Development and Validation of a Model to Predict Neonatal Abstinence Syndrome

Stephen W. Patrick, MD, MPH, MSc[1,2,3], James C. Slaughter, DrPH[4], Frank E. Harrell, Jr., PhD[4], Peter R. Martin, MD, MSc[5,6], Katherine Hartmann, MD, PhD[7], Judith Dudley, BS[2], Shannon Stratton, BS[2], and William O. Cooper, MD, MPH[1,2]

Objectives To develop and validate clinical risk prediction tools for neonatal abstinence syndrome (NAS).

Study design We developed prediction models for NAS based on a set of 30 demographic and antenatal exposure covariates collected during pregnancy. Data (outpatient prescription, vital, and administrative records), were obtained from enrollees in the Tennessee Medicaid Program from 2009 to 2014. Models were created using logistic regression and backward selection based on improvement in the Akaike information criterion, and internally validated using bootstrap cross-validation.

Results A total of 218 020 maternal and infant dyads met inclusion criteria, of whom 3208 infants were diagnosed with NAS. The general population model included age, hepatitis C virus infection, days of opioid used by type, number of cigarettes used daily, and the following medications used in the last 30 day of pregnancy: bupropion, antinausea medicines, benzodiazepines, antipsychotics, and gabapentin. Infant characteristics included birthweight, small for gestational age, and infant sex. A high-risk model used a smaller number of predictive variables. Both models discriminated well with an area under the curve of 0.89 and were well-calibrated for low-risk infants.

Conclusions We developed 2 predictive models for NAS based on demographics and antenatal exposure during the last 30 days of pregnancy that were able to risk stratify infants at risk of developing the syndrome. *(J Pediatr 2021;229:154-60)*.

As the opioid crisis spread through the US, increasing numbers of pregnant women and infants were affected.[1,2] Over the last 2 decades, the number of mothers diagnosed with opioid use disorder grew 4-fold and the rate of newborns being diagnosed with opioid withdrawal, also known as neonatal abstinence syndrome (NAS), grew nearly 7-fold.[1-4] By 2014, one infant was diagnosed with the syndrome every 15 minutes on average nationwide, eclipsing $500 million in hospital costs.[2]

Data suggest that the majority of infants with opioid exposure do not exhibit clinical signs severe enough to be diagnosed with NAS.[5] In part, because of the limitations of current tools to estimate NAS risk, the American Academy of Pediatrics recommends standard observation periods for all infants with opioid exposure based upon the type of opioid exposure of 3 to 7 days after birth, far longer than usual observation periods for uncomplicated term infants.[4,6] For infants with opioid exposure who do not develop NAS, these recommended observation periods may lead to excessive hospital stays and cost with marginal benefit. In contrast, the inability to identify infants at high risk of NAS at the time of birth may result in delays in treatment. Although previous studies have identified infant characteristics and maternal substance use patterns that may modify an infant's risk of developing NAS, no tools have been created to apply this research to guide clinical practice.[5,7,8] Our objective was to develop and validate parsimonious clinical risk prediction tools for NAS among a large population of infants exposed to medically prescribed opioids.

Methods

This retrospective study used data from maternal infant dyads enrolled in TennCare, the Tennessee Medicaid Program, using outpatient prescription claims linked to vital records and hospital and outpatient administrative data from 2009 to 2014. Because Medicaid is financially responsible for more than 80% of infants diagnosed with NAS, it is an ideal program to study the syndrome.[2,9] This study was approved with a waiver of informed consent by the Vanderbilt University Institutional Review Board, the State of Tennessee Department of Health, and the Bureau of TennCare.

HCV	Hepatitis C virus
ICD-9-CM	International Classification of Diseases 9th Revision Clinical Modification
MOUD	Medications for opioid use disorder
NAS	Neonatal abstinence syndrome

From the [1]Department of Pediatrics, [2]Department of Health Policy, [3]Mildred Stahlman Division of Neonatology, [4]Department of Biostatistics, [5]Department of Psychiatry and Behavioral Sciences, [6]Department of Pharmacology, and the [7]Department of Obstetrics and Gynecology, Vanderbilt University Medical Center, Nashville, TN

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Similar to our previous work, maternal and infant dyads were included in the study if the mother was 15-44 years old at the time of delivery, enrolled in TennCare at least 30 days before delivery, and infants were enrolled in TennCare within 30 days after delivery.[5] Last menstrual period and date of delivery were obtained from vital records.[10] Pregnancies were included if the birth occurred between January 1, 2009, and December 31, 2014.

Our outcome of interest was NAS, as defined by the *International Classification of Diseases 9th Revision Clinical Modification* (ICD-9-CM) code 779.5. We previously established the accuracy of the diagnostic code for NAS, through a review of 950 medical records of NAS with a standardized algorithm and determined the positive predictive value of the code to be more than 90%.[11] Infants did not require pharmacotherapy for NAS to be included as having a diagnosis of NAS.

Model predictors were chosen a priori based on the existing literature, clinical practice, and common medications used in pregnancy. For clinical relevance and to facilitate ease of use, we focused on medication use within the last 30 days of pregnancy and characteristics that would be readily available to clinicians at the time of birth.

Prescription claims were obtained from TennCare outpatient pharmacy records of prescriptions filled within the last 30 days of pregnancy. These claims contain information for all outpatient prescriptions that are reimbursed by the program. Opioid drug types were categorized as immediate release, (eg, hydrocodone-acetaminophen, oxycodone hydrochloride), sustained release (eg, oxycodone hydrochloride controlled-release, oxymorphone hydrochloride extended release), and medications for opioid use disorder (MOUD) (eg, buprenorphine hydrochloride). Because TennCare did not reimburse for care at opioid treatment programs during our study period, 99% of pregnant women using MOUD were prescribed buprenorphine-containing products. Naltrexone was not included as a MOUD. Opioid doses were converted to morphine milligram equivalents using established conversion guidelines to facilitate meaningful comparisons.[12] The duration of opioid use was defined as the period between the prescription start date and the end of the days of supply (allowing up to a 5-day carryover period from previous prescriptions). In addition, data were obtained for benzodiazepines, atypical antipsychotics, typical antipsychotics, antidepressants, acid reflux and nausea medications, zolpidem, and gabapentin (**Table I**; available at www.jpeds.com). To facilitate ease of clinical use, medications were grouped into classes for analyses.

