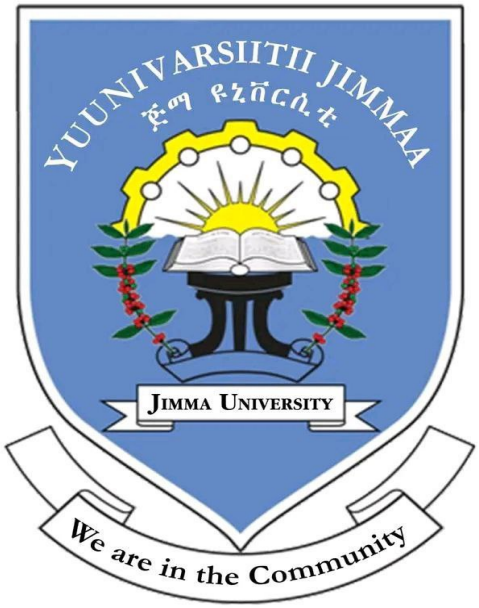

COLLEGE OF NATURAL SCIENCES

DEPARTMENT OF STATISTICS

Bayesian Method to Examine the Factors for Birth Defects in Children Admitted to CURE Ethiopia Children's Hospital: Application of a Bivariate Multinomial Regression model

By: Abenezer Yohannes

A Thesis Submitted to Jimma University, College of Natural Sciences, Department of Statistics in Partial Fulfillment of the Requirements for the Degree of Master of Science (M.Sc.) in Biostatistics.

November, 2023

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As members of the Board of Examiners for the M.Sc. thesis open defense examination on the aforementioned title, we have thoroughly reviewed and assessed the thesis, as well as conducted a comprehensive examination of the candidate.

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STATEMENT OF THE AUTHOR

I, the undersigned author of this research study, hereby affirm the authenticity and independence of this thesis. I acknowledge the support of my mentors and the assistance of various individuals. Proper acknowledgment has been given to all contributors and sources utilized in crafting this thesis. This thesis has been submitted to Jimma University as a partial fulfillment for the Degree of Master of Science in Biostatistics. The library directorate of Jimma University is authorized to archive a copy of this thesis in the university library for accessibility to students and researchers. I declare that this thesis has not been previously submitted to any other institution for academic recognition. Limited use of brief quotations from this thesis is permissible with proper acknowledgment and citation. Any other usage requires explicit consent from the author.

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Name of Candidate	Signature	Date

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List of Abbreviations and Acronyms

CL	Cleft Lip
CP	Cleft Palate
CLO	Cleft Lip only
CLP	Cleft Lip with Cleft Palate
COSECSA	College of Surgeons of East, Central, and Southern Africa
FMoH	Federal Ministry of Health
IRB	Institutional review Board
JAGS	Just Another Gibbs Sampler
LMICs	Low- and Middle-income countries
LP	likelihood principles
MCMC	Markov Chain Monte Carlo
MLE	Maximum Likelihood Estimation
MLR	Multinomial Logistic Regression
NCDs	Non-Communicable disease
OFC	Orofacial Clefts
SSA	Sub-Saharan Africa
UK	United Kingdom
WHO	World Health Organization

Abstract

Background: *Cleft Lip (CL) and Cleft Palate (CP) are holes or splits inside the upper lip and roof of the mouth (palate). These are the most prevalent congenital abnormalities of the head and neck and mainly occur when the facial structure of a growing child does not fully close. This study aimed to examine the determinants of cleft lip and cleft palate in children admitted at CURE Ethiopia Children's Hospital.*

Methods: *In this study, the data were collected from 544 children and related families cleft lip and palate patients using the cross-sectional study design. A bivariate multinomial regression model was employed to examine the determinants of cleft lip and cleft palate. Parameter estimation and inference association to the model were performed based on the Bayesian method.*

Results: *Among the study participants, unilateral, bilateral, and median cleft lip types of birth defects were observed on 360 (66.17%), 118 (21.69%) and 66 (12.13%) children, respectively. Also, 143(26.28 %) , 83 (15.25%) and 318 (58.45%) children were with muscular/soft, bony/hard and both (soft and hard) parts of the cleft palate, respectively. The results suggests that mothers consumption of alcohol for unilateral (OR = 1.127; 95% CI: 1.066, 5.546) was significant predictors for cleft lip. On the other hand, mothers consumption of alcohol for bony/hard part (OR = 1.701; 95% CI: 1.286, 5.680) was significant predictors for cleft Palate at 5% level of confidence. The choice of prior distributions significantly impact the posterior distributions.*

Conclusion: *In this study, alcohol consumption during pregnancy, maternal folic acid deficiency, history of birth defects, poor antenatal care service, and other variables were the risk factors for the prevalence of cleft lip and cleft palate in children. Therefore, in order to decrease the occurrence of these defects, special attention should be paid to specific population groups by raising awareness of the risk factors.*

Key Words*: Cleft lip and Cleft Palate, bivariate multinomial regression model, Bayesian method.*

1 Introduction

1.1 Background of the Study

Birth defects are changes to the body's structure that are present at birth[1]. They can affect any part of the body, and they can range from mild to severe. Cleft Lip (CL) and Cleft Palate (CP) are two examples of birth defects that affect the face[2]. They are the most prevalent congenital abnormalities of the head and neck, which are holes or splits inside the upper lip and the mouth's roof (palate)[3;4]. They are among the most common birth defects and are caused when a growing baby's facial structures don't fully close (between the 4^{th} and 6^{th} weeks of pregnancy, a developing baby's lip begins to form)[5;6].

Birth defects have a multifactorial aetiology, meaning that both genetic and environmental factors may affect how the anomaly develops[7;8]. Considering the non-syndrome and syndrome types of the illness, more than 70% of face congenital abnormalities are non-syndrome, while less than 30% of all facial deformities are categorised as syndrome types[9;10]. The disease often comes with a number of consequences, primarily affecting the voice and face. Most cleft patients have speech and hearing disorders, whereas patients with cleft lip and palate often have a wide range of issues, with physical loss being the most obvious[9;10;11]. A study showed that people with oral-facial clefts feel less adapted to their social environment than healthy adults do[12].

According to the WHO, CL and/or CP are heterogeneous disorders that affect the lips and oral cavity, and 70% occur either alone or as part of a syndrome, which affects more than 1 in 1000 newborns worldwide (2017). Birth defects have been the leading cause of infant mortality and represent a significant source of Childhood disability in the United States and other developed countries[13]. The prevalence of Orofacial Clefts

varies from 1:500 to 1:2500 births depending on geographic origin, racial and ethnic backgrounds, and socioeconomic status[14;15].

In Africa, most babies are born outside hospitals[16] and the results of a more extensive investigation would be valuable to understand the causes of the disease. A study conducted to determine the incidence of cleft lip and palate in Addis Ababa, Ethiopia, shows that sixty-four new cleft lip and palate patients were recorded in the study institutions, giving an incidence of 1.49 per 1000 live births, or 1 in 672 live births[16]. The incidence found in this study indicates that cleft is not rare in Ethiopia. In low-income settings, there is a high mortality rate in the neonatal period[13]. However, if lip and palate clefts are properly treated by surgery, complete rehabilitation is possible[13]. Additionally, it was reported that poor oral health has been linked in a reciprocal way with other non-communicable diseases (NCDs), such as diabetes[13]. Approximately 400 million people suffered from some form of oral disease recorded in the WHO African Region in 2017[8;16].

Moreover, the presence of facial abnormalities or congenital deformities in children affects the oro-facial area and may lead to significant health care costs, which might have a negative effect on their quality of life and mental health[17]. However, the prevalence of birth defects, including oro-facial clefts (OFC), is not well known in Ethiopia, and there is no established birth defect registration system[18].

A study conducted by Martelli et al.[19] to describe the relation between non sindromic cleft lip and/or palate and sex and severity of the cleft using multinomial logistic regression. However, Bivariate multinomial regression is specifically designed to handle categorical dependent variables with more than two categories. This makes it particularly useful when analyzing data that involve multiple outcomes. It allows for the examination of relationships between multiple independent variables and a categorical dependent variable, for the identification of the predictors that are associ-

ated with each outcome category separately, providing insights into the unique effects of different variables on each category. Other models, such as binary logistic regression, are limited to binary outcomes and may not be suitable for analyzing data with more than two categories[20;21]. Therefore, in this thesis, the factors associated with birth defects, cleft lip and palate, were investigated using the bivariate multinomial regression model to identify and quantify the risk factors.

Also, from methodological point of view, the Bayesian approach integrates additional information, known as prior information, with the data to discover the true parameter value and achieve the desired goal[22]. The posterior standard deviations for the parameters provided by a Bayesian framework are much easier to interpret than the standard deviations in a frequentist approach[23]. Various literature considered the Bayesian method to evaluate the posterior distributions of the parameters in multinomial logistic regression models[23;24;25;26]. These methods used in[23;24;25;26] also showed that a Bayesian approach surpasses the frequentist approach by providing a full representation of uncertainty in parameters. It offers a comprehensive description and a satisfactory estimation strategy, ensuring precision and accounting for uncertainty in parameters and return levels estimation. Hence, inferences associated with model employed were provided using the Bayesian method.

1.2 Statement of the Problem

Various scholarly investigations have been undertaken to explore the effects of maternal smoking, environmental tobacco smoke exposure, the risk of oro-facial clefts, and passive smoke exposure as a risk factor for oral clefts using logistic regression to assess the relationships between first-trimester maternal exposure to cigarette smoke and the risk of clefts[27;28]. For instance, Periconceptional smoking was associated with cleft lip and palate and strongly associated with bilateral CLP, while a weaker association observed for CPO[27]. It was also indicated that children whose mothers

actively smoked had an increased risk of oral clefts[28].

Although these studies provided valuable insights into the relationship between maternal smoking and specific phenotypes of oro-facial clefts, only maternal smoking and passive smoke exposure were identified as significant risk factors. Furthermore, the associated risk factors for cleft lip and palate in infants with oro-facial clefts (OFCs) were restricted to biological factors. Since, individuals with oral-facial clefts (OFCs) report lower levels of social adaptation than healthy adults[12], therefore, it is essential to investigate the risk factors associated with the development of birth defects in children.

From methodological point of view, Razzaghi et al.[29] used Poisson regression model to analyse associations between selected characteristics and high hospital resource use for birth, postbirth, and total hospitalizations among children aged below 2 years. However, only one response variable was considered in the model fitted to the dataset. To account for the dependencies between the dependent variables in the presence of different types of birth defects, it is essential to analyze the dataset using a bivariate modeling technique with binary responses. Also, MacLehose et al.[10] employed Bayesian approach using different assumptions about the sensitivity and specificity of self-reported maternal smoking data, and Tian et al.[18;30] applied conventional logistic regression to assess the risk factors for birth defects.

While these studies provided valuable insights into the response variables used, the inferences drawn about the risk factors were inconsistent. Additionally, although conventional logistic regression, Bayesian kernel regression, and weighted quantile sum regression models were employed, the predictors were examined separately for cleft lip with or without cleft palate. Therefore, to investigate the determinants of birth defects, it is crucial to consider the dependencies between the different types of birth defects in the model.

Additionally, a study conducted in Ethiopia used a multinomial logistic regression model to estimate the incidence of cleft lip and palate, and to assess the patterns of anatomical cleft lip and palate malformations in neonates[16]. Biological and environmental factors have been used to predict the risk of clefts in children, but there is a paucity of recent and robust studies that employ the bivariate multinomial logistic regression model and Bayesian inference. Therefore, it is essential to investigate both biological and environmental factors associated with cleft lip and palate in Ethiopian children using the proposed model and inference techniques to address the identified gaps in the literatures.

Generally, the following research questions were addressed in the study:

- What are the determinant factors for cleft lip and palate in children, and how can evaluate the different effects of both biological and environmental factors on its development?
- What are the factors that are most strongly associated with an increased risk of each types of cleft lip and cleft palate in children?
- How do the posterior distributions of the model parameters under the different prior distributions differ in terms of their estimation precision?

1.3 Objectives of the Study

1.3.1 General Objective

The general objective of this study was to examine the factors for Birth defects in children admitted to CURE Ethiopia Children's Hospital using a bivariate multinomial regression model.

1.3.2 Specific Objectives

- To examine and quantify the different effects of both biological and environmental risk factors on the development of cleft lip and palate in children.
- To investigate the factors that are most strongly associated with an increased risk of each types of cleft lip and cleft palate in children.
- To assess the impact of Inverse gamma prior distributions relative to Normal multivariate prior distributions on estimation precision.

1.4 Significance of the Study

The significance of this study is to investigate the risk factors for cleft lip and palate birth defects, providing valuable insights for healthcare professionals and serving as a reference for future research. It will also stimulate academic and biostatistical interest in the topic, particularly in the context of binary responses. The findings will contribute to policy formulation and strategies aimed at reducing the risk factors for cleft lip and palate.

2 Literature Review

2.1 Definition and Overview of Clefts

Cleft lip and palate are the result of tissues of the face not joining properly during development as they are a type of birth defect[31]. The cause is unknown in most cases[32]. Risk factors include smoking during pregnancy, diabetes, obesity, an older mother, and certain medications (such as some used to treat seizures)[33]. Cleft lip and cleft palate can often be diagnosed during pregnancy with an ultrasound exam[34;35]. Cleft lip is about twice as common in males as females, while cleft palate without cleft lip is more common in females[36]. In 2017, it resulted in about 3,800 deaths globally, down from 14,600 deaths in 1990[4]. The condition was formerly known as a "hare-lip" because of its resemblance to a hare or rabbit, but that term is now generally considered to be offensive[37].

2.2 Clefts and Risk Factors

A cleft lip contains an opening in the upper lip that may extend into the nose. The opening may be on one side, both sides, or in the middle[38]. The term orofacial cleft refers to either condition or to both occurring together. These disorders can result in feeding problems, speech problems, hearing problems, and frequent ear infections, Less than half the time the condition is associated with other disorders[39;40]. Several studies have focused on the incidence of CL/P in the Czech Republic in the past. The basic research in this field was done by Cerny et al[41]. He reported the occurrence of CL/P as 2 per 1000 live births among the Czech population for the 1964-1983 period, presenting CL/P anomalies as a major health problem. Peterka et al in their study presented the incidence of CL/P in Bohemia (major part of the Czech Republic) between 1964 and 1992 oscillating around 1.74 per 1000 newborns[42].

