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Article

An assessment of controllable etiological factors involved in neonatal seizure using a Monte Carlo model

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SUMMARY

Neonatal seizures occur in 0.01-0.06% of newborns. Many studies have correlated single factors with neonatal seizures, but emerging evidence indicates that the stimuli for neonatal seizures are multifactorial. To decrease neonatal seizure incidence, it is important to identify which combinations of factors have the greatest effect. The ability to identify the combinatorial influence has been restricted so far due to the limited number of case studies. Monte Carlo is a simulation method used to determine the probability of an uncertain event by simulating a large number of experiments that are otherwise unfeasible. We identified four controllable risk factors from previous studies: smoking, alcohol consumption, opioid use, and selective serotonin reuptake inhibitors use (SSRIs). Here, we used Monte Carlo simulations to examine the interplay of multiple factors simultaneously, which has not been considered in many previous studies. Previously, alcohol consumption and opioid use have only been associated with seizure through an intermediary factor (Fetal Alcohol Spectrum Disorders and Neonatal Opioid Withdrawal Syndrome, respectively). Our simulation demonstrated that there is a weak relationship between smoking and seizure and the strongest association between alcohol consumption and seizures. Similar to opioid use, SSRIs have previously been shown to have a moderate relationship with neonatal seizures. In contrast to published studies, our algorithm showed that SSRIs have a more significant role. Our work provides support for use of Monte Carlo simulations to determine the contribution of controllable factors to neonatal seizures, with the potential for ultimately allowing for more informed clinical decisions.

INTRODUCTION

A seizure is defined as the occurrence of hypersynchronous firing within neurons (1). This irregularity in electrical signaling can lead to changes in cognitive ability, muscle tension, emotions, and thought processes (2). Status epilepticus is when a patient has two or more unprovoked seizures, or a seizure that lasts for an extended period of time (3). This leads to the death of over 125,000 people in the US annually (4). Although seizures do not equate to having epilepsy, seizures have adverse effects even with a singular occurrence (5). The manifestation of a seizure in people can look visually different depending on the type, including generalized tonic-clonic seizures during an inhibitory neuronal state or absence seizures during an excitatory state (2). Despite the different manifestations, seizures are easier to identify and diagnose in children (62% accurate diagnosis) and adults (74.75% accurate diagnosis) than neonates (7.6% accurate diagnosis) (6-8). Neonates, which are infants in the 0–4 week range, can be permanently impacted by seizures. Many neonates have been diagnosed with ongoing epilepsy, developmental delays, or cerebral palsy after even one instance of a seizure (9). Thus, immediate identification and treatment of neonatal seizures is essential for the health of the child (10). However, due to the immaturity of a neonate's brain, visual signs are more difficult to ascertain and diagnose (9). Therefore, it is imperative to identify etiologies or factors that cause or strongly influence the likelihood of a neonatal seizure.

Numerous uncontrollable factors have been correlated with neonatal seizures including hypoxia-ischemia and asphyxia, hemorrhage and intracerebral infarction, physical trauma, central nervous system (CNS) infections, inborn metabolic disorders, malformations of cerebellum during development, and preterm birth (11-15). These factors are associated with 91% of all neonatal seizures (10). The most prevalent is hypoxia-ischemia, which accounts for 41% of all neonatal seizures. This is when the neonate does not receive enough oxygen to the brain (10).

Additionally, some controllable factors during pregnancy have been implicated in seizures including smoking, alcohol consumption, opioids use, and use of a category of antidepressant medication called selective serotonin reuptake inhibitors (SSRIs) (**Table 1**) (16-46)**.** Two of these risk factors, alcohol consumption and opioid use, are primarily correlated to neonatal seizure with an intermediary risk factor, respectively

	Alcohol	FASD	Opioids	NOWS	Smoking	SSRI
Lowest P(RF)	0.011	0.00106	0.00059	0.002	0.07	0.0028
Highest P(RF)	0.192	0.11322	0.099	0.0233	0.253	0.051
Range for P(NS|RF)		0.03-0.21		0.021-0.11	0.0123-0.044	0.01-0.093

Table 1: Lowest and highest probabilities applied in the Monte Carlo simulation for each risk factor are shown. Alcohol consumption and opioid use were designated intermediary risk factors and are therefore not shown to have a direct relationship with values for P(NS|RF). RF = risk factor. NS = neonatal seizure. P(RF) is the probability of the specific risk factor. P(NS|RF) is the range of probabilities identified of neonatal seizure given the specific risk factor is present. FASD = fetal alcohol spectrum disorder. NOWS = neonatal opioid withdrawal syndrome. SSRI = selective serotonin reuptake inhibitors. ND = No data. Values were obtained from literature reviews (22-46).

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being neonatal opioid withdrawal syndrome (NOWS) and fetal alcohol spectrum disorder (FASD) (47-54). Currently, the role of SSRIs in seizure is questionable, as several studies have argued that SSRIs can induce seizures while others deny this claim (55-59). Since the cause of neonatal seizures seems multifactorial, it is possible that the disagreement in these studies is due to a neglect of other variables (7,60).

Ranges for the statistical probability of each risk factor leading to neonatal seizure were identified using a literature review. We hypothesized that the variable ranges of probabilities among studies in the literature can be attributed to the compounding effect of multiple controllable factors. This compounding of factors may not have been considered by the authors in these studies. Notably, during our literature review of these articles we noticed that marginal statistics were often used. Marginal statistics define probabilities that do not consider the other variables present in the parameter and are unconditional (61). To our knowledge, the referenced articles each have their own limitations. These include a lack of specifics in detail about duration, frequency, and quantity of the toxin substance exposure to the mother and, therefore, the fetus. Therefore, there is an inevitable lack of continuity between articles, which may cause certain correlations to go unnoticed. For instance, one paper discussing the probability of a mother smoking did not mention whether or not she drank alcohol, despite the fact that smoking and drinking tendencies tend to be linked (62). Ideally, each probability would be of a singular risk factor and would ignore any possibility of overlap. Practically, however, the risk factors should have been studied without any other comorbidities or conditions to ensure statistically accurate results. Again, this may be due to inaccuracies in the categorization of samples in the datasets accumulated.