Additional maternal and infant characteristics were obtained from administrative and vital records data. Cigarette use was obtained from birth certificates and using the ICD-9-CM codes 305.1, V15.82, 989.84, and 649.0x; number of cigarettes smoked per day was obtained from the birth certificate. Infant birth weight, gestational age, and sex were obtained from the birth certificate. Maternal age and hepatitis C virus (HCV) status was used as a proxy for injection drug use and obtained from the birth certificate, augmented by ICD-9-CM codes 070.41, 070.44, 070.51, 070.54, and 070.7x. Small for gestational age was calculated using a previously published algorithm.[13]

Statistical Analyses

Multivariable logistic regression was used to develop a model for predicting NAS status using the approach outlined in the text by Harrell.[14] We were concerned with creating a robust prediction model that could readily be applied to other populations while mitigating overfitting. To that end, continuous predictors were flexibly modeled using restricted cubic splines[15] and categorical variables modeled using indicator functions. Partial effects plots were used to display the adjusted association of each predictor with the odds of NAS (**Figure 1** and **Figure 2**; available at www.jpeds.com).

Two models were created: (1) using all subjects meeting cohort inclusion criteria (hereafter "general population model") and (2) a subset of participants with HCV infection or opioid exposure in the last 30 days (hereafter "high-risk model"), based on prior work identifying these 2 factors as likely to be associated with greater risk for NAS.[5,16] We prespecified a full model that included the main effects for all potential predictors as well as 2-way interactions for maternal smoking by opioid exposure and gabapentin use by opioid exposure. We used backward selection to remove covariates that resulted in an improvement in the Akaike information criterion and arrived at a final, parsimonious model. Predictors requiring multiple degrees of freedom were removed as a group. Bootstrapping was used for both the model selection process and cross-validation (a double bootstrap) to obtain unbiased estimates of prediction fit statistics (eg, area under the curve). Additionally, we considered different penalty functions to allow for shrinkage estimation of regression coefficients, but saw no improvement in fit so report results with no penalty and no shrinkage. This process, selecting covariates a priori, double bootstrapping with different penalty functions to validate the predictive accuracy of the proposed model, reapplying the backward selection process with the validation and calibration statistics estimated at multiple iterations, exploring different penalty functions to allow for shrinkage estimation of the regression coefficients, mitigates common problems with a traditional backwards selection approach. The final prediction models were evaluated for their ability to discriminate subjects with low- and high-risk for NAS. Calibration plots of the observed vs predicted probability plots were used to internally validate the accuracy of predictions. Because the incidence of NAS increased over time in Tennessee much like rest of the US, we evaluated the interaction of Time × Covariates, but process this did not change model performance and was not included. Last, we created predicted probabilities using the high-risk model to demonstrate how common clinical scenarios influence an

infant's risk of NAS. Caution should be taken when interpreting predicted probabilities that are high because this model is not well-calibrated at the high end of risk. All analyses were conducted using the R statistical program using the "rms" package for developing and validating multivariable prediction models.[17]

Results

Between 2009 and 2014, a total of 218 020 maternal and infant dyads met inclusion criteria, of whom 3208 were diagnosed with NAS. Infants diagnosed with NAS had lower median birthweights (3204 g vs 2968 g), were more likely to be small for gestational age (34% vs 18%), and more likely to be female (44% vs 49%). Mothers of infants with NAS were older (26 years vs 23 years), were more likely to have evidence of HCV infection (15% vs 1%), had higher days use of MOUD compared with immediate release opioids, smoked more median numbers of daily cigarettes (8 vs 0), and were more likely to use benzodiazepines (2% vs 0%), antipsychotics (2% vs 0%), selective serotonin reuptake inhibitors (7% vs 2%), and bupropion (2% vs 0%; all comparisons <0.01; **Table II**). Relationships were similar among the high-risk cohort (ie, restricted to infants exposed to opioid and exposed to HCV) (**Table III**). Variable relationships were evaluated, including collinearity (**Figure 3**; available at www.jpeds.com).

General Population Model

Model variables for the general population included maternal characteristics, age, HCV status, days of opioid used by type (immediate release, sustained release, and MOUD) in the final 30 day of pregnancy, maternal smoking, number of cigarettes used daily, and use of the following medications in the last 30 day of pregnancy: bupropion, antinausea medicines, benzodiazepines, antipsychotics, and gabapentin. Infant characteristics included birthweight, small for gestational age, and infant sex (**Figure 4**, A). The model performed well, with an area under the curve of 0.89 (**Figure 5**, A) and was well-calibrated for infants with a risk of less than 40%. However, the model was less well-calibrated at higher risks, consistently underestimating infant risk for this subset of the cohort (**Figure 5**, A, b). Additional data on model covariates can be found in **Figure 6** (available at www.jpeds.com).

