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1 and 5-minute Apgar scores and child developmental health at 5 years of age, a population-based cohort study

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Short title: Apgar scores and child developmental health

ABSTRACT

Objectives: We investigated the associations between Apgar scores at 1 and 5-minutes, across the entire range of score values, and child developmental health at 5 years of age.

Setting: British Columbia, Canada.

Participants: All singleton term infants without major congenital anomalies born between 1993 and 2009, who had a developmental assessment in kindergarten between1999 and 2014.

Main outcomes and measures: Developmental vulnerability on 1 or more domains of the Early Development Instrument and special needs requirements. Adjusted rate ratios (aRRs) and 95% confidence intervals (CIs) were estimated using log-linear regression.

Results: Of the 150,081 children in the study, 45,334 (30.2%) were developmentally vulnerable and 3,644 (2.5%) had special needs. There was an increasing trend in developmental vulnerability and special needs with decreasing 1-minute and 5-minute Apgar scores. Compared with children with an Apgar score of 10 at 5-minute, the rate ratio for developmental vulnerability increased steadily with decreasing Apgar score from 1.02 (95%CI 1.00-1.04) for an Apgar score of 9 to 1.88 (95%CI 1.27-2.77) for an Apgar score of 1. Among children with 1 minute Apgar scores in the 7-10 range, changes in Apgar scores between 1 and 5-minutes were associated with significant differences in developmental vulnerability. Compared with children who had an Apgar score of 9 at 1-minute and 10 at 5-minutes, children with an Apgar score of 9 at both 1 and 5-minutes had higher rates of developmental vulnerability (aRR 1.03, 95%CI 1.01-1.05). Compared with infants with an Apgar of 10 at both 1 and 5-minutes, infants with a 1-minute score of 10 and a 5-minute score of <10 had higher rates of developmental vulnerability (aRR 1.53, 95%CI 1.08-2.17).

Conclusion: Risks of adverse developmental health and having special needs at 5 years of age are inversely associated with 1 minute and 5-minute Apgar scores across their entire range.

Article Summary:

Strengths and limitations of this study:

- Ability to access comprehensive health and education-related databases at the population level.
- Using a teacher reported instrument, no reliance was placed on parent or self-report of developmental health.
- There may be some individual differences in teachers' ability to evaluate developmental health on the EDI.
- Study was restricted to the comparatively healthy subset of all term live births, as children with disabilities may not have enrolled in kindergarten.

INTRODUCTION

In 1953, Virginia Apgar proposed a scoring system that enabled a rapid assessment of the clinical status of the newborn infant and identified infants requiring resuscitation on the basis of heart rate, respiration, color, muscle tone and reflex irritability.[1] Initially, the Apgar score at 1 minute was used to assess the need for immediate resuscitation. Subsequently, the Apgar score at 5-minute was shown to be a better predictor of neonatal survival than the Apgar score at 1 minute. Although the value of a low Apgar score for predicting adverse neonatal outcomes has been questioned,[2] low Apgar scores are well correlated with both short-term[3] and long-term outcomes, in both preterm and term infants.[4-10]

Only the lowest and more compromised Apgar scores have been conventionally regarded as predictive of maladaptive development and morbidity. Nevertheless, a few population-based studies have shown that risks of cerebral palsy, epilepsy, early developmental health status and need for special education are inversely associated with 5 minute-Apgar scores in a dose-dependent manner across the entire range of scores.[11-13] Even children with an Apgar score of 9 at 5 or 10 minutes have an increased risk of adverse neurological outcomes compared with children with 5 or 10 minutes Apgar scores of 10.[11,12] Approximately 65% to 85% of newborns receive a 1 minute or a 5-minute Apgar score in the 7 to 9 range,[12] yet, there is a dearth of information on how this impacts a child's developmental health.

Changes in Apgar score values between 1 and 5 minutes, and between 5 and 10 minutes are known to influence risks of cerebral palsy and epilepsy.[11,14,15] Our recent population-based study demonstrated elevated risks of cerebral palsy and epilepsy among children with a 5-minute Apgar

score of 7 or 8, even if their 10-minute Apgar score was 9 or 10.[11] Although it is recognized that changes in Apgar scores between 1 and 5 minutes are a useful measure of the response to resuscitation, the long-term significance of changes in such Apgar scores within the "normal" range (i.e., 7-10) is not clear.

In this population-based study, we investigated the associations between Apgar scores at 1 and 5 minutes across the entire range of score values, and developmental health at 5 years of age. We also analyzed the effect of a change in Apgar scores from 1 to 5 minutes, including changes within the normal range of Apgar scores. Specifically, we were interested in developmental health among children with 1 minute Apgar score in the 7-9 range who received a score less than 10 at 5 minutes.

METHODS

Information on the study population was obtained from several population-based linked health and demographic databases in British Columbia. The anonymized linked data used in this study included information from the Discharge Abstract Database[16] that comprised hospital admission and discharge records; the Vital Statistics Birth and Clinical Births[17] databases, which contained information on all births in the province, along with delivery and neonatal health status, including diagnoses based on International Classification of Diseases (ICD 9 or ICD-10CA) codes; Census GeoData, which provided socioeconomic status (SES) data expressed as average neighbourhood income quintiles (based on Census information from Statistics Canada and quantified using postal codes);[18] the Consolidation File,[19] which provided demographic information on study subjects and confirmed residency in the province; and the Early Development Instrument (EDI)[20] data, which provided information on early childhood developmental health, and were accessed through linkage

with the Human Early Learning Partnership.[21] Teachers completed the EDI for each child in their kindergarten class (age range 5-7 years) in February. The EDI is designed to tap five core areas of early childhood development:[20,22] physical health and well-being; social competence; emotional maturity; language and cognitive development; and communication skills and general knowledge (Supplementary Table 1).[20] It consists of 104 binary and Likert-scale items, from which scores between 0 and 10 are calculated for each domain. The EDI also records demographic information on each child and whether the child has identified special needs.

The study population included all singleton term (≥37 weeks' gestation) infants born between April 1, 1993 and December 31, 2009, who had documented 1 minute and 5-minute Apgar scores as well as a completed EDI assessment in kindergarten. Inclusion of infants with these birth dates meant that children were 5 to 7 years of age between 1999 and 2014 and part of the EDI assessment. The study population was restricted to infants without major congenital anomalies, identified using diagnosis codes from linked hospital records in the year after birth.

Apgar scores at 1 and 5 minutes were considered as the main exposures and examined both as discrete values from 0 to 10 and also as grouped categories (Apgar values of 0-3, 4-6, 7, 8, 9, and 10). Children with an Apgar score of 0 at 1 or 5 minutes who did not have a diagnostic code for birth asphyxia [ICD-9: 768.5, 768.6 and 768.9; ICD-10: P21), or an intervention code for either resuscitation or ventilation (Canadian Classification of health interventions: 1.GZ.30, 1.GZ31, 1.HZ.30, 1361, 1362, 1363, 1373, 1379, 1004) were excluded from the study (n=470), as information on these cases likely resulted from transcription errors.

Developmental health included whether a child had special needs or was developmentally vulnerable as measured by the EDI. Children were categorized as being developmentally vulnerable if their scores on the EDI fell below the 10th percentile value[23] in any of the five domains, based on the national EDI cut-off scores.[24] The 10th percentile cut-off has been recommended because it is usually higher than clinical cut-off points of 3% or 5% for clinically diagnosing behaviour[20] and should therefore include children who may be more difficult to diagnose.[25] Children with special needs were defined as requiring special assistance because of chronic medically, physically, or intellectually disabling conditions.

Other independent variables included infant sex (male vs female), birth weight-for-gestational age, age of the child in years at the time of EDI assessment, gestational age at birth in completed weeks (37, 38, 39, 40, 41, and ≥42), birth order (1, 2, 3, and +4), marital status (married vs not married) and socioeconomic status (SES). Birth weight-for-gestational age was categorized as: small (<10th percentile), appropriate (10th-90th percentile) and large (>90th percentile) for gestational age.[26] Each child's family income was derived from the median household income in the child's residential area (based on postal code) obtained from the 2006 Canadian Census data.[27-29]

The frequency of each 5-minute Apgar score value was calculated within categories of maternal and infant characteristics. Multivariable log-linear regression models with robust variance estimates[30] was used to examine the association between Apgar score at 1 and 5 minutes and developmental vulnerability and special needs. Results were expressed as rate ratios (RRs) with 95% confidence intervals (CIs). Other variables included in the final models were based on the literature[23,31] or statistical significance (P value <0.1). The full model included child's sex, child's

age at EDI completion, socioeconomic status, child's first language, birth weight-for-gestational age, birth order, and gestational age. Interactions between Apgar scores and other determinants were examined and stratified analyses were carried out when a significant interaction was present. The University of British Columbia's Clinical Research Ethics Board approved the study.

Patient and public involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

RESULTS

There were 150,081 children (mean age = 5.7 years) with a gestational age at birth of ≥37 weeks, without major malformations and complete Apgar and EDI data included in the study. Five-minute Apgar scores showed a U-shaped association with gestational age at birth, with low scores more frequent at 37 weeks and ≥42 weeks (Table 1). Low 5-minute Apgar scores were comparable for most characteristics but more frequent among males, small-for-gestational age live births, children of mothers who were nulliparous, not married and those with a low SES.

Overall, the prevalence of vulnerability in one or more domains of the EDI was 30.2%, with physical and social domains having the highest rates of vulnerability at 15.2% and 12.7%, respectively (Figure 1). There was an increasing trend in the rate of developmental vulnerability with decreasing 1 minute and 5-minute Apgar scores (P for trend <0.001; Table 2). However, this

association was much more pronounced for the 5-minute Apgar score. Compared with children with an Apgar score of 10 at 5-minute, children with a 5-minute Apgar score of 2 had 1.57 times higher rates of developmental vulnerability (95% CI 1.03-2.39). Similarly, children with a 5-minute Apgar score of 7, 8 or 9 had significantly higher rates of developmental vulnerability compared with children with a 5-minute Apgar score of 10 (adjusted rate ratios 1.08, 1.06 and 1.02 for Apgar 7, 8 and 9, respectively; Table 2). The association between 5-minute Apgar scores and developmental vulnerability was mainly due to the higher rates of vulnerability in the language and emotional domains of the EDI (Supplementary Table 2).

In total, 3,644 (2.5%) children had special needs (Table 3). The proportion of children with special needs increased linearly with decreasing 1 minute and 5-minute Apgar scores (P for trend <0.001). Compared with children who had a 1 minute Apgar score of 10, those with an Apgar score of 2 at 1 minute had significantly higher adjusted rates of having special needs (adjusted rate ratio 1.72, 95% CI 1.19-2.48), while those with an Apgar score of 5 at 1 minute had 1.39 times higher rates of having special needs (95% CI 1.05-1.85). Children with score of 7 to 9 at 1 minute were not more likely to have special needs. However, children with 5-minute Apgar scores in the 1 to 8 range had elevated adjusted rate ratios for having special needs which consistently increased with decreasing 5-minute Apgar score values: from 1.20 in children with an Apgar score of 8 at 5 minutes to 5.13 among those with an Apgar score of 1 at 5 minutes.

Table 4 shows rates of developmental vulnerability in relation to changes in Apgar score from 1 to 5 minutes, among children whose 1 minute Apgar score was in the normal range (7 to 10). Among children with a 1 minute Apgar score of 7, the rate of developmental vulnerability decreased in a

dose-response manner with greater improvement in the Apgar score from 1 to 5 minutes (P value for dose response = 0.02). Larger reductions in developmental vulnerability with greater improvements in 1 to 5-minute Apgar scores were also evident among children with a 1 minute Apgar score of 9 (P value for trend 0.009) but not among children with a 1 minute Apgar score of 8 (P for trend 0.36). Children with an Apgar score of 9 at 1 minute and 9 at 5-minute had higher rates of developmental vulnerability compared with those who had an Apgar score of 9 at 1 minute and 10 at 5-minute (adjusted rate ratio 1.03, 95% CI 1.01-1.05). Furthermore, compared with children who had Apgar scores of 10 at both 1 and 5 minutes, children whose 1 minute Apgar score decreased from 10 to a 5-minute Apgar score of <10, had 1.53 times higher rates of developmental vulnerability (adjusted rate ratio 1.53, 95% CI 1.08-2.17).

DISCUSSION

In this population-based study, we found graded, continuously increasing risks of developmental vulnerability and special needs at 5 years of age with decreasing 1 and 5-minute Apgar scores. In particular, children with "normal" 5-minute Apgar scores of 7, 8 and 9 were more likely to have developmental vulnerability compared with children with 5-minute Apgar scores of 10. Similarly, children who had Apgar scores of 7 or 8 at 5-minute had higher risks of having special needs compared with those with a 5-minute Apgar score of 10. Furthermore, children with a 1 minute Apgar score in the normal range (7 or 9) had an increased risk of developmental vulnerability, if their Apgar score at 5-minute was <10. Finally, a reduction in the Apgar score from 10 at 1 minute to 7-9 at 5-minute, substantially increased the risk of developmental vulnerability.

Our results confirm previous findings from a smaller cohort, which showed that developmental

adversity extended in a linear fashion across the full range of Apgar scores.[12] Both research and clinical practice generally emphasize the increased risks of adverse outcomes associated with very low and less common Apgar scores (i.e., <7 or <4). Our results suggest that the negative association between Apgar score and developmental adversity or special needs extends across the full range of scores. Consistent with our findings, previous studies have shown a significant linear relationship between each one-point decrease in 5- and 10-minute Apgar scores and increasing risk of epilepsy, cerebral palsy, and needing education in a special school.[11,13] While profound perinatal events can cause death or obvious neurological deficits, milder insults may sometimes cause subtle cognitive impairment only detectable as the child grows older.

Our study also showed that changes in Apgar scores from 1 to 5 minutes were associated with developmental vulnerability. This is in agreement with previous studies showing that changes in Apgar scores immediately after birth influence risks of cerebral palsy and epilepsy.[11,14,15] To our knowledge, this is the first study that examined risks of developmental adversity in relation to changes in Apgar scores from 1 to 5 minutes. Current guidelines define "normal" Apgar scores as 7 or more at 1 minute and 8 or more at 5-minute, indicating that the baby does not require assistance if scores are within these ranges.[32] However, our results reveal that small changes within the normal range (7-9) or even a slight reduction in score from 10 at 1 minute to 9 at 5-minute can significantly increase the risk of developmental vulnerability. Similarly, infants who have low Apgar scores for prolonged, or even brief periods are reported to have a higher risk of poor IQ scores at age 18, even if the infants recover subsequently.[5] These findings provide justification for monitoring all infants with 1 minute Apgar scores of 10 (to identify those whose scores may be

declining) and providing appropriate support to infants with normal Apgar scores between 7 and 9 at 1 minute (to ensure that they achieve a more optimal 5-minute score).

The strengths of our study included the ability to access comprehensive health and education-related databases at the population level. By using a teacher reported instrument, no reliance was placed on parent or self-report of developmental health. Nonetheless, there may be some individual differences in teachers' ability to evaluate developmental health on the EDI.[24] Further, our study was restricted to the comparatively healthy subset of all term live births, as children with disabilities may not have enrolled in kindergarten or may have enrolled in special needs schools. We acknowledge that the Apgar score as recorded in medical charts represents routine clinical practice,[33] and it is prone to interobserver variablitiy,[33] specifically in intubated newborn babies.[34] However, the quality of Apgar score values should not differ between children with and without later diagnosed developmental vulnerability.

In summary, our study showed that the risk of developmental vulnerability and special needs at 5 years of age was inversely associated with 1 and 5 minutes Apgar scores across their entire range. Furthermore, improvements in Apgar scores between 1 and 5 minutes among children with a 1 minute Apgar score of 7 or 9 resulted in lower risk of developmental vulnerability. These results provide clinicians with valuable prognostic information and justification to monitor and to provide appropriate support to infants who are even mildly compromised at 1 and 5 minutes.

