

Supplementary Methods & Results

Diagnosing early-onset neonatal sepsis in low-resource settings: development of a multivariable prediction model

Neal SR et al.

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Contents

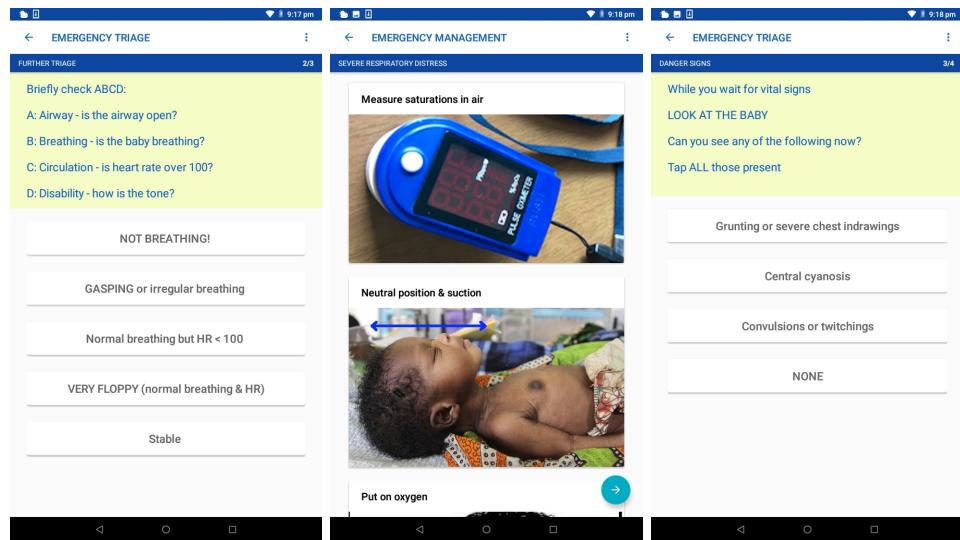
1	Neotree data collection	2
2	Candidate predictors	3
3	Preliminary data cleaning	5
4	Record linkage	8
5	Further data cleaning	17
6	Missing data	45
7	Descriptive statistics	51
8	Model development and performance	58
9	Additional analyses for reviewers' comments	79

Some supplementary data have been redacted or replaced by fictitious examples (where indicated) to remove identifying information for publication.

1 Neotree data collection

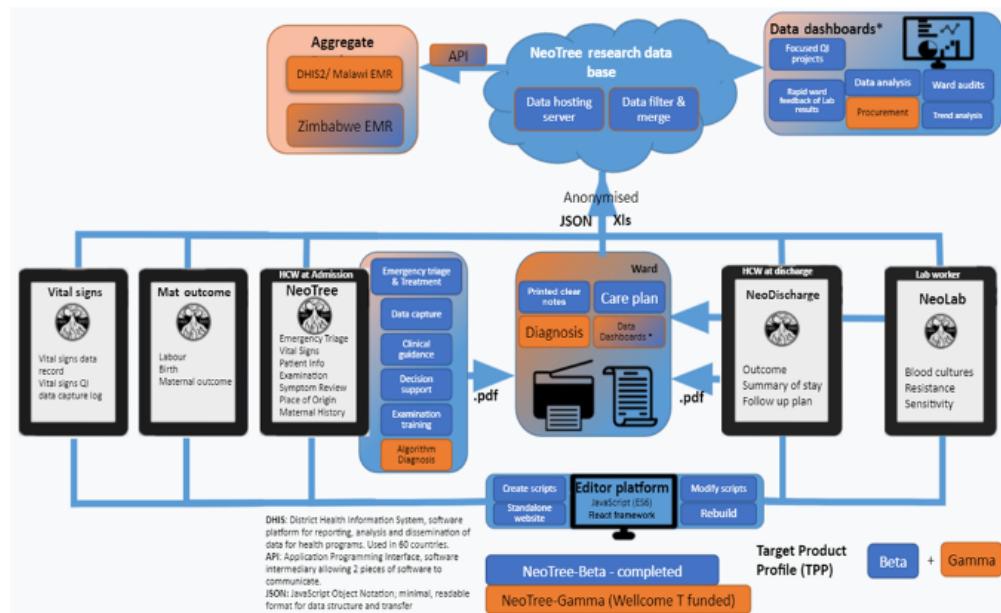
1.1 Example screens from the Neotree app

Below are example screens from the Neotree app showing data capture and integrated education on neonatal care.



1.2 Neotree data pipeline at Sally Mugabe Central Hospital

The below flow diagram summarises the current Neotree data pipeline.



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2 Candidate predictors

Predictors from literature review & expert opinion	Mapping to Neotree data (verbatim)
Risk factors	
Maternal fever >38°C in labor	“Tap all risk factors for sepsis present (some you have already asked about) these RFs will guide us on antibiotics” -> “Maternal fever in labour”
Prolonged rupture of membranes >18 hours	“When did the membranes rupture? (spontaneously or artificially)” -> “Did the membranes rupture?” -> “Yes” -> “How long between ROM and birth?” -> “>18 hours”
	“Tap all risk factors for sepsis present (some you have already asked about) these RFs will guide us on antibiotics” -> “PROM more than 18 hrs”
Foul smelling amniotic fluid	“Tap all risk factors for sepsis present (some you have already asked about) these RFs will guide us on antibiotics” -> “Offensive Liquor”
Gestation <32 weeks	“Gestation of the baby to the nearest week?” -> “Gestational age at birth (weeks)” -> <i>weeks (integer)</i>
Birth weight <1500g	“Look for birth weight in the obstetric record; Infants >24hrs old need a weight on the day of admission” -> “Birth Weight (g)” / “Admission Weight (g) (if different)” -> <i>grams (integer)</i>
Signs and symptoms	
Neonatal temperature >37.5°C	“Temperature (degs C)” -> <i>degrees Celsius (decimal, 1DP)</i>
Boil or abscess	“Examine the baby’s skin” -> “Big Boil / Abscess”
Grunting, severe respiratory distress or moderate to severely increased work of breathing	“Look at the baby. Can you see any of the following now?” -> “Grunting or severe chest indrawings”
	“Tap all that are present (more than one if necessary)” -> “Nasal flaring” / “Chest in-drawings” / “Grunting”
	“How severe is the work of breathing” -> “Mild” / “Moderate” / “Severe”
Lethargy	“How is the baby’s activity?” -> “Lethargic, quiet, decreased activity”
Umbilical redness or umbilicus draining pus	“Describe the umbilicus” -> “Red skin all around umbilicus”
Deep jaundice	“What colour is the baby?” -> “Yellow”
Tachypnoea >60 breaths per minute	“Tap the timer above to count the number of breaths in 30 seconds” -> <i>breaths per minute (integer)</i>
Convulsions, twitching or abnormal movements	“Look at the baby. Can you see any of the following now?” -> “Convulsions or twitchings”
	“How is the baby’s activity?” -> “Seizures, convulsions, or twitchings”
Many or severe skin pustules	“Examine the baby’s skin” -> “Pustules all over”

Bilious vomiting with severe abdominal distention	“Has the baby been vomiting” -> “Vomiting bright green” “Softly palpate the abdomen in all 4 quadrants” -> “Distended”
Bulging fontanelle	“Feel the fontanelle” -> “Bulging”
Not moving when stimulated	“How is the baby’s activity?” -> “Coma (unresponsive)”
Swollen red eyelids with pus	(No corresponding data collected by Neotree)
Central cyanosis	“Look at the baby. Can you see any of the following now?” -> “Central cyanosis” “What colour is the baby?” -> “Blue”
Pallor	“What colour is the baby?” -> “White”
Tachycardia >160 beats per minute	“Heart rate (beats/min)” -> <i>beats per minute (integer)</i>

DP = decimal place; PROM = prolonged rupture of membranes; RF = risk factor; ROM = rupture of membranes

3 Preliminary data cleaning

We applied several preliminary cleaning steps to the raw imported data.

- Number of rows in raw admission data frame = 99468
- Number of rows in raw outcome data frame = 105139

3.1 Removing duplicate entries

We defined exact duplicates as entries where values for all variables were identical to one or more other entries. This occurs when data are exported from a study tablet before previous data have been erased, resulting in some entries being exported in duplicate.

Number of duplicate entries:

```
## # A tibble: 2 x 2
##   form     duplicates
##   <chr>     <int>
## 1 admission 94801
## 2 outcome   100476
```

3.2 Recoding missing values

We recoded empty cells or cells containing strings that signify missingness as missing values using the following custom function:

```
## function (x)
## {
##   strings <- c("", "na", "n/a", "N/A", "NA", "Nil", "nil",
##             "-")
##   x[x %in% strings] <- NA
##   x
## }
```

3.3 Standardising variables between admission & outcome forms

We standardised `mode of delivery` and `sex` between admission and outcome forms, so they can be used for record linkage.

Labels before standardisation:

```
## $`Mode of delivery (admission)`
## [1] "1" "2" "3" "4" "5" "6"
##
## $`Mode of delivery (outcome)`
## [1] "ECS"  "ElCS" "For"  "SVD"  "Vent"
##
## $`Sex (admission)`
## [1] "F"   "M"   "NS"
##
## $`Sex (outcome)`
## [1] "F"   "M"   "U"
```

Labels after standardisation:

```
## $`Mode of delivery (admission)`  
## [1] "ECS"   "ElCS"  "For"   "SVD"   "Vent"  
##  
## $`Mode of delivery (outcome)`  
## [1] "ECS"   "ElCS"  "For"   "SVD"   "Vent"  
##  
## $`Sex (admission)`  
## [1] "F"     "M"     "U"  
##  
## $`Sex (outcome)`  
## [1] "F"     "M"     "U"
```

3.4 Removing entries without a healthcare worker identifier

We removed entries that had not been ‘signed off’ by a healthcare worker with their healthcare worker identifier (HCW ID) (commonly their initials). Entries without a HCW ID occur for several reasons, e.g. (1) a healthcare worker accidentally exits the app and starts a new form upon reopening it; (2) a healthcare worker is demonstrating how to use the app to another user so does not want to mark the form as a genuine entry.

Number of entries without a HCW ID:

```
## # A tibble: 2 x 2  
##   form      `no HCW ID`  
##   <chr>      <int>  
## 1 admission    100  
## 2 outcome       88
```

3.5 Removing outcome form entries with invalid unique identifiers

Invalid UIDs were:

```
## # A tibble: 4 x 2  
##   format          freq  
##   <chr>          <int>  
## 1 missing values     24  
## 2 strings of only zeros     84  
## 3 strings shorter than 4 characters long     12  
## 4 strings containing words      3
```

3.6 Limiting entries to the study period

We removed entries outwith the study period. This included entries prior to 01/02/2019, which constituted the ‘pilot period’ of data collection for the Neotree at SMCH.

Data import and preliminary cleaning resulted in one data frame for admission forms and one data frame for outcome forms.

- Number of rows in final admission data frame = 4137
- Number of rows in final outcome data frame = 3935

3.7 Flow diagram

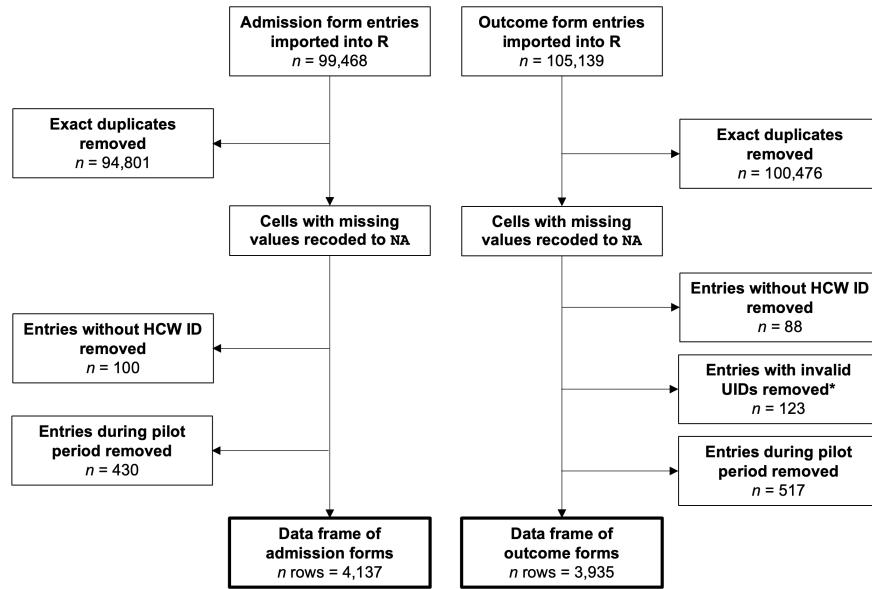


Figure 1: Flow diagram summarising preliminary data cleaning

4 Record linkage

At the time of our study, the Neotree app required users to manually enter the automatically generated admission unique identifier (UID) into a free-text field when completing the outcome form. Therefore, the outcome UID is liable to typographical errors and is not a 100% reliable key to link admission and outcome forms. Thus, we linked records using the Fellegi-Sunter framework of probabilistic record linkage.

4.1 Create data frames for linkage

4.1.1 Linkage variables

There are 8 variables common to both admission and outcome forms:

1. UID
2. Birth weight
3. Gestation at birth
4. Occipitofrontal circumference at admission
5. Length at admission
6. Mode of delivery
7. Sex
8. Place of birth

These have the following levels of missingness in the admission forms:

```
## # A tibble: 8 x 3
##   variable           n_miss pct_miss
##   <chr>              <int>    <dbl>
## 1 Admission.PlaceBirth     3637   87.9
## 2 Admission.BW                68    1.64
## 3 Admission.OFC                 5    0.121
## 4 Admission.Gestation            1    0.0242
## 5 Admission.Length                1    0.0242
## 6 Admission.UID_alphanum            0    0
## 7 Admission.ModeDelivery            0    0
## 8 Admission.Gender                  0    0
```

And in the outcome forms:

```
## # A tibble: 8 x 3
##   variable           n_miss pct_miss
##   <chr>              <int>    <dbl>
## 1 Discharge.GestBirth      2499   63.5
## 2 Discharge.OFCDis            248    6.30
## 3 Discharge.LengthDis          231    5.87
## 4 Discharge.BirthPlace            13    0.330
## 5 Discharge.Delivery               1    0.0254
## 6 Discharge.NeoTreeID_alphanum        0    0
## 7 Discharge.BWTDis                0    0
## 8 Discharge.SexDis                  0    0
```

Note Place of birth has 87.9% missing values in the admission forms. It is also coded differently between admission and outcome forms:

```

## $admission
## # A tibble: 5 x 2
##   levels definition
##   <chr>  <chr>
## 1 BBA    born before arrival
## 2 HC     health centre
## 3 Home   home
## 4 Hosp   hospital
## 5 TBA    traditional birth attendant
##
## $outcome
## # A tibble: 4 x 2
##   levels definition
##   <chr>  <chr>
## 1 H      home
## 2 HCH   Harare Central Hospital
## 3 OtH   other clinic in Harare
## 4 OtR   other clinic outside Harare

```

Although `Gestation at birth` has 63.5% missing values in the outcome forms, it is a numeric variable and, therefore, coded the same between admission and outcome forms:

```

## $admission
## [1] "40" "41" "33" "40" "40" "38"
##
## $discharge
## [1] "34" "32" "31" "27" "34" "34"

```

Thus, we used 7 variables for record linkage (excluding `Place of birth`):

1. Unique ID*
2. Birth weight
3. Gestation at birth
4. Occipitofrontal circumference at admission
5. Length at admission
6. Mode of delivery
7. Sex
8. Place of birth

* **Special note on UID:** After the first month of the project, healthcare workers were told to only enter the first 3 and last 3 characters of the UID in the outcome form. This is because the UID was initially long and laborious to type and, hence, prone to error. Therefore, most outcome form UIDs are 6 characters long, except those from the first month of the project. To avoid confusion, we used a substring of the full UIDs (called `uidsub`) for linkage. This substring consists of the first 3 and last 3 characters of the UID, converted to lowercase. E.g. (fictitious example),

```

##       full      uidsub
## [1,] "AB123456" "ab1456"
## [2,] "AB789012" "ab7012"

```

4.1.2 Linkage data frames

Below is a fictitious example of the data frame structure for record linkage:

```
## $admission
## # A tibble: 4 x 8
##   bw    gest  ofc  length mode  sex session      uidsub
##   <chr> <chr> <chr> <chr> <chr> <chr> <chr>
## 1 3000  41    32    46    SVD   M    session 10000 ab1789
## 2 4000  40    37    46    ECS   F    session 10001 ab2567
## 3 1800  35    31    44    SVD   F    session 10002 ab3689
## 4 3500  40    33    48    SVD   M    session 10003 ab1478
##
## $outcome
## # A tibble: 4 x 8
##   bw    gest  ofc  length mode  sex session      uidsub
##   <chr> <chr> <chr> <chr> <chr> <chr> <chr>
## 1 3320  <NA>  32    48    SVD   F    session 100000 cd3567
## 2 1900  32    32    47    ECS   F    session 100001 cd1378
## 3 1900  34    30    45    SVD   M    session 100002 cd8364
## 4 1300  32    29    39    ECS   M    session 100003 cd9246
```

4.2 Perform record linkage

4.2.1 Run linkage algorithm

We performed record linkage using the `fastLink` package by Enamorado, Fifield and Imai (<https://github.com/kosukeimai/fastLink>). Linkage is performed using the `fastLink::fastLink()` wrapper.

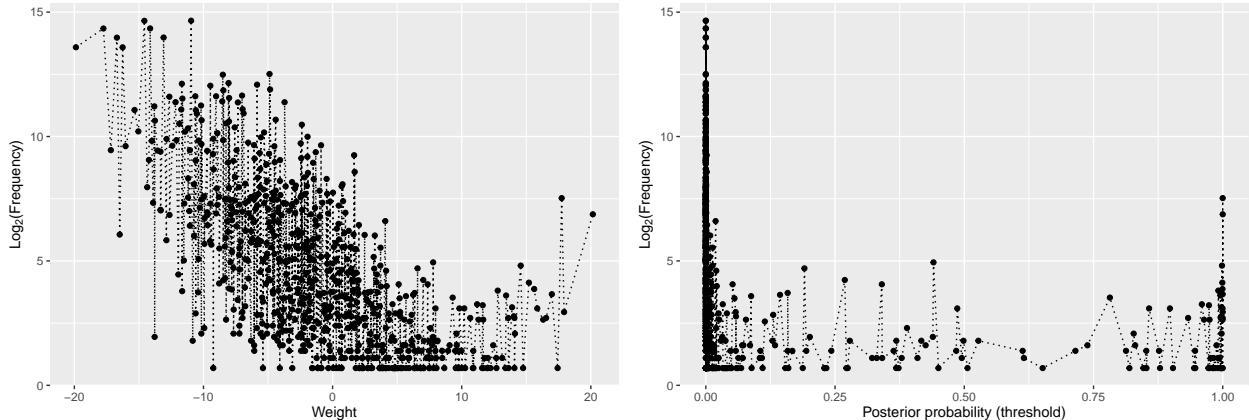
```
set.seed(123)

matches_out <- fastLink(
  dfA = adm_link,
  dfB = dis_link,
  varnames = c("uidsub", "bw", "gest", "ofc", "length", "mode", "sex"),
  stringdist.match = c("uidsub"), # use string dist matching on uidsub
  stringdist.method = "jw", # Jaro-Winkler
  jw.weight = .10, # Jaro-Winkler weight for prefix
  partial.match = c("uidsub"), # allow partial matching for uidsub
  cut.a = 0.96, # full string-distance match cut point (Winkler, 1990)
  cut.p = 0.88, # partial string-distance match cut point (Winkler, 1990)
  dedupe.matches = TRUE, # enforces one-to-one matching
  cond.indep = TRUE, # assuming conditional independence for Fellegi-Sunter model
  return.all = TRUE # sets threshold.match to 0.0001
)
```

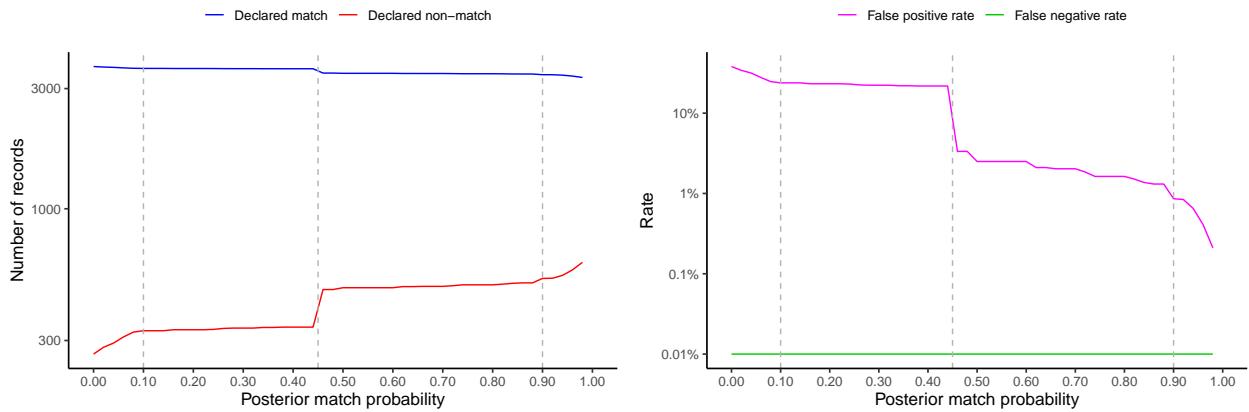
All other parameters were left as the default (see `fastLink` documentation).

4.2.2 Determine thresholds

We plot the posterior probabilities (zeta) and their corresponding Fellegi-Sunter weights, as demonstrated by Weber. Note that the y-axes values are displayed as the natural logarithm of 1 plus the number of records at each zeta or weight.



We then plot the frequencies of matches and non-matches, and the false positive rate (aka false detection rate [FDR]) and false negative rate (FNR) across the range of probability thresholds.