Table II. General population model: maternal and infant characteristics associated with NAS

Characteristics	No diagnosis of NAS (n = 214 812)	NAS (n = 3208)	*P* value
Infant characteristics			
Birthweight (g)	3204 (2870-3535)	2968 (2620-3289)	<.001
Gestational age (wk)	39 (38-40)	39 (38-40)	<.001
Small for gestational age	18 (38 711)	34 (1078)	<.001
Female	49 (104 908)	44 (1425)	<.001
Maternal characteristics			
Maternal age (y)	23 (20-27)	26 (23-29)	<.001
HCV positive	1 (1410)	15 (480)	<.001
Medication exposures in last 30 days of pregnancy			
Immediate-release opioid (d)	0 (0-0)	0 (0-0)	<.001
Sustained-release opioid (d)	0 (0-0)	0 (0-0)	<.001
MOUD (d)	0 (0-0)	0 (0-18)	<.001
Benzodiazepine	0 (331)	2 (67)	<.001
Antipsychotics	0 (739)	2 (58)	<.001
Selective serotonin reuptake inhibitor	2 (4338)	7 (226)	<.001
Zolpidem	1 (3111)	2 (76)	<.001
Bupropion	0 (850)	2 (57)	<.001
Reflux and antinausea	7 (15 646)	15 (481)	<.001
No. of cigarettes per day	0 (0-0)	8 (0-13)	<.001

Values are median (IQR) or percent (n). Medication data are obtained from filled prescriptions.

Table III. High-risk model: maternal and infant characteristics associated with NAS among infants exposed to opioids or hepatitis C

Characteristics	No diagnosis of NAS (n = 14 884)	NAS (n = 1446)	*P* value
Infant characteristics			
Birthweight (g)	3119 (2770-3430)	3005 (2665-3306)	<.001
Gestational age (wk)	39 (38-39)	39 (38-40)	.13
Small for gestational age	22 (3214)	32 (457)	<.001
Female	49 (7306)	44 (637)	<.001
Maternal characteristics			
Maternal age	25 (21-28)	26 (23-30)	<.001
HCV positive	2 (295)	16 (237)	<.001
Medication exposures in last 30 days of pregnancy			
Immediate-release opioid (d)	4 (2-10)	0 (0-3)	<.001
Sustained-release opioid (d)	0 (0-0)	0 (0-0)	<.001
MOUD (d)	0 (0-0)	22 (0-30)	<.001
Benzodiazepine	1 (125)	4 (55)	<.001
Antipsychotics	1 (122)	2 (26)	<.001
Selective serotonin reuptake inhibitor	5 (705)	8 (120)	<.001
Zolpidem	5 (764)	3 (41)	<.001
Bupropion	1 (136)	2 (24)	.006
Reflux and antinausea	26 (3920)	22 (324)	.001
No. of cigarettes per day	0 (0-8)	10 (0-13)	<.001

Values are median (IQR) or percent (n).

High-Risk Model

Model variables for the high-risk model included female sex, birthweight, gestational age, maternal age, maternal HCV infection, and the following variables related to maternal medication use in the 30 days before delivery: days of opioid use by type (immediate-release opioid, sustained-release opioid, or MOUD opioid), any benzodiazepine, and any gabapentin used (**Figure 4**, B). The model performed well, with an area under the curve of 0.89 (**Figure 5**, B, a) and, compared with the model in the full cohort, was better calibrated at the extremes of risk (**Figure 5**, B, b). Additional data on model covariates can be found in **Figure 7** (available at www.jpeds.com).

Model Application: High-Risk Model

To illustrate clinical model performance, we applied 2 distinct hypothetical clinical scenarios. Keeping other factors

