palsy associated with a motor vehicle crash were wide, overlapped the null, and ranged to more than a 100 percent increase. Taking into account term births, we estimate that future research may require a sample size exceeding 20 million patient-years of follow-up to confirm or refute our findings. We doubt such data will be available soon.

Our study has several additional limitations. Women who participate in high-risk behaviors during pregnancy (eg, alcohol) may have both an increased risk of a motor vehicle crash during pregnancy as well as an increased risk of preterm birth.

[101] [102] Maternal and delivery characteristics were unavailable (eg, APGAR scores, gestational age), as were data on minor crashes that did not receive medical attention.[103] The total number of observed motor vehicle crashes was not enormous and the totality of all-cause maternal trauma would be greater due to injuries from falls, assault, and self-harm.[104] [105] [106] Details of the severity of the crashes were also not known and most crashes did not result in cerebral palsy. More research is justified examining these and other clinical distinctions.

Previous data suggests that pregnant women have a significant incidence of a motor vehicle crash during pregnancy.[107] [108] Few studies describe the long-term consequences of maternal trauma on the surviving children. Our data suggest that a motor vehicle crash during pregnancy might increase the subsequent risk of cerebral palsy in cases of preterm birth. These results highlight an opportunity of prenatal traffic safety counseling for reducing the risks to a developing fetus.[109] [110] Injuries due to motor vehicle crashes may be particularly important and relevant since they are often preventable by following standard safety warnings. Avoiding a crash might possibly prevent a wide range of disability.

ACKNOWLEDGMENTS

We thank the following for helpful comments on specific points: Noor Ladhani, Sharon May, Nir Melamed, Jason Rajchgot, Sheharyar Raza, Jason Woodfine, and Arthur Zaltz.

FUNDING

This project was supported by a Canada Research Chair in Medical Decision Sciences, the Canadian Institutes of Health Research, and the BrightFocus Foundation. The views expressed are those of the authors and do not necessarily reflect the Ontario Ministry of Health.

ETHICS APPROVAL

This study was approved by the ethics board of Sunnybrook Health Sciences Centre including a waiver of individual consent and permissions for the necessary database linkages of mother to child. Datasets were linked using unique encoded identifiers analyzed at the Institute for Clinical Evaluative Sciences (ICES).

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DISCLOSURE OF CONFLICTS

The funding organizations had no role in the design and conduct of the study; collection, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. All authors have no financial or personal relationships or affiliations that could influence the decisions and work on this manuscript.

CONTRIBUTION TO AUTHORSHIP

The lead author (DAR) had full access to all the data in the study, takes responsibility for the integrity of the data, is accountable for the accuracy of the analysis, and wrote the first draft of the manuscript. The second author (FN) was responsible for literature review and manuscript revisions. The third author (DT) was responsible for data analysis and statistical programming). The final author (JB) was responsible for manuscript revisions and additional clinical insights. All were responsible for critical revisions.

DATA SHARING AGREEMENT

No additional data are available and all original data are available at Institute for Clinical Evaluative Sciences (ICES) through website <http://www.ices.on.ca/>.

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Table 1. Maternal and Newborn Characteristics (n = 1,325,660)

Characteristic		Motor Vehicle Crash Present (n = 7,933)	Motor Vehicle Crash Absent (n = 1,317,727)
Age	< 25	2,112 (27)	225,742 (17)
	25-35	4,887 (62)	884,878 (67)
	> 35	934 (12)	207,107 (16)
Socioeconomic status *	Higher	2,757 (35)	488,943 (37)
	Middle	1,610 (20)	266,435 (20)
	Lower	3,566 (45)	562,349 (43)
Home location	Urban	6,891 (87)	1,182,313 (90)
	Rural	1,042 (13)	135,414 (10)
Enrolment interval	First five years	4,011 (51)	645,370 (49)
	Second five years	3,922 (49)	672,357 (51)
Prenatal care †	≥ 13 clinic encounters	7,422 (94)	1,147,405 (87)
	≥ 1 hospital admission	3,253 (41)	438,570 (33)
Parity	Primiparous	3,968 (50)	597,344 (45)
	Multiparous	3,965 (50)	720,383 (55)
Pregnancy duration	Preterm	548 (7)	86,887 (7)
	At-term	6,481 (82)	1,080,323 (82)
	Post-term	904 (11)	150,517 (11)
Mode of delivery	Vaginal	5,657 (71)	952,375 (72)
	Cesarian	2,276 (29)	365,352 (28)
Newborn child	Male	3,973 (50)	669,801 (51)
	Female	3,870 (49)	635,266 (48)
	Not Recorded	90 (1)	12,660 (1)
Length of hospital stay	≤ 3 days	4,739 (60)	826,711 (63)
	≥ 4 days	3,194 (40)	491,016 (37)

<u>Footnote</u>
values are count (percentage) of each group
each pregnancy counted as separate event
* based on median neighbourhood income quintile
† In previous year

Table 2. Subsequent Cerebral Palsy Diagnosis (Events = 2,328)

