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Prediction of Risk of Preterm Birth by Neighborhood Socioeconomic Status: Neighborhood Circumstances Matters

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Abstract

Objective

This study developed and internally validated a predictive model for preterm birth (PTB) to examine the ability of neighborhood socioeconomic status (SES) to predict PTB.

Methods

Individual level data from two cohort studies in Alberta, Canada (n=5,297) were linked to neighborhood SES data. Logistic regression models (including individual level predictors e.g., parity, ethnicity, income), followed by multilevel logistic regression models that also included neighborhood SES, were developed in the bootstrapped samples. The predictive performance of the models was evaluated in the study sample by measures of model calibration and discrimination accuracy.

Results

The rates of PTB in the least and most deprived neighborhoods were 7.54% and 10.64%, respectively. Neighborhood variation in PTB was 0.20, with an intra-class correlation of 5.72%. Neighborhood SES, combined with individual level predictors, predicted PTB with an area under the receiver operating characteristic curve (AUC) of 0.75. The sensitivity was 91.80% at a low risk threshold, with a high false positive rate (71.50%), and the sensitivity was 5.70% at a highest risk threshold, with a low false positive rate (0.90%). An agreement between the predicted and observed PTB demonstrated modest model calibration. Individual level predictors alone predicted PTB with an AUC of 0.60.

Conclusion

Neighborhood SES combined with individual level predictors had poor detection rates for PTB. However, this combination improved overall prediction of PTB compared to individual level predictors alone. This indicates that knowledge of women' neighborhood context may enhance the early identification of women at risk of PTB.

Article Summary: Strengths and limitations of this study

- Use of multilevel model with random intercept at neighborhood level allowed to examine the ability of neighborhood socioeconomic status to predict preterm birth taking account the neighborhood level variation and intra-class correlation in preterm birth (relevance of neighborhood).
- Prediction model used simplest multilevel structure with individual and neighborhood level predictors of PTB, data which can be easily collected in both community and clinical setting.
- Internal validation of prediction model using bootstrapping method provided a confidence about the reproducibility of our prediction model although execution of external validation of the model is required to understand its usefulness.
- Relevant individual and neighborhood level predictors such as previous preterm birth, neighborhood access to healthcare, which may optimize the prediction, are not included in the prediction model.
- Our sample over-represents women from urban areas of Alberta, with high socioeconomic, thus limiting the generalizability of the findings to urban settings.

Introduction

Globally, 11.1% of births are preterm(1). Preterm birth (PTB), delivery prior to 37 weeks of gestation, is a major contributing factor to neonatal deaths(2, 3), and amongst survivors, PTB is also a significant risk factor for short- and long-term morbidity(3-5). The incidence of PTB and its associated mortality and morbidity could potentially be reduced if women at risk of delivering preterm were identified early in gestation and appropriately managed(6, 7). The etiology of PTB is multifactorial(8-10), and one risk factor for PTB may be neighborhood socioeconomic status (SES)(10-12): the rate of PTB in low SES neighborhoods is higher than the rate in high SES neighborhoods(13-15). Neighborhood SES is an area-level measure of SES, which aggregates individual SES (such as income, education, and employment status) at a certain geographical level(11). Neighborhood SES determines women's exposure to health-enhancing and health-damaging factors (such as access to resources, stress, environmental exposures, and lifestyle choices), which can influence the risk of PTB(11, 12).

While many studies have examined the association between neighborhood SES and PTB(13-15), our understanding about the ability of neighborhood SES to predict the risk of PTB is limited. It is possible that even strongly associated risk factors can have a low capacity to discriminate PTB in the population(16-18). Similarly, a statistically significant association between neighborhood SES and PTB may exist, with small/no variation of PTB at neighborhood level(19-21). Thus, the association may provide unreliable information about the likelihood of delivering preterm infants among women living in certain neighborhoods and may mislead decision-makers in implementing public health interventions targeted at specific areas(19, 20). As previous studies have not developed and validated a prediction model for PTB to evaluate the

predictive ability of neighborhood SES, information about the ability of neighborhood SES to predict PTB is lacking.

A better understanding of the ability of neighborhood SES to predict PTB has its own importance as it may improve our capacity to accurately discriminate between women at high and low risk for delivering preterm infants(17, 22). The accurate discrimination capacity may offer a more valid prediction about the future probability of delivering a preterm infant in an individual woman coming from certain neighborhoods(17, 22). The use of valid prediction models may help us effectively identify women at high risk of delivering preterm infants, and in planning suitable public health interventions targeting women from low SES neighborhoods, such as appropriate triage of women into low and high risk prenatal care. This is timely and relevant given that individual level risk factors (including biomarkers) have shown a low discriminatory accuracy in predicting PTB(16, 18), resulting in ineffective early identification of women at risk for delivering preterm infants. Therefore, this study developed and internally validated a predictive model to examine the ability of neighborhood SES to predict PTB.

Methods

Data sources

This study combined existing datasets from two community-based prospective pregnancy cohort studies in Alberta, Canada: All Our Families (AOF: n=3,341) and Alberta Pregnancy Outcome and Nutrition (APrON: n=2,187)) (Figure 1). The description and comparability of these two cohort studies is available elsewhere(23, 24) and justifies combining these data sources(25). Briefly, each cohort study had similar recruitment periods (2008-2012), inclusion criteria, sampling design, and data-collection methods(23, 24). Both studies collected data on

socio-demographics, lifestyle, social support, depression, and PTB (23)– the core individual-level variables necessary for this research.

We obtained two de-identified cohort datasets linked with neighborhood SES data from SAGE (Secondary Analysis to Generate Evidence), the secure data repository developed by PolicyWise for Children & Families, which houses these datasets. Neighborhood SES data were measured by the median personal income and the Pampalon material deprivation index (both measures were derived from 2011 Statistics Canada census)(26, 27), which were both aggregated at the dissemination area (DA) level. DA is the smallest geographic unit available in the Canadian census, consisting of 400-700 persons(28). The Pampalon material deprivation index is a composite measure of neighborhood SES that combines the proportion of persons without high school diplomas (education), the average personal income (income), and the rate of unemployment (employment) within the DA(26). Ethics approval for this study was obtained from the Conjoint Health Research Ethics Board at the University of Calgary.

Patient and public involvement

This study used de-identified secondary data. Patient and public were not involved in this study.

Data harmonization and combination

Individual level variables in the two studies were harmonized in each dataset considering multiple factors. These factors included whether the variables were completely or partially identical regarding question asked/responded, the response coded (value level, value definition, data type), the frequency of measurement, the pregnancy time-point of measurement, and missing values. If the variables were an exact match for each of these factors, they were pooled as is. If the variables were partially matched, data harmonization was performed considering these multiple factors. The variables deemed completely un-matched were not combined; thus,

they were not included in this study. However, no important variables had to exclude from the study due to this reason. Prenatal care visits and previous preterm birth variables were excluded from the study as these variables were not available in APrON cohort dataset. Once the selected variables were harmonized in each dataset, the two datasets were appended into a single new dataset. Women who participated in both studies (n=231) were counted only once.

Data Analysis

Univariate analysis was performed to observe the distribution of each variable. Bivariate analysis using chi-square tests was performed to identify individual level variables associated with PTB ($p<0.25$). Multivariable conventional logistic regression models, followed by multilevel logistic regression models, as outlined by Merlo et al 2016(21), were developed using bootstrapped samples with 1000 replications (training dataset) (see Supplementary File for details on the model building and validation strategies). Missing data were deleted using variable wise or pair wise deletion approach for bivariate analysis, followed by complete deletion approach for regression models. All analyses were performed using STATA/IC software – version 14.1.

Model validation and model performance assessment

The bootstrap procedure was employed for internal validation of the model(17, 29). Model performance was evaluated in the original sample (validation dataset) by measures of model calibration (the correspondence between predicted and observed outcome rates), risk stratification capacity (proportion of women categorized as low vs high risk, or the distribution of the women in each predicted risk category), and classification performance or discrimination accuracy (true positive and false positive rates, positive and negative predictive values, positive and negative likelihood ratios, and area under the receiver operating characteristic curve (AUC)).

To obtain these measures, the predicted probability of PTB for each woman was estimated and was categorized into four risk groups (<5%, ≥5 - 10%, ≥10 - 15%, and ≥15%). The difference in AUC estimates between the bootstrapped sample and the original sample was assessed as described by optimism(17, 29).

Results

The total sample size from the combined cohort was 5,297. The proportion of missing data ranged from 1.52% for depression to 7.51% for gestational age at delivery. The majority of women were under the age of 35 years, were married or living with a common-law partner, were Caucasian, and approximately half of the women were primiparous. Almost three quarters of women had completed more than high school education and had a household income ≥$70,000, while approximately one quarter of women were living in the least deprived neighborhood (Table 1). Overall, 7.25% (95% CI: 6.57, 8.07) of women delivered preterm infants, with 7.54% among women living in the least deprived neighborhoods and 10.64% among women living in the most deprived neighborhoods. Compared to women who delivered at term, a higher proportion of women who delivered preterm infants were primiparous, non-white, obese, and were living in the most deprived neighborhood (Table 1).

As shown in Table 2, a conventional logistic regression model that included individual level predictors (parity, ethnicity, body mass index, smoking, depression, and household income) showed an AUC of 0.60 (95% CI: 0.56, 0.63). The multilevel model that included individual level predictors, and a random effect at the neighborhood level showed large variation in PTB at neighborhood level (neighborhood variance: 0.20, intracluster correlation (ICC): 5.72, median odds ratio (MOR): 1.53), with an AUC of 0.75 (95% CI: 0.73, 0.78). After inclusion of

neighborhood SES (deprivation index) in the multilevel model, although deprivation index was not significantly associated with PTB (OR: 1.19, 95% CI: 0.78, 1.79), neighborhood variance decreased to 0.15, the ICC to 4.45, and the MOR to 1.46, with an AUC of 0.75 (95% CI: 0.73, 0.78). Furthermore, the multilevel model that contained median personal income, as a measure of neighborhood SES, showed similar variance as the model that contained deprivation index.

Predicted probabilities of PTB in the multilevel model that contained individual level predictors and deprivation index ranged from 2.77% - 27.00%. Calibration of the model predicting PTB was adequate, as shown by an agreement between the model-predicted probability for PTB and the proportion of observed PTB, particularly for low risk categories. Specifically, the observed PTB rate within the predicted risk category of ≥5% -10% was 7.30%, which falls within the risk category range; the same was true for the risk category of < 5%. The risk-stratification capacity of the model was adequate– it assigned women to the different risk of PTB, where almost 90% of women were assigned to low risk category (Table 3).