Also, the study which conducted to determine the incidence of cleft lip and palate

in Addis Ababa, Ethiopia showes, Sixty-four new cleft lip and palate patients were recorded in the study institutions which gives an incidence of 1.49/1000 live births or 1 in 672 live births. The female:male ratio was 1:0.6. in the cleft lip group, 1:1.8 in the cleft lip and palate group, and 1:0.5 in the cleft palate group. A family history of clefts was recorded in three babies (4.8% of cleft patients), one in cleft lip alone (1.6%) and two in cleft lip and palate (3.1%). In ten of the clefts there were associated anomalies: extremity malformation in five (Syndactyly in two, popliteal webbing polvdactyly and a congenital constricting band), central nervous malformations in three, genital malformation in one and heart anomaly in one tetralogy of Fallot (TOF) echocardiography proved, The incidence found in this study indicates that cleft is not rare in Ethiopia 64 (1.49/1000)[16].

MacLehose et al[10] accounted for misclassification using 4 Bayesian models that made different assumptions about the sensitivity and specificity of self-reported maternal smoking data. they used results from previous studies to specify the prior distributions for sensitivity and specificity of reporting and used Markov chain Monte Carlo algorithms to calculate the posterior distribution of the effect of maternal smoking on children's risk for CL/P and CPO. They found an increased risk of CL/P among children born to mothers who smoked during early pregnancy (posterior odds ratio [OR] =1.6, 95% credible interval = 1.1–2.2). The posterior effect of smoking on CPO provided less evidence of effect (posterior OR = 1.1, 95% credible interval = 0.7–1.7), and suggest that future research should emphasize validity studies, especially those of differential reporting, rather than replicating existing analyses of the relationship between maternal smoking and clefts.

Nagase et al[43] analysed gender differences in cleft pattern by the clinical statistical study of Japanese patients with cleft lip and/or cleft palate. Cleft pattern modeling was used to analyze 782 patients with cleft lip and/or cleft palate (417 males and 365 females) who had been examined at the Cleft Lip and Palate Center, Aichi-Gakuin

University Hospital, and whose details could be confirmed. Relationships between gender and cleft type were analyzed with chi-squared test.

A systematic review of literature was performed by Kruppa et al.[44] on electronic databases using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols. Literature on risks associated with CL/P in LMICs, from 2010 to 2020, to identify and review published data on the risks associated with cleft lip and/or palate (CL/P) in lower-middle-income countries (LMICs). Seventeen studies met the inclusion criteria. All studies adopted an observational study design. Biological and environmental risks were identified. Maternal and paternal age and low socioeconomic status were the most prominently associated environmental risk factors. A strong association was identified between family history of cleft and CL/P occurrence, and they concluded environmental risk factors are now being investigated more than biological risk factors in LMICs, aiding health care workers in the early identification of possible cumulative effects of risks in CL/P. Contextually relevant tools are recommended to promote early identification of at-risk infants.

Maternal Alcohol Consumption during Pregnancy: A meta-analysis was performed by Bell et al.[45] to evaluate the association between maternal consumption of alcohol during pregnancy and the occurrence of OFCs in infants, they conducted a systematic review and meta-analyses of published studies. they examined the associations between any alcohol consumption, binge level drinking, and heavy and moderate levels of consumption vs. no or low levels of consumption. After screening 737 publications, they identified 33 studies (23 case–control and 10 cohort studies). There was considerable heterogeneity in individual study design, quality measures and study results. Findings from random effects meta-analyses suggest no relationship between prenatal alcohol consumption and the occurrence of OFCs pooled odds ratios for any alcohol intake and binge level drinking respectively: cleft lip with or without cleft palate 1.00 [95%confidence interval (CI) 0.86, 1.16] from 18349 participants in

13 studies, 1.04 [95% CI 0.87, 1.24] [8763 individuals, 4 studies]; cleft palate only 1.05 [95% CI 0.92, 1.21] [21459 individuals, 17 studies], 0.94 [95% CI 0.74, 1.21] [7730 participants, 4 studies].

While they found no association between alcohol consumption during pregnancy and OFCs in infants, the influence of study design, particularly in relation to alcohol exposure measurement and OFC ascertainment cannot be ignored. Maternal consumption of alcohol during pregnancy can adversely affect the fetus, and a wide range of physical, behavioural, and neurocognitive disabilities can result. The pattern and severity of these effects depend on the dose, timing, pattern and duration of the alcohol exposure. As well, the vulnerability to alcohol-induced damage varies across cell types and tissues as well as across stages of fetal development[46;47;48].

Mother's Folic acid deficiency: The population-based infant cohort of the national Growing Up in Ireland study, which consists of 11134 9-month-old infants. to identify factors associated with suboptimal periconceptional use of folic acid and its potential effect on oral clefts. The prevalence of cleft lip and palate was 1.98 (95% confidence interval [CI] = 1.31 to 2.99) per 1000 9-month-olds. The odds ratio for cleft lip was 4.36-fold higher (95% CI = 1.55 to 12.30, P = 0.005) for infants of mothers who did not take folic acid during the first 3 months of pregnancy, when compared with those who did have a folate intake during the first trimester. Folic acid use was suboptimal in 36.3% (95% CI = 35.4 to 37.2) of the sample[49]. Folic acid supplementation during early pregnancy (400 per day) was associated with a reduced risk of isolated cleft lip with or without cleft palate after adjustment for multivitamins, smoking, and other potential confounding factors [adjusted OR, 0.61; 95% confidence interval (CI), 0.39–0.96]. Independent of supplements, diets rich in fruits, vegetables and other high-folate-containing foods reduced the risk somewhat (adjusted OR, 0.75; 95% CI, 0.50–1.11). The lowest risk of cleft lip was among women who ate folate-rich diets who also took folic acid supplements and multivitamins (adjusted OR, 0.36; 95% CI,

0.17–0.77). Folic acid provided no protection against cleft palate alone (adjusted OR, 1.07; 95% CI, 0.56–2.03)[50].

Having certain medical condition: Diabetes mellitus has been implicated in several studies as a possible etiological factor of various congenital anomalies. Oral clefts are common congenital malformations that may severely affect the quality of life.[51] The authors conducted a population-based case-control study using the 1996 National Center for Health Statistics United States Natality database to investigate whether maternal diabetes mellitus is a risk factor ($p < 0.05$) for having a newborn with an oral cleft. The patients consisted of 2,207 live births with cleft lip/palate, and the control subjects were 4,414 randomly selected live births, excluding those with other congenital defects. After adjusting for potential confounding variables, diabetic mothers were found to be 1.352 times (95% confidence interval, 1.004–1.821;$p < 0.05$) more likely than nondiabetic mothers to have a newborn with cleft lip/palate. In counseling expectant mothers, early glycemic control may be an important factor in decreasing the incidence of this congenital anomaly.

Family history of Birth defects: Family history of clefts (OR 7.4; 95% CI), folic acid consumption (OR 7.3; 95% CI) and consanguineous marriage (OR 3.2; 95% CI) were quite strongly associated with increased higher incidence in CL/P patients marriage and families with a history of CL/P should be extra cautious about the occurrence of CL/P. The study was carried out at the surgical outpatient cleft clinic of the Lagos University Teaching Hospital, Lagos, Nigeria. This was a cross-sectional descriptive study among mothers of children born with CLP, using both interviewer-administered questionnaire and a semi-structured interview. A total of 51 mothers of children with cleft lip and/or palate participated in the study. 35.3% of respondents believed cleft was an “act of God,” whereas others believed it was either due to “evil spirit” (5.9%), “wicked people” (9.8%). Seventy-three percent of the mothers were ashamed of having a child with orofacial cleft. Two of the respondents wanted to abandon

the baby in the hospital. About a quarter of the respondent wished the child was never born and 59% of the fathers were ashamed of the facial cleft. Fifty-one percent admitted that their relatives were ashamed of the orofacial cleft, and 65% admitted that their friends were ashamed of the cleft. In addition, 22% of the respondents admitted that they have been treated like an outcast by neighbors, relatives, and friends because of the cleft of their children. When asked about refusal to carry the affected children by friends, relatives, and neighbors, 20% of respondents said "Yes."[52;53]

Prenatal maternal intake and lack of multivitamin supplementation: The study found that the maternal risk factors with the strongest association for the development of cleft lip and cleft palate were the following: patients who were not taking folic acid during pregnancy [OR 3.27, 95% CI 1.32-8.09], P=0.00; patients who were not taking vitamin supplementation during pregnancy [OR 2.6, 95% CI 1.19-7.27], P=0.02; smoking during pregnancy [OR 2.05, 95% CI 1.23-3.41], P=0.01; and alcohol abuse during pregnancy [OR 1.90, 95% CI 1.17-3.08], P=0.03. The main risk factors associated with the development of cleft lip and cleft palate in a Mexican population at the Women's hospital in Culiacan, Sinaloa, Mexico were smoking, alcohol abuse, and patients not taking folic acid and multivitamins during pregnancy. of the 98787 children, 69 (0.07%) were diagnosed with cleft lip alone, 113 (0.11%) were diagnosed with cleft lip and palate, and 52 (0.05%) were diagnosed with cleft palate within 1 month after birth. Regarding the total orofacial cleft outcome, statistically significant point estimates of relative risk ratios (RR) were determined for multivitamin intake before pregnancy (RR=1.71; 95% CI 1.06 to 2.77) and during the first trimester (RR=2.00; 95% CI 1.18 to 3.37), but the association was not significant for multivitamin intake after the first trimester (RR=1.34; 95% CI 0.59 to 3.01). Maternal micro nutrient intake via food was not associated with the incidence of orofacial clefts in offspring. And concluded that intake of multivitamin supplements shortly before conception or during the first trimester of pregnancy was found to be associated

with an increased incidence of orofacial clefts at birth. Pregnant women and those intending to become pregnant should be advised of the potential risks of multivitamin supplementation[54;55].

2.3 Overview of Bayesian Regression Model

Bayesian regression models use a different approach that is based on Bayesian statistics, which emphasizes the use of prior knowledge, or assumptions about the data, in making statistical inferences. In this approach, parameters of the model are represented as probability distributions, rather than point estimations. Prior knowledge and new data are combined using Bayes' Theorem to compute posterior probability distributions for the model parameters. These posterior distributions represent updated beliefs about the model parameters given the observed data. In this method, the posterior distribution can be obtained using Markov Chain Monte Carlo (MCMC) algorithms.

2.4 Overview of bivariate multinomial regression model

Bivariate multinomial regression is a statistical technique used to analyze the relationship between two categorical variables. In this model, the response variable has more than two categories, and the goal is to determine how changes in the predictor variable(s) affect the probabilities of belonging to each category. The bivariate multinomial regression model estimates the probability of each category of the response variable, given the values of the predictor variable(s). The model assumes that the probabilities of each category are related to the predictor variable(s) through a set of coefficients, which are estimated using maximum likelihood estimation. The coefficients represent the change in the log-odds of belonging to each category for a one-unit change in the predictor variable(s).

The Bayesian version of this model can be particularly useful in allowing for more

flexibility in model assumptions and often provides more accurate estimates by taking into account prior information and uncertainty in the model parameters. However, it is important to consider factors such as interpretability and ease of implementation when choosing an appropriate approach. Overall, bivariate multinomial regression is a powerful tool for analyzing the relationship between two categorical variables with multiple categories in the response variable. It can provide valuable insights into the factors that influence the probabilities of belonging to each category and can be used to make predictions about the response variable based on the values of the predictor variable(s).

3 Data and Methodology

3.1 Description of the Study Area

The study was conducted at CURE Ethiopia Children's Hospital. CURE Ethiopia is a paediatric orthopaedic teaching hospital located in Ethiopia's capital city, Addis Ababa. Opened in 2008, the hospital is a state-of-the-art complex that provides modern medical and surgical care to physically disabled children. CURE Ethiopia performs over 2,500 life-changing reconstructive and orthopaedic surgeries every year for children suffering from treatable disabilities. The teaching hospital has 70 beds and four operating rooms. CURE International uses this facility to multiply its efforts by partnering with The College of Surgeons of East, Central, and Southern Africa (COSECSA) to serve as a regional learning institution by implementing an orthopaedic paediatric training programme at the residency and fellowship levels[56].

Currently, the hospital is in the process of a multi-year project to maximise the number of children they can heal. In addition, CURE Ethiopia fills a critical need as an orthopaedic training site in the country, providing didactic and clinical training in paediatric and advanced orthopaedic techniques and being an international COSECSA-accredited training site[56].

3.2 Study Design

A cross-sectional study design and a face-to-face interview method of data collection were employed in the study. Data were collected from the patients and their families on cases of cleft lip and cleft palate cases in children treated at CURE Ethiopia Children's Hospital. In addition, other related information about the cleft lip and cleft palate was also carefully reviewed from patients registration log book and cards. Any inadequate information was extracted from the file and excluded from analysis because it was proven to be inadequate.

3.3 Study Population and Period

The population for this study consists of all children with cleft lip and cleft palate cases registered for treatment at CURE Children's Hospital Ethiopia between May 1^{st}, 2021, and May 30^{th}, 2023, as well as their families.

3.4 Data Collection Procedure

After receiving approval from the perspective of the CURE Institutional Review Board (IRB), the cross-sectional hospital-based data was collected by a trained enumerator and principal investigator. This study incorporates primary and secondary data to identify factors associated with birth defects and cleft lip and palate. Data was collected from birth defected patients and the patient's family undergoing treatment at CURE Ethiopia Children's Hospital, Addis Ababa, by using their medical chart and by face-to-face interview.

3.5 Inclusion and Exclusion Criteria

Inclusion criteria: All children 3 years of age and younger who underwent cleft lip and palate surgery at CURE Ethiopia Children's Hospital during the study period and registered with full information in the patient registration log book and card were eligible for the study.

Exclusion criteria: All children older than 3 years of age with cleft lip and palate who had not undergone cleft lip and palate surgery and had insufficient information about one of the vital variables either in the registration book or on the card were not eligible for the study.

3.6 Variables under the Study

In this study, two dependent variables, namely Cleft lip and Cleft palate, were analyzed. Each of these response variables had three categories. The study also considered several independent variables, which were categorized into biological risk factors and environmental risk factors. The dependent variables, Cleft lip and Cleft palate, refer to specific conditions related to the development of the lip and palate during fetal development. The independent variables, on the other hand, are factors that are believed to influence the occurrence of these conditions. The descriptions of both dependent and independent variables, respectively, with their categories are given in below Table 3.1.

