Modelling perinatal and child mortality in Nepal

Pramesh Raj Ghimire

BSW, MIPH

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School of Science and Health, Western Sydney University

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Dedication

This thesis is dedicated to my late grandparents (Keshav Raj Upadhaya and Mrs. Tulasa Ghimire), my parents (Ravi Raj Ghimire and Prema Kumari Ghimire), my beloved wife (Samikshya Poudel), my son (Shreyaan P. Ghimire), my brother (Mr. Rupan Raj Ghimire), my sisters (Pramila Ghimire and Sharmila Ghimire), and all Ghimire family

Acknowledgment

First and foremost, I am deeply indebted to my primary supervisor Dr. Kingsley E. Agho for his excellent guidance throughout my academic journey and for making me reach where I am today. I would like to profoundly thank for his excellent supervision, constructive criticisms, statistical and STATA programming guidance throughout my candidature.

I would like to express my gratefulness to my co-supervisor Professor Andre MN. Renzaho for his excellent supervision, constructive feedback, and promptness in reviewing my manuscripts during my candidature.

I am also grateful to Measure DHS ICF international for providing all the data sets for this thesis.

Statement of Authentication

The work presented in this thesis is, to the best of my knowledge and belief, original except as acknowledged in the text. I hereby declare that I have not submitted this material, either in full or in part, for a degree at this or any other institution.

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Abstract

South Asia has the second largest burden of perinatal and childhood mortality in the world and Nepal has been reported as a significant contributor to this burden within the region. The main aim of this thesis was to statistically model perinatal and childhood mortality in Nepal. Specifically, this thesis will first conduct a systematic review of factors associated with perinatal mortality in South Asia including Nepal. Second, socioeconomic predictors of stillbirths in Nepal will be examined. Third, Factors associated with perinatal mortality in Nepal will be identified. Finally, this thesis will examine factors associated with under-5 mortality in Nepal.

Chapter 2 identifies the factors associated with perinatal and childhood mortality through literature review. The systematic literature review revealed the most common factors associated with perinatal mortality were: low socioeconomic status, lack of quality health care services, pregnancy/obstetric complications and lack of antenatal care. Similarly, poor socio-economic status, rural residence, higher birth order and lower birth interval, use of contraceptives, polluted fuel for cooking at home, and antenatal care were found to be associated with under-5 mortality.

Chapter 4 examined the socio-economic predictors of stillbirth in Nepal. Multivariable analysis and found maternal age (>25years), ecological zone (mountains or hills), religion (Hindu, Muslim, Christian and others), low maternal education, mother's occupation (farming) and the use of open defecation system are associated with stillbirth.

Chapter 5 presents the factors associated with Perinatal Mortality (PM) and Extended Perinatal Mortality (EPM) in Nepal. In this study, PM rate was 42 [95% Confidence Interval (CI): 39, 44] per 1000 births and the corresponding EPM rate was 49 [95% CI: 46, 51] for the five-year prior each survey (2001-2016). Multivariable analysis revealed that ecological zone,

household wealth index, birth order and birth interval; maternal age, use of contraceptives, and types of cooking fuel were associated with PM and EPM.

Chapter 6 assesses the common factors associated with neonatal, post-neonatal, infant, child, and under-5 mortality in Nepal, and the study found that the death of the previous child, non-usage of contraceptives and non-receipt of TT vaccination during pregnancy were associated with inder-5 mortality.

In summary, household with poor socio-economic status, and non-use of contraceptives among mothers were strongly associated with perinatal, and under-5 mortality in Nepal. Hence, future intervention to reduce perinatal and under-5 mortality should focus on family planning and these intervention should target mothers from socioeconomically disadvantaged groups.

Table of Contents

Publication from thesis

This thesis is based on a series of published papers. All chapters presented in the main body of the thesis have been published in peer-reviewed journals. The candidate is the principal author of each publication.

Chapter 2 Ghimire PR, Agho KE, Akombi BJ, Wali N, Dibley M, Raynes-Greenow C, Renzaho AM. Perinatal mortality in South Asia: Systematic review of observational studies (https://doi.org/10.3390/ijerph15071428)

Chapter 3 Ghimire PR, Agho KE, Renzaho A, Christou A, Nisha MK, Dibley M, Raynes-Greenow C. Socio-economic predictors of stillbirths in Nepal (2001-2011). PloS one. 2017 Jul 13; 12(7):e0181332. (https://doi.org/10.1371/journal.pone.0181332)

Chapter 4 Ghimire PR, Agho KE, Renzaho, A, Nisha MK, Dibley M, Raynes-Greenow C. Factors associated with perinatal mortality in Nepal: evidence from Nepal Demographic and Health Survey 2001-2016 (https://doi.org/10.1186/s12884-019-2234-6)

Chapter 5 Ghimire PR, Agho KE, Ezeh OK, Renzaho A, Dibley M, Raynes-Greenow C. Under-Five Mortality and Associated Factors: Evidence from the Nepal Demographic and Health

Survey (2001–2016) (https://dx.doi.org/10.3390%2Fijerph16071241)

Appendix

Ghimire PR, Agho KE, Renzaho AM, Dibley M, Raynes-Greenow C. Association between health service use and diarrhoea management approach among caregivers of under-five children in Nepal. PloS one. 2018 Mar 1; 13(3):e0191988. (https://doi.org/10.1371/journal.pone.0191988)

List of other publications during the course of this PhD

1. Agho KE, Osuagwu UL, Ezeh OK, Ghimire PR, Chitekwe S, Ogbo FA. Gender differences in factors associated with prehypertension and hypertension in Nepal: A nationwide survey. PloS one. 2018 Sep 13;13(9):e0203278 (https://journals.plos.org/plosone/article/comments?id=10.1371/journal.pone.0203278)
2. Poudel S, Upadhaya N, Khatri RB, Ghimire PR. Trends and factors associated with pregnancies among adolescent women in Nepal: Pooled analysis of Nepal Demographic and Health Surveys (2006, 2011 and 2016). PloS one. 2018 Aug 9;13(8):e0202107 (https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0202107)
3. Akombi BJ, Ghimire PR, Agho KE, Renzaho AM. Stillbirth in the African Great Lakes region: A pooled analysis of Demographic and Health Surveys. PloS one. 2018 Aug 29;13(8):e0202603 (https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0202603)
4. Ogbo FA, Dhami MV, Awosemo AO, Olusanya BO, Olusanya J, Osuagwu UL, Ghimire PR, Page A, Agho KE. Regional prevalence and determinants of exclusive breastfeeding in India. International breastfeeding journal. 2019 Dec;14(1):20

(https://internationalbreastfeedingjournal.biomedcentral.com/articles/10.1186/s13006-019-0214-0)

Author's Contribution

The work presented in this thesis was conducted by the candidate under the primary supervision of Dr Kingsley E. Agho (KEA), School of Science and Health, Western Sydney University with co-supervision of Professor Andre M. N. Renzaho (AMNR), School of Social Sciences and Psychology, Western Sydney University.

The candidate conceptualized the research, conducted the literature review, carried out the formal analyses, interpreted the findings of the analyses as well as drafted and revised the original manuscripts for submission to peer-reviewed journals. KEA and AMR were involved in reviewing and editing of each manuscript. The candidate organized, compiled and wrote this thesis.

Abbreviations

LMICs: Low and Middle Income Countries

NDHS: Nepal Demographic and Health Survey

WHO: World Health Organization

SDG: Sustainable Development Goal

CB-IMCI: Community Based Integrated Management of childhood Illness

GLLAM: Logistic regression generalized linear latent and mixed models

GDP: Gross Domestic Product

USAID: United States Agency for International Development

MOH: Ministry of Health

HIV: Human Immunodeficiency Virus

AIDS: Acquired Immune Deficiency Syndrome

STIs: Sexually Transmitted Diseases

IR: Individual Recode

OR: Odds ratios

AOR: Adjusted Odds Ratios

CI: Confidence Interval

ANC: Antenatal Care

IFA: Iron and Folic Acid

TT: Tetanus Toxoid

BSW: Bachelors of Social Work

MIPH: Masters of International Public Health

PHD: Doctor of Philosophy

SECTION I: Overview

CHAPTER 1

1. Introduction

Perinatal and child mortality remains a major public health problem in many Low and Middle-Income Countries (LMICs) including Nepal. Perinatal mortality refers to fetal death occurring after 28 weeks of gestation (stillbirth) and before the 7th day of life (early neonatal period) [1]. Child mortality refers to the death of children aged between 0 and 59 months and can be categorised into neonatal mortality (0-28 days), post-neonatal mortality (1-11 months), infant mortality (0-11 months), child mortality (12-59 years) and under-5 mortality (0-59 months) [2].

Evidence has shown that the leading causes of perinatal and child mortality include: congenital anomalies, placental abruption, placenta previa, uterine rupture, asphyxia, operative delivery, prolonged or breech labor, hypertensive disorders, hemorrhage, anemia, extremes of neonatal birth weight, fetal growth restriction, prematurity, fetal asphyxia, untreated syphilis, malaria, diarrhoeal diseases and other maternal infections [3-5]. Studies has also reported factors such as older maternal age, higher maternal body mass index, prior stillbirth, low maternal education, low socioeconomic status, large family size, use of solid cooking fuel, maternal illiteracy, unimproved water sources, geographic location, rural residence, maternal working status, lack of antenatal care and knowledge about family planning to be significantly associated with perinatal and child mortality [6-8].

Globally, an estimated 2.6 million babies are stillborn [3], and about 5.6 million children die before their fifth birthday [9]. Approximately 80% of these deaths occur in sub-Saharan Africa and South Asia with almost half reported during the perinatal period. South Asia including Nepal accounts for over 30% of the estimated global stillbirth and under-5 deaths [9, 10]. Though substantial global progress has been made in improving child survival [9], and evidence from Nepal Demographic and Health Survey (NDHS) showed that perinatal, and under-5 mortality rate has reduced from 47 and 91 per 1000 births respectively in 2001 to 39 and 31 per 1000 births in 2016 [11-14], indicating that despite the commitment of the Nepalese government in addressing child mortality, the pace of current progress is not sufficient enough to achieve the Sustainable Development Goal (SDG) child survival targets by 2030 [14]. Therefore, to accelerate child survival progress, it is imperative to identify the most common underlying factors associated with these preventable deaths in order to inform the formulation of effective high-impact interventions which could be integrated into current national child survival strategy and programs, thus making good use of limited resources.

1.1 Rationale of the study

In the past two decades, the Nepalese government has adopted different child survival policies and implemented programs such as National Newborn Health Strategy, Community Based Integrated Management of Childhood Illness (CB-IMCI), vitamin A supplementation, and the national immunisation program to reduce perinatal and under-5 deaths [11-14]. Despite these efforts, Nepal reported four times higher the burden of stillbirth and under-5 mortality compared with its regional counterpart - Sri Lanka [9, 10]. This makes achieving a substantial decline in perinatal and childhood mortality a seemingly unachievable goal. However, to improve child survival in Nepal, there is a need to statistically model perinatal and child mortality in order to identify the underlying factors associated with these untimely deaths.

Previous studies on stillbirth [15-17] and perinatal mortality [18, 19] in Nepal are mainly district level hospital-based; and a major limitation of these studies is that the findings cannot be used to inform initiatives and policy responses at the national level because the samples do not represent geographically diverse population within the country.

Similarly, previous studies on factors associated with childhood mortality in Nepal are limited in a number of ways. First, past studies on child mortality [20-22] were either community-based experimental study in smaller settings; or population based cross sectional studies with smaller sample size that may limit statistical power to detect statistical differences. Second, there is evidence to suggest that the risk of neonatal mortality due to pregnancy complications and preterm birth is higher amongst multiple births compared to singleton births [23, 24]; and hence, the inclusion of multiple births in the analysis may produce inaccurate mortality estimates. However, none of the existing studies on factors associated with child mortality in Nepal restricted their analysis to the most recent singleton live births that may likely increase the inaccurate mortality estimates. Third, studies disaggregating analyses across different age ranges of the first 59 months of life in Nepal have been limited (especially for the post-neonatal and child mortality sub-groups).

Therefore, the aim of this thesis was to identify factors associated with perinatal and under-5 mortality in Nepal. Findings from this study will help to bridge the gap on existing Nepalese public health literature as well as help Nepalese government for effective programmatic response to help achieve newborn and child survival Sustainable Development Goal.

1.2 Research objectives

The main aim of this thesis is to statistically model perinatal and child mortality in Nepal. The present study was undertaken with the following specific objectives:

1. To examine socio-economic predictors associated with stillbirths in Nepal.
2. To examine the factors associated with perinatal mortality and extended perinatal mortality in Nepal.
3. To identify common factors associated with under-five mortality in Nepal.

1.3 Quantitative study

We used quantitative methods to answer our research questions; and for this, the Logistic regression generalised linear latent and mixed models (GLLAMM), and Cox proportional hazards models that adjust for clustering and sampling weight were used. The statistical methods used are clearly outlined in each of the relevant publications.

1.4 Thesis outline

This thesis includes a total of four sections. **Section I** is an overview of the research (**chapter 1**). **Section II** consists of chapter 2 and chapter 3. **Chapter 2** identifies factors associated with perinatal and under-5 mortality through systematic literature review (https://doi.org/10.3390/ijerph15071428); whereas Chapter 3 is based on methods of the study.

Section III consists of two chapters. **Chapter 4** examines socio-economic predictors of stillbirths in Nepal (2001-2011) (https://doi.org/10.1371/journal.pone.01813322). **Chapter 5** identifies factors associated with perinatal mortality in Nepal: Evidence from Nepal Demographic and Health Survey 2001-2016 (https://doi.org/10.1186/s12884-019-2234-6).

Section IV consists of one chapter (**Chapter 6)** that assesses Under-5 mortality and associated factors: evidence from Nepal Demographic and Health Survey (2001-2016) (https://dx.doi.org/10.3390%2Fijerph16071241).

Section V consists of final chapter **(chapter 7)** which presents the summary of main findings, policy implications of findings, strengths and limitation of the study, future research and conclusion.

Supplement Diarrhoea remains a leading cause of under-five morbidity and mortality, particularly in low-and middle-income countries including Nepal [25-27]. According to Nepal Demographic and Health Survey report [12], childhood diarrhoea contributes 5% of the total under-5 mortality. The use of Oral Rehydration Solution (ORS), extra fluids, and continued feeding are the important national diarrhoea management strategy adopted by Nepalese government as part of its Community Based- Integrated Management of Childhood Illness(CB-IMCI) program. However, the uptake of ORS, extra fluids, and continued feeding is not universally adopted across the country. Therefore, this study also examined the association between health service use and diarrhoea management approach among caregivers of under-five children in Nepal as a supplementary field note, and this will be presented as an **appendix** (https://doi.org/10.1371/journal.pone.0191988).

1.5 Summary

In this chapter, the situation of perinatal and childhood mortality in Nepal has been presented. Pregnancy complications, low birth weight, prematurity, fetal growth restriction, birth asphyxia, diarrhoeal diseases, poor socio-economic status, poor maternal health care may lead to perinatal and under-5 mortality. Despite important public health indicators, the current rates of perinatal and under-5 mortality in Nepal are well above SDG targets of 12 and 20 per 1000 births respectively.

The specific objectives of this thesis has been clearly outlined in this chapter. In addition, the quantitative methods used to answer each of the research question, the rational of the study, and thesis outlines are important features of this chapter.

The next chapter of this thesis will present a literature review on perinatal and childhood mortality, location of the study, general overview of NDHS including sample size and corresponding response rates. This will be followed by Mosley and Chen theoretical framework of childhood survival in developing countries. The chapter then discuss a brief statistical modelling used in identifying factors associated with perinatal and childhood mortality in Nepal.

SECTION II: Literature review and methods

CHAPTER 2: Literature review

2. Introduction

Chapter two presents Mosley and Chen's conceptual framework for child survival in developing countries as well as literature reviews on perinatal and childhood mortality. Section 2.1 outlines Mosley and Chen conceptual framework for child survival in developing countries. As part of the literature review, section 2.2 is a systematic review of factors associated with perinatal mortality in South Asia. Section 2.3 discusses existing literature on factors associated with childhood mortality at community, household, individual, environmental, and health service level.

2.1 Conceptual framework

The Mosley and Chen's analytical framework for the study of the determinants of child survival in developing countries [5] are regarded as the most comprehensive and systematic conceptual framework for analysing childhood mortality at various levels of causality in low- and middle-income countries [6-8]. The framework bridges the gap between medical and social science by integrating research methods employed by social and medical scientists. The framework proposed that socioeconomic determinants of child mortality operate through a set of biological mechanisms, or proximate determinants, to influence childhood survival. These proximate determinants were grouped into five distinct categories which include maternal factors such as age, parity and birth interval; environmental contamination in the air, food/water/fingers, skin/soil/inanimate objects, and insect vectors; nutrient deficiency which include energy, protein, micronutrients (vitamins and minerals) deficiency; injury which could be accidental or intentional; personal illness control which include personal preventive measures and medical treatment. The socioeconomic determinants were classified into three broad levels which include the individual-level, household-level and community-level determinants. This study used variables at each level to identify the most significant factors associated with childhood mortality.

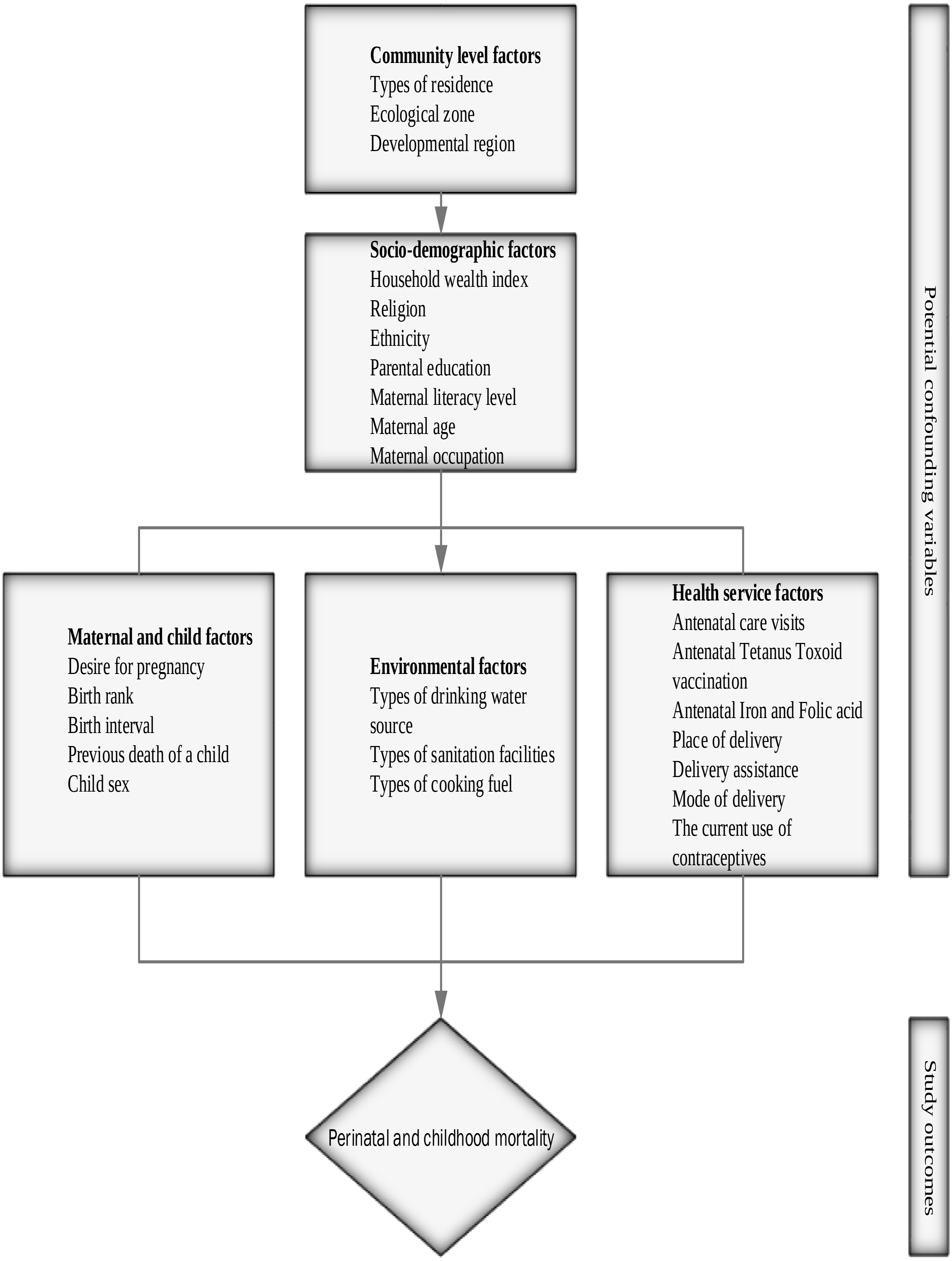

Figure 2. Modified Mosley and Chen conceptual framework for modelling perinatal and child mortality in Nepal.

2.2 Perinatal mortality in South Asia: systematic review of observational studies

(https://doi.org/10.3390/ijerph15071428)

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Review

Perinatal Mortality in South Asia: Systematic Review of Observational Studies

Pramesh Raj Ghimire [1,*], Kingsley E. Agho [1], Blessing J. Akombi [1], Nidhi Wali [2], Michael Dibley [3], Camille Raynes-Greenow [3] and Andre M. N. Renzaho [2]

1 School of Science and Health, Western Sydney University, Locked Bag1797, Penrith, NSW 2571, Australia; K.Agho@westernsydney.edu.au (K.E.A.); blessingakombi@yahoo.com (B.J.A.)
2 School of Social Sciences and Psychology, Western Sydney University, Locked Bag1797, Penrith, NSW 2751, Australia; N.Wali@westernsydney.edu.au (N.W.); Andre.Renzaho@westernsydney.edu.au (A.M.N.R.)
3 Sydney School of Public Health, The University of Sydney, Edward Ford Building (A27), Sydney, NSW 2006, Australia; michael.dibley@sydney.edu.au (M.D.); camille.raynes-greenow@sydney.edu.au (C.R.-G.)
* Correspondence: P.Ghimire@westernsydney.edu.au; Tel.: +61-422-300-960

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Abstract: Background: This study aimed to systematically review observational studies on perinatal mortality in South Asia. Methods: This review was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines. Five computerized bibliographic databases: MEDLINE, CINAHL, Embase, PsycINFO, and Scopus were searched for published studies which reported factors associated with perinatal mortality in South Asia from 1 January 2000 to 20 March 2018. All relevant observational studies (cohort, cross-sectional and case-control) were reviewed. Results: Fourteen studies met the selection criteria. The most common factors associated with perinatal mortality were: low socioeconomic status, lack of quality health-care services, pregnancy/obstetric complications and lack of antenatal care. Conclusions: Interventions to reduce perinatal mortality in the South Asia should focus on the provision of adequate antenatal care and quality healthcare services which are accessible to women of low socioeconomic status.

Keywords: perinatal mortality; South Asia; systematic review; public health

1. Introduction

Perinatal mortality is a major public health challenge in many low- and middle-income countries (LMICs). Perinatal mortality refers to fetal death after 28 weeks of gestation and before the 7th day of life [1]. In LMICs, perinatal mortality has been reported to be associated with inadequate access to quality care services [2], inadequate infant nutrition [3], and suboptimal environmental conditions such as unsafe water supply, inadequate sanitation, and poor housing facilities [4]. Almost half of the stillbirth and early neonatal mortality occurs during the period of labor and delivery [5]; with prematurity, low birth weight, obstructed labor, pregnancy complications and infections identified as the leading causes for these untimely deaths [6–8].

Globally, the number of perinatal deaths decreased from 5.7 million in 2000 to 4.1 million in 2015 [9]. However, 95% of these deaths occurred in LMICs with the largest numbers reported in South Asia and sub-Saharan Africa [9,10]. Despite the substantial global progress in improving child survival [10], perinatal mortality remains an urgent public health concern and progress made has been slower than that reported for maternal and child mortality [10–13]. Thus, reducing inequities among the most vulnerable pregnant women and newborns is an important strategy in achieving the Sustainable Development Goal (SDG) target of ending preventable perinatal deaths [14,15].

Previous studies conducted in South Asia identified distal determinants such as maternal age [16], poor socio-economic status [17], illiteracy [18], obesity and overweight [19], and poor water and sanitation [20] to be significantly associated with increased perinatal mortality. The 2014 Lancet series on Every Newborn suggested that annually 33% stillbirth can be averted with increased coverage and quality interventions such as antenatal care and skilled birth attendant services, detection and management of pregnancy-induced disorders as well as intrauterine growth restriction, and management of preterm labor [21]. In addition, the World Health Organization (WHO) recommends community-based cost-effective newborn care interventions such as immediate drying and additional stimulation, dry cord care, skin to skin contact in the first hour of life, and immediate breastfeeding [22] to reduce newborn death. However, these interventions are primarily focused on minimizing the risk factors which are prevalent around the perinatal period but do not take into cognizance the distal determinants responsible for increased perinatal mortality [16–20,23]. Previous studies conducted on perinatal mortality in developing countries reported factors such as maternal anemia [24], institutional delivery [25] and antenatal care services [26] as significantly associated with increased mortality without taking into account the predisposing socioeconomic and environmental level factors. Hence, there is a need to understand the most significant community-, household-, environmental-, and socioeconomic-related factors associated with perinatal mortality to guide the formulation of effective policies and programs to accelerate progress for newborn survival across South Asia.

Presently, no study has collectively and systematically analyzed the predisposing factors at the individual-, community-, household-, environmental-, and socioeconomic levels associated with perinatal mortality in South Asia to drive context-specific interventions which will lead to a decline in preventable perinatal death within the region. Hence, the aim of this study was to systematically review the factors associated with perinatal mortality in South Asia, thus contributing to the body of evidence needed to inform effective policy strategies to reduce perinatal mortality, and setting the region on the path to achieving the SDG target by reducing perinatal mortality to as low as 12 deaths per 1000 births by 2030 [14,15].

2. Materials and Methods

2.1. Outcome Measure

The outcome measure for this study was perinatal mortality which refers to the number of stillbirths and deaths in the first week of life [1].

2.2. Search Strategy

This systematic review was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [27]. Relevant MeSH headings and keywords were generated and used to extensively search five bibliographic databases: MEDLINE, CINAHL, Embase, PsycINFO, and Scopus for peer-reviewed articles published between 1 January 2000 and 20 March 2018. The year 2000 was used as a baseline for this review because this was the beginning of the Millennium Development Goals (MDGs) and hence will aid in tracking the progress of the region in line with the MDGs.

Retrieved articles from each database were imported into an EndNote library. To capture relevant publications that might have been omitted, a further search of the bibliographical references of all retrieved articles that met the inclusion criteria was performed, complemented by citation tracking using Google Scholar.

The search strategy was developed using Boolean operators for three major concepts: perinatal mortality, risk factors, and countries in South Asia. The following combination of keywords was used for the search:

["perinatal mortality*" or "Perinatal death*"]
AND

[risk* or "risk factor*" or predictor* or determinant* or socioeconomic* or sociodemographic* or factor*]
AND
["South Asia*" or "Southern Asia*" or Afghan* or Bangladesh* or Bhutan* or India* or Maldives or Nepal* or Pakistan* or Sri Lanka*]

2.3. Inclusion and Exclusion Criteria

Eligibility assessment was conducted and studies were included in this review if they (i) focused on perinatal mortality; (ii) were conducted in South Asia; (iii) reported factors associated with perinatal mortality; (iv) were published between 1 January 2000 and 20 March 2018; (v) were observational studies (cross-sectional studies, cohort studies and case-control studies); (vi) were published in a peer-reviewed journal (non-peer reviewed research, reviews, commentaries, letters to editors and conference presentations were excluded); (v) written in English. The inclusion of eight South Asian countries (Afghanistan, Bangladesh, Bhutan, India, Maldives, Nepal, Pakistan, and Sri Lanka) in our study is based on UNICEF regional classification [28].

2.4. Data Extraction

All articles identified from the search of each database were imported into an EndNote library and duplicates were eliminated. The first author (PRG) independently read and screened the titles and abstracts of all retrieved articles. In the final screening phase, full-texts of selected articles were identified by PRG using electronic databases, school library and contacting author via email, and studies which met the eligibility criteria were retained after reading the full text. All data extraction and appraisals of retrieved studies were independently reviewed by PRG, BJA and NW, and all disagreements among the three reviewers were resolved through discussion. The summary of the selected studies was recorded, and this included: author, year of publication, country of publication, study design, pregnancy outcome(N), factors associated with perinatal mortality, study limitations, and quality assessment score (Table 1).

Table 1. Summary of selected studies.

Author [Ref.] Year Country	Study Design	Pregnancy Outcome (N)	Factors Associated with Perinatal Mortality	Study Limitations	Quality Assessment Score
Ahmed et al. [17] 2006 India	Cross-sectional study	2199	Domestic violence, first birth, lack of maternal education, poor socioeconomic status.	Underreporting of violence because of the involvement of perpetrators for obtaining data, no direct question to justify if the violence occurred during pregnancy, and underreport of pregnancy and death due to a retrospective study.	7/14 (Fair)
Bari et al. [29] 2002 Bangladesh	Cohort study	965	Five or more pregnancy prior to index pregnancy, assisted delivery, poor economic status, anemia prevalence.	All study variables used in the analysis are not defined.	10/14 (Good)
Guidotti et al. [30] 2009 Afghanistan	Cross-sectional study	53,524	Mode of delivery, medical risk factors.	Data were obtained from hospital records that are not primarily designed for research purpose; and this has limited study findings for the adjustment of other important confounding factors.	4/14 (Poor)
Iqbal et al. [31] 2014 Pakistan	Cohort study	11,260	Antepartum hemorrhage, hypertensive disorders, mechanical problems, congenital anomalies, neonatal problems, maternal medical problems.	Small sample size.	2/14 (Poor)
Khan et al. [19] 2017 Bangladesh	Cross-sectional study	6584	Maternal overweight and obesity.	Pregnancy outcomes reported in this study are based on based on maternal recall in five years preceding the survey that may inaccurately capture the total number of perinatal death.	7/14 (Fair)
Perveen et al. [23] 2016 Pakistan	Cohort study	234	Sideropaenic anemia.	Small sample size, hospital-based study and it has the limitation of generalization of the finding into wider community level.	5/14 (Fair)
Sachar et al. [32] 2000 India	Case-control study	2424	Lower maternal weight and height, BMI, literacy, pregnancy interval, prematurity, home delivery.	The study is based on rural setting, and findings from this study cannot be generalized to make a programmatic response to urban women. The risk variables used in the study are poorly defined.	6/12 (Fair)
Shabbir et al. [33] 2014 Pakistan	Cohort study	2010	Multiparous, advanced maternal age.	Limitation of ascertainment bias.	7/14 (Fair)

Table 1. *Cont.*

Author [Ref.] Year Country	Study Design	Pregnancy Outcome (N)	Factors Associated with Perinatal Mortality	Study Limitations	Quality Assessment Score
Shah et al. [18] 2000 India	Case-control study	10,715	Antenatal care, socioeconomic status, maternal education, tobacco consumption, parity, history of abortion, history of stillbirth, history of neonatal death, history of infant death, pregnancy spacing, maternal medical problems, obstetric problems, weeks of gestation, birth weight, type of labor, rupture of membranes, type of presentation, mode of delivery, anesthesia, intrapartum medical problems, Apgar score, state of amniotic fluid, resuscitation of the newborn, placenta and cord abnormalities, congenital defects.	Data collection was not regionally homogeneous limiting to apply study findings across the country.	9/12 (Fair)
Siddalingappa et al. [34] 2013 India	Cross-sectional study	314	The intrapartum complication, intrauterine complication, small gestational size at birth, the time taken for a first cry, multiple pregnancies.	Limited sample size, limited scope for generalization.	5/14 (Fair)
Wassan et al. [35] 2009 Pakistan	Cohort study	2778	Antenatal care, birth weight, gestational age, fetal causes, types of residence, maternal risk factors.	Hospital-based study and the study lacks generalizability of findings to a wider population. The study has lacked statistical measure to examine factors associate with perinatal mortality.	4/14 (Poor)
Kusiako et al. [16] 2000 Bangladesh	Cross-sectional study	3865	Maternal age, poor obstetric history, antenatal nutritional marker, signs and symptoms of pregnancy, length of gestation, complications during labor.	As the data was collected by midwives, and lack of verbal autopsy may increase classification bias for perinatal mortality.	6/14 (Fair)
Khanam et al. [36] 2017 Bangladesh	Cross-sectional study	6285	Antepartum hemorrhage, pregnancy-induced hypertension, probable infection.	The use of cross-sectional data lacks establishment of a temporal relationship between pregnancy complication and perinatal mortality. Selective recall bias as mothers who experienced perinatal deaths were more likely to recall antepartum complications compared with those who did not experience a complication.	8/14 (Fair)
Short et al. [37] 2018 India and Pakistan	Cohort study	41,778	Obesity and overweight during pregnancy.	The findings are limited to reflect the whole of the cohort as almost 60% women who measured their weight after 12 weeks of pregnancy were excluded from the analysis.	8/14 (Fair)

2.5. Quality Assessment

The quality of all selected studies was assessed using the National Institute of Health (NIH) Study Quality Assessment Tools for observational studies [38]. The tools consist of criteria which evaluate the internal validity of studies by considering the potential risk of selection bias, information bias, measurement bias, and confounding. Case-control studies were assessed using 12 criteria, while cohort and cross-sectional studies were assessed based on 14 criteria. The reviewed studies were assigned a quality score on a scale of 0–12 points for case-control studies and 0–14 points for cohort and cross-sectional studies (0 if the study did not meet any criteria and 12 or 14 points if the study met all the criteria for the appropriate study design). The sum of points indicated the overall quality of a study. Studies were rated as poor quality (score ≤ 4); fair quality (5–9); and good quality (≥ 10) as shown in Supplementary Tables S1 and S2.

