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Drs. Kozyrskyj and Mandhane 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.

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Acquisition, analysis, or interpretation of data: Matenchuk, Tamana, Lou, Becker, Mandhane, Turvey, Subbarao, Sears, Kozyrskyj.

Drafting of the manuscript: Matenchuk, Kozyrskyj

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Statistical analysis: Matenchuk

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Administrative, technical, or material support: Matenchuk, Lou, Becker, Mandhane, Turvey, Subbarao, Lefebvre, Kozyrskyj.

Study supervision: Kozyrskyj, Mandhane

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Running head: Depression & birth mode mediate influence on sleep

Abstract

Rationale: Sleep duration is critical to growth, learning, and immune function development in infancy. Strategies to ensure that national recommendations for sleep duration in infants are met require knowledge of perinatal factors that affect infant sleep.

Objectives: To investigate the mechanistic pathways linking maternal education and infant sleep.

Methods: An observational study was conducted on 619 infants whose mothers were enrolled at the Edmonton site of the CHILD birth cohort. Infant sleep duration at 3 months was assessed using the Brief Infant Sleep Questionnaire. Maternal education was collected via maternal report. Prenatal and postnatal depression scores were obtained from the 20-item Center for Epidemiologic Studies Depression Scale (CES-D). Birth records and maternal report were the source of covariate measures. Mediation analysis (PROCESS v3.0) was used to examine the indirect effects of maternal education on infant sleep duration mediated through prenatal depression and birth mode.

Measurements and Main Results: At 3 months of age, infants slept on average 14.1 hours. Lower maternal education and prenatal depression were associated with significantly shorter infant sleep duration. Emergency cesarean section birth was associated with 1-hour shorter sleep duration at 3 months compared to vaginal birth [without intrapartum antibiotic prophylaxis] (β: -0.99 hours; 95% CI: -1.51, -0.48). Thirty percent of the effect of lower maternal education on infant total sleep duration was mediated sequentially through prenatal depression and birth mode (Total Indirect Effects: -0.12, 95%CI: -0.22, -0.03, $p<0.05$).

Conclusions: Prenatal depression and birth mode sequentially mediate the effect of maternal education on infant sleep duration.

Keywords: pediatric sleep, maternal education, prenatal depression, birth mode, emergency caesarean section

Abbreviations

CHILD - Canadian Healthy Infant Longitudinal Development; CS - Caesarean section; HPA – Hypothalamic-pituitary-adrenal; IAP - Intrapartum antibiotic prophylaxis; SES – Socioeconomic status

3.1 Introduction

Globally, over 50% of 3 month old infants obtain less than the recommended 14 hours of sleep per 24 hour period (1,2). Sleep plays a central role in growth, neurological development, learning and processing of memory, and optimal functioning of the immune system (3). In childhood, shorter sleep duration is associated with cognitive deficits (4), poor school performance and increased behavioral problems (5). Infants who sleep less are at risk for overweight (6) and those with frequent nocturnal awakenings are more likely to develop asthma (7). Sleep problems which arise in infancy and childhood tend to persist (8). In adults, short sleep duration has been linked to increased risk of mortality, diabetes mellitus, hypertension, obesity and coronary heart disease (4). Poor quality sleep in adulthood is identified as a pathway by which low socioeconomic status (SES) 'gets under the skin' to cause disease (9) and conceivably, may be a missing link in the intergenerational transmission of SES inequalities in health (10). Hence, infant sleep is a logical target for government and public health agencies.

Be it short sleep in infants or sleep problems in toddlers, there is emerging evidence of the influence of family SES, including maternal educational attainment, on sleep in young children (11,12). When examining the various household factors that affect infant sleep, such as parental sleep (11,13,14), the upstream factor which is most likely candidate to mediate the relationship between SES and infant sleep duration is maternal prenatal depression (15). Mothers in distress have sleep problems during pregnancy (16), which can be 'transmitted' to the fetus via the maternal suprachiasmatic nucleus or melatonin levels (17–19). Maternal depression also leads to elevated free cortisol levels during pregnancy (20), which in turn, appear to increase infant cortisol levels in response to stress (21,22). When cortisol levels are elevated, they preferentially bind to norepinephrine and glucocorticoid receptors and ultimately increase sleep EEG frequency, light sleep and frequent waking, and decrease short-wave sleep via stimulation of corticotropin releasing hormone (CRH) (23). Interestingly, maternal psychological health also plays a role in the birth process and birth outcomes (24–26). If birth is stressful and/or leads to unexpected events such as cesarean delivery, infant sleep can be impacted through newborn exposure to hypothalamic pituitary adrenal (HPA) axis hormones (27), reduced mother-infant bonding (28), or

additional birth-associated medical interventions. There is a gap in the literature regarding the influence of the birth process on infant sleep duration beyond the second postnatal day (29).