The classification accuracy of the model ranged from 33.09% to 92.30% in the different predicted risk categories: the proportion of women with preterm delivery who were identified as high risk for PTB (sensitivity) ranged from 5.70% to 91.80% and the proportion of women without preterm delivery who are identified as low risk (specificity) ranged from 28.50 to 99.10. The positive and negative likelihood ratios of the model for the highest predicted risk category for PTB were 6.22 and 0.95, respectively. The difference in the AUCs between the bootstrap sample (AUC: 0.75, 95% CI: 0.73, 0.78) and original sample (AUC: 0.75, 95% CI: 0.73, 0.78) was negligible (i.e., optimism: 0.0001). While the multilevel model that contained median personal income showed similar model performance as model that contained deprivation index (except for sensitivity and positive predictive values for the highest risk category), the logistic

regression model that included individual level variables showed lower model performance (Table 3 and Figure 2).

Discussion

Main findings

This study developed and internally validated a prediction model to examine the ability of neighborhood SES to predict the risk of PTB. This study found that approximately 6% of the total variance in PTB was attributable to neighborhood circumstances (ICC: 5.72%), and neighborhood SES explained one quarter of the neighborhood level variation in PTB. Neighborhood SES combined with individual level predictors (parity, ethnicity, body mass index, smoking, depression, and household income) predicted the risk of delivering a preterm infant with an AUC of 0.75. The sensitivity was 91.80% at a lowest risk threshold, with a cost of high false positive (71.50%), and the sensitivity was 5.70% at a highest risk threshold, with a low false positive (0.90%). Neighborhood SES combined with individual level predictors had a good risk-stratification and a modest calibration ability for identifying woman at risk for delivering a preterm infant.

Interpretation

Model discrimination (measured by AUC) was improved substantially when we combined individual level predictors with neighborhood level information. While it has been previously demonstrated that individual level predictors including maternal characteristics, clinical risk factors, and biomarkers have low discriminatory accuracy in predicting the risk of PTB (AUC ranged from 0. 60 – 0.67)(16, 18), our study enhances our understanding that adding the neighborhood level information we can improve the discriminatory accuracy of PTB.

Furthermore, it is important to note that a multilevel model that included a random effect for neighborhood and individual level information gives the maximum AUC that can be obtained by combining available individual level information and the neighborhood identity(21). Neighborhood identity captures the totality of potentially observable and unobservable neighborhood factors(21, 30, 31). Furthermore, in our study, reduction of some of the neighborhood variance after the inclusion of neighborhood SES would have reduced the predictive role of the neighborhood random effect(21). However, the multilevel model simultaneously improves the prediction of PTB through the addition of the regression coefficient for the neighborhood SES variable(21). This balance explains the observed unchanged discriminatory accuracy between the multilevel model with and without neighborhood SES.

As suggested by the classification performance of the model including neighborhood SES and individual level predictors, a large proportion of women who were identified as high risk actually did not deliver preterm. Positive predictive value was improved, but still too low, as the predicted risk threshold increased, which was related to the high proportion of PTB in the threshold. The model had low sensitivity (5.70%) at a highest risk threshold, with a low false positive (0.90%). This would mean that a substantial number of women who are at high risk for delivering PTB would be identified as low risk(32). The LR positive test was improved (up to 6.22) for the highest risk threshold; however, this group only includes <6% of total women who actually delivered preterm. This dichotomy between improve LR and poor detection rates has also been noted previously(33).

While the prediction of PTB risk using neighborhood SES is suboptimal, other commonly recognized risk factors for PTB also failed to sufficiently predict PTB. For example, it has been noted that a history of prior PTB has an LR+ of 3.24, short cervical length has an

LR+ of 2.0, and vaginal fetal fibronectin has an LR+ of 3 in predicting PTB(34). Similarly, for a fixed false positive rate of 10%, maternal characteristics and obstetrical history have a sensitivity of 27.5% for PTB with an AUC of 0.61(18). The less optimal predictive performance for identifying the risk of PTB may be related to the complex underlying etiology of PTB, and a combination of multiple aspects of predictors (such as biomarkers, clinical risk factors, socio-demographics, and health behaviors) may be required to adequately predict such an outcome(33, 35). Our study further shows that inclusion of neighborhood SES along with multiple individual level predictors would further improve the prediction of PTB. Altogether, it implies that identification of women at risk for delivering preterm infants should rely on multiple factors, and even women identified as low risk for PTB may need further monitoring/assessment and high quality prenatal care should be universal.

Our findings on neighborhood variation and clustering of PTB suggest that pregnant women from the same neighborhoods are more similar to each other than to women from different neighborhoods with respect to the risk of PTB, and that some portion of this variation is related to neighborhood SES. Overall, this finding reflects the presence of health disparities in PTB between neighborhoods in Alberta, and justifies the relevance of neighborhood including neighborhood SES and neighborhood targeted interventions. Furthermore, as neighborhood variation in PTB (as measured by ICC) corresponds to the predictive accuracy (as measured by AUC)(21)– when the ICC is high the AUC is also high, the information about the variation in PTB at neighborhood level offers some understanding about the ability of neighborhood level factors to predict PTB(21). However, previous research has emphasized identifying neighborhood level risk factors associated with PTB or causal effects, which is difficult to establish due to the potential challenges. These challenges include reverse causation between

neighborhood circumstances and health, unmeasured confounding, residential mobility, possibility of same individual variable being confounder and mediator, and changes in neighborhood context over the life process(11, 12, 36). Thus, a study aiming to establish a causal association demands longitudinal study design with repeated measurement of neighborhood characteristics and outcomes over time in life-course processes(11, 12, 36).

Strengths and limitations of study

To our knowledge, our study is the first to develop and validate a predication model for PTB to investigate the ability of neighbourhood SES to predict the risk of PTB, in contrast to the previous studies that examined mostly the association between neighbourhood SES and PTB. Our finding allows us to understand the relevance of area of residence (in general), and more specifically area-level SES, in predicting the risk of maternal health outcomes. Our study used the simplest multilevel structure with individual and neighborhood level predictors of PTB, data which can be easily collected in both community and clinical settings. However, our findings should be interpreted with a consideration of the limitations of our study. We were not able to separate-out spontaneous and iatrogenic PTB in the model due to data limitations– the predictive performance might be improved with a focus on spontaneous PTB. Our sample over-represents women from urban areas of Alberta, with high SES(24, 37, 38), thus limiting the generalizability of the findings to urban settings. The observed predictive ability of neighborhood SES would have been underestimated as the relevance of neighborhood SES status might be higher for those with low SES. Although the observed small difference in discriminatory accuracy between the bootstrapped sample and the original sample provided us a confidence about the reproducibility of our prediction model, as the model was internally validated, it possibly showed artificially high performance; thus, model validation should be confirmed against external data. While the

development and validation of our predictive model is an important first-step towards the early identification of women at high risk for PTB based on neighborhood risk assessment, an addition of other clinically relevant individual and neighborhood level predictors in the model and an execution of external validation of the model is required to optimize the prediction and to improve its usefulness.

Conclusion

Although the predictive performance of the model that contained neighborhood SES and individual level predictors was too low to consider its application in clinical or public health practices, the performance was better compared to the performance of individual level predictors alone. This improved performance indicates that knowledge about neighborhood context of pregnant woman matters: by understanding the context in which pregnant women live (mainly during routine prenatal care), healthcare providers and public health practitioners may improve their ability to identify woman most at risk of delivering preterm. This would allow them to make more informed decisions on their care. As such, community level interventions combined with individual-centered approach that attempts to change neighborhood circumstances (health promoting or damaging features of neighborhood including SES) and population characteristics (with focus to modifiable predictors) may be effective in reducing the incidence of PTB.

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Authors contributions

Kamala Adhikari involved in the conception and design of the study. Kamala is also responsible for conducting the analysis, interpreting the data and drafting the manuscript. Amy Metcalfe provided overall supervision to Kamala in conducting this study and contributed to conception and study design, interpretation of data, provided intellectual content and revisions to manuscript. Scott Patten, Tyler Williamson, Alka B Patel, Shahirose Premji, Suzanne Tough, Nicole Letourneau, and Gerald Giesbrecht were involved in the conception and design of the study and provided interpretation and intellectual content to subsequent drafts of the manuscript. All authors read and approved the final draft.

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Ethical approval

Ethics approval for this study was obtained from the Conjoint Health Research Ethics Board at the University of Calgary.

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Data sharing

Additional data such as statistical codes, supplementary tables, and technical appendix are available upon request (by emailing Kamala Adhikari: kamala.adhikaridahal@ucalgary.ca)

Competing interests

The authors declare that they have no competing interests.

Table 1 Distribution of maternal characteristics across preterm birth status[a]

Variables	Overall		Preterm Birth (Gestational Age <37 weeks) n= 371		Term Birth (Gestational Age ≥37 weeks) n=4743		χ2 p-value
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	
Maternal age							0.332
<35yrs	4117 (79.23)	78.10, 80.31	269 (77.08)	72.36, 81.19	3541 (79.27)	78.05, 80.43	
≥35yrs	1079 (20.77)	19.68, 21.89	80 (22.92)	18.80, 27.63	926 (20.73)	18.80, 27.63	
Marital status							0.657
Single/divorced/separated	262 (5.06)	4.49, 5.69	17 (4.96)	3.10, 7.83	198 (4.44)	3.87, 5.09	
Married/common-law	4916 (94.94)	94.30, 95.50	326 (95.04)	92.17, 96.89	4260 (95.56)	94.91, 96.13	
Ethnicity							0.004
White/Caucasian	4085 (78.98)	77.85, 80.07	253 (73.76)	68.83, 78.15	3574 (80.28)	79.08, 81.42	
Others	1087 (21.02)	19.93, 22.15	90 (26.24)	21.85, 31.16	878 (19.72)	18.58, 20.92	
Duration of stay in Canada							0.061
<5 years	473 (9.26)	8.49, 10.08	39 (11.64)	8.61, 15.54	380 (8.63)	7.84, 9.25	
Born/5 years+	4636 (90.74)	89.91, 91.51	296 (88.36)	84.45, 91.38	4022 (91.37)	90.50, 92.16	
Body mass index							0.001
Underweight (<18.5kg/m2)	214 (4.33)	3.80, 4.94	12 (3.69)	2.10, 6.39	180 (4.23)	3.66, 4.87	
Normal weight (18.5 - 24.99)	3084 (62.45)	61.09, 63.79	183 (56.31)	50.85, 61.62	2694 (63.28)	61.82, 64.72	
Overweight (25 - 29.99 kg/m2)	1066 (21.59)	20.46, 22.76	72 (22.15)	17.69, 27.00	924 (21.71)	20.49, 22.97	
Obesity (≥30 kg/m2)	574 (11.62)	10.76, 12.54	58 (17.85)	14.05, 22.40	459 (10.78)	9.88, 11.75	
Parity							0.004
Primiparous	2649 (51.27)	49.90, 52.63	201 (58.94)	54.64, 64.80	2266 (50.92)	49.45, 52.39	
Multiparous	2518 (48.73)	47.37, 50.09	140 (41.06)	35.19, 45.36	2184 (49.08)	47.61, 50.54	
Intended pregnancy							0.805
Yes	4175 (80.51)	79.40, 81.56	62 (18.02)	14.30, 22.45	829 (18.58)	17.46, 19.75	
No	1011 (19.49)	18.44, 20.60	282 (81.98)	77.54, 85.69	3633 (81.42)	80.25, 8253	
Smoked before pregnancy							0.062
Yes	1095 (21.13)	20.04, 22.26	259 (75.29)	70.44, 79.57	3547 (79.53)	78.31, 80.68	
No	4088 (78.87)	77.74, 79.96	85 (24.71)	20.43, 29.55	913 (20.47)	19.31, 21.68	
Alcohol consumption before pregnancy							0.531
Yes	4363 (84.13)	83.11, 85.10	49 (14.24)	10.93, 18.36	692 (15.51)	14.47, 16.60	
No	823 (15.87)	14.90, 16.89	295 (85.76)	81.64, 89.07	3770 (84.49)	83.39, 85.52	