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Contributor's statement:

Neda Razaz conceptualized and designed the study, analyzed the data, drafted the initial manuscript, and finalized the manuscript based on coauthor feedback. She had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Sven Cnattingius, Martina Persson, Kristina Tedroff, and Sarka Lisonkova, reviewed and commented on the initial and final analyses, provided feedback on the initial draft of the manuscript and approved the final version of the manuscript.

KS Joseph assisted with conceptualization and design of the study, and reviewed and commented on the initial and final analyses, provided feedback on the initial draft of the manuscript and approved the final version of the manuscript.

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What is already known on this topic: Risks of cerebral palsy, epilepsy, early developmental health status and need for special education are inversely associated with 5 minute-Apgar scores in a dose-dependent manner across the entire range of scores. Even children with an Apgar score of 9 at 5 or 10 minutes have an increased risk of adverse neurological outcomes compared with children with 5 or 10 minutes Apgar scores of 10.

What this study adds: Risk of adverse developmental health and having special needs at 5 years of age were inversely associated with 1 and 5 minutes Apgar scores across its entire range. Changes in Apgar scores between 1 and 5 minutes among children with 1-minute Apgar scores in the normal range (7 to 10) were associated with significant differences in rates of adverse developmental health. These findings provide justification for monitoring infants with 1 minute Apgar of 10 and providing appropriate support to infants with normal Apgar scores between 7 and 9 at 1 minute.

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Table 1. Maternal and birth characteristics according to Apgar score at five minutes among singleton term live births, British Columbia, 1993-2009

Maternal and birth characteristics	Total	Apgar 0-3	Apgar 4-6	Apgar 7	Apgar 8	Apgar 9	Apgar 10
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
Total	150081 (100)	147 (0.10)	1328 (0.88)	2375 (1.58)	7666 (5.11)	101191 (67.42)	37374 (24.90)
Maternal age (years)							
≤19	6170 (4.11)	9 (0.15)	87 (1.41)	119 (1.93)	358 (5.80)	3959 (64.17)	1638 (26.55)
20-24	24637 (16.42)	23 (0.09)	273 (1.11)	435 (1.77)	1449 (5.88)	15973 (64.83)	6484 (26.32)
25-29	43832 (29.21)	44 (0.10)	384 (0.88)	719 (1.64)	2275 (5.19)	29217 (66.66)	11193 (25.54)
30-34	47332 (31.54)	47 (0.10)	380 (0.80)	710 (1.50)	2254 (4.76)	32398 (68.45)	11543 (24.39)
≥35	28081 (18.71)	24 (0.09)	203 (0.72)	391 (1.39)	1329 (4.73)	19627 (69.89)	6507 (23.17)
Missing	29 (0.02)	0 (0)	<5 (<17.24)	<5 (<17.24)	<5 (<17.24)	17 (58.62)	9 (31.03)
Socioeconomic status							
5th quintile [highest]	27519 (18.34)	27 (0.10)	249 (0.90)	452 (1.64)	1377 (5.00)	18406 (66.88)	7008 (25.47)
4th quintile	31282 (20.84)	33 (0.11)	259 (0.83)	528 (1.69)	1682 (5.38)	20894 (66.79)	7886 (25.21)
3rd quintile	30939 (20.61)	32 (0.10)	266 (0.86)	510 (1.65)	1602 (5.18)	20875 (67.47)	7654 (24.74)
2nd quintile	31266 (20.83)	19 (0.06)	263 (0.84)	464 (1.48)	1589 (5.08)	21177 (67.73)	7754 (24.80)
1st quintile [lowest]	28889 (19.25)	36 (0.12)	289 (1.00)	419 (1.45)	1410 (4.88)	19716 (68.25)	7019 (24.30)
Missing	186 (0.12)	0 (0)	<5 (<2.69)	<5 (<2.69)	6 (3.23)	123 (66.13)	53 (28.49)
Married							
Yes	103099 (68.70)	88 (0.09)	807 (0.78)	1518 (1.47)	4880 (4.73)	70552 (68.43)	25254 (24.49)
No	43374 (28.90)	53 (0.12)	489 (1.13)	804 (1.85)	2608 (6.01)	28163 (64.93)	11257 (25.95)
Missing	3608 (2.40)	6 (0.17)	32 (0.89)	53 (1.47)	178 (4.93)	2476 (68.63)	863 (23.92)
Infant's sex							
Female	73809 (49.18)	56 (0.08)	573 (0.78)	1075 (1.46)	3626 (4.91)	49576 (67.17)	18903 (25.61)
Male	76272 (50.82)	91 (0.12)	755 (0.99)	1300 (1.70)	4040 (5.30)	51615 (67.67)	18471 (24.22)
Birth order							
1	67516 (44.99)	83 (0.12)	845 (1.25)	1408 (2.09)	4136 (6.13)	45859 (67.92)	15185 (22.49)
2	56025 (37.33)	49 (0.09)	353 (0.63)	693 (1.24)	2419 (4.32)	37822 (67.51)	14689 (26.22)
3	19239 (12.82)	13 (0.07)	89 (0.46)	202 (1.05)	794 (4.13)	12825 (66.66)	5316 (27.63)
≥4	7301 (4.86)	<5 (<0.07)	41 (0.56)	72 (0.99)	317 (4.34)	4685 (64.17)	2184 (29.91)
Gestational age							
37 weeks	8966 (5.97)	9 (0.10)	97 (1.08)	181 (2.02)	617 (6.88)	6099 (68.02)	1963 (21.89)
38 weeks	25821 (17.20)	13 (0.05)	192 (0.74)	353 (1.37)	1205 (4.67)	17612 (68.21)	6446 (24.96)
39 weeks	37408 (34.03)	34 (0.09)	286 (0.76)	494 (1.32)	1630 (4.36)	25652 (68.57)	9312 (24.89)
40 weeks	51079 (34.03)	50 (0.10)	419 (0.82)	842 (1.65)	2577 (5.05)	33871 (66.31)	13320 (26.08)

41 weeks	25040 (16.68)	38 (0.15)	306 (1.22)	468 (1.87)	1522 (6.08)	16873 (67.38)	5833 (23.29)
42-44 weeks	1767 (1.18)	<5 (<0.28)	28 (1.58)	37 (2.09)	115 (6.51)	1084 (61.35)	500 (28.3)
Birth weight-for-gestational age							
Appropriate	121035 (80.65)	110 (0.09)	1022 (0.84)	1832 (1.51)	5998(4.96)	81599 (67.42)	30474 (25.18)
Small	11581 (7.72)	22 (0.19)	156 (1.35)	255 (2.20)	713 (6.16)	7764 (67.04)	2671 (23.06)
Large	17445 (11.62)	14 (0.08)	149 (0.85)	288 (1.65)	955 (5.47)	11820 (67.76)	4219 (24.18)
Missing	20 (0.01)	<5 (<25.00)	<5 (<25.00)	0 (0)	0 (0)	8 (40.00)	10 (50.00)
Child's age at EDI data collection (years)							
Means (SD)	5.70 (0.32)	5.67 (0.30)	5.65 (0.30)	5.66 (0.30)	5.66 (0.30)	5.65 (0.30)	5.65 (0.30)

Table 2. Apgar scores at one and five minutes and rate ratios for developmental vulnerability among singleton term live births, British Columbia, Canada

		Developmental vulnerability			
				Rate Ratio (95% CI)	
Apgar Score	Total No. of children	No. with outcome	%	Crude	Adjusted*
1-Min Apgar	**150081**	**45334**	**30.2**		
0	24	9	37.5	1.25 (0.74−2.10)	1.08 (0.64−1.83)
1	469	161	34.3	1.15 (1.00−1.31)	1.16 (1.02−1.32)
2	1060	329	31.0	1.04 (0.93−1.15)	1.03 (0.93−1.14)
3	1760	546	31.0	1.04 (0.95−1.13)	1.03 (0.95−1.13)
4	2582	814	31.5	1.05 (0.97−1.14)	1.07 (0.99−1.15)
5	4069	1261	31.0	1.03 (0.96−1.11)	1.05 (0.98−1.12)
6	6975	2124	30.5	1.02 (0.95−1.08)	1.04 (0.98−1.11)
7	12019	3648	30.4	1.01 (0.95−1.08)	1.03 (0.97−1.09)
8	38671	11666	30.2	1.01 (0.95−1.06)	1.02 (0.96−1.08)
9	79369	23852	30.1	1.00 (0.95−1.06)	1.00 (0.95−1.06)
10	3083	924	30.0	1.00 (Reference)	1.00 (Reference)
P for trend					<0.001
Per one unit of Apgar					0.99 (0.98-0.99)
5-Min Apgar					
0	20	7	35.0	1.18 (0.65−2.15)	1.16 (0.62−2.17)
1	16	9	56.3	1.90 (1.24−2.93)	1.88 (1.27−2.77)
2	28	13	46.4	1.57 (1.05−2.34)	1.57 (1.03−2.39)
3	83	30	36.2	1.22 (0.92−1.63)	1.25 (0.93−1.67)
4	106	43	40.6	1.37 (1.09−1.73)	1.33 (1.06−1.67)
5	290	85	29.3	0.99 (0.83−1.19)	0.98 (0.82−1.17)
6	932	306	32.8	1.11 (1.01−1.22)	1.08 (0.99−1.18)
7	2375	740	31.2	1.05 (0.99−1.12)	1.08 (1.01−1.14)
8	7666	2387	31.1	1.05 (1.02−1.09)	1.06 (1.02−1.10)
9	101191	30668	30.3	1.03 (1.01−1.04)	1.02 (1.00−1.04)
10	37374	11046	29.6	1.00 (Reference)	1.00 (Reference)
P for trend					<0.001
Per one unit of Apgar					0.98 (0.97-0.99)

*Adjusted for child's sex (male vs female), child's age at EDI completion (years), socioeconomic status (1st quintile, 2nd quintile, 3rd quintile, 4th quintile vs 5th quintile) child's first language (other vs English), birth order (2, 3, +4 vs 1), birth weight-for-gestational age (large, small vs appropriate), gestational age (weeks).

Table 3. Apgar score at one and five minutes and rate ratios for special needs status among singleton term live births in British Columbia, Canada

		Special Needs			
				Rate Ratio (95% CI)	
Apgar Score	Total No. of children	No. with outcome	%	Crude	Adjusted*
1-Min Apgar	**148699**	**3644**	**2.5**		
0	22	<5	4.6	1.94 (0.28−13.4)	1.44 (0.23−8.97)
1	463	26	5.6	2.40 (1.55−3.72)	2.23 (1.44−3.46)
2	1054	45	4.3	1.82 (1.26−2.63)	1.72 (1.19−2.48)
3	1743	53	3.0	1.30 (0.91−1.84)	1.23 (0.86−1.74)
4	2554	69	2.7	1.15 (0.83−1.60)	1.09 (0.79−1.52)
5	4032	136	3.4	1.44 (1.09−1.91)	1.39 (1.05−1.85)
6	6894	191	2.8	1.18 (0.90−1.55)	1.16 (0.89−1.52)
7	11903	298	2.5	1.07 (0.83−1.38)	1.06 (0.82−1.37)
8	38300	946	2.5	1.06 (0.83−1.34)	1.07 (0.84−1.35)
9	78701	1808	2.3	0.98 (0.78−1.24)	1.00 (0.79−1.26)
10	3033	71	2.3	1.00 (Reference)	1.00 (Reference)
P for trend					<0.001
Per one unit of Apgar					0.99 (0.98-0.99)
5-Min Apgar					
0	17	<5	<29.4	2.51 (0.37−16.8)	2.59 (0.41−16.3)
1	15	<5	<33.3	5.69 (1.56−20.7)	5.13 (1.45−18.1)
2	28	<5	<17.9	6.10 (2.46−15.2)	5.17 (2.01−13.3)
3	83	9	10.8	4.63 (2.49−8.61)	3.78 (2.03−7.02)
4	103	7	6.8	2.90 (1.41−5.95)	2.59 (1.25−5.35)
5	289	8	2.8	1.18 (0.59−2.35)	1.10 (0.56−2.16)
6	928	36	3.9	1.66 (1.19−2.30)	1.49 (1.07−2.06)
7	2342	74	3.2	1.35 (1.07−1.70)	1.28 (1.01−1.61)
8	7597	225	3.0	1.26 (1.09−1.46)	1.20 (1.03−1.38)
9	100281	2411	2.4	1.03 (0.95−1.11)	1.01 (0.94−1.09)
10	37016	867	2.3	1.00 (Reference)	1.00 (Reference)
P for trend					<0.001
Per one unit of Apgar					0.98 (0.97-0.99)

*Adjusted for child's sex (male vs female), child's age at EDI completion (years), socioeconomic status (1st quintile, 2nd quintile, 3rd quintile, 4th quintile vs 5th quintile) child's first language (other vs English), birth order (2, 3, +4 vs 1), birth weight-for-gestational age (large, small vs appropriate), gestational age (weeks).

Table 4. Rate ratios for developmental vulnerability according to combination of Apgar scores at one and five minutes, singleton term live births, British Columbia, Canada

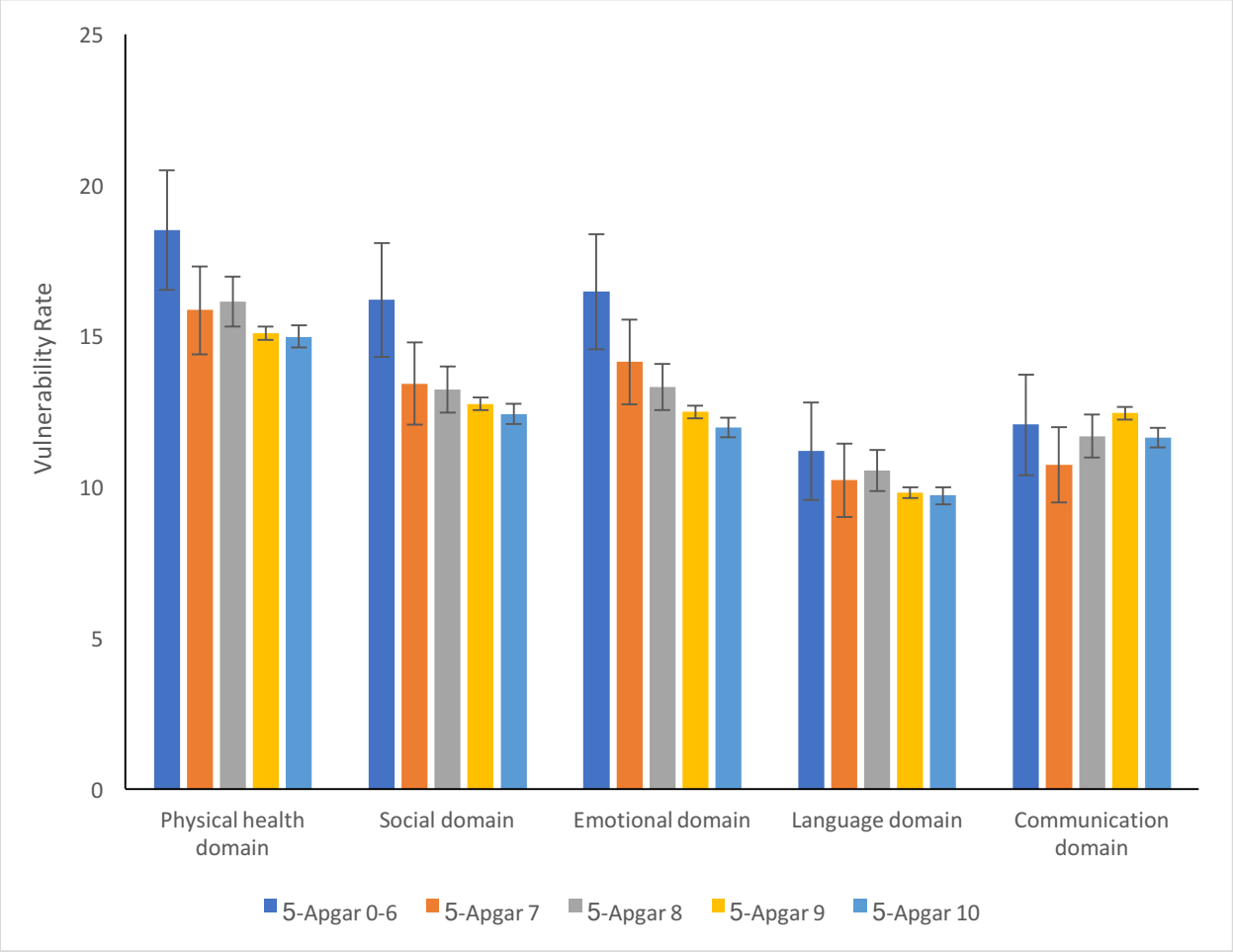
			Developmental vulnerability			
				Rate Ratio (95% CI)		
1-min Apgar	5-min Apgar	Total No. of children	No. with outcome (%)	Crude	Adjusted*	P for trend
7	<7	20	9 (45.0)	1.62 (0.99-2.65)	1.34 (0.80-2.25)	
7	7	172	56 (32.6)	1.18 (0.93-1.48)	1.18 (0.94-1.47)	
7	8	1987	629 (31.7)	1.14 (1.02-1.28)	1.12 (1.01-1.23)	
7	9	8700	2637 (30.3)	1.09 (0.99-1.20)	1.08 (0.99-1.19)	
7	10	1140	317 (27.8)	1.00 (Reference)	1.00 (Reference)	0.024
8	<8	66	17 (25.8)	0.85 (0.56-1.28)	0.71 (0.47-1.07)	
8	8	1337	420 (31.4)	1.03 (0.94-1.13)	1.01 (0.92-1.10)	
8	9	33255	10007 (30.1)	0.99 (0.94-1.04)	0.97 (0.93-1.02)	
8	10	4013	1222 (30.5)	1.00 (Reference)	1.00 (Reference)	0.36
9	<9	140	48 (34.3)	1.17 (0.93-1.47)	1.10 (0.88-1.38)	
9	9	50976	15501 (30.4)	1.03 (1.01-1.06)	1.03 (1.01-1.05)	
9	10	28253	8303 (29.4)	1.00 (Reference)	1.00 (Reference)	0.009
10	<10	26	13 (50.0)	1.68 (1.14-2.47)	1.53 (1.08-2.17)	
10	10	3057	911 (29.8)	1.00 (Reference)	1.00 (Reference)	0.016†