While maternal education status has been linked to infant sleep duration (11) and maternal psychological health (30), the relatedness of these factors has not been studied nor has the birth process been taken into account. Reported associations between cesarean delivery and postpartum depression (31) may in fact be secondary to existing prenatal depression. Importantly, potential causes of childhood sleep duration are often examined after 1 year of age, excluding the first 6 months of life when critical development of the circadian rhythm, neurological function, and behavior takes place (3,19,32). We examined the association between maternal educational attainment and infant sleep duration at 3 months of age in the Canadian healthy Infant Longitudinal Development (CHILD) birth cohort. Second, we assessed whether prenatal depression and birth mode sequentially mediated the association between maternal education status and infant sleep duration. The CHILD cohort also provided a unique opportunity to test independence from putative confounding factors such as colic, often a suspected cause of sleep problems in infants (33) and antibiotic exposure, which has been found to induce transient insomnia (34) and decrease slow wave sleep (35).

3.2 Methods

Study Design

This study involved a subsample of 619 Canadian infants from the Edmonton site of the Canadian Healthy Infant Longitudinal Development (CHILD) birth cohort (http://www.childstudy.ca) (36). The Human Research Ethics board at the University of Alberta approved this study. Written informed consent was obtained from the mother at enrollment. Mothers of studied infants were enrolled during pregnancy between 2008 and 2012. Data on covariates were obtained from hospital records (birth mode, gestational age at birth, birth weight and direct antibiotic exposure) or standardized questionnaires (maternal age, maternal race/ethnicity, household income, infant sex, breastfeeding status, weight at 3 months, and solid food intake before 3 months) (see Appendix).

Infant sleep at 3 months of age (outcome of interest). Infant total sleep duration was obtained from the parent self-reported BISQ (Appendix B) administered at 3 months of age (37). Parent self-report of infant day (7 am until 7 pm) and night (7 pm until 7 am) sleep duration in hours and minutes were combined to obtain infant total sleep duration per 24-hour period.

Maternal education (exposure of interest). Maternal education level was collected from a standardized questionnaire. Mothers chose from: "1-high school or less", "2-some university or college", and "3-university degree obtained". Categories 1 and 2 were then combined.

Depression symptoms. Depression symptoms were measured using the 20-item Center for Epidemiologic Studies Depression Scale (CES-D) (38) at 36 weeks of gestation and 6 months postpartum. Women self-reported how often they experienced various depressive cognitions, affect, and behaviors during the past week. Responses were given on a score ranging from 0 (None of the time; less than 1 day) to 3 (Most or all of the time; 5-7 days). Responses were summed, with higher scores indicating higher depressive symptoms (min=0, max=60). CES-D scores of 16 or greater represent significant risk for clinical depression (39).

Statistical analysis. The Student's t-test and ANOVA test with Tukey post-hoc test were used to examine the association between maternal education level and covariates. Univariate and multivariate linear regression modelling was performed with total sleep duration as the outcome and maternal education as the exposure of interest. A final model was chosen using purposeful selection as described by Hosmer and Lemeshow (40). Multinomial regression was used to predict having postnatal depression only, prenatal depression only, or prenatal and postnatal depression together (ref: no prenatal or postnatal depression) from maternal education level. Statistical significance of the difference in sleep duration according to birth mode was determined by ANOVA with Tukey post hoc test. Mediation analysis was conducted using the Hayes PROCESS v3.0 macro for SPSS, version 23.0 (SPSS Inc) (41). A multiple mediation path model was evaluated to determine the indirect effects of sequential mediators: prenatal depression (mediator 1) and birth mode (mediator 2) in the path between maternal education and infant total sleep duration at 3 months of age. Bootstrapping (5000 bootstrap resamples) was used to generate to 95% CIs

in mediation models. Sensitivity analyses were conducted to explore the potential confounding effect of postpartum depression on the multiple mediation model.

3.3 Results

Table 1. Associations between infant and maternal characteristics, maternal education level and total sleep duration at 3 months.