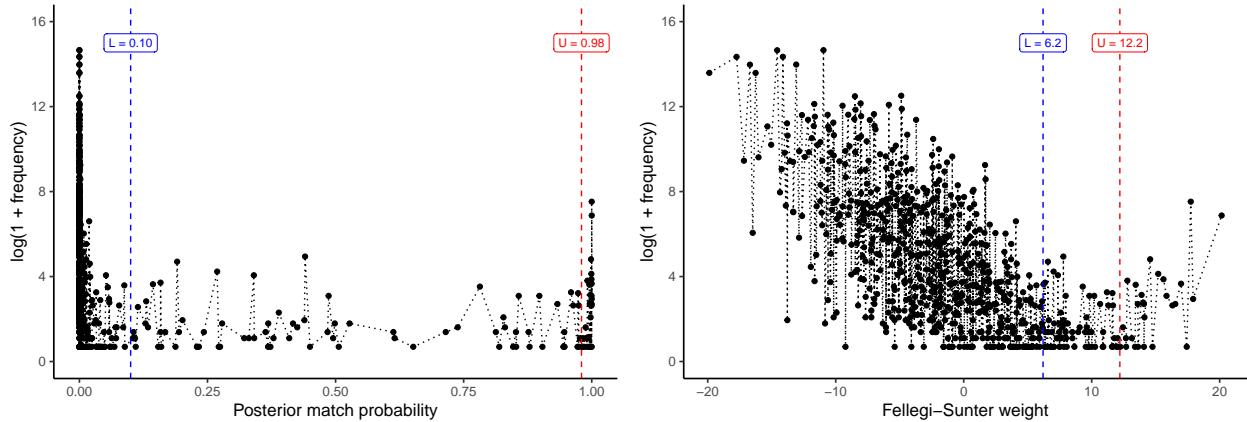


Considering the graphs, there appears to be an abrupt change in the number of matches vs. non-matches, and the FDR at zetas of ~ 0.10 , ~ 0.45 and ~ 0.90 (*dotted lines*). The FNR appears essentially constant at 0.01% across all values of zeta.

It is most important to minimise the FDR (i.e. minimise the likelihood of declaring records a match when they are not a true match). Therefore, we set the threshold for declared matches very high (**zeta = 0.98**), which yielded an FDR $< 0.5\%$. We set the lower threshold (for declaring potential matches requiring manual review) at **zeta = 0.10**, based on the abrupt changes in the above graphs at this point.

- Zeta = 0.10 corresponds to Fellegi-Sunter weight = ~ 6.2 .
- Zeta = 0.98 corresponds to Fellegi-Sunter weight = ~ 12.2 .

Below are the zeta and Fellegi-Sunter weight plots with thresholds superimposed:



The chosen thresholds result in the following confusion tables:

```
## $lower_thres
## $lower_thres$confusion.table
##           'True' Matches 'True' Non-Matches
## Declared Matches      3504.46        102.54
## Declared Non-Matches       0.27      327.73
##
## $lower_thres$addition.info
##                               results
## Max Number of Obs to be Matched 3935.00
## Sensitivity (%)                 99.99
## Specificity (%)                76.17
## Positive Predicted Value (%)   97.16
## Negative Predicted Value (%)  99.92
## False Positive Rate (%)       23.83
## False Negative Rate (%)       0.01
## Correctly Classified (%)      97.39
## F1 Score (%)                  98.55
##
##
## $upper_thres
## $upper_thres$confusion.table
##           'True' Matches 'True' Non-Matches
## Declared Matches      3320.70        1.30
## Declared Non-Matches       0.45      612.55
##
## $upper_thres$addition.info
##                               results
## Max Number of Obs to be Matched 3935.00
## Sensitivity (%)                 99.99
## Specificity (%)                99.79
## Positive Predicted Value (%)   99.96
## Negative Predicted Value (%)  99.93
## False Positive Rate (%)       0.21
## False Negative Rate (%)       0.01
## Correctly Classified (%)      99.96
## F1 Score (%)                  99.97
```

This results in **285 records for manual review**. We deemed this to be an acceptable and pragmatic

number of records to review manually.

4.2.3 Get matches and potential matches at chosen thresholds

We subset the linkage data frames to return a data frame of matches and a data frame of potential matches using the `fastLink::getMatches()` function.

```
matches_list <- vector("list")

# With zeta >0.98 (matches)
matches_list$low <- getMatches(
  dfA = adm_link,
  dfB = dis_link,
  fl.out = matches_out,
  threshold.match = 0.98,
  combine.dfs = FALSE
)

# With zeta >0.10 (matches + potential matches)
matches_list$high <- getMatches(
  dfA = adm_link,
  dfB = dis_link,
  fl.out = matches_out,
  threshold.match = 0.10,
  combine.dfs = FALSE
)

# Session IDs for potential matches
matches_list$potential_adm <-
  matches_list$high$dfA.match$session[!matches_list$high$dfA.match$session
    %in% matches_list$low$dfA.match$session]

matches_list$potential_dis <-
  matches_list$high$dfB.match$session[!matches_list$high$dfB.match$session
    %in% matches_list$low$dfB.match$session]
```

We build this into a full data frame with all Neotree variables for matches and potential matches by merging on session ID (which uniquely identifies each completed admission or outcome form). N.B. `adm` and `dis` are the complete data frames of Neotree admission forms and outcome forms, respectively.

```
# Build into data frames
# Designated matches from fastLink
matches_list$matches <- tibble(
  Admission.session = matches_list$low$dfA.match$session,
  Discharge.session = matches_list$low$dfB.match$session
) %>%
  merge(adm, by = "Admission.session") %>%
  merge(dis, by = "Discharge.session")

# Potential matches from fastLink
matches_list$potentials <- tibble(
  Admission.session = matches_list$potential_adm,
  Discharge.session = matches_list$potential_dis
```

```
) %>%
  merge(adm, by = "Admission.session") %>%
  merge(dis, by = "Discharge.session")
```

There are **3322 declared matches**, **285 declared potential matches**, and **328 non-matches** from the Fellegi-Sunter linkage algorithm.

4.3 Manual review of potential matches

Potential matches are manually reviewed to determine their true match status. We used several factors to make a clinical judgement, including:

- Admission and outcome UIDs - any discrepancies are plausible (e.g. likely to represent a typographical error).
- Admission date and outcome (discharge or death) date - congruent and plausible.
- Admission reason/diagnosis and discharge diagnosis or cause of death - congruent.
- A review of all other variables looking for any unique features on the admission and outcome form that might indicate a true match.

From manual review of the potential matches, we decided that **258** were true matches. Thus, there were **3580** declared matches at this stage.

4.3.1 Quality checks

Finally, we performed several additional ‘quality checks’ to identify false-positive matches or other irregularities.

First, we checked for duplicate admission or outcome session IDs (i.e. duplicate completed admission or outcome forms) in the final linked dataset.

- Duplicated admission forms: $n = 0$
- Duplicated outcome forms: $n = 0$

Therefore, the one-to-one matching constraint was successful.

Next, we checked for duplicate admission or outcome UIDs in the final linked dataset.

- Duplicated admission UIDs: $n = 86$
- Duplicated outcome UIDs: $n = 108$

Looking at an extract from these duplicates, it was clear that they are unique babies with, for example, different birth weights, gestational ages, admission reasons, discharge diagnosis or outcome despite the same UID.

Finally, we checked for invalid admission durations (i.e. cases where the outcome date came before the admission date, or where the interval was unusually long).

Acceptable discrepancies:

- Outcome date ≤ 1 day prior to admission date - this could occur if the admission form was completed retrospectively shortly after the outcome form (e.g. if a baby was deceased on or soon after arrival to the neonatal unit).

Unacceptable discrepancies:

- Outcome date > 1 day prior to admission date
- Admission duration shown to be > 4 months - this is not a plausible admission duration for the neonatal unit at Sally Mugabe Central Hospital.

Distribution of admission durations:

```
##          Min.           1st Qu.
##      "-5d -21H -45M -2S"      "1d 6H 51M 52.25S"
##      Median               Mean
##      "2d 13H 2M 39S"  "5d 6H 57M 15.7974860329414S"
##      3rd Qu.              Max.
##      "5d 14H 40M 59.25S"     "309d 14H 56M 13S"
```

- Outcome date prior to admission date: $n = 49$
 - ≤ 1 day prior: $n = 47$
 - > 1 day prior: $n = 2$
- Admission duration shown to be > 4 months: $n = 1$

We changed the status of these 3 cases to “non-match”, to err on the side of caution. We felt these most likely represented false-positive matches.

```
## [1] "session 70565" "session 21083"
## [1] "session 10707"
```

New distribution of admission durations:

```
##          Min.           1st Qu.
##      "-16H -59M -25S"      "1d 6H 54M 10S"
##      Median               Mean
##      "2d 13H 7M 59S"  "5d 5H 1M 47.4453452615999S"
##      3rd Qu.              Max.
##      "5d 14H 40M 46S"     "84d 22H 15M 49S"
```

A total of 3577 record pairs were thus included in the final linked dataset.

4.3.2 Flow diagram

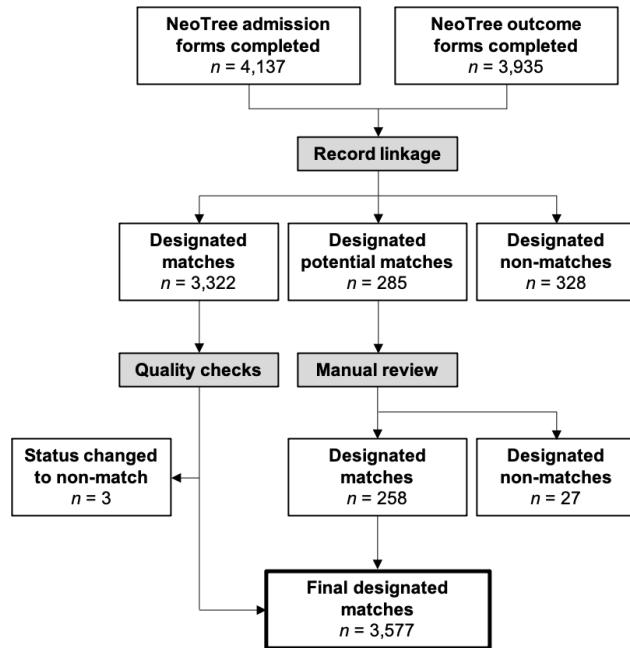


Figure 2: Flow diagram summarising record linkage

5 Further data cleaning

Elaboration on creating/extracting relevant variables required for model development from the Neotree dataset at Sally Mugabe Central Hospital.

5.1 Data collected by admission forms

There are 7 sections to the Neotree admission form at SMCH, Zimbabwe.

1. Emergency triage & vital signs
2. Patient information
3. Examination
4. Symptom review
5. Place of origin
6. Maternal history
7. Provisional diagnoses

N.B. Other data are collected by the app, but only relevant variables are detailed here.

5.1.1 Emergency triage & vital signs

The variables to be subset/created from this section are as follows:

Parent variable	New variable(s)	Comments
Admission.DangerSigns	et_grunt	“Grun” (yes/no)
“ ”	et_cyanosis	“Cyan” (yes/no)
“ ”	et_seizures	“Conv” (yes/no)
Admission.RR	et_rr	(numeric)
Admission.HR	et_hr	(numeric)
Admission.Temperature	et_temp	(numeric)
Admission.BW	et_bw	(numeric)
Admission.AW	informs et_bw	(numeric)

5.1.1.1 Admission.DangerSigns Categorical variable with four levels:

- Grun = “Grunting or severe chest indrawings”
- Cyan = “Central cyanosis”
- Conv = “Convulsions or twitchings”
- None

Recoded into three separate variables: `et_grunt`, `et_cyanosis` and `et_seizures`.

```
## [1] "Original variable"

##
##          Conv      Conv ,Grun        Cyan      Grun Grun ,Conv ,Cyan
##          11                  3                  58          1067           1
##          Grun ,Cyan        None     <NA>
##          82                  2353                 2
```

```

## [1] "New variables"

## et_grunt      et_cyanosis et_seizures
##   no :2422    no :3434    no :3560
##   yes :1153   yes : 141   yes :  15
##  NA's:     2   NA's:     2   NA's:     2

```

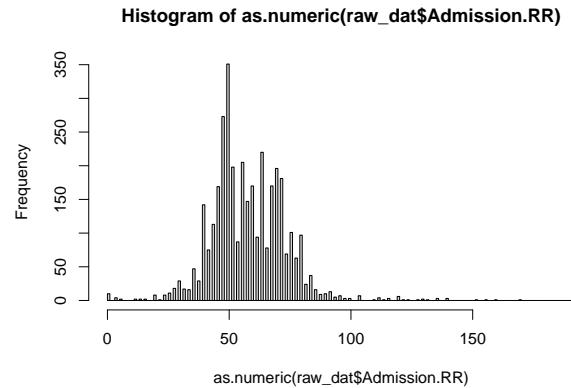
5.1.1.2 Admission.RR Continuous variable measured in breaths per minute.

- Some recorded values were very low (i.e. <20 breaths per minute).
 - On inspection, most died suggesting the recorded values were correct.
 - Some neonates were recorded as surviving to discharge with an initial RR < 10, despite receiving no resuscitation. This is implausible and their RR was set to missing.
- Similarly, some recorded values were very high (i.e. >100 breaths per minute).
 - After reviewing the distribution, we truncated these data to the 99.5th percentile, setting greater values to missing.

```

##      Min. 1st Qu. Median     Mean 3rd Qu. Max. NA's
##      0.0   48.0   56.0   58.3   68.0 192.0   6

```



```

##      0%  0.5%   1%   50%   99% 99.5% 100%
##      0.0 13.7  24.0  56.0 104.0 120.0 192.0

```

```

## [1] "Lowest 10 values"

```

```

##
##  0  4  6 12 14 16 20 22 24 26
## 10  4  2  2  2  2  8  1  8 11

```

```

## [1] "Highest 20 values"

```

```

##
##  98 100 104 110 112 114 116 120 122 124 128 130 132 136 140 152 156 160 170 192
##  3   3    7    1    4    1    3    6    1    1    2    1    3    3    1    1    1    1    1    1

```

```

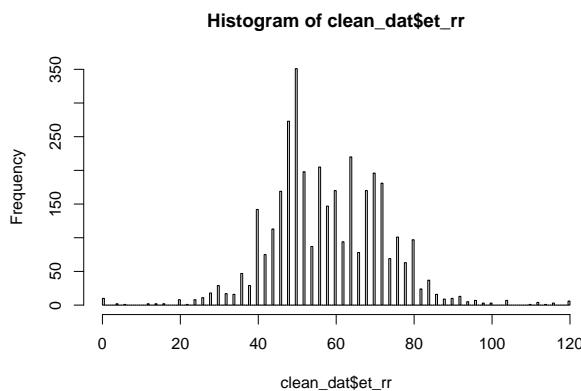
## [1] "Cases where RR <20"

## # A tibble: 22 x 3
##   Admission.RR Admission.Resus Discharge.NeoTreeOutcome
##   <dbl> <chr>          <chr>
## 1       16 Stim,02        NND
## 2        4 Stim,BVM,02,Suc  NND
## 3        0 Stim,02,Suc     NND
## 4        0 Stim,CPR,02,BVM,Suc NND
## 5        6 Stim,CPR,02,BVM,Suc NND
## 6       12 Stim,02,BVM     NND
## 7        0 Stim,CPR,BVM    NND
## 8        6 None            DC
## 9       16 Stim,02        NND
## 10       0 CPR,Suc,02,BVM  NND
## 11       0 Stim,CPR,02,BVM,Suc NND
## 12      12 Stim,BVM,02,Suc  NND
## 13       0 Stim,BVM,02,Suc  NND
## 14       4 None            DC
## 15      14 Stim,CPR,02,BVM,Suc NND
## 16       4 Stim,CPR,02,BVM,Suc NND
## 17       0 None            NND
## 18       0 Stim,CPR,02,BVM,Suc NND
## 19       0 Stim,CPR,BVM    NND
## 20       4 None            DC
## 21      14 Stim,02         DC
## 22       0 None            NND

## [1] "New variable"

##      et_rr
## Min.   :  0
## 1st Qu.: 48
## Median : 56
## Mean   : 58
## 3rd Qu.: 68
## Max.   :120
## NA's   :26

```

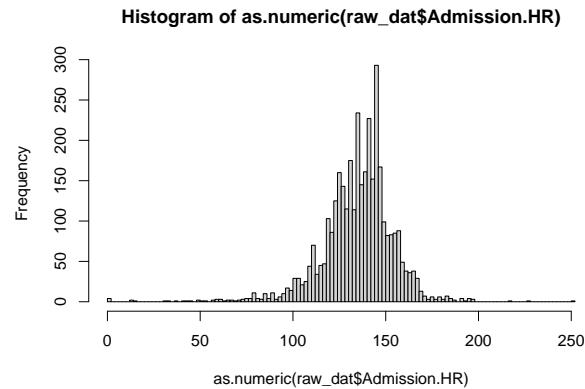


5.1.1.3 Admission.HR

Continuous variable measured in beats per minute.

- Some recorded values were very low (i.e. <50 beats per minute).
 - On inspection, most died suggesting the recorded values were correct.
 - Some neonates were recorded as surviving to discharge with an initial HR < 20, despite receiving no resuscitation. This is implausible and their HR was set to missing.

```
##      Min. 1st Qu. Median     Mean 3rd Qu.     Max.
##        0    125    138     136    146    252
```



```
##      0%    0.1%    1%    50%    99%   99.9%  100%
##    0.000  8.064  74.760 138.000 179.000 198.000 252.000

## [1] "Lowest 10 values"

##
##      0 14 15 32 34 38 42 43 45 50
##      4  2  1  1  1  1  1  1  1  2

## [1] "Highest 20 values"

##
##      178 179 180 182 183 184 185 186 187 188 191 192 193 195 196 197 198 218 228 252
##      2    2    4    3    3    4    2    2    1    1    1    3    1    1    1    3    1    2    1    1    1

## [1] "Cases where HR <50"

## # A tibble: 13 x 4
##   Admission.HR Admission.RR Admission.Resus Discharge.NeoTreeOutcome
##       <dbl>      <chr>          <chr>          <chr>
## 1         32      60            O2,Suc        NND
## 2         14      70            None          DC
## 3          0      0             Stim,CPR,BVM  NND
## 4         38      26            Stim,CPR,O2,BVM NND
## 5         42      44            Stim,CPR,O2,BVM,Suc NND
## 6         14      50            None          DC
```

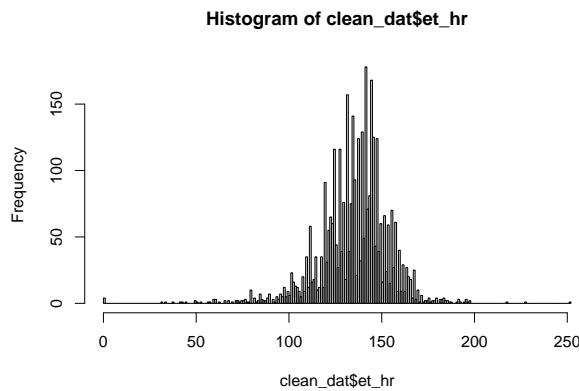
```

##   7          0 20      Stim,CPR,O2,BVM,Suc NND
##   8          0 0       Stim,BVM,O2,Suc     NND
##   9         15 48     None                  DC
##  10         43 4      Stim,CPR,O2,BVM,Suc NND
##  11         34 0      None                  NND
##  12         45 26     Stim,CPR,BVM,Suc    NND
##  13          0 0      None                  NND

## [1] "New variable"

##      et_hr
## Min. : 0
## 1st Qu.:125
## Median :138
## Mean   :136
## 3rd Qu.:146
## Max.   :252
## NA's   :3

```

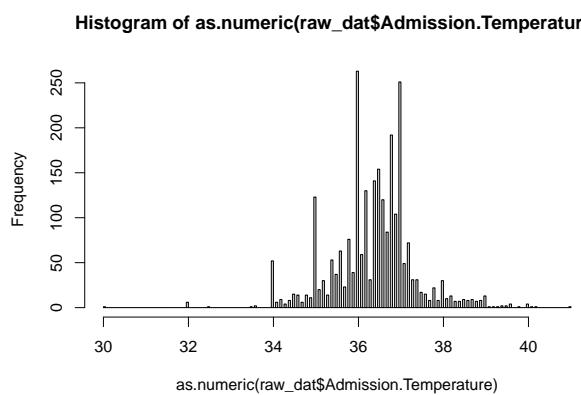


5.1.1.4 Admission.Temperature Continuous variable measured in degrees Celsius (to 0.1 precision).

```

##      Min. 1st Qu. Median      Mean 3rd Qu.      Max.    NA's
##  30.0   36.0   36.5   36.4   37.0   41.0   1027

```



```

##      et_temp
##  Min.   :30.0
##  1st Qu.:36.0
##  Median :36.5
##  Mean   :36.4
##  3rd Qu.:37.0
##  Max.   :41.0
##  NA's    :1027

```

5.1.1.5 Admission.BW & Admission.AW Continuous variables measured in grams.

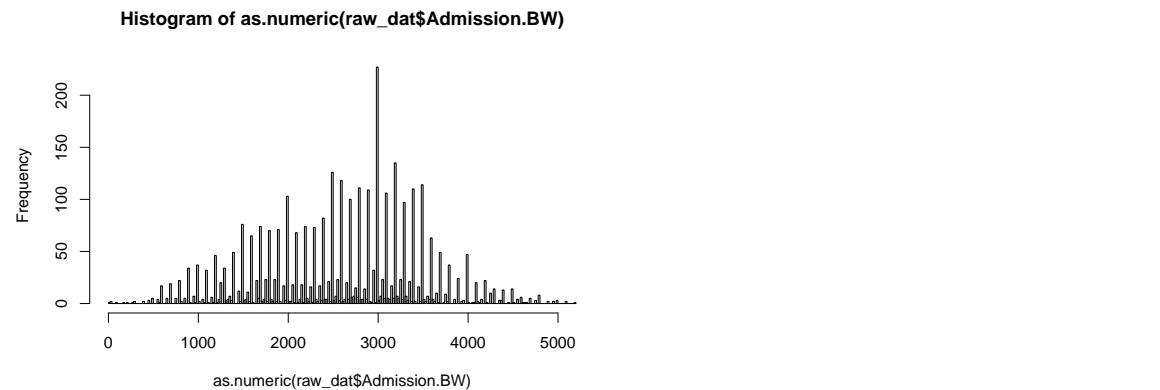
- Looking at the distributions of birth weight (BW) and admission weight (AW), some values are clearly invalid.
- It is important not to assume what these values should be (e.g., for “100” the true value may have been “1000”, or perhaps “3100”).

```
## [1] "Distribution of birth weight"
```

```

##      Min. 1st Qu. Median     Mean 3rd Qu.     Max.     NA's
##        2    1950    2700    2592    3200    5200       48