Drug abuse before pregnancy							0.519
Yes	750 (14.48)	13.54, 15.46	290 (84.30)	80.06, 87.78	3814 (85.57)	84.51, 86.57	
No	4430 (85.52)	84.53, 86.45	54 (15.70)	12.22, 19.94	643 (14.43)	13.42, 15.49	
Maternal education							0.917
Less than high school	174 (3.37)	2.91, 3.90	11 (3.22)	1.79, 5.72	126 (2.84)	2.39, 3.37	
Completed high school	893 (17.31)	16.29, 18.36	56 (16.37)	12.81, 20.69	722 (16.25)	15.19, 17.36	
More than high school	4093 (79.32)	78.19, 80.40	275 (80.41)	75.85, 84.28	3595 (80.91)	79.73, 82.04	
Household income							0.436
≥$100,000	2659 (52.52)	51.14, 53.89	176 (52.54)	47.17, 57.84	2358 (53.98)	52.50, 55.45	
$70,000 - <$100,000	1204 (23.78)	22.63, 24.97	74 (22.09)	17.96, 26.86	1059 (24.24)	22.99, 25.53	
$40,000 - <$70,000	723 (14.28)	13.34, 15.27	51 (15.22)	11.75, 19.49	591 (13.53)	12.55, 14.57	
<$40,000	477 (9.42)	8.64, 10.25	34 (10.15)	7.33, 13.88	360 (8.24)	7.46, 9.09	
Social support anytime during pregnancy							0.216
Adequate	4053 (77.93)	76.78, 79.03	263 (75.79)	70.99, 80.01	3514 (78.63)	77.40, 79.81	
Inadequate	1148 (22.07)	20.96, 23.22	84 (24.21)	19.98, 29.00	955 (21.37)	20.19, 22.59	
Depression anytime during pregnancy							
Yes	1311 (25.14)	23.98, 26.33	96 (27.67)	23.20, 32.61	1086 (24.21)	22.97, 25.48	0.149
No	3904 (74.86)	73.66, 76.02	251 (72.33)	67.38, 76.94	3400 (75.79)	74.51, 77.02	
Neighborhood deprivation index							0.002
Quintile 1 (least deprived)	1323 (27.08)	25.85, 28.35	93 (26.12)	21.81, 30.94	1176 (27.68)	26.36, 29.05	
Quintile 2	1259 (25.77)	24.56, 27.01	76 (21.35)	17.39, 25.92	1119 (26.34)	25.04, 27.69	
Quintile 3	972 (19.90)	18.80, 21.04	71 (19.94)	16.10, 24.43	839 (19.75)	18.58, 20.97	
Quintile 4	736 (15.07)	14.09, 16.09	52 (14.61)	11.30, 18.67	639 (15.04)	13.99, 16.15	
Quintile 5 (most deprived)	595 (12.18)	11.29, 13.14	64 (17.98)	14.32, 22.32	475 (11.18)	10.27, 12.16	
Neighborhood median personal income							0.054
Quintile 1 (least deprived)	1549 (31.05)	29.78, 32.35	106 (29.78)	25.24, 34.74	1369 (31.49)	30.12, 32.89	
Quintile 2	1403 (28.13)	26.89, 29.39	96 (26.97)	22.60, 31.82	1229 (28.27)	26.95, 29.63	
Quintile 3	881 (17.66)	16.62, 18.74	57 (16.01)	12.55, 20.20	776 (17.85)	16.74, 19.01	
Quintile 4	666 (13.35)	12.43, 14.32	47 (13.20)	10.06, 17.14	574 (13.20)	12.22, 14.24	
Quintile 5 (most deprived)	489 (9.80)	9.00, 10.66	50 (14.04)	10.80, 18.06	399 (9.18)	8.35, 10.07	

[a]sample size between variables differs as missing values were deleted using variable wise or pair wise deletion approach

Table 2 Predictive models for preterm birth[a]

	Model 1[b] OR (95% CI)	Model 2[c] OR (95% CI)	Model 3[d] OR (95% CI)
Ethnicity			
White/Caucasian (ref)	-	-	-
Non-white	1.50 (1.11, 2.04)	1.48 (1.11, 1.96)	1.49 (1.13, 1.99)
Parity			
Multiparous (ref)	-	-	-
Primiparous	1.49 (1.21, 1.84)	1.52 (1.19, 1.93)	1.53 (1.20, 1.95)
Body mass index			
Normal weight (ref)	-	-	-
Underweight	0.99 (0.46, 2.10)	1.01 (0.47, 1.14)	1.00 (0.35, 2.83)
Overweight	1.18 (0.88, 1.57)	1.14 (0.76, 1.68)	1.13 (0.72, 1.78)
Obesity	1.94 (1.41, 2.65)	1.95 (1.25, 3.04)	1.95 (1.16, 3.30)
Smoked before pregnancy			
No (ref)	-	-	-
Yes	1.20 (0.90, 1.60)	1.19 (0.78, 1.79)	1.19 (0.77, 1.82)
Depression during pregnancy			
No (ref)	-	-	-
Yes	1.10 (0.84, 1.46)	1.12 (0.76, 1.66)	1.13 (0.74, 1.71)
Household income			
≥$100,000 (ref)	-	-	-
$70,000 - <$100,000	0.82 (0.61, 1.12)	0.82 (0.51, 1.33)	0.84 (0.55, 1.28)
$40,000 - <$70,000	0.75 (0.70, 1.31)	0.96 (0.57, 1.62)	0.99 (0.58, 1.69)
<$40,000	0.92 (0.71, 1.66)	1.05 (0.60, 1.81)	1.10 (0.63, 1.88)
Neighbourhood SES	-		
Q1 least deprived (ref)		-	-
Q2		0.86 (0.53, 1.39)	0.97 (0.64, 1.49)
Q3		0.96 (0.58, 1.59)	0.87 (0.52, 1.47)
Q4		0.99 (0.60, 1.58)	0.90 (0.51, 1.59)
Q5 most deprived		1.20 (0.63, 1.85)	1.01 (0.55, 1.86)
Neighbourhood level variance	-	0.15 (0.03, 0.89)	0.14 (0.03, 0.88)
ICC (%)[e]	-	4.45 (0.07, 23.25)	4.27 (0.06, 23.59)
MOR	-	1.46	1.44
Proportion of neighbourhood level variance explained by neighborhood SES (%)	-	25.00	25.16
AUC	0.60 (0.56, 0.63)	0.75 (0.73, 0.78)	0.75 (0.72, 0.77)

[a]prediction models were developed in bootstrapped samples with 1000 replications; [b] conventional logistic regression model that includes individual level predictors; [c] multilevel logistic regression model that includes random intercept at neighbourhood level, neighbourhood deprivation index, and all the individual level predictors contained in the logistic regression model; [d] multilevel logistic regression model that includes random intercept at neighbourhood level, neighbourhood median personal income, and all the individual level predictors contained in the logistic regression model; [e]ICC calculation follows standard logistic distribution with variance $\pi 2/3$ for the level 1, where π denotes the mathematical constant 3.1416; MOR: median odds ratio; ICC: intra-cluster correlation; AUC: area under the receiver operating characteristic curve

Table 3: Performance of predictive models for preterm birth (n=4,357)[a]

Predictive models	Model calibration		Risk stratification capacity n (%)	Model discrimination[b]						
	Predicted probability of PTB	Observed PTB n (%) 95% CI		Sensitivity (%)	Specificity (%)	Classification accuracy (%)	PPV (%)	NPV (%)	LR+ (%)	LR- (%)
Conventional logistic regression model with individual level predictors, i.e., parity, ethnicity, body mass index, smoking, depression, and household income	<5%	42 (4.81) 3.43, 6.03	873 (20.04)	-	-	-	-		-	-
	≥5 – 10%	197 (6.96) 6.02, 7.81	2832 (65.00)	85.76	22.43	26.54	7.66	95.44	1.10	0.63
	≥10 – 15%	77 (12.56) 9.99, 15.96	613 (14.07)	20.12	89.42	84.58	12.43	93.70	1.90	0.89
	≥15	4 (10.26) 2.82, 24.37	39 (0.90)	1.55	99.14	92.31	8.82	93.03	1.80	0.99
Multilevel logistic regression model with neighbourhood deprivation index and individual level predictors	<5%	26 (2.22) 1.50, 3.22	1177 (27.01)	-	-	-	-	-	-	-
	≥5 – 10%	197 (7.30) 6.40, 8.37	2690 (61.74)	91.80	28.50	33.09	9.12	97.80	1.28	0.29
	≥10 – 15%	75 (17.24) 13.97, 21.09	435 (9.98)	29.40	90.20	85.83	19.00	94.20	3.00	0.78
	≥15	18 (32.73) 21.60, 46.20	55 (1.26)	5.70	99.10	92.30	32.80	93.10	6.22	0.95
Multilevel logistic regression model with neighbourhood median personal income and individual level predictors	<5%	31 (2.64) 1.86, 3.73	1174 (26.97)	-	-	-	-	-	-	-
	≥5 – 10%	192 (7.16) 6.24, 8.19	2683 (61.58)	90.30	28.30	33.13	8.95	97.40	1.26	0.34
	≥10 – 15%	81 (18.08) 14.78, 21.92	448 (10.28)	29.40	89.90	85.85	18.60	94.20	2.92	0.78
	≥15	12 (23.08) 13.52, 36.53	52 (1.19)	3.80	99.00	92.20	23.10	92.10	3.84	0.97

[a] model performance was assessed in the original sample (study sample); [b]model discriminatory was calculated using cumulative row values as different cut-offs to define high risk, for example, if all women with a model predicted probability of a preterm birth of 5% or higher are considered to have a positive test, model with deprivation index and individual level predictors would have a sensitivity of 91.80% and specificity of 28.50%.
PPV: positive predictive value; NPV: negative predictive value; LR+: positive likelihood ratio; LR-: negative likelihood ratio;

Figure Legends

Figure 1: Flowchart of study cohort

*Participants who were 0-13 weeks of gestation during the recruitment were eligible to fill out the questionnaire 2. ** Participants who were 0-26 weeks of gestation during recruitment were eligible to fill out the questionnaire 3.