	Maternal Education			Total Sleep Duration (hours/24 hours)	
	No University Degree n = 284/619 (45.89 %)	University Degree n = 335/619 (54.11%)	p-value	Observations	Mean (SD) 14.17 (2.14)
Maternal education, No. (%)					
No University Degree	-	-	N.A.	284	13.94 (2.20)
University Degree	-	-		335	14.36 (2.08)
Infant Characteristics					
Gestational age, No. (%)					
Below 38 weeks	28 (9.96%)	44 (13.25%)	0.357	72	14.32 (2.25)
38 to 39 weeks	138 (49.11%)	148 (44.58%)		286	14.33 (2.27)
Over 40 weeks	115 (40.93%)	140 (42.17%)		255	13.93 (1.93)
Birth weight, No. (%)					
< 2500g	6 (2.12%)	14 (4.22%)	0.332	20	14.09 (2.23)
2500-3499g	147 (51.94%)	173 (52.11%)		320	14.19 (2.23)
3500-4499g	127 (44.88)	138 (41.57%)		265	14.14 (2.05)
> 4500g	3 (1.06%)	7 (2.11%)		10	13.95 (1.44)
Weight at 3 months, No. (%)					
< 5000g	6 (2.17%)	13 (3.93%)	0.302	19	14.26 (2.24)
5000-5999g	59 (21.38%)	73 (22.05%)		132	14.34 (2.26)
6000-7999g	185 (67.03%)	203 (61.33%)		388	14.16 (2.11)
>8000g	26 (9.42%)	42 (12.69%)		68	13.91 (2.10)
Gender, No. (%)					
Boy	150 (52.82%)	161 (48.06%)	0.259	311	14.25 (2.13)
Girl	134 (47.18%)	174 (51.94%)		308	14.09 (2.16)
Antibiotic exposure, No. (%)					
Yes	149 (53.41%)	161 (49.09%)	0.291	310	13.94 (2.16)
No	130 (46.59%)	167 (50.91%)		297	14.37 (2.10)
Birth mode, No. (%)					
Vaginal –IAP	144 (51.25%)	179 (53.92%)	0.177	323	14.39 (2.08)
Vaginal +IAP	56 (19.93%)	81 (24.40%)		137	13.98 (2.18)
Scheduled CS	36 (12.81%)	35 (10.54%)		71	14.36 (2.07)
Emergency CS	45 (16.01%)	37 (11.14%)		82	13.40 (2.20)
Breastfeeding status, No. (%)					
Exclusive	138 (48.59%)	204 (61.08%)	<0.001	342	14.26 (2.06)
Partial	79 (27.82%)	95 (28.44%)		174	14.09 (2.16)
Zero	67 (23.59%)	35 (10.48%)		102	14.00 (2.38)
Solids, No. (%)					
Yes	8 (2.92%)	7 (2.12%)	0.604	15	14.83 (1.54)
No	266 (97.08%)	323 (97.88%)		589	14.16 (2.16)
Colic, No. (%)					
Yes	43 (15.30%)	52 (15.66%)	0.911	95	13.89 (2.27)

No	238 (84.70%)	280 (84.34%)		518	14.22 (2.13)
Maternal Characteristics					
Maternal age, No. (%)					
18 to 29	125 (44.01%)	60 (17.91%)	<0.001	185	14.07 (2.08)
30 to 39	150 (52.82%)	259 (77.31%)		409	14.20 (2.17)
Over 40	9 (3.17%)	16 (4.78%)		25	14.32 (2.20)
Annual household income, No. (%)					
Less than 39,999	31 (10.95%)	7 (2.09%)	<0.001	38	13.86 (1.70)
40,000-79,999	83 (29.33%)	55 (16.42%)		138	14.01 (2.20)
80,000-99,9999	43 (15.19%)	49 (14.63%)		92	14.04 (2.34)
Greater than 100,000	101 (35.69%)	207 (67.79%)		308	14.41 (1.97)
Preferred not to answer	25 (8.83%)	17 (5.07%)		42	13.59 (2.76)
Maternal race, No. (%)					
White	215 (76.24%)	258 (77.01%)	<0.001	473	14.09 (2.09)
Asian	18 (6.38%)	50 (14.93%)		68	14.64 (2.46)
Other	49 (17.38%)	27 (8.06%)		76	14.21 (2.18)
Prenatal depression, No. (%)					
Yes	69 (27.27%)	41 (13.62%)	<0.001	110	13.65 (2.11)
No	184 (72.73%)	260 (86.38%)		444	14.23 (2.14)
Postnatal depression, No. (%)					
Yes	40 (17.62%)	30 (10.71%)	0.028	70	13.43 (2.54)
No	187 (82.38%)	250 (89.29%)		437	14.26 (2.03)
Maternal prenatal smoking, No. (%)					
No	256 (91.10%)	332 (99.40%)	<0.001	588	14.18 (2.14)
Yes	25 (8.90%)	2 (0.60%)		27	13.87 (1.94)
Siblings in the home, No. (%)					
No	124 (43.82%)	152 (45.65%)	0.685	270	13.70 (2.06)
Yes	159 (56.18%)	181 (54.35%)		340	14.54 (2.13)

Notes: -IAP: no intrapartum antibiotics; +IAP: with intrapartum antibiotics; CS: caesarean section.

In our population-based cohort of 619 mother-infant dyads, 54% of mothers had a university degree. Significant differences in maternal age, annual household income, maternal race, breastfeeding status, prenatal smoking, and pre- and post- natal depression were found between mothers with and without a university degree (See Table 1). Women with a university degree were older than those without a university degree. The majority of mothers with a university degree (67.79%) had an annual household income greater than $100,000. Annual household income greater than $100,000 was less prevalent when mothers did not have a university degree (35.69%). Two percent of mothers with a university degree and 10.95% of mothers without a university degree had a household income below $39,999. Mothers with a university degree were less likely to identify as a race other than white or Asian (8.1% vs 17.4%). In contrast, 6.4%of mothers without a university degree were Asian, compared to 14.9% of mothers with a

university degree. Exclusive breastfeeding was higher at 3 months of age in mothers with a university degree (61.1% vs 48.6%).