Table 3.1: Descriptions of the dependent and independent variables.

Variables	Categories	Codes
Dependent Variables		
Cleft Lip	Unilateral	1
	Bilateral	2
	Median	3
Cleft Palate	Muscular/soft part	1
	Bony/hard part	2
	Both part(soft and hard)	3
Independent Variables		
Biological risk factors		
Child Gender	Male	1
	Female	2
Maternal cigarette smoking during pregnancy	Yes	1
	No	2
Maternal Alcohol Consumption during Pregnancy	Yes	1
	No	2
Mother's Use of certain medicines/drugs during pregnancy	Yes	1
	No	2
Maternal Having certain medical condition	Yes	1
	No	2
Mother's Exposure fore chemicals and viruses during pregnancy	Yes	1
	No	2
Mother's Folic acid deficiency	Yes	1
	No	2
History birth defects	Yes	1
	No	2
Family history of cancer	Yes	1
	No	2
History of Contraceptive use	Yes	1
	No	2
Antenatal care service during pregnancy	Yes	1
	No	2
Residence	Urban	1
	Rural	2

Environmental risk factors		
Mother's Age	< 35	1
	≥ 35	2
Maternal and secondhand/passive smoking	yes	1
	No	2
Low socioeconomic status	Yes	1
	No	2
Low maternal education level	Yes	1
	No	2
Prenatal maternal alcohol use	Yes	1
	No	2
Prenatal maternal use of medication (prescribed and herbal)	Yes	1
	No	2
Prenatal complications (eg. threatened abortion)	Yes	1
	No	2
Prenatal maternal exposure to chemicals, minerals, and/or radiation	Yes	1
	No	2
Prenatal maternal intake and lack of multivitamin supplementation	Yes	1
	No	2
Food consumption	Yes	1
	No	2

3.7 Multinomial Logistic Regression

The Multinomial Logistic Regression (MLR) model is a simple extension of the binomial logistic regression model. The multinomial response could be ordinal (ordered categories) or nominal (unordered categories). It is used when the dependent variable has more than two nominal or unordered categories, in which dummy coding of independent variables is quite common. The MLR does necessitate careful consideration of the sample size and examination for outlying cases. While a binary logistic regression model compares one dichotomy, a multinomial logistic regression model compares a number of dichotomies. A multinomial approach outputs a number of logistic regression models that make specific comparisons of the response categories. Considering a situation where we have the J category of the response variable, the model consists of $J-1$ logit equations which fit simultaneously. The probability of a categorical variable in a multinomial model is estimated using maximum likelihood estimation[57].

The simplest approach to multinomial data is to nominate one of the response categories as baseline or reference cell, calculate log-odds for all other categories relative to the baseline, and then let the log-odds be a linear function of the predictors. MLR models pairs each outcome category with a reference category. When there are J categories of the response variable, the model consists of $J-1$ logit equations which are fit simultaneously. The last category or probably the most common category is assumed to be picked as reference[58]. Suppose $x_i = (x_{i0}, x_{i1}, ..., x_{ip})^T$denote the explanatory variables for individual $1 \leq i \leq n$ and $\beta_j = (\beta_{j0}, \beta_{j1}, ..., \beta_{jp})$, $1 \leq j \leq J-1$, a row vector, represent the regression parameters for the J^{th} reference category. Suppose $y_i = (y_{i1}, y_{i2}, ..., y_{iJ})$ denote a multinomial trial for individual $1 \leq i \leq n$. The trial y_{ij} is equal to one whenever a trial occurs in category j. Let $\pi_j(xi) = Pr((yij = 1)|xi)$ be the probability that the i^{th} trial occurs in category j

given a set of covariates x_i. Then the multinomial logistic regression model is:

$$log\frac{\pi_j(x_i)}{\pi_J(x_i)} = \beta_j^T x, where j = 1, 2, ..., J-1 \tag{1}$$

With the logit link we can interpret the coefficients. The exponential of the coefficient, $exp(\beta_j)$, represents the odds of a trial falling into the category j against category J, all other things equal. A odds greater than one represents that a trial is more likely to occur in category j than J and by symmetry if it is less than one it is more likely to occur in category J than j. If the odds is equal to one, there is independence between y and covariates.

Using the logit link we have response probabilities

$$\pi_j(x) = \frac{exp(\beta_j^T x)}{1 + \sum_{k=1}^{J-1} exp(\beta_k^T x)} \tag{2}$$

In order to fit the MLR model we need to derive the log likelihood function for regression parameters. For the log likelihood of the regression parameters we use notation from[58]. The likelihood of the regression coefficients is derived from the multinomial likelihood function. For n independent observations

$$L(y|\beta) = \prod_{i=1}^{n} \prod_{j=1}^{J} \pi_j(x_i)^{y_{ij}} \tag{3}$$

by taking the log on both sides, we have expressed log likelihood as follow:

$$\ell(\beta) = log(L(y|\beta)) = \sum_{i=1}^{n} \sum_{j=1}^{J} y_{ij} log \pi_j(x_i) \tag{4}$$

Putting the response probabilities in equation (2) into equation(4) results in the log likelihood for our regression parameters as represented follow:

$$\ell(\beta) = \sum_{i=1}^{n} \sum_{j=1}^{J} y_{ij} log \frac{exp(\beta_j^T x)}{1 + \sum_{k=1}^{J-1} exp(\beta_k^T x)} \tag{5}$$

$$\ell(\beta) = \sum_{i=1}^{n} \sum_{j=1}^{J} \left\{ y_{ij} \left(log \left[exp(\beta_j^T x) \right] - log \left[1 + \Sigma_{k=1}^{J-1} exp(\beta_k^T x) \right] \right) \right\} \tag{6}$$

By taking the first partial derivatives of $\ell(\beta)$ with respect to each of the unknown parameters and setting these equations equal to zero,we can obtained the maximum likelihood estimators.

That means,

$$\frac{\partial \ell(\beta)}{\partial \beta} = 0 \tag{7}$$

As nonlinear equations, we can use similar iterative procedures like Newton-Raphson iterative method. The Hessian matrix is calculated to obtain the estimator of the covariance matrix of the ML estimator, which is the inverse of the observed information matrix. Again, the estimates of the parameters and variance covariance matrix can be obtained by any standard statistical computer packages like SPSS, and R.

3.7.1 Bivariate multinomial regression model

Bivariate multinomial data exhibit two types of structural correlations. First, the marginal multinomial responses for one response variable are correlated. Second, the multinomial responses of one variable is correlated to the multinomial responses for the other variable. This correlation is referred to as the familial correlation which is caused by a common individual random effect shared by both response variables. Thus, for two multinomial responses with dimensions J and K, respectively, there is a $(J-1) \times (K-1)$ structural correlation matrix for given individual. It is important to take these correlations into account to obtain consistent and as efficient as possible estimates for the effects of the covariates. For the purpose, in this section we indicate how some of the existing inference approaches are developed[59]. Let y_{ij} and y_{jk} denote the two multinomial response variables with $J \geq 2$ and $K \geq 2$.

$y_{ij} = (y_{i1}, ..., y_{ij}, ..., y_{i,J-1})^{'}$ and $y_{jk} = (y_{j1}, ..., y_{jk}, ..., y_{j,K-1})^{'}$, In this setup, one is interested in understanding the association between the two multinomial variables. The marginal effect of each variable is also of interest. This requires one to model the joint probabilities for understanding the associations.

3.7.2 Bivariate multinomial models involving individual level covariate

Suppose there are individual level covariate associated with the two multinomial responses. Let x_{i1} and x_{i2} denote the covariate vector associated with y_i and y_j, respectively. Note that x_{i1} and x_{i2} may contain certain common and fixed covariates. It is of scientific interest to understand the effect of x_{i1} on y_j , x_{i2} on y_i as well. Let α_k $(k = 1, ..., K-1)$and β_j $(j = 1, ..., J-1)$ represent the intercept parameters reflecting the categories, and let θ_1 and θ_2 denote the effects of x_{i1} on y_j and x_{i2} on y_i , respectively. The marginal probabilities for the multinomial variable y_j as

$$\pi_{iz}^{(k)} = Pr(y_j = (y_j^{(k)}) = \frac{\exp(\alpha_k + x_{i1}^{'}\theta_{k1})}{1 + \sum_{q=1}^{k-1}\exp(\alpha_q + x_{i1}^{'}\theta_{q1})^{'}} for k = 1, ..., K-1, and \quad (8)$$

$$\pi_{iz}^{(K)} = Pr(y_j = (y_j^{(K)}) = 1 - \sum_{k=1}^{K-1}\pi_{iz}^{(k)}\frac{1}{1 + \sum_{q=1}^{K-1}\exp(\alpha_q + x_{i1}^{'}\theta_{q1})^{'}} for k = 1, ..., K-1 \quad (9)$$

Similarly, the marginal probabilities for the multinomial variable y_i are given by

$$\pi_{iy}^{(j)} = \begin{cases} Pr(y_i = (y_i^{(j)}) = \frac{\exp(\beta_j + x_{i2}^{'}\theta_{j2})}{1 + \sum_{l=1}^{j-1}\exp(\beta_j + x_{i2}^{'}\theta_{j2})^{'}} for j = 1, ..., j-1, and \\ Pr(y_i = (y_i^{(j)}) = 1 - \sum_{j=1}^{j-1}\pi_{iy}^{(j)}\frac{1}{1 + \sum_{l=1}^{j-1}\exp(\beta_l + x_{i2}^{'}\theta_{i2})^{'}} \end{cases} \quad (10)$$

On top of the marginal properties (1), it is necessary for the bivariate multinomial data analysis to model the joint probabilities for y_i and y_j, so that correlations between y_i and y_j can be accommodated for any inferences mainly for the parameters involved in the marginal probabilities. To address the above correlation issues, that is,

- Estimation of α_k and θ_{k1} using marginal information $y_j = y_j^{(k)}$ and similarly estimating β_j and β_{j2} by exploiting $y_i = y_i^{(j)}$ can not be the same thing as estimating these parameters by accommodating correlations between y_i and y_j. It is well known that in such cases the marginal estimates loose efficiency.

- Further because in the bivariate binary or multinomial setup, it is also important to know the joint probabilities $\pi_{ijk} = Pr(y_i = y_i^{(j)}, y_j = y_j^{(k)})$. However, it should be clear that if correlations are ignored and joint probabilities π_{ijk} are computed using π_{ijk}=$\pi_{iz}^k \pi_{iy}^j$ then they will be biased estimates for actual probabilities.

For these two reasons, it is important to model π_{ijk} as a function of suitable dependence between y_i and y_j. The marginal probabilities ar modeled in a fashion similar to the models (8) and (9), but, as indicated in the last section, the joint probabilities are defined through certain odds ratios approach. To be specific, the odds ratio in terms of the joint probability π_{ijk} corresponding to response $(y_i = y^{(j)}, z_i = z^{(k)})$ is defined as

$$\pi_{ijk} = \frac{Pr(y_i = y^{(j)}, z_i = z^{(k)}), Pr(y_i \neq y^{(j)}, z_i \neq z^{(k)})}{Pr(y_i \neq y^{(j)}, z_i = z^{(k)}), Pr(y_i = y^{(j)}, z_i \neq z^{(k)})} = \frac{\pi_{ijk}(1 - \pi_{ijk})}{(\pi_{iz}^k - \pi_{ijk})(\pi_{ij}^j - \pi_{ijk})'}$$
$$for, k = 1, ..., K - 1 and j = 1, ..., J - 1 \tag{11}$$

3.7.3 Bivariate multinomial models with categorical covariates

The modeling of bivariate multinomial responses with categorical covariates. suppose that we deal with a situation where the models (8) and (9) contain one covariate x_i instead of x_{i1} and x_{i2}. Also suppose that x_i is a categorical covariate with L levels To represent these L levels, we use $L - 1$ dummy covariates $x_{i1}, ..., x_{il}, ..., x_{i,L-1}$., some authors treated the categorical covariate x also as a multinomial response, Agresti (2002, Section 8.4.2, Table 8.8). Thus, treating X as the third response variable, the

joint probability for a response to be in the l^{th} level of x, j^{th} and k^{th} categories of y and z, respectively, has been written as

$$\pi^*_{lkj} = \frac{\exp(\psi_l + \alpha_k + \beta_j + \lambda^{XZ}_{lk} + \lambda^{XY}_{lj} + \lambda^{YZ}_{kj} + \lambda^{XYZ}_{ljk})}{\sum_{l=1}^{L}\sum_{j=1}^{J}\sum_{k=1}^{K}\exp(\psi_l + \alpha_k + \beta_j + \lambda^{XZ}_{lk} + \lambda^{XY}_{lj} + \lambda^{YZ}_{kj} + \lambda^{XYZ}_{ljk})'} \quad (12)$$

Where ψ_l, α_k and β_j are the level/category effect of x, z and y to influence the response to be in the $(l, k, j)^{th}$ cell.

Statistical analysis is carried out using the Bayesian multinomial logistic regression. The effect of explanatory variables on the dependent variable can be investigated using multinomial logistic regression that can be formulated under the Bayesian setup. We considered this approach in this study.

3.8 Bayesian multinomial Logistic Regression

In Bayesian analysis, the parameters are treated as random variables. The parameters being random variables, they are given distributions. Prior distribution of the parameters is one before data is collected while posterior distribution is one realized after scaling the prior distribution with new information obtained. The posterior can be interpreted as the summary (in a probabilistic sense) of the available information on β, once x is observed. The Bayesian approach realizes somewhat the updating of prior information by observation of x, through $\pi(\beta|x)$[60]. Bayesian inference for logistic regression models is derived applying a Markov Chain Monte Carlo algorithm to simulate from the joint posterior distribution of the regression and the link parameters. In the Bayesian framework, there are three key components associated with parameter estimation: the prior distribution, the likelihood function, and the posterior distribution. The Bayesian estimation provided a framework for quantifying uncertainty by estimating the posterior distributions of the model parameters. This allowed for the interpretation of results in terms of probabilities and credible intervals and provided more accurate estimates of the model parameters than frequentist methods, such as

maximum likelihood estimation. Bayesian estimation allows for flexible modeling of complex relationships in cross-sectional data. It can incorporate various types of predictors, such as continuous, categorical, and interaction terms, allowing for a comprehensive analysis of the associations between variables.