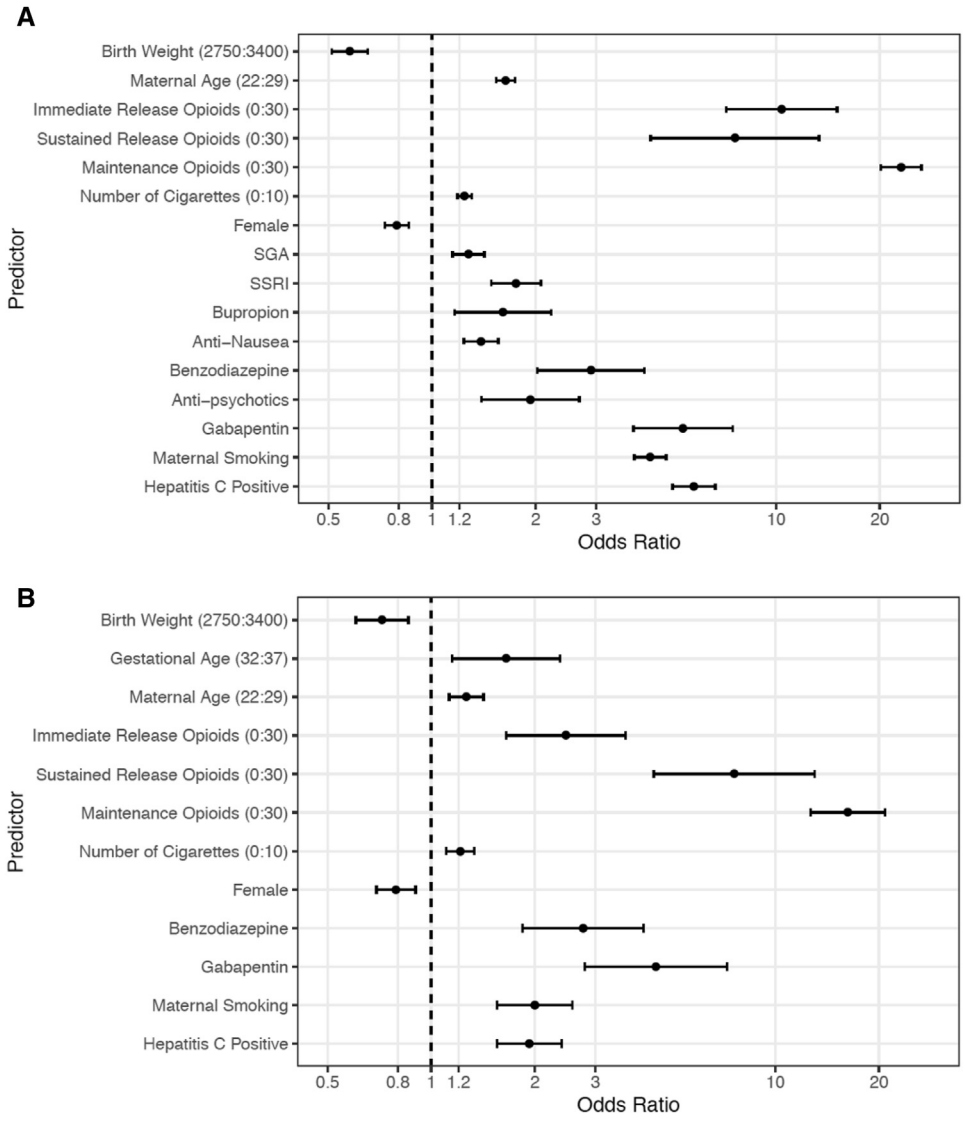

Figure 4. Factors associated with NAS risk in the **A,** general and **B,** high-risk population models. SGA, small for gestational age; SSRI, selective serotonin reuptake inhibitor.

constant, for every hypothetical patient A was exposed to 14 days of an immediate release opioid (eg, hydrocodone) in the last 30 days of pregnancy with an estimated NAS risk of 2.5% (95% CI, 1.6%-3.5%). In contrast, for every hypothetical patient B was exposed to 30 days of a MOUD opioid and also exposed to gabapentin, a benzodiazepine, and a pack of cigarettes a day with an estimated NAS risk of 87.8% (95% CI, 81.1%-94.6%). Additional predicted probabilities applying the high-risk model are in **Table IV** (available at www.jpeds.com). Model data and an interactive web tool for the clinical model can be found at: www.childpolicy.org/NASrisk.

Discussion

Using data from more than 200 000 maternal-infant dyads, we developed and validated 2 models using data available at the time of delivery that could be used to risk stratify infants exposed to opioids at the time of birth. Currently, an estimated 30 000 infants are diagnosed with NAS each year[2]; however, this number does not include the infants exposed to opioids who do not develop clinical features of withdrawal severe enough to be diagnosed with NAS. Similar to previous work, only a minority of infants exposed to opioids in this study were diagnosed with the syndrome.[5,8] Taken together, this finding suggests that there potentially tens of thousands of low-risk infants exposed to opioids who spend extended periods of time being observed in hospitals with marginal health benefit. Furthermore, excess observation may lead to separation of the maternal-infant dyad and cost to the healthcare system. Using clinically available details to tailor postnatal care based upon an individual infant's risk of developing NAS has the potential to be both more efficient

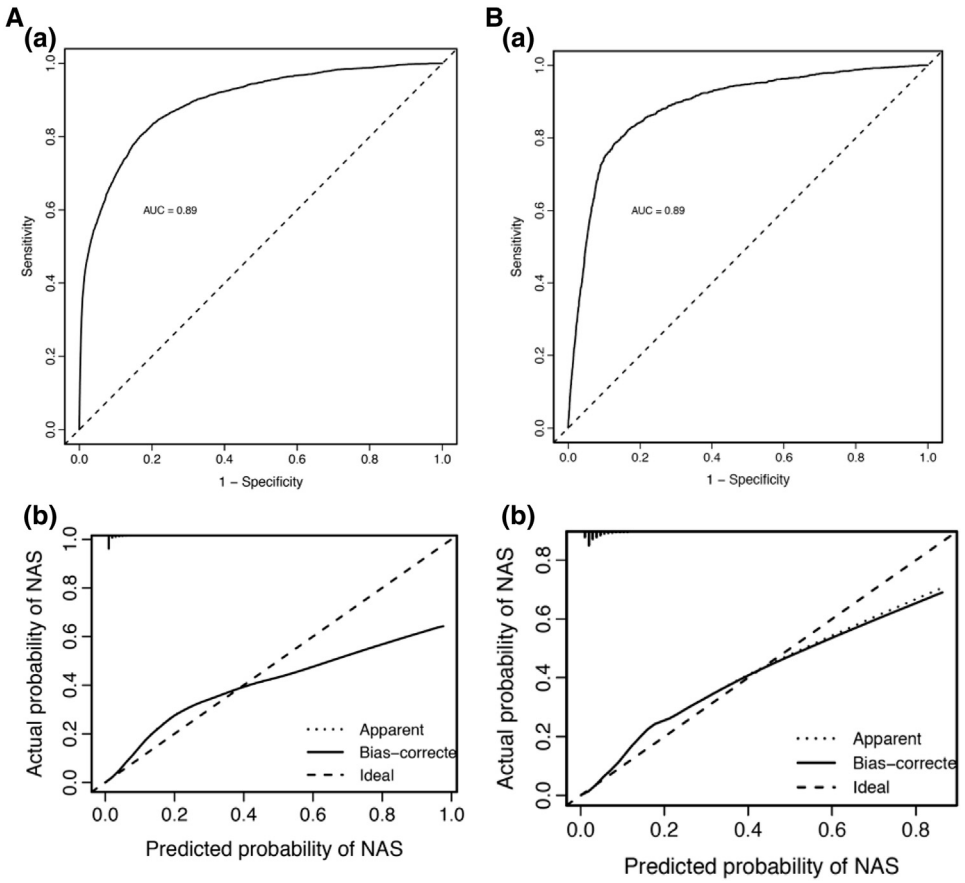

Figure 5. **A,** General population model cohort. (a) Discrimination and (b) calibration characteristics. **B,** High-risk model. (a) Discrimination and (b) calibration characteristics.

and result in less disruptive care for the maternal-infant dyad.