3. Results

A total of 2921 articles were retrieved from the five databases. After applying the selection criteria at each screening stage, a total of 14 articles were retained (Figure 1).

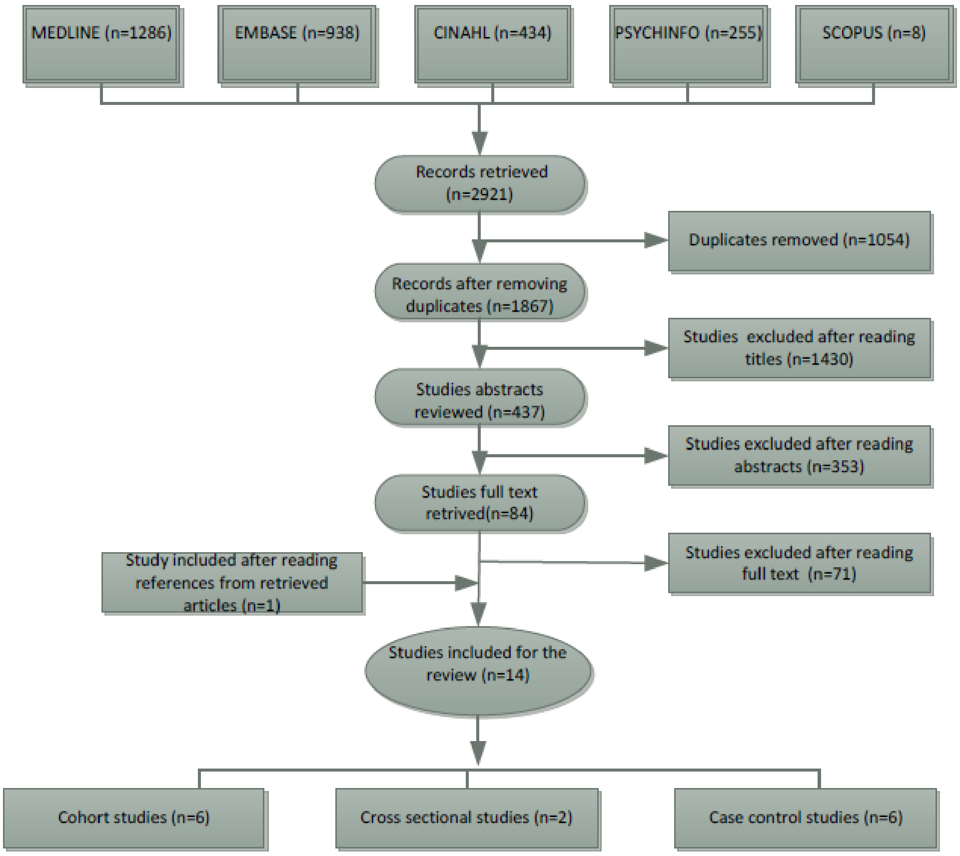

Figure 1. The flow chart for study selection based on PRISMA 2015 guidelines.

3.1. Characteristics of Selected Studies

Four studies were conducted in Pakistan, 4 studies in Bangladesh, 4 studies in India, 1 study in Afghanistan and 1 study in India and Pakistan (Table 1). There were no studies from Nepal, Maldives, Sri Lanka and Bhutan. The sample size of selected studies ranged from 55 to 57,108 women or pregnancies. Of the 14 studies selected; 6 were cohort studies [23,29,31,33,35,37], 2 were case-control studies [18,32] and 6 were cross-sectional studies [16,17,19,30,34,36]. Based on the NIH criteria, 1 study was of good quality [29], while 10 studies were of fair quality [16–19,23,32–34,36,37], and 3 studies were of poor quality [30,31,35]. The details of specific scores assigned to each quality assessment domain are provided in Supplementary Tables S1 and S2.

3.2. Summary of Reviewed Studies

Low socioeconomic status was found to be associated with perinatal mortality as reported in studies conducted in India [17,18] and Bangladesh [29] (Table 1). A cross-sectional study [17] and a case-control study [18] conducted in India also reported that uneducated women were more susceptible to perinatal mortality compared to those who were educated. Furthermore, a cohort study conducted in Pakistan reported that perinatal mortality was higher among women who reside in rural areas compared to those residing in urban areas [35].

In this review, suboptimal maternal anthropometry such as low maternal body weight and height [32] as well as maternal obesity and overweight [19,37], were found to be associated with perinatal mortality in India [32], Bangladesh and Pakistan [19,37]. Maternal medical conditions, birth and pregnancy complications such as anemia [23,29], antepartum hemorrhage [31,36], hypertensive disorders [31], congenital anomalies [31], placenta and cord abnormalities [18], pregnancy-induced hypertension [36], probable infection [36], and neonatal and intrapartum complications [18,34] were also reported to be associated with perinatal mortality in studies conducted in Pakistan [23,31], Bangladesh [29,36] and India [18,34]. A cohort study conducted in Pakistan reported that older maternal age ($\geq$40 years) was associated with perinatal mortality [33], while another cross-sectional study conducted in Bangladesh identified young maternal age ($\leq$18 years) to be associated with perinatal mortality [16]. A case-control study conducted in India reported that parity of three and above was associated with perinatal mortality [18]. Another study conducted in India found that mothers having their first birth were more susceptible to perinatal mortality [17]. Multiple pregnancies were also reported to be associated with perinatal mortality [34]. Furthermore, a cohort study conducted in Bangladesh found that women having five or more pregnancies prior to the index pregnancy were associated with perinatal mortality [29].

Home birth [18,30,32], pregnancy interval [18,30,32] and history of previous death [18] were also reported to be associated with perinatal mortality. A cross-sectional study conducted in India found that mothers who were victims of domestic violence were more susceptible to perinatal mortality [17]. Another case-control study conducted in India found that women who consumed tobacco were more predisposed to perinatal mortality [18] than women who did not consume tobacco.

Low birth weight [18], small gestational size at birth [34] and prematurity [35] were found to be associated with perinatal mortality in studies conducted in India. A case-control study conducted in India [18] and a cohort study in Pakistan [35] also reported that poor antenatal care was associated with perinatal mortality.

4. Discussion

This review appraises the methodological quality of reviewed observational studies. We used observational studies because randomized controlled trials are not feasible and only data from observational studies are available for review [39]. Findings from this study revealed that the most common factors associated with perinatal mortality in South Asia were: low socioeconomic status, lack of quality health care services, pregnancy and or obstetric complications, and lack of antenatal care.

Socioeconomic status (SES) was reported to be associated with perinatal mortality in South Asia. Women with low SES have poorer nutrition and less access to quality maternal and child health care services which adversely impacts fetal and newborn health. Previous studies conducted in low [40,41] and high income countries [42] have reported that higher SES has a protective effect on perinatal mortality, and this maybe as a result of better access and utilization of quality healthcare services such as skilled birth attendants, antenatal care, postnatal care, and institutional deliveries [7,25,43]. The utilization of antenatal care and institutional birth that provide high-quality care are well established as interventions to reduce perinatal mortality [21,25,44], and are more likely to be accessed by women from higher SES. A recent Nepalese study indicated that women of the lower socioeconomic background were significantly less likely to use institutional birth [45] and quality antenatal care [46] resulting in higher perinatal mortality.

In South Asia, countries such as India, Pakistan and Bangladesh have a health care system which is primarily financed by out-of-pocket money [47]. This may pose a great barrier to the access and utilization of quality health care services by women particularly with low SES.

In a case-control study conducted in Kuwait, it was inferred that access to free maternal health care services for women of lower SES had a significant positive impact in reducing perinatal mortality [48]. Furthermore, a low rate of perinatal mortality was reported in Sri Lanka (<10 per 1000 births) [9] which may be due to the implementation of clear policies through well-structured community-based and institutional healthcare service delivery that provides free of charge quality maternal and child health care services irrespective of socioeconomic class [49].

In this study, lack of maternal health care services such as antenatal care and home birth were reported to be associated with perinatal mortality. The presence and accessibility of quality health care service greatly influence maternal and child health outcomes. A large number of avoidable perinatal deaths are due to inadequate health care services rendered from poorly equipped health care centers with inadequate diagnostic tools and suboptimal maternal care services. Perinatal care is intimately linked to maternal and newborn survival, and thus effective care throughout the continuum of pregnancy, labor, and into the postpartum period is essential [50]. A meta-analysis of estimating perinatal mortality by place of delivery conducted in Sub-Saharan Africa reported that 14 perinatal deaths per 1000 births could be averted if birth occurred at a high-quality health facility [25]. Hence, to reduce perinatal mortality, an improvement in the quality and access of health care services is critical [51].

In this study, maternal obstetric complications such as gestational diabetes, anemia, hypertensive disorders, preterm labor, and intrauterine growth restriction were found to be associated with perinatal mortality in South Asia. These conditions can be identified in the antenatal period, thus reinforcing the need to improve the continuum of care between antenatal identification and subsequent management of complications in health facilities [21,52]. Hence, high coverage quality antenatal care and institutional delivery/skilled birth attendants have become a part of global and country level strategy to improve birth outcome [15,53,54].

In South Asia, countries such as Bangladesh, India, Nepal and Pakistan have existing public health policies which include conditional cash transfer and voucher schemes aimed at promoting antenatal, delivery and postnatal care for women of lower socioeconomic status [47]. However, despite these policies, perinatal mortality is still high within the region which indicates that these policies have not been effective in improving health outcomes [47,55]. Hence, further research into the quality of antenatal and delivery care services offered to women is needed.

4.1. Strengths and Limitations

This review is a comprehensive search of the existing literature to report factors associated with perinatal mortality across South Asia. However, this study also had some limitations. First, qualitative studies were excluded from this review. The inclusion of qualitative studies in systematic reviews provides alternative explanations and enables triangulation of findings [56,57]. Second, relevant studies may have been published in a language other than English, and hence were missed in our study. Third, there were no studies from Bhutan, Maldives, Sri Lanka and Nepal on perinatal mortality; hence, more research on perinatal mortality should be done in these countries. Fourth, most studies retained for review were fair to poor quality which may affect the external validity of our findings. Finally, with such different data sources and limited information from some countries, this review did not report the pooled estimate for the effect of each factor on perinatal mortality across all countries in the region; this is due to the fact that the factors were measured differently in each study, thus reporting an estimate for the pool effect would misrepresent the impact of the factors on perinatal mortality. Furthermore, some countries have no reported studies on perinatal mortality; hence, further research should focus on analyzing the determinants of perinatal mortality in these countries.

4.2. Policy Implications

Findings from this study are useful for identifying the underlying factors associated with perinatal mortality in South Asia in order to assist in the proper allocation of health resources. These findings will also assist policy makers in planning, developing and implementing of public health interventions which provide appropriate antenatal and obstetric care services aimed at improving maternal health and reducing perinatal mortality at both the individual and community levels. This study also serves as a needs assessment indicator to countries having no representation of research on perinatal mortality to further explore the factors associated with perinatal mortality within its populace.

5. Conclusions

This systematic review found that pregnancy complications are the major causes of perinatal mortality in South Asia. A protective effect of perinatal mortality was found in women who used antenatal care and institutional delivery as well as those with a high SES. Socioeconomic disparity remains a significant barrier to the utilization of maternal and child health services. Hence, cost-effective health care interventions such as quality antenatal care and institutional delivery are needed and should target women of low socio-economic status. Furthermore, due to there being no evidence from some countries in South Asia, there is need to improve data collection by introducing effective health information management systems (HIMS) aimed at assisting health agencies gather data on perinatal mortality to influence current and future needs for health care services.

Supplementary Materials: The following are available online at http://www.mdpi.com/1660-4601/15/7/1428/s1, Table S1: Quality assessment of selected cross-sectional and cohort studies, Table S2: Quality assessment of selected case-control studies.

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References

1. World Health Organization. *Neonatal and Perinatal Mortality: Country, Regional and Global Estimates*; World Health Organization: Geneva, Switzerland, 2006.
2. Opportunities for Africas Newborns: Practical Data Policy and Programmatic Support for Newborn Care in Africa. Available online: http://www.who.int/pmnch/media/publications/oanfullreport.pdf (accessed on 3 July 2017).
3. Paul, V.K.; Sachdev, H.S.; Mavalankar, D.; Ramachandran, P.; Sankar, M.J.; Bhandari, N.; Sreenivas, V.; Sundararaman, T.; Govil, D.; Osrin, D.; et al. Reproductive health, and child health and nutrition in India: Meeting the challenge. *Lancet* **2011**, *377*, 332–349. [CrossRef]
4. Fink, G.; Günther, I.; Hill, K. The effect of water and sanitation on child health: Evidence from the demographic and health surveys 1986–2007. *Int. J. Epidemiol.* **2011**, *40*, 1196–1204. [CrossRef] [PubMed]
5. Lehtonen, L.; Gimeno, A.; Parra-Llorca, A.; Vento, M. Early neonatal death: A challenge worldwide. *Semin. Fetal Neonatal Med.* **2017**, *22*, 153–160. [CrossRef] [PubMed]

6. Mason, E.; McDougall, L.; Lawn, J.E.; Gupta, A.; Claeson, M.; Pillay, Y.; Presern, C.; Lukong, M.B.; Mann, G.; Wijnroks, M. From evidence to action to deliver a healthy start for the next generation. *Lancet* **2014**, *384*, 455–467. [CrossRef]
7. Shah, R.; Sharma, B.; Khanal, V.; Pandey, U.K.; Vishwokarma, A.; Malla, D.K. Factors associated with neonatal deaths in Chitwan district of Nepal. *BMC Res. Notes* **2015**, *8*, 818. [CrossRef] [PubMed]
8. Lawn, J.E.; Cousens, S.; Zupan, J. Lancet Neonatal Survival Steering Team. 4 million neonatal deaths: When? Where? Why? *Lancet* **2005**, *365*, 891–900. [CrossRef]
9. Wang, H.; Bhutta, Z.A.; Coates, M.M.; Coggeshall, M.; Dandona, L.; Diallo, K.; Franca, E.B.; Fraser, M.; Fullman, N.; Gething, P.W. Global, regional, national, and selected subnational levels of stillbirths, neonatal, infant, and under-5 mortality, 1980–2015: A systematic analysis for the Global Burden of Disease Study 2015. *Lancet* **2016**, *388*, 1725–1774. [CrossRef]
10. United Nations Inter-Agency Group for Child Mortality Estimation (UN IGME). *Levels & Trends in Child Mortality: Report 2017, Estimates Developed by the UN Inter-Agency Group for Child Mortality Estimation*; United Nations Children's Fund: New York, NY, USA, 2017.
11. Hogan, M.C.; Foreman, K.J.; Naghavi, M.; Ahn, S.Y.; Wang, M.; Makela, S.M.; Lopez, A.D.; Lozano, R.; Murray, C.J.L. Maternal mortality for 181 countries, 1980–2008: A systematic analysis of progress towards Millennium Development Goal 5. *Lancet* **2010**, *375*, 1609–1623. [CrossRef]
12. Lawn, J.E.; Blencowe, H.; Waiswa, P.; Amouzou, A.; Mathers, C.; Hogan, D.; Flenady, V.; Frøen, J.F.; Qureshi, Z.U.; Calderwood, C.; et al. Stillbirths: Rates, risk factors, and acceleration towards 2030. *Lancet* **2016**, *387*, 587–603. [CrossRef]
13. Darmstadt, G.L.; Kinney, M.V.; Chopra, M.; Cousens, S.; Kak, L.; Paul, V.K.; Martines, J.; Bhutta, Z.A.; Lawn, J.E. The Lancet Every Newborn Study Group. Who has been caring for the baby? *Lancet* **2014**, *384*, 174–188. [CrossRef]
14. Lawn, J.E.; Blencowe, H.; Oza, S.; You, D.; Lee, A.C.; Waiswa, P.; Lalli, M.; Bhutta, Z.; Barros, A.J.; Christian, P.; et al. Every Newborn: Progress, priorities, and potential beyond survival. *Lancet* **2014**, *384*, 189–205. [CrossRef]
15. World Halth Organization. *Every Newborn: An Action Plan to End Preventable Deaths*; World Health Organization: Geneva, Switzerland, 2014.
16. Kusiako, T.; Ronsmans, C.; Van der Paal, L. Perinatal mortality attributable to complications of childbirth in Matlab, Bangladesh. *Bull. World Health Organ.* **2000**, *78*, 621–627. [PubMed]
17. Ahmed, S.; Koenig, M.A.; Stephenson, R. Effects of domestic violence on perinatal and early-childhood mortality: Evidence from north India. *Am. J. Public Health* **2006**, *96*, 1423–1428. [CrossRef] [PubMed]
18. Shah, D.; Shroff, S.; Ganla, K. Factors affecting perinatal mortality in India (perinatal audit). *Prenat. Neonatal Med.* **2000**, *5*, 288–302.
19. Khan, M.N.; Rahman, M.M.; Shariff, A.A.; Rahman, M.M.; Rahman, M.S.; Rahman, M.A. Maternal undernutrition and excessive body weight and risk of birth and health outcomes. *Arch. Public Health* **2017**, *75*, 12. [CrossRef] [PubMed]
20. Tarique, A.; Khan, M.; Ahmed, L. Perinatal Mortality (PNM): A discussion of social myths, socioeconomic taboos and psychosocial stress. *Med. Channel* **2013**, *19*, 8–12.
21. Bhutta, Z.A.; Das, J.K.; Bahl, R.; Lawn, J.E.; Salam, R.A.; Paul, V.K.; Sankar, M.J.; Blencowe, H.; Rizvi, A.; Chou, V.B. Can available interventions end preventable deaths in mothers, newborn babies, and stillbirths, and at what cost? *Lancet* **2014**, *384*, 347–370. [CrossRef]
22. World Health Organization. *WHO Recommended Interventions for Improving Maternal and Newborn Health: Integrated Management of Pregnancy and Childbirth*; World Health Organization: Geneva, Switzerland, 2007.
23. Perveen, S.; Soomro, T.K. Sideropaenic anaemia: Impact on perinatal outcome at tertiary care hospital. *J. Pak. Med. Assoc.* **2016**, *66*, 952–956. [PubMed]
24. Rahman, M.M.; Abe, S.K.; Rahman, M.S.; Kanda, M.; Narita, S.; Bilano, V.; Ota, E.; Gilmour, S.; Shibuya, K. Maternal anemia and risk of adverse birth and health outcomes in low-and middle-income countries: Systematic review and meta-analysis. *Am. J. Clin. Nutr.* **2016**, *103*, 495–504. [CrossRef] [PubMed]
25. Chinkhumba, J.; De Allegri, M.; Muula, A.S.; Robberstad, B. Maternal and perinatal mortality by place of delivery in sub-Saharan Africa: A meta-analysis of population-based cohort studies. *BMC Public Health* **2014**, *14*, 1014. [CrossRef] [PubMed]

26. Merali, H.S.; Lipsitz, S.; Hevelone, N.; Gawande, A.A.; Lashoher, A.; Agrawal, P.; Spector, J. Audit-identified avoidable factors in maternal and perinatal deaths in low resource settings: A systematic review. *BMC Pregnancy Childbirth* **2014**, *14*, 280. [CrossRef] [PubMed]
27. Moher, D.; Shamseer, L.; Clarke, M.; Ghersi, D.; Liberati, A.; Petticrew, M.; Shekelle, P.; Stewart, L.A. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst. Rev.* **2015**, *4*, 1. [CrossRef] [PubMed]
28. United Nations International Children's Fund. *The State of the World's Children 2014 in Numbers: Every Child Counts. Revealing Disparities, Advancing Children's Rights*; United Nations International Children's Fund: New York, NY, USA, 2014.
29. Bari, W.; Chowdhury, R.I.; Islam, M.; Chakraborty, N.; Akhter, H. The differentials and determinants of perinatal mortality in rural Bangladesh. *Eur. J. Contracept. Reprod. Health Care* **2002**, *7*, 216–222. [CrossRef] [PubMed]
30. Guidotti, R.J.; Kandasamy, T.; Betrán, A.P.; Merialdi, M.; Hakimi, F.; Van Look, P.; Kakar, F. Monitoring perinatal outcomes in hospitals in Kabul, Afghanistan: The first step of a quality assurance process. *J. Matern. Fetal Neonatal Med.* **2009**, *22*, 285–292. [CrossRef] [PubMed]
31. Iqbal, M.; Majid, A.; Khan, H.A.; Muhammad, Z. Perinatal mortality and its related obstetrics risk factors. *J. Med. Sci.* **2014**, *22*, 76–79.
32. Sachar, R.; Soni, R. Brief report. Perinatal mortality in rural Punjab—A population based study. *J. Trop. Pediatr.* **2000**, *46*, 43–45. [CrossRef] [PubMed]
33. Shabbir, S.; Zahid, M.; Qazi, A. To detect outcome of pregnancy in advanced maternal age among Pakistani women. *Pak. J. Med. Sci.* **2014**, *1*, 709–712.
34. Siddalingappa, H.; Nrayana Murthy, M.; Kulkarni, P.; Ashok, N. Prevalence and factors influencing perinatal mortality in rural Mysore, India. *J. Clin. Diagn. Res.* **2013**, *7*, 2796. [CrossRef] [PubMed]
35. Wassan, K.; Rani, S.; Haider, G. Perinatal mortality-A hazardous dilemma. *Rawal Med. J.* **2009**, *34*, 195–198.
36. Khanam, R.; Ahmed, S.; Creanga, A.A.; Begum, N.; Koffi, A.K.; Mahmud, A.; Rosen, H.; Baqui, A.H. Antepartum complications and perinatal mortality in rural Bangladesh. *BMC Pregnancy Childbirth* **2017**, *17*, 81. [CrossRef] [PubMed]
37. Short, V.L.; Geller, S.E.; Moore, J.L.; McClure, E.M.; Goudar, S.S.; Dhaded, S.M.; Kodkany, B.S.; Saleem, S.; Naqvi, F.; Pasha, O.; et al. The Relationship between Body Mass Index in Pregnancy and Adverse Maternal, Perinatal, and Neonatal Outcomes in Rural India and Pakistan. *Am. J. Perinatol.* **2018**. [CrossRef]
38. Study Quality Assessment Tools. Available online: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools (accessed on 13 January 2018).
39. Stroup, D.F.; Berlin, J.A.; Morton, S.C.; Olkin, I.; Williamson, G.D.; Rennie, D.; Moher, D.; Becker, B.J.; Sipe, T.A.; Thacker, S.B. Meta-analysis of observational studies in epidemiology: A proposal for reporting. *JAMA* **2000**, *283*, 2008–2012. [CrossRef] [PubMed]
40. McDermott, J.; Steketee, R.; Wirima, J. Perinatal mortality in rural Malawi. *Bull. World Health Organ.* **1996**, *74*, 165–171. [PubMed]
41. Nkwo, P.O.; Lawani, L.O.; Ezugwu, E.C.; Iyoke, C.A.; Ubesie, A.C.; Onoh, R.C. Correlates of poor perinatal outcomes in non-hospital births in the context of weak health system: The Nigerian experience. *BMC Pregnancy Childbirth* **2014**, *14*, 341. [CrossRef] [PubMed]
42. Flenady, V.; Koopmans, L.; Middleton, P.; Frøen, J.F.; Smith, G.C.; Gibbons, K.; Coory, M.; Gordon, A.; Ellwood, D.; McIntyre, H.D. Major risk factors for stillbirth in high-income countries: A systematic review and meta-analysis. *Lancet* **2011**, *377*, 1331–1340. [CrossRef]
43. Pal, S. Impact of hospital delivery on child mortality: An analysis of adolescent mothers in Bangladesh. *Soc. Sci. Med.* **2015**, *143*, 194–203. [CrossRef] [PubMed]
44. Gordon, A.; Raynes-Greenow, C.; McGeechan, K.; Morris, J.; Jeffery, H. Risk factors for antepartum stillbirth and the influence of maternal age in New South Wales Australia: A population based study. *BMC Pregnancy Childbirth* **2013**, *13*, 12. [CrossRef] [PubMed]
45. Karkee, R.; Lee, A.H.; Khanal, V. Need factors for utilisation of institutional delivery services in Nepal: An analysis from Nepal Demographic and Health Survey, 2011. *BMJ Open* **2014**, *4*, e004372. [CrossRef] [PubMed]

46. Joshi, C.; Torvaldsen, S.; Hodgson, R.; Hayen, A. Factors associated with the use and quality of antenatal care in Nepal: A population-based study using the demographic and health survey data. *BMC Pregnancy Childbirth* **2014**, *14*, 94. [CrossRef] [PubMed]
47. Jehan, K.; Sidney, K.; Smith, H.; de Costa, A. Improving access to maternity services: An overview of cash transfer and voucher schemes in South Asia. *Repord. Health Matters* **2012**, *20*, 142–154. [CrossRef]
48. Shah, N.M.; Shah, M.A.; Khalaf, A.A.; Mustafa, M.M.; Al-Sayed, A. Searching for socioeconomic risk factors in perinatal mortality in Kuwait: A case control study. *Soc. Sci. Med.* **2000**, *51*, 539–550. [CrossRef]
49. Haththotuwa, R.; Senanayake, L.; Senarath, U.; Attygalle, D. Models of care that have reduced maternal mortality and morbidity in Sri Lanka. *Int. J. Gynaecol. Obstet.* **2012**, *119*, S45–S49. [CrossRef] [PubMed]
50. Lawn, J.E.; Kerber, K.; Enweronu-Laryea, C.; Cousens, S. 3.6 Million Neonatal Deaths—What Is Progressing and What Is Not? *Semin. Perinatol.* **2010**, *34*, 371–386. [CrossRef] [PubMed]
51. Lawn, J.E.; Blencowe, H.; Pattinson, R.; Cousens, S.; Kumar, R.; Ibiebele, I.; Gardosi, J.; Day, L.T.; Stanton, C. The Lancet's Stillbirths Series Steering Committee. Stillbirths: Where? When? Why? How to make the data count? *Lancet* **2011**, *377*, 1448–1463. [CrossRef]
52. Vogel, J.; Souza, J.; Mori, R.; Morisaki, N.; Lumbiganon, P.; Laopaiboon, M.; Ortiz-Panozo, E.; Hernandez, B.; Pérez-Cuevas, R.; Roy, M.; et al. Maternal complications and perinatal mortality: Findings of the World Health Organization Multicountry Survey on Maternal and Newborn Health. *BJOG* **2014**, *121*, 76–88. [CrossRef] [PubMed]
53. Kerber, K.J.; de Graft-Johnson, J.E.; Bhutta, Z.A.; Okong, P.; Starrs, A.; Lawn, J.E. Continuum of care for maternal, newborn, and child health: From slogan to service delivery. *Lancet* **2007**, *370*, 1358–1369. [CrossRef]
54. Darmstadt, G.L.; Bhutta, Z.A.; Cousens, S.; Adam, T.; Walker, N.; De Bernis, L. Lancet Neonatal Survival Steering Team. Evidence-based, cost-effective interventions: How many newborn babies can we save? *Lancet* **2005**, *365*, 977–988. [CrossRef]
55. Randive, B.; Diwan, V.; De Costa, A. India's Conditional Cash Transfer Programme (the JSY) to Promote Institutional Birth: Is There an Association between Institutional Birth Proportion and Maternal Mortality? *PLoS ONE* **2013**, *8*, e67452. [CrossRef] [PubMed]
56. Grant, M.J.; Booth, A. A typology of reviews: An analysis of 14 review types and associated methodologies. *Health Inf. Libr. J.* **2009**, *26*, 91–108. [CrossRef] [PubMed]
57. Paudel, M.; Javanparast, S.; Dasvarma, G.; Newman, L. Religio-cultural factors contributing to perinatal mortality and morbidity in mountain villages of Nepal: Implications for future healthcare provision. *PLoS ONE* **2018**, *13*, e0194328. [CrossRef] [PubMed]

2.3 Previous studies on childhood mortality

This section presents existing literature around factors associated with childhood mortality, and these factors are classified into four distinct groups: community-level factors, household-level factors, individual-level factors, environmental level factors, and health service factors.

2.3.1 Community level factors

Community level factors are structural determinants that are often looked as a barrier to access to health care services. These factors include place of residence and geopolitical regions.

Place of residence: The place of residence determines child survival in many Low-and-Middle Income countries (LMICs). For example, previous studies conducted in Malawi [29], Brazil [6], Nigeria [30], and Bangladesh [31] found that mothers who reported living in rural areas were more likely to have had child mortality. The disadvantaged households within rural communities are less likely to use essential maternal and child health care services, that further contributes to higher child mortality [32].

Geopolitical regions: Nepal is divided into 3 ecological zone, and five development regions and a previous study conducted in Nepal have found that mothers who resided in the Mountain ecological zone were more likely to report child mortality compared to those who lived in the Terai (flat zone), or in the hills [20, 33]. The inequality in childhood mortality based on geopolitical differences has been identified in the previous study conducted in Indonesia [24].

2.3.2 Household level factors

In many countries in South Asia including Nepal, the health care system is financed by out of pocket money [34]. Therefore, Household economic status can be a strong predictor of receiving maternal and child health care that may affect child survival.

Household wealth Index: The lack of income and expenditure data in surveys conducted in many low- and middle-income countries have prompted researchers to use household assets as a proxy of measuring household economic status [35, 36]. Previous studies conducted in LMICs [30, 33, 37-43] have extensively used household assets to construct household wealth index covariate, and also found a significant association between wealth index and childhood mortality.

The only household factor selected for this thesis was the household wealth index, and it was constructed by using the wealth index factor scores calculated in each of the four Birth Recode (BR), and Individual Recode (IR) data files of NDHS [11-14]. The wealth index was classified into three: the bottom, 40% of households were arbitrarily referred to as poor households, the next 40% was classified as the middle households, and the top 20% was classified as rich households, consistent with previous studies [30, 41, 44].

2.3.3 Individual-level factors

For the purpose of this thesis, Individual-level factors consist of maternal, child and paternal characteristics which are discussed as follow:

Maternal Age*:* Previous studies have found that young maternal age is significantly associated with increased likelihood of child mortality [30, 45]. Similarly, Ghimire et al., also found that mothers who were <20 years were significantly more likely to have child mortality compared to their older counterparts [46]. However, the finding of higher risk of childhood mortality amongst younger mothers in above studies contradicts a previous report by Neupane et al.; and studies from developing countries [47, 48] also found no significant association between maternal age and childhood mortality.

Religion*:* The Previous study that used data from the National Family Health Survey in India reported differences in child mortality based on religious affiliation [49]. In Nepal, there is a dearth of literature explaining the reason for differences in child mortality across religious affiliations. However, another study from India indicated that access and utilisation of institutional delivery services differ by religious affiliation that may have attributed to higher child mortality in some religion [50].

Maternal Education*:* Education is a fundamental human right and also considered as one of the important determinants of health. Specifically, studies from LMICs have examined the impact of maternal education on child survival which found a significant protective effect of education against child mortality [51-53]. Previous studies from Nepal [54] Pakistan [55] and Bangladesh [56] reported that education could increase the uptake of quality health service utilisation.

Maternal occupation*:* Mustafa et al. have assessed the impact of maternal occupation on childhood mortality [57] and found a significant association of child mortality among working mothers.

The desire for pregnancy: Previous cross-sectional study conducted in Bangladesh found that mothers who reported not having a desire for previous pregnancy were more likely to have child mortality [41]. However, another cross-sectional study conducted in Indonesia found no such association [24].

Paternal education: Studies conducted in Pakistan [42] and regional Bangladesh have found that educated fathers are less likely to have infant and child mortality. Despite initiations to close gender inequality, in many parts of Nepal, mainly rural communities, gender inequalities exist, and fathers make most of the household decisions including those of child health and nutrition. Educated fathers are more likely to get employment and their belief and decision on seeking child health may attribute to child survival outcome.

Birth order: Previous studies found that first order births had a significantly greater risk of child mortality compared with subsequent infants [58, 59]. Existing literature from Nepal [60] and Nigeria [61] have argued that an increased risk of mortality among first-born children may be linked to the high number of young women below 20 years of age, in particular, having first births.

Birth Interval: The impact of short birth intervals on higher childhood mortality has been well documented in previous studies from Bangladesh [62] and South Africa [63]. Mothers having short birth interval have less time for physical and nutritional recovery and be the possible explanation for higher childhood mortality compared to those who have a long birth interval [64]. For the purpose of this thesis, we have combined birth order and birth interval in one because the impact of birth order on child mortality can be arbitrated by birth interval, and previous studies have also combined birth order and birth interval [20, 24, 30, 33, 44, 64].

Sex of child: Studies conducted in South Asia such as Bangladesh [65, 66], and India [67] found that female children are more likely to die compared to male children. The higher mortality risk among female children may be attributed to sex-selective culture because, in South Asia including Nepal, son preference has significant social and economic implications that may have impacted the pattern of fertility and mortality.

Previous death of a child: Several population-based studies conducted in South Asia have shown that childhood mortality was significantly associated with mothers who reported of having previous death of child compared to those whose previous child survived [31, 41, 68]. The higher odds of child mortality among mothers who reported of having previous death of a sibling may be aggravated due to the long-term psychological effect of sibling death on parents that the surviving child may lack essential healthcare including nutrition [69, 70].