By considering the findings of both single and conditional probabilities in separate studies, it was possible to approach a more robust prediction of each contributing risk factor. The objective of this study was to determine if the Monte Carlo simulation can be used to predict which combination of factors gives neonates the greatest likelihood of seizure. We created a Monte Carlo simulation in order to estimate the chance of a neonate developing seizures given varying parameters. To understand the functions of a Monte Carlo simulation, one must first understand its underlying principles. A Monte Carlo simulation is a computational algorithm that involves the random assignment of variables predicated on the Law of Large Numbers (63). The Law of Large Numbers argues that as more experiments are continuously repeated, the statistical mean will approach the true value (64). Monte Carlo specializes in random sampling. The more data points are generated, the closer one gets to the true value of association between an explanatory and response variable. For the Monte Carlo analysis of the role of different risk factors on neonatal seizures, we included key parameters (62). These parameters included the probability of risk factor X, the intermediary risk factor that connected either alcohol or opioids to neonatal seizure, and the identified probability of seizure given the study had either factor X or the intermediary risk factor. This is dependent on which risk factor is being analyzed. For instance, the probability that a mother abuses opioids is then related with the probability of NOWS. This is a principal component of the Monte Carlo algorithm, as the purpose of Monte Carlo is to produce an output probability considering uncertain variables. Furthermore, by oscillating the different values within a range for each risk factor, a sensitivity analysis is attainable. Following this, the probability of seizures given NOWS is inputted. However, the link between factors such as smoking and SSRIs and neonatal seizure are direct and do not require an intermediary factor. Thus, the output displayed how individual factors are associated with seizure. The output was then compared to the range of probabilities accumulated in the literature review. Moreover, using Monte Carlo simulation allowed us to consider the influence of multiple factors by implementing Bayes Theorem, a mathematical formula to calculate conditional probabilities (66).

By utilizing a Monte Carlo simulation, we were able to simulate different conditions per experiment, or neonate, in order to obtain a more precisely defined probability rather than the broad ranges cited in journals (65). We demonstrated that alcohol had the strongest association with the highest likelihood of neonatal seizure. Additionally, SSRIs increased the average probability of neonatal seizure twofold in comparison to smoking. These findings can be used to assist the direction of physician advice and increase our awareness about the role of different substances on the probability of neonatal seizure.

RESULTS

This study aimed to elucidate the influence of individual factors when considering their combinatorial probabilities. We hypothesized that there were reported probabilities in the literature that did not consider the probability of the effect of multiple factors in tandem leading to neonatal seizure. The Monte Carlo simulation used the inputted probabilities of substance use and seizures associated with that substance found from previously published studies (16-46). This was used in order to find the proportion of neonates who had a seizure. These probabilities were randomly assigned within the identified range in the literature to each neonate to reduce experimental uncertainty and to analyze the validity of conclusions reached from previous studies. Results from this simulation were then used to identify the role of individual risk factors (**Table 2**). Using the Monte Carlo simulation, the average occurrence of neonatal seizure with only the FASD risk factor was the highest at 0.1198. The probability of neonatal seizure with only NOWS as a risk factor had an average probability of 0.0659. In this study, R^2 values were determined with consideration for the presence of a combination of factors. From this study, the Monte Carlo

Risk factor	Average occurrence of neonatal seizure
FASD	0.1198
NOWS	0.0659
Smoking	0.0281
SSRI	0.0513

Table 2: The average probability of neonatal seizure given a specified risk factor. A greater probability suggests a stronger association between an individual risk factor and the final probability of neonatal seizure. FASD = fetal alcohol spectrum disorder. NOWS = neonatal opioid withdrawal syndrome. SSRI = selective serotonin reuptake inhibitors.

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simulation demonstrated that SSRIs were associated with seizures (R^2 = 0.2067, p < 0.0001). We observed that smoking had a low R^2 value of 0.00936; however, this weak association was significant (p < 0.05) (**Figure 1**).

To define an individual factor's influence, we restricted the four parameters to only a single factor that was assigned to be true. For example, among the one million neonates simulated, we selected only neonates that were evaluated as 'true' for FASD, but 'false' for NOWS, SSRIs, and smoking. This allowed us to analyze the role of an individual factor without risk of assessing the influence of others. When considering neonates with exactly one risk factor, FASD was associated with the highest probability of neonatal seizure (**Table 2**). We were able to allocate distinct values for each risk factor rather than the wide ranges originally identified. These ranges were found from all articles that gave probability of one of the four risk factors leading to neonatal seizure. Many of these articles did not consider the overlapping of risk factors, which the Monte Carlo simulation considered. Notably, the average occurrence of neonatal seizure was almost two times greater with SSRIs (R^2 = 0.0513) than smoking (R^2 = 0.0281).

DISCUSSION

Currently, there are limitations to our understanding of the impact of various controllable risk factors on the likelihood of neonatal seizure. Identifying the impact of these factors on the probability of neonatal seizure can aid in assessing the validity of claims from previously published literature and enable an objective assessment of specific controllable

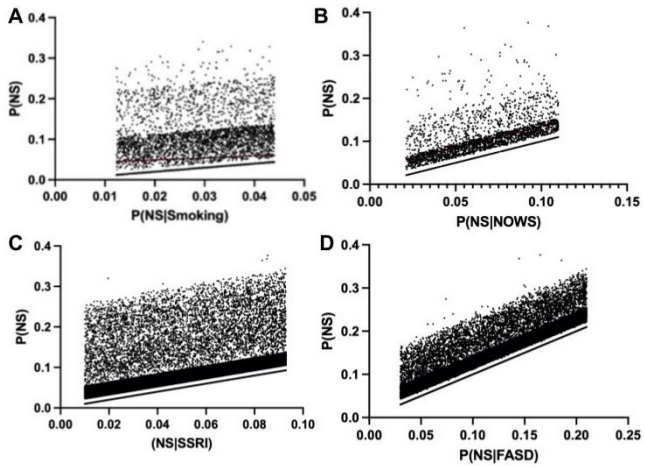

Figure 1: Regression analysis between the probability of neonatal seizure given a specific risk factor and the final probability of neonatal seizure. (A) Correlation of smoking risk factor with neonatal seizures. p < 0.0001, R = 0.09675, 95% CI [0.07874–0.1147], R^2 = 0.00936, Y = 0.5226x + 0.03857. (B) Correlation of opioid risk factor with neonatal seizures in which NOWS was used as an intermediary factor. p < 0.0001, R = 0.4418, 95% CI [0.2931–0.5697] R^2= 0.1952, Y = 0.8907x + 0.04531. (C) Correlation of SSRI risk factor with neonatal seizures. p < 0.0001, R = 0.4546, 95% CI [0.4305–4782], R^2 = 0.2067, Y = 0.8456x + 0.03319, (D) Correlation of alcohol risk factor with neonatal seizures in which FASD was used as an intermediary factor. p < 0.0001, R = 0.8651, 95% CI [0.8531–0.8762]. R^2 = 0.7484, Y = 0.9577x + 0.02939. NS = neonatal seizure. NOWS = neonatal opioid withdrawal syndrome. SSRI = selective serotonin reuptake inhibitors. FASD = fetal alcohol spectrum disorders.

factors correlation with neonatal seizure. Notably, we found that SSRIs have a greater association with neonatal seizures than shown in published literature (57-58, 71-73). On the other hand, we found that smoking was not as influential as previously regarded (17-23).