Figure 2: Receiver operating characteristic curves of models predicting preterm birth

[a] receiver operating characteristic curves of models were assessed in the original sample (study sample); predictors in Figure 2a included individual level variables, i.e., parity, ethnicity, body mass index, smoking, depression, and household income; predictors in Figure 2b included neighbourhood deprivation index and individual level variables; predictors in Figure 2c included neighbourhood median personal income and individual level variables.

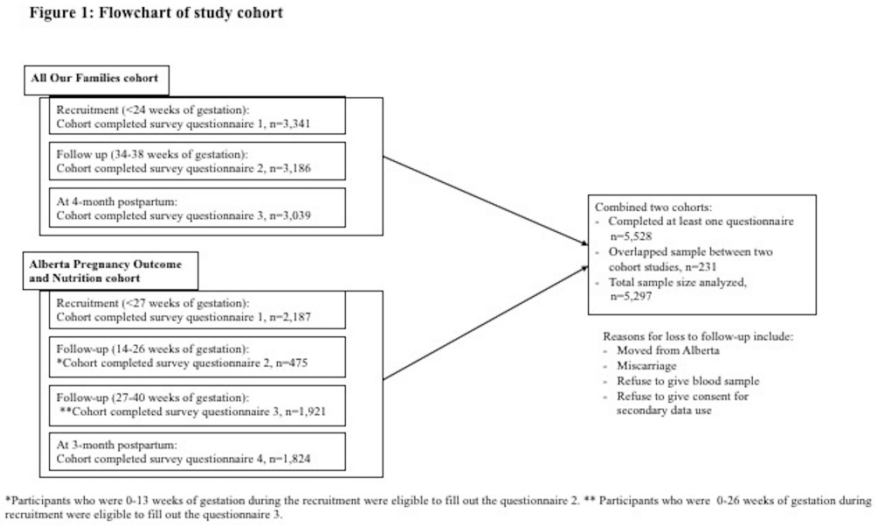

Figure 1- Flowchart of study cohort

338x190mm (300 x 300 DPI)

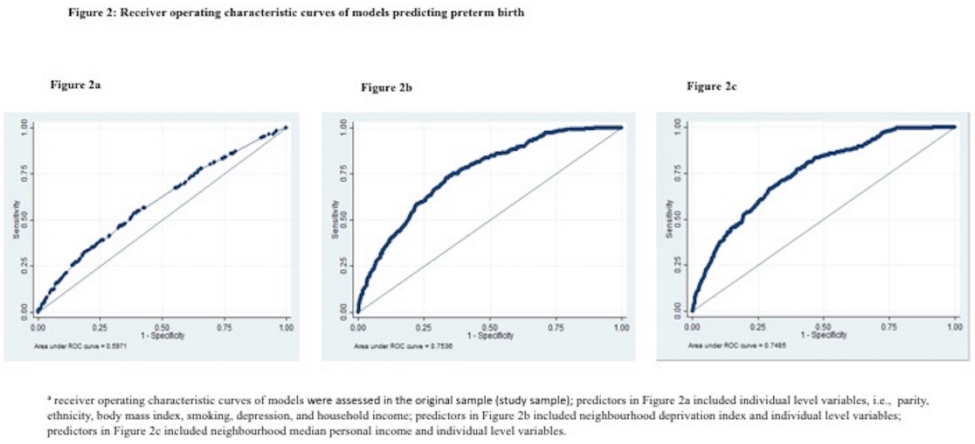

Figure 2- Receiver operating characteristics curves of models predicting preterm birth

338x190mm (300 x 300 DPI)

APPENDIX 1: Model building and validation strategy

A predictive model for PTB was developed using three consecutive model development steps as outlined by Merlo et al 2016 for multilevel data. These steps included development of a logistic regression model, followed by development of a multilevel logistic regression model with a random intercept, with and without including neighborhood SES. These three steps allow us to systematically develop a predictive model containing individual and neighborhood level variables.

Predictive models were developed in the bootstrapped sample (of equal size of the study sample) with 100 replications (training dataset). A conventional multivariable logistic regression model, which included individual level variables associated with PTB ($p<0.25$), was developed using a backward variable elimination approach. Neighborhood level information was not included in this model. The individual level variable with the largest p-value was first eliminated from the full model, then, the variable with the second largest p-value was eliminated and so on. Variables were retained in the model if the associated p-value was <0.1 or if the variable was clinically relevant.

A two-level multilevel logistic regression model with a random intercept for neighborhood (DA) was developed, with 5,297 women nested into 1,501 DAs; thus, on average each DA included three women. This model contained all of the individual level predictors identified in the conventional logistic regression model. Then, the neighborhood SES variable (Pampalon material deprivation index or median personal income) was added in the multilevel logistic regression model. Different SES measures have been used across studies to measure neighborhood SES; thus, two multilevel models (one for material deprivation index and another for median personal income) were developed to explore whether the predictive ability of neighborhood SES on the risk of PTB differs by the different measures of neighborhood SES used. Multilevel models provided estimates involving the association between neighborhood SES and PTB (odds ratio (OR)) and the neighborhood variation in PTB (including intra-class correlation coefficient (ICC) and median odds ratio (MOR)). Additionally, the proportional change in variance between multilevel models with neighborhood SES and without

neighborhood SES was calculated to assess the proportion of the neighborhood variance explained by neighborhood SES. The discriminative ability of three predictive models (conventional logistic regression model, multilevel logistic regression model with deprivation index, and multilevel regression model with median household income) was assessed in the bootstrapped sample and the study sample using the AUC of the receiver operating characteristic curve.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4 and 5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5 and 6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5, 6 and 7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5, 6 and 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	5 and 6
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	Not applicable
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	Not applicable
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, explain how loss to follow-up was addressed	Not applicable
		(*e*) Describe any sensitivity analyses	Not applicable
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	Figure 1
		(b) Give reasons for non-participation at each stage	Figure 1
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
		(c) Summarise follow-up time (eg, average and total amount)	Figure 1
Outcome data	15*	Report numbers of outcome events or summary measures over time	Table 1
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	We used regression for prediction purpose, Table 2
		(*b*) Report category boundaries when continuous variables were categorized	Not applicable
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not done
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Not done
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10, 11, 12, and 13
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
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	20

*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.

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Does Neighborhood Socioeconomic Status Predict the Risk of Preterm Birth? A Community-based Canadian Cohort Study

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Does Neighborhood Socioeconomic Status Predict the Risk of Preterm Birth? A Community-based Canadian Cohort Study

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Abstract

Objective

This study developed and internally validated a predictive model for preterm birth (PTB) to examine the ability of neighborhood socioeconomic status (SES) to predict PTB.

Design

Cohort study using individual-level data from two community-based prospective pregnancy cohort studies (All Our Families (AOF) and Alberta Pregnancy Outcomes and Nutrition (APrON)) and neighborhood SES data from the 2011 Canadian census.

Setting

Calgary, Alberta, Canada

Participants

Pregnant women who were <24 weeks of gestation and >15 years old were enrolled in the cohort studies between 2008-2012. Overall, 5,297 women participated in at least one of these cohorts: 3,341 women participated in the AOF study, 2,187 women participated in the APrON study, and 231 women participated in both studies. Women who participated in both studies were only counted once.

Primary and secondary outcome measures

Preterm birth (delivery prior to 37 weeks of gestation)

Results

The rates of PTB in the least and most deprived neighborhoods were 7.54% and 10.64%, respectively. Neighborhood variation in PTB was 0.20, with an intra-class correlation of 5.72%. Neighborhood SES, combined with individual level predictors, predicted PTB with an area under the receiver operating characteristic curve (AUC) of 0.75. The sensitivity was 91.80% at a low

risk threshold, with a high false positive rate (71.50%), and the sensitivity was 5.70% at a highest risk threshold, with a low false positive rate (0.90%). An agreement between the predicted and observed PTB demonstrated modest model calibration. Individual level predictors alone predicted PTB with an AUC of 0.60.

Conclusion

Although neighborhood SES combined with individual level predictors improved overall prediction of PTB compared to individual level predictors alone, the detection rate was insufficient for application in clinical or public health practice. A prediction model with better predictive ability is required to effectively find women at high risk of preterm delivery.

Article Summary: Strengths and limitations of this study

- Use of multilevel model with random intercept at neighborhood level allowed to examine the ability of neighborhood socioeconomic status to predict preterm birth taking account the neighborhood level variation and intra-class correlation in preterm birth (relevance of neighborhood).
- Prediction model used simplest multilevel structure with individual and neighborhood level predictors of PTB, data which can be easily collected in both community and clinical setting.
- Internal validation of prediction model using bootstrapping method provided a confidence about the reproducibility of our prediction model although execution of external validation of the model is required to fully understand its performance.
- Relevant individual and neighborhood level predictors such as previous preterm birth, neighborhood access to healthcare, which may help to optimize the prediction, are not included in the prediction model.
- Our sample over-represents women from urban areas of Alberta, with high socioeconomic, thus limiting the generalizability of the findings to urban settings.

Introduction

Globally, 11.1% of births are preterm(1). Preterm birth (PTB), delivery prior to 37 weeks of gestation, is a major contributing factor to neonatal deaths(2, 3), and amongst survivors, PTB is also a significant risk factor for short- and long-term morbidity(3-5). The incidence of PTB and its associated mortality and morbidity could potentially be reduced if women at risk of delivering preterm were identified early in gestation and appropriately managed(6, 7). The etiology of PTB is multifactorial(8-10), and one risk factor for PTB may be neighborhood socioeconomic status (SES)(10-12): the rate of PTB in low SES neighborhoods is higher than the rate in high SES neighborhoods(13-15). Neighborhood SES is an area-level measure of SES, which aggregates individual SES (such as income, education, and employment status) at a certain geographical level(11). The high rate of PTB in low SES neighborhoods is not only related to the fact that women living in these neighborhoods have higher individual-level risk factors for PTB. Neighborhoods themselves can also increase the risk of PTB by exposing individuals to elevated risk(11, 12, 16). Low SES neighborhoods influence an individual's ability to fulfill daily needs, access resources, make lifestyle choices, and cope with different situations (11, 12, 16). Accordingly, women living in low SES neighborhoods have less access to healthy foods, quality health services, opportunities for leisure activity, and social support, and have more exposure to societal stressors, crimes, and poor air and water quality. All of these neighborhood level factors can increase the risk of PTB among women living in these neighborhoods through material, psychosocial, behavioral, and biological mechanisms(11, 12, 16, 17).