2.3.4 Environmental factors

Environmental health remains one of the major contributors to morbidity and mortality in many developing countries [71]. The environmental factors, for the purpose of this thesis, include types of the drinking water source, types of sanitation facilities, and types of cooking fuel.

Types of drinking water source and sanitation facility: Unimproved water and sanitation is a leading cause of childhood diarrhoea; and diarrhoea remains one of the major cause of under-5 mortality [25-27] accounting for almost half a million deaths annually in developing countries such as Nepal [27]. Literature suggests that about 2.2 million under-5 deaths in LMICs can be averted with improved water and sanitation facilities [72]. According to the World Health Organization and the United Nations Children's Fund Joint Monitoring Program guidelines [73], piped water on premises and other improved drinking water sources such as neighbours tap or tubewell, tubewell or borehole in yard, stone tap, protected well and rainwater are categorised as improved source of drinking water; whereas unprotected well in house, unprotected public or neighbour's well, unprotected spring, bottled water, water from tanker or truck, and surface drinking water sources (river, stream, pond, lake, dam, canal, or irrigation water) are categorised as unimproved source of drinking water. Likewise, households with flush toilet, ventilated or improved pit latrine, pit latrine with the slab or composting toilet are categorised as improved sanitation; whereas traditional pit toilet, pit latrine without slab, bucket toilet, and open defecation are categorised as unimproved sanitation.

Types of cooking fuel: According to recent Demographic and Health Survey 2016, about 66% of the Nepalese household use unimproved cooking fuel such as wood, straw, and animal dung [14]. Unimproved cooking fuel is a major cause of respiratory illness [74, 75], and according to the World Health Organization, over 50% of the under-5 deaths are attributed to acute respiratory illness often caused by the use of unimproved cooking fuel. Cooking fuel is categorised as improved (biogas, natural gas, Liquefied Petroleum Gas and electricity) and unimproved (charcoal, wood, coal/lignite, animal dung, kerosene, straw/shrubs/grass, and agricultural crop).

2.3.5 Health Service Factors

Use of contraceptives: Previous population-based study by Abir et al. [41] has examined the impact of contraceptives on under-5 mortality, and found that mothers who reported of using contraceptives were less likely to have under-5 mortality compared to mothers with no contraceptives use. The use of contraceptives may help to create a long birth interval, and the impact of the birth interval has been previously discussed [20, 21, 41].

Antenatal care visits: Almost half of the newborn death occurs during delivery [76]. The major causes of these deaths are prematurity, low birth weight, obstruct labor and pregnancy complication [77-79]; and hence antenatal identification of pregnancy complications and timely management of such complications have become a part of the global strategy to reduce maternal and newborn death [80]. The protective effect of antenatal care on child mortality has been previously documented [33].

Tetanus Toxoid (TT) vaccination: The impact of TT vaccine on child survival has been well documented in previous studies conducted in Bangladesh [41, 44]. Maternal TT vaccine during pregnancy helps to protect the newborn from tetanus, and It has been reported that the TT vaccine during pregnancy reduces under-5 mortality by 95% [81].

Antenatal Iron and Folic Acid (IFA): Previous studies have shown that mothers with antenatal IFA supplementations are less likely to have under-5 mortality [33, 82]. Iron deficiency is a common cause of anaemia, and anaemia during pregnancy is associated with prematurity and low birth weight [83, 84].

The protective effect of antenatal IFA against child mortality may be aggravated because IFA help reduces anaemia during pregnancy so as the prematurity and low birth weight.

Mode of delivery: The effect of mode of delivery on child survival has been previously studied with different findings. For example, a study conducted in Nigeria revealed that mothers who delivered their baby through caesarean section were more likely to have had neonatal mortality

[39], whereas another study from Swaziland found no significant association between child mortality and mode of delivery [47].

2.4 Summary

In this chapter, literature review of factors associated with perinatal and under-5 mortality accompanied by Mosley and Chen conceptual framework for child survival in developing countries has been presented. The next chapter (chapter 3) is based on methods of this thesis which encompasses: study area, overview of demographic and health survey, study population, and statistical analysis.

CHAPTER 3: Methods

Chapter 3 explains the methods of this thesis. Section 3.1 describes the study area. Section 3.2 is a brief overview of demographic and health survey, which is followed by a table that outlines the four consecutive Nepal Demographic and Health Surveys explaining sample size and corresponding response rates. Section 3.3 and section 3.2 explains different statistical modellings used to examine factors associated with perinatal and child mortality in Nepal.

3.1 The study area

Figure 1 shows the map of Nepal. Nepal is a landlocked country in South Asia with an estimated population of 26.4 million. As shown in the figure 1, Kathmandu is the capital city as well as the largest metropolis in Nepal, with a population of roughly 5 million people. Nepal is the 93rd largest country by area and 48th largest country by population. It borders China in the north and India in the south, east, and west while Bangladesh is located within only 27 km (17 mi) of its south-eastern tip and Bhutan is separated from it by the Indian state of Sikkim. Nepal is a Himalayan state with diverse geography, including fertile plains, subalpine forested hills, and eight of the world's ten tallest mountains, including Mount Everest, which is the highest point on Earth. Nepal has a multiethnic population with Hindu and Buddhist majority. Nepal is among the least developed countries in the world, with about one-quarter of its population living below the poverty line. Nepal is heavily dependent on remittances, which amount to as much as 30% of Gross Domestic Product (GDP). Agriculture is the mainstay of the economy, providing a livelihood for almost two-thirds of the population but accounting for only one-third of GDP. Industrial activity mainly involves the processing of agricultural products, including pulses, jute, sugarcane, tobacco, and grain.

Figure 1: The map of Nepal:

(Source:https://www.google.com/search?q=map+of+nepal&tbm=isch&source=hp&sa=X&ved=2ahUKEwjlgujk7oPhAhXQ7HMBHSX6AkkQsAR6BAgFEAE&biw=1366&bih=628)

3.2 Demographic and health surveys

The DHS is a nationally representative household survey that collects, analyses, and disseminates data on fertility, family planning, maternal and child health, gender, HIV/AIDS, malaria, and nutrition [4]. Since 1984, the DHS program has provided technical assistance to more than 300 surveys in over 90 LMICs, advancing global understanding of health and population trends in developing countries. Participating countries adopt standardized methods involving uniform questionnaires, manuals, and field procedures that are developed by the DHS to gather information that is comparable across countries. The surveys have large sample sizes (usually between 5,000 and 30,000 households) and typically are conducted about every 5 years, to allow comparisons over time [4].

New ERA implemented the Nepal Demographic and Health Survey (NDHS) [11-14] under the aegis of the Ministry of Health (MOH) of the Government of Nepal, and ICF International provided technical assistance through the DHS Program, which is funded by the United States Agency for International Development (USAID). The first NDHS was conducted in 1996, and since then four NDHSs have been conducted (2001, 2006, 2011, and 2016 NDHS). The main objective of NDHS was to provide up-to-date estimates of basic demographic and health indicators in the country [4].

The NDHS uses a stratified, two-stage (cluster), random sampling design [11-14]. Nepal is divided into seven provinces with each province stratified into urban and rural areas, yielding 14 sampling strata [14]. The target groups were women and men aged 15-49 who were either permanent residents of the selected households or visitors who stayed in the households the night before the survey. The survey was conducted using 5 questionnaires namely; the household questionnaire, the woman's questionnaire, the man's questionnaire, the biomarker questionnaire, the fieldworker questionnaire, and the verbal autopsy questionnaire (for neonatal deaths).

The household questionnaire collected information on the residents of the selected household and their characteristics, such as age, sex, marital status, education, and relationship to the head of the household. The questionnaire also collected information on features of the household's dwelling unit, such as the source of water, type of toilet facilities, and materials used for the floor of the dwelling unit, as well as ownership of various durable goods, migration, and food security.

The women's questionnaire collected information on background characteristics (including age, education, and media exposure); pregnancy history and child mortality; knowledge, use, and source of family planning methods; fertility preferences (including desire for more children and ideal number of children); antenatal, delivery, and postnatal care; breastfeeding and infant feeding practices; vaccinations and childhood illnesses; women's work and husbands' background characteristics; domestic violence; knowledge, awareness, and behaviour regarding HIV/AIDS and other sexually transmitted infections (STIs); adult mortality, including maternal mortality; knowledge, attitudes, and behavior related to other health issues (e.g., tuberculosis).

The men's questionnaire collected similar information as the women's questionnaire but with the exception of a detailed reproductive history, and questions on maternal and child health, or nutrition.

The biomarker questionnaire was used to collect anthropometry measurements, haemoglobin testing, and blood pressure measurements for children age 0-59 months as well as women and men age 15 and above in the selected households.

The verbal autopsy questionnaire was administered in households where a neonatal death took place within the 5 years prior to the survey [14]. The instrument included questions on the respondent's account of the cause of death, vital registration and certification, general signs and symptoms associated with the illness, history of injury, and service utilisation to assist in the proper diagnosis of the cause of death.

Table 3.1 Household, women, and men sample and response rates in Nepal Demographic and Health Survey (NDHS) (2001-2016)

NDHS Year	Household sample (Response rate)	Women sample (Response rate)	Men sample (Response rate)
NDHS 2001	8602(99.6%)	8726(98.2%)	2261(96.1%)
NDHS 2006	8707(99.6%)	10793(98.4%)	4397(96.0%)
NDHS 2011	10826(99.4%)	12674(98.1%)	4121(95.3%)
NDHS 2016	11040(98.5%)	12862(98.3%)	4063(95.9%)

Source: NDHS reports (2001-2016)

In this thesis, we fitted the community, household, individual, environmental, and health service variables using models described by Rabe-Hesketh [85] and Cox [86]. The formula for

Logistic regression generalised linear latent and mixed models (GLLAM) [85] and the Cox proportional hazards model [86] have been described below.

3.3 Cox proportional hazards model

The letters $h(t,k)$denote the hazard function defined as the risk of dying at time t based on an n-dimensional vector of predictor variables $K = (k_1, k_2, \ldots, k_n)$, as shown in equation (1).

$$h(t,k) = h_0(t)\, exp(\sum_{i=1}^{n} \omega_i\, p_i) \qquad (1)$$

$h_o(t)$ denotes the baseline hazard at time t, where the exponential of the sum of ωi and pi provide the proportional change in hazard function in relation to changes in the predictor variables. The coefficients $\omega 1 \ldots \omega n$ are estimated by Cox regression. The hazard ratio is then obtained by dividing both sides of equation (1) by $h_o(t)$ and taking logarithms, which yields equation 2.

$$\frac{h(t,k)}{h_0(t)} = \omega_1 k_1 + \omega_2 k_2 + \omega_3 k_3 + \cdots + \omega_n k_n \qquad (2)$$

By applying equation (2), the hazard ratios of the effect of the previously discussed predictor variables were obtained for neonatal, post-neonatal, infant, child, and under-5 mortality.

3.4 Logistic regression generalised linear latent and mixed models (GLLAM)

Let the dichotomous responses are an example of being wealthy (1: death; 0: alive). The expectation of a dichotomous response y_i is just the probability that y_i =1. That is $\mu_i = \Pr(y_i = 1 | x_i)$. The logit link is:

$$g(\mu_i) = \text{log}it\,(\mu_i) = \log\left(\frac{\mu_i}{1-\mu_i}\right) = x_i^{`}\beta = v_i$$

Where the linear combination $v_i = \beta_0 + \beta_1 x_{i1} + \ldots = x_i^{`}\beta$ is called the "linear predictor" and β are fixed effect. The conditional expectation of the response given the covariate is $\mu_i = E\,[y_i \mid x_i]$ and g is a link function; linking the expected response μ_i to the linear predictor v_i.

Two-level generalised linear for logistic regression is given by:

$$g(\mu_{ij}) = \log\left(\frac{\mu_{ij}}{1-\mu_{ij}}\right) = x_{ij}^{`}\beta + \sum_{m_2=0}^{M_2-1} \eta_{m_2 j}^{(2)}\ z_{m_2 ij}^{(2)}$$

Here, $\mu_{ij} = E\,[y_{ij} \mid x_{ij,}\ z_{ij}^{(2)}, \eta_j^{(2)}]$ and $\eta_j^{(2)} = (\eta_{0j}^{(2)}, \ldots, \eta_{M_2-1,j}^{(2)})^{`}$ are random effects varying at level 2 and $z_{ij}^{(2)}$ is the corresponding covariates. It is typically assumed that the random effects are multivariate normal with $\eta_i^{(2)} \sim N(0, \psi^{(2)})$.

3.5 Summary

In this chapter, the first two sections (3.1 and 3.2) described study area, an overview of demographic and health survey, and sample population. This is followed by sections of different statistical modellings (Generalized linear latent and mixed models with the log link and binomial family and Cox proportional hazards models) that are planned to use while addressing each of the research objective.

The next chapters (chapter 4, chapter 5, and chapter 6) are designed to address the overall research objectives. Chapter 4 and chapter 5 are meant to identify predictors of stillbirth and factors associated with perinatal mortality in Nepal using GLLAMM that adjusted for clustering and sampling weights; whereas, chapter 6 is meant to identify factors associated with under-5 mortality in Nepal using Cox proportional hazards models

SECTION III: Factors associated with stillbirth and perinatal mortality in Nepal

This section presents two manuscripts titled "Socio-economic predictors of stillbirths in Nepal (2001-2011)" (https://doi.org/10.1371/journal.pone.0181332) and "Factors associated with perinatal mortality in Nepal: evidence from Nepal Demographic and Health Survey 2001-2016" (https://dx.doi.org/10.3390%2Fijerp).

CHAPTER 4: Socio-economic predictors of stillbirths in Nepal (2001-2011)

Ghimire PR, Agho KE, Renzaho AMN, Christou A, Nisha MK, Dibley M, Raynes-Greenow C. (https://doi.org/10.1371/journal.pone.01813322)

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RESEARCH ARTICLE

Socio-economic predictors of stillbirths in Nepal (2001-2011)

Pramesh Raj Ghimire[1]*, Kingsley Emwinyore Agho[1], Andre Renzaho[2], Aliki Christou[3], Monjura Khatun Nisha[3], Michael Dibley[3], Camille Raynes-Greenow[3]

1 School of Science and Health, Western Sydney University, Penrith, New South Wales, Australia, **2** School of Social Sciences and Psychology, Western Sydney University, Penrith, New South Wales, Australia, **3** Sydney School of Public Health, University of Sydney, Sydney, New South Wales, Australia

* prameshraj@hotmail.com

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Abstract

Introduction

Stillbirth has a long-lasting impact on parents and families. This study examined socio-economic predictors associated with stillbirth in Nepal for the year 2001, 2006 and 2011.

Methods

The Nepalese Demographic and Health Survey (NDHS) data for the period (2001–2011) were pooled to estimate socio-economic predictors associated with stillbirths in Nepal using binomial logistic regression while taking clustering and sampling weights into account.

Results

A total of 18,386 pregnancies of at least 28 weeks gestation were identified. Of these pregnancies, 335 stillbirths were reported. Stillbirth increased significantly among women that lived in the hills ecological zones (aRR 1.38, 95% CI 1.02, 1.87) or in the mountains ecological zones (aRR 1.71, 95% CI 1.10, 2.66). Women with no schooling (aRR 1.72, 95% CI 1.10, 2.69), women with primary education (aRR 1.81, 95% CI 1.11, 2.97); open defecation (aRR 1.48, 95% CI 1.00, 2.18), and those whose major occupation was agriculture (aRR 1.80, 95% CI 1.16, 2.78) are more likely to report higher stillbirth.

Conclusions

Low levels of education, ecological zones and open defecation were found to be strong predictors of stillbirth. Access to antenatal care services and skilled birth attendants for women in the mountainous and hilly ecological zones of Nepal is needed to further reduce stillbirth and improved services should also focus on women with low levels of education.

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Competing interests: The authors have declared that no competing interests exist.

Introduction

Stillbirth refers to the birth of a baby with no signs of life at or after 28 weeks' gestation[1]. Globally, stillbirth is a major public health problem, with more than 2.7 million stillbirths occurring annually; of these, 98% are from developing countries[2]. Sub-Sahara Africa and South Asia account for the highest numbers of stillbirth[3]. The long-lasting impact of stillbirth remains a large burden for parents, families, policy makers and public health practitioners[4]. Evidence has shown that stillbirth is associated with physical and psychological morbidity, and remains a significant source of cost for the affected family and community [2, 5, 6]. Despite the huge burden of stillbirth on families and global health, progress made in low-middle-income countries to reduce stillbirth is considerably slower than the decline in child mortality[3].

Stillbirth rates vary within and between countries; with economically disadvantaged communities having higher rates compared to their economically well-off counterparts [3, 7]. In developing countries, the major risk factors for stillbirth include advanced maternal age, maternal educational status, infections, fetal development, environmental hazards, diabetes, malaria and umbilical cord complications [8–11]. Recent studies from developed countries (such as the United Kingdom and Sweden) have also reported that psychological issues are associated with higher stillbirth rates [12, 13].

The major causes and predictors of stillbirth in South Asia are not well understood because of the huge variation in data availability and quality that underestimates the true number of stillbirths[5]. Recent case-control studies [14, 15] conducted in Nepal found that stillbirth is associated with older maternal age, lower level of maternal education, coming from the poorest households, inadequate antenatal care and antepartum haemorrhage. Similarly, a verbal autopsy study conducted in Nepal revealed that obstetric complications which included prolonged labour, antepartum haemorrhage and pregnancy induced hypertension were associated with stillbirth[16]. A community-based study from a rural area of Nepal found that a history of prior child loss, maternal age above 30 years and low socio-economic status were associated with higher stillbirth rates [17].

The 2011 Lancet series on stillbirths suggested that for better estimation and intervention, the epidemiology of stillbirths should be at a country level instead of at the regional level because of the regional variations[4]. A major limitation of these Nepalese studies is that the findings cannot be used to inform initiatives and policy responses at the national level because the samples do not represent geographically diverse population across the country. Hence, the aim of this study was to provide nationally representative evidence on the socio-economic predictors associated with stillbirths in Nepal, using pooled data from the 2001, 2006 and 2011 Nepal Demographic and Health Surveys (NDHS). Findings from this study would enable public health professionals to inform different policies and programmes to reduce stillbirth, with subsequent improvements in maternal and newborn outcomes in Nepal.

Methods

Data sources

The NDHS is nationally representative, collected by the Nepalese Ministry of Health and Population, in collaboration with New ERA and ICF International, USA using a multi-stage cluster sampling design. Data on fertility, mortality, family planning, and important aspects of nutrition, health, and health services were collected for the years 2001, 2006 and 2011 using standard model questionnaires designed for, and widely used in developing countries[18–20]. For the 2001 NDHS, 8726 women aged 15–49 were interviewed, of these 7089 pregnancies were

7+ months' gestation. Similarly in the 2006 NDHS, 10,793 women aged 15–49 years were interviewed. Of these, 5921 pregnancies were 7+ months' gestation. In the 2011 NDHS, 12,674 women aged 15–49 years were interviewed; of which 5376 reported pregnancies 7+ months' gestation. A total sample of 18,386 pregnancies 7+ months' gestation five year prior each survey was included in the final analysis. For the year 2006 and 2011, pregnancies were identified using calendar information such as pregnancy outcomes and duration of pregnancy; whereas for the year 2001, pregnancies were identified using information such as pregnancy history index, and outcome and duration of pregnancy. Further detail of the survey methodology, sampling procedure, and questionnaires are reported elsewhere[18–20]. In all surveys, the response was more than 98%.

Study outcome

The outcome variable was stillbirth, defined as the birth of a baby with no signs of life at or after 28 weeks' gestation[1]. The outcome was recorded as a binary variable in the data set coded as 1 for 'stillbirth' and 0 for 'Alive at birth'. Information on stillbirth was obtained using reproductive calendar (for 2006 and 2011 NDHS); and pregnancy history and outcome of pregnancies (for 2001 NDHS).

Exploratory variables

The exploratory variables selected for this study were based on previous studies from developing countries [8, 14, 16, 21–23] and the information available in the pooled data sets.

Fig 1 presented the modified Mosley and Chen [24] conceptual framework which comprise four groups of variables used in this study: community level factors, socio-economic level factors, maternal factor and environmental factors. The community level factors assessed included ecological zone (terai, hill and mountain), Geographical region (Eastern, Central, Western,

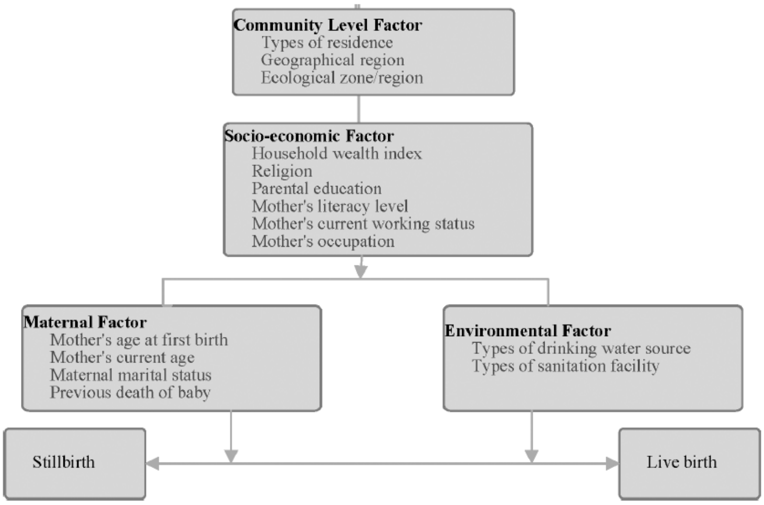

Fig 1. Conceptual framework of socio-economic predictors of stillbirth in Nepal.

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Mid-Western and Far-Western) and place of residence (rural or urban). The socio-economic level factors considered were maternal education, literacy level, occupation (categorised as not working or working in agricultural or working in non-agricultural sector), paternal education, mother's current work status and household wealth index. The household wealth index measures the economic status of the household. As a measure of household wealth index, we pooled the wealth index factor scores in each of the three original Individual Recode data files as calculated by original DHS. The pooled original household wealth index factor scores were then categorised into three: the bottom, 40% of households was referred to as poor households, the next 40% as the middle households and the top 20% as rich households[25].

Maternal factors encompass maternal age at first birth, previous death of a baby, mother's current age and maternal marital status. We also considered environmental factors consisting of drinking water source and types of sanitation facility for each household classified based on the WHO and UNICEF Joint Monitoring Program (JMP) guidelines[26]. Based on JMP guidelines, we categorized sources of drinking water as: piped water on premises (piped water system into dwelling), other improved drinking water sources (neighbours tap or tubewell, tubewell or borehole in yard, stone tap, protected well and rainwater), unimproved water sources (unprotected well in house, unprotected public or neighbour's well, unprotected spring, bottled water and water from tanker or truck) and surface drinking water sources (river, stream, pond, lake, dam, canal, or irrigation water). Similarly, we categorized types of sanitation facility as improved and unimproved. Improved sanitation facilities included (households with flush toilet, ventilated or improved pit latrine, pit latrine with slab and composting toilet). Unimproved sanitation facilities were traditional pit toilet, pit latrine without slab or open pit and bucket toilet and open defecation (bush or field for defecation).

Statistical analysis

Frequency tabulations were first conducted to describe the frequency and relative frequency of all potential confounding factors. This was followed by calculating the stillbirth rate and 95% confidence interval, using 'the number of stillbirths divided by the number of live births multiplied by 1,000'.

Generalized linear latent and mixed models (GLLAM) with the log link and binomial family[27] that adjusted for cluster and survey weights were used to identify those socio-economic predictors associated with stillbirth. A staged modelling technique[28] was adopted. Community-level factors were first entered into the baseline multivariable model with manual backward elimination process to keep statistically significant variables with p-value <0.05 (model 1). Second, socio-economic factors were added into community-level factors associated with outcome variable and those factors with p-values < 0.05 were retained after backward elimination process was conducted (model 2). Third, maternal factors were added into model 2. After applying similar approach as above, variables with p-values < 0.05 were retained in the next model (model 3). In the final stage, environmental factors were assessed with a list of significant variables from model 3. Variables with p-values < 0.05 were retained in the final model (model 4). Only those factors significantly associated with stillbirth at a 5% significance level in the final model were reported in the study. In the final model, collinearity was tested and reported. The analysis was restricted to five years preceding each of the survey.

A total of 57 missing values were excluded from the multivariate analysis, and GLLAM estimates were translated to relative risk and 95% confidence interval. All analyses were performed using STATA statistical software, version 14.1 (Stata Corporation, College Station, TX, USA) with 'Svy' commands to allow for adjustments for sampling weights and cluster sampling design.

Ethics

The DHS project obtained ethical approval from the Nepal Health Research Council-Kathmandu. The first author communicated with MEASURE DHS/ ICF International and permission was granted to download and use the data for his doctoral dissertation with the School of Science and Health at Western Sydney University, Australia.

Results

Basic characteristics of the study participants

The majority of mothers who reported higher rates of stillbirth were from rural and mountainous areas, poor households, parents with low levels of education, households with unimproved sources of drinking water and unimproved toilet facilities (sanitation) (Table 1). We also noted that mothers whose major occupation was agriculture had more stillbirths compared to those mothers who worked in non-agricultural sectors.

The prevalence of stillbirth across three ecological zones indicates that the rate was 28 per 1000 amongst mothers who resided in the mountains whereas this rate was 17 per 1000 in the terai, and 19 per 1000 in the hills (Fig 2).

Predictors of stillbirth

The univariate analyses revealed that ecological zone (mountains or hills); religion (Muslim, Christian and others); mother's literacy (illiterate); parental level of education (primary education or no schooling), currently not working mothers, mother's whose major occupation was agriculture, mother's age (25 years and above at the time of the first birth), types of drinking water source (surface drinking water sources) and types of sanitation facility (unimproved sanitation facility or open defecation) were all significantly associated with higher stillbirth (Table 2).

Multivariable analysis revealed that factors associated with stillbirth were mothers in the age bracket (>25years), mothers who lived in mountains or hills, mothers whose religion was Hindu, Muslim, Christian and others, mothers who had no schooling or only primary level of education. Further we found that mothers whose major occupation was agriculture and those who used open defecation reported higher stillbirth.

In the final model, we removed maternal education level and replaced it with father's education level; the result indicated that stillbirth increased significantly among fathers with no schooling (aRR 1.71, 95% CI 1.10, 2.64).

Discussion

This study reports the predictors associated with stillbirths in Nepal by using pooling the three most recent Nepal demographic and Health survey and found that maternal age (25 years and over), low levels of education, sanitation and ecological zones were predictors for stillbirth. Additionally, when mother education was replaced by father education in the final model, father with no education reported significantly higher stillbirth. This current study provides an evidence-base that could be used to inform the design of effective interventions, policies and programmes aimed at health professionals and individuals recognising stillbirths.

Primiparity is an established risk factor for stillbirth in both high and low income countries [29], and our results also found this association. This study demonstrated that mothers aged 25 years and above at the time of their first birth were more likely to experience stillbirth. This finding was supported by case-control studies conducted in Nepal, Bangladesh and Canada, which indicated that older mothers (35 years and above) significantly reported higher stillbirth

Table 1. Characteristics of study population as weighted counts and stillbirth, with rates with 95% confidence interval in Nepal: 2001, 2006 and 2011 (N = 18249).

Study variables	N	Stillbirth (n)	Rate (95% CI)
Type of residence			
Urban	1656	27	17(10.3 to 22.8)
Rural	16593	308	19(16.8 to 21.0)
Ecological zone			
Terai	9358	154	17(14.1 to 19.4)
Hill	7405	141	19(16.2 to 22.6)
Mountain	1487	41	28(19.7 to 37.1)
Geographical region			
Eastern	4154	75	18(14.2 to 22.5)
Central	5936	98	17(13.5 to 20.1)
Western	3363	62	19(14.1 to 23.5)
Mid-western	2596	53	21(15.2 to 26.5)
Far-western	2201	47	22(15.6 to 28.1)
Wealth index			
Rich	3615	48	13(9.5 to 17.0)
Middle	7595	163	21(18.2 to 24.8)
Poor	7040	124	18(14.5 to 20.7)
Religion			
Hindu	15288	16	12(6.0 to 17.4)
Buddhist	1385	288	19(17.0 to 21.4)
Others	1576	32	21(13.5 to 27.9)
Mother education			
Secondary or higher	3833	46	12(8.6 to 15.7)
Primary	3122	63	21(15.5 to 25.7)
No education	11295	227	21(17.8 to 23.2)
Mother's literacy level (N = 18228)			
Can read	8096	126	16(13.0 to 18.6)
Cannot read	10133	210	21(18.3 to 24.0)
Father's education			
Secondary or higher	3386	40	12(8.2 to 15.7)
Primary	6463	113	18(14.5 to 21.1)
No schooling	8400	182	22(18.9 to 25.4)
Mother current working status			
Not working	5470	72	13(10.3 to16.4)
Currently Working	12779	263	21(18.5 to 23.6)
Mother occupation (N = 18247)			
Not working	3834	46	12(8.6 to 15.7)
Agriculture	12849	271	22(19.0 to 24.1)
Non- agriculture	1565	18	12(6.3 to 17.0)
Mother's age at first birth in years (N = 18191)			
<18	8043	106	13(10.7 to 19.0)
19–24	9036	148	16(13.7 to19.0)
25+	1112	23	21(12.2 to29.1)
Mother current age			
20–29	11643	201	18(15.1 to 20.0)
<20	1198	22	19(10.9 to 26.5)

(*Continued*)

Table 1. (*Continued*)

Study variables	N	Stillbirth (n)	Rate (95% CI)
30–39	4527	94	21(16.9 to 25.5)
40–49	882	17	20(10.3 to 29.0)
Maternal marital status			
Currently married	18069	332	19(16.7 to 20.7)
Not currently married	180	4	23(0.5 to 45.0)
Previous death of baby			
No	13457	254	19(16.9 to 21.6)
Yes	4793	82	17(13.6 to 21.2)
Types of drinking water source (N = 17092)			
Piped water on premises	1843	26	14(8.7 to 19.5)
Other improved drinking water sources	12012	205	17(14.7 t019.4)
Unimproved drinking water sources	1203	26	22(13.3 to29.9)
Surface drinking water sources	2035	53	26(19.0 to33.1)
Types of sanitation facility (N = 17093)			
Improved sanitation facilities	4337	50	12(8.3 to14.7)
Unimproved sanitation facilities	1859	36	19(13.0 to 25.7)
Open defecation	10898	224	21(17.9 to23.2)

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than younger mothers [14, 22, 30]. Similarly, a hospital-based study conducted in Nigeria also revealed that mothers aged 35 years or older were significantly more likely to report higher rate of stillbirths[31]. Studies conducted in high-income countries showed a significant relationship between stillbirth and maternal age [7, 32–35]. Higher stillbirth rate in older women has been attributed to the increase likelihood of congenital anomalies, chronic hypertension, placenta praevia, uterine rupture, and breech deliveries in older mothers which may contribute to an increased fetal death [36–39]. Studies have also shown that advanced maternal age has been associated with an increased risk of abnormal chromosomes, and or decreasing uterine and hormonal function[40, 41].

Parental education is considered as one of the important determinants of health. Previous studies from Pakistan and Bangladesh reported that education could increase the uptake of

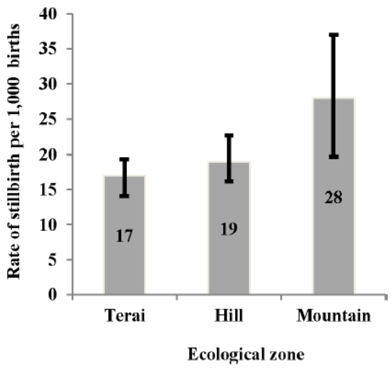

Fig 2. Pooled stillbirth rate by ecological zone in Nepal, 2001–2011.

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Table 2. Crude and adjusted Relative Risk (RR) for socio-demographic predictors of stillbirths in Nepal, 2001–2011 (N = 18249).