In both of our models, and similar to previous research, we found lower birthweight and female sex protected against developing the syndrome.[7,13,18] In addition, we found several maternal medications increased the risk of a diagnosis of NAS. Even though MOUD, including buprenorphine, improve pregnancy outcomes by decreasing the risk of preterm birth and overdose death, they come with an increased risk of drug withdrawal, which has been described in the literature.[5,19,20] Additional exposures, including selective serotonin reuptake inhibitors, antipsychotics, benzodiazepines, gabapentin, and maternal cigarette use have also been associated with development of NAS and with NAS severity.[5,7,16,18] However, data suggesting an association with bupropion and antinausea medications (eg, metoclopramide) with NAS risk are sparse. We speculate that metoclopramide's mechanism of action, antagonizing central dopamine receptors, in combination may increase NAS risk; however, this association and the proposed mechanism merit additional research.

The American Academy of Pediatrics suggests that all infants exposed to opioids be observed for 3-7 days after birth to monitor for development of NAS.[6] For infants at low risk of developing the syndrome who are exposed to licit opioids, this observation period may be disruptive and undesirable, resulting in excess use of hospital resources and possible separation of the maternal-infant dyad if care is delivered in a neonatal intensive care unit.[21] Our study suggests that, by using clinically available data at the time of birth, infants exposed to opioids can be risk stratified, potentially improving care. However, applying these data to tailor observation periods should be done in the setting of close postdischarge monitoring or a clinical trial. There could be unintended consequences of premature discharge, including hospital readmission.[22] Further, for families who received no or limited prenatal care before birth, the hospitalization period can serve as an ideal time to engage families in important postdischarge services, including potential addiction treatment for the mother.

Our study has a number of limitations. First, as with all clinical prediction tools, this NAS predictive tool may not perform as well among different populations when validated. Next, our data were obtained from Medicaid-enrolled maternal-infant dyads. Although Medicaid is financially responsible for more than 80% of NAS births nationwide, our findings may not be generalizable to privately insured dyads.[2] Although we performed a robust internal validation of our model, the model should be validated in an external population and recalibrated before it is considered for use in additional settings. We note that our general population models are not well-calibrated for high-risk infants; therefore, in their present form they may serve best to discriminate low-risk infants. We used data from filled prescriptions to estimate infant risk; however, it is possible that despite prescriptions being filled pregnant women did not take medications. Although our study included data from filled prescriptions, clinicians may not have these data available, instead having to rely on medical history taking to obtain these data, perhaps influencing the applicability of our model. This study focuses on infants exposed to medically prescribed opioids and may not be generalizable to infants exposed to illicit opioids. We could not assess differences in NAS risk between methadone and buprenorphine because methadone was not covered by TennCare for opioid use disorder during our study period. Importantly, a clinical trial found that, although methadone increased NAS severity, there was no difference in NAS incidence, which is the primary outcome in our study.[23] Future studies should evaluate differences between NAS risk among different MOUD.

We developed 2 parsimonious clinical prediction rules for the development of NAS that effectively discriminate between infants at high and low risk of developing NAS. Although future work is required to validate the clinical utility of this prediction rule, application of such a tool has the potential to limit excess hospital use among low-risk infants exposed to opioids nationwide. ■

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Reprint requests: Stephen W. Patrick, MD, MPH, Vanderbilt Center for Child Health Policy, 2525 West End Ave, Suite 1200, Nashville, TN 37203. E-mail: stephen.patrick@vanderbilt.edu

Data Statement

Data sharing statement available at www.jpeds.com.

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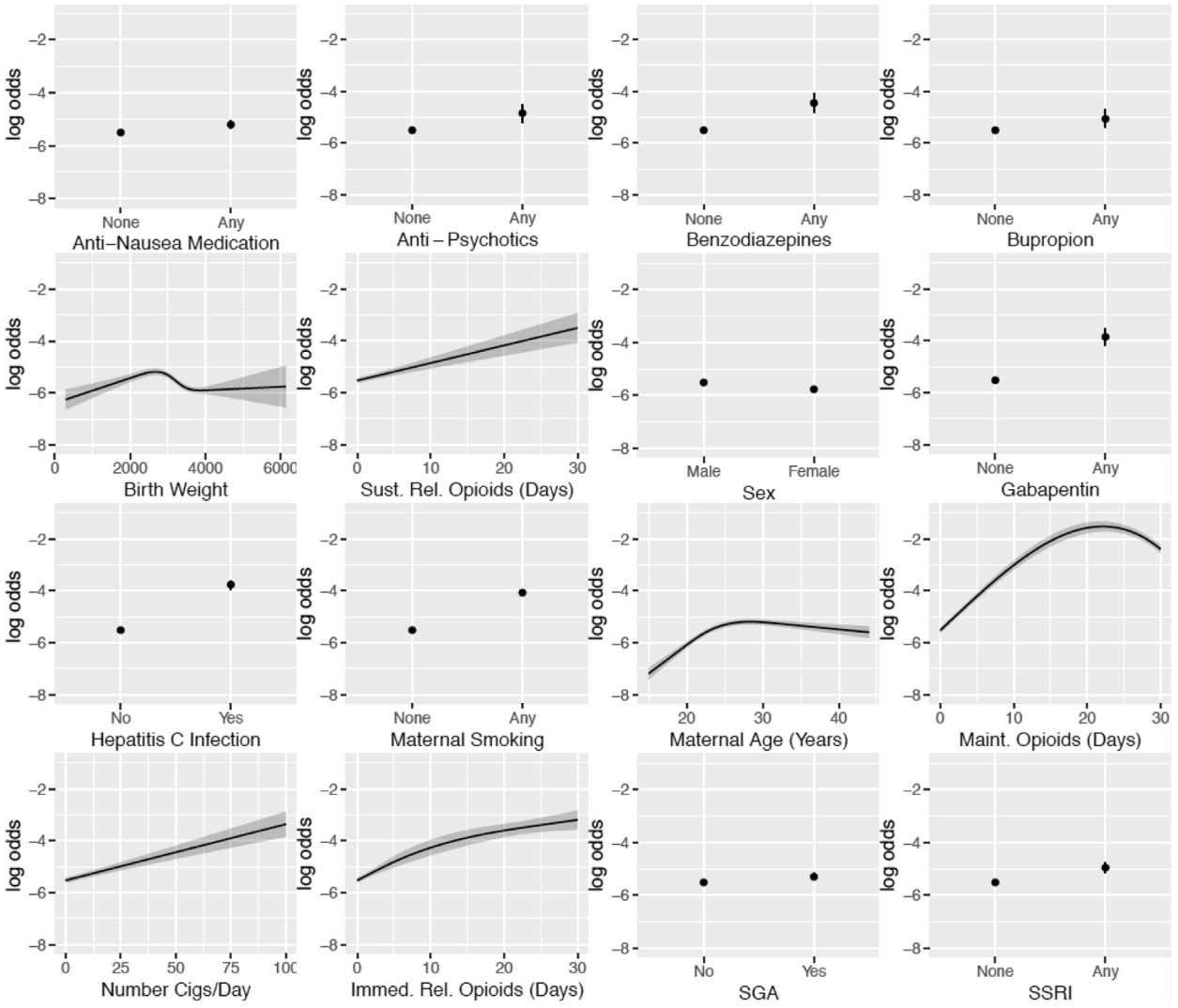