One of our objections to the conclusions of published literature was that previous studies failed to consider how multiple factors may be at play in the probability of neonatal seizure. Additionally, previous studies reported a range of probabilities rather than a single value. Often, these ranges were wide and obscure. Moreover, the many factors related to neonatal seizures contribute to the overall probability of neonatal seizure that is critical for our understanding of the condition. Consistent with published literature, our Monte Carlo simulation demonstrated a strong correlation between neonatal seizure and alcohol or opioids, supporting the restrictive use of these substances during pregnancy.

One of the surprising findings of our Monte Carlo simulation was that smoking had less of an impact on neonatal seizure than SSRIs. Many articles have purported that smoking is directly correlated with neonatal seizure (20-23). However, our findings suggest that smoking plays a minimal role in neonatal seizure. It is likely that the high correspondence between smoking and seizure that is found in the literature is stated without strong consideration of the presence of other factors. For instance, smoking has been shown to worsen the effect of hypoxia-ischemia by inducing greater cellular damage (67). Therefore, it is possible that our results reflect a Type 1 statistical error where the null hypothesis was rejected because of the significance (p < 0.00001) but corresponding data (R^2 = 0.00936) did not align (68). Nevertheless, it is important to consider the influence of smoking on neonatal seizure as a whole.

Upon analyzing a singular risk factor in our study through the Monte Carlo algorithm, SSRIs were shown to have a twofold increase in average occurrence when compared to smoking. Despite the fact that smoking was shown to have a similarly distributed probability range of being connected with neonatal seizure occurrence in the literature as SSRIs, we found that use of SSRIs was shown to be drastically more influential. There are conflicting reports as to whether SSRIs are detrimental to the development of neonates (48,57-59,69-74). These differences may be caused by small sample sizes, compounding variables that introduced experimental uncertainty, and the clustering of various types of SSRIs such as Citalopram and Fluoxetine without specificity. We found that a large number of studies argued conflicting findings, making it difficult for readers to understand the influence of SSRIs on neonatal development. The differences observed in our study concerning both smoking and SSRIs may help provide recommendations for how prenatal care is handled. Women and physicians should be aware of the potential consequences of this class of antidepressant drugs before use.

It is important to identify the various limitations of the Monte Carlo simulation. The data used in this study were gathered from literature where research was performed in different experiments and conditions. This variability is accompanied by some caveats. Notably, the simulation utilizes the inputs that were found from the literature review. Any potential inconsistencies in the acquired data may have impacted the accuracy of our findings.

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Our findings suggest limiting the use of opioids, SSRIs, and alcohol in pregnancy to minimize the risk of neonatal seizure. We found SSRIs to have a significant risk for leading to neonatal seizures. Therefore, the potential side effects of SSRIs on the neonate must be studied further to help weigh the implications on the mother and her neonate.

In our future studies we intend to expand the number of risk factors studied and run simulations in which a singular risk factor's probability is left constant while allowing for the mathematically random variation of all other factors. By employing this network, we will be able to establish the correlative relationship between these factors and neonatal seizure, see how modifying a risk factor influences the probability of neonatal seizure, and test the simulations' predictions. Furthermore, our project will be expanded to limit certain generalizations. For instance, both SSRIs and opioids have many subtypes that may have varying influence on neonates. Our future studies will consider subcategories of SSRIs (i.e. Fluoxetine or Citalopram) to help in the specification of our results on SSRIs. Analyzing each substance's effect under greater scrutiny will help in eliminating uncertainty. Furthermore, our research focused on considering the combination of risk factors and then purposefully excluding them. We identified the probability of neonates experiencing combinations of factors leading to neonatal seizure, but did not extensively interpret these data. It may prove beneficial to further analyze how a combination of risk factors alters the probability of neonatal seizure.

Our creation of a Monte Carlo computational algorithm allowed us to identify the role of different controllable risk factors in the probability of neonatal seizures. The statistical discrepancy between the literature review and our findings can be attributed to computational and organizational differences in the literature. Our Monte Carlo simulation can provide tools for healthcare providers to make comprehensive evaluations by taking the overlapping of factors into account. Understanding the factors that contribute to neonatal seizure may help decrease the prevalence of neonatal seizures in the population.

MATERIALS AND METHODS

Data Accumulation and Algorithm Design

The maximum and minimum probability of each risk factor's association with neonatal seizure were obtained from previous studies prior to the Monte Carlo simulation (**Table 2**). These ranges were either specifically identified in the article or calculated by finding the number of neonates exposed to a factor and how many experienced neonatal seizures. The influence of each risk factor can therefore be considered within the minimum and maximum values obtained from the literature review.

To obtain the ranges used in the simulation, over 30 articles were identified (16-46). These articles discussed any of the following: the probability of one of the four primary risk factors leading to neonatal seizure, the probability of an intermediary factor, if applicable, to be associated with neonatal seizure, the probability of a neonate being exposed to two or more of the risk factors during gestation, or the probability of neonatal seizure when considering uncontrollable risk factors. The probabilities were either explicitly stated in the results of the article or calculated by determining the total number of neonates studied and the number of neonates who had a seizure when exposed to the factor under examination.

Monte Carlo simulation

The Monte Carlo simulation was written in Python using random and Panda imports. The algorithm simulated one million neonates with the global probability of neonatal seizure (**Appendix**). Then, each neonate is randomly assigned a value within the range of probabilities for the initial risk factor. This value is then compared to the randomly generated value in the detcond function. This function, meant to determine if a neonate has the subsequent condition, compares each neonate's assigned value from the assigned probability to a value randomly generated between 0 and 1. If the value from this function is lower than the one generated in detcond, the neonate is assigned 'false' such that the neonate does not have the factor. However, if the generated value is greater than or equal to the value from detcond the neonate has the condition.