While many studies have examined the association between neighborhood SES and PTB(13-15), our understanding about the ability of neighborhood SES to predict the risk of PTB

is limited. It is possible that even strongly associated risk factors can have a low capacity to discriminate PTB in the population(18-20). Similarly, a statistically significant association between neighborhood SES and PTB may exist, with small/no variation of PTB at neighborhood level(21-23). Thus, the association may provide unreliable information about the likelihood of delivering preterm infants among women living in certain neighborhoods and may mislead decision-makers in implementing public health interventions targeted at specific areas(21, 22). As previous studies have not developed and validated a prediction model for PTB to evaluate the predictive ability of neighborhood SES, information about the ability of neighborhood SES to predict PTB is lacking.

A better understanding of the ability of neighborhood SES to predict PTB has its own importance as it may improve our capacity to accurately discriminate between women at high and low risk for delivering preterm infants(19, 24). The accurate discrimination capacity may offer a more valid prediction about the future probability of delivering a preterm infant in an individual woman coming from certain neighborhoods(19, 24). The use of valid prediction models may help us effectively identify women at high risk of delivering preterm infants, and in planning suitable public health interventions targeting women from low SES neighborhoods, such as appropriate triage of women into low and high risk prenatal care. This is timely and relevant given that individual level risk factors (including biomarkers) have shown a low discriminatory accuracy in predicting PTB(18, 20), resulting in ineffective early identification of women at risk for delivering preterm infants. Therefore, this study developed and internally validated a predictive model to examine the ability of neighborhood SES to predict PTB.

Methods

Data sources

This study combined existing datasets from two community-based prospective pregnancy cohort studies in Alberta, Canada: All Our Families (AOF: n=3,341) and Alberta Pregnancy Outcome and Nutrition (APrON: n=2,187)) (Figure 1). The description and comparability of these two cohort studies is available elsewhere(25, 26) and justifies combining these data sources(27). Briefly, each cohort study had similar recruitment periods (2008-2012), inclusion criteria, sampling design, and data-collection methods(25, 26). Both studies collected data on socio-demographics, lifestyle, social support, depression, and PTB(25)– the core individual-level variables necessary for this research.

We obtained two de-identified cohort datasets linked with neighborhood SES data from SAGE (Secondary Analysis to Generate Evidence), the secure data repository developed by PolicyWise for Children & Families, which houses these datasets. Neighborhood SES data were measured by the median personal income and the Pampalon material deprivation index (both measures were derived from 2011 Statistics Canada census)(28, 29), which were both aggregated at the dissemination area (DA) level. DA is the smallest geographic unit available in the Canadian census, consisting of 400-700 persons(30). The Pampalon material deprivation index is a composite measure of neighborhood SES that combines the proportion of persons without high school diplomas (education), the average personal income (income), and the rate of unemployment (employment) within the DA(28). Ethics approval for this study was obtained from the Conjoint Health Research Ethics Board at the University of Calgary.

Patient and public involvement

This study used de-identified secondary data. Patients and public were not involved in this study.

Data harmonization and combination

Individual level variables in the two studies were harmonized in each dataset considering multiple factors. These factors included whether the variables were completely or partially identical regarding question asked/responded, the response coded (value level, value definition, data type), the frequency of measurement, the pregnancy time-point of measurement, and missing values. If the variables were an exact match for each of these factors, they were pooled as is. If the variables were partially matched, data harmonization was performed considering these multiple factors. The variables deemed completely un-matched were not combined; thus, they were not included in this study. However, no important variables had to be excluded from the study due to this reason. Once the selected variables were harmonized in each dataset, the two datasets were appended into a single new dataset. Women who participated in both studies (n=231) were counted only once.

The harmonized variables included maternal age, marital status, ethnicity, duration of stay in Canada, body mass index, parity, education, household income, depression during pregnancy, and smoking, alcohol consumption, and drug abuse before the pregnancy. Deliveries that occurred before the completion of 37 weeks of gestation were considered as preterm birth.

Data Analysis

Univariate analysis was performed to observe the distribution of each variable. Bivariate analysis using chi-square tests was performed to identify individual level variables associated with PTB ($p<0.25$). Multivariable conventional logistic regression models, followed by multilevel logistic regression models, as outlined by Merlo et al 2016(23), were developed using bootstrapped samples with 1000 replications (training dataset) (Appendix 1). Missing data were deleted using variable wise or pair wise deletion approach for bivariate analysis, followed by the

listwise deletion approach for regression models. All analyses were performed using STATA/IC software – version 14.1.

Model validation and model performance assessment

The bootstrap procedure was employed for internal validation of the model(19, 31). Model performance was evaluated in the original sample (validation dataset) using measures of model calibration (the correspondence between predicted and observed outcome rates), risk stratification capacity (proportion of women categorized as low vs high risk, or the distribution of the women in each predicted risk category), and classification performance or discrimination accuracy (true positive and false positive rates, positive and negative predictive values, positive and negative likelihood ratios, and area under the receiver operating characteristic curve (AUC)). To obtain these measures, the predicted probability of PTB for each woman was estimated and was categorized into four risk groups (<5%, ≥5 - 10%, ≥10 - 15%, and ≥15%). The difference in AUC estimates between the bootstrapped sample and the original sample was assessed as described by optimism(19, 31). Data on prenatal care and previous PTB were not available in APrON cohort dataset. A sensitivity analysis was performed using only the AOB dataset, whereby two variables, previous PTB and total number of prenatal care visits, were added to the final models (conventional logistic regression model and multilevel random effect model) to assess whether addition of these variables improved model performance.

Results

The total sample size from the combined cohort was 5,297. The proportion of missing data ranged from 1.52% for depression to 7.51% for gestational age at delivery. The majority of women were under the age of 35 years, were married or living with a common-law partner, were

Caucasian, and approximately half of the women were primiparous. Almost three quarters of women had completed more than high school education and had a household income ≥$70,000, while approximately one quarter of women were living in the least deprived neighborhood (Table 1). Overall, 7.26% (95% CI: 6.57, 8.07) of women delivered preterm infants, with 7.54% among women living in the least deprived neighborhoods and 10.64% among women living in the most deprived neighborhoods. Compared to women who delivered at term, a higher proportion of women who delivered preterm infants were primiparous, non-white, obese, and were living in the most deprived neighborhood (Table 1).

As shown in Table 2, a conventional logistic regression model that included individual level predictors (parity, ethnicity, body mass index, smoking, depression, and household income) showed an AUC of 0.60 (95% CI: 0.56, 0.63). The multilevel model that included individual level predictors, and a random effect at the neighborhood level showed large variation in PTB at neighborhood level (neighborhood variance: 0.20, intracluster correlation (ICC): 5.72%, median odds ratio (MOR): 1.53), with an AUC of 0.75 (95% CI: 0.73, 0.78). After inclusion of neighborhood SES (deprivation index) in the multilevel model, although deprivation index was not significantly associated with PTB (OR: 1.19, 95% CI: 0.78, 1.79), neighborhood variance decreased to 0.15, the ICC to 4.45%, and the MOR to 1.46, with an AUC of 0.75 (95% CI: 0.73, 0.78). The MOR of 1.46 for PTB indicates that in the median case, the residual heterogeneity between neighborhoods increased by 1.46 times the individual odds of PTB when randomly picking out two persons in different neighborhoods. Furthermore, the multilevel model that contained median personal income, as a measure of neighborhood SES, showed similar variance as the model that contained deprivation index.

Predicted probabilities of PTB in the multilevel model that contained individual level predictors and deprivation index ranged from 2.77% - 27.00%. Calibration of the model predicting PTB was adequate, as shown by an agreement between the model-predicted probability for PTB and the proportion of observed PTB, particularly for low risk categories. Specifically, the observed PTB rate within the predicted risk category of ≥5% -10% was 7.30%, which falls within the risk category range; the same was true for the risk category of < 5%. The risk-stratification capacity of the model was adequate– it assigned women to the different risk of PTB, where almost 90% of women were assigned to low risk category (Table 3).

The classification accuracy of the model ranged from 33.09% to 92.30% in the different predicted risk categories: the proportion of women with preterm delivery who were identified as high risk for PTB (sensitivity) ranged from 5.70% to 91.80% and the proportion of women without preterm delivery who are identified as low risk (specificity) ranged from 28.50 to 99.10. The positive and negative likelihood ratios of the model for the highest predicted risk category for PTB were 6.22 and 0.95, respectively. The difference in the AUCs between the bootstrap sample (AUC: 0.75, 95% CI: 0.73, 0.78) and original sample (AUC: 0.75, 95% CI: 0.73, 0.78) was negligible (i.e., optimism: 0.0001). While the multilevel model that contained median personal income showed similar model performance as the model that contained the deprivation index (except for sensitivity and positive predictive values for the highest risk category), the logistic regression model that included individual level variables showed lower model performance (Table 3 and Figure 2). In the sensitivity analysis, the addition of variables related to prenatal care visits and previous PTB did not change the model performance. The AUC increased by 2.00% for the conventional logistic regression model, but did not increase for the multilevel random effect model that contained the neighborhood SES variable.

Discussion

Main findings

This study developed and internally validated a prediction model to examine the ability of neighborhood SES to predict the risk of PTB. This study found that approximately 6% of the total variance in PTB was attributable to neighborhood circumstances (ICC: 5.72%), and neighborhood SES explained one quarter of the neighborhood level variation in PTB. Neighborhood SES combined with individual level predictors (parity, ethnicity, body mass index, smoking, depression, and household income) predicted the risk of delivering a preterm infant with an AUC of 0.75. The sensitivity was 91.80% at a lowest risk threshold, with a cost of high false positive (71.50%), and the sensitivity was 5.70% at a highest risk threshold, with a low false positive (0.90%). Neighborhood SES combined with individual level predictors had a good risk-stratification and a modest calibration ability for identifying woman at risk for delivering a preterm infant.

Interpretation

Model discrimination (measured by AUC) was improved substantially when we combined individual level predictors with neighborhood level information. While it has been previously demonstrated that individual level predictors including maternal characteristics, clinical risk factors, and biomarkers have low discriminatory accuracy in predicting the risk of PTB (AUC ranged from 0. 60 – 0.67)(18, 20), our study enhances our understanding that adding the neighborhood level information can improve the discriminatory accuracy of PTB. Furthermore, it is important to note that a multilevel model that included a random effect for neighborhood and individual level information gives the maximum AUC that can be obtained by combining available individual level information and the neighborhood identity(23).

Neighborhood identity captures the totality of potentially observable and unobservable neighborhood factors(23, 32, 33).

As suggested by the classification performance of the model including neighborhood SES and individual level predictors, a large proportion of women who were identified as high risk actually did not deliver preterm. Positive predictive value was improved, but still too low, as the predicted risk threshold increased, which was related to the high proportion of PTB in the threshold. The model had low sensitivity (5.70%) at the highest risk threshold, with a low false positive (0.90%). This means that a substantial number of women who were at high risk for delivering PTB would be identified as low risk(34). The LR positive test was improved (up to 6.22) for the highest risk threshold; however, this group only includes <6% of total women who actually delivered preterm. This dichotomy between improved LR and poor detection rates has also been noted previously(35).