*Adjusted for child's sex (male vs female), child's age at EDI completion (years), socioeconomic status (1st quintile, 2nd quintile, 3rd quintile, 4th quintile vs 5th quintile) child's first language (others vs English), birth order (2, 3, +4 vs 1), birth weight-for gestational age (large, small vs appropriate), gestational age (weeks).

† P value for difference in rates.

Figure 1 Legend: Rates of vulnerability within the five Early Development Instrument domains by Apgar score at 5-minute, British Columbia, Canada

Figure 1: Rates of vulnerability within the five Early Development Instrument domains by Apgar score at 5-minute, British Columbia, Canada



Supplementary Table 1. Five domains of the Early Development Instrument

EDI domains	Characteristics addressed
Physical health and well-being	Children's fine and gross motor skills, energy levels, fatigue and clumsiness
Social competence	Self-confidence, tolerance, ability to get along with other children, to accept responsibility for their own actions, to work independently
Emotional maturity	Children's general emotional health and maturity. It also identifies minor problems with aggression, restlessness, distractibility or inattentiveness as well as excessive regular sadness
Language and cognitive skills	Mastery of the basics of reading and writing, interest in books, and numerical skills
Communication skills and general knowledge	Children's general knowledge, their ability to articulate clearly and their ability to understand and communicate in English

Supplementary Table 2. Apgar score at one and five minutes and rate ratios for vulnerability in each domain of the EDI, among singleton term live births in British Columbia, Canada

	Physical health domain			Social domain			Emotional domain		
Apgar Score	**No. with outcome**	**%**	**Adjusted***	**No. with outcome**	**%**	**Adjusted***	**No. with outcome**	**%**	**Adjusted***
1-Min Apgar									
0	<5	<20.83	0.90 (0.37−2.19)	<5	<20.83	1.01 (0.40−2.51)	<5	<20.83	0.71 (0.25−1.96)
1	88	18.76	1.24 (1.02−1.52)	82	17.48	1.30 (1.05−1.61)	83	17.7	1.25 (1.01−1.54)
2	179	16.89	1.09 (0.93−1.27)	142	13.40	0.97 (0.82−1.16)	147	13.87	0.96 (0.81−1.14)
3	283	16.08	1.06 (0.93−1.21)	246	13.98	1.03 (0.89−1.19)	273	15.51	1.09 (0.95−1.25)
4	410	15.88	1.06 (0.94−1.19)	349	13.52	1.02 (0.89−1.16)	370	14.33	1.03 (0.91−1.18)
5	644	15.83	1.04 (0.93−1.16)	569	13.98	1.06 (0.94−1.19)	563	13.84	1.01 (0.90−1.13)
6	1076	15.43	1.02 (0.93−1.13)	925	13.26	1.02 (0.92−1.14)	932	13.36	1.00 (0.89−1.11)
7	1889	15.72	1.03 (0.94−1.13)	1555	12.94	1.00 (0.90−1.11)	1500	12.48	0.94 (0.85−1.04)
8	5876	15.19	1.01 (0.93−1.10)	4993	12.91	1.01 (0.92−1.11)	4836	12.51	0.96 (0.87−1.05)
9	11839	14.92	0.99 (0.91−1.08)	9858	12.42	0.97 (0.89−1.07)	9608	12.11	0.94 (0.86−1.03)
10	472	15.31	1.00 (Reference)	393	12.75	1.00 (Reference)	399	12.94	1.00 (Reference)
5-Min Apgar									
0	<5	<25.00	0.66 (0.17−2.60)	<5	<25.00	1.13 (0.44−2.9)	<5	<25.00	1.13 (0.44−2.88)
1	6	37.5	2.42 (1.28−4.59)	<5	<31.25	1.42 (0.58−3.52)	<5	<31.25	1.92 (0.89−4.11)
2	9	32.14	2.22 (1.23−4.01)	7	25.00	1.87 (0.99−3.53)	6	21.43	1.60 (0.83−3.07)
3	21	25.30	1.75 (1.22−2.51)	15	18.07	1.37 (0.87−2.17)	12	14.46	1.08 (0.65−1.78)
4	25	23.58	1.56 (1.12−2.18)	18	16.98	1.26 (0.84−1.90)	18	16.98	1.19 (0.77−1.82)
5	46	15.86	1.06 (0.81−1.37)	34	11.72	0.86 (0.63−1.19)	33	11.38	0.84 (0.61−1.17)
6	164	17.60	1.13 (0.99−1.30)	159	17.06	1.26 (1.10−1.44)	167	17.92	1.33 (1.16−1.52)
7	377	15.87	1.08 (0.98−1.19)	319	13.43	1.05 (0.95−1.16)	336	14.15	1.11 (1.00−1.23)
8	1237	16.14	1.08 (1.02−1.14)	1014	13.23	1.04 (0.97−1.10)	1021	13.32	1.06 (1.00−1.13)
9	15272	15.09	1.03 (1.00−1.06)	12904	12.75	1.02 (0.99−1.06)	12641	12.49	1.04 (1.01−1.07)
10	5601	14.99	1.00 (Reference)	4640	12.42	1.00 (Reference)	4473	11.97	1.00 (Reference)

Supplementary Table 2 (cont.). Apgar score at one and five minutes and rate ratios for each domain of the EDI, among singleton term live births in British Columbia, Canada

	Language domain			Communication domain		
Apgar Score	**No. with outcome**	**%**	**Adjusted***	**No. with outcome**	**%**	**Adjusted***
1-Min Apgar				**18335**	**12.18**	
0	5	20.83	1.85 (0.81−4.25)	<5	<20.83	1.27 (0.50−3.22)
1	60	12.79	1.42 (1.10−1.82)	54	11.51	1.07 (0.83−1.39)
2	106	10.00	1.05 (0.86−1.29)	131	12.36	1.12 (0.93−1.35)
3	174	9.89	1.07 (0.90−1.27)	203	11.53	1.05 (0.90−1.23)
4	269	10.42	1.14 (0.98−1.32)	291	11.27	1.04 (0.90−1.19)
5	435	10.69	1.14 (1.00−1.31)	486	11.94	1.10 (0.97−1.24)
6	733	10.51	1.13 (1.00−1.28)	803	11.51	1.07 (0.96−1.20)
7	1255	10.44	1.10 (0.98−1.23)	1440	11.98	1.08 (0.97−1.20)
8	3830	9.90	1.04 (0.93−1.16)	4711	12.18	1.04 (0.95−1.15)
9	7621	9.60	0.99 (0.89−1.10)	9779	12.32	1.00 (0.91−1.10)
10	305	9.89	1.00 (Reference)	372	12.07	1.00 (Reference)
5-Min Apgar						
0	6	30.00	3.13 (1.52−6.44)	<5	<25.00	1.27 (0.43−3.70)
1	<5	<31.25	1.23 (0.38−3.92)	<5	<31.25	1.75 (0.74−4.13)
2	5	17.86	1.95 (0.86−4.43)	7	25.00	2.19 (1.09−4.41)
3	13	15.66	1.79 (1.11−2.91)	14	16.87	1.63 (1.00−2.68)
4	14	13.21	1.44 (0.89−2.34)	15	14.15	1.33 (0.84−2.12)
5	29	10.00	1.11 (0.78−1.57)	29	10.00	0.94 (0.67−1.33)
6	96	10.30	1.09 (0.90−1.31)	107	11.48	1.03 (0.87−1.23)
7	243	10.23	1.14 (1.01−1.29)	255	10.74	1.04 (0.92−1.16)
8	809	10.55	1.13 (1.06−1.22)	895	11.67	1.07 (1.00−1.14)
9	9939	9.82	1.04 (1.00−1.07)	12595	12.45	1.03 (1.00−1.06)
10	3637	9.73	1.00 (Reference)	4351	11.64	1.00 (Reference)

*Adjusted for child's sex (male vs female), child's age at EDI completion (years), socioeconomic status (1st quintile, 2nd quintile, 3rd quintile, 4th quintile vs 5th quintile) child's first language (others vs English), birth order (2, 3, +4 vs 1), birth weight-for-gestational age (large, small vs appropriate), gestational age (weeks).

STROBE Statement—checklist of items that should be included in reports of observational 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 (Page 1 and 2)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found (Page 2)
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported (Page 3, paragraph 1 and 2)
Objectives	3	State specific objectives, including any prespecified hypotheses (Page 4, paragraph 2)
Methods		
Study design	4	Present key elements of study design early in the paper (Page 4, para 1)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection (Page 6 to 9)
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (Page 4 to 7) *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed (n/a) *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable (Page 4 to 7)
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 (Page 4 to 7)
Bias	9	Describe any efforts to address potential sources of bias (n/a)
Study size	10	Explain how the study size was arrived at (n/a)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why (Page 6 to 7)
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (Page 6 to 7)
		(*b*) Describe any methods used to examine subgroups and interactions (n/a)
		(*c*) Explain how missing data were addressed (n/a)
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed

	Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy
	(*e*) Describe any sensitivity analyses

Continued on next page

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 (Page 7, para 1)
		(b) Give reasons for non-participation at each stage (n/a)
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (Page 7 and 8)
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time (Page 7 and 8)
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
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 (Page 8 -9)
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives (Page 9, last para)
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 (Page 11)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence (Page 10 to 11)
Generalisability	21	Discuss the generalisability (external validity) of the study results
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 (Page 1)

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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1 and 5 minutes Apgar scores and child developmental health at 5 years of age, a population-based cohort study in British Columbia, Canada

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ABSTRACT

Objectives: We investigated the associations between Apgar scores at 1 and 5 minutes, across the entire range of score values, and child developmental health at 5 years of age.

Setting: British Columbia, Canada.

Participants: All singleton term infants without major congenital anomalies born between 1993 and 2009, who had a developmental assessment in kindergarten between1999 and 2014.

Main outcomes and measures: Developmental vulnerability on one or more domains of the Early Development Instrument and special needs requirements. Adjusted rate ratios (aRRs) and 95% confidence intervals (CIs) were estimated using log-linear regression.

Results: Of the 150,081 children in the study, 45,334 (30.2%) were developmentally vulnerable and 3,644 (2.5%) had special needs. There was an increasing trend in developmental vulnerability and special needs with decreasing 1-minute and 5-minute Apgar scores. Compared with children with an Apgar score of 10 at 5-minute, the aRR for developmental vulnerability increased steadily with decreasing Apgar score from 1.02 (95% CI 1.00-1.04) for an Apgar score of 9 to 1.88 (95% CI 1.27-2.77) for an Apgar score of one. Among children with 1-minute Apgar scores in the 7-10 range, changes in Apgar scores between 1 and 5 minutes were associated with significant differences in developmental vulnerability. Compared with children who had an Apgar score of 9 at 1-minute and 10 at 5-minute, children with an Apgar score of 9 at both 1 and 5 minutes had higher rates of developmental vulnerability (aRR 1.03, 95%CI 1.01-1.05). Compared with infants with an Apgar of 10 at both 1 and 5 minutes, infants with a 1-minute score of 10 and a 5-minute score of <10 had higher rates of developmental vulnerability (aRR 1.53, 95% CI 1.08-2.17).

Conclusion: Risks of adverse developmental health and having special needs at 5 years of age are inversely associated with 1-minute and 5-minute Apgar scores across their entire range.

Article Summary:

Strengths and limitations of this study:

- Ability to access comprehensive health and education-related databases at the population level.
- Using a teacher reported instrument, no reliance was placed on parent or self-report of developmental health.
- There may be some individual differences in teachers' ability to evaluate developmental health on the Early Development Instrument.
- Study was restricted to the comparatively healthy subset of all term live births, as children with disabilities may not have enrolled in kindergarten.

INTRODUCTION

In 1953, Virginia Apgar proposed a scoring system that enabled a rapid assessment of the clinical status of the newborn infant and identified infants requiring resuscitation on the basis of heart rate, respiration, color, muscle tone and reflex irritability.[1] Initially, the Apgar score at 1-minute was used to assess the need for immediate resuscitation. Subsequently, the Apgar score at 5-minute was shown to be a better predictor of neonatal survival than the Apgar score at 1-minute. Although the value of a low Apgar score for accurately predicting adverse neurologic outcomes at the individual level has been questioned,[2,3] low Apgar scores are well correlated with both short-term[4] and long-term outcomes, in both preterm and term infants.[5-11]

Only the lowest and more compromised Apgar scores have been conventionally regarded as predictive of maladaptive development and morbidity. Nevertheless, a few population-based studies have shown that risks of cerebral palsy, epilepsy, early developmental health status and need for special education are inversely associated with 5-minute Apgar scores in a dose-dependent manner across the entire range of scores.[12-14] Even children with an Apgar score of 9 at 5 or 10 minutes have an increased risk of adverse neurological outcomes compared with children with 5 or 10 minutes Apgar scores of 10.[12,13] Although approximately 65% to 85% of newborns receive a 1-minute or a 5-minute Apgar score in the 7 to 9 range,[13] there is a dearth of information on how this impacts a child's developmental health.

Changes in Apgar score values between 1 and 5 minutes, and between 5 and 10 minutes are known to influence risks of cerebral palsy and epilepsy.[12,15,16] Our recent population-based study demonstrated elevated risks of cerebral palsy and epilepsy among children with a 5-minute Apgar score of 7 or 8, even if their 10-minute Apgar score was 9 or 10.[12] Although it is recognized that

changes in Apgar scores between 1 and 5 minutes are a useful measure of the response to resuscitation, the long-term significance of changes in such Apgar scores within the "normal" range (i.e., 7-10) is not clear.

In this population-based study, we investigated the associations between Apgar scores at 1 and 5 minutes across the entire range of score values, and developmental health at 5 years of age. We also analyzed the effect of a change in Apgar scores from 1 to 5 minutes, including changes within the normal range of Apgar scores. Specifically, we were interested in developmental health among children with 1-minute Apgar score in the 7-9 range who received a score less than 10 at 5-minute.