The proceeding function, probgiven, takes the results from the previous function and determines whether the neonate has an intermediary factor, if applicable (**Figure 2**). An intermediary factor was identified if the controlled substance was primarily associated with neonatal seizure via conditions developed following exposure. If it was found that the mother abuses opioids during pregnancy, then k==true and the function will assign a random value within the inputted range for the FASD factor. However, if k==false, then the standard

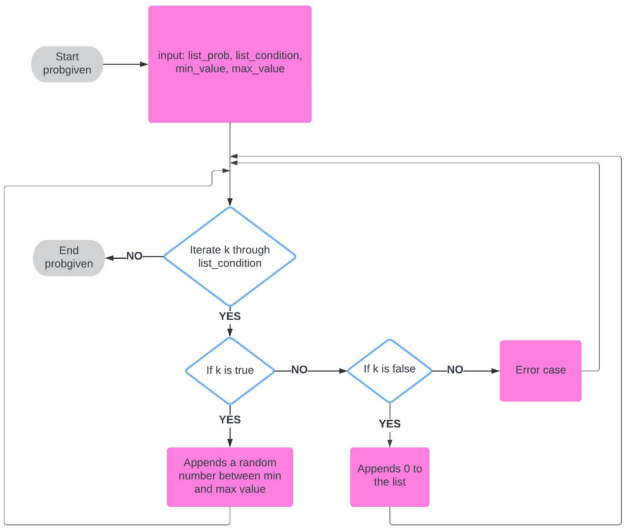

Figure 2: Logic tree of the probgiven function. The probgiven function determines the probabilistic presence of intermediary factors and assigns the factor to the simulated neonate when applicable (n = one million). List_prob is a list of floats, which will be filled with a random probability within range of min_value and max_value that a condition will be present if a correlated one is also present. If the given condition is not present, the given probability will be set to 0. List_condition is a list of boolean values that indicate whether a specific condition is present for each neonate, which is determined in prior steps. Min_value is a float that represents the lower bound for which the probability of a condition will occur, with the information that a given condition is true (value based on literature review. Max_value is a float that represents the upper bound for which the probability of a condition will occur, with the information that a given condition is true (value based on literature review). N_samples is the number of simulated neonates.

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probability of neonatal seizure without consideration of the false factor will be assigned to the neonate and appended to the list. This standard probability is the chance that the neonate will experience a seizure without influence from any controlled substance.

The function reeval then takes an identified factor in the neonate and attempts to identify the influence of any other factors. For instance, if a mother takes opioids then the probability of alcohol consumption will be the randomly generated value within the range of p(alcohol) with the addition of a randomly generated value from the p(alcohol|opioid) range (**Figure 3**). The simulation will continue to determine the likelihood of any combination of factors until all factors have been determined. Following this, the neonate's final probability of neonatal seizure is appended to the list and the simulation loop moves to the next iteration.

Due to a lack of articles focusing on less common co-etiologies such as the probability of SSRI given alcohol consumption, Bayes theorem was applied. Since a range of values were used in the Monte Carlo simulation, the minimum and maximum for each factor were considered. Additionally, articles' confidence intervals were used as part of the range when there were less than five articles identified per risk

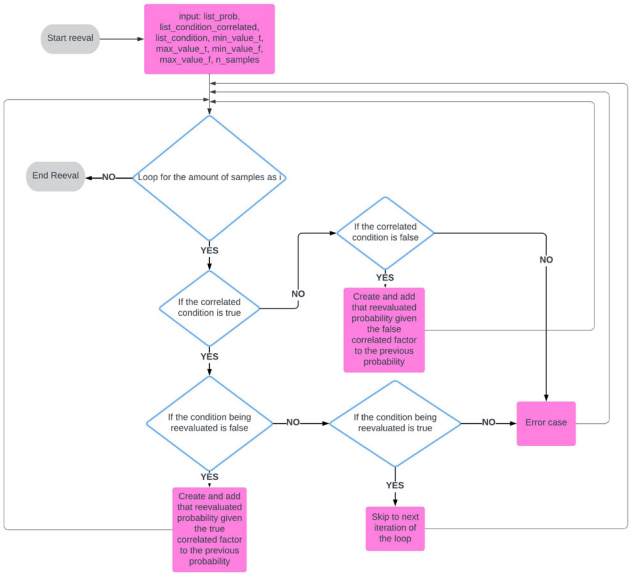

Figure 3: Logic tree of the reeval function. The reeval function determines the probability of the presence of a combination of factors and assigns numerous factors to be true to a neonate when applicable (n = one million). List_prob is list of floats, which will be filled with a probability that the condition being evaluated is true and is altered in this function depending on whether the correlated condition is also present. List_condition is a list of boolean values that indicate whether a specific condition is present for each neonate, which is determined in prior steps. List_condition_correlated is a list of boolean values that indicate whether a specific condition that is correlated with the one being evaluated is present for each neonate. Min_value is a float that represents the lower bound for which the probability of a condition will occur, with the information that a given condition is true (value based on literature review. Max_value is a float that represents the upper bound for which the probability of a condition will occur, with the information that a given condition is true (value based on literature review). N_samples is the number of simulated neonates.

factor. To find the probability of seizure for each neonate, probabilities from each factor were added together.

In order to decide whether the neonate actually has neonatal seizure, risk factors were separately considered to identify the probability of neonatal seizure for each reeval_detcond_final_probability (**Figure 4**). It was important to consider that the probability of neonatal seizure will extend beyond what was found in the literature review, as the final probability of neonatal seizure being considered is a summation. As the last function in the simulation, this function identified the final probability of seizure for each neonate. Due to the principles of the reeval function, any values greater than 1 were set to 1. Similar to detcond, a neonate is shown to have a seizure if the final probability of neonatal seizure is greater than the randomly generated number between 0 and 1. If not, the neonate is appended with 'false' for the p(NS).

The final line of code for identifying the probabilities of the neonate having neonatal seizure is shown on line 133 (**Appendix**). In the case that the neonate had none of the risk factors, the control probability of neonatal seizure was appended. However, if any of the risk factors were present, the range of probabilities for neonatal seizure given the present risk factor were added. In the case of multiple factors, probabilities were accumulated. The principles of the detcond function are then brought back to determine whether the neonate has neonatal seizure, which is appended to the probNS list in Excel.