		Total Cases of Cerebral Palsy	Relative Risk After Crash	95% Confidence Interval
FULL COHORT		2,328	1.29	0.84 to 2.10
Age	< 25	451	1.20	0.57 to 3.06
	25-35	1,479	1.48	0.88 to 2.69
	> 35	398	0.56	0.17 to 4.16
Socioeconomic	Higher	794	1.58	0.82 to 3.47
	Middle	478	0.35	0.10 to 2.58
	Lower	1,056	1.51	0.86 to 2.91
Home location	Urban	2,087	1.41	0.91 to 2.32
	Rural	241	0.54	0.16 to 4.04
Enrolment interval	First five years	1,179	1.65	0.99 to 3.01
	Second five years	1,149	0.90	0.45 to 2.11
Prenatal care	≥ 13 clinic visits	1,982	1.26	0.80 to 2.11
	≥ 1 admissions	1,069	1.14	0.64 to 2.29
Parity	Primiparous	1,179	1.16	0.64 to 2.32
	Multiparous	1,149	1.43	0.80 to 2.87
Pregnancy duration	Preterm	850	1.89	1.07 to 3.66
	At-term	1,314	0.76	0.38 to 1.79
	Post-term	164	2.06	0.73 to 8.94
Mode of delivery	Vaginal	1,285	1.05	0.57 to 2.20
	Cesarian	1,043	1.55	0.89 to 3.00
Newborn child	Male	1,339	1.52	0.91 to 2.77
	Female	989	1.00	0.50 to 2.34
Length of stay	≤ 3 days	1,026	1.37	0.74 to 2.86
	≥ 4 days	1,302	1.19	0.68 to 2.29

<u>Footnote</u>
referent indicates pregnancies with no motor vehicle crash

Table 3. Additional Predictors of Cerebral Palsy Risk in Preterm Newborns

	UNIVARIATE ANALYSIS *		MULTIVARIATE ANALYSIS †	
Predictor	Relative Risk	Confidence Interval	Relative Risk	Confidence Interval
Age (per year older)	0.82	0.73 to 0.93	0.86	0.76 to 0.97
Income (low)	0.98	0.84 to 1.14	--	--
Home (rural)	1.22	0.98 to 1.51	--	--
Enrollment (recent)	0.82	0.72 to 0.94	0.84	0.73 to 0.96
Prenatal care ≥ 13 encounters ‡	0.83	0.69 to 0.99	0.80	0.66 to 0.95
Hospital care ≥ 1 admissions ‡	1.25	1.09 to 1.43	1.24	1.08 to 1.43
Parity (multiparous)	0.85	0.74 to 0.97	0.89	0.78 to 1.03
Newborn (male)	1.32	1.15 to 1.52	1.32	1.15 to 1.52

Footnotes

analyses based on 850 events in 87,435 children (absolute risk = 9.7 per 1,000)
results from proportional hazards analysis (Cox regression)
estimates and confidence intervals calculated from normal approximation (Wald statistic)
* basic comparison with no adjustments for other baseline differences
† adjusted comparison accounting for other baseline differences
‡ in previous year

Table 4. Propensity Score Matched Analysis of Preterm Newborns (n = 4,384)

Characteristic		Motor Vehicle Crash Present (n = 548)	Motor Vehicle Crash Absent (n = 3,836)
Age	< 25	132 (24)	933 (24)
	25-35	351 (64)	2,430 (63)
	> 35	65 (12)	473 (12)
Socioeconomic status *	Higher	181 (33)	1,230 (32)
	Middle	104 (19)	762 (20)
	Lower	263 (48)	1,844 (48)
Home location	Urban	485 (89)	3,447 (90)
	Rural	63 (11)	389 (10)
Enrolment interval	First five years	277 (51)	1,970 (51)
	Second five years	271 (49)	1,866 (49)
Prenatal care †	≥ 13 clinic encounters	516 (94)	3,620 (94)
	≥ 1 hospital admission	322 (59)	2,278 (59)
Parity	Primiparous	288 (53)	2,024 (53)
	Multiparous	260 (47)	1,812 (47)
Pregnancy duration	Preterm	548 (100)	3,836 (100)
	At-term	--	--
	Post-term	--	--
Mode of delivery	Vaginal	321 (59)	2,255 (59)
	Cesarian	227 (41)	1,581 (41)
Newborn child	Male	287 (52)	2,036 (53)
	Female	252 (46)	1,761 (46)
	Not Recorded	9 (2)	39 (1)
Length of hospital stay	≤ 3 days	173 (32)	1,224 (32)
	≥ 4 days	375 (68)	2,612 (68)

<u>Footnote</u>
values are count (percentage) of each group
§ all data from propensity matched analysis of original cohort
¶ Crash present group includes all cases with preterm birth
¥ Crash absent group includes those from 1:7 matching of cases to controls
* based on median neighbourhood income quintile
† In previous year

Table 5. Crash Features and Cerebral Palsy Risk

		Total Pregnancies with a Crash	Relative Risk After Crash	95% Confidence Interval
FULL COHORT		7,933	1.29	0.84 to 2.10
Crash position	Driver	4,358	1.57	0.94 to 2.85
	Not Driver	3,575	0.96	0.48 to 2.24
Crash day	Weekend	1,982	1.73	0.86 to 4.04
	Weekday	5,951	1.15	0.69 to 2.09
Crash season	Spring /Summer	3,717	1.07	0.56 to 2.36
	Autumn / Winter	4,216	1.49	0.87 to 2.78
Pregnancy trimester	First	2,457	1.39	0.70 to 3.26
	Second	3,714	1.08	0.56 to 2.36
	Third	1,762	1.62	0.77 to 4.11
Vehicle	Car	7,100	1.12	0.69 to 1.95
	Other	833	2.74	1.22 to 7.78
Time of day	Morning	1,719	0.66	0.24 to 2.87
	Afternoon	4,488	1.91	1.19 to 3.25
	Night	1,726	0.33	0.10 to 2.46
Ambulance arrival	Yes	3,957	1.30	0.72 to 2.59
	No	3,976	1.29	0.72 to 2.58
Triage urgency	Higher	5,525	1.45	0.89 to 2.51
	Lower	2,408	0.95	0.42 to 2.69