Figure 1. General population model partial effects plots. *Cigs*, cigarettes; *Immed. Rel.*, immediate release; *Maint.*, maintenance; *Sust. Rel.*, sustained release.

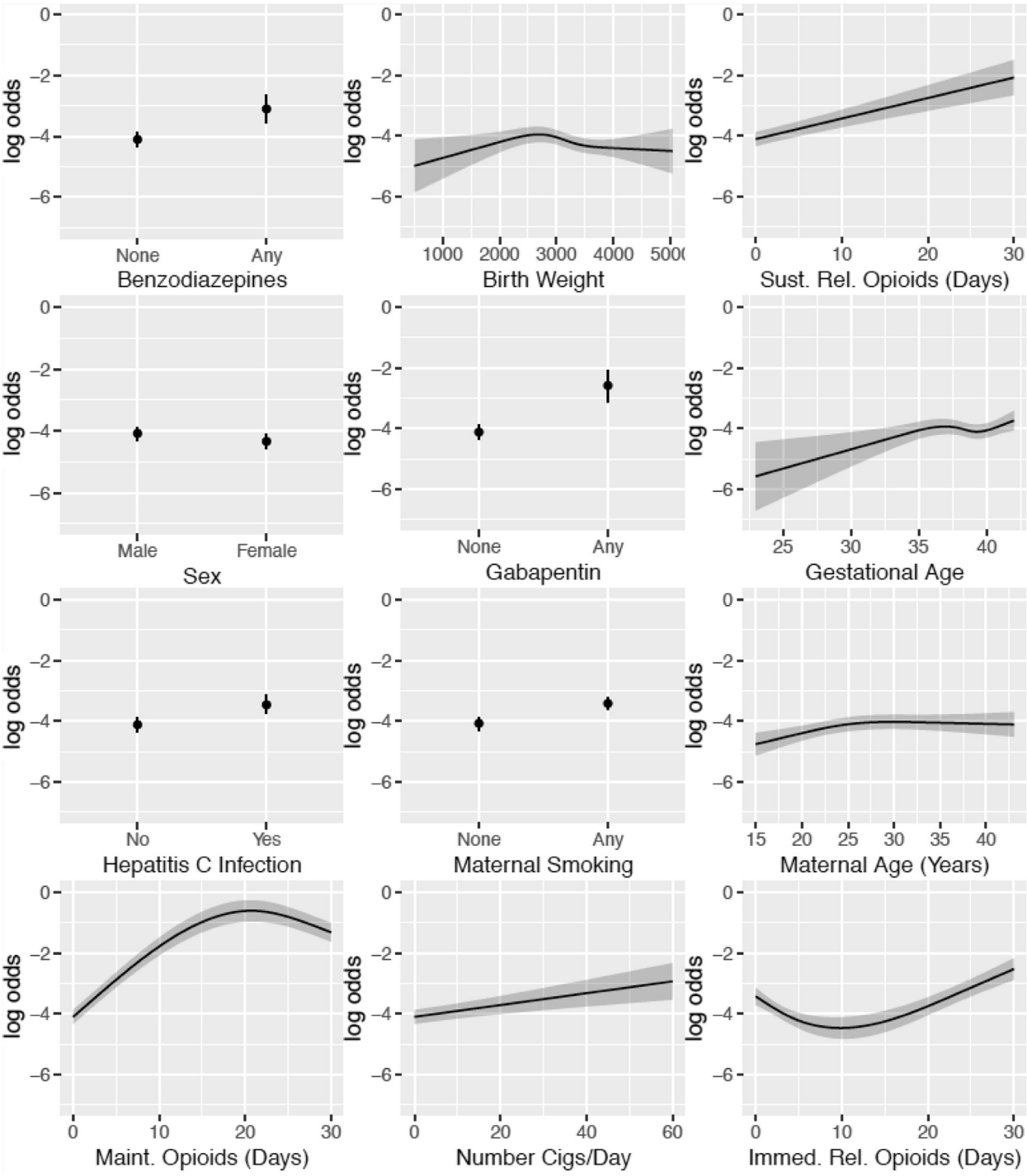

Figure 2. High-risk model partial effect plots.