The Monte Carlo simulation outputs the probability of a neonate being exposed to a specific factor. It then determined if the neonate was exposed to said factor, while simultaneously considering how this may affect the probability of another factor being present. When applicable, the same was done for the intermediary risk factor if alcohol or opioids was assigned to be true for a neonate. Lastly, the simulation determined, based on the compounding of all of the risk factors randomly assigned, if the neonate would have had a seizure.

Categorization and analysis of data

Once the simulation was performed, data were arranged into an 18 million cell Excel spreadsheet that listed the probability of each risk factor and associated intermediary risk factor if applicable, and the final probability of neonatal seizure in terms of a risk factor and as a whole. For specificity, 'true' and 'false' were also listed next to each column when identifying if a neonate had the proceeding condition. Following this, data was categorized by combinations of risk factors. In particular, we identified neonates that were only shown to have one risk factor to be true to identify this specific risk factor's role in neonatal seizure without the presence of the other three factors.

In order to measure the impact of each risk factor, outputs were categorically separated based on the four primary risk factors. The probability of neonatal seizure given a risk factor and the final output probability of neonatal seizure for each neonate with the former being the explanatory variable and the latter being its response variable. All neonates that were found to have neonatal seizure were collated and inputted into a simple linear regression graph in GraphPad Prism to study changes across experimental conditions. A statistically significant correlation ($p < 0.05$) was needed to show a strong association between risk factor X and the final probability of seizure. The *R*-value, R^2 value, *p*-value,

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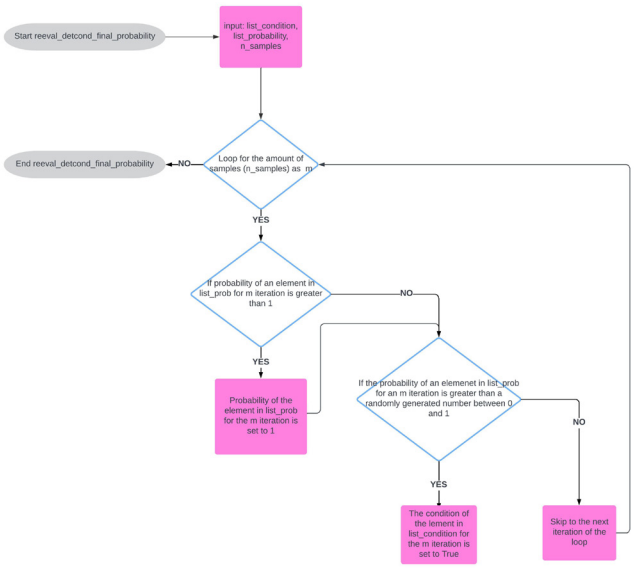

Figure 4: Logic tree of the reeval_detcond_final_probability function. The reeval_detcond_final_probability function determines whether the simulated neonate has neonatal seizure given the present factors (n = one million). List_prob is a list of floats, which will be filled with a random probability within range of min_value and max_value that a condition will be present if a correlated one is also present. If the given condition is not present, the given probability will be set to 0. List_condition is a list of boolean values that indicate whether a specific condition is present for each neonate, which is determined in prior steps. List_condition_correlated is a list of boolean values that indicate whether a specific condition that is correlated with the one being evaluated is present for each neonate. Min_value is a float that represents the lower bound for which the probability of a condition will occur, with the information that a given condition is true (value based on literature review. Max_value is a float that represents the upper bound for which the probability of a condition will occur, with the information that a given condition is true (value based on literature review). N_samples is the number of simulated neonates

and 95% Confidence Interval (CI) were gathered as well. The Coefficient of Determination (R^2) indicates to what degree an independent variable represents a percentage of the variation in the dependent variable. The R^2 value is a key component in determining how a constant variable influences the final probability of neonatal seizure. An R^2 closer to 1 indicates a strong association, while a value closer to 0 indicates a weak relationship. Graphs were made in dot-plot format with a line of best-fit and an estimation of the 95% CI (**Figure 1**). This interval was formed to show variance in results.

We used R and R^2 values to measure the strength of association between a risk factor and neonatal seizure. An R^2 describes the percent variation of the final probability of neonatal seizure as a result of the independent factor, one of the controllable etiologies.

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REFERENCES

1. "Epilepsy and Seizures." *National Institute of Neurological Disorders and Stroke*, www.ninds.nih.gov/health-information/disorders/epilepsy-and-seizures. Accessed 28 Nov, 2023
2. "Seizures - Symptoms and Causes." Mayo Clinic, www.mayoclinic.org/diseases-conditions/seizure/symptoms-causes/syc-20365711. Accessed 2 Sep, 2023
3. Glauser, Tracy *et al.* "Evidence-Based Guideline: Treatment of Convulsive Status Epilepticus in Children and Adults: Report of the Guideline Committee of the American Epilepsy Society." *Epilepsy currents* vol. 16,1 (2016). https://doi.org/10.5698/1535-7597-16.1.48.
4. Trinka, Eugen, *et al.* "Mortality, and Life Expectancy in Epilepsy and Status Epilepticus—Current Trends and Future Aspects." *Frontiers in Epidemiology*, vol. 3,23 Feb. 2023, https://doi.org/10.3389/fepid.2023.1081757.
5. Pohlmann-Eden, Bernd *et al.* "The first seizure and its management in adults and children." *BMJ* (Clinical research ed.) vol. 332, no. 7537, 2006, https://doi.org/10.1136/bmj.332.7537.339.
6. Hamiwka, L. D., *et al.* "Diagnostic Inaccuracy in Children Referred with 'First Seizure': Role for a First Seizure Clinic." *Epilepsia*, vol. 48, no. 6, June 2007, https://doi.org/10.1111/j.1528-1167.2007.01018.x.
7. Muayqil, Taim A., *et al.* "Accuracy of Seizure Semiology Obtained from First-Time Seizure Witnesses." *BMC Neurology*, vol. 18, Sept. 2018, https://doi.org/10.1186/s12883-018-1137-x
8. Malone, Aileen, *et al.* "Interobserver Agreement in Neonatal Seizure Identification." *Epilepsia*, vol. 50, no. 9, Sept. 2009, https://doi.org/10.1111/j.1528-1167.2009.02132.x.
9. Kaminiów, Konrad, *et al.* "Neonatal Seizures Revisited." *Children,* vol. 8, no. 2, 2, Feb. 2021,. https://doi.org/10.3390/children8020155.
10. Krawiec, Conrad, and Maria Rosaria Muzio. "Neonatal Seizure." *StatPearls*, StatPearls Publishing, 2023., www.ncbi.nlm.nih.gov/books/NBK554535/.
11. Spagnoli, Carlotta, *et al.* "Symptomatic Seizures in Preterm Newborns: A Review on Clinical Features and Prognosis." *Italian Journal of Pediatrics*, vol. 44, no. 1, Nov. 2018, https://doi.org/10.1186/s13052-018-0573-y.
12. Westover, M. Brandon, *et al.* "The Probability of Seizures during EEG Monitoring in Critically Ill Adults." Clinical Neurophysiology: *Official Journal of the International Federation of Clinical Neurophysiology* vol. 126, no. 3, Mar. 2015, https://doi.org/10.1016/j.clinph.2014.05.037.
13. "Seizure: What It Is, Causes, Symptoms & Types." *Cleveland Clinic*, my.clevelandclinic.org/health/diseases/22789-seizure. Accessed 3 Sep, 2023
14. Panayiotopoulos, C. P. The Epilepsies: Seizures, Syndromes and Management. *Bladon Medical Publishing*, 2005., www.ncbi.nlm.nih.gov/books/NBK2606/.
15. Soul, Janet S. "Acute Symptomatic Seizures in Term Neonates: Etiologies and Treatments." *Seminars in Fetal & Neonatal Medicine*, vol. 23, no. 3, June 2018, https://doi.org/10.1016/j.siny.2018.02.002.