METHODS

Information on the study population was obtained from several population-based linked health and demographic databases in British Columbia. The anonymized linked data used in this study included information from the Discharge Abstract Database[17] that comprised hospital admission and discharge records; the Vital Statistics Birth and Clinical Births[18] databases, which contained information on all births in the province, along with delivery and neonatal health status, including diagnoses based on International Classification of Diseases (ICD 9 or ICD-10CA) codes; Census GeoData, which provided socioeconomic status (SES) data expressed as average neighbourhood income quintiles (based on Census information from Statistics Canada and quantified using postal codes);[19] the Consolidation File,[20] which provided demographic information on study subjects and confirmed residency in the province; and the Early Development Instrument (EDI)[21] data, which provided information on early childhood developmental health, and were accessed through linkage with the Human Early Learning Partnership.[22] The EDI has been routinely administered province-wide in British Columbia every one to three years since the 1999/2000 school year, achieving at

least 85% participation of kindergarten children from each school district. Teachers completed the EDI for each child in their kindergarten class (age range 5-7 years) in February. The EDI is designed to tap five core areas of early childhood development:[21,23] physical health and well-being; social competence; emotional maturity; language and cognitive development; and communication skills and general knowledge (Supplementary Table 1).[21] It consists of 104 binary and Likert-scale items, from which scores between 0 and 10 are calculated for each domain. The EDI also records demographic information on each child and whether the child has identified special needs.

The study population included all singleton term (≥37 weeks' gestation) infants born between April 1, 1993 and December 31, 2009, who had documented 1-minute and 5-minute Apgar scores as well as a completed EDI assessment in kindergarten. Inclusion of infants with these birth dates meant that children were 5 to 7 years of age between 1999 and 2014 and part of the EDI assessment. The study population was restricted to infants without major congenital anomalies, identified using diagnosis codes from linked hospital records in the year after birth.

Apgar scores at 1 and 5 minutes were considered as the main exposures and examined both as discrete values from 0 to 10 and also as grouped categories (Apgar values of 0-3, 4-6, 7, 8, 9, and 10). Children with an Apgar score of 0 at 1 or 5 minutes who did not have a diagnostic code for birth asphyxia [ICD-9: 768.5, 768.6 and 768.9; ICD-10: P21], or an intervention code for either resuscitation or ventilation (Canadian Classification of health interventions: 1.GZ.30, 1.GZ31, 1.HZ.30, 1361, 1362, 1363, 1373, 1379, 1004) were excluded from the study (n=470), as information on these cases likely resulted from transcription errors.

Developmental health included whether a child had special needs or was developmentally

vulnerable as measured by the EDI. Children were categorized as being developmentally vulnerable if their scores on the EDI fell below the 10th percentile value[24] in any of the five domains, based on the national EDI cut-off scores.[25] The 10th percentile cut-off has been recommended because it is usually higher than clinical cut-off points of 3% or 5% for diagnosing developmental delay. [21] Developmentally vulnerable children may not manifest developmental delays but may be at risk of experiencing challenges in school and society without additional support and care.[26] Children with special needs were defined as requiring special assistance because of chronic medically, physically, or intellectually disabling conditions.

Other independent variables included infant sex (male vs female), birth weight-for-gestational age, age of the child in years at the time of EDI assessment, gestational age at birth in completed weeks (37, 38, 39, 40, 41, and ≥42), birth order (1, 2, 3, and +4), marital status (married vs not married) and socioeconomic status (SES). Birth weight-for-gestational age was categorized as: small (<10th percentile), appropriate (10th-90th percentile) and large (>90th percentile) for gestational age.[27] Each child's family income was derived from the median household income in the child's residential area (based on postal code) obtained from the 2006 Canadian Census data.[28-30]

The frequency of each 5-minute Apgar score value was calculated within categories of maternal and infant characteristics. Multivariable log-linear regression models with robust variance estimates[31] was used to examine the association between Apgar score at 1 and 5 minutes and developmental vulnerability and special needs. Results were expressed as crude and adjusted rate ratios (aRR) with 95% confidence intervals (CI). Other variables included in the final models were based on the literature[24,32] or statistical significance (P value <0.1). The full model included child's sex, child's age at EDI completion, socioeconomic status, child's first language, birth weight-for-

gestational age, birth order, and gestational age. Interactions between Apgar scores and other determinants were examined and stratified analyses were carried out when a significant interaction was present. The University of British Columbia's Clinical Research Ethics Board approved the study.

Patient and public involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for or implementation of the study. No patients were asked to advise on interpretation of the findings.

RESULTS

There were 150,081 children (mean age = 5.7 years) with a gestational age at birth of ≥37 weeks, without major malformations and complete Apgar and EDI data included in the study. Information on special needs was available in 148,699 (99.1%) children. Five-minute Apgar scores showed a U-shaped association with gestational age at birth, with low scores more frequent at 37 weeks and ≥42 weeks (Table 1). Low 5-minute Apgar scores were comparable for most characteristics but more frequent among males, small-for-gestational age live births, children of mothers who were nulliparous, not married and those with a low SES.

Overall, the prevalence of vulnerability in one or more domains of the EDI was 30.2%, with physical and social domains having the highest rates of vulnerability at 15.2% and 12.7%, respectively (Figure 1). There was an increasing trend in the rate of developmental vulnerability with decreasing 1-minute and 5-minute Apgar scores (P for trend <0.001; Table 2). However, this association was much more pronounced for the 5-minute Apgar score. Compared with children

with an Apgar score of 10 at 5-minute, children with a 5-minute Apgar score of 2 had a 57% higher rate of developmental vulnerability (aRR 1.57, 95% CI 1.03-2.39). Similarly, children with a 5-minute Apgar score of 7, 8 or 9 had significantly higher rates of developmental vulnerability compared with children with a 5-minute Apgar score of 10 (aRR 1.08, 1.06 and 1.02 for Apgar 7, 8 and 9, respectively; Table 2). The association between 5-minute Apgar scores and developmental vulnerability was mainly due to the higher rates of vulnerability in the language and emotional domains of the EDI (Supplementary Table 2).

In total, 3,644 (2.5%) children had special needs (Table 3). The proportion of children with special needs increased linearly with decreasing 1-minute and 5-minute Apgar scores (P for trend <0.001). Compared with children who had a 1-minute Apgar score of 10, those with an Apgar score of 2 at 1-minute had significantly higher adjusted rates of having special needs (aRR 1.72, 95% CI 1.19-2.48), while those with an Apgar score of 5 at 1-minute had 1.39 times the rate of having special needs (95% CI 1.05-1.85). Children with 5-minute Apgar scores in the 1 to 8 range had higher adjusted rates for having special needs which consistently increased with decreasing 5-minute Apgar score values: from 1.20 in children with an Apgar score of 8 at 5-minute to 5.13 among those with an Apgar score of 1 at 5-minute. The adjusted risk ratios for having special needs among children with 1 and 5 minutes Apgar scores in the 0-3 range had wide 95% confidence intervals because of small numbers of children in these categories.

Table 4 shows rates of developmental vulnerability in relation to changes in Apgar score from 1 to 5 minutes, among children whose 1-minute Apgar score was in the normal range (7 to 10). Among children with a 1-minute Apgar score of 7, the rate of developmental vulnerability decreased in a dose-response manner with greater improvement in the Apgar score from 1 to 5 minutes (P value

for dose response = 0.02). Larger reductions in developmental vulnerability with greater improvements in 1 to 5 minutes Apgar scores were also evident among children with a 1-minute Apgar score of 9 (P value for trend 0.009) but not among children with a 1-minute Apgar score of 8 (P for trend 0.36). Children with an Apgar score of 9 at 1-minute and 9 at 5-minute had higher rates of developmental vulnerability compared with those who had Apgar scores of 9 at 1-minute and 10 at 5-minutes (aRR 1.03, 95% CI 1.01-1.05). Furthermore, compared with children who had Apgar scores of 10 at both 1 and 5 minutes, children whose 1-minute Apgar score decreased from 10 to a 5-minute Apgar score of <10, had 1.53 times the rate of developmental vulnerability (aRR 1.53, 95% CI 1.08-2.17).

DISCUSSION

In this population-based study, we found graded, continuously increasing risks of developmental vulnerability and special needs at 5 years of age with decreasing 1- and 5-minute Apgar scores. A low Apgar score at 5-minute was more strongly associated with developmental vulnerability and special needs than a low Apgar score at 1-minute. In particular, children with "normal" 5-minute Apgar scores of 7, 8 and 9 were more likely to have developmental vulnerability compared with children with 5-minute Apgar scores of 10. Similarly, children who had Apgar scores of 7 or 8 at 5 minutes had higher risks of having special needs compared with those with a 5-minute Apgar score of 10. Furthermore, children with a 1-minute Apgar score in the normal range (7 to 10) had an increased risk of developmental vulnerability, if their Apgar score at 5-minute was <10. Particularly noteworthy was a reduction in the Apgar score from 10 at 1-minute to 7-9 at 5-minute, as this substantially increased the risk of developmental vulnerability.

Our results confirm previous findings from a smaller cohort, which showed that developmental adversity extended in a linear fashion across the full range of Apgar scores.[13] Both research and clinical practice generally emphasize the increased risks of adverse outcomes associated with very low and less common Apgar scores (i.e., <7 or <4). Our results suggest that the negative association between Apgar score and developmental adversity or special needs extends across the full range of scores. Consistent with our findings, previous studies have shown a significant linear relationship between each one-point decrease in 5 and 10 minutes Apgar scores and increasing risk of epilepsy, cerebral palsy, and needing education in a special school.[12,14] While profound perinatal events can cause death or obvious neurological deficits, milder insults may sometimes cause subtle cognitive impairment only detectable as the child grows older, and apparent only at a population level.

Our study also showed that changes in Apgar scores from 1 to 5 minutes were associated with developmental vulnerability. This is in agreement with previous studies showing that changes in Apgar scores immediately after birth influence risks of cerebral palsy and epilepsy.[12,15,16] To our knowledge, this is the first study that examined risks of developmental adversity in relation to changes in Apgar scores from 1 to 5 minutes. Current guidelines define "normal" Apgar scores as 7 or more at 1-minute and 8 or more at 5-minute, indicating that the baby does not require assistance if scores are within these ranges.[33] However, our results reveal that lower scores within the normal range (7-9) and even a slight reduction in score from 10 at 1-minute to 9 at 5-minute are both associated with a significant increase in the risk of developmental vulnerability. Similarly, infants who have low Apgar scores for prolonged, or even brief periods are reported to have a higher risk of poor IQ scores at age 18, even if the infants recover subsequently.[6] The higher developmental vulnerability observed among infants whose optimal Apgar score (of 10) at 1-minute falls with

time after birth may be important clinically; such a progression may indicate problems with circulatory, respiratory or central nervous system changes that are associated with birth. Deterioration in the Apgar score immediately after birth, therefore, warrants re-evaluation of the infant and close clinical scrutiny in order to exclude congenital abnormalities and drug induced depression of the central nervous system.

The strengths of our study included the ability to access comprehensive health and education-related databases at the population level. By using a teacher reported instrument, no reliance was placed on parent or self-report of developmental health. Nonetheless, there may be some individual differences in teachers' ability to evaluate developmental health on the EDI.[25] Further, our study was restricted to the comparatively healthy subset of all term live births, as children with disabilities may not have enrolled in kindergarten or may have enrolled in special needs schools. Furthermore, although the EDI has broad coverage across British Columbia, it is collected less frequently in independent schools (30% coverage). Since parents who enroll their children in independent schools tend to be more affluent, our study population may have under-represented families at higher income. We recognize that the Apgar score as recorded in medical charts represents routine clinical practice,[34] and is prone to interobserver variability,[34] specifically in intubated newborn babies.[35] However, the quality of Apgar score values should not differ between children with and without subsequent diagnosed developmental vulnerability. Nevertheless, measurement errors inherent in routinely recorded Apgar scores (and possibly the EDI) may potentially explain the lack of an evident dose-response relationship between Apgar scores and developmental vulnerability. Lastly, we acknowledge that the incidence of adverse outcomes in the setting of normal Apgar scores is rare and a low Apgar in the normal range is a poor predictor of developmental vulnerability for the individual infant.

In summary, our study showed that the risk of developmental vulnerability and special needs at 5 years of age was inversely associated with 1 and 5 minutes Apgar scores across their entire range. Furthermore, improvements in Apgar scores between 1 and 5 minutes among children with a 1-minute Apgar score of 7 or 9 were associated with a lower risk of developmental vulnerability. These results provide clinicians with valuable prognostic information and the justification to carefully monitor infants who are even mildly compromised at 1 and 5 minutes. Future studies should examine the underlying mechanism by which Apgar score in the normal range could influence long-term neurodevelopmental outcomes.

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Contributor's statement:

Neda Razaz conceptualized and designed the study, analyzed the data, drafted the initial manuscript, and finalized the manuscript based on coauthor feedback. She had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Sven Cnattingius, Martina Persson, Kristina Tedroff, and Sarka Lisonkova, reviewed and commented on the initial and final analyses, provided feedback on the initial draft of the manuscript and approved the final version of the manuscript.

KS Joseph assisted with conceptualization and design of the study, and reviewed and commented on the initial and final analyses, provided feedback on the initial draft of the manuscript and approved the final version of the manuscript.

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Table 1. Maternal and birth characteristics according to Apgar score at five minutes among singleton term live births, British Columbia, 1993-2009

Maternal and birth characteristics	Total	Apgar 0-3 (n=147)	Apgar 4-6 (n=1328)	Apgar 7 (n=2375)	Apgar 8 (n=7666)	Apgar 9 (n=101191)	Apgar 10 (n=37374)
	No. (%)	%	%	%	%	%	%
Total	150081 (100)						
Maternal age (years)							
≤19	6170 (4.11)	0.15	1.41	1.93	5.80	64.17	26.55
20-24	24637 (16.42)	0.09	1.11	1.77	5.88	64.83	26.32
25-29	43832 (29.21)	0.10	0.88	1.64	5.19	66.66	25.54
30-34	47332 (31.54)	0.10	0.80	1.50	4.76	68.45	24.39
≥35	28081 (18.71)	0.09	0.72	1.39	4.73	69.89	23.17
Missing	29 (0.02)	0	<17.24	<17.24	<17.24	58.62	31.03
Socioeconomic status							
5th quintile [highest]	27519 (18.34)	0.10	0.90	1.64	5.00	66.88	25.47
4th quintile	31282 (20.84)	0.11	0.83	1.69	5.38	66.79	25.21
3rd quintile	30939 (20.61)	0.10	0.86	1.65	5.18	67.47	24.74
2nd quintile	31266 (20.83)	0.06	0.84	1.48	5.08	67.73	24.80
1st quintile [lowest]	28889 (19.25)	0.12	1.00	1.45	4.88	68.25	24.30
Missing	186 (0.12)	0	<2.69	<2.69	3.23	66.13	28.49
Married							
Yes	103099 (68.70)	0.09)	0.78	1.47	4.73	68.43	24.49
No	43374 (28.90)	0.12	1.13	1.85	6.01	64.93	25.95
Missing	3608 (2.40)	0.17	0.89	1.47	4.93	68.63	23.92
Infant's sex							
Female	73809 (49.18)	0.08	0.78	1.46	4.91	67.17	25.61
Male	76272 (50.82)	0.12	0.99	1.70	5.30	67.67	24.22
Birth order							
1	67516 (44.99)	0.12	1.25	2.09	6.13	67.92	22.49
2	56025 (37.33)	0.09	0.63	1.24	4.32	67.51	26.22
3	19239 (12.82)	0.07	0.46	1.05	4.13	66.66	27.63
≥4	7301 (4.86)	<0.07	0.56	0.99	4.34	64.17	29.91
Gestational age							
37 weeks	8966 (5.97)	0.10	1.08	2.02	6.88	68.02	21.89
38 weeks	25821 (17.20)	0.05	0.74	1.37	4.67	68.21	24.96