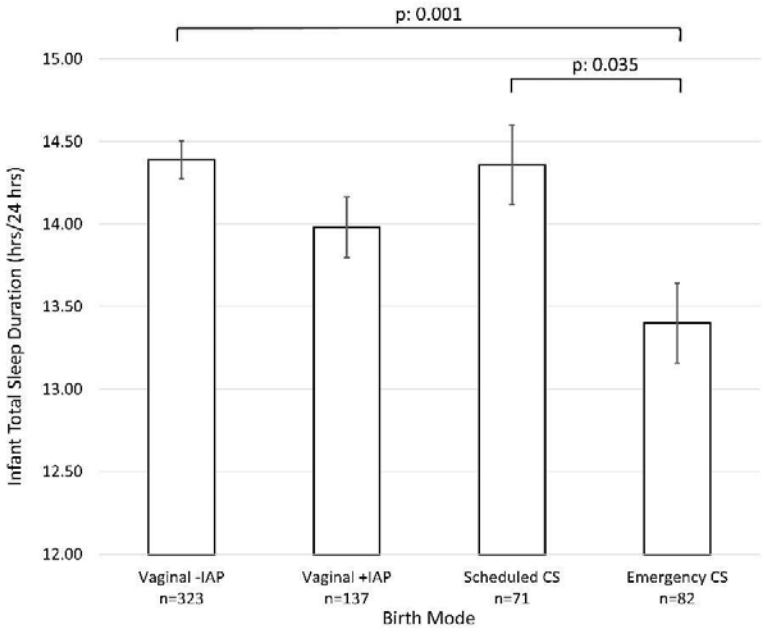

Figure 1. Infant total sleep duration at 3 months of age according to birth mode.

Note:-IAP: no intrapartum antibiotics; +IAP: with intrapartum antibiotics; CS: caesarean section.

Mean infant total sleep duration at 3 months of age was 14.2 hours (Standard deviation [SD]: 2.14; Table 1). The National Sleep Foundation recommends 14-17 hours of sleep in this age group (2). Infants born to mothers without a university degree slept an average of 13.94 hours (SD: 2.20) compared to 14.36 hours (SD: 2.08) in infants born to mothers with university degrees. Both prenatal and postnatal depression were associated with significantly shorter infant sleep duration. Total sleep duration was significantly different according to birth mode. Tukey post-hoc test showed that infants born by emergency caesarian section (CS) slept significantly shorter than infants born vaginally without IAP or by scheduled CS (Figure 1).

Maternal education is associated with prenatal and postnatal depression.

Twenty-seven percent of mothers without a university degree had prenatal depression (CES-D score ≥ 16), while 13.6% of mothers with a university degree had prenatal depression. Similarly, 17.6% of mothers without a university degree had postnatal depression while only 10.7% of mothers with a university degree had postnatal depression. Women without a university degree had an almost 2 times higher relative risk of prenatal depression without postnatal depression (relative risk [RRR]: 1.91, 95% CI: 1.06, 3.43, p=0.03; figure E1 online supplement), 4.4 times higher relative risk of both prenatal and postnatal depression (RRR: 4.39, 95% CI: 1.82, 10.62, p<0.001), but no difference in relative risk of postnatal depression without prenatal depression (RRR: 0.95, 95% CI: 0.43, 2.08, p=0.89) compared to women with a university degree.

Maternal postsecondary education is positively associated with infant sleep duration.

Infants of mothers without a university degree had reduced sleep duration at 3 months of age (β: -0.42 hours, 95% Confidence Interval [CI]: -0.76, -0.08, p<0.01; Table 2) compared to mothers with a university degree. This association remained significant following adjustment for infant factors including gestational age at birth, gender, birth mode, breastfeeding status, solids, and colic (β: -0.42 hours, 95% CI: -0.78, -0.07, p<0.05; Model 2). However, the difference in sleep duration by maternal education status was not significant (β: -0.28 hours, 95% CI: -0.67, 0.11, p=NS; Model 3) when controlling for maternal characteristics including prenatal depression, maternal age, maternal race, siblings in the home, maternal prenatal smoking and all Model 2 variables.

Table 2. Crude and multivariate linear regression analyses predicting infant total sleep duration at 3 months of age.

	Crude		Model 1		Model 2		Model 3		Model 4	
	B Coeff.	95% CI Lower, Upper	*B Coeff.*	95% CI Lower, Upper	*B Coeff.*	95% CI Lower, Upper	*B Coeff.*	95% CI Lower, Upper	*B Coeff.*	95% CI Lower, Upper
Maternal education ***(ref = university degree)***	**-0.42***	**-0.76, -0.08**	**-0.44****	**-0.78, -0.10**	**-0.42***	**-0.78, -0.07**	**-0.37**	**-0.75, 0.02**	**-0.29**	**-0.65, 0.06**
Infant Characteristics										