16. Alvik, Astrid, *et al*. "Alcohol Use before and during Pregnancy: A Population-Based Study." *Acta Obstetricia Et Gynecologica Scandinavica*, vol. 85, no. 11, 2006, https://doi.org/10.1080/00016340600589958.
17. Kataoka, Mariana Caricati, *et al*. "Smoking during Pregnancy and Harm Reduction in Birth Weight: A Cross-Sectional Study." *BMC Pregnancy and Childbirth,* vol. 18, no. 1, Mar. 2018,. https://doi.org/10.1186/s12884-018-1694-4.
18. Lechosa Muñiz, Carolina, *et al*. "Impact of Maternal Smoking on the Onset of Breastfeeding versus Formula Feeding: A Cross-Sectional Study." *International Journal of Environmental Research and Public Health*, vol. 16, no. 24, 24, Jan. 2019, https://doi.org/10.3390/ijerph16244888.
19. Rivas-Juesas, Cristina, *et al*. "Maternal Smoking during Pregnancy and Asthma during the First Year of Life: A Comparative Study between Smokers and Nonsmoker Mothers." *Allergologia et Immunopathologia*, vol. 49, no. 5, Sept. 2021, https://doi.org/10.15586/aei.v49i5.439.
20. Sequí-Canet, Jose Miguel, *et al*. "Maternal Factors Associated with Smoking during Gestation and Consequences in Newborns: Results of an 18-Year Study." *Journal of Clinical and Translational Research*, vol. 8, no. 1, Jan. 2022, http://doi.org/10.18053/jctres.08.202201.001.
21. Soneji, Samir, and Hiram Beltrán-Sánchez. "Association of Maternal Cigarette Smoking and Smoking Cessation With Preterm Birth." vol. 2, no. 4, Apr. 2019, *Silverchair*, https://doi.org/10.1001/jamanetworkopen.2019.2514.
22. Zaganjor, I., Kramer, R. D., Kofie, J. N., Sawdey, M. D., & Cullen, K. A. (2024). Trends in Smoking Before, During, and After Pregnancy in the United States from 2000 to 2020: Pregnancy Risk Assessment Monitoring System. *Journal of women's health (2002)*, *33*(3), https://doi.org/10.1089/jwh.2023.0641.
23. Yang, Lili, *et al*. "Maternal Cigarette Smoking before or during Pregnancy Increases the Risk of Birth Congenital Anomalies: A Population-Based Retrospective Cohort Study of 12 Million Mother-Infant Pairs." *BMC Medicine*, vol. 20, Jan. 2022, https://doi.org/10.1186/s12916-021-02196-x.
24. Cheng, Diana, *et al*. "Alcohol Consumption during Pregnancy: Prevalence and Provider Assessment." *Obstetrics and Gynecology*, vol. 117, no. 2 Pt 1, Feb. 2011, https://doi.org/10.1097/AOG.0b013e3182078569.
25. Flynn, Heather A., *et al*. "Rates and Correlates of Alcohol Use among Pregnant Women in Obstetrics Clinics." *Alcoholism, Clinical and Experimental Research*, vol. 27, no. 1, Jan. 2003, https://doi.org/10.1097/01.ALC.0000046595.47491.37.
26. Green, Patricia P., *et al*. "Vital Signs: Alcohol-Exposed Pregnancies--United States, 2011-2013." *MMWR. Morbidity and Mortality Weekly Report*, vol. 65, no. 4, Feb. 2016, https://doi.org/10.15585/mmwr.mm6504a6.
27. Lanting, Caren I., *et al*. "Prevalence and Pattern of Alcohol Consumption during Pregnancy in the Netherlands." *BMC Public Health,* vol. 15, July 2015, https://doi.org/10.1186/s12889-015-2070-1.
28. Leonardson, Gary, and Roland Loudenburg. "Risk Factors for Alcohol Use during Pregnancy in a Multi State Area." *Neurotoxicology and Teratology*, vol. 25, Nov. 2003, https://doi.org/10.1016/j.ntt.2003.07.002.
29. Fleming, K.M., Gomez, K.U., Goodwin, L. *et al.* Identifying the motives for and against drinking during pregnancy and motherhood, and factors associated with increased maternal alcohol use. *J Public Health,* Nov 2023 https://doi.org/10.1007/s10389-023-02141-7.
30. Pirie, Phyllis L., *et al*. "Tobacco, Alcohol, and Caffeine Use and Cessation in Early Pregnancy." *American Journal of Preventive Medicine*, vol. 18, no. 1, Jan. 2000, https://doi.org/10.1016/S0749-3797(99)00088-4.
31. Shmulewitz, Dvora, and Deborah S. Hasin. "Risk Factors for Alcohol Use among Pregnant Women, Ages 15-44, in the United States, 2002 to 2017." *Preventive Medicine,* vol. 124, July 2019, https://doi.org/10.1016/j.ypmed.2019.04.027.
32. Skagerström, Janna, *et al*. "Prevalence of Alcohol Use before and during Pregnancy and Predictors of Drinking during Pregnancy: A Cross Sectional Study in Sweden." *BMC Public Health*, vol. 13, no. 1, Aug. 2013, https://doi.org/10.1186/1471-2458-13-780.
33. Kozhimannil, Katy B., *et al*. "Non-Medical Opioid Use and Sources of Opioids among Pregnant and Non-Pregnant Reproductive-Aged Women." *Drug and Alcohol Dependence*, vol. 174, May 2017, https://doi.org/10.1016/j.drugalcdep.2017.01.003.
34. Maeda, Ayumi, *et al*. "Opioid Abuse and Dependence during Pregnancy: Temporal Trends and Obstetrical Outcomes." *Anesthesiology*, vol. 121, no. 6, Dec. 2014, https://doi.org/10.1097/ALN.0000000000000472.
35. Martin, Caitlin E., *et al*. "Recent Trends in Treatment Admissions for Prescription Opioid Abuse during Pregnancy." *Journal of Substance Abuse Treatment,* vol. 48, no. 1, Jan. 2015, https://doi.org/10.1016/j.jsat.2014.07.007.
36. Nørgaard, Mette, *et al*. "Birth and Neonatal Outcomes Following Opioid Use in Pregnancy: A Danish Population-Based Study." *Substance Abuse: Research and Treatment*, vol. 9, no. Suppl 2, 2015, https://doi.org/10.4137/SART.S23547.
37. Alwan, Sura, *et al*. "Use of Selective Serotonin-Reuptake Inhibitors in Pregnancy and the Risk of Birth Defects." *The New England Journal of Medicine*, vol. 356, no. 26, June 2007, https://doi.org/10.1056/NEJMoa066584.
38. Bérard, Anick, *et al*. "SSRI and SNRI Use during Pregnancy and the Risk of Persistent Pulmonary Hypertension of the Newborn." *British Journal of Clinical Pharmacology*, vol. 83, no. 5, May 2017, https://doi.org/10.1111/bcp.13194.
39. Hanley, Gillian E., and Barbara Mintzes. "Patterns of Psychotropic Medicine Use in Pregnancy in the United States from 2006 to 2011 among Women with Private Insurance." *BMC Pregnancy and Childbirth*, vol. 14, July 2014, https://doi.org/10.1186/1471-2393-14-242.
40. Jimenez-Solem, Espen, *et al*. "SSRI Use during Pregnancy and Risk of Stillbirth and Neonatal Mortality." *The American Journal of Psychiatry*, vol. 170, no. 3, Mar. 2013, https://doi.org/10.1176/appi.ajp.2012.11081251.
41. Jordan, Sue, *et al*. "Selective Serotonin Reuptake Inhibitor (SSRI) Antidepressants in Pregnancy and Congenital Anomalies: Analysis of Linked Databases in Wales, Norway and Funen, Denmark." *PloS One*, vol. 11, no. 12, 2016, https://doi.org/10.1371/journal.pone.0165122.