```



```
## [1] "Lowest values"
```

```

##
##      2   35   36   100   180   220   270   300   400   450   550   580   600   650   690   700   750   800   805
##      1     1     1     1     1     1     1     2     2     3     5     4     1    17     5     1    18     5    22     2
##  850  900  920  945  950  955
##      5   34   1     1     5     1

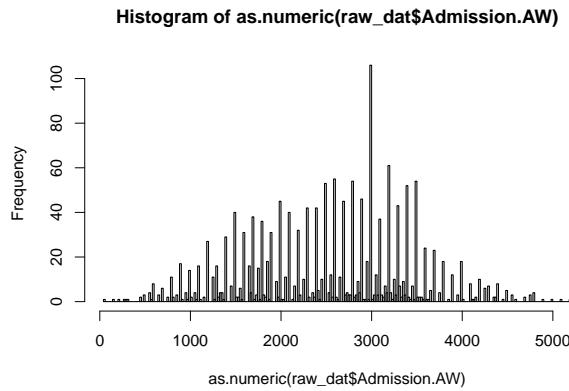
```

```
## [1] "Distribution of admission weight"
```

```

##      Min. 1st Qu. Median     Mean 3rd Qu.     Max.     NA's
##        40    1850    2600    2544    3200    5200   1877

```



```

## [1] "Lowest values"

##
##   40 150 220 280 300 310 310 450 500 550 580 600 650 690 700 750 800 805 850 900 920
##   1    1    1    1    1    1    1    2    3    4    1    8    3    1    5    2    11    2    3    17    1
## 950
##   3

## [1] "Cases where BW or AW <500g"

## # A tibble: 18 x 2
##       Admission.BW Admission.AW
##       <dbl>        <dbl>
## 1      1500        150
## 2      100         NA
## 3      300         300
## 4     3100        310
## 5      300        3000
## 6      450         450
## 7      450         NA
## 8      400         NA
## 9     2800        280
## 10     450         450
## 11     700         40
## 12      35        3375
## 13      2         NA
## 14     400         NA
## 15      36       1340
## 16     270         NA
## 17     180       1800
## 18     220        220

```

Therefore, we assessed how many cases have BW and/or AW missing, and whether it is necessary to have two weight variables (i.e., do BW and AW substantially differ?):

```

## [1] "Birth weight missing"

## [1] 48

```

```

## [1] "Admission weight missing"

## [1] 1877

## [1] "Birth weight missing but admission weight NOT missing"

## [1] 28

## [1] "Cases where BW and AW differ (and AW not missing)"

## # A tibble: 32 x 2
##   Admission.BW Admission.AW
##       <dbl>        <dbl>
## 1      1500        150
## 2      3780       3300
## 3      3100        310
## 4      2120       2100
## 5      1700       1660
## 6      1650       1700
## 7      1540       1890
## 8      2488       2408
## 9       300        3000
## 10     3400       3408
## 11     1500       1350
## 12     2630       2603
## 13     3300       3700
## 14     1700       1550
## 15     1660       1600
## 16     3000       2880
## 17     2700       2600
## 18     1800       1500
## 19     1320       1750
## 20     4800       4560
## 21     1500       1600
## 22     2000       2200
## 23     4000       3900
## 24     2800        280
## 25     1900       1980
## 26     2910       2700
## 27     3100       3400
## 28      700         40
## 29      35        3375
## 30    1470       1275
## 31      36        1340
## 32     180        1800

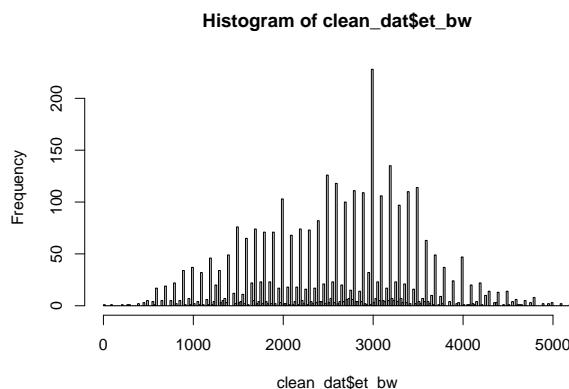
```

- There are only 32 cases where BW and AW differ.
 - Examining these cases, the differences are relatively small (excluding cases where the value is obviously erroneous). Therefore, it is unnecessary to have a separate variable for AW, and BW will suffice.
 - Some values were recorded as very low (i.e. <500g).

- If BW is consistent with the gestational age, the original value is retained.
- If BW is inconsistent with gestational age but AW is consistent, then `et_bw` takes the value of AW.
- Otherwise, if neither BW or AW consistent with gestational age (or AW missing), then original BW value retained and case will be excluded based on inclusion/exclusion criteria for birth weight (see below).
- *N.B. We used the UK-WHO Neonatal and Infant Close Monitoring Growth Chart 2009 to determine weights consistent with each gestational age.*

```
## [1] "New variable"
```

```
##      et_bw
##  Min.   :    2
##  1st Qu.:1950
##  Median :2700
##  Mean   :2595
##  3rd Qu.:3200
##  Max.   :5200
##  NA's   :48
```



5.1.2 Patient information

The variables to be subset/created from this section are as follows:

Parent variable	New variable(s)	Comments
Admission.AdmReason “ ”	<i>informs</i> pi_bba pi_admreason	“BBA” (yes/no) <i>takes original values</i> (factor)
Admission.UID	adm_uid	(string)
Admission.session	adm_session	(string)
Admission.DateTimeAdmission	adm_datetime	(date-time)
Admission.Gender	pi_sex	<i>takes original values</i> (factor)
Admission.AgeA/B/Cat/C	pi_age	(numeric)
Admission.TypeBirth	pi_type	(factor)
Admission.Gestation	pi_gest	(numeric)

5.1.2.1 Admission.AdmReason Categorical variable with many levels. No changes made to original data.

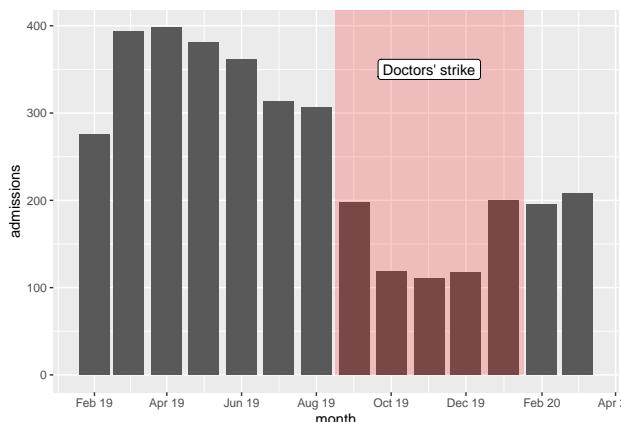
```
##          AD      Apg      BA     BBA     Cong     Conv     DIB      DU      FD      Fev
##      25     392     141    139      46       7     511      10      63     132
##      G     HIVX      J     LBW     Mac     Mec     NTD       0      OM     Prem
##      96      10    155    246    128    240      25    261      18     149
## PremRDS   Risk   Safe    SPn    <NA>
##      443     86    251       3       0
##      pi_admreason
##      DIB      : 511
##      PremRDS: 443
##      Apg      : 392
##      0        : 261
##      Safe     : 251
##      LBW     : 246
##      (Other):1473
```

5.1.2.2 Admission.UID & Admission.session String variables. No changes made to original data.

- Admission.UID = the unique identifier for each baby, automatically generated by the Neotree app when a new admission form is created.
- Admission.UID_alphanum = Admission.UID but with non-alphanumeric characters removed. Used for record linkage.
- Admission.session = a unique number assigned to each row of data when imported from the raw JSON files (i.e., `seq_along(1:nrow(data))`). Can be used to merge columns from the other data frames if needed in later analyses.

5.1.2.3 Admission.DateTimeAdmission String variable representing a date. Converted to POSIXct object.

- The period prior to 1st February 2019 was a ‘pilot period’.
 - During this period, healthcare workers were becoming accustomed to the Neotree app and only a subset of admissions and outcomes were recorded.



5.1.2.4 Admission.Gender Categorical variable with three levels.

- Male
- Female
- Unsure

No changes made to original data.

```
##  
##      F      M      U <NA>  
## 1608 1965     4     0  
  
## [1] "New variable"  
  
##  pi_sex  
##  f:1608  
##  m:1965  
##  u:    4
```

5.1.2.5 Admission.AgeA/B/Cat/C Categorical or string variables representing age at admission:

- Admission.AgeA = Is the baby aged less than 1 week?
 - Binary categorical variable: yes (Y) or no (N)
- Admission.AgeB = If AgeA = yes, the baby's age to the nearest hour
 - String variable in the format X days, Y hours
- Admission.AgeCat = If AgeA = yes, the age category that the baby falls into
 - Categorical variable with 5 levels:
 - * Fresh newborn (<2 hours-old)
 - * Newborn 2-23 hours-old
 - * Newborn 24-47 hours-old
 - * Infant 48-71 hours-old
 - * Infant 72 hours-old
- Admission.AgeC = If AgeA = no, the baby's age to the nearest day
 - String variable in the format X days

N.B. If the reason for admission is “dumped baby”, then age is not recorded.

```
## # A tibble: 4 x 3  
##   variable      n_miss pct_miss  
##   <chr>        <int>    <dbl>  
## 1 Admission.AgeC     3557    99.4  
## 2 Admission.AgeB      657    18.4  
## 3 Admission.AgeCat     109    3.05  
## 4 Admission.AgeA       13    0.363  
  
## [1] "Missing both AgeB and AgeCat"
```

```
## [1] 28
```

All age variables have a high proportion of missingness except Admission.AgeCat and Admission.AgeA.

- Since Admission.AgeA is a simple binary question of whether the baby is less than one week-old, using Admission.AgeCat is more informative.
- This means age will be a categorical variable rather than a continuous variable, but this is preferable to reduce the proportion of missing values.

We can transform Admission.AgeB into a continuous variable of age in hours, and then check to ensure Admission.AgeB is congruent with Admission.AgeCat:

```
## [1] "Admission.AgeB, original"

## [1] "18 hours"          "1 day, 9 hours"    "1 hour"        "1 day, 9 hours"
## [5] "16 hours"          "1 day, 5 hours"    "1 day, 5 hours" "1 day, 15 hours"
## [9] "6 hours"           "15 hours"        "13 hours"      "2 hours"
## [13] "19 hours"          "4 hours"         "11 hours"      "2 days, 18 hours"
## [17] "14 hours"          "11 hours"        "1 day, 3 hours" NA

## [1] "Note some anomalies: negative values or >1 week-old"

## [1] "-21 hours"          "-10 hours"
## [3] "1 month5 days, 16 hours" "1 month1 day, 4 hours"
## [5] "-17 hours"          "-10 hours"
## [7] "-3 hours"           "-18 hours"
## [9] "-5 hours"           "-11 hours"
## [11] "-23 hours"          "-20 hours"
## [13] "-20 hours"          "-23 hours"
## [15] "-23 hours"          "-23 hours"
## [17] "-20 hours"          "-5 hours"
## [19] "-10 hours"          "1 month4 days, 7 hours"
## [21] "-6 hours"           "-22 hours"
## [23] "-21 hours"          "-22 hours"
## [25] "-5 hours"           "-9 hours"
## [27] "-8 hours"           "-10 hours"

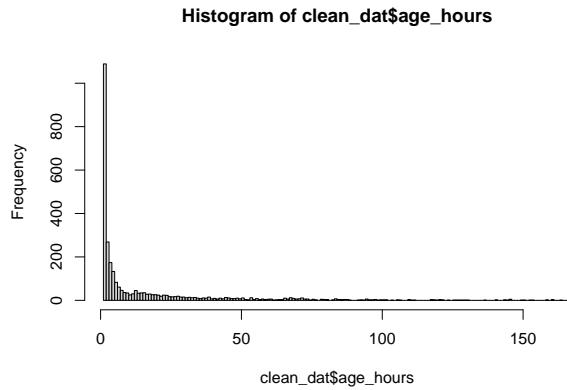
## [1] "Check this new variable, age in hours"

## # A tibble: 10 x 2
##   Admission.AgeB  age_hours
##   <chr>            <dbl>
## 1 18 hours          18
## 2 1 day, 9 hours   33
## 3 1 hour            1
## 4 1 day, 9 hours   33
## 5 16 hours          16
## 6 1 day, 5 hours   29
## 7 1 day, 5 hours   29
## 8 1 day, 15 hours  39
## 9 6 hours            6
## 10 15 hours         15
```

```

##      age_hours
##  Min.   : 1.0
##  1st Qu.: 2.0
##  Median : 4.0
##  Mean   : 15.6
##  3rd Qu.: 18.0
##  Max.   :167.0
##  NA's    :685

```



```

## [1] "Generate agecat_new based on age_hours values"
## [1] "Cases where agecat != agecat_new"
## [1] 259

## # A tibble: 6 x 5
##   Admission.AgeA age_hours agecat agecat_new Admission.AgeC
##   <chr>          <dbl>   <chr>   <fct>    <chr>
## 1 Y              33     NB24    NB48     <NA>
## 2 Y              27     NB24    NB48     <NA>
## 3 Y              95     INF72   INF      <NA>
## 4 Y              1      NB24    FNB      <NA>
## 5 Y              67     INF     INF72    <NA>
## 6 Y              38     NB24    NB48     <NA>

```

There are some discrepancies between the age from Admission.AgeB (automatically generated by the app from date-time of birth and admission date-time) and the age category selected by the healthcare workers (recorded as Admission.AgeCat).

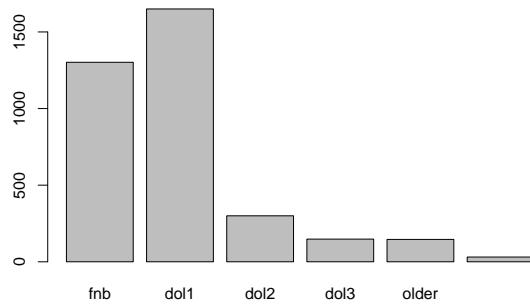
- These discrepancies occur in relatively few cases and likely represent a misunderstanding of the age category definitions by healthcare workers using the app.
- As Admission.AgeB is generated automatically by the app, it is less liable to errors than Admission.AgeCat.
- Therefore, the following rules will be applied to create the age variable:
 - Where Admission.AgeB is *not* missing, we use this variable to assign the age category.
 - Where Admission.AgeB is missing but Admission.AgeCat is *not* missing, we use the value of Admission.AgeCat.

- Where Admission.AgeCat is missing but Admission.Age == “N”, then the baby is older than one week, so is assigned to the “infant” category.
- Where all the above are missing, the new age variable is missing.

```
## [1] 14

## # A tibble: 14 x 4
##   Admission.AgeA Admission.AgeB  agecat pi_age
##   <chr>          <chr>        <chr>  <chr>
## 1 N              15 hours     <NA>    NB24
## 2 N              2 days, 6 hours <NA>    INF72
## 3 N              2 days, 3 hours <NA>    INF72
## 4 N              14 hours     <NA>    NB24
## 5 N              1 day, 17 hours <NA>    NB48
## 6 N              21 hours     <NA>    NB24
## 7 N              1 hour       <NA>    FNB
## 8 N              1 day, 3 hours <NA>    NB48
## 9 N              1 day, 20 hours <NA>    NB48
## 10 N             16 hours     <NA>    NB24
## 11 N             1 day, 3 hours <NA>    NB48
## 12 N             1 day       <NA>    NB48
## 13 N             1 day, 2 hours <NA>    NB48
## 14 N             1 day, 11 hours <NA>    NB48

##   pi_age
##   fnb   :1302
##   dol1  :1650
##   dol2  : 300
##   dol3  : 148
##   older: 146
##   NA's :  31
```



There are several cases where Admission.AgeA would suggest the baby is ≥ 1 week-old, yet Admission.AgeB (and, thus, pi_age) does not correlate with this. Admission.AgeB is likely the most accurate source of age and so this value will be used.

5.1.2.6 Admission.TypeBirth Categorical variable with six levels:

- Singleton

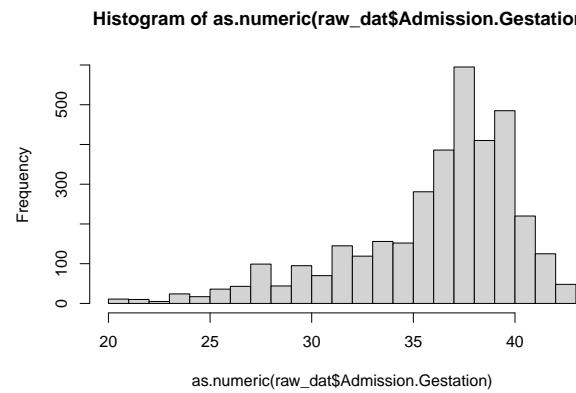
- Twin number 1
- Twin number 2
- Triplet number 1
- Triplet number 2
- Triplet number 3

No changes made to original data.

```
##  
##      S   Tr1   Tr2   Tr3   Tw1   Tw2 <NA>  
## 3217     6     5     6   187   153     3  
  
##      pi_type  
## singleton:3217  
## twin1      : 187  
## twin2      : 153  
## triplet1   :   6  
## triplet2   :   5  
## triplet3   :   6  
## NA's       :   3
```

5.1.2.7 Admission.Gestation Continuous variable measured in weeks. No changes made to original data.

```
##    Min. 1st Qu. Median     Mean 3rd Qu.     Max. NA's  
## 20.0   35.0   38.0   36.5   39.0   43.0     1
```



```
##      pi_gest  
## Min.   :20.0  
## 1st Qu.:35.0  
## Median :38.0  
## Mean   :36.5  
## 3rd Qu.:39.0  
## Max.   :43.0  
## NA's   :1
```

5.1.3 Examination

The variables to be subset/created from this section are as follows:

Parent variable	New variable(s)	Comments
Admission.Fontanelle	oe_fontanelle	<i>takes values</i> (factor)
Admission.Activity	oe_activity	<i>takes values</i> (factor)
Admission.SignsRD	oe_nasalflare	“NFL” (yes/no)
“ ”	oe_retractions	“CHI” (yes/no)
“ ”	oe_grunt	“GR” (yes/no)
Admission.WOB	oe_wob	<i>takes values</i> (factor), add “normal” if SignsRD == “None”, NA if SignsRD missing
Admission.Colour	oe_colour	<i>takes values</i> (factor)
Admission.Abdomen	oe_abdodist	“Dist” (yes/no)
Admission.Umbilicus	oe_omphalitis	“Inf” (yes/no)
Admission.Skin	oe_absskin	not “None” (yes/no)

5.1.3.1 Admission.Fontanelle Categorical variable with three levels:

- Bulging = “Bulging”
- Flat = “Flat”
- Sunken = “Sunken”

No changes made to original data.

```
##  
## Bulg Flat Sunk <NA>  
##   16 3546   15    0  
  
## oe_fontanelle  
## flat :3546  
## sunken : 15  
## bulging: 16
```

5.1.3.2 Admission.Activity Categorical variable with five levels:

- Alert = “Alert, active, appropriate”
- Coma = “Coma (unresponsive)”
- Convulsions = “Seizures, convulsions, or twitchings”
- Irritable = “Irritable”
- Lethargic = “Lethargic, quiet, decreased activity”

No changes made to original data.

```
##  
## Alert Coma Conv Irrit Leth <NA>  
## 2791    48     16    77   645      0
```

```

##      oe_activity
##  alert      :2791
##  lethargic: 645
##  irritable:  77
##  seizures :  16
##  coma       :   48

```

5.1.3.3 Admission.SignsRD Categorical variable with five levels:

- Chest retractions = “Chest in-drawings”
- Grunting = “Grunting”
- Nasal flaring = “Nasal flaring”
- ~~Gasping~~ = “~~Gasping~~”
- ~~Stridor~~ = “~~Stridor~~”
- Head nodding = “Head nodding”
- Tracheal tug = “Tracheal tug”
- None

Of these, only the first three categories are candidate predictors for this study. No changes made to original data.

```

##
##          CHI           CHI,GR        CHI,HN,NFL
##          268             71              1
##          CHI,NFL         CHI,NFL,GR      Gasp
##          488             307             45
##          Gasp,CHI         Gasp,CHI,GR    Gasp,CHI,NFL
##          16               7                19
##          Gasp,CHI,NFL,GR  Gasp,GR        Gasp,HN,CHI,NFL
##          20               4                1
##          Gasp,HN,CHI,NFL,GR  Gasp,NFL      Gasp,NFL,CHI
##          3                 3                6
##          Gasp,NFL,CHI,GR   GR              HN,CHI
##          4                 35               4
##          HN,CHI,GR         HN,CHI,NFL    HN,CHI,NFL,GR
##          5                 21               48
##          HN,NFL            HN,NFL,CHI   HN,NFL,CHI,GR
##          1                 1                7
##          HN,NFL,GR          NFL             NFL,CHI
##          1                 189              87
##          NFL,CHI,GR         NFL,GR        NFL,HN
##          31                44               1
##          NFL,HN,CHI         NFL,HN,GR    None
##          1                 1                1788
##          ST                ST,CHI        ST,CHI,NFL,GR
##          1                 1                1
##          ST,HN              ST,NFL        TT
##          1                 1                2
##          TT,CHI             TT,CHI,NFL   TT,CHI,NFL,GR
##          4                 8                10
##          TT,Gasp,CHI,NFL   TT,Gasp,CHI,NFL,GR TT,Gasp,HN,CHI,NFL,GR
##          1                 2                1
##          TT,Gasp,NFL,CHI,GR TT,HN,CHI     TT,HN,CHI,NFL,GR

```

```

##          1          1          6
##    TT,HN,NFL,CHI,GR    TT,NFL,CHI    TT,NFL,CHI,GR
##          1          3          1
##    TT,NFL,HN,CHI    TT,ST,CHI,NFL,GR <NA>
##          1          1          1
## oe_nasalflare oe_retractions oe_grunt
## no   :2253      no   :2117      no   :2964
## yes  :1323      yes  :1459      yes  : 612
## NA's:     1      NA's:     1      NA's:     1

```

5.1.3.4 Admission.WOB Categorical variable with three levels:

- Mildly increased work of breathing (WOB) = “Mild”
- Moderately increased WOB = “Moderate”
- Severely increased WOB = “Severe”

N.B. At the time of study, this variable was only completed if Admission.SignsRD was recorded as “nasal flaring”, “chest retractions”, “head nodding”, “grunting”, or “tracheal tug”. A value was *not* entered if Admission.SignsRD was recorded as “gasping” or “stridor”.