Block 1											
Gestational age at birth *(continuous)*		-0.12†	-0.24, 0.01	-0.13†	-0.26, 0.001	-0.15*	-0.28, -0.02	-0.03	-0.18, 0.12	-	-
Gender *(ref = female)*		0.16	-0.18, 0.50	0.12	-0.22, 0.46	0.09	-0.25, 0.44	0.16	-0.20, 0.52	-	-
Birth mode	Vag +IAP	-0.41†	-0.83, -0.02	-0.49*	-0.92, -0.07	-0.50*	-0.93, -0.06	-0.48*	-0.93, -0.02	-0.35	-0.80, 0.09
(ref = vaginal - IAP)	Scheduled CS	-0.02	-0.57, 0.52	-0.11	-0.67, 0.45	-0.09	-0.66, 0.48	-0.22	-0.81, 0.37	-0.24	-0.81, 0.33
	Emergency CS	-0.99***	-1.51, -0.48	-0.94***	-1.45, -0.42	-0.98***	-1.51, -0.44	-0.68*	-1.26, -0.10	-0.70*	-1.25, -0.15
Block 2											
Breastfeeding status	Partial	-0.17	-0.56, 0.22	-	-	-0.20	-0.60, 0.21	-0.35†	-0.77, 0.07	-	-
(ref = exclusive)	Zero	-0.27	-0.74, 0.21	-	-	-0.24	-0.74, 0.26	-0.30	-0.83, 0.23	-	-
Solids		0.68	-0.43, 1.78	-	-	0.89	-0.23, 2.00	0.96	-0.59, 0.43	-	-
Colic		-0.33	-0.81, 0.14	-	-	-0.40	-0.88, 0.08	-0.08	-0.59, 0.43	-	-
Maternal Characteristics											
Prenatal depression *(CES-D score)*		-0.03**	-0.06, -0.01	-	-	-	-	-0.03*	-0.06, 0.00	-0.03*	-0.05, -0.004
Maternal age	18-29	-0.14	-0.51, 0.24	-	-	-	-	-0.36†	-0.78, 0.05	-	-
(ref = 30-39)	40+	0.12	-0.75, 0.99	-	-	-	-	-0.46	-1.41, 0.49	-	-
Maternal race	Asian	0.55*	0.01, 1.10	-	-	-	-	0.66*	0.06, 1.25	-	-
(ref = white)	Other	0.12	-0.40, 0.64	-	-	-	-	0.29	-0.28, 0.87	-	-
Siblings in the home *(ref = no)*		-0.85****	0.51, 1.18	-	-	-	-	0.79***	0.41, 1.17	0.79***	0.42, 1.16
Maternal prenatal smoking		-0.31	-1.14, 0.51	-	-	-	-	0.29	-0.66, 1.24	-	-

Notes: Model 1: maternal education, gestational age at birth, gender, and birth mode. Model 2: Model 1 with breastfeeding status, solids, and colic. Model 3: Model 2 with prenatal depression, maternal age, and maternal race. Model 4: maternal education, birth mode, prenatal depression, and siblings in the home [chosen by purposeful selection]. IAP: intrapartum antibiotics; CS: caesarean section. p<0.05*; p<0.01**; p<0.001***; p<0.0001****.

Emergency CS was associated with shorter sleep duration at 3 months of age compared to the reference group of infants born vaginally without IAP (Crude β: -0.99 hours, 95% CI: -1.51, -0.48, p<0.001). Each 1-point increase in mothers' prenatal CES-D score was associated with a 0.03-hour decrease in infant sleep duration (Crude β: -0.03 hours, 95% CI: -0.06, -0.01, p<0.01). Infants of Asian mothers slept on average 0.59 hours more than infants of white mothers (Crude β: 0.59 hours, 95% CI: 0.05, 1.13, p<0.05).

Purposeful selection resulted in the inclusion of birth mode, prenatal depression (CES-D score) and siblings in the home in the regression model predicting infant sleep duration (Model 4). Maternal education was included as an exposure of interest. Emergency CS (β: -0.70 hours, 95% CI: -1.25, -0.15, p<0.05; Model 4), prenatal depression (CES-D score) (β: -0.03 hours, 95% CI: -0.05, -0.004, p<0.05) and siblings in the home (β: 0.79 hours, 95% CI: 0.42, 1.16, p<0.001), significantly contributed to the

prediction of infant sleep duration. Maternal education did not contribute to the model predicting infant sleep duration (β: -0.29 hours, 95% CI: -0.65, 0.06, *p*=NS) when adjusting for birth mode, prenatal depression and siblings in the home. Interactions between maternal education, prenatal depression, birth mode and siblings in the home did not significantly contribute to the model.

Prenatal depression and birth mode sequentially mediate the relationship between maternal education level and infant sleep duration.

Regression analysis was used to investigate the hypothesis that prenatal depression and birth mode sequentially mediate the effect of maternal education on infant total sleep duration (Figure 2). Lower maternal education was a significant predictor of prenatal depression (CES-D score) (β=2.68, SE=0.63, *p*<0.0001; Online Supplement Table E1). Furthermore, prenatal depression (CES-D score) (β=0.01, SE=0.01, *p*=0.05), but not lower maternal education (β=0.15, SE=0.09, *p*=0.11) was a significant predictor of birth mode (classified as 1 = vaginal no IAP, 2 = vaginal IAP, 3 = scheduled CS, and 4 = emergency CS) when modelled concurrently. When evaluated in regression analysis together, prenatal depression (CES-D score) (β=-0.03, SE=0.01, *p*=0.04) and birth mode (β=-0.27, SE=0.08, *p*<0.01) but not maternal education (β=-0.27, SE=0.18, *p*=0.15) predicted infant total sleep duration.