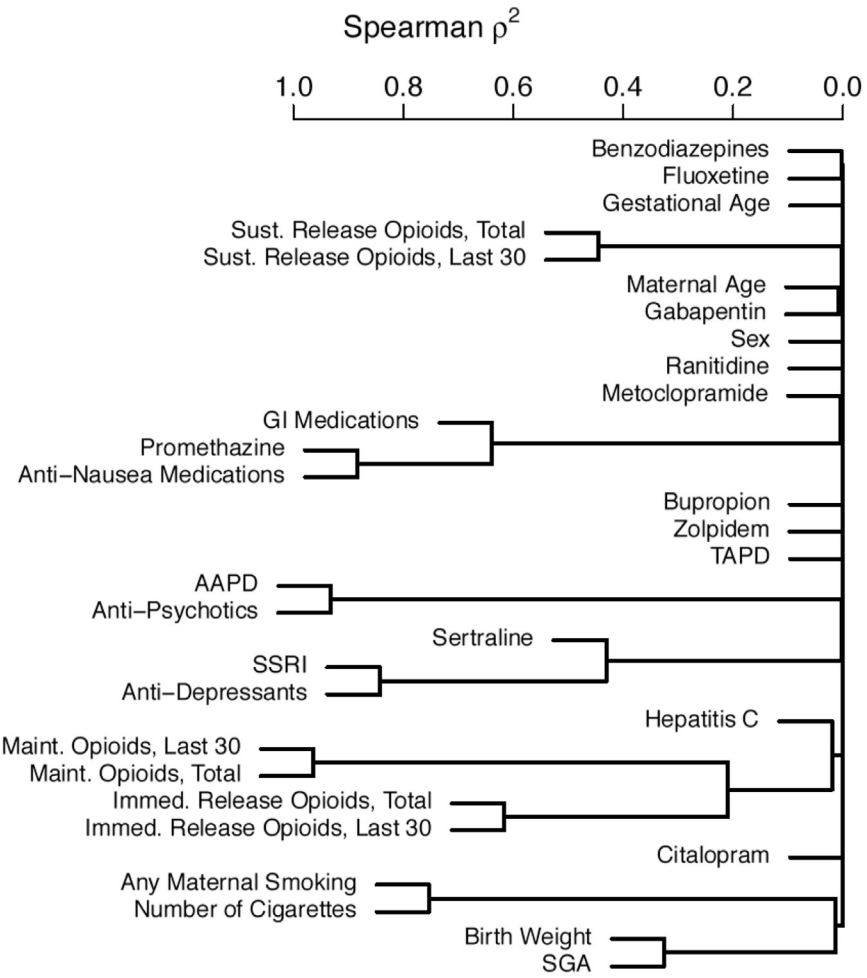

Figure 3. Relationships of model predictors. *AAPD*, atypical antipsychotic drug; *GI*, gastrointestinal; *SGA*, small for gestational age; *SSRI*, selective serotonin reuptake inhibitor; *SUST.*, sustained; *TAPD*, typical antipsychotic drug.

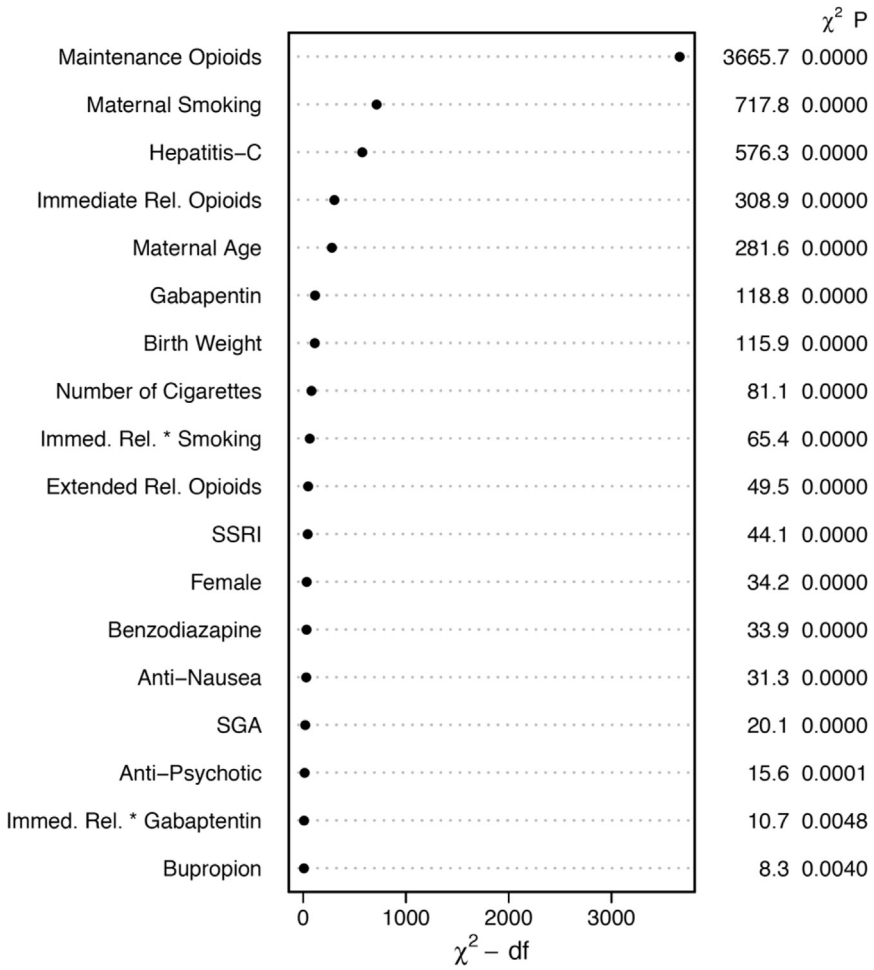

Figure 6. General population model relative contribution of each covariate to the final model using the relative χ^2. *Dot charts depicting the importance of variables in the prediction model based on clinical predictors, as measured by Wald χ^2 and χ^2 minus degrees of freedom. Statistics are provided for main effects and 2-way interactions (represented as A * B) with *P* values calculated using separate multiple degree of freedom chunk tests. *Immed. Rel.*, immediate release; *SGA*, small for gestational age; *SSRI*, selective serotonin reuptake inhibitor.

