Protocol for the development and validation of a risk prediction model for stillbirths from 35 weeks gestation in Australia

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Protocol

Keywords: fetal death, stillbirth, prediction, prognostic, risk, obstetrics, perinatal, AUROC

Posted Date: March 10th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-16494/v1

Version of Record: A version of this preprint was published on December 16th, 2020. See the published version at https://doi.org/10.1186/s41512-020-00089-w.

Abstract

Background Despite advances in the care of women and their babies in the past century, an estimated 1.7 million babies are born still each year throughout the world. A robust method to estimate a pregnant woman's individualized risk of late-pregnancy stillbirth is needed to inform decision-making around timing of birth to reduce the risk of stillbirth from 35 weeks gestation.

Methods This is a protocol for a retrospective cohort study of all late-pregnancy births in Australia (1998-2015) from 35 weeks gestation including 7,200 stillbirths among 4.9 million births at an estimated rate of 1.47 stillbirths per 1000 live births. A multivariable logistic regression model will be developed in line with current T ransparent R eporting of a multivariable prediction model for I ndividual P rognosis or D iagnosis (TRIPOD) guidelines to estimate the gestation-specific probability of stillbirth with prediction intervals. Candidate predictors were identified from systematic reviews and clinical consultation and will be assessed through univariate regression analysis. To generate a final model, elimination by backward stepwise logistic regression will be performed. The model will be internally validated using K-fold cross-validation and externally validated using a geographically unique dataset. Overall model performance will be assessed with R 2 in addition calibration and discrimination. Calibration will be visualized using a calibration plot. Discrimination will be measured by the C- statistic and visualized using area underneath the receiver-operator curves (AUROC). Clinical usefulness will be reported as positive and negative predictive values and a decision curve analysis will be considered.

Discussion A robust method to predict a pregnant woman's individualized risk of late-pregnancy stillbirth is needed to inform timely, appropriate care to reduce stillbirth. Among existing prediction models designed for obstetric use, few have been subject to internal and external validation and many fail to meet recommended reporting standards. In developing a risk prediction model for late-gestation stillbirth with both providers and pregnant women in mind, we endeavor to develop a validated model for clinical use in Australia that meets current reporting standards.

Background

Prevention of stillbirth remains one of the greatest challenges in modern maternity care. Globally, one in every 137 pregnancies that reach 20 weeks' gestation will result in stillborn child (1, 2). Despite advances in the care of women and their babies in the past century, an estimated 1.7 million babies die before birth each year throughout the world (3). The 2016 Lancet Ending Preventable Stillbirths series highlighted differences in rates of late stillbirth (≥ 28 weeks) between high-income countries ranging from 1.7 per 1,000 to 8.8 per 1,000 births (4). In Australia, over 2,000 families each year – six families each day – have a stillbirth, and there has been no improvement in stillbirth rates among late pregnancy stillbirths for over 20 years (5). Among women who were born elsewhere (6, 7), women with lower socioeconomic status (8), and women who identify as Aboriginal and Torres Strait Islander (9), the risk of stillbirth is higher (4, 10). Failure to identify and appropriately care for women with risk factors for stillbirth contributes to 20–50%

of preventable stillbirths, which has potential to avoid 400 stillbirths each year for Australian families (11–13).

Detecting women at risk for stillbirth is challenging. In the absence of a tool to assess a pregnant woman's individualized risk of late-pregnancy stillbirth, we rely on generalized, population-level information. Awareness of risk factors that increase the risk of stillbirth at or near term is a necessary first step in improving care and to ultimately reduce the number of stillbirths. Despite a high proportion of unexplained stillbirths between 39–41 weeks gestation, many women who have a stillbirth have one or more risk factors that are often unrecognized (14).