Study variables	Unadjusted		Adjusted	
	RR (95% CI)	P-value	RR (95% CI)	P-value
Type of residence				
Urban	Reference			
Rural	1.07 (0.71, 1.61)	0.738		
Ecological zone				
Terai	Reference		Reference	
Hill	1.17(0.90, 1.51)	0.241	1.37(1.02, 1.84)	0.036
Mountain	1.71(1.16, 2.52)	0.006	1.68(1.09, 2.59)	0.018
Geographical region				
Eastern	Reference			
Central	0.88(0.63, 1.25)	0.478		
Western	1.01(0.69, 1.48)	0.956		
Mid-western	1.11(0.74, 1.65)	0.621		
Far-western	1.17(0.77, 1.77)	0.459		
Wealth index				
Rich	Reference			
Middle	1.56(1.12, 2.17)	0.009		
Poor	1.28(0.91, 1.80)	0.156		
Religion				
Buddhist	Reference		Reference	
Hindu	1.64(0.97, 2.76)	0.062	2.19(1.19, 4.04)	0.012
Others including Muslim and Christian	1.87(1.00, 3.50)	0.05	2.68(1.29, 5.58)	0.008
Mother education				
Secondary or higher	Reference		Reference	
Primary	1.67(1.14, 2.45)	0.009	1.80(1.10, 2.93)	0.019
No schooling	1.65(1.20, 2.28)	0.002	1.71(1.09, 2.66)	0.019
Mother's literacy level				
Can read part or whole of the sentence	Reference			
Cannot read	1.31(1.05, 1.65)	0.018		
Father's education				
Secondary or higher	Reference			
Primary	1.47(1.02, 2.12)	0.036		
No schooling	1.83(1.30, 2.59)	0.001		
Mother current working status				
Not working	Reference			
Currently working	1.54(1.18, 2.01)	0.002		
Mother occupation				
Not working	Reference		Reference	
Agriculture	1.70(1.24, 2.34)	0.001	1.78(1.16, 2.75)	0.009
Non- Agriculture	0.99(0.57, 1.70)	0.964	1.38(0.72, 2.63)	0.328
Mother's age at first birth				
<18	Reference		Reference	
19–24	1.23(0.95, 1.58)	0.109	1.20(0.93, 1.56)	0.186
>25	1.59(1.00, 2.50)	0.046	1.77(1.12, 2.82)	0.015
Mother current age				
<20	Reference			
20–29	1.10(0.71, 1.70)	0.675		

(*Continued*)

Table 2. (*Continued*)

Study variables	Unadjusted		Adjusted	
	RR (95% CI)	P-value	RR (95% CI)	P-value
30–39	1.18(0.92, 1.51)	0.180		
40–49	1.15(0.70, 1.88)	0.590		
Maternal marital status				
Currently married	Reference			
Not currently married	1.20(0.44, 3.28)	0.720		
Previous death of baby				
No	Reference			
Yes	0.88(0.69, 1.14)	0.332		
Types of drinking water source				
Piped water on premises	Reference			
Other improved drinking water sources	1,21(0.80, 1.84)	0.371		
Unimproved drinking water sources	1.53(0.88, 2.65)	0.135		
Surface drinking water sources	1.81(1.12, 2.94)	0.016		
Types of sanitation facility				
Improved sanitation facilities	Reference		Reference	
Unimproved sanitation facilities	1.57(1.01, 2.43)	0.044	1.10(0.67, 1.82)	0.697
Open defecation	1.76(1.29, 2.41)	<0.001	1.47(1.00, 2.16)	0.049

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health service utilization [42, 43] with subsequent reduction in stillbirth. This study found that women with only primary level of education or no schooling had higher risk of stillbirth compared to those who had secondary or higher levels of education. There are very few studies from developing countries that have examined the relationship between maternal education and stillbirth. A study conducted in a province of Thailand revealed women who had low levels of education were at a higher risk of having stillbirths[44]. This finding is also consistent with previous studies from Canada and Denmark, which found that lower level of maternal education was associated with higher risk of stillbirths [45–47]. Plausible reasons for this finding may be that educated mothers are more likely to practice healthy behaviours, including health seeking, which may contribute to reducing their risk of stillbirth compared to mothers with no education. Likewise, fathers with no schooling were also associated with higher risk of stillbirth.

Our study demonstrated that the risk of stillbirth was significantly higher among women who worked in an agricultural sector, similar to a finding from a hospital-based case-control study conducted in the Nguyen province of Vietnam[44]. Our finding of higher risk of stillbirth among mothers residing in the high altitude mountains or hills was similar to a retrospective births record obtained from four regional centres in Peru, which indicated that after controlling for potential confounding factors, mothers who lived in high altitude (greater than 3000 meters) were significantly more likely to report higher stillbirths than those mothers that lived in low altitude [48]. Whether our finding is related to altitude or access to antenatal and birth service is unknown due to the limitations of the DHS data. However, literature has shown that management of pregnancy complications through quality antenatal care[49] and provision of skilled birth attendance around labour time[4] help to prevent stillbirth. Based on these evidences, it can be argued that the focused antenatal care as well as targeted skilled birth attendance for women residing in the mountainous region would help to reduce the number of stillbirth.

Our study also found an association between stillbirth and mothers religious affiliation. Mothers whose religion was Hindu and others including Muslim and Christian reported significantly higher stillbirth compared to those mothers whose religion was Buddhist. Analysis [50] conducted in India using the National Family Health Survey (NFH) reported differences in child mortality based on religious affiliation. In Nepal access and utilization of birthing services differs by religious affiliation and this may contribute to the increased stillbirth in some religious groups[51].

Unimproved water and sanitation contributes 0.9% to the global Disability Adjusted Live Years [52]. It is not surprising that women who reported open defecation were at greater risk of stillbirth compared to mothers who reported improved sanitation facilities; similar with the finding from a population-based prospective cohort study conducted in India that revealed open defecation among pregnant women was associated with adverse pregnancy outcomes [53].

The study has a number of strengths. Firstly, the analysis was based on nationally representative data (NDHS); thus, estimates from this study are generalizable to the Nepalese population and can inform national policies and initiatives in Nepal. Secondly, the response to the surveys was high (>98%), reducing a likely chance of selection bias from the observed findings. Thirdly, measurement bias is unlikely to affect the observed results as the data were collected using a standardised questionnaire developed for developing countries including Nepal [18–20]. It is however retrospective data, and there may be some bias in reporting stillbirth. Despite these advantages, this study is limited in a number of ways. Firstly, the diagnosis of stillbirth was based on self-report from mother and is subject to recall and misclassification bias. Secondly, formal verbal autopsies were not conducted on stillbirths. Finally, no information on health services factors or other factors such as tobacco, gestational diabetes and genetic abnormality that may have been associated with stillbirth were included in the NDHS data.

Policy implications

To close the equity gaps, community-based interventions need to be formulated and implemented in order to improve maternal and child health in Nepal. At the individual level intervention, uptake and quality of antenatal care should be encouraged among mothers from low socio-economic group and those mothers from hilly and mountainous ecological zones. At the community level intervention, increase awareness and access to basic and emergency obstetric care to women from hilly and mountainous ecological zones. These interventions will improve prevention strategies that could have massive and far-reaching improvement on Nepalese mothers and children in order for the country to accelerate progress towards achievement of ending preventable stillbirths by 2035[54].

Conclusions

Our findings suggest that antenatal care service should be targeted to women from low socio-economic status and those who lived in the mountainous ecological zone in order for Nepal to further reduce the rate of stillbirth to a target of 12 stillbirths per 1000 births by the year 2030.

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Author Contributions

Conceptualization: Pramesh Raj Ghimire, Kingsley Emwinyore Agho.

Formal analysis: Pramesh Raj Ghimire.

Methodology: Pramesh Raj Ghimire.

Supervision: Kingsley Emwinyore Agho, Andre Renzaho.

Writing – original draft: Pramesh Raj Ghimire.

Writing – review & editing: Kingsley Emwinyore Agho, Andre Renzaho, Aliki Christou, Monjura Khatun Nisha, Michael Dibley, Camille Raynes-Greenow.

References

1. World health Organization. Maternal, newborn, child and adolescent health, 2015. Available from: http://www.who.int/maternal_child_adolescent/epidemiology/stillbirth/en/.
2. De Bernis L, Kinney MV, Stones W, Ten Hoope-Bender P, Vivio D, Leisher SH, et al. Stillbirths: ending preventable deaths by 2030. The Lancet. 2016 Jan 18; 387: 703–716.
3. Lawn JE, Blencowe H, Waiswa P, Amouzou A, Mathers C, Hogan D, et al. Stillbirths: rates, risk factors, and acceleration towards 2030. The Lancet. 2016 Jan 18; 387: 587–603.
4. Lawn JE, Blencowe H, Pattinson R, Cousens S, Kumar R, Ibiebele I, et al. Stillbirths: Where? When? Why? How to make the data count? The Lancet. 2011 Apr 14; 377: 1448–1463.
5. Cousens S, Blencowe H, Stanton C, Chou D, Ahmed S, Steinhardt L, et al. National, regional, and worldwide estimates of stillbirth rates in 2009 with trends since 1995: a systematic analysis. The Lancet. 2011 Apr 14; 377:1319–1330.
6. Mullan Z, Horton R. Bringing stillbirths out of the shadows. The Lancet. 2011 Apr 14; 377: 1291–1292.
7. Gordon A, Raynes-Greenow C, McGeechan K, Morris J, Jeffery H. Risk factors for antepartum stillbirth and the influence of maternal age in New South Wales Australia: a population based study. BMC pregnancy and childbirth. 2013; 13:12. https://doi.org/10.1186/1471-2393-13-12 PMID: 23324309
8. McClure EM, Pasha O, Goudar SS, Chomba E, Garces NA Tshefu A, et al. Epidemiology of stillbirth in low-middle income countries: a Global Network Study. Acta obstetricia et gynecologica Scandinavica. 2011; 90: 1379–1385. https://doi.org/10.1111/j.1600-0412.2011.01275.x PMID: 21916854
9. McClure EM, Nalubamba-Phiri M, Goldenberg RL. Stillbirth in developing countries. International Journal of Gynecology & Obstetrics. 2006 May 30; 94: 82–90.
10. Goldenberg RL, McClure EM, Saleem S, Reddy UM. Infection-related stillbirths. The Lancet. 2010 Mar 10; 375: 1482–1490.
11. Aminu M, Unkels R, Mdegela M, Utz B, Adaji S, Den Broke N. Causes of and factors associated with stillbirth in low-and middle-income countries: a systematic literature review. An International Journal of Obstetrics & Gynaecology. 2014 Sep 18; 121: 141–153.
12. Turton P, Evans C, Hughes P. Long-term psychosocial sequelae of stillbirth: Phase II of a nested case-control cohort study. Archives of women's mental health. 2009 Jan 10; 12: 35–41. https://doi.org/10.1007/s00737-008-0040-7 PMID: 19137447
13. Radestad I, Steineck G, Nordin C, Sjogren B. Psychological complications after stillbirth—influence of memories and immediate management: population based study. BMJ. 1996 Jun 15; 312: 1505–1508. PMID: 8646141
14. Ashish KC, Nelin V, Wrammert J, Ewald U, Vitrakoti R, Baral GN, et al. Risk factors for antepartum stillbirth: a case-control study in Nepal. BMC Pregnancy Childbirth. 2015 Jul 5; 15: 146. https://doi.org/10.1186/s12884-015-0567-3 PMID: 26143456
15. Ashish KC, Wrammert J, Ewald U, Clark RB, Gautam J, Baral G, et al. Incidence of intrapartum stillbirth and associated risk factors in tertiary care setting of Nepal: a case-control study in Nepal. Reproductive Health. 2016 Aug 31; 13:1. https://doi.org/10.1186/s12978-016-0226-9

16. Manandhar SR, Ojha A, Manandhar DS, Shrestha B, Shrestha D, Saville N, et al. Causes of stillbirths and neonatal deaths in Dhanusha district, Nepal: a verbal autopsy study. University Medical Journal. 2010; 8: 62–72.
17. Lee AC, Mullany LC, Tielsch JM, Katz J, Khatry SK, LeClerg SC, et al. Community-based stillbirth rates and risk factors in rural Sarlahi, Nepal. International Journal of Gynecology & Obstetrics. 2011; 113: 199–204.
18. Ministry of Health [Nepal], New ERA, and ORC Macro. 2002. Nepal Demographic and Health Survey 2001. Calverton, Maryland, USA: Family Health Division, Ministry of Health; New ERA; and ORC Macro.
19. Ministry of Health and Population (MOHP) [Nepal], New ERA, and Macro International Inc. 2007. Nepal Demographic and Health Survey 2006. Kathmandu, Nepal: Ministry of Health and Population, New ERA, and Macro International Inc.
20. Ministry of Health and Population (MOHP) [Nepal], New ERA, and ICF International Inc. 2012. Nepal Demographic and Health Survey 2011. Kathmandu, Nepal: Ministry of Health and Population, New ERA, and ICF International, Calverton, Maryland.
21. Cherry N, Shaikh K, McDonald C, Chowdhury Z. Stillbirth in rural Bangladesh: arsenic exposure and other etiological factors: a report from Gonoshasthaya Kendra. Bulletin of the World Health Organization. 2008 Jan 25; 86: 172–177. https://doi.org/10.2471/BLT.07.043083 PMID: 18368203
22. Nahar S, Rahman A, Nasreen HE. Factors influencing stillbirth in Bangladesh: a case-control study. Paediatric Perinatal Epidemiology. 2013; 27: 158–164. https://doi.org/10.1111/ppe.12026 PMID: 23374060
23. Kumar R, Singhi S. Risk factors for stillbirths in a rural community. Indian Journal of Paediatrics. 1992 Jul; 59: 455–461.
24. Mosley WH, Chen LC. An analytical framework for the study of child survival in developing countries. Population and development review. 1984 10: 25–45.
25. UNICEF. Childhood under threat: the state of the world's children. 2004
26. World Health Organization. Progress on sanitation and drinking water: 2015 update and MDG Assessment. World Health Organization, Geneva, Switzerland; 2015
27. Skrondal A, Rabe-Hesketh S. Generalized latent variable modeling: Multilevel, longitudinal, and structural equation models, Crc Press; 2004.
28. Victora CG, Huttly SR, Fuchs SC, Olinto MT. The role of conceptual frameworks in epidemiological analysis: a hierarchical approach. International journal of epidemiology. 1997 Feb 1; 26: 224–227. PMID: 9126524
29. Flenady V, Koopmans L, Middleton P, Froen JF, Smith GC, Gibbons K, et al. Major risk factors for stillbirth in high income countries: a systematic review and meta-analysis. The lancet. 2011 Apr 14; 377: 1331–1340.
30. Dodds L, King WD, Fell DB, Armson BA, Allen A Nimrod K. Stillbirth risk factors according to timing of exposure. Annals of epidemiology. 2006 Aug; 16: 607–613. https://doi.org/10.1016/j.annepidem.2005.11.006 PMID: 16431134
31. Suleiman BM, Ibrahim HM, Abdulkarim N. Determinants of stillbirths in katsina, Nigeria: a hospital-based study. Paediatric reports. 2015; 7: 5615. https://doi.org/10.4081/pr.2015.5615 PMID: 25918622
32. Naeye RL. Maternal Age, Obstetric Complications, and the Outcome of Pregnancy. Obstetrics & Gynecology. 1983 Feb; 61: 210–216.
33. Forman MR, Meirik O, Berendes HW. Delayed childbearing in Sweden. Jama. 1984 Dec 14; 252: 3135–3139. PMID: 6502882
34. Leyland AH, Boddy FA. Maternal age and outcome of pregnancy. New England Journal Medicine. 1990 Aug 9; 323: 413–416.
35. Cnattingius S, Forman MR, Berendes HW, Isotalo L. Delayed childbearing and risk of adverse perinatal outcome: a population-based study. Jama. 1992 Aug 19; 268: 886–890. PMID: 1640617
36. Biggs J. Pregnancy at 40 years and over. Obstetrical & Gynecological Survey. 1973 Oct 1; 28: 710–711.
37. Booth RT, Williams GL. Elderly primigravidae. An International Journal of Obstetrics & Gynaecology. 1964 Apr 1; 71: 249–254.
38. Kajanoja P, Widholm O. Pregnancy and delivery in women aged 40 and over. Obstetrics & Gynecology. 1978 Jan; 51: 47–51.
39. Naeye RL. The duration of maternal cigarette smoking, fetal and placental disorders. Early Human Development. 1979 Sep; 3: 229–237. PMID: 527525

40. Hassold T, Chiu D. Maternal age-specific rates of numerical chromosome abnormalities with special reference to trisomy. Human genetics. 1985 May; 70: 11–17. PMID: 3997148
41. Cano F, Simon C, Remohi J, Pellicer A. Effect of aging on the female reproductive system: evidence for a role of uterine senescence in the decline in female fecundity. Fertility and sterility. 1995 Sep 30; 64: 584–589. PMID: 7543864
42. Shaikh BT, Hatcher J. Health seeking behaviour and health service utilization in Pakistan: challenging the policy makers. Journal of public health. 2005 Mar; 27: 49–54. https://doi.org/10.1093/pubmed/fdh207 PMID: 15590705
43. Chakraborty N, Islam MA, Chowdhury RI, Bari W, Akhter HH. Determinants of the use of maternal health services in rural Bangladesh. Health promotion international. 2003 Dec 1; 18: 327–337. PMID: 14695364
44. Cripe SM, Phung T, Nguyen T, Williams MA. Risk factors associated with stillbirth in Thai Nguyen Province, Vietnam. Journal of tropical paediatrics. 2007 Oct 1; 53: 366–367.
45. Auger N, Delezire P, Harper S, Platt RW. Maternal education and stillbirth: Estimating gestational-age-specific and cause-specific associations. Epidemiology. 2012 Mar; 23: 247–254. https://doi.org/10.1097/EDE.0b013e31824587bc PMID: 22266894
46. Luo ZC, Wilkins R, Kramer MS. Effect of neighbourhood income and maternal education on birth outcomes: a population-based study. Canadian Medical Association Journal. 2006 May 9; 174: 1415–1420. https://doi.org/10.1503/cmaj.051096 PMID: 16682708
47. Olsen O, Madsen M. Effects of maternal education on infant mortality and stillbirths in Denmark. Scandinavian Journal of Public Health. 1999 Jun 16; 2: 128–136.
48. Gonzales GF, Tapia V, Carrillo CE. Stillbirth rates in Peruvian populations at high altitude. International Journal of Gynecology and Obstetrics. 2008 March; 100: 221–227. https://doi.org/10.1016/j.ijgo.2007.08.009 PMID: 17977541
49. Lawn JE, Lee CC, Kinney M, Sibley L, Carlo WA, Paul MK, et al. Two million intrapartum-related stillbirths and neonatal deaths: where, why, and what can be done? International Journal of Gynecology & Obstetrics. 2009 Oct; 107: S5–S19.
50. Guillot M, Allendorf K. Hindu-Muslim differentials in child mortality in India. Genus. 2010 May 1; 66: 43–68.
51. Thind A, Mohani A, Banerjee K, Hagigi F. Where to deliver? Analysis of choice of delivery location from a national survey in India. BMC Public Health. 2008 Jan 24; 8: 29. https://doi.org/10.1186/1471-2458-8-29 PMID: 18218093
52. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. The Lancet. 2012 Dec 15; 380: 2224–2260.
53. Padhi BK, Baker KK, Dutta A, Cumming O, Freeman MC, Satpathy R, et al. Risk of Adverse Pregnancy Outcomes among Women Practicing Poor Sanitation in Rural India: a Population-Based Prospective Cohort Study. Plos Medicine. 2015 Jul 7; 12: e1001851. https://doi.org/10.1371/journal.pmed.1001851 PMID: 26151447
54. World Health Organization. Every Newborn: An action plan to end preventable deaths. 2014

CHAPTER 5: Factors associated with perinatal mortality in Nepal: evidence from Nepal demographic and health survey 2001-2016

Ghimire PR, Agho KE, Renzaho, AMN, Nisha MK, Dibley M, Raynes-Greenow C.

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RESEARCH ARTICLE Open Access

Factors associated with perinatal mortality in Nepal: evidence from Nepal demographic and health survey 2001–2016

Pramesh Raj Ghimire[1*], Kingsley E. Agho[1], Andre M. N. Renzaho[2], Monjura K. Nisha[3], Michael Dibley[3] and Camille Raynes-Greenow[3]

Abstract

Background: Perinatal mortality is a devastating pregnancy outcome affecting millions of families in many low and middle-income countries including Nepal. This paper examined the more distant factors associated with perinatal mortality in Nepal.

Methods: A sample of 23,335 pregnancies > 28 weeks' gestation from the Nepal Demographic and Health Survey datasets for the period (2001–2016) was analysed. Perinatal Mortality (PM) is defined as the sum of stillbirth (fetal deaths in pregnancies > 28 weeks' gestation) and early neonatal mortality (deaths within the first week of life), while Extended Perinatal Mortality (EPM) is denoted as the sum of stillbirth and neonatal mortality (deaths within the first 28 days of life). Rates of PM and EPM were calculated. Logistic regression generalized linear latent and mixed models (GLLAMM) that adjusted for clustering and sampling weight was used to examine the factor associated with perinatal mortality.

Results: Over the study period, the PMR was 42 [95% Confidence Interval (CI): 39, 44] per 1000 births for the five-year before each survey; while corresponding EPMR was 49 (95% CI, 46, 51) per 1000 births. Multivariable analyses revealed that women residing in the mountains, who did not use contraceptives, women aged 15–18 years or 19–24 years, and women having no education were associated with increased PM and EPM. The study also identified households using biomass as cooking fuel, and households who reported unimproved sanitation or open defecation were significantly more likely to experience PM and EPM.

Conclusions: Interventions aimed to improve use of contraceptives, and reduce biomass as a source of cooking fuel are needed to achieve the recommended target of < 12 perinatal deaths per 1000 births by 2030.

Keywords: Perinatal mortality, Extended perinatal mortality, NDHS, Nepal

Background

Availability and quality of healthcare of both mother and newborn is reflected in the perinatal mortality rate, and perinatal mortality remains one of the devastating pregnancy outcomes for millions of families in low-and-middle-income countries including Nepal [1]. A recent Lancet systematic review for the Global Burden of Disease estimated that every year over 4 million perinatal deaths occur worldwide; and almost all (98%) of these deaths occur in low-and-middle-income countries, mostly in sub-Saharan Africa and South Asia, including Nepal [2]. The perinatal mortality rate is five times higher in low as compared to high income countries, with 10 deaths per 1000 total births in high income countries; 50 per 1000 total deaths in low and middle income countries and over 60 per 1000 in the most deprived countries [1].

In Asia, the perinatal mortality rate is estimated to be 50 per 1000 births, but as high as 65 per 1000 in South-central Asia, the third-highest rate among the sub-regions [1]. Past studies indicated that preterm birth, intrapartum complications and infections are the three leading causes of perinatal death [3], and millions

* Correspondence: prameshraj@hotmail.com
[1]School of Science and Health, Western Sydney University, Locked Bag1797, Penrith, NSW 2571, Australia
Full list of author information is available at the end of the article

of these deaths can be averted with high coverage quality interventions along with a population-specific action plan for women who are socially marginalized based on issues such as ethnicity, geography and socioeconomic status [4]. A case-control study conducted in Pakistan identified that maternal literacy, poor socio-economic household, primigravida, and lack of knowledge of family planning were associated with perinatal mortality [5]. Similarly, a population-based cross-sectional study conducted in Bangladesh that examined the impact of maternal excessive body weight on a range of maternal and child health outcomes reported that overweight and obesity among women aged 25 years and older increased the risk of perinatal mortality by 1.8 [95% Confidence Interval (1.5, 2.1)] [6].

Perinatal mortality rates play an increasingly important role in childhood mortality, and there are currently no effective community-based intervention programs in Nepal particularly targeting perinatal mortality including stillbirth. Despite the high burden of perinatal mortality globally, there have been very limited epidemiological studies that examine potential factors associated with perinatal mortality in Nepal. Previous studies conducted in Eastern and Central districts of Nepal found that birth asphyxia, infection, and prematurity were the major causes of stillbirth and neonatal mortality [7, 8]. A multi-centre prospective study conducted in the Jhapa and Kathmandu districts revealed that higher parity (> 4), low birthweight (< 1999 g) and older maternal age (≥35 years) were reported to be associated with PM [9]. In contrast, a cross-sectional study conducted in central Nepal found that teenage women were more likely to report higher perinatal mortality [10]. Similarly, another prospective study conducted in Kathmandu concluded that perinatal mortality occurred more frequently among primigravid women, and those having preterm birth reported a higher risk of perinatal mortality [11]. However, the external validity of these studies was limited because they were not population-based, hence may not be generalised to inform effective interventional policy that will significantly reduce perinatal death. The Nepal Demographic and Health Survey (NDHS) dataset provides an opportunity to examine factors associated with perinatal mortality using a population-based sample. Using a national population-based sample will allow the formulation of an integrated policy and programmatic response to address perinatal mortality in Nepal.

The main aim of this study was to determine more distant factors associated with Perinatal Mortality (PM) and Extended Perinatal Mortality (EPM) by using the four most recent nationally representative household data of NDHS for the years 2001, 2006, 2011, and 2016.

Methods

Data sources and sample

This study combined data of NDHS for the years 2001 [12], 2006 [13], 2011 [14] and 2016 [15]; which were nationally representative household surveys, using multistage cluster sampling designs, stratified by geographical regions and urban and rural areas. All four surveys sampling methods were similar and routinely collected with the objective of estimating socio-demographic; and maternal and child health indicators at national and district level.

A total of 32,193 women aged 15–49 years were interviewed in the four surveys (8726 women in 2001 NDHS, 10,793 women in 2006 NDHS, 12,674 women in 2011 NDHS, and 12,862 in 2016 NDHS), with the average response rate over 97%. In the 2001 NDHS [12] women were asked to report all pregnancies they had in their lifetime records of pregnancy loss and the duration of such pregnancies included; whereas in the 2006 NDHS [13], the 2011 NDHS [14], and the 2016 NDHS [15] women were asked to report on any pregnancy loss and the duration of such pregnancy that occurred five years preceding the surveys. Information such as pregnancy, pregnancy loss and duration of pregnancy was used to identify the number of livebirth, stillbirth and pregnancies > 28 weeks' gestation. For this study 23,335 pregnancies > 28 weeks' gestation were identified ($N = 7134$ in 2001, $N = 5671$ in 2006, $N = 5444$ in 2011, and $N = 5086$ in 2016). Details of the survey methodology, sampling procedures, and questionnaires are provided in the respective NDHS reports [12–15].

Outcome

Outcome variables for this study were: (I) Perinatal Mortality (PM) defined as the sum of stillbirth (fetal deaths in pregnancies > 28 weeks' gestation) and early neonatal mortality (deaths within the first week of life) [12–15], and (II) Extended Perinatal Mortality (EPM) defined as the sum of stillbirth and neonatal mortality (deaths within the first 28 days of life) [12–16].

Potential explanatory variables

The selection of potential explanatory variables for this study was based on past studies that have examined factors associated with perinatal mortality in different low-and middle-income countries [9, 17–19]. We also adopted Mosley and Chen's analytical framework for the study of child survival in low income countries [20]. Figure 1 illustrates the factors used to examine their relation with PM and EPM in that framework. Based on Mosley and Chen's framework, 19 explanatory variables were classified into five categories as community level factors (types of residence and ecological zone); socioeconomic factors (wealth index, religion, mother's education, mother's literacy level,

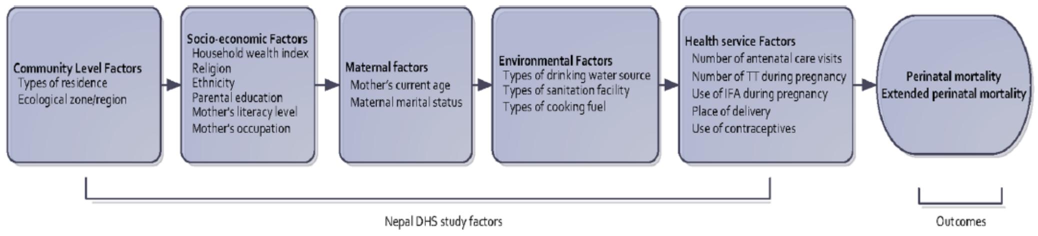

Fig. 1 Framework for factors associated with perinatal mortality in Nepal, adopted from Mosley and Chen analytical framework for the study of child survival in low income countries

father's education and mother's occupation); maternal factors (mother's current age, maternal marital status, and birth order and birth interval); environmental factors (types of drinking water sources, types of sanitation facility and types of cooking fuel); and health service factors (number of antenatal care visits, number of Tetanus Toxoid (TT) vaccines during pregnancy, place of delivery and use of contraceptives). Birth order and birth interval were combined because a previous study found that the impact of birth order may be mediated by birth interval [21]. A household wealth index variable was constructed using principle component analysis [22] of the common household facilities across four NDHS, 2001–2016 (electricity, radio, television, bicycle, telephone, and main material of floor). For the purpose of this study, the household wealth index was divided into three categories. The bottom 40% of households were arbitrarily referred to as poor households, the next 40% was classified as the middle households and the top 20% was classified as rich households, consistent with previous studies [18, 21].

The World Health Organization and the United Nations Children's Fund Joint Monitoring Program guidelines were used to categorize the source of drinking water and types of sanitation facility [23]. Categories of source of drinking water included (1) piped water on premises, (2) other improved drinking water sources, (3) unimproved drinking water sources, and (4) surface drinking water sources. Households with piped water system into dwelling were categorised as piped water on premises. Households relying on neighbour's tap or tubewell, borehole in yard, stone tap, protected well and rainwater for drinking were categorised as other improved drinking water sources. Households who reported unprotected well in-house, unprotected public or neighbour's well, unprotected spring, bottled water or water from tanker or truck as sources of drinking water were categorised as unimproved water sources. Households who reported river, stream, pond, lake, dam, canal, or irrigation water for drinking were categorised as surface drinking water sources. Likewise, categories of sanitation facility included (1) improved sanitation facilities, (2) unimproved sanitation facilities, and (3) open defecation. Households having flush toilet, ventilated or improved pit latrine, pit latrine with slab or composting toilet were categorised as improved sanitation facilities. Households who reported traditional pit toilet, pit latrine without slab, bucket toilet were categorised as unimproved sanitation facilities. Households relying on bush or open field for defecation were categorised as open defecation.

Statistical analysis

Weighted frequencies for all explanatory variables were calculated (Table 2). Perinatal Mortality Rate (PMR) and Extended Perinatal Mortality Rate (EPMR) with 95% confidence interval across all explanatory variables were calculated (Table 2). The sample was restricted to five years preceding each survey. Data were analysed using STATA 14.1 (Stata Corp, College Station, Texas, US). SVY functions were used to adjust for sampling weights. Logistic regression generalized linear latent and mixed models (GLLAMM) with the logit link and binomial family [24] that adjusted for clustering and sampling weights were used to measure the level of association between outcomes and explanatory variables. Multivariate analysis was conducted using staged technique described by Victora et al. [25] and based on this technique, the effect of distal determinants can be assessed without adjustment of proximal or intermediate determinants [21]. Therefore, at the first stage, all community-level factors (more distal determinants) were assessed in the baseline multivariable model with manual backward elimination to keep statistically significant factors (model 1). Second, socioeconomic factors were added with model 1 and manual backward elimination process was repeated to keep statistically significant factors (model 2). This procedure was followed when maternal, environmental and health service variables were included in the third (model 3), in the fourth (model 4) and in the fifth stage (model 5) respectively. Variables significantly associated at the 5% significance level were included in model 5 and reported in the study. In the final model (Model 5), we tested and reported any collinearity. Unadjusted and adjusted odd ratios with 95% confidence interval of the final model were reported.

Table 1 Rates and 95% Confidence Intervals (CI) of stillbirth, early neonatal mortality, late neonatal mortality, neonatal mortality, perinatal mortality, and extended perinatal mortality in Nepal (2001–2016)

Birth and mortality rate	Birth/Mortality	Rate (95% CI)
All births, N[a]	23,335	–
Stillbirth, rate[b] per 1000 births (95% CI)	414	18 (16, 19)
Early neonatal mortality, rate[c] per 1000 live births (95% CI)	561	24 (22, 27)
Late neonatal mortality, rate[d] per 1000 live births (95% CI)	160	7 (6, 8)
Neonatal mortality, rate[e] per 1000 live births (95% CI)	721	31 (29, 34)
Perinatal mortality, rate[f] (95% CI)	975	42 (39, 44)
Extended perinatal mortality, rate[g] (95% CI)	1135	49 (46, 51)

[a]N included stillbirths and live births from pregnancies > 28 weeks' gestation
[b]The rate of stillbirth was calculated from the number of stillbirths divided by all births multiplied by 1000
[c]Early neonatal mortality rate is early neonatal mortality divided by total live births multiplied by 1000
[d]Late neonatal mortality rate is late neonatal mortality divided by total live births multiplied by 1000
[e]Neonatal mortality rate is neonatal mortality divided by total live births multiplied by 1000
[f]Perinatal mortality rate is stillbirths plus mortality within the first week of life per 1000 births
[g]Extended perinatal mortality rate is stillbirths plus mortality within the first 28 days of life per 1000 births

"We double checked our findings by re-normalising the sampling weights for each year of survey to add up to 1. This process involved computing the total sum of weights for each survey round and divide each year of survey sampling weights with the total sum of weights. The results obtained from using each year of survey sampling weights presented in the manuscript and those obtained from re-normalized sampling weights were similar (see Additional files 1 and 2).

Results

Over the study period (2001–2016), PMR was 42 (95% CI: 39, 44) per 1000 births; whereas EPMR was 49 (95% CI: 46, 51) per 1000 births (Table 1). PMR and EPMR decreased significantly in 2011 and 2016 compared to 2001 (Fig. 2a, b). Similarly, PMR and EPMR decreased significantly in 2016 compared to 2006. However, there was no significant decrease in PMR and EPMR in 2016 compared to 2011.

Mothers residing in the mountains reported significantly higher PMR and EPMR than those who resided in the Terai or the hills (Table 2). Lower rates of perinatal and extended perinatal mortality were observed among women with aged between 25 to 49 years. Households with improved sanitation facilities, as well as those who used natural gas for cooking at home reported lower PMRs and EPMRs. Women who currently used contraceptives also reported lower PMR and EPMR.