3.8.1 Prior settings

In Bayesian estimation, the choice of a prior for unknown parameters is crucial. It's especially critical with small samples but less so with larger samples, as the data becomes more influential than the prior. If the posterior heavily relies on the prior, it indicates a lack of sufficient information in the data.

The major challenge in Bayesian statistics is the correct specification of a Bayesian prior distribution, because appropriate prior specification is key in Bayesian modeling.[61;62] indicated that the prior distribution is an important part of Bayesian inference, representing information about an uncertain parameter β which is combined with the probability distribution of the likelihood of new data to produce the posterior distribution. This is then used for future inference on β. Therefore, necessary precaution should be taken in selecting priors because inappropriate choices of priors may result to wrong inference. In specifying priors, a number of points need to be considered. A key point among them is the fact that priors can be not sure. Because inference is assumed to be dependent on prior choice, alternative priors are examined to explore how sensitive the main conclusions are to alterations in the prior.

There are two types of prior distribution namely, informative and non-informative prior distributions can be used. Informative prior distributions are applied if something is known about the likely values of the unknown parameters. On the other hand, Non informative priors are the property of allowing prior information into a statistical analysis is a unique feature of Bayesian methods. The prior that expresses lack of information or ignorance was initially called a noninformative (NI) prior

distribution with the flat prior as an obvious first candidate. However, this choice creates confusion for a continuous parameter since a flat prior for β implies a nonflat prior for a transformed parameter $\psi = h(\beta)$[63].

The most common choice of non-informative priors is the flat prior, which assigns equal likelihood to all possible values of the parameters. In our case, there is no enough information or little prior knowledge about the value of parameters, therefore, non informative prior distribution are employed since we want prior information to play a very little role in our analysis which makes the data to remain influential in the analysis. For this purpose, the most common priors for logistic regression parameters is normal distributed, and we assume a multivariate normal prior on β with a large variance. In the case of Bayesian approach, prior distributions were assigned to all the parameters and the prior distribution of β is assumed to be multivariate normal with parameter $\beta_j \sim N(\mu_\beta, \Sigma_\beta)$.

$$p(\beta) \propto \left[\frac{1}{2\pi|\Sigma_\beta|}\right]^{p/2} exp\left\{-\frac{1}{2}\left(\left(\beta-\mu_\beta\right)' \Sigma_\beta^{-1}\left(\beta-\mu_\beta\right)\right)\right\} \tag{13}$$

Where, p is the size of the design matrix X.

The most common choice for μ_β is zero vectors, and Σ_β is usually chosen to be a diagonal matrix ($\Sigma = diag(\sigma_0^2, \sigma_1^2, ..., \sigma_k^2)$) with large variances that to be considered as non-informative prior.

The inverse gamma distribution is a continuous probability distribution that is often used as a prior distribution in Bayesian statistics. It is a conjugate prior distribution for the variance of a normal distribution with known mean.

The equation for the inverse gamma distribution with parameter $\theta_j \sim IG(\alpha_\theta, \beta_\theta)$ is as follows:

$$p(\theta|\alpha_\theta, \beta_\theta) = \frac{\beta_\theta^\alpha}{\Gamma(\alpha_\theta)\beta^{\alpha_\theta+1}} e^{-\beta_\theta/\theta} \tag{14}$$

where: θ is the parameter to be estimated, α is the shape parameter, and β is the scale parameter. In this case, the inverse gamma distribution, the shape parameter α and the scale parameter β controls the informativeness of the prior distribution. A large value of α and β were used for more non-informative prior distributions.

3.8.2 Likelihood Function of multinomial logistic regression

The one part to a Bayesian analysis are the likelihood function, which reflects information about the parameters contained in the data, and the prior distribution, which quantifies what, is known about the parameters before observing data.

3.8.3 Posterior distributions

The Bayesian approach is first introduced by the Reverend Thomas Bayes. Today the Bayesian concept has gained popularity among many researchers across different fields as a result of its ability to handle complex models. Bayesian methods have also been embraced in other fields of science due to their ability to handle complexity in real-world problems. In addition, Bayesian inference has means of incorporating prior knowledge about the parameters under consideration since they influence the posterior inference. In the case of Bayesian methods, parameters are assumed to follow a probability distribution while model parameters are considered as random variables. The main object of interest in Bayesian inference is the posterior distribution. Classical inference estimation depends solely on approximations as well as asymptotic results.

The posterior distribution in Bayesian analysis combines the prior distribution with the likelihood function, incorporating all available knowledge about the model's parameters. It is derived by multiplying the prior distribution by the likelihood function based on observed data. Bayes' rule allows us to express the posterior

distribution explicitly[64;65].

$$p(\beta|y) = \frac{L(\beta, y)}{L(y)} = \frac{L(y|\beta)p(\beta)}{\int_\beta L(\beta, y)p(\beta)d_\beta} \propto L(y|\beta)p(\beta) \tag{15}$$

where $L(y|\beta)$ is likelihood function, $p(\beta)$ is the prior distribution, and $p(\beta|y)$ is the posterior distribution. To obtain the posterior distribution we substitute the equation (3 and 13) in to equation (15), then it becomes:

$$p(\beta|y) \propto \prod_{i=1}^{n}\prod_{j=1}^{J} \pi_j(x_i)^{y_{ij}} \times \left[\frac{1}{2\pi|\Sigma_\beta|}\right]^{p/2} exp\left\{-\frac{1}{2}\left(\left(\beta - \mu_\beta\right)' \Sigma_\beta^{-1}\left(\beta - \mu_\beta\right)\right)\right\} \tag{16}$$

The posterior distribution has multivariate normal distribution.

- Given X, Y, Σ and β sample size Z_{ij} for all $i = 1, 2, ..., n$ and $j = 1, 2, ..., J-1$, $Z_{ij} \sim N\left(d_{ij}, \tau_{ij}^2\right)$
- Given X, Σ and Z

  $$\beta|X, Z, \Sigma \sim N\left(\mu_1, \wedge_1\right)$$

  Where, $\wedge_1 = \left(\wedge_0^{-1} + X_0' X_0\right)^{-1}$, $\mu_1 = \wedge_1\left(\wedge_0^{-1}\mu_0 + X_0' Z_0\right)$ N MVN $X_0 = C'X$, $Z_0 = C'Z$, $Z_i = X_i\beta + \epsilon_i$,$\epsilon \sim N\left(0, I\right)$ and μ_0 and $\wedge_0$ are prior mean and covariance matrix of $X\beta$ and $\Sigma^{-1} = C'C$
- Given X,β and Z sample Σ such that $\Sigma|X, Z, \beta \sim W\left(v + n, (v_0 + S)^{-1}\right)$,where v_0 is wishart distribution and $S = \epsilon'\epsilon$

The Wishart distribution is the sampling distribution of the matrix of sums of squares and products of normal distributional assumption.

Estimation of β on the posterior distribution may be difficult, for this reason we need to use non-analytic method. The most popular method of simulation technique is Markov Chain Monte Carlo (MCMC) methods. MCMC is a class of methods in which we can simulate draws that are slightly dependent and are approximately

from a (posterior) distribution. The most commonly used MCMC techniques are Metropolis-Hasting and Gibbs sampler techniques which will use in this study.

3.8.3.1 Markov Chain Monte Carlo Methods

Bayesian inference is solved by randomly drawing a very large sample from the posterior distribution. The idea of drawing a large sample from the posterior distribution is called Markov Chain Monte Carlo. Using MCMC techniques such as Gibbs sampling or the Metropolis–Hastings algorithm, we can directly sample sequences of values from the posterior distribution of interest, giving up the need for analytic solutions. MCMC methods have transformed Bayesian inference to a practical area of modern statistics[22;66]. Solving the posterior distribution analytically is often not feasible due to the difficulty in determining the integration constant Computing the integral using numerical integration methods is a practical alternative if only a few parameters are involved, New computational approach is needed With Markov chain Monte Carlo (MCMC) methods: 1. Gibbs sampler, 2. Metropolis-(Hastings) algorithm[63].

3.8.3.2 Gibbs sampler

The standard likelihood approach to this problem involves integration of the two component models over the distribution of random effects, which requires numerical integration since the two models are not conjugate. As an alternative, we focus on the posterior distribution of model parameters, which approximates the likelihood function if we use flat priors. We estimate the joint posterior distribution of all unknown model parameters using Gibbs sampling. This is a Monte Carlo method for generating samples from the joint posterior distribution of unknown parameters in a model, conditional only on the observed data. The method involves iteratively sampling from the full conditional distributions of each parameter given the current assignment of all other parameters and data. Thus, the method is most useful when

the joint distribution of parameters is intractable, but the generation of samples from each full conditional distribution is feasible[63;67].

3.8.3.3 The Metropolis-(Hastings) algorithm

Metropolis–Hastings algorithm is a general Markov chain Monte Carlo (MCMC) method for obtaining a sequence of random samples from a probability distribution. The Metropolis-Hastings algorithm works by generating a sequence of sample values. In such a way that, as more and more sample values are produced, the distribution of values more closely approximates the desired distribution. The Metropolis-Hastings algorithm does not need availability of full conditionals because it uses a proposal distribution and an acceptance-rejection step to explore and sample from the target distribution. It only requires the product of the prior and the likelihood to sample from the posterior[63].

3.9 Model diagnostics

Tests for Convergence: Several diagnostic tests have been developed to monitor the convergence of Markov Chain Monte Carlo (MCMC) algorithms. To detect poorly sampled Markov Chains, it is beneficial to consider different methods for examining convergence. Once a model has been developed, assessing its effectiveness in describing the outcome is crucial, which is known as goodness of fit. The most common ways to check goodness of fit include diagnosing convergence and mixing, as well as conducting posterior-predictive checks[68]. In this study, the researcher was utilized the most popular and straightforward convergence assessment methods, which encompass the following four potential tests of convergence.

Trace plots: Iteration numbers on $x - axis$ and parameter value on the y-axis are commonly used to assess convergence. If the plot looks like a horizontal band, with no long upward or downward trends, then researcher as evidence that the chain has

converged[69].

Autocorrelation: High correlation between the parameters of a chain tends to give slow convergence, whereas high autocorrelation within a single parameter chain leads to slow mixing and possibly individual non-convergence to the limiting distribution because the chain tends to explore less space in finite time. That is, low or high values indicate fast or slow convergence, respectively. In analyzing Markov chain autocorrelation, it is helpful to identify lags in the series in order to calculate the longer- run trends in correlation, and in particular whether they decrease with increasing lags[69].

Density plot: This is also another method or technique which can be taken for checking convergence in the Bayesian analysis. The idea is that the Markov chain has attained its posterior distribution when the Density plots of the independent variables coefficients are normally distributed[69].

Effective sample size: A related concept to the MCMC convergence would be the inefficiency factor which is useful to measure the efficiency of the MCMC sampling algorithm.

3.9.1 Accuracy of Bayesian Logistic Regression model

If the convergence has been achieved, we need to run the simulation for a further number of iterations to obtain samples that can be used for posterior inference. One way to assess the accuracy of the posterior estimates is by calculating the Monte Carlo error for each parameter[70]. As a rule of thumb, the simulation should be run until the Monte Carlo error for each. parameter of interest is less than about 5% of the parameter's standard deviation. Running multiple chains with different starting values is also as a way of assessing convergence.

4 Results and Discussion

4.1 Descriptive summaries

4.1.1 Socio-Demographic characteristics of patients

The descriptive summaries for the categories of the independent variables corresponding to cleft types are given in Table 4.1. The factors that were frequently observed are presented here in sequence. Among the study participants, more than half of children, 284 (52.2%), were boys. Of the male patients, 210 (47.8%), 32 (3.3%), and 32 (3.3%) had unilateral, bilateral, and median Cleft lips, while 103 (18.93%), 39 (7.18%), and 142 (26.16%) had Soft, hard, and both parts of cleft palate, respectively. More than nine-tenths (93.8%) of the children‘s mothers did not smoke, and of these children, 334 (61.39%), 89 (16.36%), and 118 (21.70%) had unilateral, bilateral, and median cleft lips, while 143 (26.3%), 49(9.00%), and 318 (58.5%) had soft, hard and both parts cleft palates, respectively.

More than half of children (296) born to mothers who drank alcohol during pregnancy, and 189 (34.74%), 57 (10.47%), and 50 (9.19%) of them had unilateral, bilateral, and median cleft lips, whereas 93 (17.1%), 50(9.19%), and 40(7.35%) had Soft, hard, and both parts of the cleft palates, respectively. Considering the children (72.97%) born to mothers with folic acid deficiency, 256(47.1%), 87(16.0%), and 54(9.9%) children had unilateral, bilateral, and median cleft lips, while 101(18.6%), 61(11.2%), and 235(43.2%) had soft, hard, and both parts of cleft palates, respectively. Children (397) born to mothers who had folic acid deficiency, 256(47.1%), 87(16.0%), and 54(9.9%) had unilateral, bilateral, and median cleft lips, while 101(18.6%), 61(11.2%), and 235(43.2%) had soft, hard, and both parts of cleft palates, respectively.

Additionally, the children (392) born to mothers who had a history of contraceptive, 254(46.7%), 88(16.2%), and 50(9.2%) had unilateral, bilateral, and median cleft lip,

while 108(19.9%), 67(12.3%), and 21(39.9%) had soft, hard, and both parts of cleft palate, respectively. Nearly 90% of the birth defect patients (89.5%) to born mothers who had antenatal care service during pregnancy, 318(58.5%), 103(18.9%), and 66(12.1%) children had unilateral, bilateral, and median cleft lips, while 143(26.3%), 65(11.9%), and 297(51.3%) had soft, hard, and both parts of cleft palates, respectively. Of the children 487(89.52%) born to mothers who had a antenatal care service during pregnancy, 318(58.5%), 103(18.9%), and 66(12.1%) had unilateral, bilateral, and median cleft lip, while 143(26.3%), 65(11.9%), and 297(51.3%) had soft, hard, and both parts of cleft palate, respectively.

Children born to mothers aged below 35 years were 394 (72.42%), and 251 (46.1%), 110(20.2%), and 33(6.1%) had unilateral, bilateral, and median cleft lips, while 106(19.5)%), 57(10.5%), and 231(42.5%) had soft, hard, and both parts of a cleft palates, respectively. Children 319 (58.6%) born to mothers who are in low socioeconomic status, 204 (37.5%), 92 (16.9%), and 23 (4.2%) had unilateral, bilateral, and median cleft lips, whereas 69 (12.7%), 47 (8.6%), and 203 (37.3%) had soft, hard, and both parts of cleft palates, respectively. Comparatively, more than half of children 427 (78.49%) born to mothers in low maternal education level, 285 (52.4%), 105 (19.3%), and 37 (6.8%) had unilateral, bilateral, and median Cleft lips, whereas 109 (20.0%), 57 (10.5%), and 261(48.0%) had soft, hard, and both parts of a cleft palate, respectively.