While the prediction of PTB risk using neighborhood SES is suboptimal, other commonly recognized risk factors for PTB also failed to sufficiently predict PTB. For example, it has been noted that a history of prior PTB has an LR+ of 3.24, short cervical length has an LR+ of 2.0, and vaginal fetal fibronectin has an LR+ of 3 in predicting PTB(36). Similarly, for a fixed false positive rate of 10%, maternal characteristics and obstetrical history have a sensitivity of 27.5% for PTB with an AUC of 0.61(20). The less optimal predictive performance for identifying the risk of PTB may be related to the complex underlying etiology of PTB, and a combination of multiple aspects of predictors (such as biomarkers, clinical risk factors, socio-demographics, and health behaviors) may be required to adequately predict such an outcome(35, 37). Our study further shows that inclusion of neighborhood SES along with multiple individual level predictors would further improve the prediction of PTB. Altogether, it implies that

identification of women at risk for delivering preterm infants should rely on multiple factors, and even women identified as low risk for PTB may need further monitoring/assessment and high quality prenatal care should be universal.

Our findings on neighborhood variation and clustering of PTB suggest that pregnant women from the same neighborhoods are more similar to each other than to women from different neighborhoods with respect to the risk of PTB, and that some portion of this variation is related to neighborhood SES. Overall, this finding reflects the presence of health disparities in PTB between neighborhoods in Alberta, and justifies the relevance of neighborhood including neighborhood SES and neighborhood targeted interventions. Furthermore, the share of the variance in PTB that are explained by neighborhood level variance (as measured by ICC) offers understanding about the discriminatory accuracy as it corresponds to the AUC(23)– when the ICC is high the AUC is also high(23). However, previous research has emphasized identifying neighborhood level risk factors associated with PTB or causal effects, which is difficult to establish due to the potential challenges. These challenges include reverse causation between neighborhood circumstances and health, unmeasured confounding, residential mobility, possibility of same individual variable being confounder and mediator, and changes in neighborhood context over the life process(11, 12, 38). Thus, a study aiming to establish a causal association demands longitudinal study design with repeated measurement of neighborhood characteristics and outcomes over time in life-course processes(11, 12, 38).

Strengths and limitations of study

To our knowledge, our study is the first to develop and internally validate a predication model for PTB to investigate the ability of neighbourhood SES to predict the risk of PTB, in contrast to the previous studies that examined mostly the association between neighbourhood

SES and PTB. Our finding allows us to understand the relevance of area of residence (in general), and more specifically area-level SES, in predicting the risk of maternal health outcomes. Our study used the simplest multilevel structure with individual and neighborhood level predictors of PTB, data which can be easily collected in both community and clinical settings.

Our findings should be interpreted with a consideration of the limitations of our study. We were not able to separate-out spontaneous and iatrogenic PTB in the model due to data limitations– the predictive performance might be improved with a focus on spontaneous PTB. Our sample over-represents women from urban areas of Alberta, with high SES(26, 39, 40), thus limiting the generalizability of the findings to urban settings. The observed predictive ability of neighborhood SES would have been underestimated as the relevance of neighborhood SES status might be higher for those with low SES. Although the observed small difference in discriminatory accuracy between the bootstrapped sample and the original sample provided us a confidence about the reproducibility of our prediction model, as the model was internally validated, it possibly showed artificially high performance; thus, model validation should be confirmed against external data. Use of area-based variables, where women living in the same area share the same value for the variable, can be a methodological problem. Results on outcomes could be affected by what geographical level or unit we choose to define area in the study. Individuals who live in the same area may also experience different contextual influences from many other areal units, and the timing and duration in which individuals experienced these contextual influences is also uncertain. Thus, it is hard to interpret neighborhood influences on outcomes, including the performance of the model that contains neighborhood level variable. However, we defined neighborhoods using smallest area (i.e., dissemination area), where people

living in the smallest area are more likely to be similar for the outcomes, and used multilevel analysis that accounts for area-level variation, an appropriate analytical approach for multilevel data.

Conclusion

Although the predictive performance of the model that contained neighborhood SES and individual level predictors was better compared to the performance of individual level predictors alone, the performance was too low to consider its application in clinical or public health practices. While the development and validation of our predictive model is an important first-step towards the early identification of women at high risk for PTB based on neighborhood risk assessment, a clinically-relevant validated model to predict the risk of PTB is yet to be identified. Future studies could develop a prediction model for PTB considering other clinically relevant individual and neighborhood level predictors, separating out spontaneous and iatrogenic PTB in the model, and externally validating their results to optimize the prediction and to improve its usefulness. The application of clinically useful prediction model would support healthcare providers and public health practitioners to make informed decisions on their care by improving their ability to identify woman most at risk of delivering preterm. As such, community level interventions combined with an individual-centered approach that attempts to change neighborhood circumstances (health promoting or damaging features of neighborhood including SES) and population characteristics (with focus to modifiable predictors) may be effective in reducing the incidence of PTB.

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Authors contributions

Kamala Adhikari involved in the conception and design of the study. Kamala is also responsible for conducting the analysis, interpreting the data, and drafting the manuscript. Amy Metcalfe provided overall supervision to Kamala in conducting this study and contributed to conception and study design, interpretation of data, provided intellectual content and revisions to manuscript. Scott Patten, Tyler Williamson, Alka B Patel, Shahirose Premji, Suzanne Tough, Nicole Letourneau, and Gerald Giesbrecht were involved in the conception and design of the study and provided interpretation and intellectual content to subsequent drafts of the manuscript. All authors read and approved the final draft.

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Ethical approval

Ethics approval for this study was obtained from the Conjoint Health Research Ethics Board at the University of Calgary.

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Data sharing

Additional data such as statistical codes, supplementary tables, and technical appendix are available upon request (by emailing Kamala Adhikari: kamala.adhikaridahal@ucalgary.ca)

Competing interests

The authors declare that they have no competing interests.

Table 1 Distribution of maternal characteristics across preterm birth status[a]

Variables	Overall (n=5297)		Preterm Birth (Gestational Age <37 weeks) n=356		Term Birth (Gestational Age ≥37 weeks) n=4546		χ^2 p-value
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	
Maternal age							0.332
<35yrs	4117 (79.23)	78.10, 80.31	269 (77.08)	72.36, 81.19	3548 (79.27)	78.05, 80.43
≥35yrs	1079 (20.77)	19.68, 21.89	80 (22.92)	18.80, 27.63	928 (20.73)	18.80, 27.63
Marital status							0.657
Single/divorced/separated	262 (5.06)	4.49, 5.69	17 (4.96)	3.10, 7.83	198 (4.44)	3.87, 5.09
Married/common-law	4916 (94.94)	94.30, 95.50	326 (95.04)	92.17, 96.89	4262 (95.56)	94.91, 96.13
Ethnicity							0.004
White/Caucasian	4085 (78.98)	77.85, 80.07	253 (73.76)	68.83, 78.15	3554 (80.28)	79.08, 81.42
Others	1087 (21.02)	19.93, 22.15	90 (26.24)	21.85, 31.16	878 (19.72)	18.58, 20.92
Duration of stay in Canada							0.061
<5 years	473 (9.26)	8.49, 10.08	39 (11.64)	8.61, 15.54	386 (8.63)	7.84, 9.25
Born/5 years+	4636 (90.74)	89.91, 91.51	296 (88.36)	84.45, 91.38	4072 (91.37)	90.50, 92.16
Body mass index							0.001
Underweight (<18.5kg/m2)	214 (4.33)	3.80, 4.94	12 (3.69)	2.10, 6.39	186 (4.33)	3.66, 4.87
Normal weight (18.5 - 24.99)	3084 (62.45)	61.09, 63.79	183 (56.31)	50.85, 61.62	2684 (63.28)	61.82, 64.72
Overweight (25 - 29.99 kg/m2)	1066 (21.59)	20.46, 22.76	72 (22.15)	17.69, 27.00	924 (21.71)	20.49, 22.97
Obesity (≥30 kg/m2)	574 (11.62)	10.76, 12.54	58 (17.85)	14.05, 22.40	456 (10.78)	9.88, 11.75
Parity							0.004
Primiparous	2649 (51.27)	49.90, 52.63	201 (58.94)	54.64, 64.80	2226 (50.92)	49.45, 52.39
Multiparous	2518 (48.73)	47.37, 50.09	140 (41.06)	35.19, 45.36	2134 (49.08)	47.61, 50.54
Intended pregnancy							0.805
Yes	4175 (80.51)	79.40, 81.56	62 (18.02)	14.30, 22.45	829 (18.58)	17.46, 19.75
No	1011 (19.49)	18.44, 20.60	282 (81.98)	77.54, 85.69	3633 (81.42)	80.25, 8253
Smoked before pregnancy							0.062
Yes	1095 (21.13)	20.04, 22.26	259 (75.29)	70.44, 79.57	3547 (79.53)	78.31, 80.68
No	4088 (78.87)	77.74, 79.96	85 (24.71)	20.43, 29.55	913 (20.47)	19.31, 21.68
Alcohol consumption before pregnancy							0.531
Yes	4363 (84.13)	83.11, 85.10	49 (14.24)	10.93, 18.36	692 (15.51)	14.47, 16.60