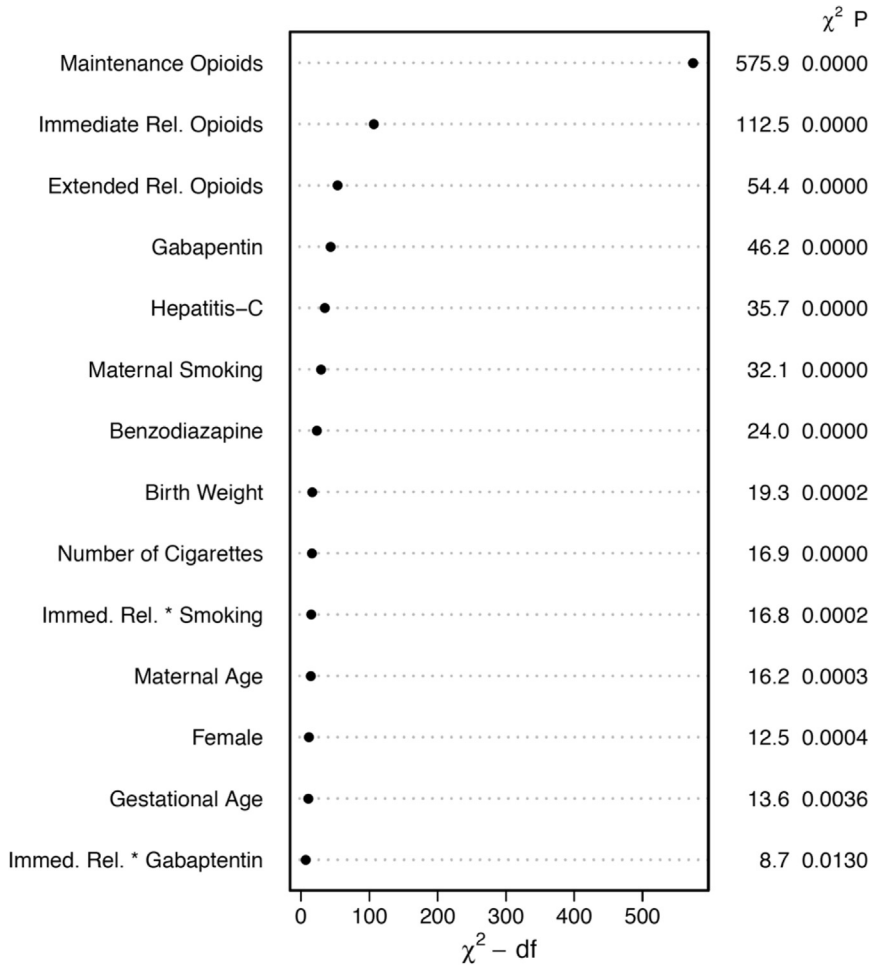

Figure 7. High-risk model relative contribution of each covariate to the final model using the relative χ^2. *Dot charts depicting the importance of variables in the prediction model for high risk patients, as measured by Wald χ^2 and χ^2 minus degrees of freedom. Statistics are provided for main effects and 2-way interactions (represented as A * B) with *P* values calculated using separate multiple degree of freedom chunk tests. *Immed. Rel.*, immediate release.

Table I. Included benzodiazepines, atypical antipsychotics, and typical antipsychotics

Medication classes	Medications
Benzodiazepines	Alprazolam, bromazepam, chlordiazepoxide hydrochloride, clonazepam, clorazepate dipotassium, diazepam, estazolam, flurazepam, halazepam, lorazepam, midazolam hydrochloride, oxazepam, prazepam, quazepam, temazepam, triazolam
Atypical antipsychotics	Aripiprazole, asenapine, clozapine, fluoxetine-olanzapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone-inj, risperidone-oral, ziprasidone
Antipsychotics	Carphenazine, chlorpromazine hydrochloride, chlorprothixene, droperidol, fluphenazine decanoate, fluphenazine enanthate, fluphenazine hydrochloride, haloperidol, haloperidol decanoate, loxapine succinate, mesoridazine besylate, molindone hydrochloride, perphenazine, pimozide, piperacetazine, thioridazine, thiothixene hydrochloride, trifluoperazine hydrochloride, trifluprom azine hydrochloride
Antidepressants	Fluoxetine, sertraline, citalopram, bupropion
Medications for acid reflux and nausea	Metoclopramide, ranitidine, promethazine

Table IV. Predicted probabilities of high-risk using different clinical scenarios among infants exposed to 14 days of an immediate release opioid and a MOUD in the last 30 days of pregnancy

Models	14 Days immediate release opioid	30 Days MOUD
No additional exposures	2.5 (1.6-3.5)	46.5 (40.0-53.0)
Gabapentin	11.4 (3.6-19.1)	61.8 (50.0-73.7)
No cigarettes		
No benzodiazepines		
Gabapentin	33.8 (17.8-49.8)	69.6 (59.3-80.0)
10 Cigarettes per day		
No benzodiazepines		
Gabapentin used	54.4 (34.3-74.5)	84.2 (75.9-92.5)
10 cigarettes per day Benzodiazepines		
Gabapentin	61.7 (42.5-81.0)	87.8 (81.1-94.6)
20 cigarettes per day		
Benzodiazepines used		

Values are percent (95% CI). Predicted probabilities calculated used predicted marginal means. Caution should be taken when interpreting predicted probabilities that are high because this model is not well-calibrated at the high-end of risk.