Additionally, Children 286 (52.57%) born to mothers who had prenatal complications (eg. threatened abortion), 164 (30.1%), 78 (14.3%), and 44 (8.1%) had unilateral, bilateral, and median cleft lips, whereas 64 (11.8%), 61(11.2%), and 161(29.6%) had soft, hard, and both parts of a cleft palates, respectively. Nearly third-fourth of the birth defect patients (73.0%) born to parents who had prenatal maternal intake and lack of multivitamin supplementation, 299(55.0%), 85(15.6%), and 13(2.4%) had unilateral, bilateral, and median cleft lips, while 104(19.1%), 75(13.8%), and 218(40.1%) had

soft, hard, and both parts of cleft palates, respectively. Children 260(59.19%) born to mothers who had medium food consumption, 222(40.8%), 75(13.8%), and 25(4.6%) had unilateral, bilateral, and median cleft lips, whereas 97(17.8%), 67(12.3%), and 158(29.0%) had soft, hard, and both parts of a cleft palates, respectively.

Table 4.1: Descriptive summaries of the biological and environmental factors.

Variables	Cleft lip			Cleft palate			
(categories)	Unilateral(%)	Bilateral(%)	Median(%)	Soft(%)	Hard(%)	Both(%)	Total(%)
Child Gender							
Male	210(38.64)	32(5.88)	42(07.72)	103(18.93)	39(07.18)	142(26.16)	284(52.23)
Female	150(27.57)	86(15.80)	24(4.41)	40(7.35)	44(8.08)	176(32.35)	260(47.85)
Residence							
Urban	209(38.4)	79(14.5)	22(4.0)	115(21.1)	34(6.2)	161(29.6)	310(56.98)
Rural	151(27.8)	39(7.2)	44(8.1)	28(5.1)	49(9.0)	157(28.9)	234(43.01)
Maternal cigarette							
Yes	26(4.80)	0(0.00)	8(0.73)	0(0.00)	34(6.20)	0(0.00)	34(6.2)
No	334(61.39)	89(16.36)	118(21.70)	143(26.30)	49(9.00)	318(58.5)	510(93.8)
Maternal Alcohol							
Yes	189(34.74)	57(10.47)	50(9.19)	93(17.1)	43(9.19)	160(7.35)	296(54.4)
No	171(31.4)	61(11.2)	16(2.9)	50(9.19)	40(7.35)	158(29.04)	248(45.6)
Use of certain medicines							
Yes	222(40.8)	76(13.97)	21(3.86)	7(14.15)	45(8.3)	197(36.2)	319(58.63)
No	138(25.4)	42(7.7)	45(8.3)	66(12.1)	38(7.0)	121(22.2)	225(41.36)
Exposure fore chemicals							
Yes	177(32.5)	55(10.1)	35(6.4)	70(12.9)	51(9.4)	146(26.8)	267(49.08)
No	183(33.6)	63(11.6)	31(5.7)	73(13.4)	32(5.9)	172(31.6)	277(50.91)
Folic acid deficiency							
Yes	256(47.1)	87(16.0)	54(9.9)	101(18.6)	61(11.2)	235(43.2)	397(72.97)
No	104(19.1)	31(5.7)	12(2.2)	42(7.7)	22(4.0)	83(15.3)	147(27.02)
History birth defects							
Yes	78(14.3)	27(5.0)	0(0.0)	23(4.2)	0(0.0)	82(15.1)	105(19.30)
No	282(51.8)	91(16.7)	66(12.1)	120(22.1)	83(15.3)	236(43.4)	439(80.69)
Certain medical condition							
Yes	99(18.2)	35(6.4)	28(5.1)	53(9.7)	0(0.0)	109(20.0)	162(29.77)
No	261(48.0)	83(15.3)	38(7.0)	90(16.5)	83(15.3)	209(38.4)	382(70.22)
History of cancer							
Yes	95(17.5)	70(12.9)	17(3.1)	51(9.4)	26(4.8)	105(19.3)	182(33.45)
No	265(48.7)	48(8.8)	49(9.0)	92(16.9)	57(10.5)	213(39.2)	362(66.54)
Contraceptive use							
Yes	254(46.7)	88(16.2)	50(9.2)	108(19.9)	67(12.3)	21(39.9)7	392(72.05)
No	106(19.5)	30(5.5)	16(2.9)	35(6.4)	16(2.9)	101(18.6)	152(27.94)
Antenatal care							
Yes	318(58.5)	103(18.9)	66(12.1)	143(26.3)	65(11.9)	297(51.3)	487(89.52)
No	42(7.7)	15(2.8)	0(0.0)	0(0.0)	18(3.3)	39(7.2)	57(10.477)
Mother's Age							
< 35	251(46.1)	110(20.2)	33(6.1)	106(19.5)	57(10.5)	231(42.5)	394(72.42)
≥ 35	109(20.0)	8(1.5)	33(6.1)	37(6.8)	26(4.8)	87(16.0)	150(27.57)
passive smoking							
Yes	91(16.7)	9(1.7)	38(7.0)	39(7.2)	24(4.4)	75(13.8)	138(25.36)
No	269(49.4)	109(20.0)	28(5.1)	104(19.1)	59(10.8)	243(44.7)	406(74.63)
Low socioeconomic status							
Yes	204(37.5)	92(16.9)	23(4.2)	69(12.7)	47(8.6)	203(37.3)	319(58.6)
No	156(28.7)	26(4.8)	43(7.9)	74(13.6)	36(6.6)	115(21.1)	225(41.36)

Low education level							
Yes	285(52.4)	105(19.3)	37(6.8)	109(20.0)	57(10.5)	261(48.0)	427(78.49)
No	75(13.8)	13(2.4)	29(5.3)	34(6.2)	26(4.8)	57(4.8)	117(21.50)
Prenatal alcohol							
Yes	180(33.1)	49(9.0)	46(8.5)	64(11.8)	57(10.5)	154(28.3)	275(50.55)
No	180(33.1)	69(12.7)	20(3.7)	79(14.5)	26(4.8)	164(30.1)	269(49.44)
Prenatal use of medication							
Yes	164(30.1)	33(6.1)	45(8.3)	58(10.7)	0(0.0)	184(33.8)	242(44.5)
No	196(36.0)	85(15.6)	21(3.9)	85(15.6)	83(15.3)	134(24.6)	305(55.5)
Prenatal complications							
Yes	164(30.1)	78(14.3)	44(8.1)	64(11.8)	61(11.2)	161(29.6)	286(52.57)
No	196(36.0)	40(7.4)	22(4.0)	79(14.5)	22(4.0)	157(28.9)	258(47.42)
Prenatal exposure to chemicals							
Yes	177(32.5)	16(2.9)	30(5.5)	46(8.5)	75(13.8)	102(18.8)	223(40.99%)
No	183(33.6)	102(18.8)	36(6.6)	97(17.8)	8(1.5)	216(39.7)	321(59.0)
lack of multivitamin							
Yes	299(55.0)	85(15.6)	13(2.4)	104(19.1)	75(13.8)	218(40.1)	397(73.0)
No	61(11.2)	33(6.1)	53(9.7)	39(7.2)	8(1.5)	100(18.4)	147(27.02)
Food consumption							
Low	117(21.5)	29(5.3)	41(7.5)	41(7.5)	8(1.5)	138(25.4)	187(34.37)
Medium	222(40.8)	75(13.8)	25(4.6)	97(17.8)	67(12.3)	158(29.0)	260(59.19)
High	21(3.9)	14(2.6)	0(0.0)	5(0.9)	8(1.5)	22(4.0)	35(6.43)

4.1.2 Characteristics of the Birth defects types of patients

The frequency distribution of the dependent variables are also given in Table 4.2. Among the total 544 patients included in the study, unilateral, bilateral, and median cleft lip types were observed in 360 (66.17%), 118 (21.69%), and 66 (12.13%) children, respectively. Considering the cleft palate types of birth defects, muscular/soft part, bony/hard part, and both parts of cleft Palates in 143(26.28%), 83 (15.25%), and 318 (58.45%) children, respectively.

Table 4.2: Frequency distribution of response variables.

Variables	Categories	Count(%)
Cleft Lip	Unilateral	360(66.17)
	Bilateral	118(21.69)
	Median	66(12.13)
Cleft Palate	Muscular/soft part	143 (26.28)
	Bony/hard part	83(15.25)
	Both parts(soft and hard)	318(58.45)
Total number of patients		544(100)

4.2 Results of the Bayesian bivariate multinomial regression model

A bivariate multinomial regression model was used to analyze the relationship between birth defects (specifically cleft lip and palate) and independent variables using Bayesian approach. The Gibbs sampling of a Markov chain Monte Carlo (MCMC) method was employed to sample posterior samples from the posterior distributions of the parameters. The JAGS program in combination with R was used to compute MCMC samples. Then the independent variables were declared to have a significant impact on birth defects at 5% level of significance. Various diagnostic approaches were used to assess the convergence of the Markov chains to the target distribution before interpreting the estimated parameter values or analysis results.

4.2.1 Formulation of the priors

Non-informative priors were used to allow for greater data impact, minimizing prior influence. They are preferred for their objectivity, assuming no additional information and assigning equal probabilities to a wide range of parameter values. This ensures a strong data influence on the posterior distribution. Refer to the expression (13), for the regression coefficients $\boldsymbol{\beta}$, a non-informative multivariate normal prior is specified with parameter $\boldsymbol{\beta}_j \sim N(\boldsymbol{\mu}_\beta, \boldsymbol{\Sigma}_\beta)$. The preferred choice of the priors for $\boldsymbol{\mu}$ is 0 ($\boldsymbol{\mu}$ = 0) and and precision matrix $\boldsymbol{\Sigma}$ = 0.001 [62;71;72]. To compare how different prior distributions affect the posterior distributions of the model parameters, inverse gamma prior distributions were used with parameter $\boldsymbol{\theta}_j \sim IG(\boldsymbol{\alpha}_\theta, \boldsymbol{\beta}_\theta)$, with the choice of priors for $\boldsymbol{\alpha}$ is 0.001 and for $\boldsymbol{\beta}$ = 0.001 [62;71;72], refer to the expression (14).

4.2.2 Posterior sampling

For the method, posteriors were calculated using 50,000 MCMC iterations. Convergence was assessed through time series, density, and autocorrelation diagnostics plot. Refer to the expression (16), the posterior distribution combines prior knowledge

and observed data by multiplying the prior distribution with the likelihood function, representing all available knowledge about the model's parameters[73]. The authors employed the MCMC technique with the Metropolis-Hastings (MH) algorithm to estimate the multivariate normal posterior distribution, denoted as $p(\boldsymbol{\beta}|\mathbf{y})$, of the parameters $\boldsymbol{\beta}$. Because it works by generating a sequence of sample values that converge to the target distributions.

4.2.3 Assessment of Model Convergence

In this part of the requirement for the Bayesian statistics, it is important to check for the convergence of the Markov chain Monte Carlo (MCMC). Before proceeding to examine the results of the model, it is essential to do some diagnostics to assess whether the Markov chain has converged to its stationary or posterior distribution. There are several ways to examine convergence. These include a time series plot, a density plot, autocorrelation plot a comparison of the MC error to its posterior standard errors, and Gelman-Rubin statistics[74].

In Bayesian simulation, the time series plots are frequently used to evaluate convergence and presented in Figure 1. For instance the time series plots for Antenatal care services and low socioeconomic status ensures satisfactory convergence, as it resembles a horizontal band with no discernible upward or downward trends. These plots are provided by the rjags package and have the iteration number on the $X-axis$ and the parameter value on the $Y-axis$. The two independently created plots are depicts convergence (See Figure 1). All the plots demonstrated convergences of two parameters have been attained.

By determining whether or not the Markov chain has converged to its stationary distribution, the kernel density, a graphical approach, is also employed as a substitute to determine model convergence. Figure 1, shows that the independent variable coefficients were normally distributed, indicating, the Markov chain had reached its

posterior distribution (the simulated parameter values had converged).

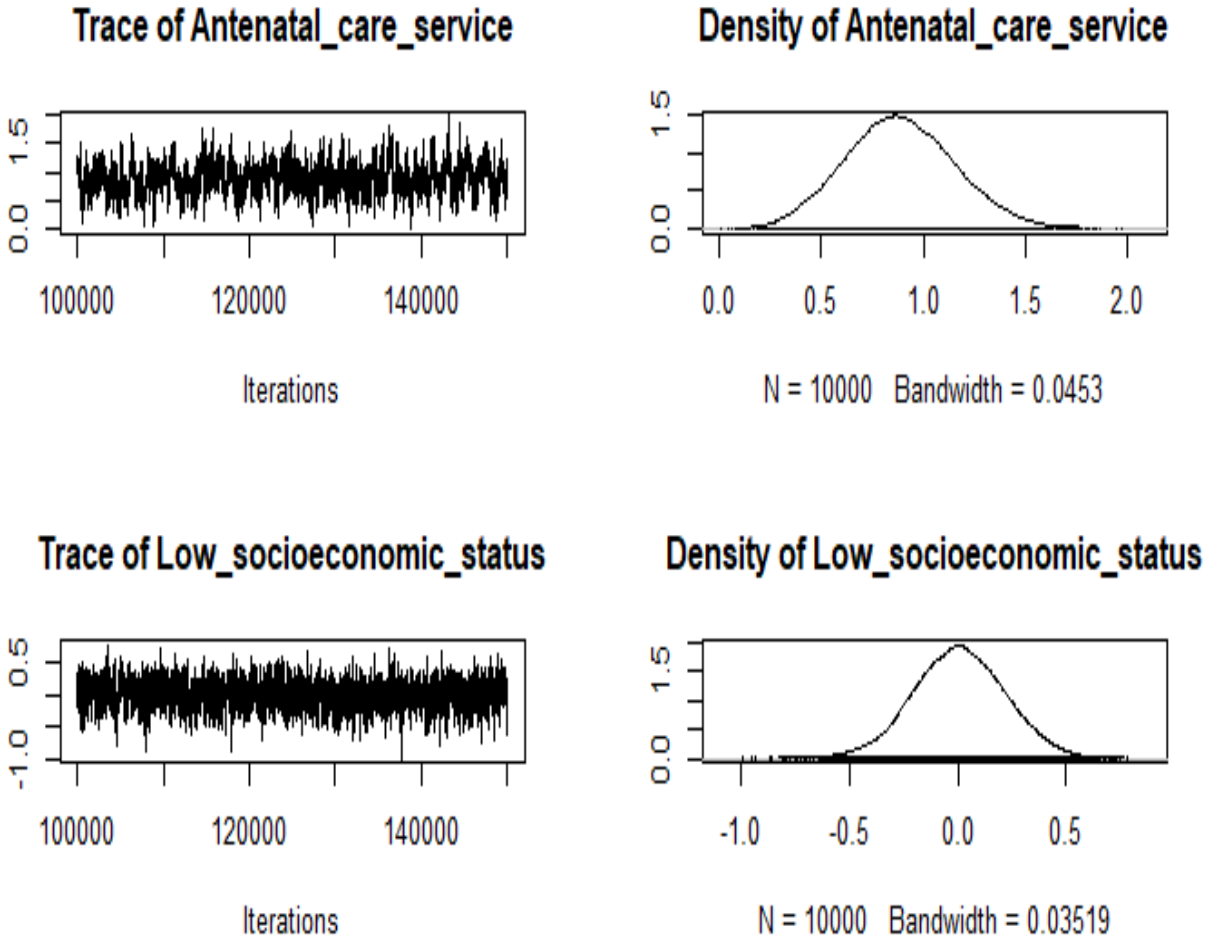

Figure 1: Trace and Density plots for Antenatal care services and low socioeconomic status

For the measured parameters inside each parameter, the autocorrelation plot generates lag-autocorrelations. In order to compute the long-run trends in correlation in Markov chain autocorrelation analysis, and in particular if they decline with increasing delays, it is important to detect lags in the series. For all parameters, the autocorrelations become minimal after lag 150 as shown in Figure 2. This proves the convergences the parameters have been achieved.