https://doi.org/10.59720/24-054

42. Koren, Gideon, and Hedvig Nordeng. "Antidepressant Use during Pregnancy: The Benefit-Risk Ratio." *American Journal of Obstetrics and Gynecology*, vol. 207, no. 3, Sept. 2012, https://doi.org/10.1016/j.ajog.2012.02.009.
43. Malm, Heli, *et al*. "Risks Associated With Selective Serotonin Reuptake Inhibitors in Pregnancy." *Obstetrics & Gynecology*, vol. 106, no. 6, Dec. 2005, https://doi.org/10.1097/01.AOG.0000187302.61812.53.
44. Molenaar, Nina Maren, *et al*. "Dispensing Patterns of Selective Serotonin Reuptake Inhibitors before, during and after Pregnancy: A 16-Year Population-Based Cohort Study from the Netherlands." *Archives of Women's Mental Health*, vol. 23, no. 1, 2020, https://doi.org/10.1007/s00737-019-0951-5.
45. Palmsten, Kristin, *et al*. "Antidepressant Use and Risk for Preeclampsia." Epidemiology (*Cambridge, Mass.*), vol. 24, no. 5, Sept. 2013, https://doi.org/10.1097/EDE.0b013e31829e0aaa.
46. Pedersen, Lars Henning, *et al*. "Selective Serotonin Reuptake Inhibitors in Pregnancy and Congenital Malformations: Population Based Cohort Study." *BMJ* (Clinical Research Ed.), vol. 339, Sept. 2009, https://doi.org/10.1136/bmj.b3569.
47. Toh, Sengwee, *et al*. "Selective Serotonin Reuptake Inhibitor Use and Risk of Gestational Hypertension." *The American Journal of Psychiatry*, vol. 166, Feb. 2009, https://doi.org/10.1176/appi.ajp.2008.08060817.
48. Zoega, Helga, *et al*. "Use of SSRI and SNRI Antidepressants during Pregnancy: A Population-Based Study from Denmark, Iceland, Norway and Sweden." *PloS One*, vol. 10, no. 12, 2015, https://doi.org/10.1371/journal.pone.0144474.
49. Desai, Rishi, *et al*. "Exposure to Prescription Opioid Analgesics in Utero and Risk of Neonatal Abstinence Syndrome: Population Based Cohort Study." *BMJ (Clinical Research Ed.),* vol. 350, May 2015, https://doi.org/10.1136/bmj.h2102.
50. Jones, H. E., *et al*. "Smoking in Pregnant Women Screened for an Opioid Agonist Medication Study Compared to Related Pregnant and Non-Pregnant Patient Samples." *The American Journal of Drug and Alcohol Abuse*, vol. 35, no. 5, 2009, https://doi.org/10.1080/00952990903125235.
51. Patrick, Stephen W., *et al*. "Prescription Opioid Epidemic and Infant Outcomes." *Pediatrics*, vol. 135, no. 5, May 2015, https://doi.org/10.1542/peds.2014-3299.
52. May PA, Chambers CD, Kalberg WO, *et al*. Prevalence of Fetal Alcohol Spectrum Disorders in 4 US Communities. *JAMA*. 2018;319(5) https://doi.org/10.1001/jama.2017.21896.
53. Popova, Svetlana, *et al*. "Prevalence of Fetal Alcohol Spectrum Disorder among Special Subpopulations: A Systematic Review and Meta-Analysis." *Addiction* (Abingdon, England), vol. 114, no. 7, July 2019, https://doi.org/10.1111/add.14598.
54. Roozen, Sylvia, *et al*. "Systematic Literature Review on Which Maternal Alcohol Behaviors Are Related to Fetal Alcohol Spectrum Disorders (FASD)." *BMJ Open,* vol. 8, no. 12, Dec. 2018, Maastricht University, https://doi.org/10.1136/bmjopen-2018-022578.
55. Hill, Trevor, *et al*. "Antidepressant Use and Risk of Epilepsy and Seizures in People Aged 20 to 64 Years: Cohort Study Using a Primary Care Database." *BMC Psychiatry*, vol. 15, Dec. 2015, https://doi.org/10.1186/s12888-015-0701-9.
56. Potokar, John, *et al*. "Do SSRIs Prolong Seizure Duration during ECT?" *International Journal of Psychiatry in Clinical Practice*, vol. 1, no. 4, Jan. 1997, https://doi.org/10.3109/13651509709024739.
57. Wiggs, Kelsey Kathleen, *et al*. "Maternal Serotonergic Antidepressant Use in Pregnancy and Risk of Seizures in Children." *Neurology*, vol. 98, no. 23, June 2022, https://doi.org/10.1212/WNL.0000000000200516.
58. LaFrance, W. C., *et al*. "Pilot Pharmacologic Randomized Controlled Trial for Psychogenic Nonepileptic Seizures." *Neurology*, vol. 75, no. 13, Sept. 2010, https://doi.org/10.1212/WNL.0b013e3181f4d5a9.