The following rules were applied to create the new WOB variable:

- NA if Admission.SignsRD is NA;
- “normal” if Admission.SignsRD == “none”;
- NA if Admission.SignsRD == “gasping” or “stridor”.

```

##          Mild  Mod  Sev <NA>
##    520  885  339 1833

##          oe_wob
## normal   :1788
## mild     : 519
## moderate: 885
## severe   : 338
## NA's     :  47

## [1] normal normal severe mild   mild   severe
## Levels: normal mild moderate severe

```

5.1.3.5 Admission.Colour Categorical variable with four levels:

- Pink = “Pink”
- Blue = “Blue”
- White = “White”
- Yellow = “Yellow”

No changes made to original data.

```

## 
##   Blue  Pink White  Yell  <NA>
##   129   3353    21     74      0

##   oe_colour
##   pink   :3353
##   pale   :  21
##   blue   : 129
##   yellow:  74

```

5.1.3.6 Admission.Abdomen

Categorical variable with eight levels:

- Distended = “Distended”
- Hepatomegaly = “Hepatomegaly”
- Splenomegaly = “Splenomegaly”
- Abdominal mass = “Abdominal mass”
- Gastrochisis = “Gastrochisis”
- Omphalocele = “Omphalocele”
- Prune belly = “Prune belly”
- Normal = “Soft and normal”

Of these, only abdominal distention is a candidate predictor for this study. No changes made to original data.

```

## 
##       AbMass        AbMass,Dist      AbMass,PrunB      Dist
##           4                  4                 1             45
##       Dist,PrunB          GSchis        HepMeg      HepMeg,Dist
##           1                  75                 2             1
##       Norm            Omph      Omph,Norm      PrunB,Norm
##           3419            15                 1             5
##       SplMeg,Dist  SplMeg,Dist,HepMeg      <NA>
##           1                  1                 2
## 

##   oe_abdodist
##   no   :3522
##   yes  : 53
##   NA's:   2

```

5.1.3.7 Admission.Umbilicus

Categorical variable with four levels:

- Infected = “Red skin all around umbilicus”
- Blood-stained = “Bleeding”
- Meconium-stained = “Meconium stained”
- Abnormal = “Abnormal looking”
- Hernia = “Umbilical hernia”
- Normal = “Healthy and clean”

Of these, only omphalitis (i.e. “infected” umbilicus) is a candidate predictor for this study. No changes made to original data.

```

##          Abn      Abn,H      Bl      Bl,H      H      Inf  Inf ,Abn      Mec      Norm      <NA>
##          52         1         6         1         4        16         1        64      3432         0
## oe_omphalitis
## no :3560
## yes: 17

```

5.1.3.8 Admission.Skin Categorical variable with four levels:

- Pustules = “Pustules all over”
- Abscess = “Big boil/abscess”
- Rash = “Other skin rash”
- None = “Normal”

Due to distribution of categories, dichotomised into “abnormal skin” yes/no.

```

##          None      Rash  Rash,PUST      <NA>
##          3540       36         1         0
## oe_abskin
## no :3540
## yes: 37

```

5.1.4 Symptom review

The variables to be subset/created from this section are as follows:

Parent variable	New variable(s)	Comments
Admission.Vomiting	hx_vomit	<i>modified values</i> (factor)

5.1.4.1 Admission.Vomiting Categorical variable with five levels:

- Yes, vomiting = “Vomiting all feeds”
- Yes, green vomit = “Vomiting bright green”
- Yes, bloody vomit = “Vomiting with blood”
- Posseting = “Small milky possets after feeds (normal)”
- No vomiting = “NONE”

In the original variable, some cases were coded with multiple categories. The new variable was recoded to ensure mutually exclusive groups.

```

##          No      Poss      Yes  Yes ,YesGr      YesBl      YesGr      <NA>
##          3482       21        18         2           6        48           0
##          hx_vomit
## no :3503
## yellow : 18
## bilious: 50
## bloody : 6

```

5.1.5 Maternal history (obstetric history)

The variables to be subset/created from this section are as follows:

Parent variable	New variable(s)	Comments
Admission.ROMlength	oh_prom2	“PROM” (yes/no)
Admission.RFSepsis	oh_prom	“PROM” (yes/no)
“ ”	oh_matfever	“MF” (yes/no)
“ ”	oh_offliquor	“OL” (yes/no)
Both of the above	co_prom	“yes” if oh_prom OR oh_prom2 == “yes” (yes/no)
Admission.ModeDelivery	oh_delivery	<i>takes values (factor)</i>

5.1.5.1 Admission.ROMlength Binary categorical variable:

- PROM = “>18 hours”
- NOPROM = “<18 hours”

No changes made to original data.

N.B. This is one of two PROM-related data points collected:

1. Admission.ROMlength (this variable)
2. Admission.RFSepsis (categorical variable with one category for PROM) - see below

```
##
##  NOPROM    PROM    <NA>
##    1894     361    1322

##
##  no    yes <NA>
##  1894   361  1322
```

5.1.5.2 Admission.RFSepsis Categorical variable with seven levels:

- Prolonged rupture of membranes = “PROM more than 18 hrs”
- Maternal fever during labour = “Maternal fever in labour”
- Offensive liquor = “Offensive liquor”
- Prematurity = “Prematurity <37 weeks”
- Prolonged second stage of labour = “Prolonged second stage”
- Born before arrival to hospital = “Born before arrival (BBA)”
- None

Of these, only the first three are candidate predictors for this study. Although prematurity is also a candidate predictor, this information is obtained more precisely from Admission.Gestation (*see above*).

No changes made to original data.

```

##          BBA        BBA,OL      BBA,Prem       MF      MF,BBA,Prem
##          127           1          27            8            2
## MF,Pr2nd,OL MF,Pr2nd,PROM MF,Prem MF,Prem,BBA MF,PROM
##          1           2          4            1            3
## MF,PROM,OL MF,PROM,Prem,OL NONE OL OL,Prem
##          1           1          2029          89            2
## Pr2nd      Pr2nd,OL     Pr2nd,Prem   Pr2nd,PROM Pr2nd,PROM,OL
##          63           16          5            16            5
## Pr2nd,PROM,Prem      Prem      Prem,BBA Prem,OL PROM
##          1           773          69            11            167
## PROM,BBA    PROM,BBA,Prem PROM,OL PROM,OL,Prem PROM,Prem
##          1           1           39            2            100
## PROM,Prem,BBA    PROM,Prem,OL <NA>
##          2           7            1
## oh_prom      oh_matfever oh_offliquor
## no :3228     no :3553    no :3401
## yes : 348    yes : 23    yes : 175
## NA's: 1     NA's: 1     NA's: 1

```

5.1.5.3 Creating a single variable to capture PROM As mentioned above, there are two PROM-related data points collected:

1. Admission.ROMlength - now oh_prom2 from above
2. Admission.RFSepsis == "PROM" - now oh_prom from above

Recoded into a single variable with “yes” if either of the above variables suggest the presence of PROM.

```

## [1] "Compare coding & distribution between both PROM variables..."

## oh_prom      oh_prom2
## no :3228     no :1894
## yes : 348    yes : 361
## NA's: 1     NA's:1322

##          no  yes
## no  1881   36
## yes  12   325

## [1] "New combined variable..."

## no  yes
## 3193 384

```

5.1.5.4 Admission.ModeDelivery Categorical variable with five levels:

- Emergency caesarean section = “Emergency caesarean section”
- Elective caesarean section = “Elective caesarean section”

- Forceps = “Forceps extraction”
- Spontaneous vaginal delivery = “Spontaneous vaginal delivery”
- Ventouse = “Vacuum extraction”

No changes made to original data.

```
##  
##  ECS  E1CS  For  SVD  Vent <NA>  
##  726   186     1 2620    44      0  
  
##          oh_delivery  
##  svd       :2620  
##  electiveCS : 186  
##  emergencyCS: 726  
##  forceps    :    1  
##  ventouse   :   44
```

5.2 Data collected by outcome forms

There are two groups of outcome variables to consider:

1. Participant demographics
2. Model outcome data

5.2.1 Participant demographics

The variables to be subset/created from this section are as follows:

Parent variable	New variable(s)	Comments
Discharge.session	dis_session	(string)
Discharge.NeoTreeID	dis_uid	(string)
Discharge.NeoTreeOutcome	outcome	takes values (factor)
Discharge.DateTimeDischarge	outcome_datetime	(date-time)
Discharge.DateTimeDeath	outcome_datetime	(date-time)
<i>several</i>	adm_dur	(period)

5.2.1.1 Discharge.NeoTreeID & Discharge.session String variables.

- Discharge.NeoTreeID = the unique identifier for each baby, automatically generated by the Neotree app when a new admission form is created. Entered manually by the healthcare worker completing the outcome form.
- Discharge.NeoTreeID_alphanum = the unique identifier but with non-alphanumeric characters removed. Used for record linkage.
- Discharge.session = a unique number assigned to each row of data when imported from the raw JSON files (i.e., `seq_along(1:nrow(data))`). Can be used to merge columns from other data frames if required in future analyses.

No changes made to original data.

```
##  dis_uid      dis_session  
##  Length:3577      Length:3577  
##  Class :character  Class :character  
##  Mode  :character  Mode  :character
```

5.2.1.2 Discharge.NeoTreeOutcome Categorical variable with five levels:

- Discharged = “Discharged”
- Death = “Died”
- Transferred within the hospital = “Transferred to other ward”
- Transferred to another hospital or facility = “Transferred to other hospital”
- Absconded = “Absconded”

Dichotomised into died/discharged. For this study, we considered a participant to be discharged if any outcome other than “death” was recorded.

```
##  
##   ABS    DC    NND    TRH    TRO <NA>  
##   3 2887  679     6     2     0  
  
##           outcome  
##   died      : 679  
##   discharged:2898
```

5.2.1.3 Discharge.DateTimeDischarge & Discharge.DateTimeDeath String variables representing dates.

```
## [1] "Ensure outcome matches date variable recorded..."  
  
## [1] "Discharge.DateTimeDischarge missing..."  
  
## [1] 2900  
  
## [1] "Discharge.DateTimeDeath missing..."  
  
## [1] 681  
  
## [1] "Both missing..."  
  
## [1] 4
```

There are 4 cases where both a discharge date and date of death are recorded. For these, we used the date corresponding to the recorded outcome.

5.2.1.4 Admission duration It is useful to have a variable denoting the admission duration for each participant. Calculated from the admission and outcome dates.

```
##   Min. 1st Qu. Median   Mean 3rd Qu.   Max.  
## -0.708   1.288   2.547   5.204   5.612  85.053  
  
## [1] 48
```

There are 48 cases where admission duration is ≤ 0 .

- These most likely represent errors when inputting the admission and/or outcome date.
- Although a tolerance of outcome date ≤ 1 day prior to admission date was allowed for record linkage, cases with negative admission durations were excluded from the main analysis because this anomaly questioned the accuracy of some other variables for that participant, e.g., chronological age (which is calculated automatically within the app from birth date-time and admission date-time).

5.3 Model outcome data

The primary outcome was early-onset sepsis, defined as sepsis with onset within the first 72 hours of life, as diagnosed by the treating consultant neonatologist.

5.3.1 Supporting variables

The variables required to create the outcome variable are as follows:

Variable	Comments
Discharge.DIAGDIS1	Primary discharge diagnosis
Discharge.DIAGDIS1OT	Free text field if primary discharge diagnosis == "other"
Discharge.OthProbs	Other problems during admission
Discharge.OthProbsOth	Free text field if other problems == "other"
Discharge.CauseDeath	Primary cause of death
Discharge.CauseDeathOther	Free text field if primary cause of death == "other"
Discharge.ContCauseDeath	Contributory cause(s) of death
Discharge.ContCauseDeathOth	Free text field of contributory cause of death == "other"

```
##
##      AN    BBA     BI     BO     CHD    DEHY   EONS     FD      G     HIE    HIVX HIVXH HIVXL
##      4     95     11     4      8      8    197     38      8    376     11     15     48
##  JAUN    LBW    LONS     MA    Mac     MD     NB    OCA     OM    OTH     PN     PR PRRDS
##  231    126     26    119    134      4     40     29     12    314      9    166    269
##    Ri  Safe    TTN   Twin <NA>
##    72    220    294     11    678

##
##      ASP      CA    EONS Gastro     HIE    LONS     MAS     NEC     OTH      PN      PR
##      22      17     35     75    117     10      5      2     63      6     39
##  PRRDS <NA>
##  288    2898

## [1] "Ensure all discharges have discharge diagnosis recorded...""

## [1] 0

## [1] 0

## [1] "Ensure all deaths have cause of death recorded...""

## [1] 0

## [1] 0

## [1] "New variables..."
```

```

##      diagnosis   diagnosis_other      diagnosis2   diagnosis2_other
## HIE      : 376    Length:3577      NONE     :1449    Length:3577
## OTH      : 314    Class  :character  OTH      : 231    Class  :character
## TTN      : 294    Mode   :character  LBW      : 181    Mode   :character
## PRRDS    : 269                JAU      : 147
## JAUN     : 231                HIVX     :  95
## (Other):1415               (Other): 795
## NA's     : 678    NA's     : 679
## cause_death cause_death_other cause_death2 cause_death2_other
## PRRDS    : 288    Length:3577      NONE     : 221    Length:3577
## HIE      : 117    Class  :character  LBW      :  78    Class  :character
## Gastro   :  75    Mode   :character  OTH      :  45    Mode   :character
## OTH      :  63                PRRDS     :  33
## PR       :  39                EONS      :  25
## (Other):  97               (Other): 277
## NA's     :2898               NA's      :2898

```

5.3.2 Outcome variable (early-onset neonatal sepsis)

Binary categorical variable of early-onset sepsis yes/no.

First, we explored the free text fields for variations of “early-onset sepsis” that would need to be captured by the outcome variable:

```

# Explore free text (too long to print in full):

# clean_dat %>%
#   select(diagnosis_other) %>%
#   filter(grepl("sepleons/early", diagnosis_other, ignore.case = T))
#
# clean_dat %>%
#   select(diagnosis2_other) %>%
#   filter(grepl("sepleons/early", diagnosis2_other, ignore.case = T))
#
# clean_dat %>%
#   select(cause_death_other) %>%
#   filter(grepl("sepleons/early", cause_death_other, ignore.case = T))
#
# clean_dat %>%
#   select(cause_death2_other) %>%
#   filter(grepl("sepleons/early", cause_death2_other, ignore.case = T))

```

Relevant free text entries identified:

Variable	Relevant free text entries
Discharge.DIAGDIS1OT	<i>None</i>
Discharge.OthProbsOth	“Early Onset Neonatal Sepsis”
Discharge.CauseDeathOther	“Early onset neonatal sepsis”, “earlyonset neonatal sepsis”
Discharge.ContCauseDeathOth	<i>None</i>

N.B. “Risk of sepsis”, “unconfirmed sepsis” or “sepsis” were not included.

Next, we created the outcome variable.

```

# Create variable
clean_dat <- clean_dat %>%
  mutate(sepsis = factor(
    case_when(
      # 1. Discharge diagnosis of EONS:
      diagnosis == "EONS" ~ "yes",
      # 2. Other discharge problem includes EONS:
      grepl("EONS", diagnosis2) ~ "yes",
      grepl("Early Onset Neonatal Sepsis", diagnosis2_other) ~ "yes",
      # 3. Cause of death of EONS:
      cause_death == "EONS" ~ "yes",
      grepl(
        "Early onset neonatal sepsis|earlyonset neonatal sepsis",
        cause_death_other
      ) ~ "yes",
      # 4. Contributory cause of death includes EONS:
      grepl("EONS", cause_death2) ~ "yes",
      # Else, no diagnosis of EONS:
      TRUE ~ "no"
    )
  )))
}

# Check new variable
clean_dat %>%
  select(sepsis) %>%
  summary()

```

```

##  sepsis
##  no :3170
##  yes: 407

```

5.3.3 Inclusion and exclusion criteria

Our inclusion and exclusion criteria were:

Inclusion criteria	Exclusion criteria
Chronological age <72 hours	Not singletons or first-born multiples
Gestation 32+0 weeks at birth	Died at admission to the unit (HR or RR = 0)
Birth weight 1500 grams	Major congenital anomalies*
-	Anomalous admission duration (<0 days)

*Major congenital anomalies included congenital heart defects, open spina bifida, gastroschisis or omphalocele, and/or genetic syndromes.

The counts of participants excluded due to each criterion are:

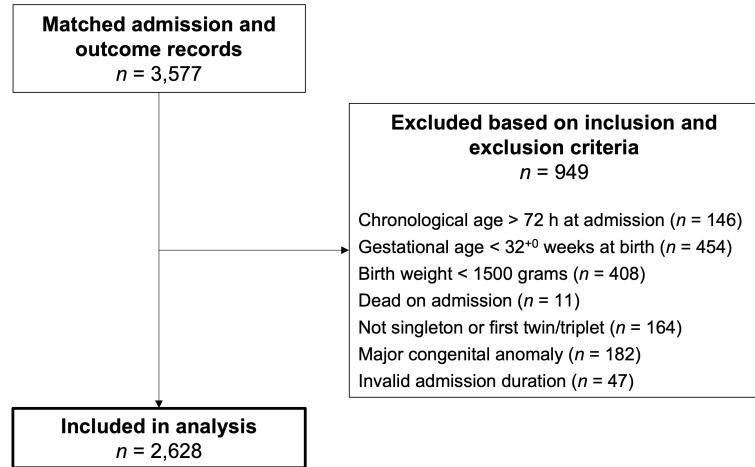
```

## # A tibble: 7 x 2
##   criterion           count
##   <chr>                <int>
## 1 Admitted 72h of life     146
## 2 Very premature          454

```

## 3 Very low birth weight	408
## 4 Dead on admission	11
## 5 Not singleton or first-born multiple	164
## 6 Major congenital anomaly	182
## 7 Anomalous admission duration	47

5.3.4 Flow diagram of participant inclusion



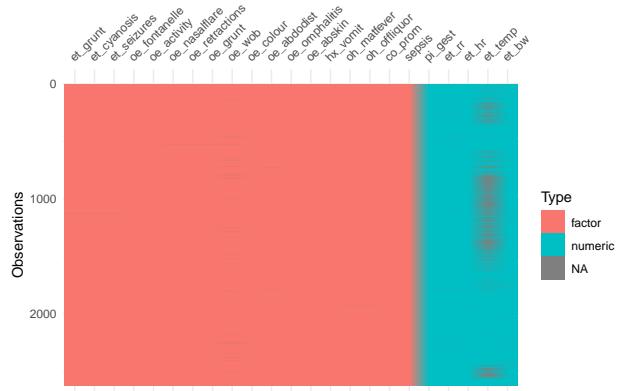
6 Missing data

Description of missing data analysis.

6.1 Assess missingness

6.1.1 Visualise data frame

A graphical representation of the data types and proportion of missing values for each variable is shown below. Ancillary variables that are not required for modelling are not shown. Variables in the data frame are plotted on the x-axis and each observation (i.e. participant) is plotted on the y-axis. Missing values are shaded grey.



6.1.2 Variable-wise missingness

The number and percentage of missing values for each variable is shown below. In total, 14 variables had missing values.

```
## # A tibble: 23 x 3
##   variable      n_miss pct_miss
##   <chr>        <int>    <dbl>
## 1 et_temp       814    31.0
## 2 et_bw         32     1.22
## 3 oe_wob        26    0.989
## 4 et_rr         22    0.837
## 5 et_hr          3    0.114
## 6 oe_abdodist   2    0.0761
## 7 et_grunt       1    0.0381
## 8 et_cyanosis    1    0.0381
## 9 et_seizures    1    0.0381
## 10 oe_nasalflare 1    0.0381
## 11 oe_retractions 1    0.0381
## 12 oe_grunt       1    0.0381
## 13 oh_matfever    1    0.0381
## 14 oh_offliquor   1    0.0381
## 15 pi_gest        0     0
## 16 oe_fontanelle   0     0
## 17 oe_activity      0     0
```

```

## 18 oe_colour          0  0
## 19 oe_omphalitis      0  0
## 20 oe_abskin          0  0
## 21 hx_vomit           0  0
## 22 co_prom            0  0
## 23 sepsis             0  0

```

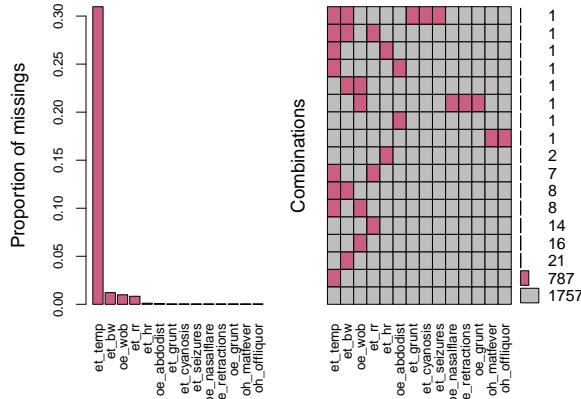
6.1.3 Case-wise missingness

Most participants had no missing data and, among those who did, the majority were only missing values for one predictor (most commonly temperature at admission).

```

## # A tibble: 6 x 3
##   n_miss_in_case n_cases pct_cases
##       <int>     <int>     <dbl>
## 1 0           1757    66.9
## 2 1           841     32.0
## 3 2           27      1.03
## 4 3           1       0.0381
## 5 4           1       0.0381
## 6 5           1       0.0381

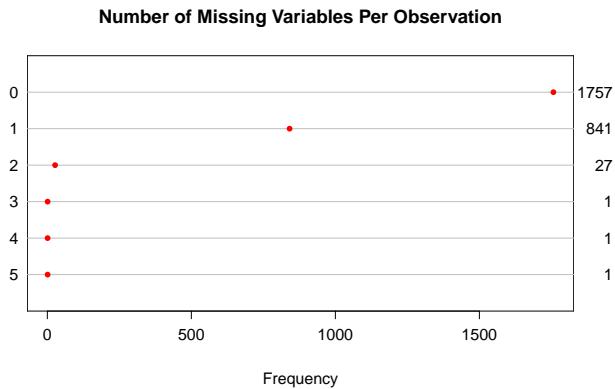
```



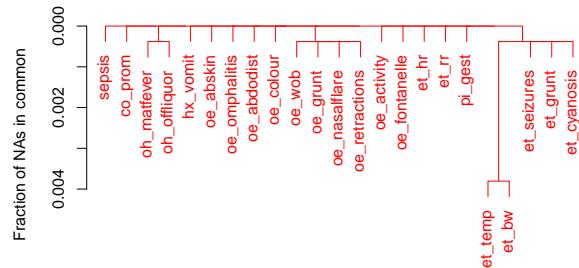
```

##
## Variables sorted by number of missings:
##           Variable      Count
## 1 et_temp        0.309741248
## 2 et_bw          0.012176560
## 3 oe_wob         0.009893455
## 4 et_rr          0.008371385
## 5 et_hr          0.001141553
## 6 oe_abdodist    0.000761035
## 7 et_grunt        0.000380518
## 8 et_cyanosis     0.000380518
## 9 et_seizures     0.000380518
## 10 oe_nasalflare 0.000380518
## 11 oe_retractions 0.000380518
## 12 oe_grunt        0.000380518
## 13 oh_matfever     0.000380518
## 14 oh_offliquor    0.000380518

```



The dendrogram below shows predictors that were commonly missing together.