39 weeks	37408 (34.03)	0.09	0.76	1.32	4.36	68.57	24.89
40 weeks	51079 (34.03)	0.10	0.82	1.65	5.05	66.31	26.08
41 weeks	25040 (16.68)	0.15	1.22	1.87	6.08	67.38	23.29
42-44 weeks	1767 (1.18)	<0.28	1.58	2.09	6.51	61.35	28.3
Birth weight-for-gestational age							
Appropriate	121035 (80.65)	0.09	0.84	1.51	4.96	67.42	25.18
Small	11581 (7.72)	0.19	1.35	2.20	6.16	67.04	23.06
Large	17445 (11.62)	0.08	0.85	1.65	5.47	67.76	24.18
Missing	20 (0.01)	<25.00	<25.00	0	0	40.00	50.00
Child's age at EDI data collection (years)							
Means (SD)	5.70 (0.32)	5.67 (0.30)	5.65 (0.30)	5.66 (0.30)	5.66 (0.30)	5.65 (0.30)	5.65 (0.30)

Table 2. Apgar scores at one and five minutes and rate ratios for developmental vulnerability among singleton term live births, British Columbia, Canada

		Developmental vulnerability			
				Rate Ratio (95% CI)	
Apgar Score	Total No. of children	No. with outcome	%	Crude	Adjusted*
1-Min Apgar	**150081**	**45334**	**30.2**		
0	24	9	37.5	1.25 (0.74−2.10)	1.08 (0.64−1.83)
1	469	161	34.3	1.15 (1.00−1.31)	1.16 (1.02−1.32)
2	1060	329	31.0	1.04 (0.93−1.15)	1.03 (0.93−1.14)
3	1760	546	31.0	1.04 (0.95−1.13)	1.03 (0.95−1.13)
4	2582	814	31.5	1.05 (0.97−1.14)	1.07 (0.99−1.15)
5	4069	1261	31.0	1.03 (0.96−1.11)	1.05 (0.98−1.12)
6	6975	2124	30.5	1.02 (0.95−1.08)	1.04 (0.98−1.11)
7	12019	3648	30.4	1.01 (0.95−1.08)	1.03 (0.97−1.09)
8	38671	11666	30.2	1.01 (0.95−1.06)	1.02 (0.96−1.08)
9	79369	23852	30.1	1.00 (0.95−1.06)	1.00 (0.95−1.06)
10	3083	924	30.0	1.00 (Reference)	1.00 (Reference)
P for trend					<0.001
Per one unit of Apgar					0.99 (0.98-0.99)
5-Min Apgar					
0	20	7	35.0	1.18 (0.65−2.15)	1.16 (0.62−2.17)
1	16	9	56.3	1.90 (1.24−2.93)	1.88 (1.27−2.77)
2	28	13	46.4	1.57 (1.05−2.34)	1.57 (1.03−2.39)
3	83	30	36.2	1.22 (0.92−1.63)	1.25 (0.93−1.67)
4	106	43	40.6	1.37 (1.09−1.73)	1.33 (1.06−1.67)
5	290	85	29.3	0.99 (0.83−1.19)	0.98 (0.82−1.17)
6	932	306	32.8	1.11 (1.01−1.22)	1.08 (0.99−1.18)
7	2375	740	31.2	1.05 (0.99−1.12)	1.08 (1.01−1.14)
8	7666	2387	31.1	1.05 (1.02−1.09)	1.06 (1.02−1.10)
9	101191	30668	30.3	1.03 (1.01−1.04)	1.02 (1.00−1.04)
10	37374	11046	29.6	1.00 (Reference)	1.00 (Reference)
P for trend					<0.001
Per one unit of Apgar					0.98 (0.97-0.99)

*Adjusted for child's sex (male vs female), child's age at EDI completion (years), socioeconomic status (1st quintile, 2nd quintile, 3rd quintile, 4th quintile vs 5th quintile) child's first language (other vs English), birth order (2, 3, +4 vs 1), birth weight-for-gestational age (large, small vs appropriate), gestational age (weeks).

Table 3. Apgar score at one and five minutes and rate ratios for special needs status among singleton term live births in British Columbia, Canada

		Special Needs			
				Rate Ratio (95% CI)	
Apgar Score	Total No. of children	No. with outcome	%	Crude	Adjusted*
1-Min Apgar	**148699**	**3644**	**2.5**		
0	22	<5	4.6	1.94 (0.28−13.4)	1.44 (0.23−8.97)
1	463	26	5.6	2.40 (1.55−3.72)	2.23 (1.44−3.46)
2	1054	45	4.3	1.82 (1.26−2.63)	1.72 (1.19−2.48)
3	1743	53	3.0	1.30 (0.91−1.84)	1.23 (0.86−1.74)
4	2554	69	2.7	1.15 (0.83−1.60)	1.09 (0.79−1.52)
5	4032	136	3.4	1.44 (1.09−1.91)	1.39 (1.05−1.85)
6	6894	191	2.8	1.18 (0.90−1.55)	1.16 (0.89−1.52)
7	11903	298	2.5	1.07 (0.83−1.38)	1.06 (0.82−1.37)
8	38300	946	2.5	1.06 (0.83−1.34)	1.07 (0.84−1.35)
9	78701	1808	2.3	0.98 (0.78−1.24)	1.00 (0.79−1.26)
10	3033	71	2.3	1.00 (Reference)	1.00 (Reference)
P for trend					<0.001
Per one unit of Apgar					0.99 (0.98-0.99)
5-Min Apgar					
0	17	<5	<29.4	2.51 (0.37−16.8)	2.59 (0.41−16.3)
1	15	<5	<33.3	5.69 (1.56−20.7)	5.13 (1.45−18.1)
2	28	<5	<17.9	6.10 (2.46−15.2)	5.17 (2.01−13.3)
3	83	9	10.8	4.63 (2.49−8.61)	3.78 (2.03−7.02)
4	103	7	6.8	2.90 (1.41−5.95)	2.59 (1.25−5.35)
5	289	8	2.8	1.18 (0.59−2.35)	1.10 (0.56−2.16)
6	928	36	3.9	1.66 (1.19−2.30)	1.49 (1.07−2.06)
7	2342	74	3.2	1.35 (1.07−1.70)	1.28 (1.01−1.61)
8	7597	225	3.0	1.26 (1.09−1.46)	1.20 (1.03−1.38)
9	100281	2411	2.4	1.03 (0.95−1.11)	1.01 (0.94−1.09)
10	37016	867	2.3	1.00 (Reference)	1.00 (Reference)
P for trend					<0.001
Per one unit of Apgar					0.98 (0.97-0.99)

*Adjusted for child's sex (male vs female), child's age at EDI completion (years), socioeconomic status (1st quintile, 2nd quintile, 3rd quintile, 4th quintile vs 5th quintile) child's first language (other vs English), birth order (2, 3, +4 vs 1), birth weight-for-gestational age (large, small vs appropriate), gestational age (weeks).

Table 4. Rate ratios for developmental vulnerability according to combination of Apgar scores at one and five minutes, singleton term live births, British Columbia, Canada

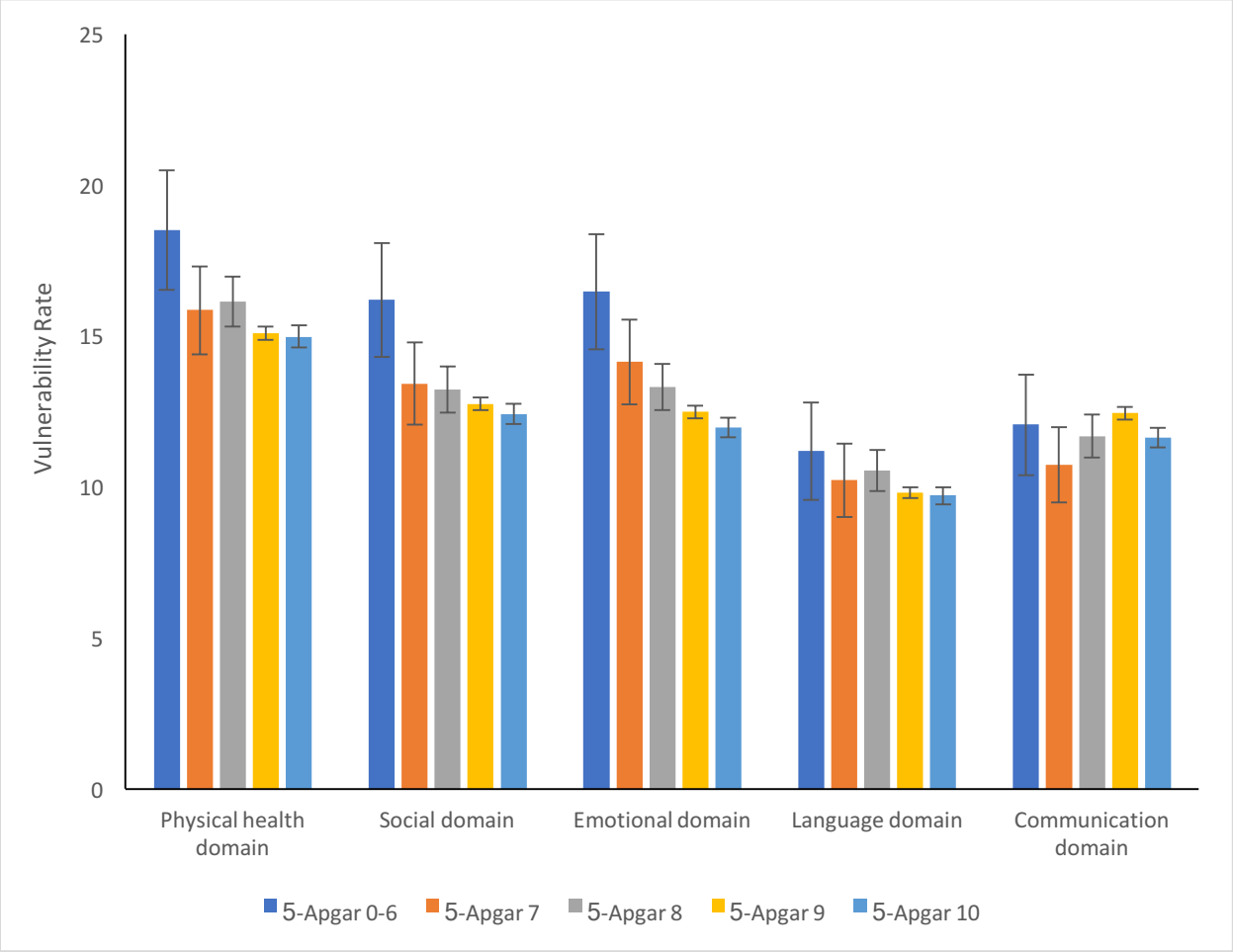
			Developmental vulnerability			
				Rate Ratio (95% CI)		
1-min Apgar	5-min Apgar	Total No. of children	No. with outcome (%)	Crude	Adjusted*	P for trend
7	<7	20	9 (45.0)	1.62 (0.99-2.65)	1.34 (0.80-2.25)	
7	7	172	56 (32.6)	1.18 (0.93-1.48)	1.18 (0.94-1.47)	
7	8	1987	629 (31.7)	1.14 (1.02-1.28)	1.12 (1.01-1.23)	
7	9	8700	2637 (30.3)	1.09 (0.99-1.20)	1.08 (0.99-1.19)	
7	10	1140	317 (27.8)	1.00 (Reference)	1.00 (Reference)	0.024
8	<8	66	17 (25.8)	0.85 (0.56-1.28)	0.71 (0.47-1.07)	
8	8	1337	420 (31.4)	1.03 (0.94-1.13)	1.01 (0.92-1.10)	
8	9	33255	10007 (30.1)	0.99 (0.94-1.04)	0.97 (0.93-1.02)	
8	10	4013	1222 (30.5)	1.00 (Reference)	1.00 (Reference)	0.36
9	<9	140	48 (34.3)	1.17 (0.93-1.47)	1.10 (0.88-1.38)	
9	9	50976	15501 (30.4)	1.03 (1.01-1.06)	1.03 (1.01-1.05)	
9	10	28253	8303 (29.4)	1.00 (Reference)	1.00 (Reference)	0.009
10	<10	26	13 (50.0)	1.68 (1.14-2.47)	1.53 (1.08-2.17)	
10	10	3057	911 (29.8)	1.00 (Reference)	1.00 (Reference)	0.016†

*Adjusted for child's sex (male vs female), child's age at EDI completion (years), socioeconomic status (1st quintile, 2nd quintile, 3rd quintile, 4th quintile vs 5th quintile) child's first language (others vs English), birth order (2, 3, +4 vs 1), birth weight-for gestational age (large, small vs appropriate), gestational age (weeks).

† P value for difference in rates.

Figure 1 Legend: Rates of vulnerability within the five Early Development Instrument domains by Apgar score at 5-minute, British Columbia, Canada

Figure 1: Rates of vulnerability within the five Early Development Instrument domains by Apgar score at 5-minute, British Columbia, Canada



Supplementary Table 1. Five domains of the Early Development Instrument

EDI domains	Characteristics addressed
Physical health and well-being	Children's fine and gross motor skills, energy levels, fatigue and clumsiness
Social competence	Self-confidence, tolerance, ability to get along with other children, to accept responsibility for their own actions, to work independently
Emotional maturity	Children's general emotional health and maturity. It also identifies minor problems with aggression, restlessness, distractibility or inattentiveness as well as excessive regular sadness
Language and cognitive skills	Mastery of the basics of reading and writing, interest in books, and numerical skills
Communication skills and general knowledge	Children's general knowledge, their ability to articulate clearly and their ability to understand and communicate in English

Supplementary Table 2. Apgar score at one and five minutes and rate ratios for vulnerability in each domain of the EDI, among singleton term live births in British Columbia, Canada

	Physical health domain			Social domain			Emotional domain		
Apgar Score	**No. with outcome**	**%**	**Adjusted***	**No. with outcome**	**%**	**Adjusted***	**No. with outcome**	**%**	**Adjusted***
1-Min Apgar									
0	<5	<20.83	0.90 (0.37−2.19)	<5	<20.83	1.01 (0.40−2.51)	<5	<20.83	0.71 (0.25−1.96)
1	88	18.76	1.24 (1.02−1.52)	82	17.48	1.30 (1.05−1.61)	83	17.7	1.25 (1.01−1.54)
2	179	16.89	1.09 (0.93−1.27)	142	13.40	0.97 (0.82−1.16)	147	13.87	0.96 (0.81−1.14)
3	283	16.08	1.06 (0.93−1.21)	246	13.98	1.03 (0.89−1.19)	273	15.51	1.09 (0.95−1.25)
4	410	15.88	1.06 (0.94−1.19)	349	13.52	1.02 (0.89−1.16)	370	14.33	1.03 (0.91−1.18)
5	644	15.83	1.04 (0.93−1.16)	569	13.98	1.06 (0.94−1.19)	563	13.84	1.01 (0.90−1.13)
6	1076	15.43	1.02 (0.93−1.13)	925	13.26	1.02 (0.92−1.14)	932	13.36	1.00 (0.89−1.11)
7	1889	15.72	1.03 (0.94−1.13)	1555	12.94	1.00 (0.90−1.11)	1500	12.48	0.94 (0.85−1.04)
8	5876	15.19	1.01 (0.93−1.10)	4993	12.91	1.01 (0.92−1.11)	4836	12.51	0.96 (0.87−1.05)
9	11839	14.92	0.99 (0.91−1.08)	9858	12.42	0.97 (0.89−1.07)	9608	12.11	0.94 (0.86−1.03)
10	472	15.31	1.00 (Reference)	393	12.75	1.00 (Reference)	399	12.94	1.00 (Reference)
5-Min Apgar									
0	<5	<25.00	0.66 (0.17−2.60)	<5	<25.00	1.13 (0.44−2.9)	<5	<25.00	1.13 (0.44−2.88)
1	6	37.5	2.42 (1.28−4.59)	<5	<31.25	1.42 (0.58−3.52)	<5	<31.25	1.92 (0.89−4.11)
2	9	32.14	2.22 (1.23−4.01)	7	25.00	1.87 (0.99−3.53)	6	21.43	1.60 (0.83−3.07)
3	21	25.30	1.75 (1.22−2.51)	15	18.07	1.37 (0.87−2.17)	12	14.46	1.08 (0.65−1.78)
4	25	23.58	1.56 (1.12−2.18)	18	16.98	1.26 (0.84−1.90)	18	16.98	1.19 (0.77−1.82)
5	46	15.86	1.06 (0.81−1.37)	34	11.72	0.86 (0.63−1.19)	33	11.38	0.84 (0.61−1.17)
6	164	17.60	1.13 (0.99−1.30)	159	17.06	1.26 (1.10−1.44)	167	17.92	1.33 (1.16−1.52)
7	377	15.87	1.08 (0.98−1.19)	319	13.43	1.05 (0.95−1.16)	336	14.15	1.11 (1.00−1.23)
8	1237	16.14	1.08 (1.02−1.14)	1014	13.23	1.04 (0.97−1.10)	1021	13.32	1.06 (1.00−1.13)
9	15272	15.09	1.03 (1.00−1.06)	12904	12.75	1.02 (0.99−1.06)	12641	12.49	1.04 (1.01−1.07)
10	5601	14.99	1.00 (Reference)	4640	12.42	1.00 (Reference)	4473	11.97	1.00 (Reference)