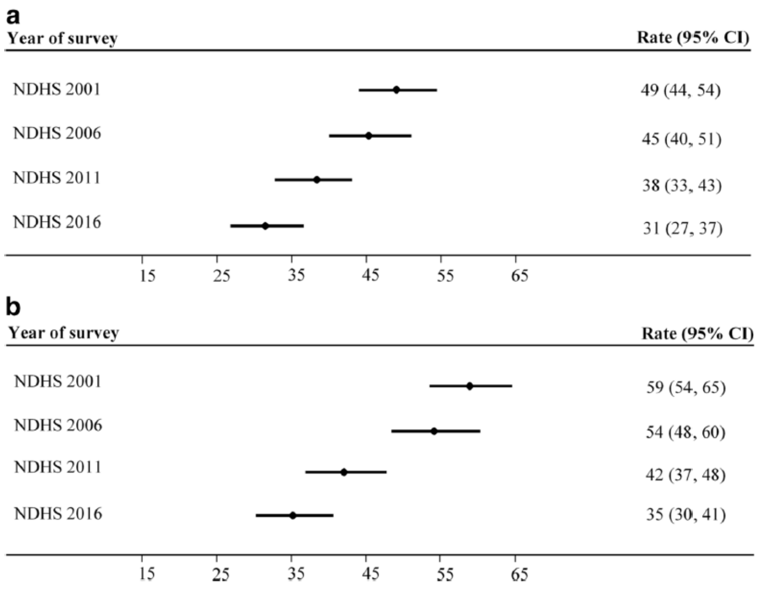

Fig. 2 **a** Rate and 95% Confidence Interval (CI) of perinatal mortality per 1000 births in NDHS 2001, 2006, 2011, and 2016. **b** Rate and 95% Confidence Interval (CI) of extended perinatal mortality per 1000 births in NDHS 2001, 2006, 2011, and 2016

Table 2 Characteristics of study population as weighted counts, and Perinatal Mortality (PM) and Extended Perinatal Mortality (EPM) rates with 95% Confidence Interval (CI) in Nepal (2001–2016), (*N* = 23,335)

Explanatory Variables	N[a]	PM Rate (95% CI)	EPM Rate (95% CI)
Community level factor			
Types of residence			
Urban	4395	31 (28, 33)	34 (32, 37)
Rural	18,940	44 (42, 47)	52 (49, 55)
Ecological zone			
Terai	12,169	42 (40, 45)	49 (46, 52)
Hill	9319	38 (35, 40)	45 (42, 47)
Mountain	1847	56 (53, 59)	67 (63, 70)
Socio-economic factor			
Wealth index			
Rich	4946	26 (24, 28)	29 (27, 31)
Middle	9644	44 (41, 47)	51 (48, 54)
Poor	8745	48 (45, 51)	57 (54, 60)
Religion			
Buddhist	1601	31 (28, 33)	41 (39, 44)
Hindu	19,639	42 (40, 45)	49 (46, 52)
Others[b]	2096	45 (42, 48)	48 (45, 51)
Ethnicity			
Brahmin/chettry	6323	37 (34, 39)	43 (40, 46)
Dalit	3716	51 (48, 54)	61 (58, 64)
Janajati	7647	37 (35, 40)	43 (40, 46)
Madhesi	5649	47 (44, 50)	55 (52, 58)
Mother education			
Secondary or higher	6151	29 (27, 32)	33 (31, 36)
Primary	4148	42 (39, 45)	48 (45, 51)
No education	13,036	47 (45, 50)	56 (53, 59)
Mother's literacy level (*N* = 23,333)			
Can read part or whole of the sentence	11,391	32 (30, 35)	37 (34, 39)
Cannot read	11,942	51 (48, 54)	60 (57, 63)
Father education (*N* = 23,299)			
Secondary or higher	11,382	36 (33, 38)	41 (38, 44)
Primary	5923	43 (40, 46)	51 (48, 54)
No education	5994	52 (49, 55)	61 (58, 64)
Mother occupation (*N* = 23,333)			
Not working	5906	34 (32, 36)	39 (36, 41)
Agriculture	15,157	45 (43, 48)	53 (50, 56)
Non- Agriculture[c]	2270	36 (33, 38)	41 (38, 43)
Maternal factor			
Mother's current age (years)			
25–49	14,131	39 (37, 42)	45 (42, 47)
15–18	821	67 (64, 70)	77 (73, 80)
19–24	8383	44 (41, 46)	53 (50, 56)
Maternal marital status			

Table 2 Characteristics of study population as weighted counts, and Perinatal Mortality (PM) and Extended Perinatal Mortality (EPM) rates with 95% Confidence Interval (CI) in Nepal (2001–2016), (*N* = 23,335) *(Continued)*

Explanatory Variables	N[a]	PM Rate (95% CI)	EPM Rate (95% CI)
Not currently married	219	32 (30, 34)	32 (30, 34)
Currently married	23,116	42 (39, 45)	49 (46, 52)
Birth order and birth interval			
2nd/3rd birth order, interval > 2 years	7065	19 (18, 21)	24 (22, 26)
1st birth order	7074	36 (33, 38)	44 (41, 46)
2nd/3rd birth order, interval ≤ 2 years	2613	42 (39, 45)	52 (49, 55)
4th or higher birth order, interval > 2 years	1727	82 (78, 85)	86 (83, 90)
4th or higher birth order, interval ≤ 2 years	4856	45 (42, 47)	59 (56, 62)
Environmental factor			
Types of drinking water source (*N* = 21,779)			
Piped water on premises	2990	31 (29, 33)	36 (34, 39)
Other improved drinking water sources	15,231	40 (38, 43)	47 (45, 50)
Unimproved drinking water sources	1434	45 (42, 47)	50 (47, 52)
Surface drinking water sources	2124	52 (49, 55)	59 (56, 62)
Types of sanitation facility (*N* = 21,775)			
Improved sanitation facilities	7931	30 (27, 32)	34 (31, 36)
Unimproved sanitation facilities	1924	42 (39, 45)	50 (47, 53)
Open defecation	11,920	47 (45, 50)	56 (53, 59)
Types of cooking fuel (*N* = 21,782)			
Natural gas	3035	22 (20, 24)	25 (23, 27)
Biomass energy	18,747	44 (41, 46)	51 (48, 54)
Health service factor			
Number of antenatal care (ANC) visits (*N* = 23,164)			
4+	8442	29 (27, 32)	34 (32, 37)
(1–3)	8330	37 (34, 39)	44 (41, 46)
No ANC	6392	40 (37, 42)	49 (47, 52)
Number of TT during pregnancy (*N* = 23,164)			
2 + TT	13,461	33 (31, 36)	39 (37, 42)
1 TT	3551	34 (32, 36)	40 (38, 43)
Never	6152	39 (36, 41)	48 (46, 51)
IFA supplementation during pregnancy(*N* = 23,168)			
Yes	13,460	33 (30, 35)	38 (35, 40)
No	9708	38 (36, 41)	47 (44, 50)
Place and assistance during delivery (*N* = 23,154)			
Health facility	6816	31 (29, 34)	35 (33, 37)
Home delivery with skilled attendants[d]	167	48 (45, 51)	54 (51, 57)
Home delivery without skilled attendants	16,171	36 (34, 39)	44 (42, 47)
Use of contraceptives			
Yes	8483	24 (22, 26)	29 (27, 32)
No	14,852	52 (49, 55)	60 (57, 63)

[a]Weighted study population. N varies between categories because of missing values
[b]other religion includes mainly Christians, Muslims, and Kirats
[c]Non-agriculture occupation includes skilled or professional jobs; [d]Skilled attendants: doctors/nurses/midwives

Table 3 Unadjusted and adjusted Odd Ratios (OR) for factors associated with perinatal mortality in Nepal, 2001–2016 (*N* = 23,335)

Explanatory Variables	Unadjusted	Adjusted
	OR (95% CI)	OR (95% CI)
Year of survey		
2001	1.00 (Reference)	1.00 (Reference)
2006	0.92 (0.78, 1.10)	0.95 (0.78, 1.16)
2011	0.77 (0.64, 0.93)	0.98 (0.80, 1.21)
2016	0.62 (0.51, 0.77)	0.72 (0.56, 0.92)
Community level factor		
Types of residence		
Urban	1.00 (Reference)	
Rural	1.46 (1.20, 1.79)	
Ecological zone		
Terai	1.00 (Reference)	1.00 (Reference)
Hill	0.89 (0.75, 1.05)	1.02 (0.83, 1.26)
Mountain	1.35 (1.09, 1.66)	1.44 (1.07, 1.95)
Socio-economic factor		
Wealth index		
Rich	1.00 (Reference)	
Middle	1.73 (1.41, 2.13)	
Poor	1.93 (1.57, 2.39)	
Religion		
Buddhist	1.00 (Reference)	
Hindu	1.37 (0.99, 1.91)	
Others including Muslim and Christian	1.47 (0.97, 2.21)	
Ethnicity		
Brahmin/chettri	1.00 (Reference)	1.00 (Reference)
Dalit	1.44 (1.13, 1.82)	1.30 (1.02, 1.65)
Janajati	1.02 (0.83, 1.26)	1.05 (0.84, 1.31)
Madhesi	1.31 (1.07, 1.62)	1.28 (0.99, 1.65)
Mother education		
Secondary or higher	1.00 (Reference)	
Primary	1.44 (1.11, 1.85)	
No education	1.64 (1.33, 2.03)	
Mother's literacy level		
Can read part or whole of the sentence	1.00 (Reference)	
Cannot read	1.42 (1.24, 1.63)	
Father education		
Secondary or higher	1.00 (Reference)	
Primary	1.21 (1.00, 1.46)	
No education	1.47 (1.23, 1.77)	
Mother occupation		
Not working	1.00 (Reference)	
Agriculture	1.28 (1.05, 1.56)	
Non-agriculture	0.95 (0.66, 1.36)	

Table 3 Unadjusted and adjusted Odd Ratios (OR) for factors associated with perinatal mortality in Nepal, 2001–2016 (*N* = 23,335) *(Continued)*

Explanatory Variables	Unadjusted	Adjusted
	OR (95% CI)	OR (95% CI)
Maternal factor		
Mother's current age (years)		
25–49	1.00 (Reference)	1.00 (Reference)
15–18	1.76 (1.27, 2.45)	1.99 (1.30, 3.09)
19–24	1.12 (0.95, 1.33)	1.71 (1.39, 2.11)
Maternal marital status		
Not currently married	1.00 (Reference)	
Currently married	1.43 (0.63, 3.26)	
Birth order and birth interval		
2nd/3rd birth order, interval > 2 years	1.00 (Reference)	1.00 (Reference)
1st birth order	1.90 (1.54, 2.35)	1.32 (1.03, 1.69)
2nd/3rd birth order, interval ≤ 2 years	2.20 (1.71, 2.85)	1.83 (1.39, 2.42)
4th or higher birth order, interval > 2 years	4.48 (3.67, 5.47)	3.27 (2.58, 4.15)
4th or higher birth order, interval ≤ 2 years	2.35 (1.76, 3.12)	2.41 (1.76, 3.29)
Environmental factor		
Types of drinking water source		
Piped water on premises	1.00 (Reference)	
Other improved drinking water sources	1.30 (1.00, 1.68)	
Unimproved drinking water sources	1.45 (1.00, 2.12)	
Surface drinking water sources	1.70 (1.24, 2.35)	
Types of sanitation facility		
Improved sanitation facilities	1.00 (Reference)	
Unimproved sanitation facilities	1.44 (1.06, 1.95)	
Open defecation	1.63 (1.37, 1.94)	
Types of cooking fuel		
Natural gas	1.00 (Reference)	1.00 (Reference)
Biomass energy	2.05 (1.54, 2.73)	1.46 (1.08, 1.97)
Health service factor		
Number of antenatal care (ANC) visits		
4+	1.00 (Reference)	
(1–3)	1.25 (1.04, 1.51)	
No ANC	1.37 (1.10, 1.70)	
Number of TT during pregnancy		
2 + TT	1.00 (Reference)	
1 TT	1.02 (0.80, 1.30)	
Never	1.18 (0.97, 1.43)	
IFA supplementation during pregnancy		
Yes	1.00 (Reference)	
No	1.18 (0.99, 1.41)	

Table 3 Unadjusted and adjusted Odd Ratios (OR) for factors associated with perinatal mortality in Nepal, 2001–2016 ($N = 23{,}335$) *(Continued)*

Explanatory Variables	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Place and assistance during delivery		
Health facility	1.00 (Reference)	
Home delivery with skilled attendants	1.59 (0.76, 3.32)	
Home delivery without skilled attendants	1.12 (0.94, 1.32)	
Use of contraceptives		
Yes	1.00 (Reference)	1.00 (Reference)
No	2.25 (1.87, 2.70)	1.93 (1.61, 2.31)

Multivariate analysis

Table 3 shows unadjusted and adjusted Odd Ratios (OR) for the association between perinatal mortality and exploratory variables, while Table 4 summarizes the corresponding ORs for extended perinatal mortality.

Factors associated with perinatal mortality (PM)

After adjusting for potential explanatory variables, perinatal mortality has decreased significantly by 28% (aOR: 0.72; 95% CI: 0.56, 0.92) between 2001 and 2016. Women residing in the mountain ecological zone and women of the dalit ethnic group had increased risk of perinatal mortality compared to those who reside in the terai ecological zone and belong to Brahmin/Chettri ethnic group. A significant increment of perinatal mortality was observed among women having 4th or higher birth order with any years of interval compared to women having 2nd or 3rd birth order with > 2 years of interval. Women aged 15 to 18 years or19 to 24 years, and those not using contraception reported higher risk of perinatal mortality compared to those with aged 25 to 49 years, and who were using contraception. Women who used biomass energy for cooking at home had significantly higher odds of having perinatal mortality compared to those who used natural gas for cooking.

In the final model of PM, when types of cooking fuel were removed and replaced by household wealth index, we found that women from the middle households were more likely to report PM (aOR: 1.44; 95% CI: 1.13, 1.83) compared to their richer counterparts.

Factors associated with extended perinatal mortality (EPM)

Our results showed similar factors to be associated with EPM as those mentioned for PM. We replaced household wealth index with types of cooking fuel in the final model; and our results indicated that women from middle households were more likely to report EPM (aOR: 1.42; 95% CI: 1.13, 1.78) compared to their richer counterparts.

Discussion

This study identified more distant factors associated with PM and EPM in Nepal. Over the study period (2001–2016), there has been a significant decline in PM and EPM. However, the pace of progress is not sufficient enough to achieve SDG target of 12 or fewer perinatal deaths per 1000 births by the year 2030. We found that the factors that were consistent across PM and EPM were ecological zone, household wealth index, birth order and birth interval; maternal age, use of contraceptives, and type of cooking fuel. Similarly, the study also found that maternal ethnic background was associated with PM; whereas maternal literacy level was found to be associated with EPM.

In this study, the odds of PM and EPM were significantly higher among women residing in the mountain ecological zone compared to those who lived in the terai ecological zone. This finding is consistent with a past study conducted in a landlocked country of Peru which has shown that high altitude (≥3000 m above the sea level) was associated with perinatal mortality [26]. Similarly, a study conducted in Nepal revealed that mothers who lived in mountainous region, with altitude ranges from 4877 m to 8848 m above the sea level were significantly more likely to report an increased risk of perinatal mortality [27]. Aadditionally, higher perinatal mortality in the mountains could be connected to access to services. Absence of adequate medical facilities would be an important contributor to the increased risk of perinatal mortality due to difficulties in timely accessing maternal and newborn health care services including emergency obstetric care during labour.

Women who were illiterate had a higher risk of EPM. This finding was consistent with a prospective longitudinal study conducted in Northwest Ethiopia [19]. Similarly, a case-control study conducted in Mashonaland East Province of Zimbabwe revealed that mothers who completed Primary education or no schooling were 5.4 times more likely to report PM compared with educated mothers [28]. These findings contradict a study carried out in Bangladesh that used prospective data on maternal morbidity which indicated that women who completed secondary or more level of education reported higher risks of perinatal mortality compared with women with no schooling [29].

Higher PM and EPM among younger age women reported in this study were similar to those reported in a population-based nested case-control conducted in Ethiopia [30]. Younger women are more likely to receive inadequate health care including family planning than older women due to the low level of women's autonomy regarding health care decisions in the households [31], psychological problems and less social support from family members [32]. Higher odds of perinatal mortality among younger women may be due to inadequate weight gain during pregnancy,

Table 4 Unadjusted and adjusted Odd Ratios (OR) for factors associated with extended perinatal mortality in Nepal, 2001–2016 ($N = 23{,}335$)

Explanatory Variables	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Year of survey		
2001	1.00 (Reference)	1.00 (Reference)
2006	0.92 (0.79, 1.08)	0.98 (0.82, 1.18)
2011	0.70 (0.58, 0.83)	0.88 (0.73, 1.08)
2016	0.58 (0.48, 0.70)	0.69 (0.54, 0.86)
Types of residence		
Urban	1.00 (Reference)	
Rural	1.54 (1.27, 1.86)	
Ecological zone		
Terai	1.00 (Reference)	1.00 (Reference)
Hill	0.91 (0.78, 1.06)	0.99 (0.84, 1.18)
Mountain	1.39 (1.15, 1.68)	1.37 (1.06, 1.76)
Socio-economic factor		
Wealth index		
Rich	1.00 (Reference)	
Middle	1.66 (1.33, 2.08)	
Poor	1.53 (1.13, 1.81)	
Religion		
Buddhist	1.00 (Reference)	
Hindu	1.21 (0.89, 1.63)	
Others including Muslim and Christian	1.18 (0.80, 1.74)	
Ethnicity		
Brahmin/chettri	1.00 (Reference)	
Dalit	1.45 (1.16, 1.80)	
Janajati	1.00 (0.83, 1.22)	
Madhesi	1.28 (1.05, 1.57)	
Mother education		
Secondary or higher	1.00 (Reference)	
Primary	1.46 (1.14, 1.86)	
No education	1.73 (1.42, 2.11)	
Mother's literacy level		
Can read part or whole of the sentence	1.00 (Reference)	1.00 (Reference)
Cannot read	1.51 (1.33, 1.72)	1.23 (1.05, 1.45)
Father education		
Secondary or higher	1.00 (Reference)	
Primary	1.27 (1.08, 1.50)	
No education	1.52 (1.28, 1.81)	
Mother occupation		
Not working	1.00 (Reference)	
Agriculture	1.32 (1.09, 1.59)	
Non-agriculture	0.94 (0.68, 1.32)	

Table 4 Unadjusted and adjusted Odd Ratios (OR) for factors associated with extended perinatal mortality in Nepal, 2001–2016 ($N = 23{,}335$) *(Continued)*

Explanatory Variables	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Maternal factor		
Mother's current age (years)		
25–49	1.00 (Reference)	1.00 (Reference)
15–18	1.79 (1.32, 2.42)	2.15 (1.45, 3.18)
19–24	1.19 (1.03, 1.39)	1.78 (1.47, 2.15)
Maternal marital status		
Not currently married	1.00 (Reference)	
Currently married	1.68 (0.74, 3.82)	
Birth order and birth interval		
2nd/3rd birth order, interval > 2 years	1.00 (Reference)	1.00 (Reference)
1st birth order	1.86 (1.54, 2.25)	1.30 (1.04, 1.63)
2nd/3rd birth order, interval ≤ 2 years	2.17 (1.72, 2.74)	1.80 (1.41, 2.31)
4th or higher birth order, interval > 2 years	3.79 (3.15, 4.55)	2.75 (2.20, 3.43)
4th or higher birth order, interval ≤ 2 years	2.52 (1.96, 3.25)	2.56 (1.94, 3.38)
Environmental factor		
Types of drinking water source		
Piped water on premises	1.00 (Reference)	
Other improved drinking water sources	1.33 (1.05, 1.69)	
Unimproved drinking water sources	1.40 (0.97, 2.00)	
Surface drinking water sources	1.68 (1.25, 2.26)	
Types of sanitation facility		
Improved sanitation facilities	1.00 (Reference)	
Unimproved sanitation facilities	1.51 (1.10, 2.07)	
Open defecation	1.70 (1.44, 2.01)	
Types of cooking fuel		
Natural gas	1.00 (Reference)	1.00 (Reference)
Biomass energy	2.11 (1.60, 2.79)	1.44 (1.09, 1.91)
Health service factor		
Number of antenatal care (ANC) visits		
4+	1.00 (Reference)	
(1–3)	1.29 (1.07, 1.54)	
No ANC	1.47 (1.21, 1.80)	
Number of TT during pregnancy		
2 + TT	1.00 (Reference)	
1 TT	1.03 (0.83, 1.29)	
Never	1.25 (1.04, 1.50)	
IFA supplementation during pregnancy		
Yes	1.00 (Reference)	
No	1.25 (1.07, 1.47)	

Table 4 Unadjusted and adjusted Odd Ratios (OR) for factors associated with extended perinatal mortality in Nepal, 2001–2016 (*N* = 23,335) *(Continued)*

Explanatory Variables	Unadjusted	Adjusted
	OR (95% CI)	OR (95% CI)
Place and assistance during delivery		
Health facility	1.00 (Reference)	
Home delivery with skilled attendants	1.69 (0.87, 3.31)	
Home delivery without skilled attendants	1.23 (1.05, 1.43)	
Use of contraceptives		
Yes	1.00 (Reference)	1.00 (Reference)
No	2.10 (1.77, 2.51)	1.79 (1.52, 2.11)

low socioeconomic status, and inadequate prenatal care [33]. In Nepal, early marriage and pregnancy is still a common practice with about 17% of girls married before the age of 19 years [15]. Early marriage is a deeply rooted and widely practised socio-cultural norm. For example, in the regional part of Nepal, bride family are required to pay extra money when young unmarried girls grow older [34].

In agreement with our findings a previous study in Nepal and India showed that mothers with 4th or higher birth order had higher probability of perinatal death [9, 35]. Obstetric complications are important causes of perinatal mortality in South Asia [17]; and a previous study has suggested that women with 4th or higher birth order were at greater risk of having any obstetric complication compared to women with birth order < 3 [36].

In Asia, while environmental factors (unimproved water, sanitation, and smoke from unimproved cooking fuel) are considered among the ten leading risks for disease [37], Nepal has made substantial improvements in the use of improved drinking water sources and sanitation facilities over the past 15 years [12–15]. Yet, the majority (over 65%) of households in the same period have constantly been using biomass energy for cooking at home [12–15]. The finding of an increased risk of PM and EPM has also been reported in a hospital-based surveillance and case-control study, linked with a population survey in India [38]. Past studies suggested that chronic exposure to carbon monoxide from biomass energy will deteriorate newborn respiratory health that may lead to a lower chance of survival especially in the first month of infant life [39]. In Nepal, natural gas is expensive; and the use of natural gas is more prevalent among rich households [12–15]. Our study also revealed that women from a rich household wealth index were less likely to report PM and EMP compared to women from a lower household wealth index. Access to affordable renewal energy both at home and community could benefit health and thus help in reducing perinatal deaths.

A plausible reason for the finding of a higher PM among Dalit women may be because Dalits were ethnic minority women, less empowered, and socio-economically marginalised with limited ability to improve their health and the health of their newborn. It has been documented that 90% of total Dalit populations living below the poverty line in Nepal have limited access to health care [40].

The higher perinatal mortality rate in home births with skilled birth attendants compared to those without skilled birth attendants in this study may be the reflection of high-risk pregnancies which may be difficult to manage in home settings.

This study has many strengths, including the use of the pooled Nepal DHS (2001–2016) with large sample sizes, and higher response rates (almost 97%). Second, the study investigated factors associated with PM and EPM using household national-wide representative surveys; and findings from a population-based study can be used by public health practitioners to formulate and inform national level policies to improve fetal and newborn survival. Third, the same questionnaires were used to collect information in all four surveys which increase accuracy and promote coherence of the data used for analysis. Despite these strengths, this study also has limitations. First, information about duration of pregnancy and birth intervals (which may be complex for illiterate women) may lead to reporting bias. Second, twin stillbirths are recorded as one stillbirth in the calendar that may undercount the number of total stillbirths, but they are very rare events. Third, this study is limited by the fact that data on important explanatory variables such as a history of previous stillbirth, prematurity, fetal growth, low birthweight, maternal anaemia, obstetric complications such as breech delivery, and birth asphyxia were not collected in the four NDHS. Fourthly, maternal body mass index, an important confounder, was not included in our multivariate analysis due to large numbers of missing data (23%) which if included could have biased the results.

Conclusions

Our analyses examined more distant factors associated with PM and EPM in Nepal using pooled population-based surveys for the year 2001, 2006, 2011, and 2016. Women who lived in the mountains, women who did not use contraceptives at the time of the survey, younger women, and women having 4th or higher birth order had significantly higher risks of PM and EPM. At household level, educating illiterate women about the benefits of using contraceptives is required to further reduce perinatal mortality. At community level, modern energy technologies such as the use of liquefied petroleum gas or electricity to all households may help to reduce perinatal mortality; and these interventions should target rural women and women from low socioeconomic households.

Additional files

Additional file 1: Adjusted Odd Ratios (aOR) for factors associated with perinatal mortality in Nepal, 2001–2016 (N = 23,335). (DOCX 19 kb)

Additional file 2: Adjusted Odd Ratios (aOR) for factors associated with extended perinatal mortality in Nepal, 2001–2016 (N = 23,335). (DOCX 19 kb)

Abbreviations

ANC: Antenatal Care; EPM: Extended Perinatal Mortality; EPMR: Extended Perinatal Mortality Rate; IFA: Iron and Folic Acid; NDHS: Nepal Demographic and Health Survey; OR: Odd Ratio; PM: Perinatal Mortality; PMR: Perinatal Mortality Rate; TT: Tetanus Toxoid

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Availability of data and materials

The first author lodged a request application via online DHS program (https://dhsprogram.com/data/available-datasets.cfm) to use NDHS data (2001–2016) for this study, and permission was granted. The authors were not able to share the data directly.

Authors' contributions

PRG and KEA conceptualized the study. PRG performed the data analysis and drafted the manuscript. PRG, KEA, AMNR, MKN, MD and CRG critically reviewed the manuscript and also involved in editing and writing of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study is a secondary analysis of the NDHS data. The NDHS obtained ethical clearance from the Ethical Review Board of Nepal Health Research Council, Kathmandu and ICF Institutional Review Board, Maryland, USA. Data for this study are free to download and use by completing a request application via online DHS program (https://dhsprogram.com). The first author got permission from online DHS program to use data for this study. All four NDHS received informed consent from all the study participants, and the process for obtaining informed consent is also available from https://www.dhsprogram.com/What-We-Do/Protecting-the-Privacy-of-DHS-Survey-Respondents.cfm.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests. KEA is a member of the editorial board (Associate Editor) of BMC Pregnancy and Childbirth, and does not have any role in the journal review and decision making process for this manuscript.

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Author details

[1]School of Science and Health, Western Sydney University, Locked Bag1797, Penrith, NSW 2571, Australia. [2]School of Social Sciences and Psychology, Western Sydney University, Locked Bag1797, Penrith, NSW 2571, Australia. [3]Sydney School of Public Health, University of Sydney, Edward Ford Building (A27), Sydney, NSW 2006, Australia.

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References

1. World Health Organization. Neonatal and perinatal mortality: country, regional and global estimates. Geneva: WHO; 2006.
2. Wang H, Bhutta ZA, Coates MM, Coggeshall M, Dandona L, Diallo K, et al. Global, regional, national, and selected subnational levels of stillbirths, neonatal, infant, and under-5 mortality, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016;388:1725.
3. Mason E, McDougall L, Lawn JE, Gupta A, Claeson M, Pillay Y, et al. From evidence to action to deliver a healthy start for the next generation. Lancet. 2014;384:455–67.
4. Bhutta ZA, Das JK, Bahl R, Lawn JE, Salam RA, Paul VK, et al. Can available interventions end preventable deaths in mothers, newborn babies, and stillbirths, and at what cost? Lancet. 2014;384:347–70.
5. Fikree FF, Gray RH. Demographic survey of the level and determinants of perinatal mortality in Karachi, Pakistan. Paediatr Perinat Epidemiol. 1996;10:86–96.
6. Khan MN, Rahman MM, Shariff AA, Rahman MM, Rahman MS, Rahman MA. Maternal undernutrition and excessive body weight and risk of birth and health outcomes. Arch Public Health. 2017;75:12.
7. Manandhar DS, Osrin D, Shrestha BP, Mesko N, Morrison J, Tumbahangphe KM, et al. Effect of a participatory intervention with women's groups on birth outcomes in Nepal: cluster-randomised controlled trial. Lancet. 2004; 364:970–9.
8. Manandhar SR, Ojha A, Manandhar DS, Shrestha B, Shrestha D, Saville N, et al. Causes of stillbirths and neonatal deaths in Dhanusha district, Nepal: a verbal autopsy study. Kathmandu Univ Med J (KUMJ). 2010;8:62–72.
9. Geetha T, Chenoy R, Stevens D, Johanson R. A multicentre study of perinatal mortality in Nepal. Paediatr Perinat Epidemiol. 1995;9:74–89.
10. Suwal A. Obstetric and perinatal outcome of teenage pregnancy. JNHRC. 2012;10:52–6.
11. Shrestha M, Manandhar D, Dhakal S, Nepal N. Two year audit of perinatal mortality at Kathmandu medical college teaching hospital. Kathmandu Univ Med J. 2006;4:176–81.
12. Ministry of Health [Nepal], New ERA, and ORC Macro. 2002. Nepal Demographic and Health Survey 2001. Calverton, Maryland, USA: Family Health Division, Ministry of Health; New ERA; and ORC Macro.
13. Ministry of Health and Population (MOHP) [Nepal], New ERA, and Macro International Inc. 2007. Nepal Demographic and Health Survey 2006. Kathmandu, Nepal: Ministry of Health and Population, New ERA, and Macro International Inc.
14. Ministry of Health and Population (MOHP) [Nepal], New ERA, and ICF International Inc. 2012. Nepal Demographic and Health Survey 2011. Kathmandu, Nepal: Ministry of Health and Population, New ERA, and ICF International, Calverton, Maryland.
15. Ministry of Health and Population (MOHP) [Nepal], New ERA, and ICF International Inc. 2017. Nepal Demographic and Health Survey 2016. Kathmandu, Nepal: Ministry of Health and Population, New ERA, and ICF International, Calverton, Maryland.
16. Neasham D, Dolk H, Vrijheid M, Jensen T, Best N. Stillbirth and neonatal mortality due to congenital anomalies: temporal trends and variation by small area deprivation scores in England and Wales, 1986–96. Paediatr Perinat Epidemiol. 2001;15:364–73.
17. Ghimire PR, Agho K, Akombi B, Wali N, Dibley M, Raynes-Greenow C, et al. Perinatal mortality in South Asia: systematic review of observational studies. Int J Environ Res. 2018;15:1428.
18. Nisha MK, Alam A, Raynes-Greenow C. Variations in perinatal mortality associated with different polluting fuel types and kitchen location in Bangladesh. Int J Occup Environ Health. 2018;24:47–54.
19. Andargie G, Berhane Y, Worku A, Kebede Y. Predictors of perinatal mortality in rural population of Northwest Ethiopia: a prospective longitudinal study. BMC Public Health. 2013;13:168.
20. Mosley WH, Chen LC. An analytical framework for the study of child survival in developing countries. Popul Dev Rev. 1984;10:25–45.
21. Abir T, Agho KE, Ogbo FA, Stevens GJ, Page A, Hasant MA, et al. Predictors of stillbirths in Bangladesh: evidence from the 2004–2014 nation-wide household surveys. Glob Health Action. 2017;10:1410048.

22. Filmer D, Pritchett LH. Estimating wealth effects without expenditure data-- or tears: an application to educational enrollments in states of India. Demography. 2001;38:115–32.
23. UNICEF/WHO. Progress on Sanitation and Drinking-Water: 2015 Update and MDG assessment. Geneva: UNICEF/WHO; 2015.
24. Skrondal A, Rabe-Hesketh S. Generalized latent variable modeling: multilevel, longitudinal, and structural equation models. Chapman and Hall/ CRC; 2004.
25. Victora CG, Huttly SR, Fuchs SC, Olinto M. The role of conceptual frameworks in epidemiological analysis: a hierarchical approach. Int J Epidemiol. 1997;26:224–7.
26. Gonzales GF, Tapia V, Carrillo CE. Stillbirth rates in Peruvian populations at high altitude. Int J Gynaecol Obstet. 2008;100:221–7.
27. Ghimire PR, Agho KE, Renzaho A, Christou A, Nisha MK, Dibley M, et al. Socio-economic predictors of stillbirths in Nepal (2001-2011). PLoS One. 2017;12:e0181332.
28. Tachiweyika E, Gombe N, Shambira G, Chadambuka A, Mufuta T, Zizhou S. Determinants of perinatal mortality in Marondera district, Mashonaland East Province of Zimbabwe, 2009: a case control study. Pan Afr Med J. 2011;8:7.
29. Bari W, Chowdhury RI, Islam MA, Chakraborty N, Akhter HA. The differentials and determinants of perinatal mortality in rural Bangladesh. Eur J Contracept Reprod Health Care. 2002;7:216–22.
30. Yirgu R, Molla M, Sibley L, Gebremariam A. Perinatal mortality magnitude, determinants and causes in west Gojam: population-based nested case-control study. PLoS One. 2016;11:e0159390.
31. Sharma AK, Verma K, Khatri S, Kannan A. Determinants of pregnancy in adolescents in Nepal. Indian J Pediatr. 2002;69:19–22.
32. Choe MK, Thapa S, Mishra V. Early marriage and early motherhood in Nepal. J Biosoc Sci. 2005;37:143–62.
33. Weng Y-H, Yang C-Y, Chiu Y-W. Risk assessment of adverse birth outcomes in relation to maternal age. PLoS One. 2014;9:e114843.
34. Shrestha R. Maternal mortality in Nepal: addressing the issue. Inquiries J. 2012;4:1–4.
35. Viswanath K, Ps R, Chakraborty A, Prasad JH, Minz S, George K. A community based case control study on determinants of perinatal mortality in a tribal population of southern India. Rural Remote Health. 2015;15:3388.
36. Bai J, Wong FW, Bauman A, Mohsin M. Parity and pregnancy outcomes. Am J Obstet Gynecol. 2002;186:274–8.
37. Guilbert JJ. The world health report 2002 - reducing risks, promoting healthy life. Educ Health. 2003;16:230.
38. Mavalankar DV, Trivedi C, Gray RH. Levels and risk factors for perinatal mortality in Ahmedabad, India. Bull World Health Organ. 1991;69:435.
39. Kim K-H, Jahan SA, Kabir E. A review of diseases associated with household air pollution due to the use of biomass fuels. J Hazard Mater. 2011;192:425–31.
40. Bishwakarma P. The situation analysis for dalit women of Nepal. National Seminar on Raising Dalit Participation in governance Centre for Economic and Technical Studies; 2004.