6.1.4 Relationship between missing temperature and the study outcome

There was no evidence of an association between having a missing value for temperature at admission and the primary outcome of early-onset sepsis:

```
##  
##      no   yes  
##    0 1596  218  
##    1  735   79  
  
##  
## Call:  
## glm(formula = sepsis ~ na_temp, family = "binomial", data = dat)  
##  
## Deviance Residuals:  
##      Min       1Q     Median       3Q      Max  
## -0.506  -0.506  -0.506  -0.452   2.160  
##  
## Coefficients:  
##             Estimate Std. Error z value Pr(>|z|)  
## (Intercept) -1.9908     0.0722 -27.57  <2e-16 ***  
## na_temp     -0.2397     0.1387  -1.73   0.084 .
```

```

## ---
## Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## (Dispersion parameter for binomial family taken to be 1)
##
## Null deviance: 1854.2 on 2627 degrees of freedom
## Residual deviance: 1851.1 on 2626 degrees of freedom
## AIC: 1855
##
## Number of Fisher Scoring iterations: 4

```

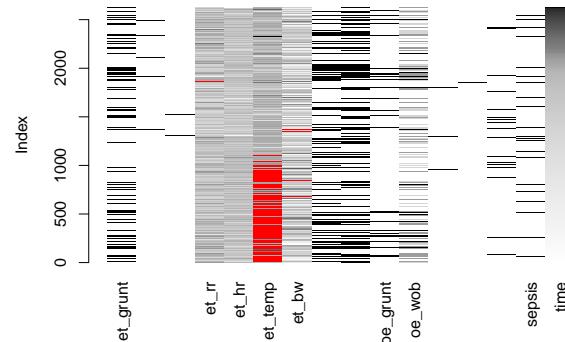
Characteristic	**OR**	**95% CI**	**p-value**
na_temp	0.79	0.60, 1.03	0.084

6.1.5 Relationship between missing temperature and time

Towards the start of the Neotree project, there was a limited number of thermometers available to measure temperature and, therefore, time since the start of the study is a plausible predictor of missingness.

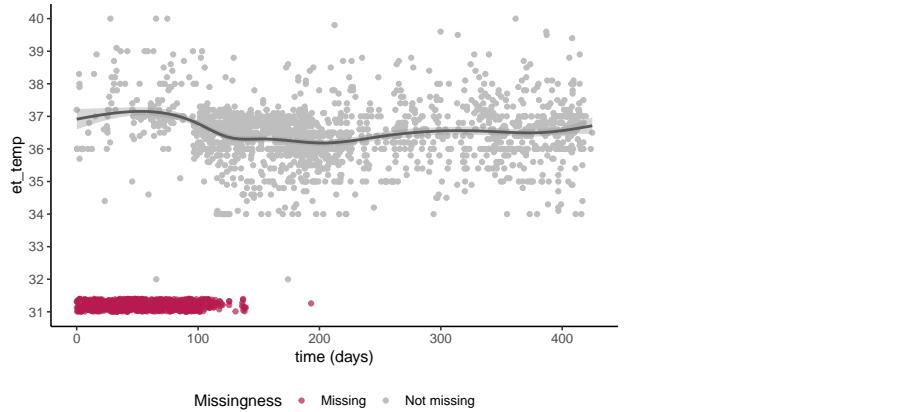
Indeed, most missing values for temperature at admission occurred near the start of data collection. This suggests that temperature was missing at random (MAR) conditional on time since start of the project.

The matrix plot below shows missing values in red, with each participant sorted by their admission date (i.e. time since the start of data collection).



Furthermore, the below figure and a logistic regression analysis demonstrate that time since the start of data collection was a significant predictor of temperature at admission being missing.

Notably, the average recorded temperature was approximately 0.5°C higher during the first 100 days compared to the rest of the data collection period. It is plausible that, during the first 100 days, healthcare workers were more likely to record temperature for ‘sicker’ babies who were thus more likely to have an elevated temperature. Nevertheless, a wide range of participant characteristics were collected by the Neotree app and were included in the imputation model.



```
##
## Call:
## glm(formula = na_temp ~ time, family = "binomial", data = dat)
##
## Deviance Residuals:
##      Min       1Q   Median       3Q      Max
## -2.6405  -0.3237  -0.0218   0.3853   2.9314
##
## Coefficients:
##             Estimate Std. Error z value Pr(>|z|)
## (Intercept) 3.45556   0.16478   21.0 <2e-16 ***
## time        -0.04006   0.00172  -23.2 <2e-16 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## (Dispersion parameter for binomial family taken to be 1)
##
## Null deviance: 3252.9 on 2627 degrees of freedom
## Residual deviance: 1462.6 on 2626 degrees of freedom
## AIC: 1467
##
## Number of Fisher Scoring iterations: 7
```

Characteristic	**OR**	**95% CI**	**p-value**
time	0.96	0.96, 0.96	<0.001

6.2 Impute missing values

The imputation model contained all candidate predictors, the outcome of sepsis, and ancillary variables included in the descriptive analysis or that were determined to predict missingness (i.e. time, see above).

Data were assumed to be MAR and 40 imputed datasets were created with 20 iterations. There is no consensus on the optimal number of imputations for multiple imputation, but 40 was chosen based on 33.1% of participants having at least one missing value.

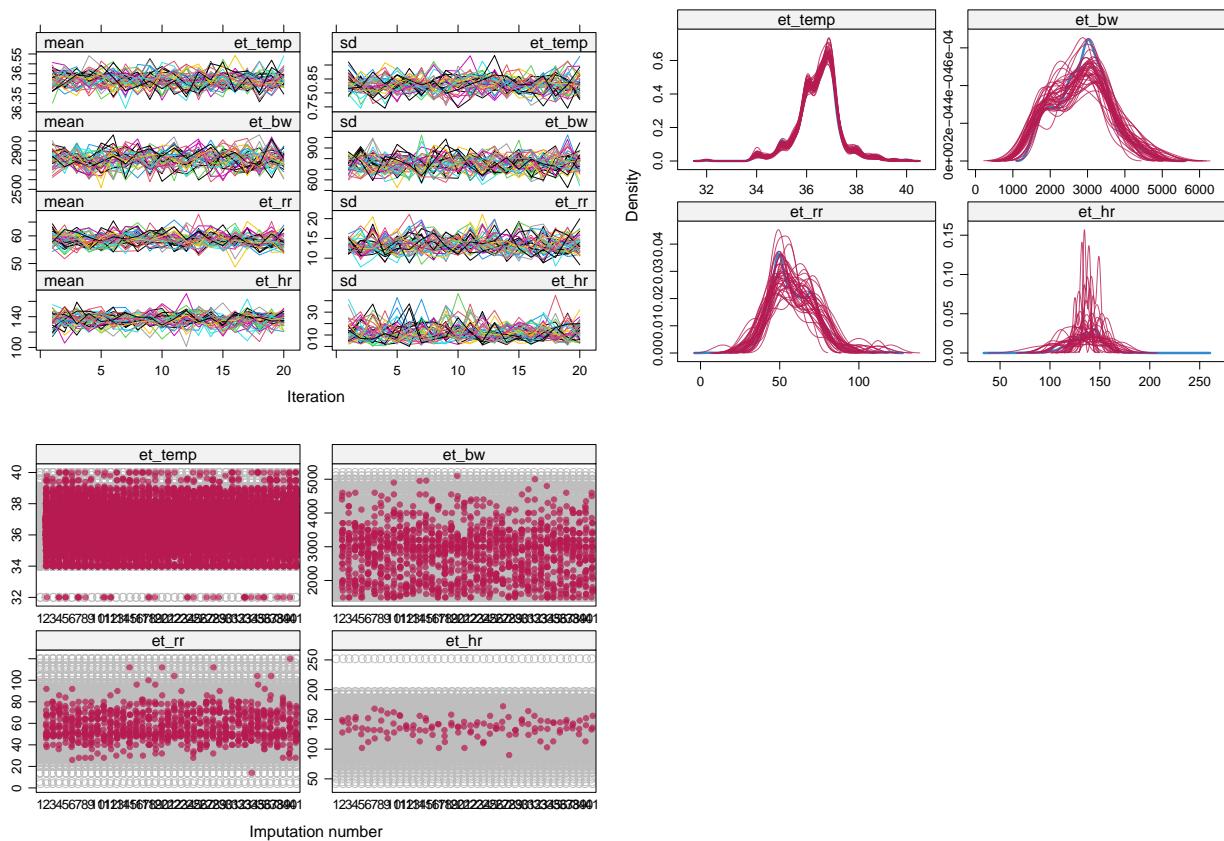
The performance of the imputation model is shown below:

```
## [1] "Imputation method for each variable..."
```

```

##      pi_gest      et_bw      oh_matfever      oh_offliquor      co_prom
##      ""          "pmm"       "logreg"        "logreg"        ""
##      et_grunt     et_rr       et_hr          et_temp         oe_activity
##      "logreg"    "pmm"       "pmm"          "pmm"          ""
##      oe_nasalflare oe_retractions oe_grunt        oe_wob        et_cyanosis
##      "logreg"    "logreg"    "logreg"       "polyreg"     "logreg"
##      et_seizures  oe_fontanelle oe_colour       oe_abdodist oe_omphalitis
##      "logreg"    ""          ""           "logreg"      ""
##      oe_abskin    hx_vomit    sepsis        time          pi_sex
##      ""          ""          ""           ""           ""
##      pi_age       outcome    "polyreg"
##      "polyreg"
## [1] "Diagnostic plots..."

```

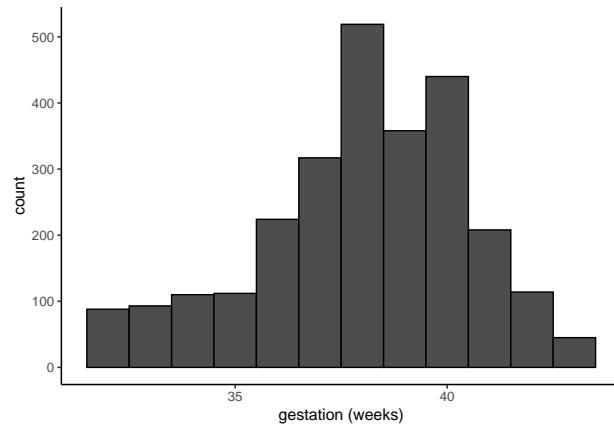


7 Descriptive statistics

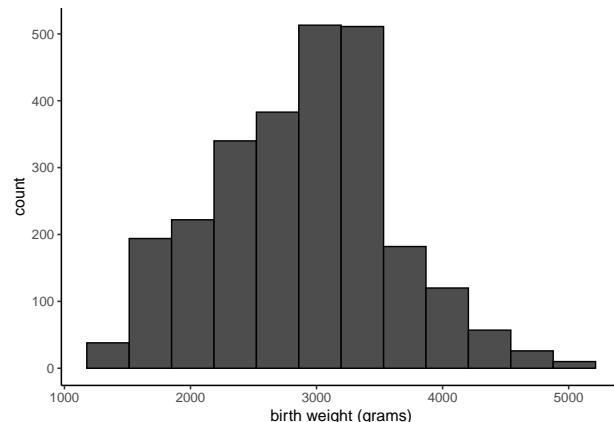
Descriptive analysis of included participants. Data are presented for the observed data only (i.e. before MICE) using pairwise deletion of missing values.

7.1 Distribution of continuous variables

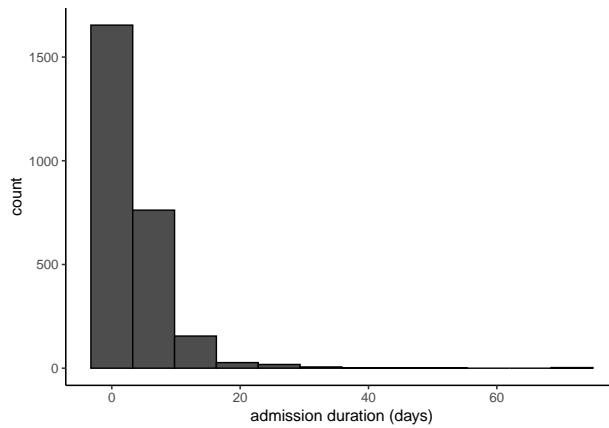
```
## $pi_gest
```



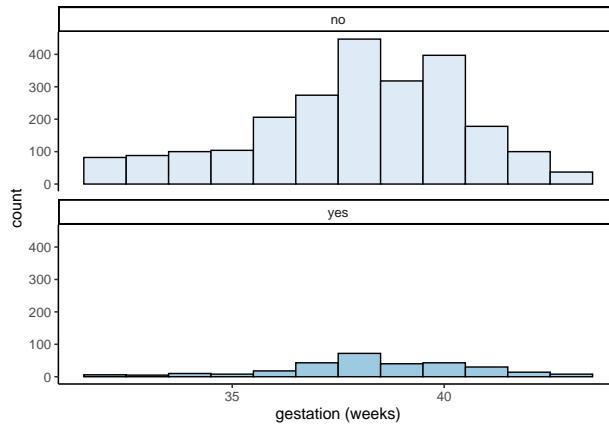
```
##  
## $et_bw
```



```
##  
## $adm_dur
```

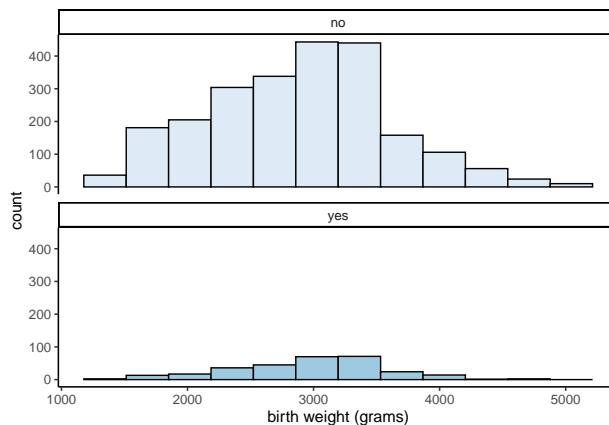


```
## $pi_gest
```



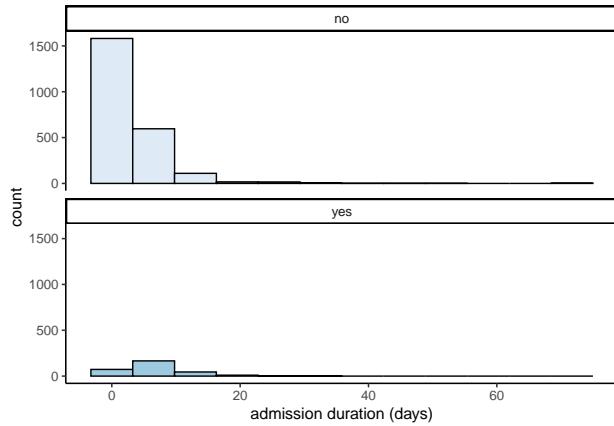
```
##
```

```
## $et_bw
```



```
##
```

```
## $adm_dur
```



“Gestation” and “birth weight” are approximately normally distributed, while “admission duration” is very right-skewed.

7.2 Table 1

Table summarising the characteristics of included participants:

Characteristic	Overall, N = 2,628	no, N = 2,331	yes, N = 297	p-value
Sex, n (%)				0.7
f	1,122 (43%)	990 (42%)	132 (44%)	
m	1,503 (57%)	1,338 (57%)	165 (56%)	
u	3 (0.1%)	3 (0.1%)	0 (0%)	
Gestational age, mean weeks (SD)	38.00 (2.50)	37.96 (2.52)	38.36 (2.29)	0.005
Birth weight, mean grams (SD)	2,889 (703)	2,881 (716)	2,950 (595)	0.067
Chronological age, n (%)				<0.001
fnb	1,001 (38%)	901 (39%)	100 (34%)	
dol1	1,257 (48%)	1,136 (49%)	121 (41%)	
dol2	235 (9.0%)	181 (7.8%)	54 (18%)	
dol3	110 (4.2%)	91 (3.9%)	19 (6.5%)	
Type of birth, n (%)				0.032
singleton	2,496 (95%)	2,205 (95%)	291 (98%)	
twin1	127 (4.8%)	121 (5.2%)	6 (2.0%)	
triplet1	2 (<0.1%)	2 (<0.1%)	0 (0%)	
Mode of delivery, n (%)				0.074
svd	1,889 (72%)	1,663 (71%)	226 (76%)	
electiveCS	136 (5.2%)	124 (5.3%)	12 (4.0%)	
emergencyCS	561 (21%)	510 (22%)	51 (17%)	
instrumental	42 (1.6%)	34 (1.5%)	8 (2.7%)	
Admission duration, median days [Q1-Q3]	2.3 [1.3-4.9]	2.1 [1.2-4.1]	6.0 [3.5-8.8]	<0.001
Death, n (%)	221 (8.4%)	184 (7.9%)	37 (12%)	0.008

p-values are from Welch’s two-sample t-test for gestational age and birth weight; the Wilcoxon-Mann-Whitney U test for admission duration; Pearson’s chi-squared test for age at admission and death; and Fisher’s exact test for sex, type of birth and mode of delivery.

Data are presented for the observed data only (i.e. before MICE) using pairwise deletion of missing values. The number of missing values for each variable in the above table are as follows:

```
## # A tibble: 9 x 3
```

```

##   variable    n_miss pct_miss
##   <chr>        <int>    <dbl>
## 1 et_bw         32     1.22
## 2 pi_age        25     0.951
## 3 pi_type        3     0.114
## 4 pi_sex         0      0
## 5 pi_gest        0      0
## 6 oh_delivery    0      0
## 7 adm_dur        0      0
## 8 outcome         0      0
## 9 sepsis         0      0

```

7.3 Distribution of candidate predictors

Characteristic	Overall, N = 2,628	no, N = 2,331	yes, N = 297	p-value ¹
pi_gest	38.00 [37.00-40.00]	38.00 [37.00-40.00]	38.00 [37.00-40.00]	0.032
et_bw	2,950 [2,400-3,350]	2,900 [2,400-3,350]	3,000 [2,600-3,350]	0.035
oh_matfever	14 (0.5%)	8 (0.3%)	6 (2.0%)	0.003
oh_offliquor	163 (6.2%)	131 (5.6%)	32 (11%)	0.001
co_prom	303 (12%)	257 (11%)	46 (15%)	0.027
et_grunt	750 (29%)	654 (28%)	96 (32%)	0.13
et_cyanosis	69 (2.6%)	60 (2.6%)	9 (3.0%)	0.6
et_seizures	14 (0.5%)	10 (0.4%)	4 (1.3%)	0.064
et_rr	56 [48-68]	56 [48-68]	60 [50-72]	<0.001
et_hr	138 [126-146]	138 [126-146]	139 [127-150]	0.011
et_temp	36.50 [36.00-37.00]	36.50 [36.00-36.90]	36.90 [36.20-38.00]	<0.001
oe_fontanelle				0.9
flat	2,608 (99%)	2,312 (99%)	296 (100%)	
sunken	10 (0.4%)	9 (0.4%)	1 (0.3%)	
bulging	10 (0.4%)	10 (0.4%)	0 (0%)	
oe_activity				<0.001
alert	2,152 (82%)	1,933 (83%)	219 (74%)	
lethargic	382 (15%)	327 (14%)	55 (19%)	
irritable	62 (2.4%)	45 (1.9%)	17 (5.7%)	
seizures	14 (0.5%)	9 (0.4%)	5 (1.7%)	
coma	18 (0.7%)	17 (0.7%)	1 (0.3%)	
oe_nasalflare	912 (35%)	791 (34%)	121 (41%)	0.023
oe_retractions	986 (38%)	848 (36%)	138 (46%)	<0.001
oe_grunt	421 (16%)	360 (15%)	61 (21%)	0.029
oe_wob				<0.001
normal	1,405 (54%)	1,263 (55%)	142 (48%)	
mild	413 (16%)	378 (16%)	35 (12%)	
moderate	614 (24%)	529 (23%)	85 (29%)	
severe	170 (6.5%)	139 (6.0%)	31 (11%)	
oe_colour				0.11
pink	2,507 (95%)	2,220 (95%)	287 (97%)	
pale	10 (0.4%)	7 (0.3%)	3 (1.0%)	
blue	62 (2.4%)	58 (2.5%)	4 (1.3%)	
yellow	49 (1.9%)	46 (2.0%)	3 (1.0%)	
oe_abdodist	28 (1.1%)	26 (1.1%)	2 (0.7%)	0.8
oe_omphalitis	6 (0.2%)	4 (0.2%)	2 (0.7%)	0.14
oe_abskin	27 (1.0%)	23 (1.0%)	4 (1.3%)	0.5

hx_vomit				0.3
no	2,605 (99%)	2,309 (99%)	296 (100%)	
yellow	7 (0.3%)	7 (0.3%)	0 (0%)	
bilious	13 (0.5%)	13 (0.6%)	0 (0%)	
bloody	3 (0.1%)	2 (<0.1%)	1 (0.3%)	

¹Data are presented as median [Q1-Q3] for continuous predictors or n (%) for categorical predictors. p-values are from the Wilcoxon-Mann-Whitney U test for continuous predictors and Fisher's exact test for categorical predictors.