Around 38 weeks gestation, the risk of stillbirth increases overall and varies by maternal and clinical characteristics while the decision on whether or not to intervene becomes more challenging (5, 9, 15, 16). The balance between benefit and harm is complicated by potentially avoiding a stillbirth at the risk of neonatal morbidity (17). Following 35 weeks gestation, the rate of stillbirth increases overall and varies by maternal and clinical characteristics A robust prediction model to assess a woman's individualized risk of late-pregnancy stillbirth has potential to alleviate some interventional uncertainty by informing antenatal care and decision-making around intervening in timing of birth.

A key limitation of developing a late-gestation stillbirth risk prediction model for clinical use is the lack of high-quality data from a complete population. With recent quality improvements for population-level data in Australia, it is now possible to leverage population-based data to develop, internally validate, and externally validate a model to predict potentially preventable and rare pregnancy outcomes (18). Therefore, the objective of this study is to develop and validate a prognostic model for late-pregnancy stillbirth risk that is designed to inform decision-making around timing of birth.

Methods

Aim

We endeavor to develop a multiple logistic regression prediction model to estimate risk of late-pregnancy stillbirth from 35 weeks using a national dataset of all births in Australia to ultimately inform decision-making around timing of birth.

Study design

This is a protocol for a retrospective cohort study using the total population of singleton term gestation births in Australia (1998–2015) included in the National Perinatal Data Collection (NPDC)(10). The dataset includes 7,200 stillbirths among 4.9 million births at an estimated rate of 1.47 stillbirths per 1000 births (10). Multiple pregnancies and congenital abnormalities will be excluded. A congenital abnormality is defined as a stillbirth classified as code 0100 "Congenital Abnormality" using the Perinatal Society of Australia and New Zealand (PSANZ) Perinatal Death Classification System (19). Candidate predictors

identified in a meta-analysis and through clinical consultation will be assessed for inclusion in the full model to ensure adjustment prior to reverse stepwise elimination.

Data source

All births from 35 weeks gestation in Australia (1998–2015) included in the NPDC will be included and made available via the AIHW Maternal and Perinatal Health Unit. The NPDC is a national population-based cross-sectional collection of data for all pregnancies and births established in 1991 (20). The NPDC includes all births from the 6 states and 2 territories of Australia. Perinatal data are collected for each birth in each state and territory, usually by midwives and other birth attendants (10). The data is collated by the relevant state or territory health department and a standard de-identified extract is provided to the AIHW on an annual basis to form the NPDC (10). Stillbirths in Australia are defined by the PSANZ as fetal deaths from gestational age of at least 20 weeks or birthweight of at least 400 grams, except in Victoria and Western Australia, where births are included if gestational age is at least 20 weeks or, if gestation is unknown, birthweight is at least 400 grams (10, 19).

Model development

A multiple logistic regression model will be developed where the outcome (stillbirth) is binary and the independent variables are either continuous or categorical. Reference group coding will be informed by literature and existing reporting recommendations. Descriptive statistics will be used to characterize the study cohort and illustrate censoring and survivability throughout gestation.

The predictor selection process is illustrated in Fig. 1. Previous meta-analyses have established characteristics and conditions associated with an increased risk of stillbirth that will be considered as candidate predictors (15, 21–23). Frequencies (%) will be presented for categorical variables and mean/standard deviation, median/interquartile range (IQR), minimum, and maximum will be presented for continuous (numerical) variables. If clinically appropriate and statistically justifiable, independent continuous variables will be logically grouped according to published guidelines and recommendations (10, 24).

We will first fit a multivariable logistic regression model containing all candidate predictors (Table 1). Clinical background knowledge and existing meta-analyses will further inform variable selection for the final model. In addition, reverse stepwise elimination will be explored to remove non-significant factors with P-values greater than 0.100 in line with Akaike's Information Criterion (25). Redundant variables demonstrating multi- or collinearity will be logically excluded through clinical consultation. Single value imputation will be considered for predictors with greater than 5% missing values or will be excluded. To alleviate risk of bias in the model, no births will be excluded due to missing data.

Table 1

Original dataset characteristics of candidate predictors for all births in Australia, 1998–2015.