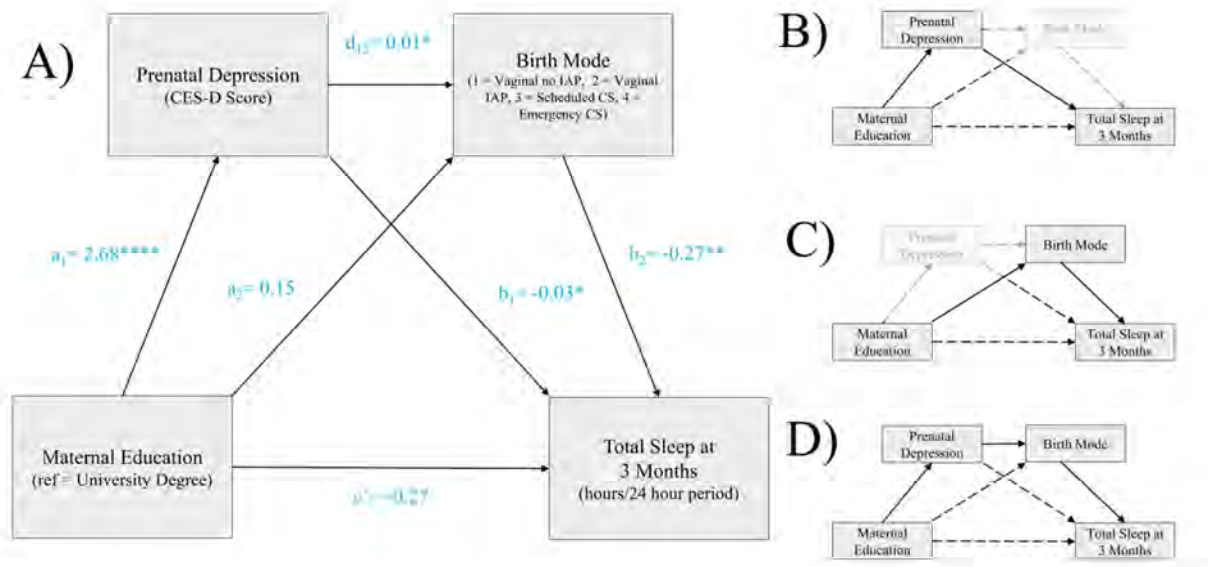

Figure 2. Sequential mediation model of associations between maternal education, prenatal depression, birth mode, and infant sleep duration. -IAP: no intrapartum antibiotics; +IAP: with intrapartum antibiotics; CS: caesarean section. p<0.1†; p<0.05*; p<0.01**; p<0.001***; p<0.0001****.

Prenatal depression and birth mode sequentially mediate the relationship between maternal education and infant sleep duration. Following sequential mediation, the direct association of lower maternal education with infant total sleep duration (path c`) was no longer significant (Effect: -0.27, 95% CI: -0.63, 0.09, *p*=0.15; Table 3); however, the total indirect effects of lower maternal education on infant total sleep duration mediated sequentially through prenatal depression and birth mode were significant (Effect: -0.12, 95% CI: -0.22, -0.03, *p*<0.05). Combined, the direct and indirect effects of lower maternal education on infant sleep duration were significant (Effect: -0.38, 95% CI: -0.74, -0.03, *p*<0.05). Eighteen percent of the effect of lower maternal education on infant total sleep duration was mediated through prenatal depression alone (Effect: -0.07, 95% CI: -0.15, -0.01, *p*<0.05). The indirect effect of maternal education through birth mode alone was not significant (Effect: -0.04, 95% CI: -0.11, 0.01, *p*=NS). The effect of lower maternal education on infant total sleep duration (2.3% of the total effect) was mediated

sequentially through prenatal depression and birth mode directly (Effect: -0.01, 95% CI: -0.02, -0.0004, p<0.05). These associations were robust to sensitivity analyses for imputed missing values. Due to the high correlation between prenatal and postnatal CES-D scores, sequential mediation of the relationship between maternal education and infant sleep duration through prenatal and subsequently postnatal depression, as well as postnatal depression alone, was explored. Postnatal CES-D score was not found to mediate the relationship between maternal education and infant sleep duration with prenatal CES-D score or on its own.

Table 3. Breakdown of direct and indirect effects of maternal education on infant sleep duration at 3 months of age through prenatal depression (CES-D score) and birth mode.

	% Effect Explained	Effect	SE	p	95% CI
A) Total effect of maternal education (indirect + direct effects)	100%	-0.38*	0.18	0.04	-0.74, -0.03
B) Indirect effect 1 Maternal education → prenatal depression → sleep duration	17.7%	-0.07*	0.03	<0.05	-0.15, -0.01
C) Indirect effect 2 Maternal education → birth mode → sleep duration	10.5%	-0.04	0.03	NS	-0.11, 0.01
D) Indirect effect 3 Maternal education → prenatal depression → birth mode → sleep duration	2.3%	-0.01*	0.006	<0.05	-0.02, -0.0004
Total indirect effects (1 + 2 + 3)	30.4%	-0.12*	0.05	<0.05	-0.22, -0.03
Direct effect of maternal education	69.5%	-0.27	0.18	NS	-0.63, 0.09

Notes: p <0.05*.