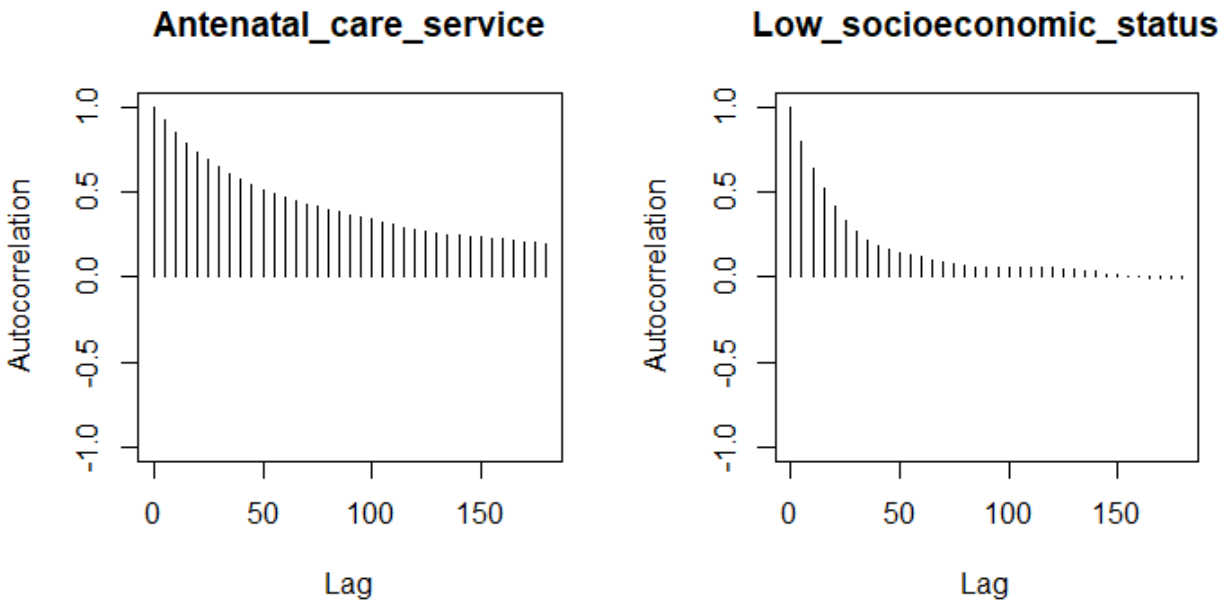

Figure 2: Autocorrelation plots for Antenatal care services and low socioeconomic status

4.2.4 Assessing Accuracy of the Bayesian Regression model

To assess the accuracy of Bayesian model estimates, the Monte Carlo standard error and credible intervals are used. The Monte Carlo standard error estimates the difference between the estimate and the true posterior mean. Credible intervals provide plausible parameter values and reflect uncertainty, with narrower intervals indicating more precise estimates. Accurate estimates rely on appropriate priors, model assumptions, and proper convergence of MCMC sampling, requiring convergence checks and diagnostics for reliability. Tables 4.3 and 4.4 demonstrates that the credible intervals (CI) for significant independent variables in the Bayesian regression model

exclude one at a 5% level of confidence. This implied that convergence and accuracy of posterior estimates has been attained and the model was appropriate to estimate the posterior statistics. The exclusion of one provides evidence of the variables' significance effect on the outcome.

4.3 Determinants of cleft lip and cleft palate among children

The posterior means of the parameter estimates (standard errors), the posterior Odds ratios (OR) with their associated 95% credible intervals (CI) of the posterior OR, which are obtained from Bayesian bivariate multinomial regression model are presented in Tables 4.3 and 4.4, for Cleft lip and Cleft Palate, respectively. In this case, the parts of the estimates that are important for the model are identified using the 95% credible intervals. Each of the observed predictors' 95% (2.5%, 97.5%) credible intervals exclude one, hence rendering them all significant. Since we used Bayesian approach with non-informative priors.

Based on the results, covariates such as mothers alcohol use during pregnancy, mother's folic acid deficiency, history of birth defects, antenatal care service during pregnancy, low socioeconomic status, prenatal complications (e.g., threatened abortion), prenatal maternal use of medication (prescribed and herbal), prenatal maternal intake, and lack of multivitamin supplementation were significant predictors for the existence of unilateral and bilateral types of cleft lip and soft and hard types of cleft palate. Bayesian credible intervals are directly interpreted as the probability that the parameter is in the credible interval, given the data and any prior information.

According to the results shown in the tables, maternal alcohol use during pregnancy is a significant predictor for patients with a unilateral type of cleft lip and soft and hard types of cleft palate. The risk of developing unilateral cleft lip is higher by 12.7% times (OR = 1.127; 95% CI: 1.066, 5.546) in children born to alcoholic mothers than non-alcoholic mothers. On the other hand, the risk of developing soft and hard types

of cleft palate is higher by 1.1% times (OR = 1.011; 95% CI: 1.001, 3.651) and 70.1% times (OR = 1.701; 95% CI: 1.286, 5.680) in children born to alcoholic mothers than non-alcoholic mothers, respectively.

Additionally, covariates such as a mother's folic acid deficiency are significant predictors for both unilateral and bilateral types of cleft lip. The risk of developing unilateral and bilateral types of cleft lip is higher by 2 times (OR = 2.293; 95% CI: 1.694, 5.730) and 9 times (OR = 9.079; 95% CI: 1.555, 14.78) in children born to mothers who are folic acid deficient than mothers who are folic acid sufficient, respectively. The risk of developing soft and hard types of cleft palate is higher by 49.1% times (OR = 1.491; 95% CI: 1.002, 8.525) and 3 times (OR = 2.998; 95% CI: 1.301, 9.192) in children born to mothers who are folic acid deficient than mothers who are folic acid sufficient, respectively.

A history of birth defects is also a significant predictor of a unilateral type of cleft lip and soft and hard types of cleft palate. The risk of developing a unilateral type of cleft lip is lower by 0.9% (OR = 0.991; 95% CI: 0.034, 0.697) times in children born to parents with a history of birth defects than in those without a history of birth defects. In contrast, the risk of developing soft and hard types of cleft palate is lower by 2.5% (OR = 0.975; 95% CI:0.144, 0.996) and higher by 10% (OR = 1.100; 95% CI: 1.000, 4.350) times in children born to parents with a history of birth defects than in parents without a history of birth defects, respectively.

Antenatal care service during pregnancy is a significant predictor of unilateral cleft lip. The risk of developing a unilateral type of cleft lip is lower by 57.1% (OR = 0.429; 95% CI: 0.284, 0.940) times in children born to antenatal care services during pregnancy than mothers with out these service during the pregnancy. Moreover, soft type of cleft palate was a significant predictor; the risk of developing soft type of cleft palate is lower by 5.9% (OR = 0.941; 95% CI: 0.152, 0.995) times in children born to

an antenatal care service during pregnancy than mothers did not obtained prenatal care service during the pregnancy.

The covariate parental low socioeconomic status, was a significant predictor for unilateral types of cleft lip and soft and hard types of cleft palate. The risk of developing a unilateral type of cleft lip is lower by 73.9% (OR = 0.261; 95% CI: -2.414,-1.0197) times in children born to low-parental socioeconomic status mothers than in mothers without low socioeconomic status. The risk of developing soft and hard types of cleft palate is higher almost by 4 times (OR = 3.82; 95% CI: 2.572, 11.46) and lower by 0.6% (OR = 0.994; 95% CI: 0.0043, 0.668) times in children born to parents of low socioeconomic status than in parents without low socioeconomic status, respectively.

Furthermore, the covariate prenatal complications (e.g., threatened abortion) was significant predictors for unilateral, bilateral, and hard types of cleft lip and palate. The risk of developing unilateral and bilateral types of cleft lip is higher by 55% times (OR = 1.55; 95% CI: 1.124, 6.910) and 2 times (OR = 2.499; 95% CI: 1.383, 7.793) in children born to mother with prenatal complications than mothers without these complications, respectively. The risk of developing a hard type of cleft palate is higher by 2 times (OR = 2.237; 95% CI: 1.350, 17.292) in children born to mothers prenatal complications than without prenatal complications.

Additionally, the covariate, such as prenatal maternal use of medication (prescribed and herbal), was a significant predictor for unilateral, soft, and hard types of cleft palate. The risk of developing a unilateral type of cleft lip is higher by 5 times (OR = 5.025; 95% CI: 3.212, 18.03) in children born to prenatal maternal use of medication than without prenatal maternal use of medication. The risk of developing soft and hard types of cleft palate are higher almost by 2 times (OR = 1.986; 95% CI: 1.270, 8.961) and almost 2 times (OR = 1.941; 95% CI: 1.482, 4.246) in children born to an prenatal maternal use of medication mothers than without prenatal maternal use of

medication, respectively.

Accordingly, the prenatal maternal intake and no multivitamin supplementation was significant predictors for the unilateral type of cleft lip and the soft and hard types of cleft palate. The risk of developing a unilateral type of cleft lip is higher by 1 times (OR = 1.431; 95% CI: 1.29, 3.67) in children born to prenatal maternal intake and no multivitamin supplementation mothers than with out prenatal maternal intake and no multivitamin supplementation mothers. On the other hand, The risk of developing soft and hard types cleft palate was higher by 7 times (OR = 7.367; 95% CI: 3.601, 9.975) and 5 times (OR = 5.511; 95% CI: 2.165, 17.31) in children born to prenatal maternal intake and no multivitamin supplementation mothers than with out prenatal maternal intake and no multivitamin supplementation mothers, respectively.

In this thesis, the factors for cleft lip and palate in children were examined based on the odds ratios (OR) with their associated 95% credible intervals (CI). The estimated accuracy of the identified the risk factors was then evaluated using standard errors. A small standard error indicates a strong association between significant factors and the likelihood of cleft lip and palate. Additionally, a high values of odds ratio (OR) indicates the most strongest associated factor with an increased risk of each types of clefts. The study revealed that the biological and environmental risk factors have varying impacts on the development of cleft lip and palate. Maternal folic acid deficiency is strongly linked to an increased risk of unilateral and bilateral cleft lip, as well as the hard type of cleft palate. Low socioeconomic status is strongly associated with a higher risk of the soft type of cleft palate. Prenatal complications, such as threatened abortion, is strongly connected to a greater chance of unilateral cleft lip and hard cleft palate. The use of medication during pregnancy, whether prescribed or herbal, is also associated with an increased risk of unilateral cleft lip. Inadequate prenatal maternal intake and a lack of multivitamin supplementation is significant factor contributing to a higher risk of both soft and hard types of cleft palate (See Tables 4.3 and 4.4).

Diagnostic tools confirmed that the MCMC sampler converged and the choice of prior distributions significantly impacted the posterior distributions. The authors used diagnostic tools to make sure that the MCMC sampler was working properly and that the posterior distributions were accurate. Based on the diagnostic plots, found that the normal multivariate prior distributions led to the most precise estimates of the model parameters than inverse gamma prior distributions.

For instance, as shown in Figure 3 of the paper in Appendix A, normal multivariate prior distributions led to more precise estimates of the model parameters than inverse gamma prior distributions (see Figure 7 of the paper in Appendix B). This indicates that the normal multivariate posterior distributions of the model parameters generally led to the most precise estimates under the prior distributions. The inverse gamma distribution is a conjugate prior distribution for the variance of a normal distribution, and a conjugate prior distribution is a probability distribution of the same family as the likelihood function. Convergence and prior distributions are crucial for Bayesian inference.