<u>Footnote</u>
referent indicates pregnancies with no motor vehicle crash

BMJ Open

Motor Vehicle Crashes During Pregnancy and Cerebral Palsy During Infancy: A Longitudinal Cohort Analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-011972.R1
Article Type:	Research
Date Submitted by the Author:	28-Jun-2016
Complete List of Authors:	Redelmeier, Donald; University of Toronto, Medicine; Sunnybrook Research Institute, Evaluative Clinical Sciences Naqib, Faisal; University of Toronto; Institute for Clinical Evaluative Sciences Thiruchelvam, Deva; Institute for Clinical Evaluative Sciences; Sunnybrook Research Institute Barrett, Jon; Sunnybrook Health Sciences Centre, Obstetrics and Gynecology; University of Toronto Faculty of Medicine, Obstetrics and Gynecology
Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Emergency medicine, Epidemiology, Health services research, Paediatrics
Keywords:	cerebral palsy, traffic crash, preterm birth, prenatal care, car accident, motor vehicle trauma

Motor Vehicle Crashes During Pregnancy and Cerebral Palsy During Infancy: A Longitudinal Cohort Analysis

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Conflicts of Interest: The authors report no conflicts of interest.

Short Title: Crashes during pregnancy and cerebral palsy

Single Sentence:
Motor vehicle crashes during pregnancy were associated with an increased subsequent risk of cerebral palsy in children with preterm birth.

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words: 2,567 abstract: 269 Tables 5

Abstract

Objectives: To assess the incidence of cerebral palsy among children born to mothers who had their pregnancy complicated by a motor vehicle crash.

Design: Retrospective longitudinal cohort analysis of children born from April 1, 2002 to March 31, 2012 in Ontario, Canada.

Participants: Cases defined as pregnancies complicated by a motor vehicle crash and controls as remaining pregnancies with no crash.

Main Outcome: Subsequent diagnosis of cerebral palsy by age three years.

Results: A total of 1,325,660 newborns were analyzed, of whom 7,933 were involved in a motor vehicle crash during pregnancy. A total of 2,328 were subsequently diagnosed with cerebral palsy, equal to an absolute risk of 1.8 per 1,000 newborns. For the entire cohort, motor vehicle crashes correlated with a 29% increased risk of subsequent cerebral palsy that was not statistically significant (95% confidence interval: -16 to +110, p = 0.274). The increased risk was only significant for those with preterm birth who showed an 89% increased risk of subsequent cerebral palsy associated with a motor vehicle crash (95% confidence interval: +7 to +266, p = 0.037). No significant increase was apparent for those with a term delivery (95% confidence interval: -62 to +79, p = 0.510). Propensity score matched analysis of preterm births (n = 4,384) yielded a 138% increased relative risk of cerebral palsy associated with a motor vehicle crash (95% confidence interval +27 to +349, p = 0.007), equal to an absolute increase of about 10.9 additional cases per 1,000 newborns (18.2 vs 7.3, p = 0.010).

Conclusion: Motor vehicle crashes during pregnancy may be associated with an increased risk of cerebral palsy among the subgroup of cases with preterm birth. The increase highlights a specific role for traffic safety advice in prenatal care.

Key Words: cerebral palsy, traffic crash, preterm birth, prenatal care, car accident

Article Summary

Strengths and Limitations

- Motor vehicle crashes in pregnancy were identified in a large comprehensive population cohort of women who subsequently gave birth
- Long-term outcomes among children were tracked longitudinally for 3 years to examine a subsequent diagnosis of cerebral palsy after delivery
- The non-randomized design means an association of motor vehicle crashes in pregnancy with an increased relative risk cerebral palsy may not be causal
- Children born preterm following a motor vehicle crash do not have a large increase in the absolute risk of cerebral palsy
- Children born at term despite a motor vehicle crash have no statistically significant increase in the absolute risk of cerebral palsy

Background

Cerebral palsy is a leading cause of disability during childhood, with about 25 children diagnosed with cerebral palsy each day in the United States.[1] The severity spectrum spans from individuals living independently in the community to those needing comprehensive care in an institution. The average lifetime cost of cerebral palsy amounts to about $1 million in the United States.[2] Several risk factors for cerebral palsy have been identified including prematurity [3 4 5 6], abnormal genetics [7], multiple pregnancy [8], maternal infections [9 10], and birth asphyxia.[11 12] However, most cases of cerebral palsy are unexplained and considered due to an unidentified injury to the young developing brain.[13 14 15]

Motor vehicle crashes are a common cause of maternal trauma [16 17 18], complicating over 2,000 per 100,000 pregnancies.[19 20] The consequences include maternal death (1 per 100,000 pregnancies) and fetal death (4 per 100,000 pregnancies).[21] The non-fatal short-term consequences of a motor vehicle crash include placental abruption, premature rupture of membranes, uterine disruption, or early delivery.[22 23 24] Fetal injury following a motor vehicle crash correlates imperfectly with the severity of maternal injury, can occur without direct uterine injury, and may have a delayed presentation.[25] Maternal trauma from a motor vehicle crash, therefore, might cause injury to a young developing brain.

Several mechanisms could contribute to a possible association between a motor vehicle crash during pregnancy and subsequent cerebral palsy during infancy. The most direct mechanism is acute trauma leading to preterm birth.[26] Less direct mechanisms include fetal cerebral hypoxia caused by maternal hypotension.[27 28] Other possibilities include a stress response involving the maternal autonomic vascular or metabolic systems that compromises uterine perfusion.[29 30] A further mechanism relates to chronic placental insufficiency from clot formation or traumatic shear stresses.[31 32] These mechanisms, however, are speculative and no population-based study has tested whether cerebral palsy during infancy might be linked to a motor vehicle crash during pregnancy.