Candidate predictor	Reported value	Reported label
Model of care (mother insurance status)	1	Public
	2	Private
	8	Not applicable (e.g., home birth)
	Missing	Jurisdiction did not provide any data
	9	Not stated
Hospital sector	1	Public
	2	Private
	8	Not applicable (e.g., home birth)
	Missing	Jurisdiction did not provide any data
	9	Not stated
Maternal age in years	< 19	Less than 19
	19–44	Single values
	>=45	45 and over
	99	Not stated
Maternal Indigenous status	1	Indigenous - Aboriginal and/or Torres Strait Islander
	2	Non-Indigenous
	Missing	Jurisdiction did not provide any data
	9	Not stated
Maternal country of birth	ASCSS, SACC codes	ASCSS, SACC 1st edition, SACC 2nd edition, SACC 2011 or pre-arranged groupings
Pre-existing diabetes during pregnancy	0	None/not stated
	1	Pre-existing diabetes
	Missing	Jurisdiction did not provide any data
Gestational diabetes	0	None/not stated
	1	Pre-existing diabetes

Candidate predictor	Reported value	Reported label
	2	Gestational diabetes mellitus (GDM)
	Missing	Jurisdiction did not provide any data
Chronic hypertension during pregnancy	0	None/not stated
	1	Chronic hypertension
	Missing	Jurisdiction did not provide any data
Maternal medical conditions: Essential hypertension	0	None/not stated
	1	Gestational hypertension
	Missing	Jurisdiction did not provide any data
2006 Socio-Economic Indexes for Areas (SEIFA) Index of Relative Socio-Economic Disadvantage (IRSD)	1	Quintile 1 (most disadvantaged)
	2	Quintile 2
	3	Quintile 3
	4	Quintile 4
	5	Quintile 5 (least disadvantaged)
	9	Not stated
2011 Socio-Economic Indexes for Areas (SEIFA) Index of Relative Socio-Economic Disadvantage (IRSD)	1	Quintile 1 (most disadvantaged)
	2	Quintile 2
	3	Quintile 3
	4	Quintile 4
	5	Quintile 5 (least disadvantaged)
	Missing	Jurisdiction did not provide any data
	9	Not stated
Remoteness Area as per the Australian Standard Geographical Classification (ASGC)	0	Major cities
	1	Inner regional
	2	Outer regional
	3	Remote
	4	Very remote
	Missing	Jurisdiction did not provide any data

Candidate predictor	Reported value	Reported label
	9	Not stated
Remoteness Area as per the Australian Statistical Geography Standard (ASGS)	0	Major cities
	1	Inner regional
	2	Outer regional
	3	Remote
	4	Very remote
	Missing	Jurisdiction did not provide any data
	Blank	Not able to be assigned, non-Australian resident and not stated
Marital status	1	Never married
	2	Widowed, divorced, separated
	3	Married (including de facto)
	Missing	Jurisdiction did not provide any data
	9	Not stated
Total number of previous pregnancies resulting in a livebirth or a stillbirth	0–4	Single values
	>=5	5 and over (grouped)
	Missing	Jurisdiction did not provide any data
	9	Not stated
Previous caesarean sections	0–4	Single values
	>=5	5 and over (grouped)
	Missing	Jurisdiction did not provide any data
	9	Not stated
Caesarean section for last birth	1	Yes
	2	No
	7	Not applicable
	Missing	Jurisdiction did not provide any data
	9	Not stated

Candidate predictor	Reported value	Reported label
Previous pregnancies resulting in stillbirths	0–1	Single values
	>=2	2 and over (grouped)
	Missing	Jurisdiction did not provide any data
	9	Not stated
Smoking status during pregnancy	1	Smoked
	2	Did not smoke
	Missing	Jurisdiction did not provide any data
	9	Not stated
Smoking status during first twenty weeks of pregnancy	1	Smoked
	2	Did not smoke
	Missing	Jurisdiction did not provide any data
	9	Not stated
Smoking status after twenty weeks of pregnancy	1	Smoked
	2	Did not smoke
	Missing	Jurisdiction did not provide any data
	9	Not stated
Pre-pregnancy Body Mass Index (BMI)	≥ 9.0	Continuous values rounded to the nearest 5 kg/m2
	Missing	Jurisdiction did not provide any data
	99.9	Not stated
Plurality	1–8	Single values
	9	Not stated
Assisted reproduction technology flag	0	No
	1	Yes
	missing	Jurisdiction did not provide any data
	9	Not stated
Baby's birth order	1–8	Single values