Supplementary Table 2 (cont.). Apgar score at one and five minutes and rate ratios for each domain of the EDI, among singleton term live births in British Columbia, Canada

	Language domain			Communication domain		
Apgar Score	**No. with outcome**	**%**	**Adjusted***	**No. with outcome**	**%**	**Adjusted***
1-Min Apgar				**18335**	**12.18**	
0	5	20.83	1.85 (0.81−4.25)	<5	<20.83	1.27 (0.50−3.22)
1	60	12.79	1.42 (1.10−1.82)	54	11.51	1.07 (0.83−1.39)
2	106	10.00	1.05 (0.86−1.29)	131	12.36	1.12 (0.93−1.35)
3	174	9.89	1.07 (0.90−1.27)	203	11.53	1.05 (0.90−1.23)
4	269	10.42	1.14 (0.98−1.32)	291	11.27	1.04 (0.90−1.19)
5	435	10.69	1.14 (1.00−1.31)	486	11.94	1.10 (0.97−1.24)
6	733	10.51	1.13 (1.00−1.28)	803	11.51	1.07 (0.96−1.20)
7	1255	10.44	1.10 (0.98−1.23)	1440	11.98	1.08 (0.97−1.20)
8	3830	9.90	1.04 (0.93−1.16)	4711	12.18	1.04 (0.95−1.15)
9	7621	9.60	0.99 (0.89−1.10)	9779	12.32	1.00 (0.91−1.10)
10	305	9.89	1.00 (Reference)	372	12.07	1.00 (Reference)
5-Min Apgar						
0	6	30.00	3.13 (1.52−6.44)	<5	<25.00	1.27 (0.43−3.70)
1	<5	<31.25	1.23 (0.38−3.92)	<5	<31.25	1.75 (0.74−4.13)
2	5	17.86	1.95 (0.86−4.43)	7	25.00	2.19 (1.09−4.41)
3	13	15.66	1.79 (1.11−2.91)	14	16.87	1.63 (1.00−2.68)
4	14	13.21	1.44 (0.89−2.34)	15	14.15	1.33 (0.84−2.12)
5	29	10.00	1.11 (0.78−1.57)	29	10.00	0.94 (0.67−1.33)
6	96	10.30	1.09 (0.90−1.31)	107	11.48	1.03 (0.87−1.23)
7	243	10.23	1.14 (1.01−1.29)	255	10.74	1.04 (0.92−1.16)
8	809	10.55	1.13 (1.06−1.22)	895	11.67	1.07 (1.00−1.14)
9	9939	9.82	1.04 (1.00−1.07)	12595	12.45	1.03 (1.00−1.06)
10	3637	9.73	1.00 (Reference)	4351	11.64	1.00 (Reference)

*Adjusted for child's sex (male vs female), child's age at EDI completion (years), socioeconomic status (1st quintile, 2nd quintile, 3rd quintile, 4th quintile vs 5th quintile) child's first language (others vs English), birth order (2, 3, +4 vs 1), birth weight-for-gestational age (large, small vs appropriate), gestational age (weeks).

STROBE Statement—checklist of items that should be included in reports of observational 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 (Page 1 and 2)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found (Page 2)
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported (Page 3, paragraph 1 and 2)
Objectives	3	State specific objectives, including any prespecified hypotheses (Page 4, paragraph 2)
Methods		
Study design	4	Present key elements of study design early in the paper (Page 4, para 1)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection (Page 6 to 9)
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (Page 4 to 7) *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed (n/a) *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable (Page 4 to 7)
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 (Page 4 to 7)
Bias	9	Describe any efforts to address potential sources of bias (n/a)
Study size	10	Explain how the study size was arrived at (n/a)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why (Page 6 to 7)
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (Page 6 to 7)
		(*b*) Describe any methods used to examine subgroups and interactions (n/a)
		(*c*) Explain how missing data were addressed (n/a)
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed

	Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy
	(*e*) Describe any sensitivity analyses

Continued on next page

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 (Page 7, para 1)
		(b) Give reasons for non-participation at each stage (n/a)
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (Page 7 and 8)
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time (Page 7 and 8)
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
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 (Page 8 -9)
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives (Page 9, last para)
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 (Page 11)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence (Page 10 to 11)
Generalisability	21	Discuss the generalisability (external validity) of the study results
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 (Page 1)

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

1-minute and 5-minute Apgar scores and child developmental health at 5 years of age, a population-based cohort study in British Columbia, Canada

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1-minute and 5-minute Apgar scores and child developmental health at 5 years of age, a population-based cohort study in British Columbia, Canada

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ABSTRACT

Objectives: We investigated the associations between Apgar scores at 1 and 5 minutes, across the entire range of score values, and child developmental health at 5 years of age.

Setting: British Columbia, Canada.

Participants: All singleton term infants without major congenital anomalies born between 1993 and 2009, who had a developmental assessment in kindergarten between1999 and 2014.

Main outcomes and measures: Developmental vulnerability on one or more domains of the Early Development Instrument and special needs requirements. Adjusted rate ratios (aRRs) and 95% confidence intervals (CIs) were estimated using log-linear regression.

Results: Of the 150,081 children in the study, 45,334 (30.2%) were developmentally vulnerable and 3,644 (2.5%) had special needs. There was an increasing trend in developmental vulnerability and special needs with decreasing 1-minute and 5-minute Apgar scores. Compared with children with an Apgar score of 10 at 5 minutes, the aRR for developmental vulnerability increased steadily with decreasing Apgar score from 1.02 (95%CI 1.00-1.04) for an Apgar score of 9 to 1.57 (95%CI 1.03-2.39) for an Apgar score of two. Among children with 1-minute Apgar scores in the 7-10 range, changes in Apgar scores between 1- and 5-minute were associated with significant differences in developmental vulnerability. Compared with children who had an Apgar score of 9 at 1-minute and 10 at 5-minute, children with an Apgar score of 9 at both 1- and 5-minute had higher rates of developmental vulnerability (aRR 1.03, 95%CI 1.01-1.05). Compared with infants with an Apgar of 10 at both 1 and 5 minutes, infants with a 1-minute score of 10 and a 5-minute score of <10 had higher rates of developmental vulnerability (aRR 1.53, 95%CI 1.08-2.17).

Conclusion: Risks of adverse developmental health and having special needs at 5 years of age are inversely associated with 1-minute and 5-minute Apgar scores across their entire range.

Article Summary:

Strengths and limitations of this study:

- Ability to access comprehensive health and education-related databases at the population level.
- Using a teacher reported instrument, no reliance was placed on parent or self-report of developmental health.
- There may be some individual differences in teachers' ability to evaluate developmental health on the Early Development Instrument.
- Study was restricted to the comparatively healthy subset of all term live births, as children with severe disabilities may not have enrolled in kindergarten.

INTRODUCTION

In 1953, Virginia Apgar proposed a scoring system that enabled a rapid assessment of the clinical status of the newborn infant and identified infants requiring resuscitation on the basis of heart rate, respiration, color, muscle tone and reflex irritability.[1] Initially, the Apgar score at 1 minute was used to assess the need for immediate resuscitation. Subsequently, the Apgar score at 5 minutes was shown to be a better predictor of neonatal survival than the Apgar score at 1 minute. Although the value of a low Apgar score for accurately predicting adverse neurologic outcomes at the individual level has been questioned,[2,3] low Apgar scores are well correlated with both short-term[4] and long-term outcomes, in both preterm and term infants.[5-11]

Only the lowest and more compromised Apgar scores have been conventionally regarded as predictive of maladaptive development and morbidity. Nevertheless, a few population-based studies have shown that risks of cerebral palsy, epilepsy, early developmental health status and need for special education are inversely associated with 5-minute Apgar scores in a dose-dependent manner across the entire range of scores.[12-14] Even children with an Apgar score of 9 at 5 or 10 minutes have an increased risk of adverse neurological outcomes compared with children with 5- or 10-minute Apgar scores of 10.[12,13] Although approximately 65% to 85% of newborns receive a 1-minute or a 5-minute Apgar score in the 7 to 9 range,[13] there is a dearth of information on how this impacts a child's developmental health.

Changes in Apgar score values between 1 and 5 minutes, and between 5 and 10 minutes are known to influence risks of cerebral palsy and epilepsy.[12,15,16] Our recent population-based study demonstrated elevated risks of cerebral palsy and epilepsy among children with a 5-minute Apgar score of 7 or 8, even if their 10-minute Apgar score was 9 or 10.[12] Although it is recognized that

changes in Apgar scores between 1 and 5 minutes are a useful measure of the response to resuscitation, the long-term significance of changes in such Apgar scores within the "normal" range (i.e., 7-10) is not clear.

In this population-based study, we investigated the associations between Apgar scores at 1 and 5 minutes across the entire range of score values, and developmental health at 5 years of age. We also analyzed the effect of a change in Apgar scores from 1 to 5 minutes, including changes within the normal range of Apgar scores. Specifically, we were interested in developmental health among children with 1-minute Apgar scores in the 7-9 range who received a score less than 10 at 5 minutes.

METHODS

The study was based on all singleton term infants without major congenital anomalies born between 1993 and 2009, who had a developmental assessment in kindergarten between1999 and 2014. Information on the study population was obtained from several population-based linked health and demographic databases in British Columbia. The anonymized linked data used in this study included information from the Discharge Abstract Database[17] that comprised hospital admission and discharge records; the Vital Statistics Birth and Clinical Births[18] databases, which contained information on all births in the province, along with delivery and neonatal health status, including diagnoses based on International Classification of Diseases (ICD 9 or ICD-10CA) codes; Census GeoData, which provided socioeconomic status (SES) data expressed as average neighbourhood income quintiles (based on Census information from Statistics Canada and quantified using postal codes);[19] the Consolidation File,[20] which provided demographic information on study subjects and confirmed residency in the province; and the Early Development

Instrument (EDI)[21] data, which provided information on early childhood developmental health, and were accessed through linkage with the Human Early Learning Partnership.[22] The EDI has been routinely administered province-wide in British Columbia every one to three years since the 1999/2000 school year, achieving at least 85% participation of kindergarten children from each school district. Teachers completed the EDI for each child in their kindergarten class (age range 5-7 years) in February. The EDI is designed to tap five core areas of early childhood development:[21-23] physical health and well-being; social competence; emotional maturity; language and cognitive development; and communication skills and general knowledge (Supplementary Table 1).[21] It consists of 104 binary and Likert-scale items, from which scores between 0 and 10 are calculated for each domain. The EDI also records demographic information on each child and whether the child has identified special needs.

The study population included all singleton term (≥37 weeks' gestation) infants born between April 1, 1993 and December 31, 2009, who had documented 1-minute and 5-minute Apgar scores as well as a completed EDI assessment in kindergarten. Inclusion of infants with these birth dates meant that children were 5 to 7 years of age between 1999 and 2014 and part of the EDI assessment. The study population was restricted to infants without major congenital anomalies, identified using diagnosis codes from linked hospital records in the year after birth.

Apgar scores at 1 and 5 minutes were considered as the main exposures and examined both as discrete values from 0 to 10 and also as grouped categories (Apgar values of 0-3, 4-6, 7, 8, 9, and 10). Children with an Apgar score of 0 at 1 or 5 minutes who did not have a diagnostic code for birth asphyxia [ICD-9: 768.5, 768.6 and 768.9; ICD-10: P21], or an intervention code for either resuscitation or ventilation (Canadian Classification of health interventions: 1.GZ.30, 1.GZ31,

1.HZ.30, 1361, 1362, 1363, 1373, 1379, 1004) were excluded from the study (n=470), as information on these cases likely resulted from transcription errors.

Developmental health assessment included whether a child had special needs or was developmentally vulnerable as measured by the EDI. Children were categorized as being developmentally vulnerable if their scores on the EDI fell below the 10th percentile value[24] in any of the five domains, based on the national EDI cut-off scores.[25] The 10th percentile cut-off has been recommended because it is higher and hence more sensitive than clinical cut-off points of 3% or 5% for diagnosing developmental delay. [21] Developmentally vulnerable children may not manifest developmental delays but may be at risk of experiencing challenges in school and society without additional support and care.[26] Children with special needs were defined as requiring special assistance because of chronic medical, physical, or intellectually disabling conditions.

Other independent variables examined included infant sex (male vs female), birth weight-for-gestational age, age of the child in years at the time of EDI assessment, gestational age at birth in completed weeks (37, 38, 39, 40, 41, and ≥42), birth order (1, 2, 3, and +4), marital status (married vs not married) and socioeconomic status (quintiles). Birth weight-for-gestational age was categorized as: small (<10th percentile), appropriate (10th-90th percentile) and large (>90th percentile) for gestational age.[27] Each child's family income was derived from the median household income in the child's residential area (based on postal code) obtained from the 2006 Canadian Census data.[28-30]

The frequency of each 5-minute Apgar score value was calculated within categories of maternal and infant characteristics. Multivariable log-linear regression models with robust variance

estimates[31] was used to examine the association between Apgar scores at 1 and 5 minutes and developmental vulnerability and special needs. Results were expressed as crude and adjusted rate ratios (aRR) with 95% confidence intervals (CI). Other variables included in the final models were based on the literature[24 32] or statistical significance (P value <0.10). The full model included child's sex, child's age at EDI completion, socioeconomic status, child's first language, birth weight-for-gestational age, birth order, and gestational age. Interactions between Apgar scores and other determinants were examined and stratified analyses were carried out when a significant interaction was present. The University of British Columbia's Clinical Research Ethics Board approved the study.

Patient and public involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for or implementation of the study. No patients were asked to advise on interpretation of the findings.

RESULTS

There were 150,081 children (mean age = 5.7 years) with a gestational age at birth of ≥37 weeks, without major malformations and complete Apgar and EDI data included in the study. Information on special needs was available in 148,699 (99.1%) children. Five-minute Apgar scores showed a U-shaped association with gestational age at birth, with low scores more frequent at 37 weeks and ≥42 weeks (Table 1). Low 5-minute Apgar scores were comparable for most characteristics but more frequent among males, small-for-gestational age live births, children of mothers who were nulliparous, not married and those with a low socioeconomic status.