Methods

Study Setting

We conducted a retrospective longitudinal population-based cohort study using datasets from the Institutes for Clinical Evaluative Sciences (ICES).[33] These datasets integrate information from medical encounters by patients throughout the Ontario healthcare system as covered by the universal health insurance plan.[34] This plan provided all-inclusive access to care with no cost to patients for emergency and prenatal treatments, thereby providing comprehensive longitudinal patient data for analysis. Patients were not involved in setting the research agenda and this study was approved by the ethics board of Sunnybrook Health Sciences Centre including a waiver for consent and permission for database linkages.

Pregnancy Identification

We identified women (age 14 to 50 years) who gave birth between April 1, 2002 to March 31, 2012 by screening physician codes for a newborn delivery (codes P006, P018, P020) using the MOM-BABY database at ICES.[35] [36] Abortions were excluded and repeat pregnancies were counted as separate events.[37] One woman, therefore, was counted for each birth and twins were counted as separate observations. Each pregnancy was categorized as complicated or not complicated by a motor vehicle crash, defined as a traffic event sending the woman to an emergency department.[38] Regardless of crashes, we also distinguished each pregnancy as cases of pre-term delivery (ICD version 10 codes O60) or cases followed by at-term or post-term delivery.

Newborn Identification

Children were identified using the MOM-BABY database at ICES that linked maternal and birth records with 98% completeness.[39] [40] The database has been used extensively.[41] [42] [43] [44] We excluded individuals with faulty medical records, living outside Ontario, or high-order multiple births; otherwise, the sampling was comprehensive and complete. Limitations of the database include the lack of direct information on sibling relationships, paternal connections, and home environment. The database also lacks information about multiple lifestyle behaviors including smoking, alcohol, substance abuse, domestic violence, dietary intake, toxin exposure, marital status, and other social determinants of health.

Identification of Crashes

We identified motor vehicle crashes using validated diagnostic codes from all emergency departments throughout Ontario (International Statistical Classification of Diseases version 10 codes V00 -V69).[45] This definition reflected motor vehicle crashes that sent the woman as a patient to an emergency department, including events as drivers, passengers, or other road users and excluding events related to aircraft or watercraft. Additional crash characteristics included day, season, clock-time (morning, afternoon, night), position (driver, passenger, other), enrolment interval (first five years, second five years), ambulance involvement (yes, no), and triage urgency (higher, lower). For each case we also determined whether subsequent newborn delivery occurred within 48 hours of the crash.

Identification of Cerebral Palsy

Newborns were followed for three years to determine survival and subsequent diagnosis since most cerebral palsy is diagnosed by age three.[46 47] Diagnostic codes were used to search for a physician diagnosis of cerebral palsy (International Statistical Classification of Diseases version 9 code 343, version 10 code G80).[48] We further distinguished cerebral palsy cases as explained or unexplained according to known antecedents; namely, congenital abnormalities, maternal infection, birth asphyxia, illicit drug use, and bleeding complication[49 50 51 52] (ICD version 10 codes Q00 to Q99; P02 to P04; P10-P15; P20-P21; P36 to P39). We did not define prematurity as a direct explanation because it might be an intermediate mechanism (explored in secondary analysis).

Identification of Additional Predictors

The demographic registry was used to obtain maternal data on age, socioeconomic status, and home location (urban, rural).[53] Prenatal care, pregnancy duration, mode of delivery, twin gestations, and length of hospital stay were determined based on linked identifiers.[54 55 56] Primiparity and multiparity was based on birth records from the previous 20 years. Neonatal variables included prematurity (binary), sex (binary), day of delivery (weekend vs weekday), and enrolment interval (first five years, second five years). [57 58 59 60 61] The databases did not contain driving history, roadway infractions, chosen destinations, license status, travel diaries, vehicle distances, injury severity, or impact velocity.

Statistical Analysis

The primary study outcome was the risk of a subsequent diagnosis of cerebral palsy by age three. The main analysis used proportional hazards analysis to compare children born after a pregnancy complicated by a motor vehicle crash to children born after a pregnancy not complicated by a motor vehicle crash. Hazard ratios were used for relative risk estimates and interval deaths were censored in the primary analysis (considered in secondary analysis). Stratified analyses assessed differences according to individual characteristics with special attention to preterm births. [62 63] We also used propensity matched analysis to reexamine preterm births and reevaluate the risk of cerebral palsy after accounting for other baseline characteristics. More extensive regressions with interaction terms were not conducted due to small numerators in some groups.

Results

Maternal Characteristics

A total of 884,897 women gave birth to 1,325,660 newborn children, of whom 7,933 newborns (1-in-170) had the pregnancy complicated by a motor vehicle crash. As expected, motor vehicle crashes involved women across a wide spectrum of age, socio-economic status, and experience (Table 1). The mean maternal age was 29.9 years and slightly lower for those pregnancies complicated by a motor vehicle crash compared to those pregnancies not complicated by a motor vehicle crash. Otherwise, the distributions of socioeconomic status, home location, prenatal care visits, parity, pregnancy duration, mode of delivery, and hospital length of stay were similar for the two groups. A total of 38 women had more than 1 crash during pregnancy. A total of 52 women delivered within 48 hours of a crash.