Candidate predictor	Reported value	Reported label
	9	Not stated
Baby's sex	1	Male
	2	Female
	9	Indeterminate and not stated

Validation

A geographic validation approach will be considered whereby gestation-specific models will be developed using eight combinations of jurisdictionally grouped data for internal and external validation (Fig. 2). Population characteristics and performance measures will be reported for all individual models (26).

Internal validation

Internal validation will be performed using a cross-validation approach (100- or 200-fold) on all birth data for respective population groups per Fig. 1 where we anticipate greater than 100 events per predictor for populations exceeding 5000 stillbirths (27). Summary stillbirth rates will be reported to characterize fluctuating stillbirth prevalence across folds.
External validation

Final models will be externally validated using data derived from the excluded jurisdictions (28). Assessment of performance will include calibration, discrimination, positive predictive value (PPV), and negative predictive value (NPV).

Model performance

The performance of development and validation datasets will be assessed via overall performance (R^2), calibration, discrimination, and clinical usefulness (PPV and NPV).

Calibration characterizes model performance in terms of agreement between predicted (expected) risk and observed risk and be visualized using a calibration plot (29). An intercept of zero and ratio of observed and expected equal to one (O/E = 1) is defined as best possible calibration (30). Confidence intervals (95%) will be prepared alongside calibration plots to visualize the degree of calibration between observed outcomes and predictions.

Discrimination is defined as the model's ability to distinguish stillbirths and non-stillbirths and will be measured via calculation of the concordance (C) statistic and visualized with a receiver operator characteristic (AUROC) curve. An AUROC curve is used to visualize the performance of a categorical classifier and is a plot of sensitivity (true positive rate) versus 1-specificity (false positive rate) where different points on the curve correspond to different cut-off points used to designate positive

identification/classification. (31). Using the AUROC curve, the performance of the predictors will be further quantified by calculating the area under the curve, or AUC. The AUC score range is 0.0–1.0, where a score of 0.5 can be equated to a 'coin flip,' 0.0 is perfectly inaccurate, and 1.0 is perfectly accurate (32). A non-parametric comparison of AUC will be performed using the Mann-Whitney U-statistic for individual models (26).

In addition to calibration and discrimination, PPV and NPV will be reported to characterize clinical usefulness. A decision curve analysis will be considered to visualize potential decision thresholds (33).

Discussion

Prediction models designed for obstetrics hold enormous promise. However, unlike other clinical prediction models, we do not yet understand whether their application improves birth outcomes (34). With many models for adverse pregnancy outcomes being developed through various approaches, it is inevitable that only a minority have been subject to full internal and external validation and fail to meet recommended reporting standards. By utilizing a population-based, individual-level dataset, our study is expected to provide a sufficient sample size of stillbirths and livebirths to develop and validate gestation-specific prediction models that can be translated into clinical tools or decision aids.