3.4 Discussion

In our general population cohort of infants from an urban center in Canada, 38% of infants slept less than the recommended 14 hours per day; lower than global estimates of infant short sleep at 3 months of age (1). Infants born to mothers with a university degree slept an average of 0.42 hours longer than infants of mothers without a university degree. The association between maternal level of education and

infant sleep duration persisted following adjustment for infant factors but diminished with additional adjustment for maternal characteristics, notably maternal prenatal depression (14). Further, we found that birth mode independently predicted infant sleep duration, with infants delivered by emergency cesarean sleeping approximately one hour less than infants born by vaginal birth. When combined, we found that maternal prenatal depression status and birth mode jointly mediated the association between maternal level of education and infant sleep duration. Previously, prenatal depression was found to be associated with shorter sleep duration in 1-2 year olds independent of household SES, and postnatal depressive symptoms in caregivers reported to influence the relationship between family demographics and sleep problems in toddlers (11,42). Our study is the first to suggest that prenatal depression has the capacity to mediate the relationship between maternal education level and infant sleep in the 3 months of age. Almost one-third of the indirect effect of maternal education was mediated through the joint action of prenatal depression and emergency cesarean.

The additional novelty of our study is the reduction in infant sleep three months after emergency cesarean delivery; this was not observed with scheduled cesarean or in vaginal deliveries with maternal antibiotic prophylaxis. Compared to vaginal delivery, both emergency and scheduled cesarean delivery have been shown to reduce active sleep in newborns on the first but not second postnatal day; however, an observed lack of diurnal rhythms in infant sleep/wakefulness with both surgical groups seems to persist (29). Netsi et al did not find an association between birth mode and sleep duration at age 3 months in a Brazilian cohort, in which many of the cesarean births would have been scheduled (43). One aspect of modern birth, the induction and augmentation of labour using synthetic oxytocin, is very common in birth by emergency cesarean (44). In animal studies, synthetic oxytocin increases wakefulness (45), hypothesized to occur due to oxytocin's influence on the HPA axis through an excitatory action on CRH (23,46,47). Upregulation of the CRH system has been implicated in the impairment of sleep quality in both human and animal studies (46).

Furthermore, emergency cesarean co-mediated with prenatal depression, the association between maternal SES and infant sleep. Little is known about the maternal physiological impact of emergency CS

on the infant (48). Unexpected cesarean delivery can be a traumatic birth experience for the mother (49), interfering with parenting behaviours that promote self-soothing in the infant and longer sleep duration (50). Interestingly, both maternal depression during pregnancy and emergency cesarean birth have the capacity to disrupt development of the infant HPA axis and alter regulation of circadian rhythm (27,32). Smith et al. found that infants born by emergency but not scheduled cesarean, had higher levels of free cortisol in umbilical cord blood samples than vaginally born infants (27). Elevated cortisol levels can increase CRH, which are associated with reduced sleep quality (23). However, due to the development of the circadian clock genes and HPA axis during late gestation and early infancy, elevated cortisol at birth may have a lasting effect on the programming of these systems (32). Furthermore, infants born by emergency but not scheduled cesarean, have been found to have elevated C-reactive protein in the cord blood following birth (51). The administration of pro-inflammatory cytokines in animal studies promotes non-REM sleep, which is more common after sleep deprivation (52). Lastly, infants born by emergency cesarean are also more likely to exhibit gut microbial dysbiosis than infants born vaginally or by scheduled CS (53), compositional changes that may ultimately alter circadian rhythm and sleep patterns (54).

Our results also support the thesis that prenatal depression influences infant sleep through a fetal programming pathway (15). Infants born to mothers with prenatal depression slept on average 0.56 hours shorter than infants born to mothers without prenatal depression. The prenatal stress model, which is an approximate animal model of stress and depression in pregnancy, results in prolonged corticosterone production after acute stress and reduced expression of glucocorticoids in the hippocampus in adult offspring (32). As a result, infants of mothers with prenatal depression may have an exaggerated stress-response which negatively impacts their sleep duration after birth. Prenatal depression is strongly linked to low SES (55); stressful life events during pregnancy and concern over finances have both been associated with frequent nocturnal awakening in toddlers (7). In our study, women without a university degree were much more likely to experience prenatal depression with or without postnatal depression but not postnatal depression without prenatal depression.

Strengths and Limitations

Our study has several strengths, including the ability to investigate birth mode in greater detail than previously examined in a birth cohort with a representative and large sample size. Also, the universal healthcare context of the Canadian populace provides an opportunity to study SES independent of accessibility to prenatal care healthcare (56). Limitations of this study include the unavailability of measures on maternal prenatal sleep, parenting behaviour and depressive symptoms in the postpartum period prior to 6 months.