SECTION IV: Factors associated with childhood mortality in Nepal

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This section presents a manuscript titled "Under-Five Mortality and Associated Factors: Evidence from the Nepal Demographic and Health Survey (2001–2016)" (https://dx.doi.org/10.3390%2Fijerph16071241)

CHAPTER 6: Under-Five Mortality and Associated Factors: Evidence from the Nepal Demographic and Health Survey (2001–2016)

Ghimire PR, Agho KE, Ezeh OK, Renzaho AMN, Dibley M, Raynes-Greenow C.

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Article

Under-Five Mortality and Associated Factors: Evidence from the Nepal Demographic and Health Survey (2001–2016)

Pramesh Raj Ghimire [1,*], Kingsley E. Agho [1], Osita Kingsley Ezeh [1], Andre M. N. Renzaho [2], Michael Dibley [3] and Camille Raynes-Greenow [3]

1 School of Science and Health, Western Sydney University, Locked Bag1797, Penrith, NSW 2571, Australia; K.Agho@westernsydney.edu.au (K.E.A.); ezehosita@yahoo.com (O.K.E.)
2 School of Social Sciences and Psychology, Western Sydney University, Locked Bag1797, Penrith, NSW 2751, Australia; andre.renzaho@westernsydney.edu.au
3 Sydney School of Public Health, The University of Sydney, Edward Ford Building (A27), Sydney, NSW 2006, Australia; michael.dibley@sydney.edu.au (M.D.); camille.raynes-greenow@sydney.edu.au (C.R.-G.)
* Correspondence: P.Ghimire@westernsydney.edu.au; Tel.: +61-422-300-960

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Abstract: Child mortality in Nepal has reduced, but the rate is still above the Sustainable Development Goal target of 20 deaths per 1000 live births. This study aimed to identify common factors associated with under-five mortality in Nepal. Survival information of 16,802 most recent singleton live births from the Nepal Demographic and Health Survey for the period (2001–2016) were utilized. Survey-based Cox proportional hazard models were used to examine factors associated with under-five mortality. Multivariable analyses revealed the most common factors associated with mortality across all age subgroups included: mothers who reported previous death of a child [adjusted hazard ratio (aHR) 17.33, 95% confidence interval (CI) 11.44, 26.26 for neonatal; aHR 13.05, 95% CI 7.19, 23.67 for post-neonatal; aHR 15.90, 95% CI 11.38, 22.22 for infant; aHR 16.98, 95% CI 6.19, 46.58 for child; and aHR 15.97, 95% CI 11.64, 21.92 for under-five mortality]; nonuse of tetanus toxoids (TT) vaccinations during pregnancy (aHR 2.28, 95% CI 1.68, 3.09 for neonatal; aHR 1.86, 95% CI 1.24, 2.79 for post-neonatal; aHR 2.44, 95% CI 1.89, 3.15 for infant; aHR 2.93, 95% CI 1.51, 5.69 for child; and aHR 2.39, 95% CI 1.89, 3.01 for under-five mortality); and nonuse of contraceptives among mothers (aHR 1.69, 95% CI 1.21, 2.37 for neonatal; aHR 2.69, 95% CI 1.67, 4.32 for post-neonatal; aHR 2.01, 95% CI 1.53, 2.64 for infant; aHR 2.47, 95% CI 1.30, 4.71 for child; and aHR 2.03, 95% CI 1.57, 2.62 for under-five mortality). Family planning intervention as well as promotion of universal coverage of at least two doses of TT vaccine are essential to help achieve child survival Sustainable Development Goal (SDG) targets of <20 under-five deaths and <12 neonatal deaths per 1000 births by the year 2030.

Keywords: risk factors; child mortality; infants; mortality rates; Nepal

1. Introduction

Globally, approximately 5.6 million deaths of children under-five years of age (under-five deaths) were reported in the year 2016. Of these deaths, three million occurred between 1 and 59 months of age while the remainder occurred between birth and the first month of life [1]. Deaths occurring at these age periods remain a huge public health concern, especially in sub-Saharan Africa (SSA) and South Asia (SA) including Nepal. An overwhelming majority (80%) of the world's estimated under-five deaths occurred in SSA and SA, and most are preventable or treatable. Preterm birth complications, pneumonia, malaria and diarrhea contribute approximately 16%, 13%, 5% and 8% of these deaths, respectively [1,2]. In 2015, neonatal tetanus accounted for about 10,000 neonatal deaths in South Asia including Nepal [3].

A recent Nepal Demographic and Health Survey (NDHS) report revealed that over a 15-year period, Nepal's under-five mortality rate (U5MR) decreased by approximately 57%, from 91 deaths per 1000 live births in 2001 to 39 in 2016 [4]. However, under-five mortality in Nepal still remains higher than the Sustainable Development Goal (SDG) target of 20 per 1000 live births [4]. Therefore, to achieve the child survival SDG target, substantial efforts are needed mainly in developing countries such as Nepal.

Previous studies that examined child mortality in Nepal found that the use of antenatal Iron and folic acid (IFA) supplementation; tetanus toxoid (TT) vaccination during pregnancy; lack of skilled birth attendance, lack of antenatal care (ANC) visits; older maternal age; use of polluting fuel; higher parity, mortality inequality among poor household and mothers with no schooling were linked with child mortality [5–11]. However, these studies were either community-based experimental in smaller settings or community-based or population based cross-sectional studies; and did not restrict their analysis to the most recent singleton live births in order to reduce recall bias. There is evidence to suggest that multiple births are biologically more likely to die during infancy than with singletons [12]. Additionally, studies disaggregating analyses by different age ranges of the first 59 months of life have been limited in Nepal, especially for the post-neonatal and child mortality subgroups.

This study aimed to identify common factors associated with mortality across all age subgroups from 0 to 59 months of life (neonatal: 0–30 days, post-neonatal: 1–11 months, infant: 0–11 months, child: 12–59 months, and under-five: 0–59 months) using survival information of most recent singleton live births from the NDHS data for the years 2001, 2006, 2011, and 2016. Findings obtained will assist health administrators and public health researchers, as well as government policy makers, to re-evaluate and revitalize existing intervention strategies to accelerate the reduction of under-five mortality in Nepal.

2. Materials and Methods

2.1. Data Source

The NDHS data for the year 2001 [13], 2006 [14], 2011 [15] and 2016 [4] were combined to yield a large sample size of reported deaths. Stratified multi-stage cluster sampling design was used to collect NDHS data and the procedures for collecting data were similar across the surveys (2001–2016). The details of survey methods, sampling techniques and questionnaires used in the NDHS surveys have been described elsewhere [4,13–15]. A weighted sample of 16,802 singleton most recent live births five years preceding each survey was used for the analysis (2001: $n = 4714$; 2006: $n = 4029$; 2011: $n = 4118$; and 2016: $n = 3941$). In our analyses, 125 multiple births were excluded because of known higher risk of neonatal mortality due to pregnancy complications and preterm birth amongst multiple births compared to singleton births [12,16,17].

2.2. Study Outcomes

Study outcomes for this study were derived from reported deaths of under-five children [4,13–15], which was disaggregated as neonatal mortality (0–30 days), post-neonatal mortality (1–11 months), infant mortality (0–11 months), child mortality (12–59 months) and under-five mortality (0–59 months). Direct estimates of childhood mortality were calculated using complete maternal birth histories that include date of every live birth (singleton and multiple birth), survival status, current age for living children and age at death of children [4,13–15].

2.3. Covariates

The selection of covariates for this study was based on Mosley and Chen conceptual framework for child survival in developing countries [18], previous studies on child mortality [5–8,10,11,19], and information available in combined NDHS datasets [4,13–15]. Selected covariates variables were categorized into five distinct groups: community level factors, household level factor, individual level factors, environmental factors and health service factors. The community-level factors consist of types of residence (rural or urban) and ecological zone (Terai, Hill and Mountain). The household factor selected was household wealth index which was constructed by using a principle component analysis [20] of the household facilities and assets (electricity, radio, television, bicycle, telephone, and main material of floor) that was common in the four datasets. For the purpose of this study, the household wealth index was divided into three categories. The bottom, 40% of households were arbitrarily referred to as poor households, the next 40% was classified as the middle households and the top 20% was classified as rich households, consistent with previous study [19].

The individual-level factors consist of maternal, child and paternal characteristics. Maternal characteristics were religion (Buddhist, Hindu or others), ethnicity (Brahmin/Chettri, Dalit, Janajati or Madhesi), education (secondary/higher, primary or no education), literacy level (can read or cannot read), age (40–49, 30–39, 20–29 or <20), desire for pregnancy (wanted then, wanted later or no more), and occupation (not working, agriculture or skilled/professional). Child characteristics were combined birth rank and birth interval (2nd/3rd birth rank and >2 years' interval, 1st birth, 2nd/3rd birth rank and $\leq$2 years' interval, 4th/higher birth rank and >2 years' interval or 4th/higher birth rank and $\leq$2 years' interval), previous death of a child (no or yes), and child sex (male or female). The only paternal characteristic was education (secondary/higher, primary or no education).

The environmental factors were types of drinking water source, types of sanitation facilities, and types of cooking fuel. We used World Health Organization and the United Nations Children's Fund Joint Monitoring Program guidelines [21] to construct types of drinking water source and types of sanitation facilities. Types of cooking fuel were categorized as improved (biogas, natural gas, liquefied petroleum gas and electricity) and unimproved (charcoal, wood, coal/lignite, animal dung, kerosene, straw/shrubs/grass, and agricultural crops).

The health service factors were ANC visits (4+ANC visits, 1–3 ANC visits or no ANC visits), TT vaccination during pregnancy (Two or more TT, one TT or no TT), antenatal IFA supplementation (yes or no), place of delivery (health facility or home facility), delivery assistance (doctors/nurses or others), mode of delivery (vaginal or caesarean) and current use of contraceptive at the time of the survey (yes or no).

2.4. Statistical Analysis

STATA (version 14.1, Stata Corp, College Station, TX, USA) was used for the study analysis and Survey "SVY" function was employed to adjust for stratified multi-stage cluster sampling procedure. Weighted counts, and percentage of all covariates were first performed. Mortality rates and 95% confidence interval (CI) by year of survey were obtained by using Roja's approach [22]. In multivariable analysis, survey Cox proportional hazard models were used to examine the independent factors for each of the study outcome. Tobit and truncreg commands in Stata were used to account for censoring and truncation.

A staged technique [23] was used to determine the final multivariate regression model. In the first stage, year of survey and community level factors (types of residence, and ecological zone) were entered into the baseline model with manual backward elimination process to remove statistically nonsignificant variables (Model 1). In the second stage, household wealth status and individual level factors (religion, ethnicity, mother's education, father's education, mother's literacy level, mother's age, desire for pregnancy, mother's occupation, combined birth rank and birth interval, previous death of a child and child sex) were assessed with Model 1 with manual backward elimination process to remove statistically nonsignificant variables (Model 2). This procedure was followed when environmental (types of drinking water source, types of sanitation facilities, and types of cooking fuel), and health service variables (ANC visits, TT vaccination during pregnancy, antenatal IFA supplementation, place of delivery, delivery assistance, mode of delivery and current use of contraceptive) were included in the third (Model 3), and in the fourth (Model 4), respectively. In each stage, the significance level was set at 0.05; and variables that were statistically significant with the study outcomes in the final model (Model 4) were reported in the study. Variables that were statistically significant with the study outcomes in models 1–3 are presented in supplementary tables (Supplementary Tables S1 and S2). Collinearity was tested and reported in the final model.

We also estimated total risk of deaths in each of the sub-age groups in the population between 2001 and 2016 attributable to each of the common significant independent variables across the age groups in the final multivariable model, under the assumption that the association were causal. The adjusted Population Attributable Risk (PAR) was estimated using the formula below, which is similar to that described by Stafford et al. [24].

$$PAR = \Psi \times (aHR-1)/(aHR) \quad (1)$$

where Ψ is the weighted proportion of deaths during neonatal, post-neonatal, infant, child and under-five period and aHR is the adjusted hazard ratio.

2.5. Ethical Considerations

The ethics committees of the ICF International, USA and the Nepal Health Research Council, Kathmandu, approved all surveys. The first author obtained approval from Measure DHS to download and use the data as part of his doctoral dissertation with the School of Science and Health, Western Sydney University, Australia.

3. Results

Over the study period, a total of 1474 deaths occurred consisting of 287 (19%) neonatal mortality, 163 (11%) post-neonatal mortality, 450 (31%) infant mortality, 62 (4%) child mortality, and 512 (35%) under-five mortality. A total of 16,290 observations were left-censored, 512 observations were uncensored and 0 observations were right-censored and truncated for under-five mortality.

The majority (79%) of mothers were rural residents, whereas over half (52%) of the study population were from Terai ecological zone (Table 1). Women who received at least two doses of TT vaccine or those who used antenatal IFA were almost equally represented (60% and 61% respectively).

Figure 1 presents the trends in rates of neonatal, post-neonatal, infant, child, and under-five mortality in Nepal. The mortality rates across the five age subgroups were higher among mothers who resided in the mountain ecological zone, who were rural residents, who could not read, who used unimproved sanitation facilities, and those who reported of having a history of previous death of a child (Table 1). It is worthy to note that mortality rates in this study differ sharply from those reported by NDHS because multiple births were excluded, and analysis was restricted to the most recent live births five years prior each survey.

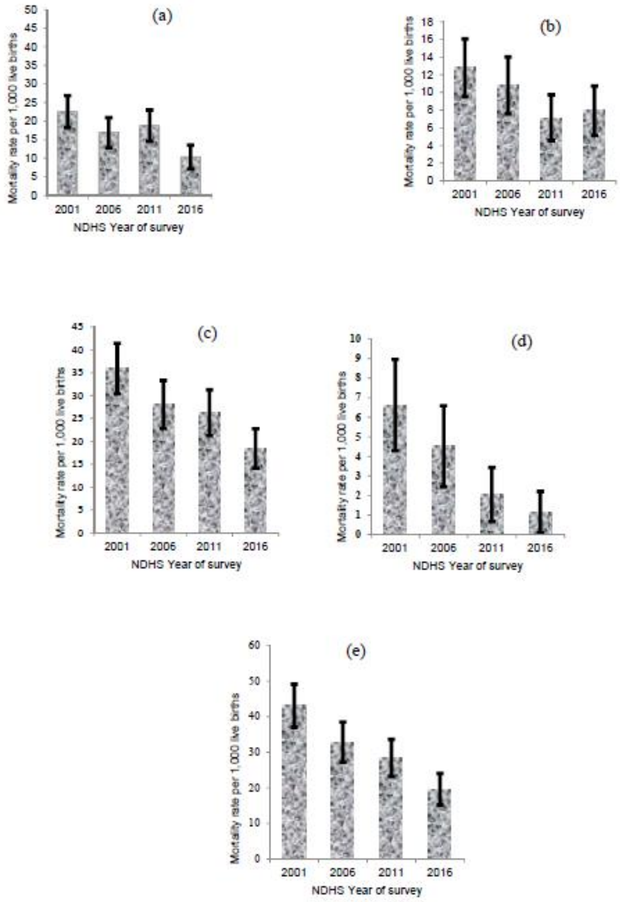

Figure 1. (**a**) Neonatal, (**b**) post-neonatal, (**c**) infant, (**d**) child and (**e**) under-five mortality per 1000 live births with 95% CI by year of survey, Nepal.

Factors Associated with Childhood Mortality

Mothers with a history of previous death of a child, who did not receive TT vaccine during pregnancy, or who were not using contraceptives at the time of the survey were significantly associated with neonatal, post-neonatal, infant, child and under-five mortality (Table 2). In order to investigate collinearity in the final model, when TT vaccine was removed and replaced with IFA supplementation; the results indicated that mothers who did not receive IFA supplementation had the higher risk of neonatal [adjusted HR (aHR) 1.49, 95% CI 1.12, 2.00; *p*-value: 0.007], infant (aHR 1.50, 95% CI 1.20, 1.87; *p*-value: <0.001), child (aHR 2.46, 95% CI 2.08, 9.58; *p*-value: <0.001), and under-five mortality (aHR 1.54, 95% CI 1.24, 1.93; *p*-value: <0.001).

During the study period, the estimated proportion of deaths in children attributed to mothers who had had a previous death of a child was 58.2% for neonatal deaths, 51.6% for post-neonatal deaths, 55.9% for infant deaths, 68.6% for child deaths and 57.4% for the overall under-five deaths. Similarly, 23.8%, 50.9%, 39.9%, 35.6% and 24.7% of neonatal, post-neonatal, infant, child and under-five deaths, respectively, were attributed to children whose mothers were not vaccinated for TT during pregnancy (Table 3).

Table 1. Characteristics of the population in Nepal for the 2001–2016 waves (n = 16,802).

Study Variable	n (% *)	NMR [a] (95% CI [f])	PNMR [b] (95% CI)	IMR [c] (95% CI)	CMR [d] (95% CI)	U5MR [e] (95% CI)
Year of survey						
2001	4714 (28)	22 (20, 23)	13 (12, 14)	35 (32, 37)	7 (5, 8)	42 (37, 45)
2006	4029 (24)	17 (15, 19)	11 (9, 12)	28 (24, 31)	4 (3, 5)	32 (27, 36)
2011	4118 (25)	18 (16, 21)	7 (6, 8)	25 (22, 29)	2 (1, 3)	27 (23, 32)
2016	3941 (23)	10 (9, 12)	8 (7, 9)	18 (16, 21)	1 (1, 2)	19 (17, 23)
Type of residence						
Urban	3461 (21)	9 (8, 11)	9 (7, 10)	18 (15, 21)	2 (1, 3)	20 (16, 24)
Rural	13,341 (79)	19 (17, 21)	10 (8, 11)	29 (25, 32)	4 (3, 5)	33 (28, 37)
Ecological zone						
Terai	8663 (52)	18 (16, 20)	9 (8, 11)	27 (24, 31)	4 (3, 5)	31 (27, 36)
Hill	6871 (41)	16 (14, 18)	8 (7, 10)	24 (21, 28)	3 (2, 4)	27 (23, 32)
Mountain	1268 (8)	20 (18, 22)	19 (17, 21)	39 (35, 43)	5 (4, 6)	44 (39, 49)
Wealth index						
Rich	3239 (19)	9 (8, 11)	6 (5, 7)	15 (14, 18)	2 (1, 3)	17 (14, 21)
Middle	6220 (37)	18 (16, 20)	10 (8, 11)	28 (24, 31)	3 (2, 4)	31 (26, 35)
Poor	7343 (44)	20 (18, 22)	11 (9, 13)	31 (27, 35)	5 (4, 6)	36 (31, 41)
Religion						
Buddhist	1191 (7)	14 (12, 16)	5 (4, 6)	19 (16, 22)	4 (3, 5)	23 (19, 27)
Hindu	14,191 (84)	17 (15, 19)	10 (8, 11)	27 (23, 30)	4 (3, 5)	31 (26, 35)
Others	1420 (8)	18 (16, 20)	11 (10, 13)	29 (26, 33)	2 (1, 3)	31 (27, 36)
Ethnicity						
Brahmin/chettri	4735 (28)	15 (13, 16)	9 (8, 11)	24 (21, 27)	2 (1, 3)	26 (22, 30)
Dalit	2550 (15)	22 (20, 24)	10 (9, 12)	32 (29, 36)	5 (4, 6)	37 (33, 42)
Janajati	5694 (34)	12 (11, 14)	8 (7, 10)	20 (18, 24)	4 (3, 5)	24 (21, 29)
Madhesi	3824 (23)	24 (22, 27)	12 (10, 13)	36 (32, 40)	4 (3, 5)	40 (35, 45)
Mother education						
Secondary or higher	5000 (30)	10 (9, 12)	6 (5, 8)	16 (14, 20)	2 (1, 3)	18 (15, 23)
Primary	3010 (18)	14 (12, 16)	11 (10, 13)	25 (22, 29)	2 (1, 3)	27 (23, 32)
No education	8792 (52)	22 (20, 24)	11 (9, 13)	33 (29, 37)	6 (5, 7)	39 (34, 44)
Mother's literacy level (n = 16,800)						
Can read	8828 (53)	12 (10, 13)	8 (6, 9)	20 (16, 22)	2 (1, 3)	22 (17, 25)
Cannot read	7972 (47)	23 (21, 25)	12 (10, 13)	35 (31, 38)	6 (5, 7)	41 (36, 45)
Father's education (n = 16,770)						
Secondary or higher	8647 (51)	14 (12, 15)	9 (7, 10)	23 (19, 24)	3 (2, 4)	26 (21, 28)
Primary	4136 (25)	19 (17, 21)	11 (9, 12)	30 (26, 33)	5 (4, 6)	35 (30, 39)
No education	3986 (24)	23 (21, 25)	11 (9, 13)	34 (30, 38)	5 (4, 6)	39 (35, 44)

Table 1. *Cont.*

Study Variable	n (% *)	NMR [a] (95% CI [f])	PNMR [b] (95% CI)	IMR [c] (95% CI)	CMR [d] (95% CI)	U5MR [e] (95% CI)
Mother occupation (16,800)						
Not working	4226 (25)	15 (13, 17)	6 (5, 7)	21 (18, 24)	2 (1, 2)	22 (20, 24)
Agriculture	10,725 (64)	17 (15, 19)	11 (10, 13)	28 (25, 32)	5 (4, 6)	33 (31, 36)
Skilled/professional	1850 (11)	19 (17, 22)	10 (8, 11)	29 (25, 33)	3 (2, 4)	32 (30, 35)
Mother's age						
40–49	824 (5)	21 (18, 23)	11 (9, 13)	32 (27, 36)	15 (13, 16)	47 (40, 52)
30–39	4089 (24)	15 (14, 17)	10 (8, 11)	25 (22, 28)	4 (3, 5)	29 (25, 33)
20–29	10,525 (63)	16 (14, 18)	9 (8, 11)	25 (22, 29)	3 (2, 4)	28 (24, 33)
<20	1364 (8)	28 (25, 30)	12 (11, 14)	40 (36, 44)	1 (1, 2)	41 (37, 46)
Mother's desire for Pregnancy (n = 16,801)						
Wanted then	11,695 (70)	18 (16, 20)	10 (9, 12)	28 (25, 32)	4 (3, 5)	32 (28, 37)
Wanted later	2165 (13)	14 (12, 16)	7 (6, 9)	21 (19, 25)	NA	21 (19, 25)
No more	2940 (18)	17 (15, 19)	10 (8, 11)	27 (23, 30)	6 (5, 7)	33 (28, 37)
Birth rank and birth interval						
2nd/3rd birth rank, >2 years	5607 (33)	13 (11, 15)	9 (7, 10)	22 (18, 25)	2 (1, 3)	24 (19, 28)
1st child	4881 (29)	20 (18, 22)	10 (8, 11)	32 (26, 33)	3 (2, 4)	35 (28, 37)
2nd/3rd child, interval ≤2 years	1740 (10)	20 (18, 22)	9 (7, 10)	29 (25, 32)	3 (2, 4)	32 (27, 36)
4th/higher child, interval >2 years	3503 (21)	14 (12, 16)	11 (10, 13)	25 (22, 29)	5 (4, 6)	30 (26, 35)
4th/higher child, interval ≤ 2 years	1072 (6)	31 (28, 33)	11 (10, 13)	42 (38, 46)	11 (10, 13)	53 (48, 59)
Previous Death of a child						
No	13,809 (82)	8 (7, 9)	5 (4, 6)	13 (11, 15)	1 (1, 2)	14 (12, 17)
Yes	2993 (18)	59 (55, 63)	30 (28, 33)	89 (83, 96)	15 (13, 17)	104 (96, 113)
Child Sex						
Male	8822 (53)	17 (15, 19)	8 (7, 10)	25 (22, 29)	4 (3, 5)	29 (25, 34)
Female	7980 (47)	17 (15, 19)	11 (10, 13)	28 (26, 32)	4 (3, 5)	32 (29, 37)
Types of drinking water source (15,659)						
Improved	13,199 (79)	16 (14, 18)	9 (8, 11)	25 (22, 29)	3 (2, 4)	28 (24, 33)
Unimproved	2460 (15)	15 (13, 17)	12 (10, 13)	27 (23, 30)	7 (5, 8)	34 (28, 38)
Types of sanitation facilities (n = 15,652)						
Improved	6302 (38)	12 (11, 14)	9 (7, 10)	21 (18, 24)	1 (1, 2)	22 (20, 24)
Unimproved	9350 (56)	19 (16, 21)	10 (9, 12)	29 (25, 33)	5 (4, 6)	34 (29, 39)
Types of Cooking Fuel (15,659)						
Improved	2478 (15)	8 (6, 9)	8 (6, 9)	16 (12, 18)	2 (1, 3)	18 (13, 21)
Unimproved	13,182 (78)	18 (16, 20)	10 (9, 12)	28 (25, 32)	4 (3, 5)	32 (28, 37)

Table 1. *Cont.*

Study Variable	n (% *)	NMR [a] (95% CI [f])	PNMR [b] (95% CI)	IMR [c] (95% CI)	CMR [d] (95% CI)	U5MR [e] (95% CI)
Number of ANC visits (n = 16,792)						
4+ANC visits	6660 (40)	9 (8, 11)	8 (6, 9)	17 (14, 20)	2 (1, 3)	19 (15, 23)
1–3 ANC visits	5825 (35)	19 (17, 22)	8 (7, 9)	27 (24, 31)	2 (1, 3)	29 (25, 34)
No ANC visits	4307 (26)	26 (23, 28)	15 (13, 17)	41 (36, 45)	9 (7, 10)	50 (43, 55)
TT Pregnancy Times (n = 16,798)						
Two or more TT	10,143 (60)	12 (10, 13)	7 (6, 9)	19 (16, 22)	2 (1, 3)	21 (17, 25)
One TT	2441 (15)	20 (18, 22)	10 (9, 12)	30 (27, 34)	3 (2, 4)	33 (29, 38)
No TT	4214 (25)	29 (26, 31)	15 (13, 17)	44 (39, 48)	8 (6, 9)	52 (45, 57)
IFA supplementation (16,801)						
Yes	10,168 (61)	13 (11, 15)	8 (7, 9)	21 (18, 24)	1 (1, 2)	22 (19, 26)
No	6633 (39)	23 (21, 25)	13 (11, 14)	36 (32, 39)	7 (6, 9)	43 (38, 48)
Place of delivery (16,801)						
Health facility	5462 (33)	12 (11, 14)	8 (7, 10)	20 (18, 24)	1 (1, 2)	21 (19, 26)
Home facility	11,338 (67)	19 (17, 21)	10 (9, 12)	29 (28, 33)	5 (4, 6)	34 (32, 39)
Delivery assistance (16,801)						
Doctors/nurses	4544 (27)	12 (10, 14)	9 (8, 11)	21 (18, 25)	1 (1, 2)	22 (19, 27)
Others	12,257 (73)	19 (17, 21)	10 (8, 11)	29 (25, 32)	5 (4, 6)	34 (29, 38)
Mode of delivery (16,801)						
Non caesarean	16,006 (95)	18 (16, 20)	10 (8, 11)	28 (24, 31)	4 (3, 5)	32 (27, 36)
Caesarean	796 (5)	6 (5, 7)	10 (9, 12)	16 (14, 19)	2 (1, 3)	18 (15, 22)
Current use of contraceptives at the time of the survey						
Yes	6422 (38)	10 (8, 11)	5 (4, 6)	15 (12, 17)	2 (1, 3)	17 (13, 20)
No	10,380 (62)	22 (19, 24)	13 (11, 14)	35 (30, 38)	5 (4, 6)	40 (35, 44)

* Percentage did not add up to 100% because of missing values. [a] Neonatal Mortality Rates; [b] Post-neonatal Mortality Rates; [c] Infant Mortality Rates; [d] Child Mortality Rates (CMR); [e] Under-five Mortality Rates; [f] Confidence Interval.

Table 2. aHR (95% CI) for factors associated with neonatal, post-neonatal, infant, child and under-five mortality in Nepal, 2001–2016, (n = 15,750).

Variables	Neonatal Mortality (0–30 Days)		Post-Neonatal Mortality (1–11 Months)		Infant Mortality (0–11 Months)		Child Mortality (12–59 Months)		Under-Five Mortality (0–59 Months)	
	aHR (95% CI)	p-value	aHR (95% CI)	p-value	aHR (95% CI)	p-value	aHR (95% CI)	p-value	aHR (95% CI)	p-value
Religion										
Buddhist			1.00							
Hindu			2.48 (1.02, 6.03)	0.046						
Others			3.55 (1.27, 9.93)	0.016						
Ethnicity										
Brahmin/chettri					1.00				1.00	
Dalit					1.19 (0.86, 1.65)	0.285			1.16 (0.85, 1.59)	0.341
Janajati					0.84 (0.63, 1.12)	0.239			0.90 (0.70, 1.16)	0.426
Madhesi					1.82 (1.35, 2.45)	<0.001			1.73 (1.29, 2.32)	<0.001
Mother's literacy level										
Can read	1.00								1.00	
Cannot read	1.57 (1.13, 2.17)	0.007							1.33 (1.03, 1.72)	0.031
Mother's occupation										
Not working			1.00		1.00				1.00	
Agriculture			1.82 (1.03, 3.22)	0.040	1.45 (1.06, 2.00)	0.022			1.45 (1.06, 1.96)	0.018
Skilled/professional			2.33 (0.99, 5.46)	0.053	2.15 (1.38, 3.35)	0.001			2.15 (1.40, 3.30)	<0.001
Mother's age										
40–49	1.00		1.00		1.00				1.00	
30–39	1.46 (0.83, 2.58)	0.192	2.20 (1.08, 4.50)	0.031	1.68 (1.07, 2.63)	0.025			1.41 (0.95, 2.08)	0.085
20–29	1.71 (0.97, 3.01)	0.065	3.28 (1.39, 7.77)	0.007	2.09 (1.30, 3.37)	0.002			1.88 (1.24, 2.86)	0.003
<20	2.39 (1.13, 5.05)	0.022	5.04 (1.73, 14.7)	0.003	3.05 (1.64, 5.66)	<0.001			2.76 (1.57, 4.85)	<0.001
Birth rank and birth interval										
2nd/3rd birth rank, >2 years	1.00		1.00		1.00		1.00		1.00	
1st child	2.91 (1.79, 4.74)	<0.001	2.12 (1.10, 4.10)	0.025	2.56 (1.72, 3.80)	<0.001	1.87 (0.54, 6.47)	0.322	2.55 (1.77, 3.68)	<0.001
2nd/3rd birth rank, interval ≤2 years	1.22 (0.75, 1.99)	0.421	1.01 (0.53, 1.92)	0.985	1.15 (0.76, 1.73)	0.501	1.43 (0.44, 4.58)	0.551	1.16 (0.78, 1.73)	0.463
4th/higher birth rank, interval >2 years	0.29 (0.17, 0.50)	<0.001	0.54 (0.27, 1.07)	0.078	0.37 (0.24, 0.56)	<0.001	0.33 (0.14, 0.78)	0.011	0.36 (0.24, 0.52)	<0.001
4th/higher birth rank, interval ≤ 2 years	0.62 (0.34, 1.11)	0.109	0.52 (0.26, 1.05)	0.066	0.60 (0.38, 0.95)	0.028	0.78 (0.39, 1.59)	0.499	0.62 (0.42, 0.91)	0.015
Previous death of a child										
No	1.00		1.00		1.00		1.00		1.00	
Yes	17.33 (11.44, 26.26)	<0.001	13.05 (7.19, 23.67)	<0.001	15.90 (11.38, 22.22)	<0.001	16.98 (6.19, 46.58)	<0.001	15.97 (11.64, 21.92)	<0.001
TT Pregnancy Times										
Two or more TT	1.00		1.00		1.00		1.00		1.00	
One TT	1.65 (1.04, 2.60)	0.033	1.34 (0.78, 2.29)	0.289	1.51 (1.06, 2.16)	0.022	1.62 (0.58, 4.54)	0.353	1.54 (1.09, 2.16)	0.013
No TT	2.28 (1.68, 3.09)	<0.001	1.86 (1.24, 2.79)	0.003	2.44 (1.89, 3.15)	<0.001	2.93 (1.51, 5.69)	0.002	2.39 (1.89, 3.01)	<0.001
Contraceptive use										
yes	1.00		1.00		1.00		1.00		1.00	
No	1.69 (1.21, 2.37)	0.002	2.69 (1.67, 4.32)	<0.001	2.01 (1.53, 2.64)	<0.001	2.47 (1.30, 4.71)	0.005	2.03 (1.57, 2.62)	<0.001

aHR: adjusted Hazard Ratio; Hazard ratio adjusted for: model 3; and number of ANC visits, TT pregnancy times, IFA supplementation, place of delivery, delivery assistance, mode of delivery, and current use of contraceptives at the time of the survey.