Table 4.3: The posterior means (SEs) of the parameter estimates and the Odds ratio (OR) with associated 95% Credible Interval (CI)

	Cleft Lip			
	Unilateral Vs Median		**Bilateral Vs Median**	
Variables	β **(se)**[a]	**OR (95%CI)**[b]	β **(se)**	**OR (95%CI)**
Intercept	-1.396(0.0019)	0.247(0.167, 0.356)*	-0.408(0.0015)	0.665(0.484, 0.906)*
Maternal Alcohol				
Yes	0.120(0.0033)	1.127(1.066, 5.546)*	0.007(0.0034)	1.007(0.0006, 1.995)
No(Ref)				
Maternal Folic acid				
Yes	0.832(0.0027)	2.293(1.694, 5.730)*	2.206(0.0738)	9.079(1.555, 14.78)*
No(Ref)				
History of birth defects				
Yes	-0.009(0.0021)	0.991(0.034, 0.697)*	0.002(0.0018)	1.002(0.699, 1.447)
No(Ref)				
Antenatal care service				
Yes	-0.847(0.0670)	0.429(0.284, 0.940)*	-0.798(0.0024)	0.451(0.271, 1.721)
No(Ref)				
Low socioeconomic status				
Yes	-1.344(0.0677)	0.261(0.089, 0.360)*	0.413(0.0022)	1.511(0.357, 2.332)
No(Ref)				
Prenatal complications				
Yes	0.435(0.0028)	1.55(1.124, 6.910)*	0.916(0.0245)	2.499(1.383, 7.793)*
No(Ref)				
Prenatal use of medication				
Yes	1.616(0.0020)	5.025(3.212, 18.03)*	-0.941(0.0248)	0.390(0.030, 8.250)
No(Ref)				
Lack of multivitamin				
Yes	0.355(0.0245)	1.431(1.29, 3.67)*	-2.215(0.0738)	0.109(0.202, 1.954)
No(Ref)				

[a] Posterior means (Naive Standard Error)
[b] Posterior Odds Ratio (95% Credible Interval)
* Significance variables of the categories

Table 4.4: The posterior means (SEs) of the parameter estimates and the Odds ratio (OR) with associated 95% Credible Interval (CI)

	Cleft Palate			
	Soft vs Both		Hard vs Both	
Variables	β **(se)**	**OR (95%CI)**	β **(se)**	**OR (95%CI)**
Intercept	-1.394(0.0019)	0.248(0.168, 0.357)*	-0.408(0.0015)	0.665(0.486, 0.907)*
Maternal Alcohol				
Yes	0.011(0.0043)	1.011(1.001, 3.651)*	0.533(0.0034)	1.701(1.286, 5.680)*
No(Ref)				
Maternal Folic acid				
Yes	0.398(0.0547)	1.491(1.002, 8.525)*	1.098(0.0369)	2.998(1.301, 9.192)*
No(Ref)				
History of birth defects				
yes	-0.025(0.0018)	0.975(0.144, 0.996)*	0.095(0.0018)	1.100(1.000, 4.350)*
No(Ref)				
Antenatal care service				
Yes	-0.025(0.0029)	0.941(0.152, 0.995)*	-1.210(0.0022)	0.298(0.128, 1.458)
No(Ref)				
Low socioeconomic status				
Yes	1.342(0.0027)	3.82(2.572, 11.46)*	-0.006(0.0021)	0.994(0.0043, 0.668)*
No(Ref)				
Prenatal complications				
Yes	-0.016(0.0259)	0.984(0.908, 1.897)	0.806(0.0361)	2.237(1.350, 17.292)*
No(Ref)				
Prenatal use of medication				
Yes	0.686(0.0281)	1.986(1.270, 8.961)*	0.664(0.0364)	1.941(1.482, 4.246)*
No(Ref)				
Lack of multivitamin				
Yes	1.998(0.0546)	7.367(3.601, 9.975)*	1.710(0.0369)	5.511(2.165, 17.31)*
No(Ref)				

4.4 Discussion

In this study, a bivariate multinomial logistic regression model was employed to determine the associated factors related to cleft lip and cleft palate types of birth defects in children. The Bayesian method was used to estimate the model parameters using non-informative prior, and inferences related to the model were made based on the estimated parameters and posterior odds ratio values.

The posterior odds ratio (OR) values for children with unilateral cleft lip defect born to alcoholics mothers was 1.127 times higher than non-alcoholic mothers. This shows that the risk of developing unilateral cleft lip birth defect was higher by 12.7% (OR = 1.127; 95% CI: 1.066, 5.546) in children born to alcoholics mothers than non-alcoholics mothers during pregnancy. This result agrees with earlier study[48], which indicated that children born to alcoholics mothers were more likely to develop unilateral cleft lip defect than children born to non-alcoholic mothers. According to the analyses of bivariate multinomial regression model, the odds ratio (OR) for children with hard cleft palate defects born to alcoholic mothers was 1.701 times higher than that for non-alcoholic mothers. This shows that the risk of developing a hard-type cleft palate is more than one and a half times as high as for mothers who abstained from using alcohol during pregnancy. This outcome is in line with the investigation made by Bell et al.[45] in Australia. Hence, it can be concluded that children whose mothers were using alcohol during pregnancy were at higher risk of having unilateral cleft lip. The risk of alcohol consumptions patterns observed in both cleft lip and palate may be explained by rising rates of alcohol consumption due to individual preferences and circumstances as well as a decline in the likelihood of obtaining medical attention and guidance following birth defects, which have been identified in cleft lip and palate research studied in other areas[46]. Analogous research was done by Yin et al.[47] also showed a higher risk of having birth defects, cleft lips,

and a cleft palate in children for mothers who used alcohol during pregnancy.

In response to the Bayesian bivariate multinomial regression model, the odds ratio (OR) values in children with unilateral and bilateral cleft lips for mothers who had folic acid deficiency were 2.293 and 9.079 times more likely to develop cleft lips compared to mothers who did not have folic acid deficiency, respectively. This outcome aligns with the findings of the research done by Kelly et al.[49] in Ireland. Consequently, it may be deduced that children to born mothers who had folic acid deficiency had a higher probability of having unilateral and bilateral cleft lips. This tendency, which has also been noticed in birth disorders, folic acid deficiency study conducted in other locations[50], provided strong evidence that it is a real effect.

The odds ratio (OR) values of Bayesian bivariate multinomial regression model for children with hard cleft palate defect born to mothers with a history of birth defects was 1.100 times higher than mothers without a history of birth defects. This shows that the risk of developing hard cleft palate birth defect was higher by 10% in children born to parents with a history of birth defects than parents without a history of birth defects. This result is in agreement with the study conducted in Iran[53]. Similar studies conducted by Acuña-González et al.[75] also showed a higher risk of family history of birth defects. This could take place because some birth defects are caused by changes in genes that can be inherited from parents[76].

Additionally, the odds ratio (OR) values for children with unilateral cleft lip defects born to mothers who obtained antenatal care services during the entire pregnancy was 0.429 times lower than mothers who did not obtain antenatal care services during the entire pregnancy. This shows that the risk of developing hard cleft palate birth defect was higher by 42.9% in children born to mothers who obtained antenatal care services during the entire pregnancy than mothers who did not obtain antenatal care services during the entire pregnancy. This may occur due to genetic factors, environmental

exposures, or other unknown causes, and its possible because antenatal care does monitor the mother's and developing baby's health, identify any risks or issues, and offer necessary support and interventions[77]. This result is inline with research studied in other areas[78]. Similar research was done by Shibui, et al.[79] also showed a higher risk of giving birth defects, cleft lip and palate to their children in mothers who did not obtained antenatal care services during pregnancy.

Aside from that, the odds ratio (OR) values for children with soft cleft palate defects born to parents with a low socioeconomic status was 3.82 times higher than parents without a low socioeconomic status. This shows that the risk of developing soft cleft palate birth defect was higher by 82% (OR = 3.82, 95% CI: 2.572, 11.46) in children born to parents with a low socioeconomic status than parents without a low socioeconomic status. This result agrees with the study conducted by Kruppa et al.[44] to determine the association with birth defects like cleft lip or palate. The study suggested that low socioeconomic status was an independent risk factor for orofacial clefts. Being a parent in a poor socioeconomic status is also linked to an increase in the possibility that their child was born with birth defects such as cleft lip and palate, with a significance level of (p.v = 0.042). This results may due to individuals with low socioeconomic status often face barriers in accessing quality healthcare services, including prenatal care. Limited access to healthcare may result in inadequate prenatal screenings, delayed diagnosis, and sub optimal management of maternal health conditions, and may have limited access to nutritious food and may experience food insecurity[80]. Inadequate maternal nutrition during pregnancy can impact fetal development, which can contribute to an increased risk of birth defects[81].

According to the Bayesian regression model, the odds ratio (OR) values for children with bilateral cleft lip and hard cleft palate defects born to mothers who experience prenatal complications (such as being threatened with abortion) was 2.499 and 2.237 times higher than mothers who did not experience prenatal complications (such as

being threatened with abortion), respectively. This shows that the risk of developing bilateral cleft lip and hard cleft palate defects were higher by 49.9% and 23.7% in children born to mothers who experience prenatal complications (such as being threatened with abortion) mothers who did not experience prenatal complications (such as being threatened with abortion), respectively. This could happen as a result of pregnancy challenges, such as threatening abortion, which could sometimes be a sign of underlying problems that might raise the likelihood of cleft lip and palate, some chromosomal or genetic diseases might result in difficulties as well as birth defects[82]. From the Bayesian perspective, the results agrees with study conducted in Estonia[83]. This result also agrees with other study conducted by Vrijheid et al.[84].

Additionally, the odds ratio (OR) values for children with unilateral cleft lip and soft and hard types of cleft palate defects born to parents with a prenatal maternal use of medication (prescribed and herbal) was 5.025, 1.986 and 1.941 times higher than parents without a prenatal maternal use of medication (prescribed and herbal), respectively. This shows that the risk of developing unilateral cleft lip and soft and hard types of cleft palate defects were higher by 0.25% (OR = 5.025, 95% CI: 3.212, 18.03), 98.6% (OR = 1.986, 95% CI: 1.270, 8.961) and 94.1% (OR = 1.941, 95% CI: 1.482, 4.246) in children born to parents with a prenatal maternal use of medication (prescribed and herbal) than parents without a prenatal maternal use of medication (prescribed and herbal), respectively. This result agrees with the study conducted by Chimedtseren et al.[85] to determine the the association between maternal drug use in early pregnancy and orofacial cleft in the infant. Their study suggested that parents with a prenatal maternal use of medication (prescribed and herbal) an independent risk factor for orofacial clefts.

In response to the odds ratio (OR) values for children with soft and hard types of cleft palate defects born to parents with mothers who had prenatal intake and lack of multivitamin supplementation were 7.367 and 5.511 times times higher than mothers

who had not prenatal intake and lack of multivitamin supplementation, respectively. This shows that the risk of developing soft and hard types of cleft palate defects were higher by 36.7% (OR = 7.367, 95% CI: 3.601, 9.975) and 55.1% (OR = 5.511, 95% CI: 2.165, 17.31) in children born to parents with mothers who had prenatal intake and lack of multivitamin supplementation than mothers who had not prenatal intake and lack of multivitamin supplementation, respectively. This outcome aligns with the findings of the research done by Zou et al.[86] in China. This tendency, which has also been noticed in birth disorders, such as cleft lip and palate studies conducted in other locations[54], may be explained by increased a position rates and reduced likelihood of seeking medical treatment after the beginning of suspected birth defects, such as cleft lip and palate. Comparable research was done by Yoshida et al.[55].

Overall, Bayesian regression is a powerful approach for examining factors associated with birth defects, providing a more comprehensive understanding of the parameters and their uncertainty. This is because Bayesian approach allowed us to use our existing knowledge about the relationship between birth defects and other factors to make better inferences about the relationship. In summary, Bayesian approaches provide a more complete understanding of uncertainty, enabling researchers to consider the analysis and make appropriate choices regarding the association between different risk factors and birth defects, such as cleft lip and palate.

5 Conclusions and Recommendations

5.1 Conclusion

In this study, the bivariate multinomial regression model using Bayesian approach was employed to investigate factors for birth defects in children at CURE Ethiopia Children's Hospital. The study concluded that Ethiopian children's birth defects are significantly influenced by biological and environmental factors.

The results show that maternal alcohol use during pregnancy, mother's folic acid deficiency, history of birth defects, antenatal care service during pregnancy, low socioeconomic status, prenatal complications, prenatal maternal use of medication, and prenatal maternal intake and lack of multivitamin supplementation were significant determinants of cleft lip and palate in Addis Ababa, Ethiopia.

To sum up, it is evident that maternal folic acid deficiency plays a crucial role in the increased risk of both unilateral and bilateral cleft lip, as well as the hard type of cleft palate. Additionally, low socioeconomic status has been strongly associated with a higher risk of the soft type of cleft palate. Prenatal complications (threatened abortion) is also connected to a greater chance of unilateral cleft lip and hard cleft palate. Furthermore, inadequate prenatal maternal intake and a lack of multivitamin supplementation have been identified as significant factors contributing to a higher risk of both soft and hard types of cleft palate. These findings emphasize the importance of proper nutrition and healthcare during pregnancy to minimize the risk of these congenital abnormalities.

The choice of prior distributions significantly impacts the posterior distributions of the model parameters. Based on the diagnostic tools, Normal prior led to more precise estimates than Inverse gamma prior distributions. Since, the inverse gamma distribution is a conjugate prior for the variance parameter in a normal distribution.

5.2 Recommendations

The research recommends that hospital administrators pay careful attention to the covariate identified as risk factors for cleft lip and cleft palate. Because patients in these groups experienced a high likelihood of cleft lip and cleft palate. Furthermore, the information obtained in this study can help to identify patients who are at high risk of having birth with cleft lip and cleft palate and useful to provide targeted healthcare interventions.

This prevents children from being born with birth defects, ensures mothers receive the best possible care, and ensures that treatments are given properly to improve their outcomes. One of the most important things is to make sure that all women have access to prenatal care. It can help to identify and manage risk factors for birth defects, and it can also provide early intervention for women who have a baby with cleft lip and cleft palate. Public health professionals and communities can also play a role in educating women about the risk factors for cleft lip and cleft palate and the importance of prenatal care.

Furthermore, using Bayesian methods prospective cohort studies beginning with preconception and ending with birth in the study area and other parts of the country should be carried out in order to properly determine the probability and its determinant factors and this is the subject of future researches. By conducting prospective cohort studies using Bayesian methods and regression modeling, researchers can gain a better understanding of the probability and determinants of birth defects of cleft lip and cleft palate. This information can be used to develop targeted interventions to reduce the risk of birth defects in different populations.

5.2.1 Limitation of the study

This study has some limitations, including:

- The use of a cross-sectional design limits the ability to establish causal relationships. A prospective cohort design would be more appropriate for future research, as it would allow for stronger causal inference.
- Social desirability bias: People may give answers they think are socially acceptable, rather than their true answers. This can lead to inaccurate data collection and results.