No	823 (15.87)	14.90, 16.89	295 (85.76)	81.64, 89.07	3780 (84.49)	83.39, 85.52	
Drug abuse before pregnancy							0.519
Yes	750 (14.48)	13.54, 15.46	290 (84.30)	80.06, 87.78	3814 (85.57)	84.51, 86.57	
No	4430 (85.52)	84.53, 86.45	54 (15.70)	12.22, 19.94	643 (14.43)	13.42, 15.49	
Maternal education							0.917
Less than high school	174 (3.37)	2.91, 3.90	11 (3.22)	1.79, 5.72	126 (2.84)	2.39, 3.37	
Completed high school	893 (17.31)	16.29, 18.36	56 (16.37)	12.81, 20.69	724 (16.25)	15.19, 17.36	
More than high school	4093 (79.32)	78.19, 80.40	275 (80.41)	75.85, 84.28	3554 (80.91)	79.73, 82.04	
Household income							0.436
≥$100,000	2659 (52.52)	51.14, 53.89	176 (52.54)	47.17, 57.84	2338 (53.98)	52.50, 55.45	
$70,000 - <$100,000	1204 (23.78)	22.63, 24.97	74 (22.09)	17.96, 26.86	1054 (24.24)	22.99, 25.53	
$40,000 - <$70,000	723 (14.28)	13.34, 15.27	51 (15.22)	11.75, 19.49	591 (13.53)	12.55, 14.57	
<$40,000	477 (9.42)	8.64, 10.25	34 (10.15)	7.33, 13.88	366 (8.44)	7.46, 9.09	
Social support anytime during pregnancy							0.216
Adequate	4053 (77.93)	76.78, 79.03	263 (75.79)	70.99, 80.01	3514 (81.63)	77.40, 79.81	
Inadequate	1148 (22.07)	20.96, 23.22	84 (24.21)	19.98, 29.00	953 (21.37)	20.19, 22.59	
Depression anytime during pregnancy							
Yes	1311 (25.14)	23.98, 26.33	96 (27.67)	23.20, 32.61	1086 (24.21)	22.97, 25.48	0.149
No	3904 (74.86)	73.66, 76.02	251 (72.33)	67.38, 76.94	3400 (75.79)	74.51, 77.02	
Neighborhood deprivation index							0.002
Quintile 1 (least deprived)	1323 (27.08)	25.85, 28.35	93 (26.12)	21.81, 30.94	1175 (27.68)	26.36, 29.05	
Quintile 2	1259 (25.77)	24.56, 27.01	76 (21.35)	17.39, 25.92	1119 (26.34)	25.04, 27.69	
Quintile 3	972 (19.90)	18.80, 21.04	71 (19.94)	16.10, 24.43	839 (19.75)	18.58, 20.97	
Quintile 4	736 (15.07)	14.09, 16.09	52 (14.61)	11.30, 18.67	636 (15.04)	13.99, 16.15	
Quintile 5 (most deprived)	595 (12.18)	11.29, 13.14	64 (17.98)	14.32, 22.32	475 (11.18)	10.27, 12.16	
Neighborhood median personal income							0.054
Quintile 1 (least deprived)	1549 (31.05)	29.78, 32.35	106 (29.78)	25.24, 34.74	1309 (30.49)	30.12, 32.89	
Quintile 2	1403 (28.13)	26.89, 29.39	96 (26.97)	22.60, 31.82	1229 (28.27)	26.95, 29.63	
Quintile 3	881 (17.66)	16.62, 18.74	57 (16.01)	12.55, 20.20	776 (17.85)	16.74, 19.01	
Quintile 4	666 (13.35)	12.43, 14.32	47 (13.20)	10.06, 17.14	574 (13.20)	12.22, 14.24	
Quintile 5 (most deprived)	489 (9.80)	9.00, 10.66	50 (14.04)	10.80, 18.06	399 (9.18)	8.35, 10.07	

[a]sample size between variables differs as missing values were deleted using variable wise or pair wise deletion approach

Table 2 Predictive models for preterm birth[a]

	Model 1[b] OR (95% CI)	Model 2[c] OR (95% CI)	Model 3[d] OR (95% CI)
Ethnicity			
White/Caucasian (ref)	-	-	-
Non-white	1.50 (1.11, 2.04)	1.48 (1.11, 1.96)	1.49 (1.13, 1.99)
Parity			
Multiparous (ref)	-	-	-
Primiparous	1.49 (1.21, 1.84)	1.52 (1.19, 1.93)	1.53 (1.20, 1.95)
Body mass index			
Normal weight (ref)	-	-	-
Underweight	0.99 (0.46, 2.10)	1.01 (0.47, 1.14)	1.00 (0.35, 2.83)
Overweight	1.18 (0.88, 1.57)	1.14 (0.76, 1.68)	1.13 (0.72, 1.78)
Obesity	1.94 (1.41, 2.65)	1.95 (1.25, 3.04)	1.95 (1.16, 3.30)
Smoked before pregnancy			
No (ref)	-	-	-
Yes	1.20 (0.90, 1.60)	1.19 (0.78, 1.79)	1.19 (0.77, 1.82)
Depression during pregnancy			
No (ref)	-	-	-
Yes	1.10 (0.84, 1.46)	1.12 (0.76, 1.66)	1.13 (0.74, 1.71)
Household income			
≥$100,000 (ref)	-	-	-
$70,000 - <$100,000	0.82 (0.61, 1.12)	0.82 (0.51, 1.33)	0.84 (0.55, 1.28)
$40,000 - <$70,000	0.75 (0.70, 1.31)	0.96 (0.57, 1.62)	0.99 (0.58, 1.69)
<$40,000	0.92 (0.71, 1.66)	1.05 (0.60, 1.81)	1.10 (0.63, 1.88)
Neighbourhood SES	-		
Q1 least deprived (ref)		-	-
Q2		0.86 (0.53, 1.39)	0.97 (0.64, 1.49)
Q3		0.96 (0.58, 1.59)	0.87 (0.52, 1.47)
Q4		0.99 (0.60, 1.58)	0.90 (0.51, 1.59)
Q5 most deprived		1.20 (0.63, 1.85)	1.01 (0.55, 1.86)
Neighbourhood level variance	-	0.15 (0.03, 0.89)	0.14 (0.03, 0.88)
ICC (%)[e]	-	4.45 (0.07, 23.25)	4.27 (0.06, 23.59)
MOR	-	1.46	1.44
Proportion of neighbourhood level variance explained by neighborhood SES (%)	-	25.00	25.16
AUC	0.60 (0.56, 0.63)	0.75 (0.73, 0.78)	0.75 (0.72, 0.77)

[a]prediction models were developed in bootstrapped samples with 1000 replications; [b] conventional logistic regression model that includes individual level predictors; [c] multilevel logistic regression model that includes random intercept at neighbourhood level, neighbourhood deprivation index, and all the individual level predictors contained in the logistic regression model; [d] multilevel logistic regression model that includes random intercept at neighbourhood level, neighbourhood median personal income, and all the individual level predictors contained in the logistic regression model; [e]ICC calculation follows standard logistic distribution with variance $\pi 2/3$ for the level 1, where π denotes the mathematical constant 3.1416; MOR: median odds ratio; ICC: intra-cluster correlation; AUC: area under the receiver operating characteristic curve

Table 3: Performance of predictive models for preterm birth (n=4,357)[a]

Predictive models	Model calibration		Risk stratification capacity n (%)	Model discrimination[b]						
	Predicted probability of PTB (%)	Observed PTB n (%) 95% CI		Sensitivity (%)	Specificity (%)	Classification accuracy (%)	PPV (%)	NPV (%)	LR+ (%)	LR- (%)
Conventional logistic regression model with individual level predictors, i.e., parity, ethnicity, body mass index, smoking, depression, and household income	<5	42 (4.81) 3.43, 6.03	873 (20.04)	-	-	-	-		-	-
	≥5 – 10	197 (6.96) 6.02, 7.81	2832 (65.00)	85.76	22.43	26.54	7.66	95.44	1.10	0.63
	≥10 – 15	77 (12.56) 9.99, 15.96	613 (14.07)	20.12	89.42	84.58	12.43	93.70	1.90	0.89
	≥15	4 (10.26) 2.82, 24.37	39 (0.90)	1.55	99.14	92.31	8.82	93.03	1.80	0.99
Multilevel logistic regression model with neighbourhood deprivation index and individual level predictors	<5	26 (2.22) 1.50, 3.22	1177 (27.01)	-	-	-	-	-	-	-
	≥5 – 10	197 (7.30) 6.40, 8.37	2690 (61.74)	91.80	28.50	33.09	9.12	97.80	1.28	0.29
	≥10 – 15	75 (17.24) 13.97, 21.09	435 (9.98)	29.40	90.20	85.82	19.00	94.20	3.00	0.78
	≥15	18 (32.73) 21.60, 46.20	55 (1.26)	5.70	99.10	92.30	32.80	93.10	6.22	0.95
Multilevel logistic regression model with neighbourhood median personal income and individual level predictors	<5	31 (2.64) 1.86, 3.73	1174 (26.97)	-	-	-	-	-	-	-
	≥5 – 10	192 (7.16) 6.24, 8.19	2683 (61.58)	90.30	28.30	33.13	8.95	97.40	1.26	0.34
	≥10 – 15	81 (18.08) 14.78, 21.92	448 (10.28)	29.40	89.90	85.85	18.60	94.20	2.92	0.78
	≥15	12 (23.08) 13.52, 36.53	52 (1.19)	3.80	99.00	92.20	23.10	92.10	3.84	0.97

[a] model performance was assessed in the original sample (study sample); [b]model discriminatory was calculated using cumulative row values as different cut-offs to define high risk, for example, if all women with a model predicted probability of a preterm birth of 5% or higher are considered to have a positive test, model with deprivation index and individual level predictors would have a sensitivity of 91.80% and specificity of 28.50%.
PPV: positive predictive value; NPV: negative predictive value; LR+: positive likelihood ratio; LR-: negative likelihood ratio;

Figure Legends

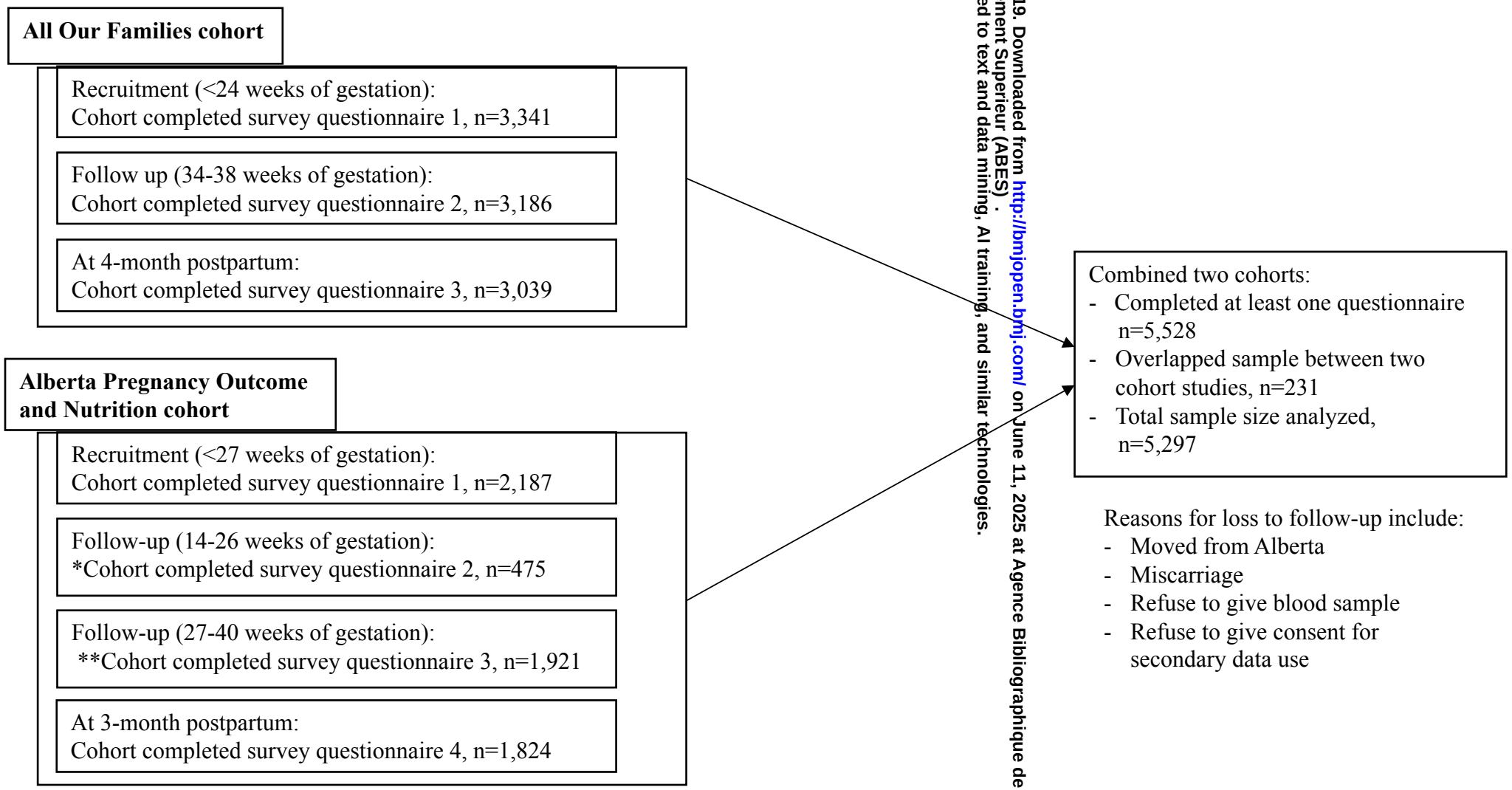
Figure 1: Flowchart of study cohort

*Participants who were 0-13 weeks of gestation during the recruitment were eligible to fill out the questionnaire 2. ** Participants who were 0-26 weeks of gestation during recruitment were eligible to fill out the questionnaire 3.