*** Table 1 About Here ***

Table 1. Maternal and Newborn Characteristics (n = 1,325,660)

Characteristic		Motor Vehicle Crash Present (n = 7,933)	Motor Vehicle Crash Absent (n = 1,317,727)
Age	< 25	2,112 (27)	225,742 (17)
	25-35	4,887 (62)	884,878 (67)
	> 35	934 (12)	207,107 (16)
Socioeconomic status *	Higher	2,757 (35)	488,943 (37)
	Middle	1,610 (20)	266,435 (20)
	Lower	3,566 (45)	562,349 (43)
Home location	Urban	6,891 (87)	1,182,313 (90)
	Rural	1,042 (13)	135,414 (10)
Enrolment interval	First five years	4,011 (51)	645,370 (49)
	Second five years	3,922 (49)	672,357 (51)
Prenatal care †	≥ 13 clinic encounters	7,422 (94)	1,147,405 (87)
	≥ 1 hospital admission	3,253 (41)	438,570 (33)
Parity	Primiparous	3,968 (50)	597,344 (45)
	Multiparous	3,965 (50)	720,383 (55)
Pregnancy duration	Preterm ¶	548 (7)	86,887 (7)
	At-term	6,481 (82)	1,080,323 (82)
	Post-term ¥	904 (11)	150,517 (11)
Mode of delivery	Vaginal	5,657 (71)	952,375 (72)
	Cesarian	2,276 (29)	365,352 (28)
Newborn child	Male	3,973 (50)	669,801 (51)
	Female	3,870 (49)	635,266 (48)
	Not Recorded	90 (1)	12,660 (1)
Length of hospital stay	≤ 3 days	4,739 (60)	826,711 (63)
	≥ 4 days	3,194 (40)	491,016 (37)

Footnote
values are count (percentage) of each group
each pregnancy counted as separate event
* based on median neighbourhood income quintile
† In previous year
¶ maternal ICD-10 code O60

¥ maternal ICD-10 code O48

Subsequent Child Outcomes

A total of 2,328 children were diagnosed with cerebral palsy by age 3 years (1,325,660 identified newborns, 5,425 interval deaths). The median age at cerebral palsy diagnosis was 586 days and median age at death was 7 days. The most common identified reasons linked to cerebral palsy were perinatal disorders and congenital abnormalities, collectively accounting for 1,225 children (53%). The remaining 1,103 children (47%) were classified as having unexplained cerebral palsy. The median age for diagnosing unexplained cerebral palsy was 610 days. The overall rate of cerebral palsy per 1,000 pregnancies was about the same in the first five years of the study and the second five years of the study (1.82 vs 1.70, respectively).

Motor Vehicle Crashes and Cerebral Palsy Risk

A total of 18 children diagnosed with cerebral palsy were born following 7,933 pregnancies complicated by a motor vehicle crash. In contrast, 2,310 children with cerebral palsy were born following 1,317,727 pregnancies with no motor vehicle crash. The difference in risk equaled a marginally increased incidence of cerebral palsy associated with motor vehicle crashes per 1,000 pregnancies (2.27 vs 1.75, p = 0.274), equal to a 29% relative increase in risk (95% confidence interval -16 to +110). The absolute difference amounted to 685 fewer cases of cerebral palsy among those who did not have a crash during pregnancy. The increased risk was most apparent before age 2 years (Appendix).

Patient Characteristics

The increased risk of cerebral palsy associated with a motor vehicle crash was evident for subgroups with different characteristics (Table 2). The highest observed relative risks were among pregnancies followed by a preterm delivery that showed a 89% relative increase in risk (95% confidence interval +7 to +266, p = 0.037). No significant increase was apparent among the large number of pregnancies followed by a term delivery or among the small number of pregnancies followed by post-term delivery. All confidence intervals were wide, almost all upper bounds overlapped a 100% relative increase in risk, and no subgroup showed a statistically significant contrary pattern.

*** Table 2 About Here ***

Table 2. Subsequent Cerebral Palsy Diagnosis (Events = 2,328)

		Total Cases of Cerebral Palsy	Relative Risk After Crash	Confidence Interval
FULL COHORT		2,328	1.29	0.84 to 2.10
Age	< 25	451	1.20	0.57 to 3.06
	25-35	1,479	1.48	0.88 to 2.69
	> 35	398	0.56	0.17 to 4.16
Socioeconomic	Higher	794	1.58	0.82 to 3.47
	Middle	478	0.35	0.10 to 2.58
	Lower	1,056	1.51	0.86 to 2.91
Home location	Urban	2,087	1.41	0.91 to 2.32
	Rural	241	0.54	0.16 to 4.04
Enrolment interval	First five years	1,179	1.65	0.99 to 3.01
	Second five years	1,149	0.90	0.45 to 2.11
Prenatal care	≥ 13 clinic visits	1,982	1.26	0.80 to 2.11
	≥ 1 admissions	1,069	1.14	0.64 to 2.29
Parity	Primiparous	1,179	1.16	0.64 to 2.32
	Multiparous	1,149	1.43	0.80 to 2.87
Pregnancy duration	Preterm	850	1.89	1.07 to 3.66
	At-term	1,314	0.76	0.38 to 1.79
	Post-term	164	2.06	0.73 to 8.94
Mode of delivery	Vaginal	1,285	1.05	0.57 to 2.20
	Cesarian	1,043	1.55	0.89 to 3.00
Newborn child	Male	1,339	1.52	0.91 to 2.77
	Female	989	1.00	0.50 to 2.34
Length of stay	≤ 3 days	1,026	1.37	0.74 to 2.86
	≥ 4 days	1,302	1.19	0.68 to 2.29

Footnote
estimates provide results from subgroup analyses (full cohort listed at top)
referent based on pregnancies with no motor vehicle crash
relative risk estimate from proportional hazards analysis (Cox regression)

confidence interval based on 95% limits using normal approximation (Wald statistic)

Additional Predictors in Cases with Preterm Birth

Several baseline characteristics were also associated with cerebral palsy following a preterm birth (Table 3). Older age predicted lower risk whereas socio-economic status and home location were not significant predictors. Those born in more recent years had a lower risk. Prenatal care visits were associated with lower risk. Conversely, past hospitalizations predicted higher risk (perhaps as a proxy for underlying patient illnesses). As expected, cerebral palsy was more frequent in boys. The absolute rate of cerebral palsy averaged about 9.7 per 1,000 pregnancies among all newborns with preterm birth (estimate essentially unchanged in analyses that excluded interval deaths or analyses that excluded the 12 cases with preterm birth who delivered within 48 hours of a crash).