3.5 Conclusions

Socioeconomic factors in early life have a strong influence on virtually all aspects of early human development (57). In our general population cohort from the CHILD study, infant sleep duration at 3 months of age was predicted by maternal education level, prenatal depression and birth mode. The maternal educational association with infant sleep was sequentially mediated by prenatal depression and birth mode. Our study provides evidence for a prenatal-birth pathway by which parental SES can impact infant sleep. Mothers who experience prenatal depression or emergency cesarean birth may benefit from advice on parenting style and infant stimulus control to increase infant sleep duration (50), so that these problems do not persist in childhood. While we are at an early stage to discern the underlying biologic mechanisms, this study identifies prenatal depression and birth mode as targets for policy makers to improve infant sleep duration. Future work is required to determine if the impact of these exposures is mediated by oxytocin administration, cortisol level, maternal sleep, postpartum depression or parental behaviours.

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3.7 Appendix

Covariate Measures

Birth mode. Birth mode was collected from maternal hospital records. Birth mode was categorized a vaginal birth without intrapartum antibiotic prophylaxis (IAP), vaginal birth with IAP, scheduled caesarean section (CS) and emergency CS.

Colic. Infant colic status was determined from parent-reported infant medication questionnaires. Infants were classified as having colic before 3 months of age if they were taking a medication indicated for the treatment of colic or if colic was listed as the reason for taking a medication.

Breastfeeding status. Infant feeding status was collected from parental report at 3 months of age. Breastfeeding status was categorized as exclusive (breast milk only following hospital discharge from 0-3 months), partial (both breastmilk and formula consumed from 0-3 months), and formula (formula only from 0-3 months).

Household income. Household income was collected from maternal report at 18-36 weeks gestational age and was categorized as: 1) less than or equal to 39,999; 2) 40,000 to 79,999; 3) 80,000 to 99,999; 4) 100,000 or greater; 5) prefer not to answer.

Maternal race/ethnicity. Maternal race/ethnicity was collected from maternal report at 18-36 weeks gestational age. For the purposes of this study, maternal race was categorized as Caucasian, Asian (East Asian, South Asian and South East Asian) or other (Black, Hispanic, Middle Eastern and First Nations).

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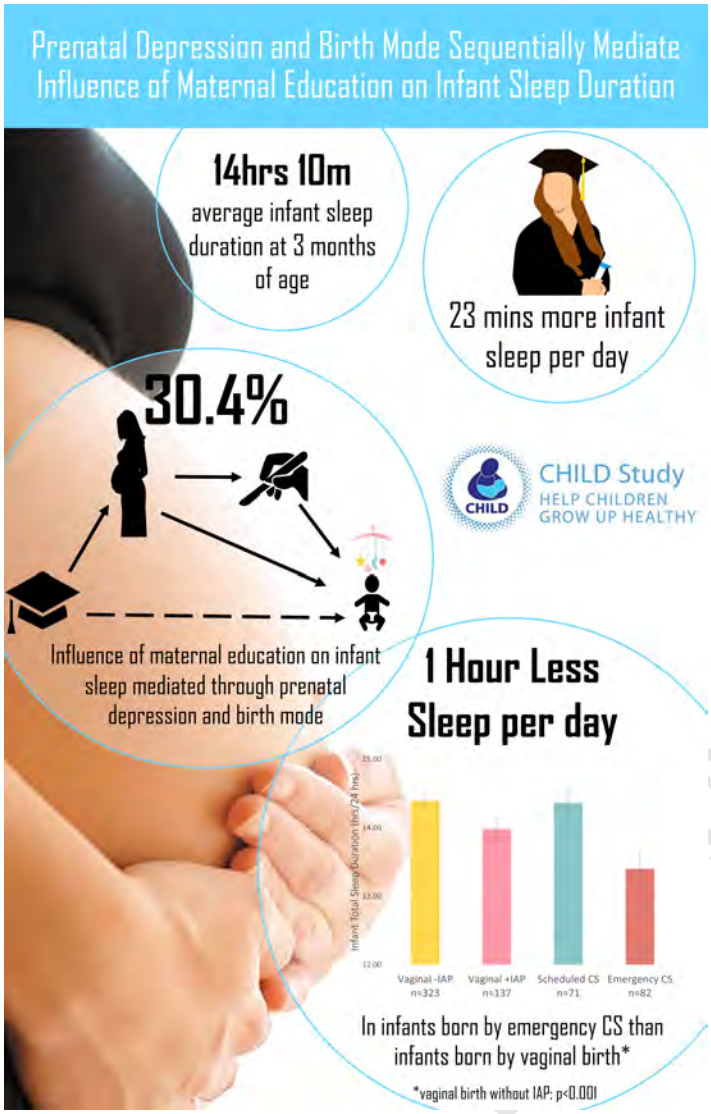

Highlights:

- Mean sleep duration at 3 months of age was 14.1 hours in 619 infants in Canada
- Maternal education & prenatal depression were associated with infant sleep duration
- Emergency cesarean section babies slept 1-hour less than those born vaginally
- Prenatal depression & birth mode mediate maternal education impact on infant sleep