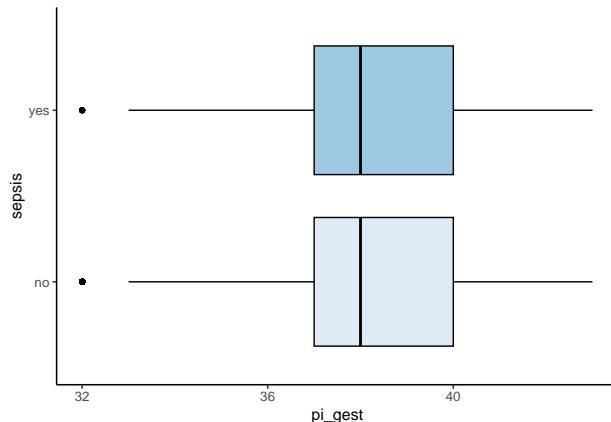
Data are presented for the observed data only (i.e. before MICE) using pairwise deletion of missing values. The number of missing values for each variable in the above table are as follows:

```
## # A tibble: 22 x 3
##   variable     n_miss pct_miss
##   <chr>       <int>    <dbl>
## 1 et_temp      814    31.0
## 2 et_bw        32     1.22
## 3 oe_wob       26    0.989
## 4 et_rr        22    0.837
## 5 et_hr         3    0.114
## 6 oe_abdodist   2    0.0761
## 7 oh_matfever   1    0.0381
## 8 oh_offliquor  1    0.0381
## 9 et_grunt      1    0.0381
## 10 et_cyanosis   1    0.0381
## # ... with 12 more rows
```

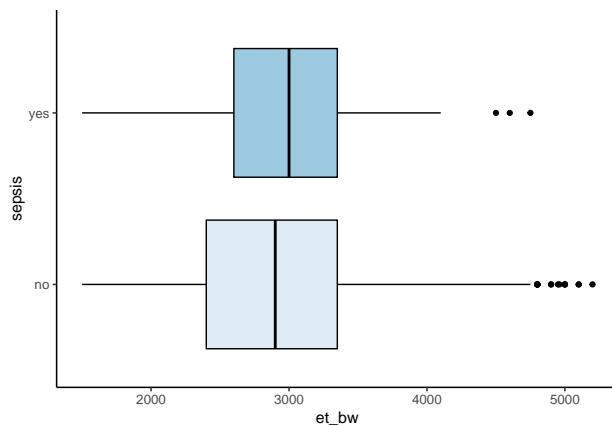
7.3.1 Box plots of continuous candidate predictors

The box plots below show the distribution of the continuous candidate predictors between participants with and without sepsis.

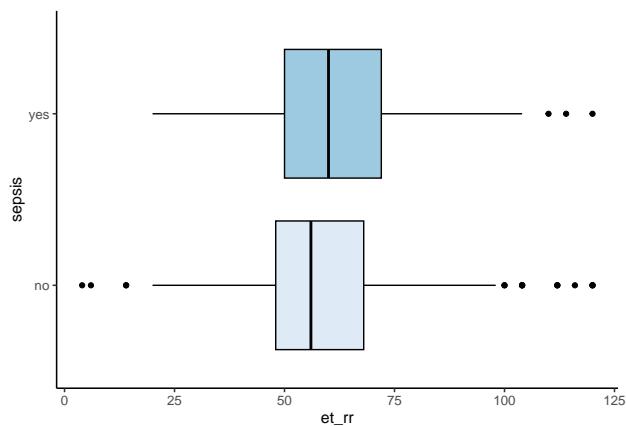
```
## $pi_gest
```



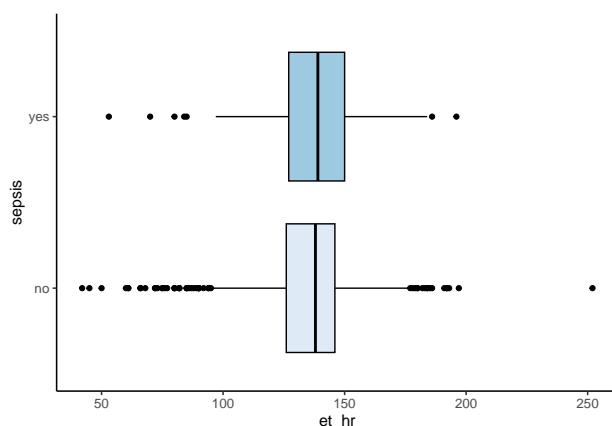
```
##
## $et_bw
```



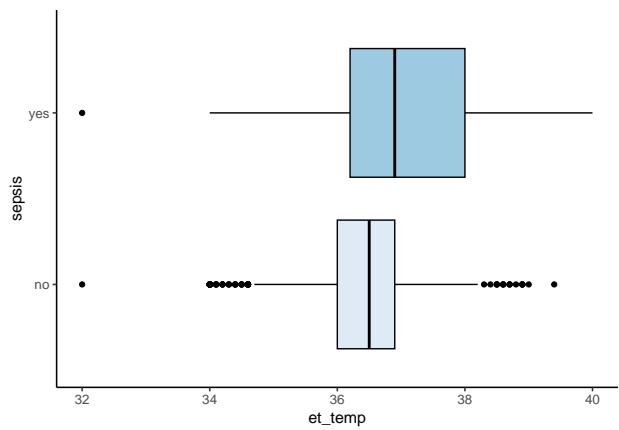
```
##  
## $et_rr
```



```
##  
## $et_hr
```



```
##  
## $et_temp
```



8 Model development and performance

Description of model development.

8.1 Univariable association of candidate predictors with EOS

Below is a univariable logistic regression showing the univariable association between each candidate predictor and the outcome of EOS. The results are pooled across all imputed datasets.

N.B. To make interpretation easier, birth weight has been converted to kilograms, respiratory rate and heart rate have been divided by 5 (i.e. 5 breaths per minute), and “activity” has been collapsed into “alert”, “lethargic”, or “other”.

```
## # A tibble: 17 x 7
##   predictor      beta     SE     OR    LCL    UCL     p
##   <fct>     <dbl>  <dbl>  <dbl>  <dbl>  <dbl>  <dbl>
## 1 pi_gest    0.067  0.026  1.07   1.02   1.12  0.009
## 2 et_bw      0.131  0.087  1.14   0.961  1.35  0.133
## 3 oh_matfeveryes  1.79  0.544  5.99   2.06  17.4  0.001
## 4 oh_offliquoryes  0.707 0.208  2.03   1.35   3.05  0.001
## 5 co_promyes  0.391  0.173  1.48   1.05   2.08  0.024
## 6 et_gruntyes  0.203  0.132  1.23   0.945  1.59  0.126
## 7 et_rr       0.093  0.022  1.10   1.05   1.14  0
## 8 et_hr       0.047  0.019  1.05   1.01   1.09  0.012
## 9 et_temp     0.886  0.087  2.42   2.04   2.88  0
## 10 oe_activitylethargic 0.395  0.162  1.48   1.08   2.04  0.015
## 11 oe_activityother  1.05   0.25   2.86   1.75   4.67  0
## 12 oe_nasalflareyes  0.29   0.126  1.34   1.04   1.71  0.021
## 13 oe_retractionsyes  0.417  0.124  1.52   1.19   1.93  0.001
## 14 oe_gruntyes   0.346  0.155  1.41   1.04   1.92  0.025
## 15 oe_wobmild    -0.207  0.197  0.813  0.552  1.20  0.293
## 16 oe_wobmoderate  0.345  0.146  1.41   1.06   1.88  0.018
## 17 oe_wobsevere  0.674  0.217  1.96   1.28   3.00  0.002
```

8.2 Model selection

8.2.1 Randomly select a single imputed dataset

To facilitate comparison between models, we randomly select a single imputed dataset (from the 40 imputations) and use this imputation throughout model selection.

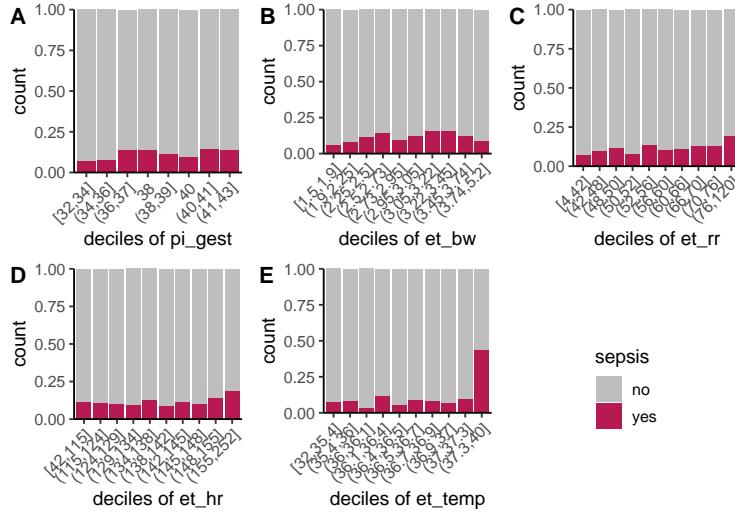
```
set.seed(37)
rand <- floor(runif(1, min = 1, max = 30))
rand

## [1] 16

si <- as_tibble(complete(imp, rand))
saveRDS(si, "Data/si.rds")
```

8.2.2 Assess linearity assumption

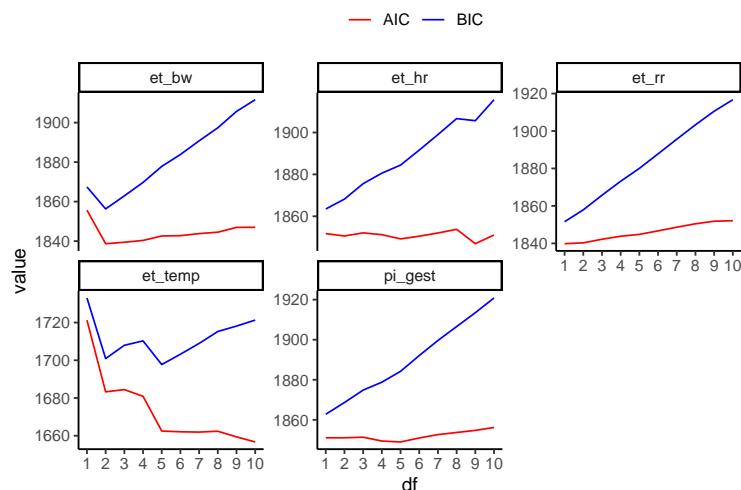
8.2.2.1 Histograms We first assessed the linearity assumption – that the outcome of sepsis is modelled by a linear combination of predictors – graphically, by plotting histograms of the proportion of included neonates with sepsis per decile of each continuous predictor.



If the relationship between the predictor and the probability of EOS were linear, we would expect the proportion of cases of sepsis to increase or decrease at a constant rate across deciles. Therefore, the above figure suggests some non-linearity for all continuous candidate predictors but most pronounced for temperature.

8.2.2.2 Splines We explored non-linear effects of continuous predictors by fitting univariable logistic regression models to predict the outcome of sepsis and modelling each continuous predictor as a natural cubic spline (NCS) function with varying degrees of freedom from 1 (linear) to 10.

We plotted the AIC and BIC of these models for each predictor to visually determine the optimal degrees of freedom for the NCS function.



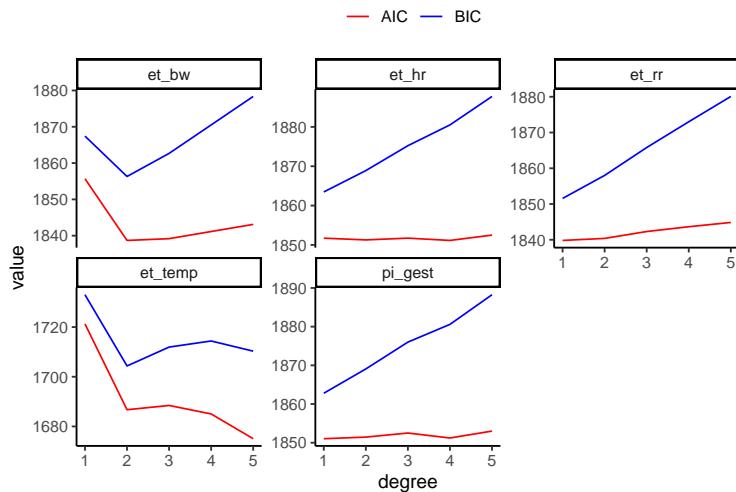
The above figure shows that the AIC and BIC increased monotonically or remained approximately constant across all degrees of freedom for heart rate, respiratory rate and gestational age. This suggests that using the untransformed predictor (i.e. assuming linearity) resulted in a better model than defining these predictors with natural cubic splines.

However, for birth weight, minimum values for AIC and BIC were determined by a natural cubic spline with 2 degrees of freedom (top left panel, above). Similarly, for temperature, the BIC was minimal for natural cubic splines with 2 or 5 degrees of freedom before increasing monotonically. The AIC had minima at 5 or 7 degrees of freedom (bottom left panel, above).

The above figure suggests that transforming birth weight using a natural cubic spline with 2 degrees of freedom and transforming temperature using a natural cubic spline with 5 degrees of freedom produced the optimal univariable models of the natural cubic spline transformations explored.

8.2.2.3 Polynomials We further explored non-linear effects by modelling each continuous predictor with polynomial transformations instead of natural cubic spline functions.

Again, we plotted the AIC and BIC of these models for each predictor to visually determine the optimal degree of polynomial.



The above figure shows that the AIC and BIC increased monotonically or remained approximately constant across all degrees of polynomials for heart rate, respiratory rate and gestational age. This suggests that using the untransformed predictor (i.e. assuming linearity) resulted in a better model than transforming these predictors with polynomial functions.

However, for birth weight, minimum values for AIC and BIC were determined by a second-degree polynomial (top left panel, above). Similarly, for temperature, the BIC was minimal for a second-degree polynomial and the AIC was minimal for a second-degree or fifth-degree polynomial (bottom left panel, above).

The above figure suggests that transforming birth weight and temperature using a second-degree polynomial produced the optimal univariable models of the polynomial transformations explored.

8.2.2.4 Univariable models with non-linear transformations - birth weight Based on the above results, we fit a univariable model to predict early-onset sepsis with birth weight modelled as a natural cubic spline with 2 degrees of freedom.

Characteristic	**log(OR)**	**SE**	**95% CI**	**p-value**
ns(et_bw, df = 2)				
ns(et_bw, df = 2)1	1.5	0.468	0.62, 2.5	0.001
ns(et_bw, df = 2)2	-1.4	0.555	-2.5, -0.34	0.013

```
## 50%
## 2.95
```

While both components of the spline were significant, their coefficients were unstable with large SEs.

Thus, we subsequently modelled birth weight as a second-degree polynomial.

Characteristic	**log(OR)**	**SE**	**95% CI**	**p-value**
et_bw				
et_bw	5.7	3.70	-1.6, 13	0.13
et_bw ²	-16	4.03	-24, -8.4	<0.001

This model suffered similar numerical issues. Adding random noise did not improve estimations in either the natural cubic spline or polynomial models:

Characteristic	**log(OR)**	**SE**	**95% CI**	**p-value**
ns(et_bw_noise, df = 2)				
ns(et_bw_noise, df = 2)1	1.6	0.496	0.67, 2.6	0.001
ns(et_bw_noise, df = 2)2	-1.4	0.569	-2.5, -0.31	0.016
Characteristic	**log(OR)**	**SE**	**95% CI**	**p-value**
et_bw_noise				
et_bw_noise	5.5	3.69	-1.8, 13	0.14
et_bw_noise ²	-16	4.02	-24, -8.2	<0.001

Therefore, birth weight was assumed to be linear in subsequent models.

8.2.2.5 Univariable models with non-linear transformations - temperature Based on the above results, we fit a univariable model to predict early-onset sepsis with temperature modelled as a natural cubic spline with 5 degrees of freedom and with 2 degrees of freedom.

Characteristic	**log(OR)**	**SE**	**95% CI**	**p-value**
ns(et_temp, df = 5)				
ns(et_temp, df = 5)1	-1.1	1.24	-3.4, 1.8	0.4
ns(et_temp, df = 5)2	-2.3	1.32	-4.7, 0.86	0.088
ns(et_temp, df = 5)3	2.3	0.713	1.0, 3.9	0.001
ns(et_temp, df = 5)4	-0.93	2.80	-6.2, 5.6	0.7
ns(et_temp, df = 5)5	3.3	0.805	1.8, 5.1	<0.001

```
## 20% 40% 60% 80%
## 36.0 36.4 36.7 37.0
```

Characteristic	**log(OR)**	**SE**	**95% CI**	**p-value**
ns(et_temp, df = 2)				
ns(et_temp, df = 2)1	-1.4	1.36	-4.0, 1.4	0.3
ns(et_temp, df = 2)2	5.1	0.428	4.3, 6.0	<0.001

```
## 50%
## 36.5
```

Similar numerical issues were encountered for these models as were encountered when fitting non-linear functions of birth weight.

Again, we subsequently modelled temperature as a second-degree polynomial and tried adding random noise, neither of which produced satisfactory models.

Characteristic	**log(OR)**	**SE**	**95% CI**	**p-value**
et_temp				
et_temp	28	3.13	22, 34	<0.001
et_temp ²	19	2.89	14, 25	<0.001

Characteristic	**log(OR)**	**SE**	**95% CI**	**p-value**
ns(et_temp_noise, df = 2)				
ns(et_temp_noise, df = 2)1	-1.5	1.41	-4.1, 1.5	0.3
ns(et_temp_noise, df = 2)2	5.2	0.436	4.3, 6.0	<0.001
Characteristic	**log(OR)**	**SE**	**95% CI**	**p-value**
et_temp_noise				
et_temp_noise	27	3.13	21, 34	<0.001
et_temp_noise ²	19	2.87	13, 24	<0.001

Therefore, temperature was also assumed to be linear in subsequent models.

8.2.3 Selecting main effects

8.2.3.1 Fit full main effects model (model M1) We next fit a full main effects model to predict sepsis, including all 14 candidate predictors (those remaining after consideration of skewed predictor distributions). The AIC and BIC of this full model were the benchmark to which subsequent models were compared.

```

## sepsis ~ et_temp + et_rr + et_hr + et_bw + pi_gest + oh_matfever +
##      oh_offliquor + co_prom + et_grunt + oe_activity + oe_nasalflare +
##      oe_retractions + oe_grunt + oe_wob

##
## Call:
## glm(formula = main_form, family = "binomial", data = si)
##
## Deviance Residuals:
##    Min      1Q  Median      3Q     Max
## -2.005  -0.492  -0.384  -0.276   3.443
##
## Coefficients:
##                               Estimate Std. Error z value Pr(>|z|)
## (Intercept)             -3.90e+01  3.20e+00 -12.18 <2e-16 ***
## et_temp                  9.48e-01  8.56e-02  11.08 <2e-16 ***
## et_rr                   6.17e-02  2.71e-02   2.28  0.023 *
## et_hr                  -9.88e-04  1.95e-02  -0.05  0.960
## et_bw                  -1.28e-01  1.25e-01  -1.03  0.305
## pi_gest                 3.79e-02  3.34e-02   1.13  0.256
## oh_matfeveryes          1.47e+00  6.25e-01   2.35  0.019 *
## oh_offliquoryes         5.31e-01  2.28e-01   2.33  0.020 *
## co_promyes               3.67e-01  1.90e-01   1.93  0.054 .
## et_gruntyes              -3.05e-01  2.07e-01  -1.47  0.142
## oe_activitylethargic   4.54e-01  1.90e-01   2.40  0.017 *
## oe_activityother        6.91e-01  2.83e-01   2.44  0.015 *
## oe_nasalflareyes        1.02e-01  2.39e-01   0.43  0.669
## oe_retractionsyes       7.37e-01  3.23e-01   2.28  0.023 *
## oe_gruntyes              1.98e-01  2.19e-01   0.90  0.367
## oe_wobmild                -7.52e-01  3.83e-01  -1.96  0.049 *
## oe_wobmoderate           -2.56e-01  4.18e-01  -0.61  0.541
## oe_wobsevere              1.62e-01  5.08e-01   0.32  0.749
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## (Dispersion parameter for binomial family taken to be 1)

```

```

## Null deviance: 1854.2 on 2627 degrees of freedom
## Residual deviance: 1632.0 on 2610 degrees of freedom
## AIC: 1668
##
## Number of Fisher Scoring iterations: 5

##          AIC      BIC
## [1,] 1668.05 1773.78

```

This model assumed linearity of all continuous candidate predictors and additivity at the predictor scale. The regression coefficients and SEs of each predictor in this model (estimated in the single imputed dataset) are as follows:

Characteristic	**OR**	**95% CI**	**p-value**
et_temp	2.58	2.19, 3.06	<0.001
et_rr	1.06	1.01, 1.12	0.023
et_hr	1.00	0.96, 1.04	>0.9
et_bw	0.88	0.69, 1.12	0.3
pi_gest	1.04	0.97, 1.11	0.3
oh_matfever	4.33	1.22, 14.6	0.019
oh_offliquor	1.70	1.07, 2.63	0.020
co_prom	1.44	0.98, 2.08	0.054
et_grunt	0.74	0.49, 1.11	0.14
oe_activity			
alert	1.00		
lethargic	1.57	1.08, 2.27	0.017
other	2.00	1.13, 3.43	0.015
oe_nasalflare	1.11	0.70, 1.79	0.7
oe_retractions	2.09	1.15, 4.10	0.023
oe_grunt	1.22	0.79, 1.87	0.4
oe_wob			
normal	1.00		
mild	0.47	0.21, 0.97	0.049
moderate	0.77	0.33, 1.71	0.5
severe	1.18	0.42, 3.12	0.7