Overall, the prevalence of vulnerability in one or more domains of the EDI was 30.2%, with physical and social domains having the highest rates of vulnerability at 15.2% and 12.7%, respectively (Figure 1). There was an increasing trend in the rate of developmental vulnerability with decreasing 1-minute and 5-minute Apgar scores (P for trend <0.001; Table 2). However, this association was much more pronounced for the 5-minute Apgar score. Compared with children with an Apgar score of 10 at 5 minutes, children with a 5-minute Apgar score of 2 had a 57% higher rate of developmental vulnerability (aRR 1.57, 95% CI 1.03-2.39). Similarly, children with a 5-minute Apgar score of 7, 8 or 9 had significantly higher rates of developmental vulnerability compared with children with a 5-minute Apgar score of 10 (aRR 1.08, 1.06 and 1.02 for Apgar 7, 8 and 9, respectively; Table 2). The association between 5-minute Apgar scores and developmental vulnerability was mainly due to the higher rates of vulnerability in the language and emotional domains of the EDI (Supplementary Table 2).

In total, 3,644 (2.5%) children had special needs (Table 3). The proportion of children with special needs increased linearly with decreasing 1-minute and 5-minute Apgar scores (P for trend <0.001). Compared with children who had a 1-minute Apgar score of 10, those with an Apgar score of 2 at 1 minute had significantly higher adjusted rates of having special needs (aRR 1.72, 95% CI 1.19-2.48), while those with an Apgar score of 5 at 1 minute had 1.39 times the rate of having special needs (95% CI 1.05-1.85). Children with 5-minute Apgar scores in the 1 to 8 range had higher adjusted rates for having special needs, which consistently increased with decreasing 5-minute Apgar score values: from 1.20 in children with an Apgar score of 8 at 5-minute to 5.13 among those with an Apgar score of 1 at 5-minute. The adjusted rate ratios for having special needs among children with 1- and 5-minute Apgar scores in the 0-3 range had wide 95% confidence intervals because of small numbers of children in these categories.

Table 4 shows rates of developmental vulnerability in relation to changes in Apgar score from 1 to 5 minutes, among children whose 1-minute Apgar score was in the normal range (7 to 10). Among children with a 1-minute Apgar score of 7, the rate of developmental vulnerability decreased in a dose-response manner with greater improvement in the Apgar score from 1 to 5 minutes (P value for dose response = 0.02). Larger reductions in developmental vulnerability with greater improvements in 1- to 5-minute Apgar scores were also evident among children with a 1-minute Apgar score of 9 (P value for trend 0.009) but not among children with a 1-minute Apgar score of 8 (P value for trend 0.36). Children with an Apgar score of 9 at 1 minute and 9 at 5 minutes had higher rates of developmental vulnerability compared with those who had Apgar scores of 9 at 1 minute and 10 at 5 minutes (aRR 1.03, 95% CI 1.01-1.05). Furthermore, compared with children who had Apgar scores of 10 at both 1 and 5 minutes, children whose 1-minute Apgar score decreased from 10 to a 5-minute Apgar score of <10, had 1.53 times the rate of developmental vulnerability (aRR 1.53, 95% CI 1.08-2.17).

DISCUSSION

In this population-based study, we found graded, continuously increasing risks of developmental vulnerability and special needs at 5 years of age with decreasing 1- and 5-minute Apgar scores. A low Apgar score at 5 minutes was more strongly associated with developmental vulnerability and special needs than a low Apgar score at 1 minute. In particular, children with “normal” 5-minute Apgar scores of 7, 8 and 9 were more likely to have developmental vulnerability compared with children with 5-minute Apgar scores of 10. Similarly, children who had Apgar scores of 7 or 8 at 5 minutes had higher risks of having special needs compared with those with a 5-minute Apgar score of 10. Furthermore, children with a 1-minute Apgar score in the normal range (7 to 10) had an

increased risk of developmental vulnerability, if their Apgar score at 5 minutes was <10. Particularly noteworthy was a reduction in the Apgar score from 10 at 1 minute to 7-9 at 5 minutes, as this substantially increased the risk of developmental vulnerability.

Our results confirm previous findings from a smaller cohort, which showed that developmental adversity extended in a linear fashion across the full range of Apgar scores.[13] Both research and clinical practice generally emphasize the increased risks of adverse outcomes associated with very low and less common Apgar scores (i.e., <7 or <4). Our results suggest that the negative association between Apgar score and developmental adversity or special needs extends across the full range of scores. Consistent with our findings, previous studies have shown a significant linear relationship between each one-point decrease in 5 and 10 minutes Apgar scores and increasing risk of epilepsy, cerebral palsy, and needing education in a special school.[12 14] While profound perinatal events can cause death or obvious neurological deficits, milder insults may sometimes cause subtle cognitive impairment only detectable as the child grows older, and apparent only at a population level.

Our study also showed that changes in Apgar scores from 1 to 5 minutes were associated with developmental vulnerability. This is in agreement with previous studies showing that changes in Apgar scores immediately after birth influence risks of cerebral palsy and epilepsy.[12 15 16] To our knowledge, this is the first study that examined risks of developmental adversity in relation to changes in Apgar scores from 1 to 5 minutes. Current guidelines define "normal" Apgar scores as 7 or more at 1 minute and 8 or more at 5 minutes, indicating that the baby does not require assistance if scores are within these ranges.[33] However, our results reveal that lower scores within the normal range (7-9) and even a slight reduction in score from 10 at 1 minute to 9 at 5 minutes are both

associated with a significant increase in the risk of developmental vulnerability. Similarly, infants who have low Apgar scores for prolonged, or even brief periods are reported to have a higher risk of poor IQ scores at age 18, even if the infants recover subsequently.[6] The higher developmental vulnerability observed among infants whose optimal Apgar score (of 10) at 1 minute falls with time after birth may be important clinically; such a progression may indicate problems with physiologic circulatory, respiratory or central nervous system changes that follow delivery. Deterioration in the Apgar score immediately after birth, therefore, warrants re-evaluation of the infant and close clinical scrutiny in order to exclude congenital abnormalities and drug induced depression of the central nervous system.

The strengths of our study included the ability to access comprehensive health and education-related databases at the population level. By using a teacher reported instrument, no reliance was placed on parent or self-report of developmental health. Nonetheless, there may be some individual differences in teachers' ability to evaluate developmental health on the EDI.[25] Further, our study was restricted to the comparatively healthy subset of all term live births, as children with severe disabilities may not have enrolled in kindergarten or may have enrolled in special needs schools. Furthermore, although the EDI has broad coverage across British Columbia, it is collected less frequently in independent schools (30% coverage). We recognize that the Apgar score as recorded in medical charts represents routine clinical practice,[34] and is prone to interobserver variability,[34] specifically in intubated newborn babies.[35] However, the quality of Apgar score values should not differ between children with and without subsequent diagnosed developmental vulnerability. Nevertheless, measurement errors inherent in routinely recorded Apgar scores (and possibly the EDI) may potentially explain the lack of an evident dose-response relationship between Apgar scores and developmental vulnerability. Lastly, we acknowledge that the incidence of adverse

outcomes in the setting of normal Apgar scores is rare and a low Apgar in the normal range is a poor predictor of developmental vulnerability for the individual infant.

In summary, our study showed that the risk of developmental vulnerability and special needs at 5 years of age was inversely associated with 1- and 5-minute Apgar scores across their entire range. Furthermore, improvements in Apgar scores between 1 and 5 minutes among children with a 1-minute Apgar score of 7 to 9 were associated with a lower risk of developmental vulnerability. These results provide clinicians with valuable prognostic information and the justification to carefully monitor infants who are even mildly compromised at 1 and 5 minutes. Future studies should examine the underlying mechanism by which Apgar scores in the normal range could influence long-term neurodevelopmental outcomes.

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Contributor's statement:

Neda Razaz conceptualized and designed the study, analyzed the data, drafted the initial manuscript, and finalized the manuscript based on coauthor feedback. She had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Sven Cnattingius, Martina Persson, Kristina Tedroff, and Sarka Lisonkova, reviewed and commented on the initial and final analyses, provided feedback on the initial draft of the manuscript and approved the final version of the manuscript.

KS Joseph assisted with conceptualization and design of the study, and reviewed and commented on the initial and final analyses, provided feedback on the initial draft of the manuscript and approved the final version of the manuscript.

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Table 1. Maternal and birth characteristics according to Apgar score at five minutes among singleton term live births, British Columbia, 1993-2009

Maternal and birth characteristics	Total	Apgar 0-3 (n=147)	Apgar 4-6 (n=1328)	Apgar 7 (n=2375)	Apgar 8 (n=7666)	Apgar 9 (n=101191)	Apgar 10 (n=37374)
	No. (%)	%	%	%	%	%	%
Total	150081 (100)						
Maternal age (years)							
≤19	6170 (4.11)	0.15	1.41	1.93	5.80	64.17	26.55
20-24	24637 (16.42)	0.09	1.11	1.77	5.88	64.83	26.32
25-29	43832 (29.21)	0.10	0.88	1.64	5.19	66.66	25.54
30-34	47332 (31.54)	0.10	0.80	1.50	4.76	68.45	24.39
≥35	28081 (18.71)	0.09	0.72	1.39	4.73	69.89	23.17
Missing	29 (0.02)	0	<17.24	<17.24	<17.24	58.62	31.03
Socioeconomic status							
5th quintile [highest]	27519 (18.34)	0.10	0.90	1.64	5.00	66.88	25.47
4th quintile	31282 (20.84)	0.11	0.83	1.69	5.38	66.79	25.21
3rd quintile	30939 (20.61)	0.10	0.86	1.65	5.18	67.47	24.74
2nd quintile	31266 (20.83)	0.06	0.84	1.48	5.08	67.73	24.80
1st quintile [lowest]	28889 (19.25)	0.12	1.00	1.45	4.88	68.25	24.30
Missing	186 (0.12)	0	<2.69	<2.69	3.23	66.13	28.49
Married							
Yes	103099 (68.70)	0.09)	0.78	1.47	4.73	68.43	24.49
No	43374 (28.90)	0.12	1.13	1.85	6.01	64.93	25.95
Missing	3608 (2.40)	0.17	0.89	1.47	4.93	68.63	23.92
Infant's sex							
Female	73809 (49.18)	0.08	0.78	1.46	4.91	67.17	25.61
Male	76272 (50.82)	0.12	0.99	1.70	5.30	67.67	24.22
Birth order							
1	67516 (44.99)	0.12	1.25	2.09	6.13	67.92	22.49
2	56025 (37.33)	0.09	0.63	1.24	4.32	67.51	26.22
3	19239 (12.82)	0.07	0.46	1.05	4.13	66.66	27.63
≥4	7301 (4.86)	<0.07	0.56	0.99	4.34	64.17	29.91
Gestational age							
37 weeks	8966 (5.97)	0.10	1.08	2.02	6.88	68.02	21.89

38 weeks	25821 (17.20)	0.05	0.74	1.37	4.67	68.21	24.96
39 weeks	37408 (34.03)	0.09	0.76	1.32	4.36	68.57	24.89
40 weeks	51079 (34.03)	0.10	0.82	1.65	5.05	66.31	26.08
41 weeks	25040 (16.68)	0.15	1.22	1.87	6.08	67.38	23.29
42-44 weeks	1767 (1.18)	<0.28	1.58	2.09	6.51	61.35	28.3
Birth weight-for-gestational age							
Appropriate	121035 (80.65)	0.09	0.84	1.51	4.96	67.42	25.18
Small	11581 (7.72)	0.19	1.35	2.20	6.16	67.04	23.06
Large	17445 (11.62)	0.08	0.85	1.65	5.47	67.76	24.18
Missing	20 (0.01)	<25.00	<25.00	0	0	40.00	50.00
Child's age at EDI data collection (years)							
Means (SD)	5.70 (0.32)	5.67 (0.30)	5.65 (0.30)	5.66 (0.30)	5.66 (0.30)	5.65 (0.30)	5.65 (0.30)

Table 2. Apgar scores at one and five minutes and rate ratios for developmental vulnerability among singleton term live births, British Columbia, Canada

		Developmental vulnerability			
				Rate Ratio (95% CI)	
Apgar Score	Total No. of children	No. with outcome	%	Crude	Adjusted*
1-Min Apgar	**150081**	**45334**	**30.2**		
0	24	9	37.5	1.25 (0.74−2.10)	1.08 (0.64−1.83)
1	469	161	34.3	1.15 (1.00−1.31)	1.16 (1.02−1.32)
2	1060	329	31.0	1.04 (0.93−1.15)	1.03 (0.93−1.14)
3	1760	546	31.0	1.04 (0.95−1.13)	1.03 (0.95−1.13)
4	2582	814	31.5	1.05 (0.97−1.14)	1.07 (0.99−1.15)
5	4069	1261	31.0	1.03 (0.96−1.11)	1.05 (0.98−1.12)
6	6975	2124	30.5	1.02 (0.95−1.08)	1.04 (0.98−1.11)
7	12019	3648	30.4	1.01 (0.95−1.08)	1.03 (0.97−1.09)
8	38671	11666	30.2	1.01 (0.95−1.06)	1.02 (0.96−1.08)
9	79369	23852	30.1	1.00 (0.95−1.06)	1.00 (0.95−1.06)
10	3083	924	30.0	1.00 (Reference)	1.00 (Reference)
P for trend					<0.001
Per one unit of Apgar					0.99 (0.98-0.99)
5-Min Apgar					
0	20	7	35.0	1.18 (0.65−2.15)	1.16 (0.62−2.17)
1	16	9	56.3	1.90 (1.24−2.93)	1.88 (1.27−2.77)
2	28	13	46.4	1.57 (1.05−2.34)	1.57 (1.03−2.39)
3	83	30	36.2	1.22 (0.92−1.63)	1.25 (0.93−1.67)
4	106	43	40.6	1.37 (1.09−1.73)	1.33 (1.06−1.67)
5	290	85	29.3	0.99 (0.83−1.19)	0.98 (0.82−1.17)
6	932	306	32.8	1.11 (1.01−1.22)	1.08 (0.99−1.18)
7	2375	740	31.2	1.05 (0.99−1.12)	1.08 (1.01−1.14)
8	7666	2387	31.1	1.05 (1.02−1.09)	1.06 (1.02−1.10)
9	101191	30668	30.3	1.03 (1.01−1.04)	1.02 (1.00−1.04)
10	37374	11046	29.6	1.00 (Reference)	1.00 (Reference)
P for trend					<0.001
Per one unit of Apgar					0.98 (0.97-0.99)

*Adjusted for child's sex (male vs female), child's age at EDI completion (years), socioeconomic status (1st quintile, 2nd quintile, 3rd quintile, 4th quintile vs 5th quintile) child's first language (other vs English), birth order (2, 3, +4 vs 1), birth weight-for-gestational age (large, small vs appropriate), gestational age (weeks).

Table 3. Apgar score at one and five minutes and rate ratios for special needs status among singleton term live births in British Columbia, Canada

		Special Needs			
				Rate Ratio (95% CI)	
Apgar Score	Total No. of children	No. with outcome	%	Crude	Adjusted*
1-Min Apgar	**148699**	**3644**	**2.5**		
0	22	<5	4.6	1.94 (0.28−13.4)	1.44 (0.23−8.97)
1	463	26	5.6	2.40 (1.55−3.72)	2.23 (1.44−3.46)
2	1054	45	4.3	1.82 (1.26−2.63)	1.72 (1.19−2.48)
3	1743	53	3.0	1.30 (0.91−1.84)	1.23 (0.86−1.74)
4	2554	69	2.7	1.15 (0.83−1.60)	1.09 (0.79−1.52)
5	4032	136	3.4	1.44 (1.09−1.91)	1.39 (1.05−1.85)
6	6894	191	2.8	1.18 (0.90−1.55)	1.16 (0.89−1.52)
7	11903	298	2.5	1.07 (0.83−1.38)	1.06 (0.82−1.37)
8	38300	946	2.5	1.06 (0.83−1.34)	1.07 (0.84−1.35)
9	78701	1808	2.3	0.98 (0.78−1.24)	1.00 (0.79−1.26)
10	3033	71	2.3	1.00 (Reference)	1.00 (Reference)
P for trend					<0.001
Per one unit of Apgar					0.99 (0.98-0.99)
5-Min Apgar					
0	17	<5	<29.4	2.51 (0.37−16.8)	2.59 (0.41−16.3)
1	15	<5	<33.3	5.69 (1.56−20.7)	5.13 (1.45−18.1)
2	28	<5	<17.9	6.10 (2.46−15.2)	5.17 (2.01−13.3)
3	83	9	10.8	4.63 (2.49−8.61)	3.78 (2.03−7.02)
4	103	7	6.8	2.90 (1.41−5.95)	2.59 (1.25−5.35)
5	289	8	2.8	1.18 (0.59−2.35)	1.10 (0.56−2.16)
6	928	36	3.9	1.66 (1.19−2.30)	1.49 (1.07−2.06)
7	2342	74	3.2	1.35 (1.07−1.70)	1.28 (1.01−1.61)
8	7597	225	3.0	1.26 (1.09−1.46)	1.20 (1.03−1.38)
9	100281	2411	2.4	1.03 (0.95−1.11)	1.01 (0.94−1.09)
10	37016	867	2.3	1.00 (Reference)	1.00 (Reference)
P for trend					<0.001
Per one unit of Apgar					0.98 (0.97-0.99)

*Adjusted for child's sex (male vs female), child's age at EDI completion (years), socioeconomic status (1st quintile, 2nd quintile, 3rd quintile, 4th quintile vs 5th quintile) child's first language (other vs English), birth order (2, 3, +4 vs 1), birth weight-for-gestational age (large, small vs appropriate), gestational age (weeks).