59. Ribot, Ramses, *et al*. "The Impact of Antidepressants on Seizure Frequency and Depressive and Anxiety Disorders of Patients with Epilepsy: Is It Worth Investigating?" *Epilepsy & Behavior*, vol. 70, May 2017, https://doi.org/10.1016/j.yebeh.2017.02.032.
60. Meador, Kimford J. "Seizure Reduction with Fluoxetine in an Adult Woman with Dravet Syndrome." *Epilepsy & Behavior Case Reports,* vol. 2, 2014, https://doi.org/10.1016/j.ebcr.2014.03.001.
61. "Marginal and Conditional Distributions (Video)." Khan Academy, www.khanacademy.org/math/ap-statistics/analyzing-categorical-ap/distributions-two-way-tables/v/marginal-distribution-and-conditional-distribution. Accessed 4 Sep, 2023.
62. van Amsterdam, Jan, and Wim van den Brink. "The effect of alcohol use on smoking cessation: A systematic review." *Alcohol (Fayetteville, N.Y.)* vol. 109: 13-22, June 2023 https://doi.org/10.1016/j.alcohol.2022.12.003.
63. Pishro-Nik, Hossein. "Law of Large Numbers." Probability Course, 24 Aug. 2014, www.probabilitycourse.com/chapter7/7_1_1_law_of_large_numbers.php. Accessed 4 Sep, 2023.
64. González Dan, J. R., *et al*. "Monte Carlo Simulation as a Tool to Show the Influence of the Human Factor into the Quantitative Risk Assessment." *Process Safety and Environmental Protection*, vol. 102, July 2016, https://doi.org/10.1016/j.psep.2016.04.024.
65. Raychaudhuri, Samik. "Introduction to Monte Carlo Simulation." 2008 Winter Simulation Conference, 2008, https://doi.org/10.1109/WSC.2008.4736059.
66. Joyce, James. "Bayes' Theorem (Stanford Encyclopedia of Philosophy)." Stanford.edu, 2016, https://plato.stanford.edu/entries/bayes-theorem/. Accessed 5 Sep, 2023.
67. Chan, Y. L., Saad, S., Machaalani, R., Oliver, B. G., Vissel, B., Pollock, C., Jones, N. M., & Chen, H. (2017). Maternal Cigarette Smoke Exposure Worsens Neurological Outcomes in Adolescent Offspring with Hypoxic-Ischemic Injury. *Frontiers in molecular neuroscience*, *10*, https://doi.org/10.3389/fnmol.2017.00306.
68. Banerjee, A., Chitnis, U. B., Jadhav, S. L., Bhawalkar, J. S., & Chaudhury, S. (2009). Hypothesis testing, type I and type II errors. *Industrial psychiatry journal*, *18*(2), https://doi.org/10.4103/0972-6748.62274.
69. Levinson-Castiel, Rachel *et al*. "Neonatal abstinence syndrome after in utero exposure to selective serotonin reuptake inhibitors in term infants." *Archives of pediatrics*

https://doi.org/10.59720/24-054

& adolescent medicine vol. 160,2 (2006): https://doi.org/10.1001/archpedi.160.2.173.
70. Moses-Kolko, Eydie L *et al.* "Neonatal signs after late in utero exposure to serotonin reuptake inhibitors: literature review and implications for clinical applications." *JAMA* vol. 293,19 (2005): https://doi.org/10.1001/jama.293.19.2372.
71. Cornet, Marie-Coralie *et al.* "Maternal treatment with selective serotonin reuptake inhibitors during pregnancy and delayed neonatal adaptation: a population-based cohort study." *Archives of disease in childhood. Fetal and neonatal edition* vol. 109,3 18 Apr. 2024, https://doi.org/10.1136/archdischild-2023-326049.
72. Leung, Miriam T Y *et al.* "Gestational exposure to antidepressants and risk of seizure in offspring: A systematic review and meta-analysis." *Neuroscience and biobehavioral reviews* vol. 131 (2021): https://doi.org/10.1016/j.neubiorev.2021.09.040.
73. Levy, Michal *et al.* "Maternal use of selective serotonin reuptake inhibitors (SSRI) during pregnancy-neonatal outcomes in correlation with placental histopathology." *Journal of perinatology : Official journal of the California Perinatal Association* vol. 40,7 (2020): https://doi.org/10.1038/s41372-020-0598-0.
74. LaFrance, W C Jr *et al.* "Pilot pharmacologic randomized controlled trial for psychogenic nonepileptic seizures." *Neurology* vol. 75,13 (2010): https://doi.org/10.1212/WNL.0b013e3181f4d5a9.

APPENDIX

GitHub access link: https://github.com/emily-smuks/Neonatal-Seizure.git