The highest VIF values were for the ‘moderate’ and ‘severe’ categories of work of breathing and retractions. All other VIF values were < 5. Pearson’s chi-squared test showed that these two predictors were highly correlated with each other:

```

## # A tibble: 17 x 2
##   predictor           VIF
##   <chr>              <dbl>
## 1 oe_wobmoderate     8.26
## 2 oe_retractionsyes  6.06
## 3 oe_wobsevere       5.08
## 4 oe_wobmild         3.79
## 5 oe_nasalflareyes  3.20
## 6 et_gruntyes        2.18
## 7 oe_gruntyes        1.76
## 8 et_bw               1.63
## 9 pi_gest             1.57
## 10 et_rr              1.45

```

```

## 11 oe_activitylethargic 1.21
## 12 et_temp 1.21
## 13 oh_offliquories 1.09
## 14 co_promyes 1.08
## 15 et_hr 1.08
## 16 oe_activityother 1.05
## 17 oh_matfeveryes 1.02

##
##      normal  mild moderate severe
##    no     1431   131      77      3
##   yes       0    282     537    167

##
## Pearson's Chi-squared test
##
## data: table(si$oe_retractions, si$oe_wob)
## X-squared = 1947, df = 3, p-value <2e-16

```

8.2.3.2 Models M2 & M2a Next, we fit model M2 as the above full model (model M1), but without work of breathing (the predictor with the highest VIF in model M1). This model had a higher AIC compared to model M1, but a lower BIC. Removing work of breathing from the model also reduced collinearity between predictors.

```

## sepsis ~ et_temp + et_rr + et_hr + et_bw + pi_gest + oh_matfever +
##        oh_offliquor + co_prom + et_grunt + oe_activity + oe_nasalflare +
##        oe_retractions + oe_grunt

##
## Call:
## glm(formula = sepsis ~ et_temp + et_rr + et_hr + et_bw + pi_gest +
##       oh_matfever + oh_offliquor + co_prom + et_grunt + oe_activity +
##       oe_nasalflare + oe_retractions + oe_grunt, family = "binomial",
##       data = si)
##
## Deviance Residuals:
##    Min      1Q  Median      3Q      Max
## -1.934  -0.495  -0.389  -0.280   3.416
##
## Coefficients:
##                               Estimate Std. Error z value Pr(>|z|)
## (Intercept)             -39.0553   3.1937 -12.23  <2e-16 ***
## et_temp                  0.9489   0.0852  11.13  <2e-16 ***
## et_rr                   0.0552   0.0267   2.07   0.0386 *
## et_hr                  -0.0024   0.0194  -0.12   0.9019
## et_bw                  -0.1216   0.1245  -0.98   0.3286
## pi_gest                 0.0401   0.0333   1.20   0.2296
## oh_matfeveryes          1.3996   0.6140   2.28   0.0226 *
## oh_offliquories          0.5146   0.2261   2.28   0.0229 *
## co_promyes                0.3768   0.1895   1.99   0.0468 *
## et_grunties              -0.2461   0.1991  -1.24   0.2164
## oe_activitylethargic     0.5402   0.1811   2.98   0.0029 **

```

```

## oe_activityother      0.7470    0.2804    2.66   0.0077 **
## oe_nasalflareyes    -0.0213    0.1877   -0.11   0.9095
## oe_retractionsyes    0.4878    0.2034    2.40   0.0165 *
## oe_gruntyes          0.3449    0.2043    1.69   0.0914 .
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## (Dispersion parameter for binomial family taken to be 1)
##
## Null deviance: 1854.2  on 2627  degrees of freedom
## Residual deviance: 1644.3  on 2613  degrees of freedom
## AIC: 1674
##
## Number of Fisher Scoring iterations: 5

##           AIC      BIC
## [1,] 1674.27 1762.38

## # A tibble: 14 x 2
##   predictor        VIF
##   <chr>            <dbl>
## 1 oe_retractionsyes 2.42
## 2 et_gruntyes       2.04
## 3 oe_nasalflareyes 2.00
## 4 et_bw             1.63
## 5 pi_gest           1.57
## 6 oe_gruntyes       1.55
## 7 et_rr              1.39
## 8 et_temp            1.19
## 9 oe_activitylethargic 1.13
## 10 co_promyes        1.08
## 11 oh_offliquories  1.08
## 12 et_hr              1.08
## 13 oe_activityother  1.04
## 14 oh_matfeveryes   1.02

```

For comparison, model M2a instead dropped retractions from model M1. This model had a slightly improved AIC compared to model M2, but a higher BIC.

```

## sepsis ~ et_temp + et_rr + et_hr + et_bw + pi_gest + oh_matfever +
##         oh_offliquor + co_prom + et_grunt + oe_activity + oe_nasalflare +
##         oe_grunt + oe_wob

##
## Call:
## glm(formula = sepsis ~ et_temp + et_rr + et_hr + et_bw + pi_gest +
##       oh_matfever + oh_offliquor + co_prom + et_grunt + oe_activity +
##       oe_nasalflare + oe_grunt + oe_wob, family = "binomial", data = si)
##
## Deviance Residuals:
##    Min      1Q  Median      3Q     Max
## -2.001  -0.492  -0.391  -0.279   3.469
##
```

```

## Coefficients:
##                               Estimate Std. Error z value Pr(>|z|)
## (Intercept)           -39.0775   3.2012 -12.21 <2e-16 ***
## et_temp                0.9496   0.0856  11.10 <2e-16 ***
## et_rr                  0.0648   0.0270   2.40  0.016 *
## et_hr                  0.0021   0.0194   0.11  0.914
## et_bw                 -0.1471   0.1244  -1.18  0.237
## pi_gest                 0.0375   0.0334   1.12  0.261
## oh_matfeveryes        1.5304   0.6270   2.44  0.015 *
## oh_offliquoryes       0.5260   0.2277   2.31  0.021 *
## co_promyes              0.3758   0.1900   1.98  0.048 *
## et_gruntyes             -0.2214   0.2038  -1.09  0.277
## oe_activitylethargic   0.4658   0.1893   2.46  0.014 *
## oe_activityother        0.7155   0.2821   2.54  0.011 *
## oe_nasalflareyes       0.0261   0.2349   0.11  0.911
## oe_gruntyes              0.1593   0.2172   0.73  0.463
## oe_wobmild               -0.1941   0.2807  -0.69  0.489
## oe_wobmoderate            0.4129   0.2896   1.43  0.154
## oe_wobsevere              0.8900   0.3953   2.25  0.024 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## (Dispersion parameter for binomial family taken to be 1)
##
## Null deviance: 1854.2 on 2627 degrees of freedom
## Residual deviance: 1637.9 on 2611 degrees of freedom
## AIC: 1672
##
## Number of Fisher Scoring iterations: 5

##          AIC      BIC
## [1,] 1671.94 1771.8

```

8.2.3.3 Models M3 & M4 Note that the sign of the regression coefficient for grunting at emergency triage (et_grunt) and nasal flaring in model M2 (above) was inconsistent with established subject knowledge of neonatal sepsis. We would expect the presence of these clinical features would increase the probability of sepsis, yet they had negative regression coefficients.

Therefore, model M3 was fitted as model M2, but without grunting at emergency triage or nasal flaring. This model had a slightly lower AIC and BIC compared to model M2.

```

## sepsis ~ et_temp + et_rr + et_hr + et_bw + pi_gest + oh_matfever +
##         oh_offliquor + co_prom + oe_activity + oe_retractions + oe_grunt

##
## Call:
## glm(formula = sepsis ~ et_temp + et_rr + et_hr + et_bw + pi_gest +
##       oh_matfever + oh_offliquor + co_prom + oe_activity + oe_retractions +
##       oe_grunt, family = "binomial", data = si)
##
## Deviance Residuals:
##      Min        1Q    Median        3Q       Max
## -1.859   -0.497   -0.390   -0.280    3.414

```

```

## 
## Coefficients:
##                               Estimate Std. Error z value Pr(>|z|)
## (Intercept)           -39.11391   3.18931 -12.26 <2e-16 ***
## et_temp                0.95273   0.08506  11.20 <2e-16 ***
## et_rr                  0.05134   0.02594   1.98  0.0478 *
## et_hr                 -0.00169   0.01933  -0.09  0.9302
## et_bw                 -0.12153   0.12441  -0.98  0.3286
## pi_gest                 0.03810   0.03329   1.14  0.2523
## oh_matfeveryes        1.38993   0.60746   2.29  0.0221 *
## oh_offliquoryes       0.52515   0.22542   2.33  0.0198 *
## co_promyes              0.37897   0.18909   2.00  0.0450 *
## oe_activitylethargic   0.53091   0.18070   2.94  0.0033 **
## oe_activityother        0.73425   0.27960   2.63  0.0086 **
## oe_retractionsyes      0.37793   0.16978   2.23  0.0260 *
## oe_gruntyes              0.23686   0.18293   1.29  0.1954
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## (Dispersion parameter for binomial family taken to be 1)
##
## Null deviance: 1854.2 on 2627 degrees of freedom
## Residual deviance: 1645.9 on 2615 degrees of freedom
## AIC: 1672
##
## Number of Fisher Scoring iterations: 5

##          AIC      BIC
## [1,] 1671.88 1748.24

```

Looking at the above model, the regression coefficient for heart rate was close to zero and it was not found to be a significant predictor in the model. Therefore, heart rate was dropped from model M3 to fit model M4. This model had a lower AIC and BIC compared to model M3. Also, this model had minimal collinearity between predictors.

```

## sepsis ~ et_temp + et_rr + et_bw + pi_gest + oh_matfever + oh_offliquor +
##         co_prom + oe_activity + oe_retractions + oe_grunt

##
## Call:
## glm(formula = sepsis ~ et_temp + et_rr + et_bw + pi_gest + oh_matfever +
##       oh_offliquor + co_prom + oe_activity + oe_retractions + oe_grunt,
##       family = "binomial", data = si)
##
## Deviance Residuals:
##      Min        1Q     Median        3Q       Max
## -1.854    -0.498    -0.389    -0.280     3.415
##
## Coefficients:
##                               Estimate Std. Error z value Pr(>|z|)
## (Intercept)           -39.1032   3.1868 -12.27 <2e-16 ***
## et_temp                  0.9512   0.0833  11.42 <2e-16 ***
## et_rr                   0.0511   0.0258   1.98  0.0478 *

```

```

## et_bw          -0.1214    0.1244   -0.98   0.3292
## pi_gest       0.0381    0.0333    1.14    0.2522
## oh_matfeveryes 1.3928    0.6065   2.30    0.0216 *
## oh_offliquoryes 0.5252    0.2254   2.33    0.0198 *
## co_promyes    0.3795    0.1890   2.01    0.0447 *
## oe_activitylethargic 0.5316    0.1805   2.94    0.0032 **
## oe_activityother 0.7347    0.2796   2.63    0.0086 **
## oe_retractionsyes 0.3767    0.1692   2.23    0.0260 *
## oe_gruntyes    0.2371    0.1829   1.30    0.1948
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## (Dispersion parameter for binomial family taken to be 1)
##
## Null deviance: 1854.2 on 2627 degrees of freedom
## Residual deviance: 1645.9 on 2616 degrees of freedom
## AIC: 1670
##
## Number of Fisher Scoring iterations: 5

##           AIC      BIC
## [1,] 1669.89 1740.38

## # A tibble: 11 x 2
##   predictor        VIF
##   <chr>            <dbl>
## 1 oe_retractionsyes 1.68
## 2 et_bw             1.62
## 3 pi_gest           1.56
## 4 et_rr              1.31
## 5 oe_gruntyes       1.25
## 6 et_temp            1.14
## 7 oe_activitylethargic 1.12
## 8 co_promyes         1.08
## 9 oh_offliquoryes   1.08
## 10 oe_activityother  1.04
## 11 oh_matfeveryes   1.01

```

Note that two non-significant predictors were retained in the regression model (premature rupture of membranes and grunting on examination) as the sign of their regression coefficient was consistent with established knowledge and the corresponding p -values were reasonably small. Also, birth weight and gestational age were retained in the model despite being non-significant to test for interactions between these two predictors, as described ahead.

8.2.4 Assess additivity assumption

We then assessed the additivity assumption – that the effects of predictors can be added at the linear predictor scale (and thus multiplied at the odds scale) - by assessing for a biologically plausible interaction between birth weight and gestational age.

8.2.4.1 Interaction plots There was a significant interaction between birth weight and gestational age in a logistic regression model of these two predictors predicting EOS:

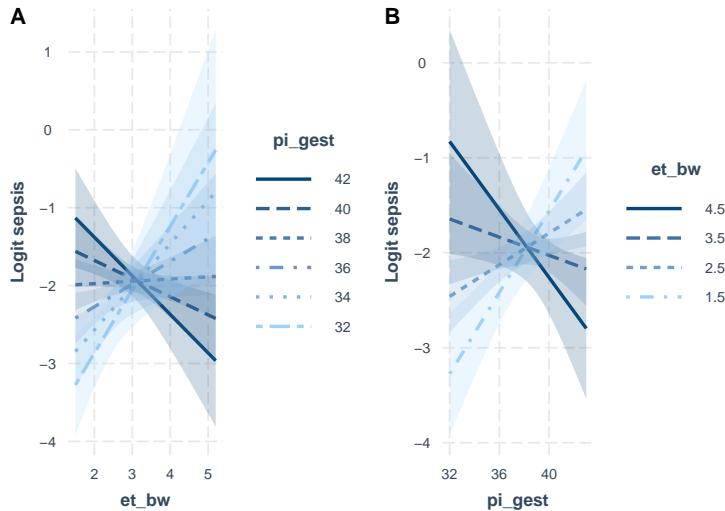
```

## sepsis ~ et_bw * pi_gest

##
## Call:
## glm(formula = sepsis ~ et_bw * pi_gest, family = "binomial",
##      data = si)
##
## Deviance Residuals:
##    Min      1Q  Median      3Q     Max
## -0.693 -0.519 -0.502 -0.425  2.574
##
## Coefficients:
##             Estimate Std. Error z value Pr(>|z|)
## (Intercept) -17.6505   4.2952  -4.11   4e-05 ***
## et_bw        5.0104   1.5822   3.17  0.00154 **
## pi_gest      0.4110   0.1141   3.60  0.00032 ***
## et_bw:pi_gest -0.1311   0.0413  -3.17  0.00152 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## (Dispersion parameter for binomial family taken to be 1)
##
## Null deviance: 1854.2 on 2627 degrees of freedom
## Residual deviance: 1836.2 on 2624 degrees of freedom
## AIC: 1844
##
## Number of Fisher Scoring iterations: 5

```

A plot of this interaction is shown below. Panel A shows the logit of the probability of sepsis across all values of birth weight at six selected values of gestational age. Panel B shows the same interaction but displayed across all values of gestational age at four selected values of birth weight.



At lower birth weights, those with a higher gestational age appeared to have a greater probability of sepsis compared to those with lower gestational ages (panel A, above). However, at approximately 3200 grams, this relationship reversed, after which the probability of sepsis appeared higher for those with lower gestational ages. The above figure suggests that the probability of sepsis decreased with increasing birth weight for gestational ages > 38 weeks but increased with increasing birth weight for gestational ages < 38 weeks.

This relationship can also be interpreted such that, for lower gestational ages, those with higher birth weights had a greater probability of sepsis compared to those with lower birth weights (panel B, above). For higher gestational ages (above around 38 weeks), those with a higher birth weight had the lowest probability of sepsis.

8.2.4.2 Models M5 & M5a The interaction between birth weight and gestational age was included in the selected multivariable model M4 to produce model M5.

The main effects and the interaction term were significant for birth weight and gestational age in this model. However, the coefficients and standard errors were extreme for these terms, with large VIF values.

```

## sepsis ~ et_temp + et_rr + oh_matfever + oh_offliquor + co_prom +
##      oe_activity + oe_retractions + oe_grunt + et_bw + pi_gest +
##      et_bw:pi_gest

##
## Call:
## glm(formula = sepsis ~ et_temp + et_rr + oh_matfever + oh_offliquor +
##      co_prom + oe_activity + oe_retractions + oe_grunt + et_bw +
##      pi_gest + et_bw:pi_gest, family = "binomial", data = si)
##
## Deviance Residuals:
##    Min      1Q  Median      3Q     Max
## -1.723  -0.496  -0.386  -0.274   3.503
##
## Coefficients:
##                               Estimate Std. Error z value Pr(>|z|)
## (Intercept)             -52.4430    5.5372  -9.47  <2e-16 ***
## et_temp                  0.9539    0.0836   11.42  <2e-16 ***
## et_rr                   0.0529    0.0259    2.04   0.0415 *
## oh_matfeveryes          1.3536    0.6044    2.24   0.0251 *
## oh_offliquoryes         0.4682    0.2261    2.07   0.0384 *
## co_promyes               0.3710    0.1895    1.96   0.0503 .
## oe_activitylethargic   0.5568    0.1807    3.08   0.0021 **
## oe_activityother         0.6909    0.2806    2.46   0.0138 *
## oe_retractionsyes       0.4082    0.1696    2.41   0.0161 *
## oe_gruntypes              0.2282    0.1830    1.25   0.2123
## et_bw                   4.9863    1.6892    2.95   0.0032 **
## pi_gest                  0.3874    0.1214    3.19   0.0014 **
## et_bw:pi_gest            -0.1338    0.0442   -3.03   0.0025 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## (Dispersion parameter for binomial family taken to be 1)
##
## Null deviance: 1854.2  on 2627  degrees of freedom
## Residual deviance: 1636.1  on 2615  degrees of freedom
## AIC: 1662
##
## Number of Fisher Scoring iterations: 5

##          AIC      BIC
## [1,] 1662.07 1738.43

```

```

## # A tibble: 12 x 2
##   predictor          VIF
##   <chr>            <dbl>
## 1 et_bw:pi_gest    349.
## 2 et_bw             265.
## 3 pi_gest           18.0
## 4 oe_retractionsyes 1.68
## 5 et_rr              1.31
## 6 oe_gruntyes       1.24
## 7 et_temp            1.14
## 8 oe_activitylethargic 1.12
## 9 oh_offliquoryes   1.08
## 10 co_promyes        1.08
## 11 oe_activityother  1.04
## 12 oh_matfeveryes   1.01

```

Refitting this model but with birth weight and gestational age centred by subtracting their respective sample means from each observation greatly improved the estimates (model M5a). However, the main effects of these terms were no longer significant despite a significant interaction. This is consistent with the crossover interaction effect seen in the interaction plot shown previously.

```

## sepsis ~ et_temp + et_rr + oh_matfever + oh_offliquor + co_prom +
##       oe_activity + oe_retractions + oe_grunt + et_bw_centred +
##       pi_gest_centred + et_bw_centred:pi_gest_centred

##
## Call:
## glm(formula = sepsis ~ et_temp + et_rr + oh_matfever + oh_offliquor +
##       co_prom + oe_activity + oe_retractions + oe_grunt + et_bw_centred +
##       pi_gest_centred + et_bw_centred:pi_gest_centred, family = "binomial",
##       data = si)
##
## Deviance Residuals:
##    Min      1Q  Median      3Q     Max 
## -1.723  -0.496  -0.386  -0.274   3.503 
##
## Coefficients:
##                               Estimate Std. Error z value Pr(>|z|)    
## (Intercept)                 -38.0075   3.0916  -12.29 <2e-16 ***
## et_temp                      0.9539   0.0835   11.42 <2e-16 ***
## et_rr                         0.0529   0.0259   2.04  0.0415 *  
## oh_matfeveryes                1.3536   0.6045   2.24  0.0251 *  
## oh_offliquoryes                0.4682   0.2261   2.07  0.0384 *  
## co_promyes                     0.3710   0.1895   1.96  0.0503 .  
## oe_activitylethargic            0.5568   0.1807   3.08  0.0021 ** 
## oe_activityother                  0.6909   0.2806   2.46  0.0138 *  
## oe_retractionsyes                0.4082   0.1696   2.41  0.0161 *  
## oe_gruntyes                      0.2282   0.1830   1.25  0.2123 
## et_bw_centred                   -0.0999   0.1239   -0.81  0.4200 
## pi_gest_centred                  0.0010   0.0353   0.03  0.9774 
## et_bw_centred:pi_gest_centred   -0.1338   0.0442   -3.03  0.0025 ** 
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```

```

## 
## (Dispersion parameter for binomial family taken to be 1)
##
## Null deviance: 1854.2 on 2627 degrees of freedom
## Residual deviance: 1636.1 on 2615 degrees of freedom
## AIC: 1662
##
## Number of Fisher Scoring iterations: 5

##          AIC      BIC
## [1,] 1662.07 1738.43

## # A tibble: 12 x 2
##   predictor            VIF
##   <chr>                <dbl>
## 1 oe_retractionsyes    1.68
## 2 pi_gest_centred      1.52
## 3 et_bw_centred        1.43
## 4 et_rr                 1.31
## 5 oe_gruntyes          1.24
## 6 et_bw_centred:pi_gest_centred 1.16
## 7 et_temp               1.14
## 8 oe_activitylethargic 1.12
## 9 oh_offliquoryes     1.08
## 10 co_promyes          1.08
## 11 oe_activityother    1.04
## 12 oh_matfeveryes      1.01

```

Given that allowing for an interaction between birth weight and gestational age (model M5a) showed only minor improvements in the AIC and BIC compared to the model assuming additivity (model M4), we selected model M4 as it was the simpler model.

This decision was reinforced since the distributions of birth weight and gestational age in our cohort suggested that higher birth weights and gestational ages had a higher probability of sepsis than lower birth weights and gestational ages. This contradicted what is expected from established subject knowledge.

8.2.4.3 Models M6 and M7 Since the interaction between birth weight and gestational age was no longer included in the model, model M4 was refitted but without gestational age (model M6) as the sign of its regression coefficient contradicted established knowledge and it was not significant in model M4. This improved both the AIC and BIC compared to model M4.