Table 4. Rate ratios for developmental vulnerability according to combination of Apgar scores at one and five minutes, singleton term live births, British Columbia, Canada

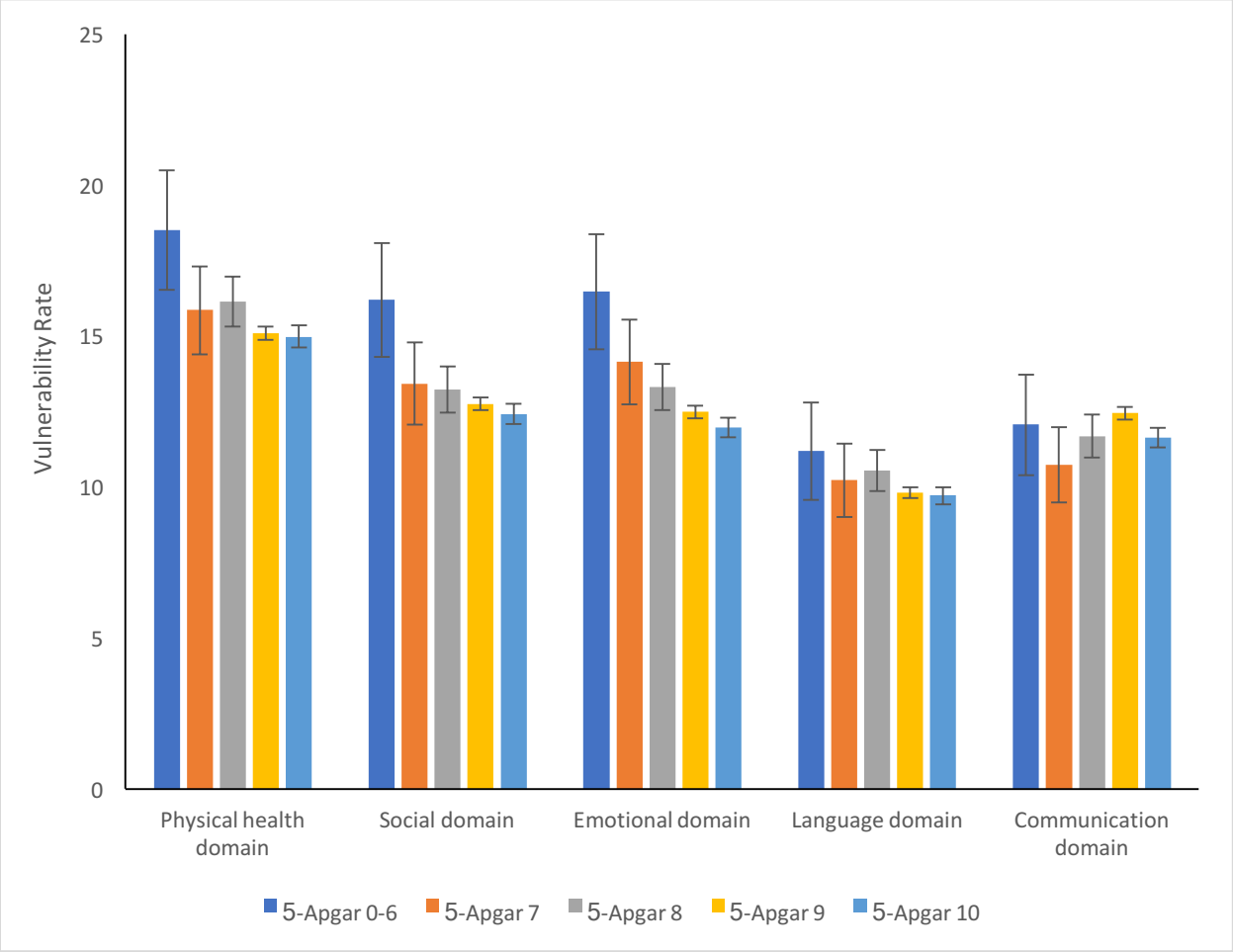
			Developmental vulnerability			
				Rate Ratio (95% CI)		
1-min Apgar	5-min Apgar	Total No. of children	No. with outcome (%)	Crude	Adjusted*	P for trend
7	<7	20	9 (45.0)	1.62 (0.99-2.65)	1.34 (0.80-2.25)	
7	7	172	56 (32.6)	1.18 (0.93-1.48)	1.18 (0.94-1.47)	
7	8	1987	629 (31.7)	1.14 (1.02-1.28)	1.12 (1.01-1.23)	
7	9	8700	2637 (30.3)	1.09 (0.99-1.20)	1.08 (0.99-1.19)	
7	10	1140	317 (27.8)	1.00 (Reference)	1.00 (Reference)	0.024
8	<8	66	17 (25.8)	0.85 (0.56-1.28)	0.71 (0.47-1.07)	
8	8	1337	420 (31.4)	1.03 (0.94-1.13)	1.01 (0.92-1.10)	
8	9	33255	10007 (30.1)	0.99 (0.94-1.04)	0.97 (0.93-1.02)	
8	10	4013	1222 (30.5)	1.00 (Reference)	1.00 (Reference)	0.36
9	<9	140	48 (34.3)	1.17 (0.93-1.47)	1.10 (0.88-1.38)	
9	9	50976	15501 (30.4)	1.03 (1.01-1.06)	1.03 (1.01-1.05)	
9	10	28253	8303 (29.4)	1.00 (Reference)	1.00 (Reference)	0.009
10	<10	26	13 (50.0)	1.68 (1.14-2.47)	1.53 (1.08-2.17)	
10	10	3057	911 (29.8)	1.00 (Reference)	1.00 (Reference)	0.016†

*Adjusted for child's sex (male vs female), child's age at EDI completion (years), socioeconomic status (1st quintile, 2nd quintile, 3rd quintile, 4th quintile vs 5th quintile) child's first language (others vs English), birth order (2, 3, +4 vs 1), birth weight-for gestational age (large, small vs appropriate), gestational age (weeks).

† P value for difference in rates.

Figure 1 Legend: Rates of vulnerability within the five Early Development Instrument domains by Apgar score at 5 minutes, British Columbia, Canada

Figure 1: Rates of vulnerability within the five Early Development Instrument domains by Apgar score at 5-minute, British Columbia, Canada



Supplementary Table 1. Five domains of the Early Development Instrument

EDI domains	Characteristics addressed
Physical health and well-being	Children's fine and gross motor skills, energy levels, fatigue and clumsiness
Social competence	Self-confidence, tolerance, ability to get along with other children, to accept responsibility for their own actions, to work independently
Emotional maturity	Children's general emotional health and maturity. It also identifies minor problems with aggression, restlessness, distractibility or inattentiveness as well as excessive regular sadness
Language and cognitive skills	Mastery of the basics of reading and writing, interest in books, and numerical skills
Communication skills and general knowledge	Children's general knowledge, their ability to articulate clearly and their ability to understand and communicate in English

Supplementary Table 2. Apgar score at one and five minutes and rate ratios for vulnerability in each domain of the EDI, among singleton term live births in British Columbia, Canada

	Physical health domain			Social domain			Emotional domain		
Apgar Score	**No. with outcome**	**%**	**Adjusted***	**No. with outcome**	**%**	**Adjusted***	**No. with outcome**	**%**	**Adjusted***
1-Min Apgar									
0	<5	<20.83	0.90 (0.37−2.19)	<5	<20.83	1.01 (0.40−2.51)	<5	<20.83	0.71 (0.25−1.96)
1	88	18.76	1.24 (1.02−1.52)	82	17.48	1.30 (1.05−1.61)	83	17.7	1.25 (1.01−1.54)
2	179	16.89	1.09 (0.93−1.27)	142	13.40	0.97 (0.82−1.16)	147	13.87	0.96 (0.81−1.14)
3	283	16.08	1.06 (0.93−1.21)	246	13.98	1.03 (0.89−1.19)	273	15.51	1.09 (0.95−1.25)
4	410	15.88	1.06 (0.94−1.19)	349	13.52	1.02 (0.89−1.16)	370	14.33	1.03 (0.91−1.18)
5	644	15.83	1.04 (0.93−1.16)	569	13.98	1.06 (0.94−1.19)	563	13.84	1.01 (0.90−1.13)
6	1076	15.43	1.02 (0.93−1.13)	925	13.26	1.02 (0.92−1.14)	932	13.36	1.00 (0.89−1.11)
7	1889	15.72	1.03 (0.94−1.13)	1555	12.94	1.00 (0.90−1.11)	1500	12.48	0.94 (0.85−1.04)
8	5876	15.19	1.01 (0.93−1.10)	4993	12.91	1.01 (0.92−1.11)	4836	12.51	0.96 (0.87−1.05)
9	11839	14.92	0.99 (0.91−1.08)	9858	12.42	0.97 (0.89−1.07)	9608	12.11	0.94 (0.86−1.03)
10	472	15.31	1.00 (Reference)	393	12.75	1.00 (Reference)	399	12.94	1.00 (Reference)
5-Min Apgar									
0	<5	<25.00	0.66 (0.17−2.60)	<5	<25.00	1.13 (0.44−2.9)	<5	<25.00	1.13 (0.44−2.88)
1	6	37.5	2.42 (1.28−4.59)	<5	<31.25	1.42 (0.58−3.52)	<5	<31.25	1.92 (0.89−4.11)
2	9	32.14	2.22 (1.23−4.01)	7	25.00	1.87 (0.99−3.53)	6	21.43	1.60 (0.83−3.07)
3	21	25.30	1.75 (1.22−2.51)	15	18.07	1.37 (0.87−2.17)	12	14.46	1.08 (0.65−1.78)
4	25	23.58	1.56 (1.12−2.18)	18	16.98	1.26 (0.84−1.90)	18	16.98	1.19 (0.77−1.82)
5	46	15.86	1.06 (0.81−1.37)	34	11.72	0.86 (0.63−1.19)	33	11.38	0.84 (0.61−1.17)
6	164	17.60	1.13 (0.99−1.30)	159	17.06	1.26 (1.10−1.44)	167	17.92	1.33 (1.16−1.52)
7	377	15.87	1.08 (0.98−1.19)	319	13.43	1.05 (0.95−1.16)	336	14.15	1.11 (1.00−1.23)
8	1237	16.14	1.08 (1.02−1.14)	1014	13.23	1.04 (0.97−1.10)	1021	13.32	1.06 (1.00−1.13)
9	15272	15.09	1.03 (1.00−1.06)	12904	12.75	1.02 (0.99−1.06)	12641	12.49	1.04 (1.01−1.07)
10	5601	14.99	1.00 (Reference)	4640	12.42	1.00 (Reference)	4473	11.97	1.00 (Reference)

Supplementary Table 2 (cont.). Apgar score at one and five minutes and rate ratios for each domain of the EDI, among singleton term live births in British Columbia, Canada

	Language domain			Communication domain		
Apgar Score	**No. with outcome**	**%**	**Adjusted***	**No. with outcome**	**%**	**Adjusted***
1-Min Apgar				**18335**	**12.18**	
0	5	20.83	1.85 (0.81−4.25)	<5	<20.83	1.27 (0.50−3.22)
1	60	12.79	1.42 (1.10−1.82)	54	11.51	1.07 (0.83−1.39)
2	106	10.00	1.05 (0.86−1.29)	131	12.36	1.12 (0.93−1.35)
3	174	9.89	1.07 (0.90−1.27)	203	11.53	1.05 (0.90−1.23)
4	269	10.42	1.14 (0.98−1.32)	291	11.27	1.04 (0.90−1.19)
5	435	10.69	1.14 (1.00−1.31)	486	11.94	1.10 (0.97−1.24)
6	733	10.51	1.13 (1.00−1.28)	803	11.51	1.07 (0.96−1.20)
7	1255	10.44	1.10 (0.98−1.23)	1440	11.98	1.08 (0.97−1.20)
8	3830	9.90	1.04 (0.93−1.16)	4711	12.18	1.04 (0.95−1.15)
9	7621	9.60	0.99 (0.89−1.10)	9779	12.32	1.00 (0.91−1.10)
10	305	9.89	1.00 (Reference)	372	12.07	1.00 (Reference)
5-Min Apgar						
0	6	30.00	3.13 (1.52−6.44)	<5	<25.00	1.27 (0.43−3.70)
1	<5	<31.25	1.23 (0.38−3.92)	<5	<31.25	1.75 (0.74−4.13)
2	5	17.86	1.95 (0.86−4.43)	7	25.00	2.19 (1.09−4.41)
3	13	15.66	1.79 (1.11−2.91)	14	16.87	1.63 (1.00−2.68)
4	14	13.21	1.44 (0.89−2.34)	15	14.15	1.33 (0.84−2.12)
5	29	10.00	1.11 (0.78−1.57)	29	10.00	0.94 (0.67−1.33)
6	96	10.30	1.09 (0.90−1.31)	107	11.48	1.03 (0.87−1.23)
7	243	10.23	1.14 (1.01−1.29)	255	10.74	1.04 (0.92−1.16)
8	809	10.55	1.13 (1.06−1.22)	895	11.67	1.07 (1.00−1.14)
9	9939	9.82	1.04 (1.00−1.07)	12595	12.45	1.03 (1.00−1.06)
10	3637	9.73	1.00 (Reference)	4351	11.64	1.00 (Reference)

*Adjusted for child's sex (male vs female), child's age at EDI completion (years), socioeconomic status (1st quintile, 2nd quintile, 3rd quintile, 4th quintile vs 5th quintile) child's first language (others vs English), birth order (2, 3, +4 vs 1), birth weight-for-gestational age (large, small vs appropriate), gestational age (weeks).

STROBE Statement—checklist of items that should be included in reports of observational 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 (Page 1 and 2)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found (Page 2)
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported (Page 3, paragraph 1 and 2)
Objectives	3	State specific objectives, including any prespecified hypotheses (Page 4, paragraph 2)
Methods		
Study design	4	Present key elements of study design early in the paper (Page 4, para 1)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection (Page 6 to 9)
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (Page 4 to 7) *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed (n/a) *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable (Page 4 to 7)
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 (Page 4 to 7)
Bias	9	Describe any efforts to address potential sources of bias (n/a)
Study size	10	Explain how the study size was arrived at (n/a)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why (Page 6 to 7)
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (Page 6 to 7)
		(*b*) Describe any methods used to examine subgroups and interactions (n/a)
		(*c*) Explain how missing data were addressed (n/a)
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed

	Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy
	(*e*) Describe any sensitivity analyses

Continued on next page

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 (Page 7, para 1)
		(b) Give reasons for non-participation at each stage (n/a)
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (Page 7 and 8)
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time (Page 7 and 8)
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
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 (Page 8 -9)
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives (Page 9, last para)
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 (Page 11)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence (Page 10 to 11)
Generalisability	21	Discuss the generalisability (external validity) of the study results
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 (Page 1)

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.