Figure 2: Receiver operating characteristic curves of models predicting preterm birth

[a] receiver operating characteristic curves of models were assessed in the original sample (study sample); predictors in Figure 2a included individual level variables, i.e., parity, ethnicity, body mass index, smoking, depression, and household income; predictors in Figure 2b included neighbourhood deprivation index and individual level variables; predictors in Figure 2c included neighbourhood median personal income and individual level variables.

Figure 1: Flowchart of study cohort



*Participants who were 0-13 weeks of gestation during the recruitment were eligible to fill out the questionnaire 2. **Participants who were 0-26 weeks of gestation during recruitment were eligible to fill out the questionnaire 3.

Figure 2: Receiver operating characteristic curves of models predicting preterm birth

Figure 2a

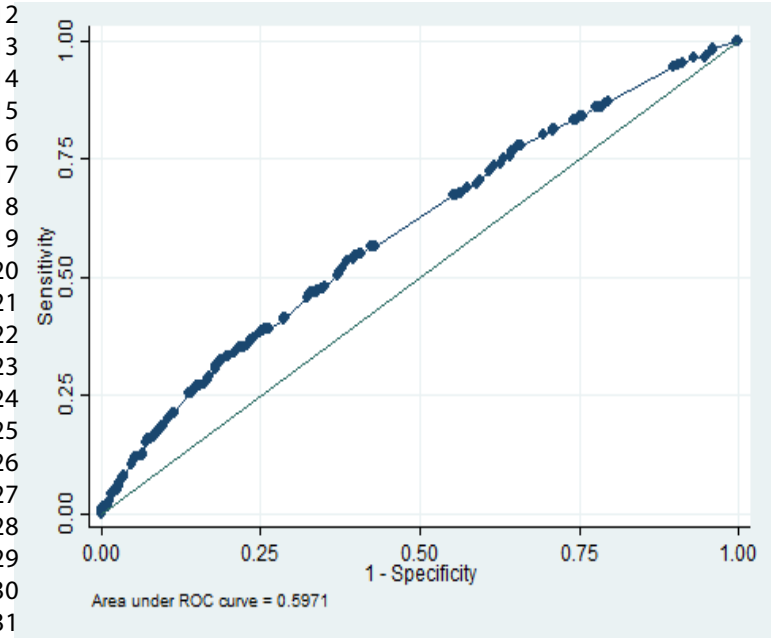


Figure 2b

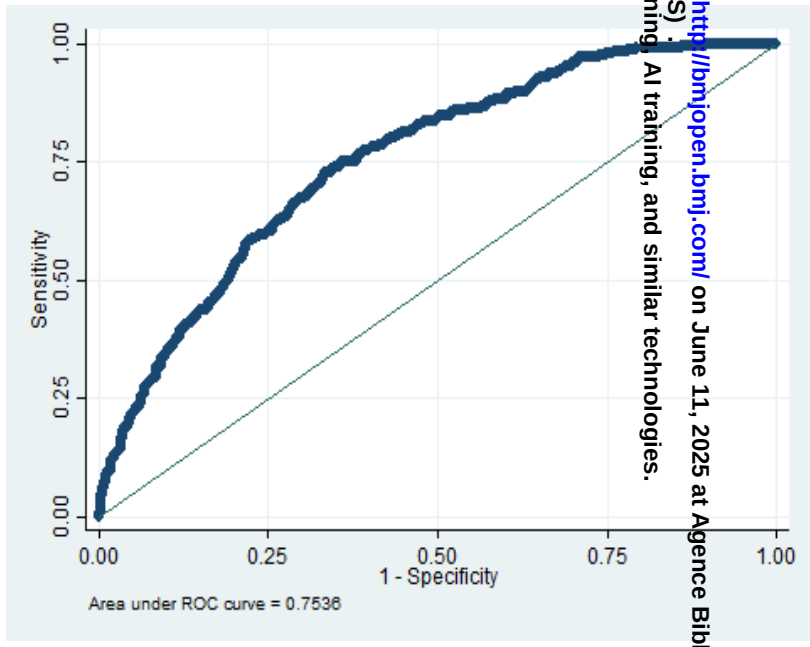
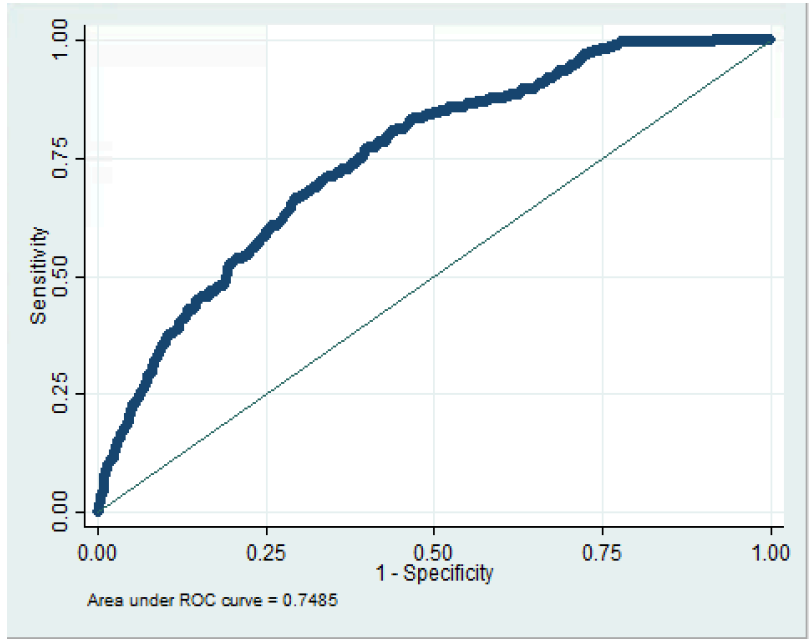


Figure 2c



[a] receiver operating characteristic curves of models were assessed in the original sample (study sample); predictors in Figure 2a included individual level variables, i.e., parity, ethnicity, body mass index, smoking, depression, and household income; predictors in Figure 2b included neighbourhood deprivation index and individual level variables; predictors in Figure 2c included neighbourhood median personal income and individual level variables.

Appendix 1: Model building and validation strategy

A predictive model for PTB was developed using three consecutive model development steps as outlined by Merlo et al 2016 for multilevel data. These steps included development of a logistic regression model, followed by development of a multilevel logistic regression model with a random intercept, with and without including neighborhood SES. These three steps allow us to systematically develop a predictive model containing individual and neighborhood level variables.

Predictive models were developed in the bootstrapped sample (of equal size of the study sample) with 100 replications (training dataset). A conventional multivariable logistic regression model, which included individual level variables associated with PTB ($p<0.25$), was developed using a backward variable elimination approach. Neighborhood level information was not included in this model. The individual level variable with the largest p-value was first eliminated from the full model, then, the variable with the second largest p-value was eliminated and so on. Variables were retained in the model if the associated p-value was <0.1 or if the variable was clinically relevant. We used a p-value <0.1, instead of the conventional p-value <0.05 to increase the chance of retention of individual level variables in the final model.

A two-level multilevel logistic regression model with a random intercept for neighborhood (DA) was developed, with 5,297 women nested into 1,501 DAs; thus, on average each DA included three women. This model contained all of the individual level predictors identified in the conventional logistic regression model. Then, the neighborhood SES variable (Pampalon material deprivation index or median personal income) was added in the multilevel logistic regression model. Different SES measures have been used across studies to measure neighborhood SES; thus, two multilevel models (one for material deprivation index and another for median personal income) were developed to explore whether the predictive ability of neighborhood SES on the risk of PTB differs by the different measures of neighborhood SES used. Multilevel models provided estimates involving the association between neighborhood SES and PTB (odds ratio (OR)) and the neighborhood variation in PTB (including intra-class correlation coefficient (ICC) and

median odds ratio (MOR)). Additionally, the proportional change in variance between multilevel models with neighborhood SES and without neighborhood SES was calculated to assess the proportion of the neighborhood variance explained by neighborhood SES. The discriminative ability of three predictive models (conventional logistic regression model, multilevel logistic regression model with deprivation index, and multilevel regression model with median household income) was assessed in the bootstrapped sample and the study sample using the AUC of the receiver operating characteristic curve.

TRIPOD Checklist: Prediction Model Development and Validation

Section/Topic	Item		Checklist Item	Page
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	2, 3
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	5, 6
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	6
Methods				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	7
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	7
Participants	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	7
	5b	D;V	Describe eligibility criteria for participants.	7
	5c	D;V	Give details of treatments received, if relevant.	not applicable
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	8
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	not applicable
Predictors	7a	D;V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	8, 26, 27
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	not applicable
Sample size	8	D;V	Explain how the study size was arrived at.	not applicable
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	9
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	8,9, appendix
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	8, 9,appendix
	10c	V	For validation, describe how the predictions were calculated.	9, appendix
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	9, appendix
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	9(sens. analysis)
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	9
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	not applicable
Results				
Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	fig. 1
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	9, 10 , 24, 25
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	not applicable
Model development	14a	D	Specify the number of participants and outcome events in each analysis.	9, 10, 24, 25
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	briefly in appendix
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	10, 26
	15b	D	Explain how to the use the prediction model.	not applicable
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	11, 27
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	11 (sensitivity analysis)
Discussion				
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	15
Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	12, 13 , 14
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	13, 14
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	15, 16
Other information				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	appendix 1
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	22

*Items relevant only to the development of a prediction model are denoted by D, items relating solely to a validation of a prediction model are denoted by V, and items relating to both are denoted D;V. We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.