*** Table 3 About Here ***

Table 3. Additional Predictors of Cerebral Palsy Risk in Preterm Newborns

	UNIVARIATE ANALYSIS *		MULTIVARIABLE ANALYSIS †	
Predictor	Relative Risk	Confidence Interval	Relative Risk	Confidence Interval
Age (per year older)	0.82	0.73 to 0.93	0.86	0.76 to 0.97
Socioeconomic (low)	0.98	0.84 to 1.14	--	--
Home (rural)	1.22	0.98 to 1.51	--	--
Enrollment (recent)	0.82	0.72 to 0.94	0.84	0.73 to 0.96
Prenatal care ≥13 encounters ‡	0.83	0.69 to 0.99	0.80	0.66 to 0.95
Hospital care ≥1 admissions ‡	1.25	1.09 to 1.43	1.24	1.08 to 1.43
Parity (multiparous)	0.85	0.74 to 0.97	0.89	0.78 to 1.03
Newborn (male)	1.32	1.15 to 1.52	1.32	1.15 to 1.52

Footnotes
analyses based on 850 events in 87,435 children (absolute risk = 9.7 per 1,000)
relative risk estimate from proportional hazards analysis (Cox regression)
confidence interval based on 95% limits using normal approximation (Wald statistic)
* basic univariate comparison with no adjustments for other baseline differences
† adjusted multivariable comparison accounting for significant univariate predictors
‡ in previous year

Propensity Matched Analysis in Preterm Birth

Propensity score matching yielded a cohort of 4,384 newborns with preterm birth, of whom 548 had the pregnancy complicated by a motor vehicle crash and the remaining 3,836 had no complicating motor vehicle crash (matching ratio 1-in-7 by design). As expected, the distribution of maternal characteristics was similar for the two groups (Table 4). A total of 38 children were subsequently diagnosed with cerebral palsy, equal to a 138% increased relative risk of cerebral palsy associated with a motor vehicle crash (95% confidence interval +27 to +349, p = 0.007). The absolute risk of cerebral palsy equaled 10.9 additional cases per 1,000 pregnancies complicated by a motor vehicle crash (18.2 vs 7.3, p = 0.010). Repeating the analysis after excluding twins yielded a similar absolute increase (17.7 vs 7.9, p = 0.034).

*** Table 4 About Here ***

Table 4. Propensity Score Matched Analysis of Preterm Newborns (n = 4,384) §

Characteristic		Motor Vehicle Crash Present ¶ (n = 548)	Motor Vehicle Crash Absent ¥ (n = 3,836)
Age	< 25	132 (24)	933 (24)
	25-35	351 (64)	2,430 (63)
	> 35	65 (12)	473 (12)
Socioeconomic status *	Higher	181 (33)	1,230 (32)
	Middle	104 (19)	762 (20)
	Lower	263 (48)	1,844 (48)
Home location	Urban	485 (89)	3,447 (90)
	Rural	63 (11)	389 (10)
Enrolment interval	First five years	277 (51)	1,970 (51)
	Second five years	271 (49)	1,866 (49)
Prenatal care †	≥ 13 clinic encounters	516 (94)	3,620 (94)
	≥ 1 hospital admission	322 (59)	2,278 (59)
Parity	Primiparous	288 (53)	2,024 (53)
	Multiparous	260 (47)	1,812 (47)
Pregnancy duration	Preterm	548 (100)	3,836 (100)
	At-term	--	--
	Post-term	--	--
Mode of delivery	Vaginal	321 (59)	2,255 (59)
	Cesarian	227 (41)	1,581 (41)
Newborn child	Male	287 (52)	2,036 (53)
	Female	252 (46)	1,761 (46)
	Not Recorded	9 (2)	39 (1)
Length of hospital stay	≤ 3 days	173 (32)	1,224 (32)
	≥ 4 days	375 (68)	2,612 (68)

Footnote
values are count (percentage) of each group
§ all data from propensity matched analysis of original cohort

¶ Crash present group includes all cases with preterm birth
¥ Crash absent group includes those from 1:7 matching of cases to controls
* based on median neighbourhood income quintile
† In previous year

Crash Features

The increased overall risk of cerebral palsy associated with a motor vehicle crash was evident for crashes with different features (Table 5). The most frequent time for a crash was a weekday and no large seasonal variation was apparent. The second trimester accounted for a disproportionate number of crashes and afternoon hours accounted for more than half of the crashes. All secondary estimates overlapped the primary analysis, most showed a nominal increase in relative risk, and most were not statistically significant in isolation. Afternoon crashes were a high outlier and associated with a 91% increased relative risk of cerebral palsy (95% confidence interval +19 to +225, p = 0.011). About half of the crashes received subsequent ambulance transport and most assigned high triage urgency.

*** Table 5 About Here ***

Table 5. Crash Features and Cerebral Palsy Risk

		Total Pregnancies with a Crash	Relative Risk After Crash	Confidence Interval
FULL COHORT		7,933	1.29	0.84 to 2.10
Crash position	Driver	4,358	1.57	0.94 to 2.85
	Not Driver	3,575	0.96	0.48 to 2.24
Crash day	Weekend	1,982	1.73	0.86 to 4.04
	Weekday	5,951	1.15	0.69 to 2.09
Crash season	Spring /Summer	3,717	1.07	0.56 to 2.36
	Autumn / Winter	4,216	1.49	0.87 to 2.78
Pregnancy trimester	First	2,457	1.39	0.70 to 3.26
	Second	3,714	1.08	0.56 to 2.36
	Third	1,762	1.62	0.77 to 4.11
Vehicle	Car	7,100	1.12	0.69 to 1.95
	Other	833	2.74	1.22 to 7.78
Time of day	Morning	1,719	0.66	0.24 to 2.87
	Afternoon	4,488	1.91	1.19 to 3.25
	Night	1,726	0.33	0.10 to 2.46
Ambulance arrival	Yes	3,957	1.30	0.72 to 2.59
	No	3,976	1.29	0.72 to 2.58
Triage urgency	Higher	5,525	1.45	0.89 to 2.51
	Lower	2,408	0.95	0.42 to 2.69