Table 3. Estimated PAR with 95% CI for common significant factors for child mortality across the five age groups in Nepal, 2001–2016 (n = 15,750).

Variable	Neonatal Mortality			Post-Neonatal Mortality			Infant Mortality			Child Mortality			Under-Five Mortality		
Previous death of a child	n *	aHR $	PAR (95% CI)	n *	aHR $	PAR (95% CI)	n *	aHR $	PAR (95% CI)	n *	aHR $	PAR (95% CI)	n *	aHR $	PAR (95% CI)
No	38.2	1.00		44.1	1.00		40.4	1.00		27.1	1.00		38.8	1.00	
Yes	61.8	17.3	58.2 (50.5–65.2)	55.9	13.05	51.6 (40.2–62.0)	59.6	15.9	55.9 (49.6–61.7)	72.9	16.98	68.6 (48.7–82.1)	61.2	15.97	57.4 (51.5–62.9)
TT pregnancy times															
Two or more	40.8	1.00		46.8	1.00		43.0	1.00		33.6	1.00		41.8	1.00	
One TT	16.7	1.65	6.58 (0.45–14.2)	15.3	1.34	—	16.2	1.51	5.47 (0.70–11.3)	12.4	1.62	—	15.8	1.54	5.54 (1.01–10.9)
No TT	42.4	2.28	23.8 (14.6–33.2)	37.9	1.86	17.5 (5.81–29.8)	40.8	2.44	24.1 (16.8–31.5)	54.0	2.93	35.6 (14.2–54.5)	42.4	2.39	24.7 (17.7–31.7)
Contraceptive use															
Yes	21.7	1.00		19.0	1.00		20.7	1.00		27.7	1.00		21.0	1.00	
No	78.3	1.69	32.0 (12.5–48.3)	81.0	2.69	50.9 (29.6–66.6)	79.3	2.01	39.9 (25.9–51.6)	77.3	2.47	46.0 (15.1–67.8)	79.0	2.03	40.1 (27.2–51.1)

* Weighted proportion of deaths in each of the five age groups. aHR: adjusted Hazard Ratio; PAR: Population Attributable Risk; CI: Confidence Interval. $ Adjusted model included: model 3; and number of ANC visits, TT pregnancy times, IFA supplementation, place of delivery, delivery assistance, mode of delivery, and current use of contraceptives at the time of the survey.
— PAR was not estimated because variables were not significant.

4. Discussion

In Nepal, rates of neonatal, post-neonatal, infant, child and under-five mortality have declined over the past 15 years. In this study, mothers who reported previous death of a child, who did not receive TT vaccines during pregnancy, and nonuse of contraceptives among mothers were found to be associated with neonatal, post-neonatal, infant, child or under-five mortality. We also found that mothers aged <20 years, and those who reported of having a first birth were significantly associated with neonatal, post- neonatal, infant and under-five mortality. In addition, mothers who did not use antenatal IFA supplementation were at greater risk of having neonatal, infant, child and under-five mortality.

Despite substantial improvements in reducing overall under-five mortality within the Asia Pacific region, the progress made during MDG period has been uneven across countries [1], and in a country like Nepal, the current child mortality rate stands well above child survival SDG targets (20 under-five mortality and 12 neonatal mortality per 1000 births by the year 2030).

Our study identified that rates of neonatal, post-neonatal, infant, child and under-five mortality were significantly associated with mothers who reported of having previous death of a child compared to mothers whose previous child survived. This finding is consistent with a previous population-based study conducted in Bangladesh [19]. A plausible reason for this higher risk of mortality may be attributed due to long-term psychological effect of child death on parents [25] resulting in poor nutrition and inadequate essential healthcare given to the surviving children.

The global burden of disease study conducted in 2015 estimated that the neonatal tetanus mortality rate per 100,000 persons in Nepal (778.52) was higher than Bangladesh (442.94), India (314.21), and Pakistan (358.50) [3]. This study found that mothers who did not receive at least two doses of TT vaccines during pregnancy were more likely to report child mortality across all five age subgroups. This finding is consistent with previous population-based studies in Nepal and Bangladesh [8,19]. Blencowe et al. argued that if mothers received the two recommended dosages of TT vaccination during pregnancy, tetanus related under-five mortality would reduce by 94%, particularly during the neonatal period (0–30 days) [26].

In Nepal, 26% of married women of reproductive age have an unmet need for family planning [4,13–15]. Our study found that mothers who were nonusers of contraception were significantly more likely to have a child death in all age subgroups. Shah et al. suggested that the use of contraceptives would reduce child mortality by creating a long birth interval [27] and the impact of short birth intervals on child survival has been well documented in previous studies [5,19].

Higher risk of neonatal, post-neonatal, infant and under-five mortality with mothers aged < 20 years compared to older mothers in our study is in agreement with previous studies [19,28]. An increased risk of mortality observed in the current study may be attributed to inadequate use of obstetric and or antenatal care by younger mothers [29], which often leads to preterm births and low birth weights [30]. Additionally, younger mothers are more likely to be poor, uneducated and unemployed [31], which may affect the health of their infants.

Our study found that first order births had a significantly greater risk of neonatal, post neonatal, infant and under-five mortality compared with subsequent infants. Existing research has argued that an increased risk of mortality among first-born children may be linked to the high number of young women <20 years of age, in particular, having first births [32]. The increased risk of mortality among the first-born children in this study may be attributed to the fact that a substantial proportion (18%) of Nepalese women gave birth before they reached 20 years of age [4,13–15]. A conceivable explanation to this may be due to younger mother's physical and reproductive immaturity as well as poor nutritional intake during pregnancy, which often leads to low birth weight. More importantly, young mothers are infrequent users of maternal health care services [33].

Similar to the findings from studies conducted in Nepal and Indonesia [5,7,34], this study showed that neonatal, infant, child, and under-five mortality were significantly higher among mothers who did not use antenatal IFA supplementation. Literature suggests that iron deficiency is the most common cause of maternal anaemia; and anaemia during pregnancy is associated with higher risk of prematurity and low birth weight [35,36]. The protective effect of antenatal IFA against child mortality may be aggravated due to the fact that IFA help reduce anaemia during pregnancy so as the prematurity and low birth weight.

The nonsignificant mortality decline in the post-neonatal group in this study may be due to the focus on neonatal mortality of the IFA intervention in Nepal aimed at reducing neonatal mortality. The IFA program in Nepal was expanded across all districts by 2012, which may have resulted a significant reduction of neonatal mortality in 2016 compared with 2011 [37].

Strengths and Limitations

This study has several strengths and limitations. First, the study has a great statistical power to detect statistical differences because four NDHS datasets that lies within MDGs period were combined; and the findings can shed light for effective intervention to help achieve SDG child survival targets. Second, the most recent singleton live births five years prior to each survey were considered for analyses to reduce maternal recall bias [5,34]. Third, the data used in this study was nationally representative with average response rate of 97%; therefore, the findings from this study can be generalizable to the entire Nepalese population. Despite these strengths, this study also has some limitations. First, we cannot make casual inference with observational data such as cross-sectional data used in this study. Second, it is also possible that the number of deaths may have been under-reported because only surviving mothers gave an account of their child's birth and death during the surveys; and hence, the mortality estimates reported in this study may have been under estimated or overestimated. Third, information on the medical history of the child and mother as well as the cause of child death was unknown as verbal autopsy was not conducted in 2001 and 2011 NDHS. Fourth, information on respiratory infections, diarrhea, nutritional and vaccination status were only collected for surviving children and we were not able to include these important variables in this study.

5. Conclusions

We found that mothers with a previous death of a child, who did not receive TT vaccines during pregnancy, and those who were nonusers of contraceptives were at greater risk of having neonatal, post-neonatal, infant, child and under-five mortality in Nepal. Hence, to achieve child survival SDG targets, our findings indicate the need for community-based family planning interventions such as the promotion of contraceptives as well as universal coverage of two recommended doses of TT vaccines during pregnancy, and these interventions should target women from socioeconomically marginalized groups as well as those who have had previous death of a child.

Supplementary Materials: The following are available online at http://www.mdpi.com/1660-4601/16/7/1241/s1, Table S1: aHR and 95% Confidence Interval (CI) for factors associated with neonatal, post-neonatal, and infant mortality in Nepal (2001–2016), Table S2: aHR and 95% Confidence Interval (CI) for factors associated with child, and under-five mortality in Nepal (2001–2016).

Author Contributions: P.R.G. and K.E.A. were involved in the conceptualization of this study. P.R.G. carried out the formal analysis and drafted the manuscript. P.R.G., K.E.A., O.K.E., A.M.N.R., M.D., and C.R.-G. were involved in the revision and editing of the manuscript. All authors read and approved the final manuscript.

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References

1. United Nations Inter-Agency Group for Child Mortality Estimation (UN IGME). *Levels & Trends in Child Mortality: Report 2017, Estimates Developed by the UN Inter-Agency Group for Child Mortality Estimation*; United Nations Children's Fund: New York, NY, USA, 2017.
2. Liu, L.; Oza, S.; Hogan, D.; Chu, Y.; Perin, J.; Zhu, J.; Lawn, J.E.; Cousens, S.; Mathers, C.; Black, R.E. Global, regional, and national causes of under-five mortality in 2000–2015: An updated systematic analysis with implications for the Sustainable Development Goals. *Lancet* **2016**, *388*, 3027–3035. [CrossRef]
3. Kyu, H.H.; Mumford, J.E.; Stanaway, J.D.; Barber, R.M.; Hancock, J.R.; Vos, T.; Murray, C.J.; Naghavi, M. Mortality from tetanus between 1990 and 2015: Findings from the global burden of disease study 2015. *BMC Public Health* **2017**, *17*, 179. [CrossRef]
4. Ministry of Health and Population (MOHP) [Nepal], New ERA, and ICF International Inc. *Nepal Demographic and Health Survey 2016*; Ministry of Health and Population, New ERA, and ICF International: Kathmandu, Nepal; Calverton, MD, USA, 2017.
5. Nisar, Y.B.; Dibley, M.J.; Mebrahtu, S.; Paudyal, N.; Devkota, M. Antenatal Iron-Folic Acid Supplementation Reduces Neonatal and Under-five Mortality in Nepal. *J. Nutr.* **2015**, *145*, 1873–1883. [CrossRef] [PubMed]
6. Khadka, K.B.; Lieberman, L.S.; Giedraitis, V.; Bhatta, L.; Pandey, G. The socio-economic determinants of infant mortality in Nepal: Analysis of Nepal Demographic Health Survey, 2011. *BMC Pediatr.* **2015**, *15*, 152. [CrossRef] [PubMed]
7. Christian, P.; Stewart, C.P.; LeClerq, S.C.; Wu, L.; Katz, J.; West, K.P., Jr.; Khatry, S.K. Antenatal and postnatal iron supplementation and childhood mortality in rural Nepal: A prospective follow-up in a randomized, controlled community trial. *Am. J. Epidemiol.* **2009**, *170*, 1127–1136. [CrossRef] [PubMed]
8. Katz, J.; West, K.P., Jr.; Khatry, S.K.; Christian, P.; LeClerq, S.C.; Pradhan, E.K.; Shrestha, S.R. Risk factors for early infant mortality in Sarlahi district, Nepal. *Bull. World Health Organ.* **2003**, *81*, 717–725.
9. Lamichhane, R.; Zhao, Y.; Paudel, S.; Adewuyi, E.O. Factors associated with infant mortality in Nepal: A comparative analysis of Nepal demographic and health surveys (NDHS) 2006 and 2011. *BMC Public Health* **2017**, *17*, 53. [CrossRef]
10. Sreeramareddy, C.T.; Kumar, H.H.; Sathian, B. Time trends and inequalities of under-five mortality in Nepal: A secondary data analysis of four demographic and health surveys between 1996 and 2011. *PLoS ONE* **2013**, *8*, e79818. [CrossRef] [PubMed]
11. Naz, S.; Page, A.; Agho, K.E. Potential impacts of modifiable behavioral and environmental exposures on reducing burden of under-five mortality associated with household air pollution in Nepal. *Matern. Child Health J.* **2018**, *22*, 59–70. [CrossRef] [PubMed]
12. Hong, R. Effect of multiple birth on infant mortality in Bangladesh. *J. Paediatr. Child Health* **2006**, *42*, 630–635. [CrossRef]
13. Ministry of Health [Nepal], New ERA, and ORC Macro. *Nepal Demographic and Health Survey 2001*; Family Health Division, Ministry of Health, New ERA, and ORC Macro: Calverton, MD, USA, 2002.
14. Ministry of Health and Population (MOHP) [Nepal], New ERA, and Macro International Inc. *Nepal Demographic and Health Survey 2006*; Ministry of Health and Population, New ERA, and Macro International Inc.: Kathmandu, Nepal, 2007.
15. Ministry of Health and Population (MOHP) [Nepal], New ERA, and ICF International Inc. *Nepal Demographic and Health Survey 2011*; Ministry of Health and Population, New ERA, and ICF International: Kathmandu, Nepal; Calverton, MD, USA, 2012.
16. Keith, L.G.; Oleszczuk, J.J.; Keith, D.M. Multiple gestation: Reflections on epidemiology, causes, and consequences. *Int. J. Fertil. Women's Med.* **2000**, *45*, 206–214.
17. Titaley, C.R.; Dibley, M.J.; Agho, K.; Roberts, C.L.; Hall, J. Determinants of neonatal mortality in Indonesia. *BMC Public Health* **2008**, *8*, 232. [CrossRef]
18. Mosley, W.H.; Chen, L.C. An analytical framework for the study of child survival in developing countries. *Popul. Dev. Rev.* **1984**, *10*, 25–45. [CrossRef]
19. Abir, T.; Agho, K.E.; Page, A.N.; Milton, A.H.; Dibley, M.J. Risk factors for under-five mortality: Evidence from Bangladesh Demographic and Health Survey, 2004–2011. *BMJ Open* **2015**, *5*, e006722. [CrossRef]
20. Filmer, D.; Pritchett, L.H. Estimating wealth effects without expenditure data-or tears: An application to educational enrollments in states of India. *Demography* **2001**, *38*, 115–132.

21. UNICEF; WHO. *Progress on Drinking Water and Sanitation Joint Monitoring Programme Update 2015*; UNICEF: New York, NY, USA, 2015.
22. Rutstein, S.O.; Rojas, G. *Guide to DHS Statistics: Demographic and Health Surveys Methodology*; ORC Macro: Calverton, MD, USA, 2006.
23. Victora, C.G.; Huttly, S.R.; Fuchs, S.C.; Olinto, M.T. The role of conceptual frameworks in epidemiological analysis: A hierarchical approach. *Int. J. Epideliol.* **1997**, *26*, 224–227. [CrossRef]
24. Stafford, R.J.; Schluter, P.J.; Wilson, A.J.; Kirk, M.D.; Hall, G.; Unicomb, L.; OzFoodNet Working Group. Population-attributable risk estimates for risk factors associated with Campylobacter infection, Australia. *Emerg. Infect. Dis.* **2008**, *14*, 895–901. [CrossRef]
25. Krell, R.; Rabkin, L. The effects of sibling death on the surviving child: A family perspective. *Fam. Process* **1979**, *18*, 471–477. [CrossRef]
26. Blencowe, H.; Lawn, J.; Vandelaer, J.; Roper, M.; Cousens, S. Tetanus toxoid immunization to reduce mortality from neonatal tetanus. *Int. J. Epidemiol.* **2010**, *39*, i102–i109. [CrossRef]
27. Saha, U.R.; van Soest, A. Contraceptive use, birth spacing, and child survival in Matlab, Bangladesh. *Stud. Fam. Plann.* **2013**, *44*, 45–66. [CrossRef]
28. Ghosh, R.; Bharati, P. Determinants of infant and child mortality in periurban areas of Kolkata city, India. *Asia Pac. J. Public Health* **2010**, *22*, 63–75. [CrossRef]
29. Loto, O.M.; Ezechi, O.C.; Kalu, B.K.E.; Loto, A.B.; Ezechi, L.O.; Ogunniyi, S.O. Poor obstetric performance of teenagers: Is it age-or quality of care-related? *J. Obstet. Gynaecol.* **2004**, *24*, 395–398. [CrossRef]
30. Yadav, S.; Choudhary, D.; Narayan, K.C.; Mandal, R.K.; Sharma, A.; Chauhan, S.S.; Agrawal, P. Adverse reproductive outcomes associated with teenage pregnancy. *McGill J. Med.* **2008**, *11*, 141–144.
31. Sayem, A.M.; Nury, A.T. Factors associated with teenage marital pregnancy among Bangladeshi women. *Reprod. Health* **2011**, *8*, 16. [CrossRef]
32. Oyefara, J.L. Maternal age at first birth and childhood mortality in yoruba society: The case of Osun State, Nigeria. *Res. Humanit. Soc. Sci.* **2013**, *3*, 246–254.
33. Kamal, S.M. What is the association between maternal age and neonatal mortality? An analysis of the 2007 Bangladesh Demographic and Health Survey. *Asia Pac. J. Public Health* **2015**, *27*, 1106–1117. [CrossRef]
34. Dibley, M.J.; Titaley, C.R.; d'Este, C.; Agho, K. Iron and folic acid supplements in pregnancy improve child survival in Indonesia. *Am. J. Clin. Nutr.* **2011**, *95*, 220–230. [CrossRef]
35. Haider, B.A.; Olofin, I.; Wang, M.; Spiegelman, D.; Ezzati, M.; Fawzi, W.W. Anaemia, prenatal iron use, and risk of adverse pregnancy outcomes: Systematic review and meta-analysis. *BMJ* **2013**, *346*, f3443. [CrossRef]
36. Imdad, A.; Bhutta, Z.A. Routine iron/folate supplementation during pregnancy: Effect on maternal anaemia and birth outcomes. *Paediatr. Perinat. Epidemiol.* **2012**, *26*, 168–177. [CrossRef]
37. Nisar, Y.B.; Dibley, M.J. Earlier initiation and use of a greater number of iron-folic acid supplements during pregnancy prevents early neonatal deaths in Nepal and Pakistan. *PLoS ONE* **2014**, *9*, e112446. [CrossRef]

SECTION V: Summary

CHAPTER 7: summary and recommendations for future research

This section presents an overview of the main research findings, Policy implications, the strengths and limitations of the study, recommendations for future research and conclusion.

7.1 Overview of the main findings

In order to achieve the main aim of this thesis, four specific objectives were each addressed in individual studies. First, a systematic review and meta-analysis of observational studies were conducted to estimate rates and identify factors associated with perinatal mortality across South Asia. Second, the socio-economic predictors of stillbirth in Nepal were examined. Third, the factors associated with perinatal mortality in Nepal were identified. Finally, under-5 mortality and common associated factors were examined. An overview of the main findings from each study is provided below:

Systematic review of observational studies on factors associated with perinatal mortality in South Asia

A total of 2,921 articles were retrieved from five databases, of which 14 studies were retained after meeting the selection criteria. The most common factors associated with perinatal mortality in South Asia were: low socioeconomic status, lack of quality health care services, pregnancy complications, and lack of antenatal care**.** The meta-analysis reported the pooled perinatal mortality rate across South Asia as 49 [95% CI: 41, 57] per 1000 births.

Socio-economic predictors of stillbirths in Nepal

A total of 18,386 pregnancies of at least 28 weeks' gestation were identified. Of these pregnancies, 335 stillbirths were reported. The predictors of stillbirth were older maternal age (>25years); mothers residing in mountainous or hilly regions; mothers whose religion was Hindu, Muslim, Christian and others; parents with no schooling or only primary level of education; mothers whose major occupation was agriculture and those who used open defecation.

Factors associated with Perinatal Mortality in Nepal: Evidence from Nepal Demographic and Health Survey

Over the study period (2001-2016), the Perinatal Mortality (PM) rate was 42[95% CI: 39, 44] per 1000 births, whereas the Extended Perinatal Mortality (EPM) rate was 49 (95% CI: 46, 51) per 1000 births. In this study, women who did not use contraceptives, women aged 19-24 years, women with no education and women residing in the mountains were more predisposed to PM and EPM. This study also reported higher PM and EPM within households using biomass as the cooking fuel, and households with unimproved sanitation practices.

Under-5 Mortality and Associated Factors: Evidence from the Nepal Demographic and Health Survey

A weighted total of 16,802 most recent singleton live births were reported in the five years preceding each survey conducted between 2001 and 2016. In this weighted total, 512 under-5 deaths were reported. Our study found that the rate of under-5 mortality decreased significantly by 53% over 15 years. The most common factors associated with under-5 mortality across all age sub-groups included: previous death of a child, inadequate Tetanus Toxoid vaccination during pregnancy (< 2 doses), and non-usage of contraceptives.

7.2 Policy implications of findings

The findings reported in this thesis will assist policy-makers in evaluating existing child survival health interventions as well as formulating effective public health policies aimed at reducing perinatal and childhood mortality at the individual, household, and community level.

Individual-level policy

Maternal and child health interventions such as antenatal care, institutional birthing services, basic and emergency obstetric care could improve child survival, especially if accessible to all women irrespective of geographical location, ethnic or religious background and socioeconomic status. Hence, health promotion programs on emphasising the benefits of using available maternal and child health care services are essential, and these programs should be scaled up in rural areas as well as for the poor and marginalised communities.

Household level policy

Findings from this study suggest the need for public health intervention strategies towards improving household sanitation and the use of environmental-friendly cooking fuels. Such interventions should focus on creating awareness on the health hazard of using solid fuel and the provision of affordable and accessible efficient cooking stoves, particularly in rural areas. In addition, public awareness campaigns on the benefits of maintaining optimal household sanitation practices in relation to effective control of environmental pollution should be conducted, and such campaigns should target rural and low socioeconomic status households to enhance child survival in Nepal.

Community-level policy

The health system in Nepal is primarily financed by out-of-pocket money [34]. Therefore, community-based income generating programs which empower women with a poor socioeconomic background to afford the use of essential maternal and child health care services are needed. In addition, to close the health-related equity gap and promote social justice, maternal and child health care service provided by the government should be accessible to those who are socio-economically marginalised.

7.3 Strengths and limitations of the research

This research has several key strengths. First, the four NDHS datasets that lies in between the MDGs period (2001-2016) were combined for increased sample size to detect any statistical differences including sub-group analysis. Second, the NDHS is a nationally representative, population-based survey with high response rate of 99.6%, 99.6%, 99.4%, and 99.6% for the year 2001 [11], 2006 [12], 2011 [13], and 2016 [14] respectively and the findings and the findings from our study can be generalizable to the entire Nepalese population. Third, the most recent live births five years prior to each survey were considered for analyses for under-5 mortality to reduce maternal recall bias, as well as to minimise bias that may also occur due to changes in household characteristics. Fourth, to capture more accurate estimates, our study on factors associated with under-5 mortality excluded multiple births because past studies have shown the higher risk of neonatal mortality due to pregnancy complications and preterm birth among multiple births compared to singleton births [23, 24].

Despite aforementioned strengths, this study also has some limitations. First, data on antenatal care, Iron and Folic Acid (IFA) supplementation, Tetanus Toxoid vaccine during pregnancy, and types of delivery (institutional vs. home delivery) were not collected for stillbirth. Second, NDHS did not collect data on timing of stillbirths; and hence, this study could not distinguish whether the death was antepartum or intrapartum. However, it is important to know that the risk factors for antepartum stillbirth may differ from intrapartum stillbirth that may require different intervention [15, 16, 87]. Third, formal verbal autopsies were not collected in NDHS (2001-2016). Hence, causes more proximal to perinatal deaths such as history of previous stillbirth, prematurity, fetal growth, low birth weight, obstetric complications such as breech delivery, and birth asphyxia mm [19, 88-90] could not be included. Fourth, due to the cross-sectional nature of the study design, this study is limited in its ability to establish causal effects between the explanatory variables and the outcome variables (stillbirth, perinatal and child mortality). Fifth, only surviving mothers were interviewed, and this might have resulted in under-reporting of the number of deaths.

7.4 Future research

This thesis has also identified number of research gaps, and future studies can build upon those gaps. First, obstetric complications including gestational diabetes, placenta previa, breech delivery, and birth asphyxia have been documented as important causes of perinatal mortality which can be identified and managed through quality antenatal and delivery care. Because NDHS did not collect data on antenatal and delivery care for stillborn babies, future population based studies are essential to allow comprehensive understanding of the impact of quality of antenatal and delivery care for pregnancies that ended in stillbirths.

Studies that can quantify the burden as well as identify the risk factors associated with antepartum and intrapartum stillbirths at a national level could be future research to inform effective population specific intervention.

Third, important medical and non-medical factors such as child respiratory infections, diarrhoea, nutritional and vaccination status, road accidents and burns have been considered as important contributors to child death in developing countries (including Nepal). NDHS did not collect data on these important medical and non-medical causes of under-5 mortality. Therefore, incorporating different medical and non-medical causes of under-5 mortality in future research may help validate the estimates obtained from this study.

7.5 Conclusion

This study has provided detailed evidence on factors associated with perinatal and under-5 mortality in Nepal by using the NDHS data for the period (2001-2016). The study of socio-economic predictors of stillbirth in Nepal highlights women residing in the mountain ecological zone, and those who are socio-economically marginalized are associated with stillbirth. This study also confirmed that lower socio-economic status, non-use of contraceptives, and the use of biomass for cooking at home were the key drivers for perinatal mortality in Nepal. Similarly, mothers who reported previous death of a child, non-use of contraceptives, and those who did not receive at least 2 doses of TT vaccine during pregnancy were found to be associated with under-5 mortality. Findings from this study will help to improve maternal and child health intervention in Nepal.

Appendix

Ghimire PR, Agho KE, Renzaho AM, Dibley M, Raynes-Greenow C. Association between health service use and diarrhoea management approach among caregivers of under-five children in Nepal. PloS one. 2018 Mar 1; 13(3):e0191988.

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RESEARCH ARTICLE

Association between health service use and diarrhoea management approach among caregivers of under-five children in Nepal

Pramesh Raj Ghimire[1] *, **Kingsley Emwinyore Agho**[1], **Andre M. N. Renzaho**[2], **Michael Dibley**[3], **Camille Raynes-Greenow**[3]

1 School of Science and Health, Western Sydney University, Penrith, New South Wales, Australia, **2** School of Social Sciences and Psychology, Western Sydney University, Penrith, New South Wales, Australia, **3** Sydney School of Public Health, University of Sydney, Sydney, New South Wales, Australia

* prameshraj@hotmail.com

Abstract

Introduction

Diarrhoea among children under-five is a serious public health problem in many developing countries, including Nepal. This study aimed to examine the association between health service utilization and diarrhoea management approaches among children under-five years in Nepal.

Methods

The combined 2001, 2006 and 2011 Nepal Demographic and Health Survey (NDHS) data sets were examined and the sample included 2,655 children aged 0–59 months who had diarrhoea 2-weeks prior to the each survey. Multilevel logistic regression analyses that adjust for clustering and sampling weight were used to examine the association between health service utilization and diarrhoea management approaches (Oral Rehydration Solution, increased fluids and/or continued feeding).

Results

The prevalence of extra fluids decreased significantly from 27% in 2001 to 15% in 2011 while that of ORS increased significantly from 32% in 2001 to 40% in 2011. The prevalence of continued feeding fluctuated between 83–89%. Multivariate analysis revealed that caregivers whose children received treatment or advice from health care providers during diarrhoea were 5.78 times more likely to treat diarrhoea with Oral Rehydration Solution (ORS) [adjusted Odds Ratio (aOR) 5.78, 95% confidence interval (CI) 4.50, 7.44], 1.56 (aOR 1.56, 95% CI 1.19, 2.05) times more likely to offer extra fluids, and 2.25 (aOR 2.25, 95% CI 1.50, 3.39) times more likely to use continued feeding than those who did not seek advice.

Conclusions

Our findings indicate that health service utilization significantly improves diarrhoea management among under-five children. However, a broader national diarrhoeal disease control program to further reduce diarrhoea related morbidity and mortality in Nepal should focus on

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educating caregivers about the importance of the use of ORS as well as increase fluid intake to children under-five years with diarrhoea.

Introduction

Globally, diarrhoea remains a leading cause of under-five mortality and morbidity, particularly in low-and middle-income countries including Nepal [1, 2, 3]. The 2015 global burden of disease study estimated that nearly half a million under-five deaths were caused by diarrhoea, and south Asia (including Nepal) stands second to sub-Saharan Africa with the highest number of these under-five deaths [3].

During the past three decades, international organizations such as World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) have proposed various management approaches for diarrhoea[4]. The first line approaches include: the use of oral rehydration solutions (ORS), increasing fluid intake, use of zinc supplements and continued feeding (including breastfeeding)[4, 5]. The impact of diarrhoeal disease control programs on childhood mortality have been documented in previous studies conducted in Egypt and the Philippines[6, 7]. These studies revealed that the decline in child mortality associated with diarrhoea may be due to increased use of ORS, extra fluids and continued feeding [6, 7], and other research concluded that diarrhoea management approaches are cost effective in reducing the overall burden of diarrhoea [8–14].

In Nepal, the national diarrhoeal disease control program emphasizes the use of the four treatment approaches for childhood diarrhoea; ORS, zinc supplementation, counselling on continued feeding to the caregivers, and the use of extra fluids; which are provided at all levels of the Nepalese health care system [15, 16]. Despite these initiatives, diarrhoea remains a public health concern, particularly in remote regions[17, 18]. Recently, the prevalence estimates for diarrhoea increased from 12% in 2006[19] to 14% in 2011[15]. Almost 50% of Nepalese children who experience diarrhoea do not have access to basic diarrhoea treatment approaches such as ORS or extra fluids[15].

There is substantial variation in uses around ORS, extra fluids and continued feeding as reported in the Nepal Demographic and Health Surveys of 2001, 2006 and 2011[15, 19, 20]. Hence, studies that examine the impact of health service use on ORS, continued feeding and/or extra fluids during childhood diarrhoea would provide important locally-relevant evidence to inform context-specific interventions geared towards reducing diarrhoea-related morbidity and mortality among children under-five years. Therefore, the aim of this study was to examine the association between health service use and diarrhoea management approaches among children aged 0–5 years in Nepal using nationally representative data from the Nepal Demographic and Health Survey (NDHS) for the years 2001, 2006 and 2011. This paper also provide insights into the three main diarrhoeal management approaches used by Nepalese government in order to be able to recommend the changes necessary for the successful implementation of the national diarrheal disease control program.

Methods

Data sources

The present study used nationally representative data from the Nepal Demographic and Health Survey (NDHS) for the period (2001–2011). The present analyses is based on publicly available NDHS datasets collected for the years 2001, 2006 and 2011[21]. Using multi-stage cluster sampling design, all NDHS collected data on various socio-demographic and health indicators including diarrhoea prevalence and its management approaches. The average response of three recent NDHS was 98.2% and the sample represents more than 98% of Nepal's population. The details of survey methodology, sampling techniques and standard questionnaires are described elsewhere[15, 19, 20].

From 17,714 children aged 0–5 years (N = 6978 in 2001 NDHS[15], N = 5545 in 2006 NDHS[19], and N = 5391 in 2011 NDHS[20]), a sample of 2655 children (n = 1320 in 2001 NDHS, n = 624 in 2006 NDHS, and n = 711 in 2011 NDHS) who had diarrhoea 2 weeks prior the interviews of each survey were identified. The sample population was weighted to adjust for the multi stage cluster sampling effect.

Outcome variables

In the NDHS, if a child had diarrhoea two weeks prior to each survey, mothers were asked how much a child was given to drink (including breastmilk), how much a child was given to eat, and was a child given a fluid made from ORS packets during the diarrhoea. The outcome variables are: (a) use of ORS, (b) use of increased fluids, (c) use of continued feeding (d) combination of all treatment approaches (ORS & extra fluids & continued feeding) and (e) combination of any treatment approaches (ORS or extra fluids or continued feeding) during recent diarrhoeal episodes. If a child had diarrhoea and was given fluid made from ORS packets, it was coded as 1, otherwise 0. If a child had diarrhoea and was given more liquids to drink, it was coded as 1, otherwise 0. If a child had diarrhoea and was given more, same as usual, or somewhat less food, it was coded as 1, otherwise 0.

Exposure variable

The exposure variable of the study was derived from the women's questionnaire for the section of immunization and health (Did you seek advice or treatment for the diarrhoea from any source?). The exposure variable was coded as 1 if the parents or carer of a child with diarrhoea sought treatment or advice from health care providers (except from pharmacies, shops and traditional practitioners), otherwise coded as 0.

Potential confounding factors

The confounding factors examined in the study were based on the modified Anderson behavioural model[22] to examine the relationship between health service use and diarrhoea management approaches (Fig 1). We analysed 15 key confounding factors and they were classified as: external environment, predisposing factor, enabling factor and need factor. The external environmental factors consisted of: type of residence (Rural and Urban), ecological zone (Mountain, Hill and Terai), and geographical region (Eastern, Central, Western, Mid-Western and Far-Western). Nepal was divided into five Development Regions: Mid-Western, Western, Eastern, Central and Far-Western [15,19,20,23]. The Mid-Western Development Region comprised of three zones (Karnali, Bheri, Rapti) whereas, Western Development Region comprised of three zones (Gandaki. Lumbini, Daulagiri). Similarly, Eastern Development Region and Central Development Region covered three zones (Mechi, Koshi, Sagarmatha) and (Janakpur, Bagmati, Narayani), respectively. Far-Western Development Region only comprised two zones (Seti, Mahakali). Mid-Western, Western, Eastern, Central and Far-Western Development Regions covered 28%, 20%, 19%, 19% and 14%, respectively of the total land of Nepal [15,19,20,23]. The predisposing factors included mother's current age, mother's education, mother's literacy level, father's education, parity, mother's religion, and mother's working status. The enabling factors examined were mother's occupation, household wealth index and the sex of the child. The household wealth index measures the economic status of the household. We used the wealth index factor scores as calculated by original DHS[15, 19, 20]. The combined original household wealth index factor scores were categorised into three: the bottom, 40% of households was referred to as poor households, the next 40% as the middle households and the top 20% as rich households, consistent with previous studies[24, 25].