There have been attempts to develop risk prediction models for stillbirth, yet none are designed to predict stillbirth risk at- or near-term or use a population-level data source (35). Among existing prediction models designed for obstetrics, logistic regression models are widely utilized (35). Yerlikaya et al. reported a prediction model for stillbirth with low predictive accuracy beyond the early term period (36). Trudell et al. reported a clinical prediction tool for antenatal testing with modest discrimination for stillbirth at or beyond 32 weeks' gestation that included risk factors such as maternal age, African-American/Black race, nulliparity, body mass index, smoking, chronic hypertension, and pre-gestational diabetes (37). Although there is growing interest in algorithmic methods such as machine learning, evidence suggests that performance is highly comparative to statistical modelling (38, 39). Regarding approaches to validation, the most commonly used methods include split-sample, bootstrap, and cross-validation. Bootstrapping tends to demonstrate increased variability and split-sampling often results in unreliable assessments of model performance. Cross-validation appears to be most appropriate for validating a prediction model for low-prevalence obstetric outcomes like stillbirth due to stability and ability to use a larger part of the study sample for model development (32, 40). Cross-validation is an extension of split-sample validation that uses a larger part of the sample for model development (> 80% vs. 50%) (29). While not the most computationally efficient approach, the repeated procedure is expected to produce stable results (41, 42). In our proposed validation design, a geographic approach to externally validate the model will be employed. While this is not considered a 'fully independent external validation,' it is expected to provide an additional layer of assessment not yet reported for any existing stillbirth prediction model.

While there are numerous benefits to utilizing large observational datasets for the development of prediction models – particularly for rare pregnancy outcomes, there are certain limitations (43).

Completeness of routinely reported variables and potentially relevant risk factors not captured by the NPDC, such as maternal ethnicity, will have an impact on the final model. Certain variables collected by NPDC that are not available for release due to quality issues include maternal asthma, type of assisted reproductive therapy, fetal growth restriction, and other pregnancy-specific medical conditions. Environmental exposures are not currently captured by the NPDC and other spatial risk factors cannot be explored due to sensitivity restrictions. However, many key risk factors identified in literature and nominated by clinicians will be included and are expected to produce a full prediction model for stillbirth using routinely collected data.

Lastly, subsequent pregnancy outcomes depend heavily on the outcome of previous pregnancies where each birth is not independent of births (44–46). An anticipated complication of our analysis that will impact interpretation of results is the absence of a unique identifier for mothers to account for potential clustering. Parity and birth order will be assessed to distinguish first versus subsequent births (47), but lack of independence of births in our models will be limited. There are recommendations for the generalized estimating equation approach, but will not be possible due to an inability to appropriately cluster pregnancies according to unique mothers (47, 48).

In developing a risk prediction model for late-gestation stillbirth with both providers and pregnant women in mind, we endeavor to develop a validated model for clinical use in Australia that meets all TRIPOD standards and recommendations (49). Such a prediction model could be used in a narrow or broad impact analysis that explores decision rules to reduce stillbirth by improving decision-making around timing of birth (33, 40).

Abbreviations

TRIPOD	Transparent Reporting of a multivariable logistic regression model for Individual Prognosis or Diagnosis
AIHW	Australian Institute of Health and Welfare
NPDC	National Perinatal Data Collection
AUROC	Area under the receiver-operator curve
HREC	Human research ethics committee(s)
PSANZ	Perinatal Society of Australia and New Zealand
NHMRC	National Health and Medical Research Council
ASGS	Remoteness Area as per the Australian Statistical Geography Standard
ASGC	Australian Standard Geographical Classification (ASGC)
SEIFA	Socio-Economic Indexes for Areas
IRSD	Index of Relative Socio-Economic Disadvantage

Declarations

Ethics approval and consent to participate

This study was jointly approved with a waiver of consent by the AIHW Ethics Committee (EO2018/2/451 “Stillbirths in Australia: An epidemiological study to identify and quantify stillbirth risk”) and Mater Research Human Research Ethics Committee (HREC) (HREC/15/MHS/36). Bilateral approvals were received from the following jurisdictions: Australian Capital Territory (2019/LRE/00011), Aboriginal Health Council (04-19-825), Northern Territory (2019-3306), Queensland Department of Health (EO2018/2/451), South Australia (HREC/19/SAH/28), and New South Wales Ministry of Health (H20/12350).

Consent for publication

A waiver of consent is justified and has been approved under all HREC jurisdictions involved in this study. In Australia, only an HREC may grant waiver of consent for research using personal information in medical research, or personal health information (50).