Footnote

estimates provide results from subgroup analyses (full cohort listed at top)
referent based on pregnancies with no motor vehicle crash
relative risks estimate from proportional hazards model
confidence interval based on 95% limits

Discussion

We studied over a million newborn children and found that a motor vehicle crash during pregnancy was associated with an increased subsequent risk of cerebral palsy among cases with preterm birth. The baseline rate of cerebral palsy was similar to past reports and the most frequent predictor was preterm birth (observed in 1-in-15 newborns and 1-in-3 cases of cerebral palsy, equal to a five-fold increased cerebral palsy risk).[64 65] The relative risk of cerebral palsy associated with a motor vehicle crash was particularly large for those with preterm birth after propensity score adjustment for imbalances in measured baseline characteristics. The most vulnerable interval was afternoon traffic that explained more than half the crashes.

Our research supports past reports describing an increased risk of cerebral palsy following a motor vehicle crash. A case series of ten children with cerebral palsy following pregnancies complicated by motor vehicle crash found brain lesions on MRI consistent with cerebral-vascular damage from trauma.[66] Individual case reports have also described maternal injury causing fetal intracranial hemorrhage.[67 68 69 70 71 72] Direct injury to fetal brain tissue or diffuse axonal injury without brain deformation may be other possible mechanisms described in animal models.[73 74] In contrast, no study to our knowledge suggests that a motor vehicle crash in pregnancy might decrease the risk of cerebral palsy.

A different set of possible mechanisms involves indirect injury to the fetus from placental compromise. Blunt trauma may cause the placenta to shear from the uterus resulting in placental blood flow insufficiency.[75] The extreme case is placental abruption and preterm birth; however, less severe trauma might result in small degrees of sheering and losses in perfusion that chronically deprive the fetus of nutrients needed for brain development.[76] A related speculative mechanism is transient placental under-perfusion due to maternal catecholamine surges from acute stress that shunt blood flow away from uterine arteries.[77 78] Regardless of potential mechanisms, our study also indicates the fetus is resilient because the vast majority of motor vehicle crashes during pregnancy do not result in cerebral palsy.

An important limitation of our research relates to random chance and statistical imprecision (since a high number of term births can mask a significant difference among the preterm group). Collectively, the observed frequency of motor vehicle crashes exceeded 1 per 200 pregnant women and the sample size for the whole cohort amounted to about four million patient-years of follow-up. However, the estimated relative risks of cerebral palsy associated with a motor vehicle crash were wide, overlapped the null, and ranged to more than a 100 percent increase. Taking into account term births, we estimate that future research may require a sample size exceeding 20 million patient-years of follow-up to confirm or refute our findings. We doubt such data will be available soon.

Our study has several other limitations. Women who have adverse behaviors during pregnancy (eg, alcohol) may have both an increased risk of a motor vehicle crash during pregnancy as well as an increased risk of preterm birth.[79] Maternal and delivery characteristics were unavailable (eg, APGAR scores, differing degrees of prematurity), as were data on biomechanical forces and minor crashes receiving no medical attention.[80] The total number of observed crashes was not enormous and the totality of all-cause maternal trauma would be greater due to injuries from falls, assault, and self-harm.[81] Details of the severity of the crashes were also not known and most crashes did not result in cerebral palsy. Subgroup analyses are also prone to chance findings and analyses adjusting for an intermediate along a causal pathway can lead to underestimated risks.[82 83] More research is justified examining these and other clinical distinctions.

Previous data suggests that pregnant women have a significant incidence of a motor vehicle crash during pregnancy.[84 85] Few studies describe the long-term consequences of maternal trauma on the surviving children. Our data suggest that a motor vehicle crash during pregnancy might increase the subsequent risk of cerebral palsy in cases of preterm birth. These results highlight an opportunity around prenatal traffic safety counseling for reducing the risks to a developing fetus.[86 87] Injuries due to motor vehicle crashes may be particularly important and relevant since they are often preventable by following standard safety warnings. Avoiding a crash might possibly prevent a wide range of disability.

ACKNOWLEDGMENTS

We thank the following for helpful comments on specific points: Noor Ladhani, Sharon May, Nir Melamed, Jason Rajchgot, Sheharyar Raza, Jason Woodfine, and Arthur Zaltz.

FUNDING

This project was supported by a Canada Research Chair in Medical Decision Sciences, the Canadian Institutes of Health Research, and the BrightFocus Foundation. The views expressed are those of the authors and do not necessarily reflect the Ontario Ministry of Health.

ETHICS APPROVAL

This study was approved by the ethics board of Sunnybrook Health Sciences Centre including a waiver of individual consent and permissions for the necessary database linkages of mother to child. Datasets were linked using unique encoded identifiers analyzed at the Institute for Clinical Evaluative Sciences (ICES).

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DISCLOSURE OF CONFLICTS

The funding organizations had no role in the design and conduct of the study; collection, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. All authors have no financial or personal relationships or affiliations that could influence the decisions and work on this manuscript.

CONTRIBUTION TO AUTHORSHIP

The lead author (DAR) had full access to all the data in the study, takes responsibility for the integrity of the data, is accountable for the accuracy of the analysis, and wrote the first draft of the manuscript. The second author (FN) was responsible for literature review and manuscript revisions. The third author (DT) was responsible for data analysis and statistical programming). The final author (JB) was responsible for manuscript revisions and additional clinical insights. All were responsible for critical revisions.