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Appendix A: Statistical Figures of Bayesian analysis for Normal distribution

I. Posterior probability trace and density plots.

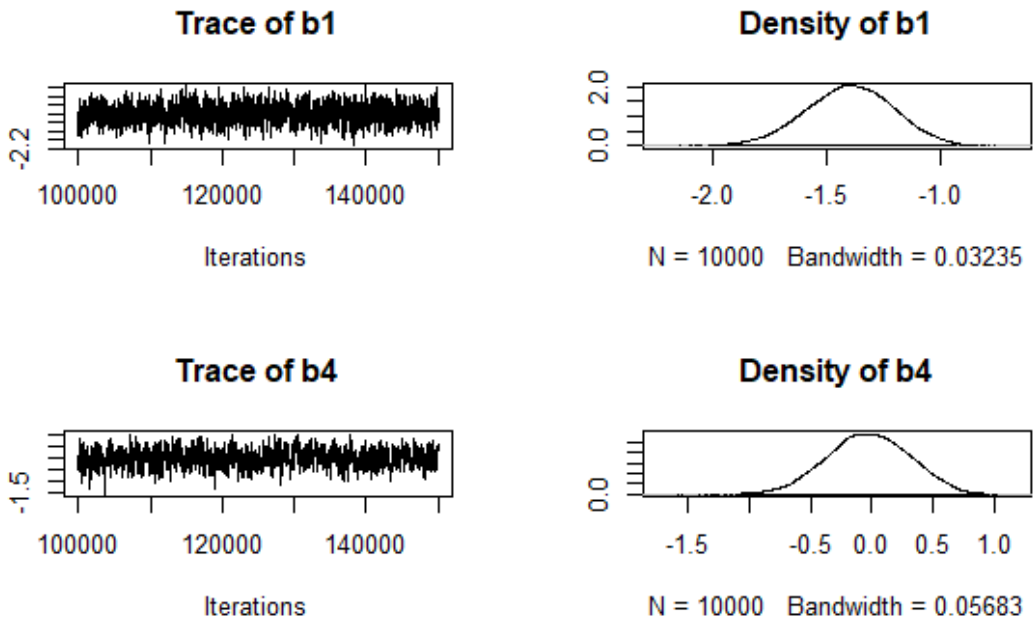

Figure 3: Trace and density plots for Intercept and maternal alcohol

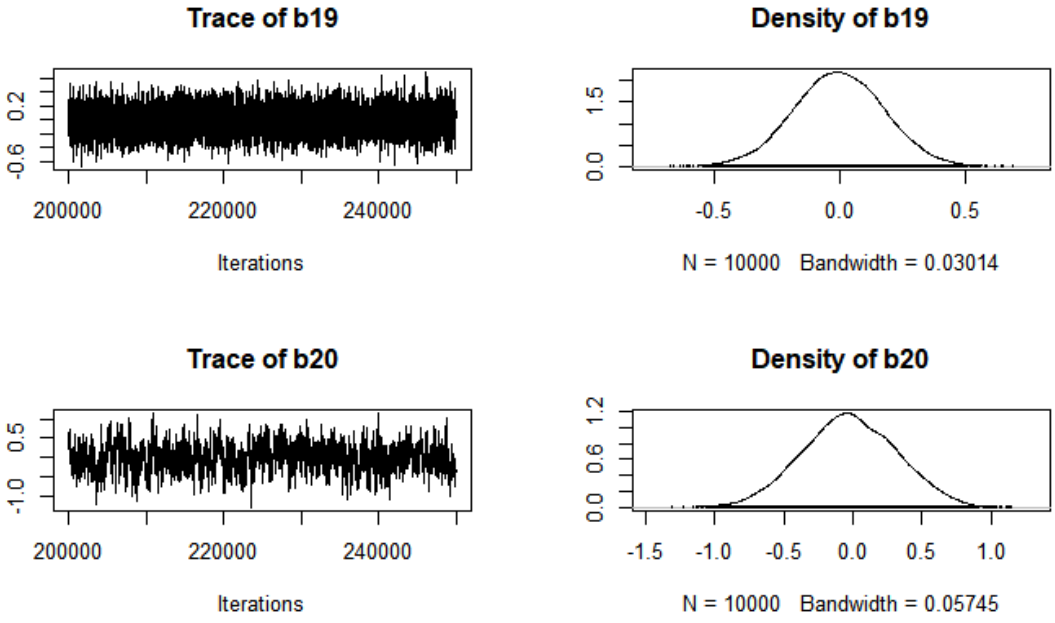

Figure 4: Trace and density for mothers folic acid deficiency and history of birth defects

II. Posterior probability Autocorrelation plots.

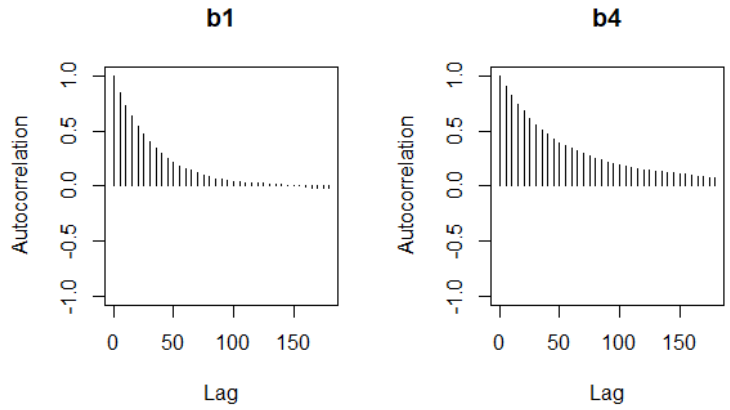

Figure 5: Autocorrelation plots for Intercept and maternal alcohol

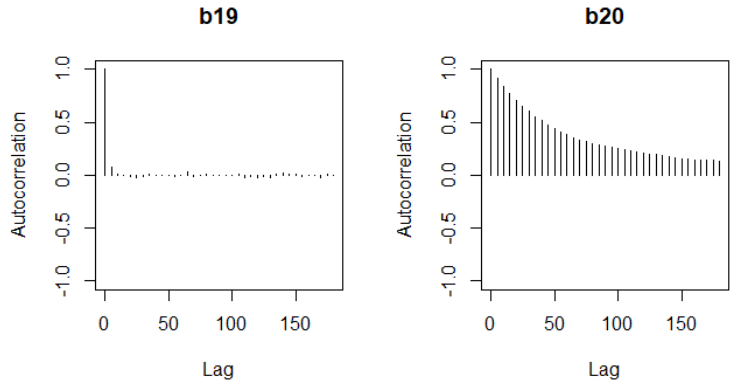

Figure 6: Autocorrelation plots for prenatal complications and prenatal use of medications

Appendix B: Statistical Figures of Bayesian analysis for Inverse Gamma distribution

I. Posterior probability trace and density plots.

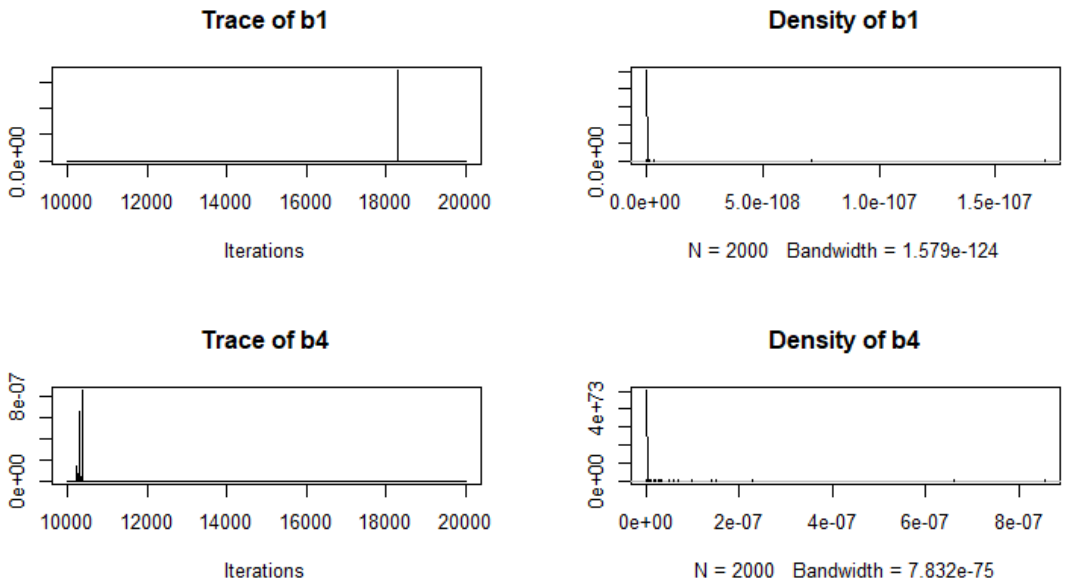

Figure 7: Trace and density plots for Intercept and maternal alcohol

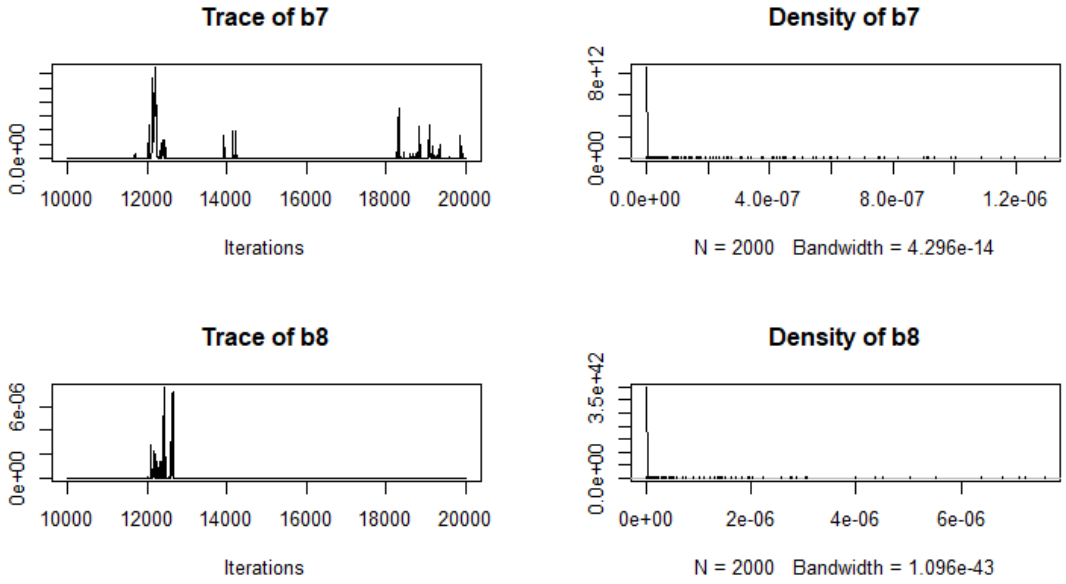

Figure 8: Trace and density plots for mothers folic acid deficiency and history of birth defects

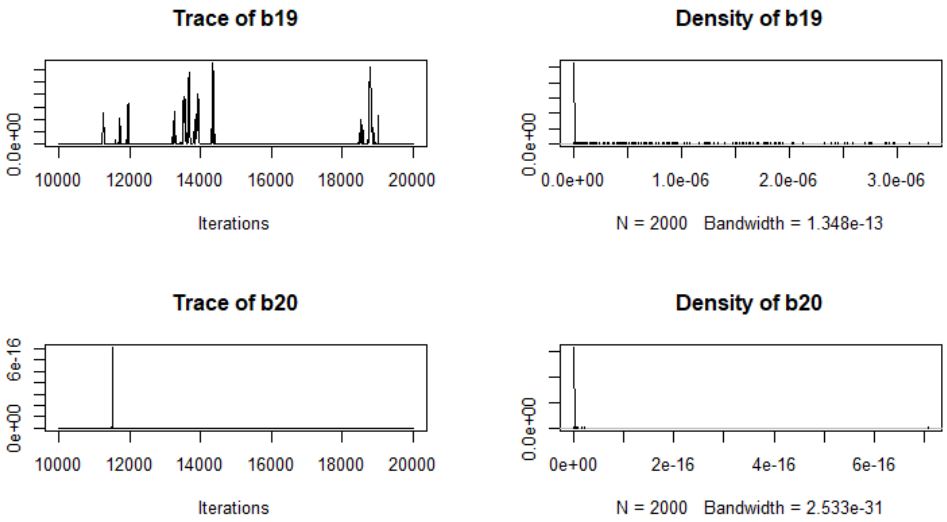

Figure 9: Trace and density plots for prenatal complications and prenatal use of medications

II. Posterior probability Autocorrelation plots.

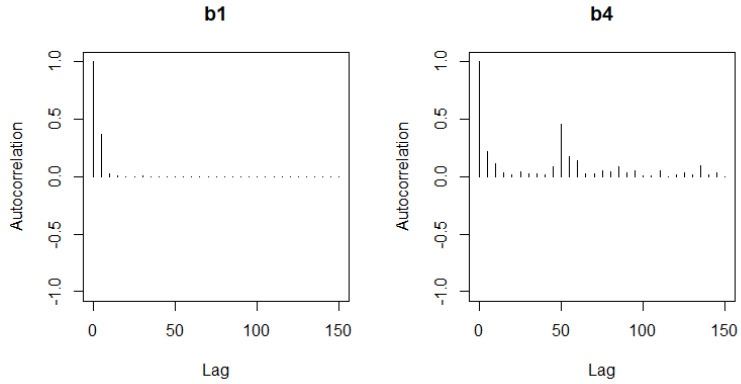

Figure 10: Autocorrelation plots for Intercept and maternal alcohol

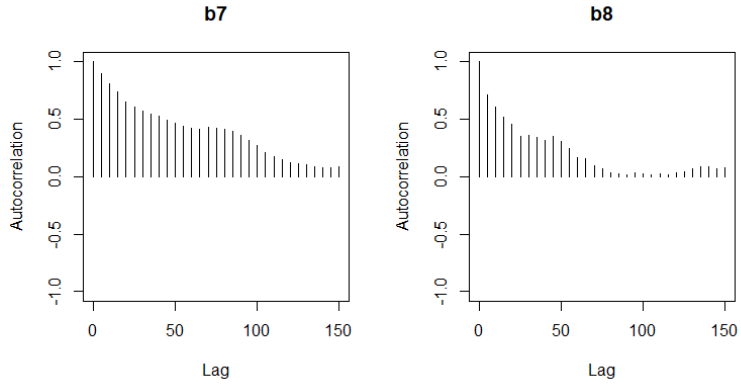

Figure 11: Autocorrelation plots for mothers folic acid deficiency and history of birth defects