```

## sepsis ~ et_temp + et_rr + et_bw + oh_matfever + oh_offliquor +
##       co_prom + oe_activity + oe_retractions + oe_grunt

##
## Call:
## glm(formula = sepsis ~ et_temp + et_rr + et_bw + oh_matfever +
##       oh_offliquor + co_prom + oe_activity + oe_retractions + oe_grunt,
##       family = "binomial", data = si)
##
## Deviance Residuals:
##      Min        1Q    Median        3Q        Max
## -1.832   -0.498   -0.392   -0.280    3.398

```

```

## 
## Coefficients:
##                               Estimate Std. Error z value Pr(>|z|)
## (Intercept)           -38.0449    3.0407 -12.51  <2e-16 ***
## et_temp                0.9552    0.0832  11.48  <2e-16 ***
## et_rr                  0.0517    0.0258   2.00   0.0452 *
## et_bw                 -0.0386    0.1004  -0.38   0.7004
## oh_matfeveryes       1.3756    0.6051   2.27   0.0230 *
## oh_offliquoryes      0.5378    0.2249   2.39   0.0168 *
## co_promyes             0.3735    0.1891   1.98   0.0482 *
## oe_activitylethargic  0.5410    0.1804   3.00   0.0027 **
## oe_activityother       0.7488    0.2790   2.68   0.0073 **
## oe_retractionsyes     0.3790    0.1693   2.24   0.0252 *
## oe_gruntyes            0.2366    0.1828   1.29   0.1956
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## (Dispersion parameter for binomial family taken to be 1)
##
## Null deviance: 1854.2 on 2627 degrees of freedom
## Residual deviance: 1647.2 on 2617 degrees of freedom
## AIC: 1669
##
## Number of Fisher Scoring iterations: 5

##          AIC      BIC
## [1,] 1669.2 1733.81

```

Finally, in model M7, we refitted model M6 without birth weight as the *p*-value for this term in model M6 was large.

```

## sepsis ~ et_temp + et_rr + oh_matfever + oh_offliquor + co_prom +
##       oe_activity + oe_retractions + oe_grunt

##
## Call:
## glm(formula = sepsis ~ et_temp + et_rr + oh_matfever + oh_offliquor +
##       co_prom + oe_activity + oe_retractions + oe_grunt, family = "binomial",
##       data = si)
##
## Deviance Residuals:
##    Min      1Q      Median      3Q      Max
## -1.846  -0.497  -0.393  -0.280   3.402
##
## Coefficients:
##                               Estimate Std. Error z value Pr(>|z|)
## (Intercept)           -37.9468    3.0286 -12.53  <2e-16 ***
## et_temp                 0.9493    0.0818  11.61  <2e-16 ***
## et_rr                  0.0517    0.0258   2.00   0.0451 *
## oh_matfeveryes       1.3841    0.6051   2.29   0.0222 *
## oh_offliquoryes      0.5327    0.2245   2.37   0.0177 *
## co_promyes             0.3770    0.1889   2.00   0.0459 *
## oe_activitylethargic  0.5410    0.1804   3.00   0.0027 **

```

```

## oe_activityother      0.7446    0.2785    2.67   0.0075 **
## oe_retractionsyses  0.3866    0.1682    2.30   0.0215 *
## oe_gruntyes          0.2364    0.1828    1.29   0.1960
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## (Dispersion parameter for binomial family taken to be 1)
##
## Null deviance: 1854.2  on 2627  degrees of freedom
## Residual deviance: 1647.3  on 2618  degrees of freedom
## AIC: 1667
##
## Number of Fisher Scoring iterations: 5

##           AIC      BIC
## [1,] 1667.35 1726.09

## # A tibble: 9 x 2
##   predictor        VIF
##   <chr>            <dbl>
## 1 oe_retractionsyses 1.66
## 2 et_rr              1.31
## 3 oe_gruntyes        1.25
## 4 oe_activitylethargic 1.12
## 5 et_temp             1.10
## 6 co_promyes         1.08
## 7 oh_offliquories   1.07
## 8 oe_activityother   1.04
## 9 oh_matfeveryes    1.01

```

8.2.5 Selected model

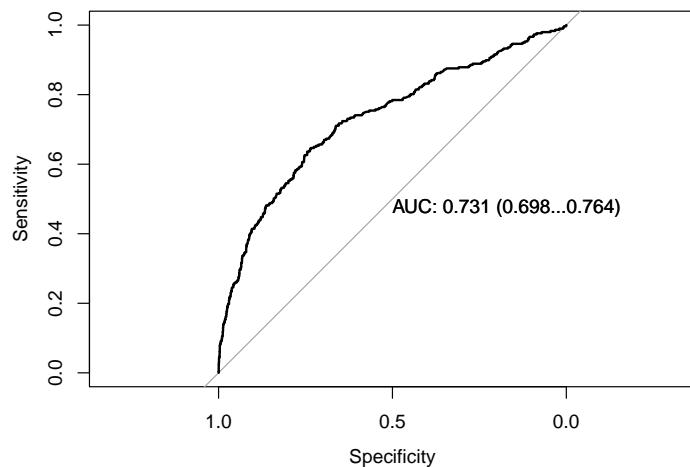
Model M7 was favoured by both the AIC and BIC and was thus selected as the optimal model. This model included 8 of the 14 candidate predictors. The regression coefficients and SEs of each predictor in this model (estimated in the single imputed dataset) are as follows:

Characteristic	**OR**	**95% CI**	**p-value**
et_temp	2.58	2.21, 3.04	<0.001
et_rr	1.05	1.00, 1.11	0.045
oh_matfever	3.99	1.17, 13.0	0.022
oh_offliquor	1.70	1.08, 2.62	0.018
co_prom	1.46	1.00, 2.09	0.046
oe_activity			
alert	1.00	—	
lethargic	1.72	1.20, 2.43	0.003
other	2.11	1.20, 3.58	0.008
oe_retractions	1.47	1.06, 2.05	0.022
oe_grunt	1.27	0.88, 1.81	0.2

8.3 Model performance

8.3.1 In the single imputed dataset

The ROC curve for the optimal model in the single imputed dataset (imputation number 16) is shown below.

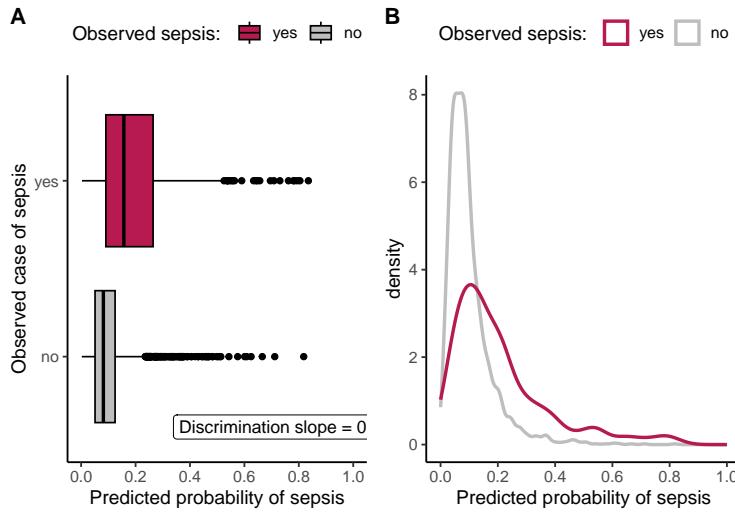


We calculated Yates' discrimination slope as the absolute difference in mean predicted probabilities between the two observed outcome groups. We obtained 95% confidence intervals using bootstrap (calculated using the normal approximation and 10,000 resamples).

```
##  
## ORDINARY NONPARAMETRIC BOOTSTRAP  
##  
##  
## Call:  
## boot(data = si, statistic = yatesBootstrap, R = 10000, model = M7)  
##  
##  
## Bootstrap Statistics :  
##      original     bias    std. error  
## t1* 0.105251  0.00581465  0.0178995  
  
## BOOTSTRAP CONFIDENCE INTERVAL CALCULATIONS  
## Based on 10000 bootstrap replicates  
##  
## CALL :  
## boot.ci(boot.out = yates, type = c("norm", "perc"))  
##  
## Intervals :  
## Level      Normal          Percentile  
## 95%  ( 0.0644,  0.1345 )  ( 0.0781,  0.1476 )  
## Calculations and Intervals on Original Scale
```

A boxplot and density plot of predicted probabilities of EOS by observed outcome are shown below. On average, the predicted probability was higher for observed cases of sepsis than observed cases without sepsis. Nevertheless, there was substantial overlap in predicted probabilities, with cases of sepsis with a low predicted

probability (below the median for observed cases without sepsis) and cases without sepsis with a high predicted probability (above the median for observed cases with sepsis).



Performance of the optimal model in the selected imputed dataset at various thresholds of predicted probability are shown below. We obtained 95% confidence intervals for likelihood ratios using bootstrap (calculated using the empirical method and 10,000 resamples).

```
## $best
##      obs
## pred   yes   no
##   yes  192  617
##   no   105 1714
##
## $`^0.8`
##      obs
## pred   yes   no
##   yes  239 1311
##   no    58 1020
##
## $`^0.85`
##      obs
## pred   yes   no
##   yes  251 1448
##   no    46  883
##
## $`^0.9`
##      obs
## pred   yes   no
##   yes  268 1816
##   no    29  515
##
## $`^0.95`
##      obs
## pred   yes   no
##   yes  283 2068
##   no    14  263

## # A tibble: 5 x 19
```

```

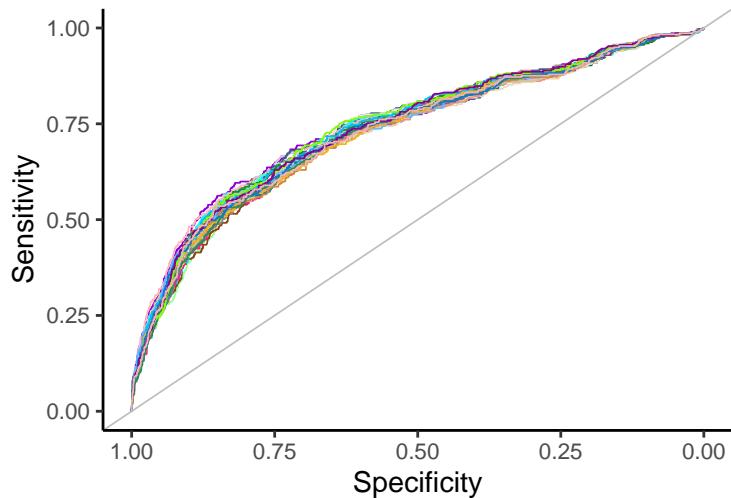
##   thres sens sens.lcl sens.ucl spec spec.lcl spec.ucl   PPV PPV.lcl PPV.ucl
##   <dbl> <dbl>   <dbl>   <dbl> <dbl>   <dbl> <dbl>   <dbl> <dbl>   <dbl> <dbl>
## 1 0.121 64.6    58.9    70.1 73.5    71.7    75.3 23.7    20.8    26.8
## 2 0.075 80.5    75.5    84.8 43.8    41.7    45.8 15.4    13.7    17.3
## 3 0.067 84.5    79.9    88.4 37.9    35.9    39.9 14.8    13.1    16.6
## 4 0.047 90.2    86.3    93.4 22.1    20.4    23.8 12.9    11.5    14.4
## 5 0.034 95.3    92.2    97.4 11.3     10     12.6 12      10.7    13.4
##   NPV NPV.lcl NPV.ucl   PLR PLR.lcl PLR.ucl   NLR NLR.lcl NLR.ucl
##   <dbl> <dbl>   <dbl> <dbl>   <dbl>   <dbl> <dbl>   <dbl> <dbl>
## 1 94.2 93.1    95.3 2.44    1.58    2.88 0.481 0.402 0.595
## 2 94.6 93.1    95.9 1.43    1.04    1.57 0.446 0.378 0.547
## 3 95     93.5    96.4 1.36    1.21    1.59 0.409 0.219 0.476
## 4 94.7 92.4    96.4 1.16    0.9     1.22 0.442 0.334 0.632
## 5 94.9 91.7    97.2 1.07    0.976   1.12 0.418 0.265 0.592

```

The ‘optimal’ classification threshold according to Youden’s J statistic was 0.120643.

8.3.2 Pooled across all imputed datasets

The ROC curve for the optimal model in each of the 40 multiply imputed datasets is shown below.



We then applied Rubin’s rules to get the pooled AUC across all imputed datasets.

```

##       auc      lcl      ucl
## [1,] 0.73648 0.700954 0.772006

```

The pooled AUC across the imputed datasets was 0.736 (95% CI 0.701-0.772%).

Finally, we estimated the regression coefficients and odds ratios for the optimal model, pooled across all imputed datasets:

```

## # A tibble: 10 x 7
##   predictor          beta     SE     OR   lcl   ucl p.value
##   <chr>        <dbl> <dbl> <dbl> <dbl> <dbl>   <dbl>
## 1 (Intercept) -39.4   3.52   0     0     0     0
## 2 et_temp       0.987  0.095  2.68  2.23  3.23  0

```

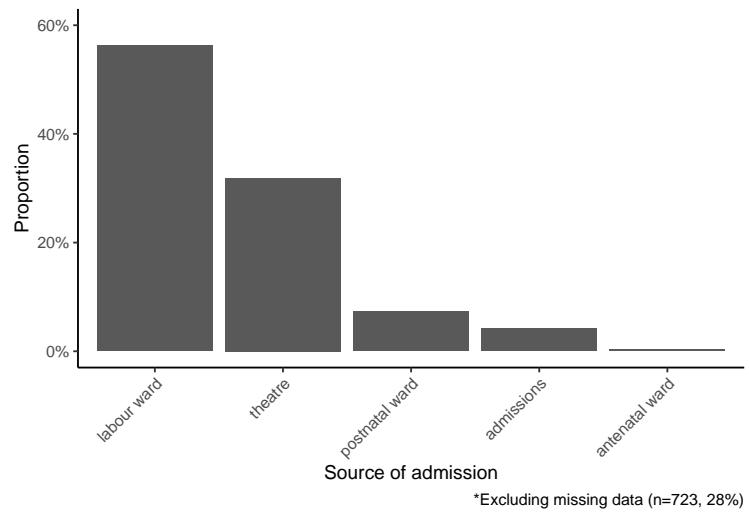
```
## 3 et_rr          0.055 0.026 1.06 1      1.11 0.0373
## 4 oh_matfeveryes 1.44  0.612 4.21 1.27 14.0  0.0189
## 5 oh_offliquoryes 0.543 0.228 1.72 1.1   2.69  0.0174
## 6 co_promyes     0.36  0.192 1.43 0.98 2.09  0.0612
## 7 oe_activitylethargic 0.586 0.184 1.8  1.25 2.58  0.0015
## 8 oe_activityother 0.84  0.286 2.32 1.32 4.06  0.0033
## 9 oe_retractionsyes 0.406 0.172 1.5  1.07 2.1   0.0187
## 10 oe_gruntyes    0.179 0.186 1.2  0.83 1.72  0.337
```

9 Additional analyses for reviewers' comments

Additional analyses in response to reviewers' comments.

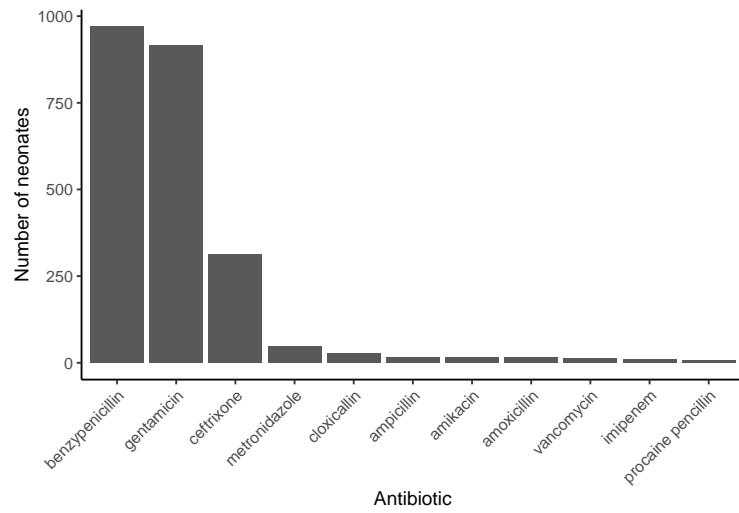
9.1 Source of admission

The below figure shows the source of admission for neonates included in our study.



9.2 Antibiotic usage

The below figure shows the distribution of antibiotic usage for neonates included in our study.



Below is the distribution of antibiotic usage for those with and without EOS.

```
##          sepsis (n)
## abx (n)   no   yes
##      0 1457   30
##      1  874  267
```

```

##          sepsis (%)
## abx (%) no yes
##      0 63 10
##      1 37 90

##
## Pearson's Chi-squared test with Yates' continuity correction
##
## data: table(abx_dat$abx, abx_dat$sepsis)
## X-squared = 292.4, df = 1, p-value <2e-16

```

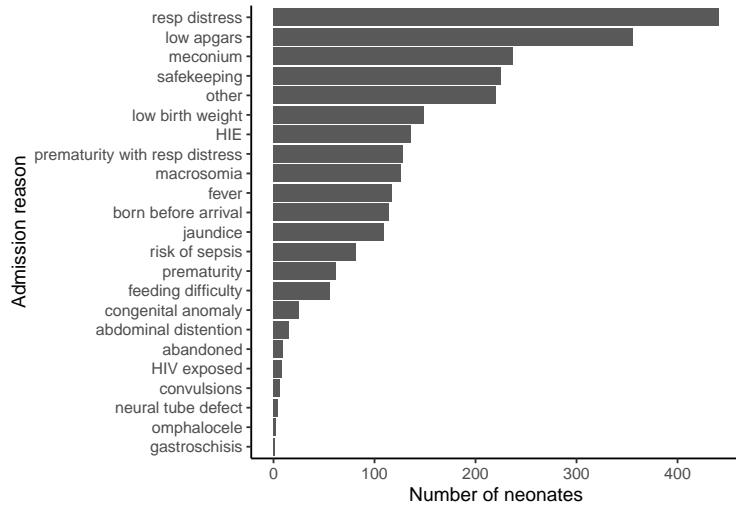
9.3 Characteristics of neonates in whom sepsis ‘missed’ by model

The table below compares characteristics between those with EOS who were classified as EOS by our model (true positives) and those with EOS who were classified as ‘no EOS’ by our model (false negatives, i.e. ‘missed’ EOS) at the optimal classification threshold determined by Youden’s J statistic (0.121).

Characteristic	Overall, N = 297	0, N = 191	1, N = 106	p-value
Sex, n (%)				0.038
f	132 (44%)	76 (40%)	56 (53%)	
m	165 (56%)	115 (60%)	50 (47%)	
u	0 (0%)	0 (0%)	0 (0%)	
Gestational age, mean weeks (SD)	38.36 (2.29)	38.65 (2.13)	37.85 (2.48)	0.006
Birth weight, mean grams (SD)	2.95 (0.60)	3.02 (0.55)	2.82 (0.65)	0.007
Chronological age, n (%)				0.005
fnb	100 (34%)	55 (29%)	45 (43%)	
dol1	121 (41%)	76 (40%)	45 (43%)	
dol2	54 (18%)	44 (23%)	10 (9.6%)	
dol3	19 (6.5%)	15 (7.9%)	4 (3.8%)	
Type of birth, n (%)				>0.9
singleton	291 (98%)	187 (98%)	104 (98%)	
twin1	6 (2.0%)	4 (2.1%)	2 (1.9%)	
triplet1	0 (0%)	0 (0%)	0 (0%)	
Mode of delivery, n (%)				0.3
svd	226 (76%)	145 (76%)	81 (76%)	
electiveCS	12 (4.0%)	5 (2.6%)	7 (6.6%)	
emergencyCS	51 (17%)	36 (19%)	15 (14%)	
instrumental	8 (2.7%)	5 (2.6%)	3 (2.8%)	
Admission duration, median days [Q1-Q3]	6.0 [3.5-8.8]	5.3 [2.9-8.4]	6.9 [4.7-9.2]	0.006
Death, n (%)	37 (12%)	21 (11%)	16 (15%)	0.4
sepsis, n (%)	297 (100%)	191 (100%)	106 (100%)	>0.9

9.4 Reasons for admission

The below figure shows the reasons for admission of neonates included in our study.



9.5 Sample size calculations

The below code shows post hoc sample size calculations as per Riley *et al.* BMJ 2020 (doi: <https://doi.org/10.1136/bmj.m441>).

```
# a. estimate the overall outcome proportion with sufficient precision
# aiming for margin of error \leq 0.05
outprop <- sum(si$sepsis == "yes")/nrow(si) #outcome proportion
(1.96 / 0.05)^2 * outprop*(1-outprop) #=154

## [1] 154.035

# b. target a small mean absolute prediction error (p \leq 30)
n <- nrow(si) #sample size of development dataset
P <- 9 #number of candidate predictor parameters
MAPE <- 0.05 #mean absolute prediction error
exp((-0.508 + 0.259*log(outprop) + 0.504*log(P) - log(MAPE))/0.544) #=263 for MAPE 0.05

## [1] 262.613

# c. target a shrinkage factor of 0.9
# (although shrinkage not used in our study)
S <- 0.9 #target shrinkage factor of 10%
R2CS <- 0.1 #anticipated R2(CS) of at least 0.1
P / ((S-1) * log(1 - (R2CS/S))) #=764

## [1] 764.117

# d. target small optimism of 0.05 in the apparent R2(Nagelkerke)
lnLnull <- (outprop*n)*log(outprop*n/n) + (n - outprop*n)*log(1 - outprop*n/n)
maxR2CS <- 1 - exp(2*lnLnull / n) #maximum possible value of R2CS
S2 <- R2CS / (R2CS + 0.05*maxR2CS) #assuming expected optimism \leq 0.05
P / ((S2 - 1)*log(1 - R2CS/S2)) #=333

## [1] 332.842
```

9.6 Model calibration

The below statistics and figure shows calibration of our optimal model with a flexible calibration curve using a loess smoother.

```
##          Dxy      C (ROC)        R2         D    D:Chi-sq       D:p
## 4.61505e-01 7.30752e-01 1.49516e-01 7.83152e-02 2.06812e+02 0.00000e+00
##          U      U:Chi-sq       U:p         Q     Brier   Intercept
## -7.61035e-04 -6.82121e-13 1.00000e+00 7.90763e-02 8.91469e-02 -6.99611e-10
##      Slope      Emax Brier scaled      Eavg       ECI
## 1.00000e+00 4.14697e-10 1.10680e-01 1.72905e-02 4.15562e-02
```