Availability of data and materials

Study outputs including full model details will be published in a peer-reviewed journal; however, the dataset is not publicly available due to sensitivity and individual privacy protection restrictions as stipulated by human research ethics. Study data can be accessed through a formal request from the AIHW (https://www.aihw.gov.au/our-services/data-on-request).

Funding and competing interests

This study is being undertaken as part of the existing strategic work under the National Health and Medical Research Council (“NHMRC”) Centre of Research Excellence in Stillbirth (“Stillbirth CRE”) at the University of Queensland – Mater Research Institute. The project has received funding from the National Health and Medical Research Council through the Centre for Research Excellence (GNT1116640). The authors declare no competing interests or conflicts of interest.

Authors’ contributions

VF conceived and JS developed the methods and wrote the protocol in consultation with MC, SK, and SL. All authors provided intellectual contributions to and approved the final version of this protocol manuscript.

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Figures

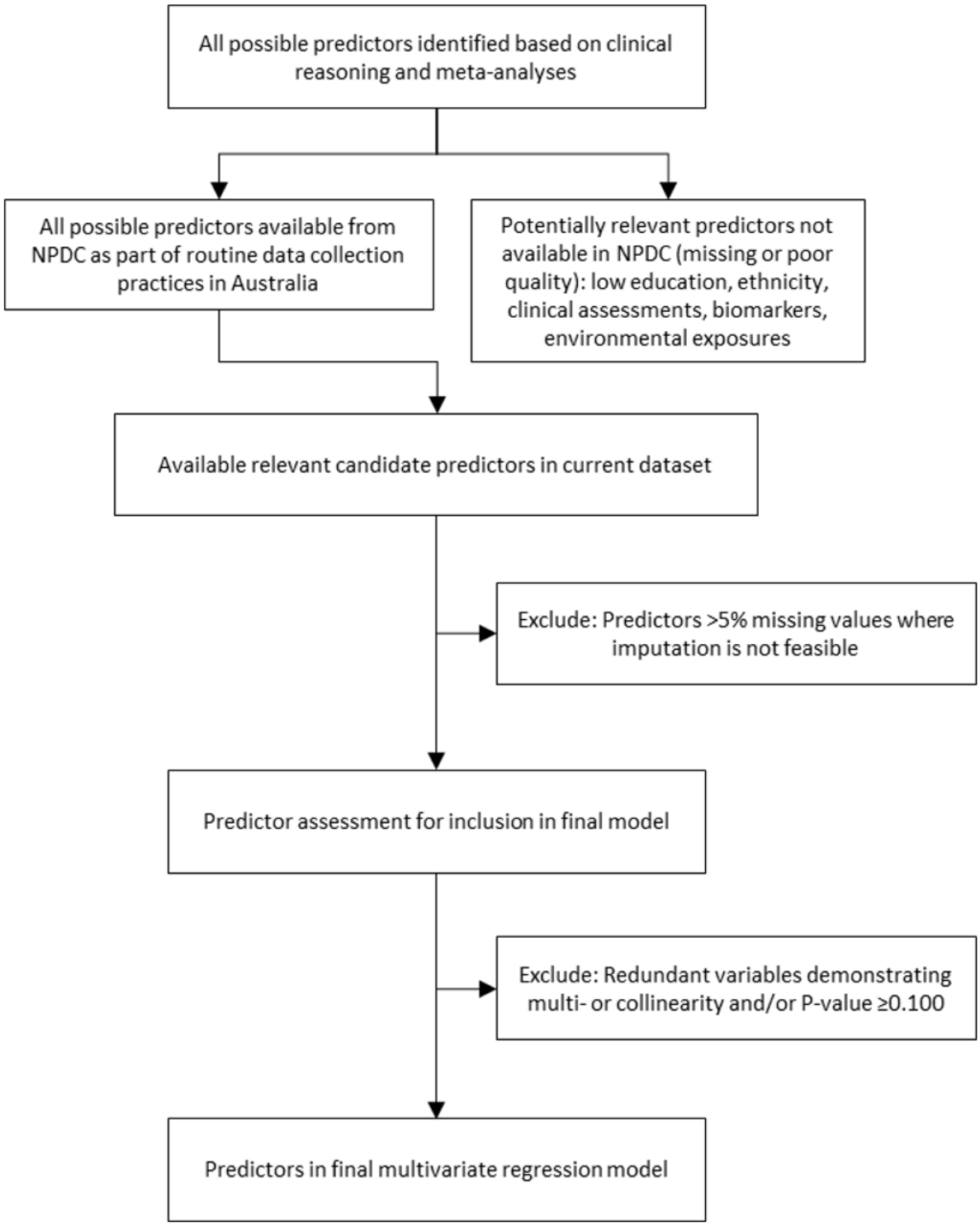

Figure 1

Selection of predictors in a study developing a multivariable logistic regression model for stillbirth.

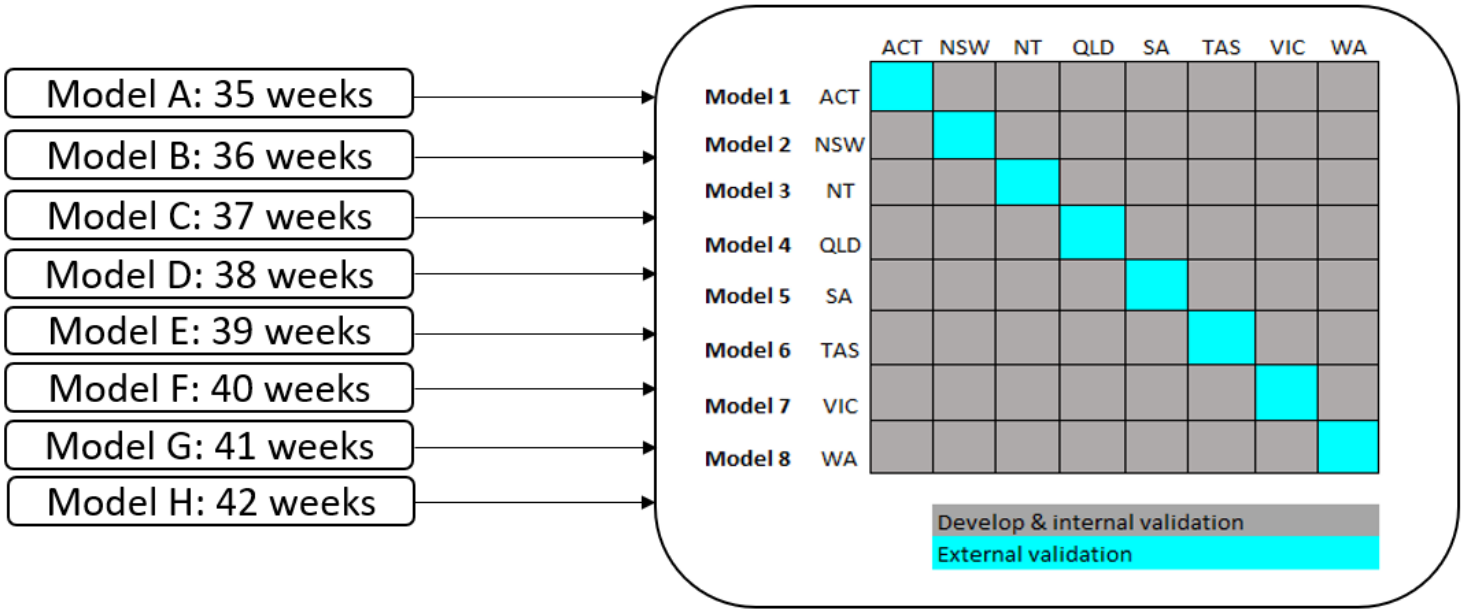

Figure 2

Map of data sources for internal and external validation of gestation-specific prediction models.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- TRIPODChecklistProtocolAustralianstillbirthmodel.docx