DATA SHARING AGREEMENT

No additional data are available and all original data are available at Institute for Clinical Evaluative Sciences (ICES) through website <http://www.ices.on.ca/>.

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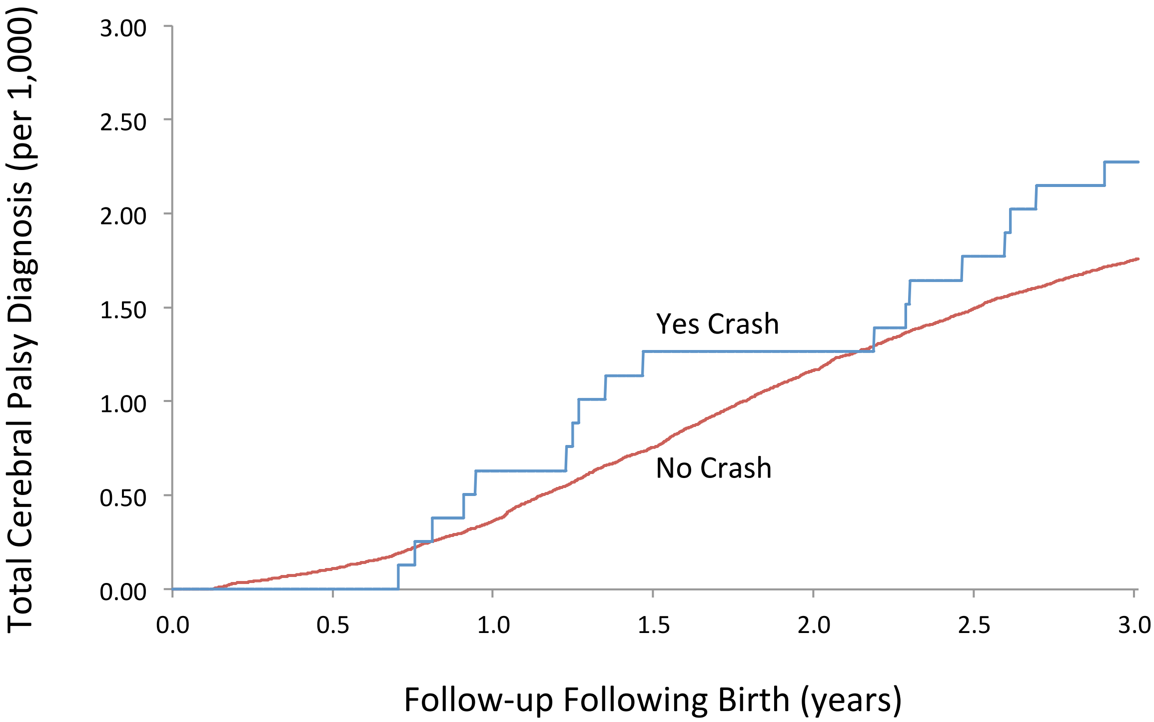
Appendix. Subsequent Risk of Cerebral Palsy



Footnote

Kaplan Meier plots of cerebral palsy following birth. X-axis shows time following birth and spans 3 years. Y-axis shows proportion diagnosed with cerebral palsy. Blue line for newborns with motor vehicle crash during pregnancy and red line for newborns with no motor vehicle crash during pregnancy. Main findings show early difference in risks that is not statistically significant for aggregate cohort of preterm births, at-term births, and post-term births. Test of proportional hazards assumption based on Schoenfield residuals and shows no significant correlation with time (p>0.20)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract XX Page 2 XX
		(*b*) Provide in the abstract an informative and balanced summary XX Page 2 XX
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation XX Pages 2, 3 XX
Objectives	3	State specific objectives, including any prespecified hypotheses XX Page 2, 3 XX
Methods		
Study design	4	Present key elements of study design early in the paper XX Page 4, 5, 6 XX
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection XX Page 2, 4, XX
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up XX Page 4, 5 XX
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed XX Table 1 and Table 4 XXX
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable XX Page 3 4, 5, 6, XX
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group XX Page 3, 5, 6 XX
Bias	9	Describe any efforts to address potential sources of bias XX Page 6 XX
Study size	10	Explain how the study size was arrived at XX Page 4 XX
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why XX Not Applicable XX
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding XX Page 6 XX
		(*b*) Describe any methods used to examine subgroups and interactions XX Page 6, 8, Table 1, Table 2, Table 3, Table 4 XX
		(*c*) Explain how missing data were addressed XX Not Applicable XX
		(*d*) If applicable, explain how loss to follow-up was addressed XX Not applicable XX
		(*e*) Describe any sensitivity analyses XX Not applicable XX

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed XX Page 6, 7, 8, 9, Table 1, Table 4 XX
		(b) Give reasons for non-participation at each stage XX not applicable XX
		(c) Consider use of a flow diagram XX not applicable XX
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders XX Table 1, Table 4 XX
		(b) Indicate number of participants with missing data for each variable of interest XX not applicable XX
		(c) Summarise follow-up time (eg, average and total amount) XX Page 7 XX
Outcome data	15*	Report numbers of outcome events or summary measures over time XX Page 7, 8 XX
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included XX Table 2 XX
		(*b*) Report category boundaries when continuous variables were categorized XX not applicable XX
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period XX Page 7, 8 XX
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses XX Page 8, 9 XX
Discussion		
Key results	18	Summarise key results with reference to study objectives XX Page 9 XX
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias XX Page 4, 5, 6, 10, 11, XX
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence XX Page 11 XX
Generalisability	21	Discuss the generalisability (external validity) of the study results XX Page 3, 4, 10 XX
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based XX Page 12 XX