Statistical analysis

As part of the analysis, weighted frequency tabulation and percentage of study variables were first performed for exposure and all confounding factors. This was followed by univariate analyses that independently examined the association of all potential confounding and exposure variables. Multivariate analyses were used to examine the association between health service use and diarrhoea management approaches. As part of the multivariate analyses, staged modelling technique[26] was employed. As a process of staged hierarchical modelling technique, all external environmental factors were first entered into the baseline multivariable model with backward elimination to remove statistically non-significant variables (Model 1). Similarly, in the next stage, predisposing factors were examined with model 1 (Model 2). Next, enabling factors were assessed with model 2 (Model 3). Afterward, need factors were examined with model 3 (Model 4). In the final model (model 5), we examined the use of health service variable with the statistically significant environmental, predisposing, enabling, and need factors identified in the previous model. Variables significantly associated at the 5% significance level with each outcome measure were included in model 5 and reported in the study. We also tested collinearity and reported these findings. The analyses were performed using STATA (version 14.1). The Survey (SVY) function was applied, which allowed for adjustments for sampling weights for cluster sampling. We reported adjusted and unadjusted odds ratios and 95% confidence intervals.

Ethics

The consent statement was read to each respondent in all three surveys and informed verbal consent from each respondent was signed by the interviewer. The Nepal Health Research

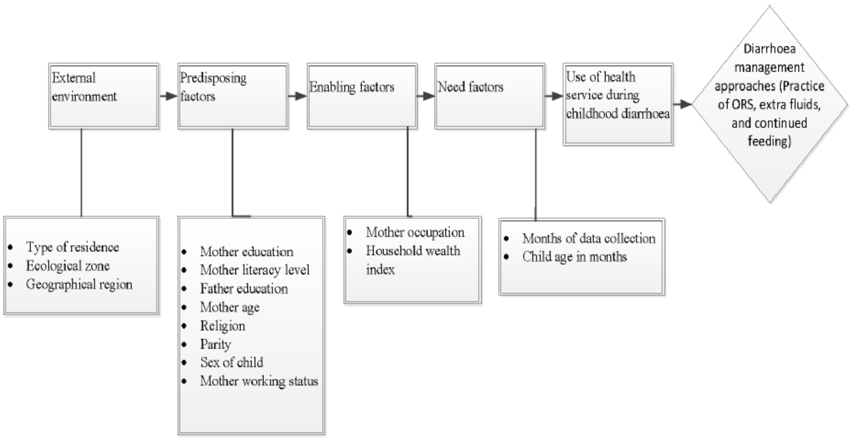

Fig 1. Conceptual framework for health service utilization and diarrhoea management approaches among children aged 0–5 years in Nepal, adopted from Anderson behavioural model.

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Council (NHRC) in Kathmandu, Nepal and the ICF Institutional Review Board in Maryland, USA, approved all surveys. The first author sought and obtained permission from Measure DHS/ ICF International to use data as part of his doctoral dissertation within the School of Science and Health at Western Sydney University, Australia.

Results

Of the 2655 children with diarrhoea, only 27% of their caregivers sought treatment or advice from health care providers (Table 1). Of the 27% who sought treatment or advice from the health care providers during diarrhoea, 17% used ORS and sought treatment and 10% sought treatment but did not use ORS. About half (46.5%) of the diarrhoea cases in the study occurred during the high diarrhoea prevalence period (April–August). The majority of children (92%)

Table 1. Characteristics of children under-five years of age with diarrhoea in Nepal, NDHS 2001–2011.

Study variables	n(%)	Study variables	n(%)
Type of Residence		**Parity**	
Rural	2443(92.0)	6+	332(12.5)
Urban	211(8.0)	(4–5)	505(19.0)
Ecological zone		(2–3)	1144(43.1)
Mountain	219(8.3)	1	674(25.4)
Hill	1030(38.8)	**Sex of child**	
Terai	1405(53.0)	Female	1220(46.0)
Geographical region		Male	1435(54.1)
Central	948(35.7)	**Mother working status (n = 2628)**	
Eastern	632(23.8)	Currently working	1829(68.9)
Western	480(18.1)	Currently not working	798(31.1)
Mid-western	312(11.8)	**Mother occupation (n = 2611)**	
Far-western	283(10.7)	Agriculture	1827(68.8)
Mother education		Non- agriculture	191(7.2)
No education	1723(64.9)	Not working	593(23.3)
Primary	442(16.7)	**Household wealth index**	
Some secondary to higher	489(18.4)	Poor	1300(49.0)
Mother literacy level (n = 2651)		Middle	577(21.7)
Cannot read at all	1567(59.0)	Rich	777(29.3)
Able to read	1084(40.8)	**Months of data collection**	
Father education		January- March	1420(53.5)
No education	1288(48.5)	April- August	1235(46.5)
Primary	869(32.7)	**Child age in months**	
Some secondary to higher	498(18.7)	(0–11)	690(26.0)
Mother age		(12–23)	819(30.9)
30–49	787(39.6)	(24–59)	1145(43.1)
20–29	1662(62.6)	**Use of health service during diarrhoea**	
<20	206(7.8)	No	1937(73.0)
Religion		Yes	718(27.0)
Buddhist	218(8.2)		
Hindu	2166(81.6)		
Others	271(10.2)		

n: Weighted counts. Other religion Includes mainly Christian, Muslims and Kirat; Non-agriculture occupation includes skilled and professional jobs; Counts and percentages vary between categories because of missing values.

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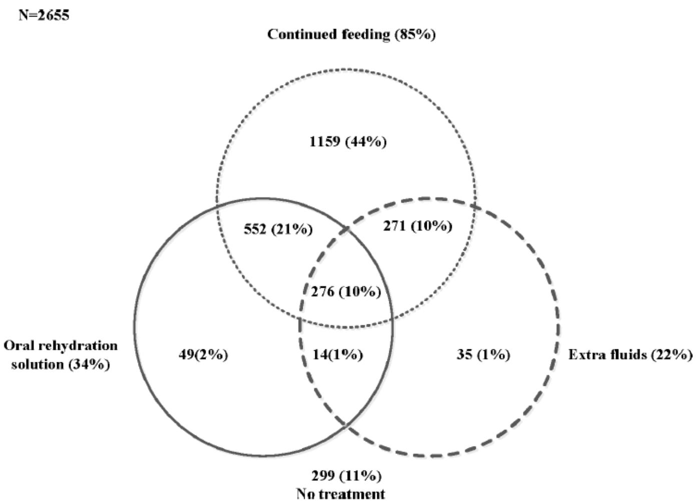

Fig 2. Number and percentage of children who received ORS, continued feeding and/or extra fluids during diarrhoea in Nepal (2001–2011).

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were rural residents, and 74% were at least two years of age. Nearly half (49%) of the children were from poor socioeconomic households.

The Venn diagram shows all the three treatment approaches in Nepal, 2001–2011 (Fig 2). In the figure, 21%, 10% and 1% of children aged 0–59 months were given ORS and continued feeding, continued feeding and extra fluids, and ORS and extra fluids, respectively. 10% of children were given ORS, extra fluids and continued feeding and 11% of children did not use any of three treatment approaches.

Trends in diarrhoea management approaches

We found that the prevalence of ORS use increased significantly from 29% in 2006 to 40% in 2011, whereas the use of extra fluids decreased significantly from 27% in 2001 to 15% in 2011 (Fig 3). Over the 10 years, the prevalence of continued feeding fluctuated from between 83% in 2001, 89% in 2006, and 85% in 2011, and the prevalence of continued feeding significantly increased by 6% in 2006 compared to 2001, and a non-statistically significant reduction of 4% in 2011 compared to 2006.

Univariate and multivariate logistic analyses

Univariate analyses revealed that caregivers who sought treatment or advice from the health care providers were significantly more likely to use at least one the three prescribed approaches, ORS or extra fluids or continued feeding (OR 3.64, 95% CI 2.24, 5.90) for the treatment of childhood diarrhoea compared to those who did not seek treatment or advice from the health care providers (S1 Table). We also found increasing use of all approaches, ORS (OR 5.48, 95% CI 4.36, 6.88), extra fluids (OR 1.67, 95% CI 1.30, 2.15), continued feeding (OR 2.04, 95%CI 1.49, 2.80) among caregivers who sought treatment or advice from health care providers compared to those who did not seek treatment or advice from health care providers. This

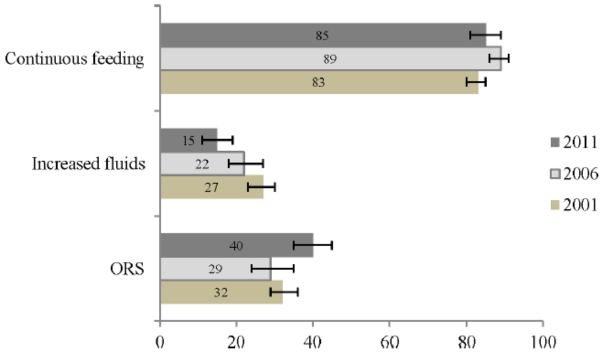

Fig 3. Trends in prevalence of Oral Rehydration Solution (ORS), increased fluids, and continued feeding during childhood diarrhoea in Nepal (2001–2011).

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result was also found for the combination of all treatment approaches, ORS and extra fluids and continued feeding (OR 3.44, 95% CI 2.52, 4.72). These results remained significant in the adjusted model: ORS or extra fluids or continued feeding (aOR 4.05, 95% CI 2.37, 6.93), ORS (aOR 5.63, 95% CI 4.43, 7.26), extra fluids (aOR 1.56, 95% CI 1.20, 2.04), continued feeding (aOR 2.25, 95% CI 1.52, 3.31), ORS and extra fluids and continued feeding (aOR 3.27, 95% CI 2.31, 4.62) (Fig 4).

There were several socio-demographic variables that were important determinants of use of the management approaches, including geographical area of residence, maternal education, paternal education, and household wealth index. The use of all treatment approaches was significantly higher among mothers residing in the eastern geographical region (aOR 1.88, 95% CI 1.09, 3.26) compared to mothers residing in the central geographical region, mothers with primary education (aOR 1.48, 95% CI 1.00, 2.19) or secondary to higher education (aOR 2.93, 95% CI 1.86, 4.63) compared to uneducated mothers, fathers with primary education (aOR 1.55, 95% CI 1.11, 2.17) or secondary to higher education (aOR 1.58, 95% CI 1.01, 2.49) compared to uneducated fathers, and the family with middle household wealth index (aOR 2.25, 95% CI 1.53, 3.32) or rich household wealth index (aOR 1.63, 95% CI 1.02, 2.60) compared to the family with poor household wealth index. Among mothers who reported childhood diarrhoea, the majority (24%) of the illiterate women were from Central Geographical Region compared to 14% in Eastern, 7% in Mid-western, 6% in Far-western, and 8% in Western Geographical Region.

Discussion

Despite the established benefits of using ORS, extra fluids and continued feeding as strategies to reduce mortality and morbidity from diarrhoea [6, 7, 11], optimal management is still not universally adopted in Nepal. Our study found that caregivers who sought treatment or advice from the health care providers were more likely to use treatment approaches (ORS, extra fluids and/or continued feeding) for childhood diarrhoea compared to those who did not seek treatment or advice from the health care providers.

The knowledge of ORS is almost universal in Nepal [27, 20]. However, this study found that the aggregate prevalence of ORS was about one-third whereas approximately a quarter of the sample reported extra fluids. The difference between knowledge and practice may be as a

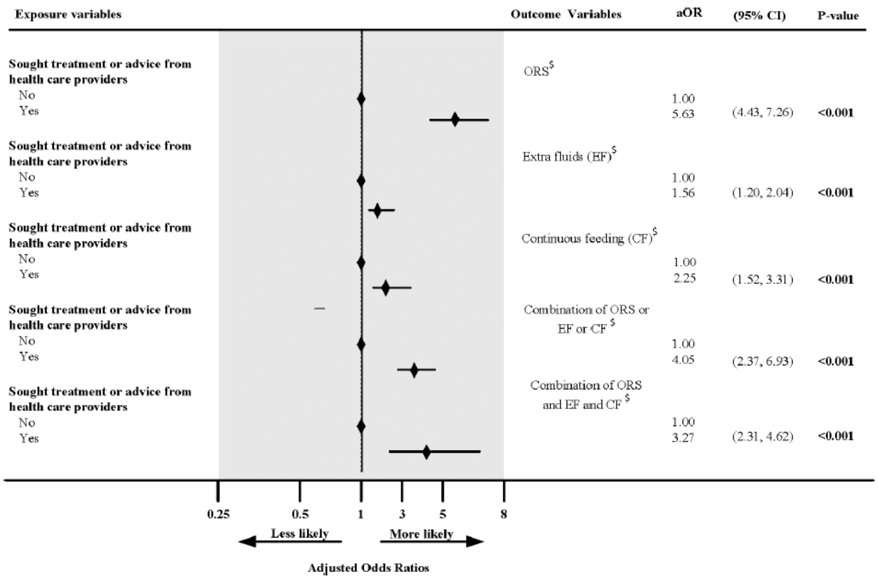

Fig 4. Impact of health service use on diarrhoea treatment approaches among children aged 0–59 months in Nepal (2001–2011).
$Adjusted for type of residence, ecological zone, geographical region, mother education, mother literacy level, father education, mother age, religion, parity, sex of child, mother working status, mother occupation, household wealth, months of data collection, age of child, and use of health service during diarrhoea.

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result of socio-cultural values related to help seeking for childhood illness and different ethnical views about causes and consequences of diarrhoea which prevented mothers from accessing modern healthcare for management of diarrhoea[28]. Similarly, the study conducted in a rural part of Nigeria reported that large improvements in knowledge of Oral Rehydration Therapy (ORT) from about 6 to 47 percent did not translate into practice with only 10 percent using ORT during diarrhoeal episodes[29]. The gap between knowledge and ORS use was also reported in hospital based studies in India, and a hospital based cross-sectional study in Pakistan [30–32]. These studies recommended that community outreach programs[30], widespread health education for mothers[31], and awareness programs around diarrhoea management approaches can bridge the knowledge and practice gap among mothers.

Our study found that attending a health service improved the management of diarrhoea (Fig 4). We found a strong association between health service utilization and the use of ORS, extra fluids and/or continued feeding during diarrhoea treatment. This finding is similar to a study conducted in a poor neighbourhood in Nicaragua[33] which reported that that ORS use was significantly associated to health service utilization. The authors concluded that mothers did not use ORS until they visited the health professional. A study conducted in Uganda by Nanyonjo et al [34] revealed that Integrated Community Case Management attendance for diarrhoea was associated with ORS use. It is useful to note that studies from developing countries including Nepal have documented some beliefs such as high fluid intake worsened diarrhoea, children with diarrhoea should be given only water due to teething, some forms of diarrhoea require traditional methods like exorcism, and intensity of diarrhoea is decreased with food restriction [28, 35–37]. These beliefs might have negatively affected the management of diarrhoea. Hence, knowledge, attitude and practice, which are deeply rooted into local cultural values and norms, appear to be important and health professionals can change cultural beliefs and improve knowledge about the use of diarrhoea treatment approach. For example, health care workers proving information to caregivers were found to improve the use of ORS and extra fluids as indicated in a study conducted in Ethiopia[38]. The government of Nepal policy to provide counselling on continued feeding during diarrhoea while patients are sought treatment or advice from health care providers may have contributed for the significant role for patient's adherence to continued feeding[15]. Hence, widespread heath education for caregivers as well as awareness programs to improve knowledge, attitude and practice could bridge the widening gap and motivate caregivers to use recommended treatment approaches during diarrhoea. Past studies [34, 38, 39] have also suggested that a proper interaction between health worker and patient/care giver is crucial to improve the rate of treatment use and recovery. These findings suggest the need for educating family members particularly, mothers, their husbands and mother in-law about the importance and how to adequately use complementary and ORS to the children during diarrhoea.

Our study found that caregivers of children aged 0–59 months who received treatment or advice from health care provider reported higher odds of practicing ORS compared to other diarrhoea management approaches (extra fluids, continued feeding, combination of ORS & extra fluids & continued feeding, and combination of ORS or extra fluids or continued feeding). This finding was supported by a recent systematic review that estimated the effectiveness of ORS on diarrhoea mortality and the study concluded that ORS is more effective in reducing mortality related childhood diarrhoea in home, community and facility settings[11].

The major strengths of this study include the use of a nationally representative pooled sample, with an average response of 97%, use of standardised survey questionnaires, and the adjustment for the cluster sampling design with sampling weight. However, findings from this study do not accurately capture changes in diarrhoea management in Nepal as the Nepalese government introduced zinc in the treatment protocol for the management of childhood diarrhoea in 2007. We could not retain the use of the zinc variable into our pooled study because NDHS 2001 had no zinc related data. Similarly, the use of antibiotics or other medicine, an important confounder was excluded from this study due to no observations recorded in 2001 NDHS dataset.

Conclusions

Our study concludes that caregivers of children aged 0–59 months of age are more likely to adhere with all three treatment approaches if they seek care or advice from health care providers. However, community based complete intervention packages such as the use of ORS, extra fluids and continued feeding are needed to further manage childhood diarrhoea in Nepal and such intervention should target caregivers of children from low socioeconomic disadvantaged group.

Supporting information

S1 Table. Unadjusted odd ratios (95% confidence interval (CI)) for the use of ORS, extra fluids and/or continued feeding during childhood diarrhoea in Nepal, NDHS 2001–2011. (DOCX)

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Author Contributions

Conceptualization: Pramesh Raj Ghimire, Kingsley Emwinyore Agho.

Formal analysis: Pramesh Raj Ghimire.

Methodology: Pramesh Raj Ghimire.

Supervision: Kingsley Emwinyore Agho, Andre M. N. Renzaho.

Writing – original draft: Pramesh Raj Ghimire.

Writing – review & editing: Pramesh Raj Ghimire, Kingsley Emwinyore Agho, Andre M. N. Renzaho, Michael Dibley, Camille Raynes-Greenow.

References

1. Santosham M, Chandran A, Fitzwater S, Fischer-Walker C, Baqui AH, Black R. Progress and barriers for the control of diarrhoeal disease. The Lancet. 2010 Jul 3; 376: 63–7. https://doi.org/10.1016/S0140-6736(10)60356-X
2. Walker CL, Rudan I, Liu L, Nair H, Theodoratou E, Bhutta ZA, et al. Global burden of childhood pneumonia and diarrhoea. The Lancet. 2013 Apr 12; 381: 1405–16. https://doi.org/10.1016/S0140-6736(13)60222-6
3. Collaborators, Global Burden of Diseases. Estimates of global, regional, and national morbidity, mortality, and aetiologies of diarrhoeal diseases: A systematic analysis for the global burden of disease study. The Lancet Infectious Diseases. 2017 June 1. http://dx.doi.org/10.1016/.S1473-3099(17)30276-1
4. UNICEF. Pneumonia and diarrhoea: tackling the deadliest diseases for the world's poorest children. New York: UNICEF. 2014 June.
5. The World Health Organization. The treatment of diarrhoea: a manual for physicians and other senior health workers, 2005.
6. Baltazar JC, Nadera DP, Victora CG. Evaluation of the national control of diarrhoeal disease programme in the philippines, 1980–93. Bulletin of World Health Organization. 2002 Aug; 80: 637–643.
7. Miller P, Hirschhorn N. The effect of a national control of diarrheal diseases program on mortality: the case of Egypt. Social Science and Medicine.1995 May; 40, S1–S30. PMID: 7638641
8. Bhutta ZA, Das JK, Rizvi A, Gaffey MF, Walker N, Horton S, et al. Evidence-based interventions for improvement of maternal and child nutrition: what can be done and at what cost? The Lancet. 2013 Aug 9; 382: 452–477. https://doi.org/10.1016/S0140-6736(13)60996-4
9. Jones G, Steketee RW, Black RE, Bhutta ZA, Morris SS, Bellagio Child Survival Study Group. How many child deaths can we prevent this year? The Lancet. 2003 Jul 5; 362: 65–71, https://doi.org/10.1016/S0140-6736(03)13811-1
10. Bhutta ZA, Das JK, Walker N, Rizvi A, Campbell H, Rudan I et al. Interventions to address deaths from childhood pneumonia and diarrhoea equitably: what works and at what cost? The Lancet. 2013 Apr 26; 381: 1417–1429, https://doi.org/10.1016/S0140-6736(13)60648-0
11. Munos MK, Walker CLF, Black RE. The effect of oral rehydration solution and recommended home fluids on diarrhoea mortality. International Journal of Epidemiology. 2010 Mar 23; 39: i75–i87. https://doi.org/10.1093/ije/dyq025 PMID: 20348131
12. Duggan C, Nurko S. Feeding the gut: the scientific basis for continued enteral nutrition during acute diarrhea. The Journal of Pediatrics. 1997 Dec 1; 131: 801–808. PMID: 9427881
13. Nel E. Diarrhoea and malnutrition. South African Journal of Clinical Nutrition. 2010 Jan 1; 23: 15–18.
14. Rohde J, Northrup R. Diarrhea is a nutritional disease. Indian pediatrics. 1988; 25: 914–929. PMID: 3248865
15. Ministry of Health and Population (MOHP) [Nepal], New ERA, ICF International Inc. 2012. Nepal Demographic and Health Survey 2011. Kathmandu, Nepal: Ministry of Health and Population, New ERA, and ICF International, Calverton, Maryland.
16. Ghimire M, Pradhan YV, Maskey MK. Community-based interventions for diarrhoeal diseases and acute respiratory infections in nepal. Bulletin of the World Health Organization. 2010 Mar; 88: 216–221. https://doi.org/10.2471/BLT.09.065649 PMID: 20428390
17. Bhandari G, Bhusal C. Cholera outbreak in far-western region of nepal. Journal of Nepal Health Research Council. 2013 May 10; 11: 6–8. PMID: 23787517

18. International Federation of Red Cross and Red Crescent Socities. Diarrhoea outbreak kills hundreds, 2009. Available from: http://www.ifrc.org/en/nouvelles/nouvelles/asia-pacific/nepal/nepal-diarrhoea-outbreak-kills-hundreds/.

19. Ministry of Health and Population (MOHP) [Nepal], New ERA, and Macro International Inc. 2007. Nepal Demographic and Health Survey 2006. Kathmandu, Nepal: Ministry of Health and Population, New ERA, and ICF International, Calverton, Maryland.

20. Ministry of Health [Nepal], New ERA, and ORC Macro. 2002. Nepal Demographic and Health Survey 2001. Calverton, Maryland, USA: Family Health Division, Ministry of Health; New ERA; and ORC Macro.

21. The Demographic and health survey. Available from: http://dhsprogram.com/data/available-datasets.cfm. Accessed 10 March 2013.

22. Andersen RM. Revisiting the behavioral model and access to medical care: Does it matter? Journal of Health and Social Behavior.1995 Mar 1; 36: 1–10. PMID: 7738325

23. Gurung H, Nepal Regional Strategy for Development. 2005

24. Agho KE, Dibley MJ, Odiase JI, Ogbonmwan SM. Determinants of exclusive breastfeeding in nigeria. BMC Pregnancy and Childbirth 2011 Jan 11; 11: 2. https://doi.org/10.1186/1471-2393-11-2 PMID: 21219659

25. Ghimire PR, Agho KE, Renzaho A, Christou A, Nisha MK, Dibley M et al. Socio-economic predictors of stillbirths in nepal (2001–2011). PloS One. 2017 Jul 13; 12: e0181332, https://doi.org/10.1371/journal.pone.0181332 PMID: 28704548

26. Victora CG, Huttly SR, Fuchs SC, Olinto M. The role of conceptual frameworks in epidemiological analysis: a hierarchical approach. International Journal of Epidemiology. 1997 Feb 1; 26: 224–227. PMID: 9126524

27. Jha N, Singh R, Baral D. Knowledge, attitude and practices of mothers regarding home management of acute diarrhoea in Sunsari, Nepal. Nepal Medical College Journal. 2006 Mar; 8: 27–30. PMID: 16827086

28. Ansari M, Ibrahim MIM, Hassali MA, Shankar PR, Koirala A,Thapa NJ. Mothers' beliefs and barriers about childhood diarrhea and its management in Morang district, Nepal. BMC Research Notes. 2012 Oct 24; 5: 576. https://doi.org/10.1186/1756-0500-5-576 PMID: 23095352

29. Jinadu MK, Olusi S, Alade O, Ominiyi C. Effectiveness of primary health-care nurses in the promotion of oral rehydration therapy in a rural area of nigeria. International Journal of Nursing Studies. 1988 Jan 1; 25: 185–190. PMID: 3225125

30. Pahwa S, Kumar GT, Toteja GS. Performance of a community-based health and nutrition-education intervention in the management of diarrhoea in a slum of delhi, India. Journal of Health, Population, and Nutrition. 2010 Dec; 28: 553–559. PMID: 21261200

31. Datta V, John R, Singh VP, Chaturvedi P. Maternal knowledge, attitude and practices towards diarrhea and oral rehydration therapy in rural maharashtra. Indian Journal of Pediatrics. 2001 Nov 1; 68: 1035–7. PMID: 11770237

32. Masiha SA, Khalid A, Malik B, Shah SMA. Oral rehydration therapy-knowledge, attitude and practice (kap) survey of pakistani mothers. J. Rawal Med. Coll. 2015; 19: 51–54.

33. Hudelson PM. ORS and the treatment of childhood diarrhea in managua, Nicaragua. Social Science and Medicine. 1993 Jul 1; 37: 97–103. PMID: 8332930

34. Nanyonjo A, Ssekitooleko J, Counihan H, Makumbi F, Tomson G, Källander K. Impact of an integrated community case management programme on uptake of appropriate diarrhoea and pneumonia treatments in uganda: a propensity score matching and equity analysis study. International Journal for Equity in Health 2015 Sep 4; 14: 74. https://doi.org/10.1186/s12939-015-0202-y PMID: 26337975

35. Olango P, Aboud F. Determinants of mothers' treatment of diarrhea in rural ethiopia. Social Science and Medicine. 1990 Jan 1; 31: 1245–1249. PMID: 2291122

36. Kumar V, Clements C, Marwah K, Diwedi P. Beliefs and therapeutic preferences of mothers in management of acute diarrhoeal disease in children. Journal of Tropical Pediatrics. 1985 Apr 1; 31: 109–12. PMID: 4009776

37. Pokhrel D, Viraraghavan T. Diarrhoeal diseases in Nepal vis-à-vis water supply and sanitation status. Journal of Water and Health. 2004 Jun 1; 2: 71–81. PMID: 15387131

38. Mengistie B, Berhane Y, Worku A. Predictors of oral rehydration therapy use among under-five children with diarrhea in eastern ethiopia: a community based case control study. BMC public health. 2012 Nov 24; 12: 1029. https://doi.org/10.1186/1471-2458-12-1029 PMID: 23176055

39. Olson CK, Blum LS, Patel KN, Oria PA, Feikin DR, Laserson KF, et al. Community case management of childhood diarrhea in a setting with declining use of oral rehydration therapy: findings from cross-sectional studies among primary household caregivers, kenya, 2007. The American Journal of Tropical Medicine and Hygiene. 2011 Dec 1; 85: 1134–1140. https://doi.org/10.4269/ajtmh.2011.11-0178 PMID: 22144458

References

1. World Health Organization. Neonatal and perinatal mortality: Country, regional and global estimates. 2006.
2. World Health Organization and United Nations Children Fund. Levels and trends in child mortality. New york: United Nations Children Fund. 2013.
3. Lawn, J.E., Blencowe, H., Waiswa, P., Amouzou, A., Mathers, C., Hogan, D., Flenady, V., Frøen, J.F., Qureshi, Z.U., Calderwood, C., Shiekh, S., Jassir, F.B., You, D., McClure, E.M., Mathai, M..Cousens, S. Stillbirths: Rates, risk factors, and acceleration towards 2030. The Lancet, 2016. 387(10018): p. 587-603.
4. The DHS program. Demographic and health survey [cited 2015 August]; Available from: https://dhsprogram.com/Data/.
5. Mosley, W.H; Chen, L.C. An analytical framework for the study of child survival in developing countries. Population and development review, 1984. 10: p. 25-45.
6. Sastry, N. What explains rural-urban differentials in child mortality in brazil? Social science & medicine, 1997. 44(7): p. 989-1002.
7. Berger, U., Fahrmeir, L., Klasen, S. Dynamic modelling of child mortality in developing countries: Application for zambia. 2002.
8. Eberstein, I.W. Demographic research on infant mortality. in Sociological Forum. 1989. Springer.
9. Hug, L., Sharrow, D..You, D. Levels & trends in child mortality: Report 2017. Estimates developed by the un inter-agency group for child mortality estimation. 2017.
10. Wang, H., Bhutta, Z.A., Coates, M.M., Coggeshall, M., Dandona, L., Diallo, K., Franca, E.B., Fraser, M., Fullman, N..Gething, P.W. Global, regional, national, and selected subnational levels of stillbirths, neonatal, infant, and under-5 mortality, 1980–2015: A systematic analysis for the global burden of disease study 2015. The Lancet, 2016. 388(10053): p. 1725-1774.
11. Ministry of Health [Nepal], New ERA, and ORC Macro. 2002. Nepal Demographic and Health Survey 2001. Calverton, Maryland, USA: Family Health Division, Ministry of Health; New ERA; and ORC Macro.
12. Ministry of Health and Population (MOHP) [Nepal], New ERA, and Macro International Inc. 2007. Nepal Demographic and Health Survey 2006. Kathmandu, Nepal: Ministry of Health and Population, New ERA, and Macro International Inc.
13. Ministry of Health and Population (MOHP) [Nepal], New ERA, and ICF International Inc. 2012. Nepal Demographic and Health Survey 2011. Kathmandu, Nepal: Ministry of Health and Population, New ERA, and ICF International, Calverton, Maryland.
14. Ministry of Health and Population (MOHP) [Nepal], New ERA, and ICF International Inc. 2017. Nepal Demographic and Health Survey 2016. Kathmandu, Nepal: Ministry of Health and Population, New ERA, and ICF International, Calverton, Maryland.
15. Ashish, K., Nelin, V., Wrammert, J., Ewald, U., Vitrakoti, R., Baral, G.N..Målqvist, M. Risk factors for antepartum stillbirth: A case-control study in nepal. BMC pregnancy and childbirth, 2015. 15(1): p. 146.
16. Ashish, K., Wrammert, J., Ewald, U., Clark, R.B., Gautam, J., Baral, G., Baral, K.P., Målqvist, M. Incidence of intrapartum stillbirth and associated risk factors in tertiary care setting of nepal: A case-control study. Reproductive health, 2016. 13(1): p. 103.
17. Lee, A.C., Mullany, L.C., Tielsch, J.M., Katz, J., Khatry, S.K., LeClerq, S.C., Adhikari, R.K., Darmstadt, G.L. Community-based stillbirth rates and risk factors in rural sarlahi, nepal. International Journal of Gynecology & Obstetrics, 2011. 113(3): p. 199-204.

18. Geetha, T., Chenoy, R., Stevens, D., Johanson, R. A multicentre study of perinatal mortality in nepal. Paediatric and Perinatal Epidemiology, 1995. 9(1): p. 74-89.
19. Shrestha, M., Manandhar, D., Dhakal, S., Nepal, N. Two year audit of perinatal mortality at kathmandu medical college teaching hospital. 2006.
20. Khadka, K.B., Lieberman, L.S., Giedraitis, V., Bhatta, L., Pandey, G. The socio-economic determinants of infant mortality in nepal: Analysis of nepal demographic health survey, 2011. BMC pediatrics, 2015. 15(1): p. 152.
21. Lamichhane, R., Zhao, Y., Paudel, S., Adewuyi, E.O. Factors associated with infant mortality in nepal: A comparative analysis of nepal demographic and health surveys (ndhs) 2006 and 2011. BMC public health, 2017. 17(1): p. 53.
22. Neupane, S., Doku, D.T. Neonatal mortality in nepal: A multilevel analysis of a nationally representative. Journal of epidemiology and global health, 2014. 4(3): p. 213-222.
23. Hong, R. Effect of multiple birth on infant mortality in bangladesh. Journal of paediatrics and child health, 2006. 42(10): p. 630-635.
24. Titaley, C.R., Dibley, M.J., Agho, K., Roberts, C.L., Hall, J. Determinants of neonatal mortality in indonesia. BMC public health, 2008. 8(1): p. 232.
25. Santosham, M., Chandran, A., Fitzwater, S., Fischer-Walker, C., Baqui, A.H., Black, R. Progress and barriers for the control of diarrhoeal disease. The Lancet, 2010. 376(9734): p. 63-67.
26. Walker, C.L.F., Rudan, I., Liu, L., Nair, H., Theodoratou, E., Bhutta, Z.A., O'Brien, K.L., Campbell, H., Black, R.E. Global burden of childhood pneumonia and diarrhoea. The Lancet, 2013. 381(9875): p. 1405-1416.
27. Troeger, C., Forouzanfar, M., Rao, P.C., Khalil, I., Brown, A., Reiner Jr, R.C., Fullman, N., Thompson, R.L., Abajobir, A., Ahmed, M. Estimates of global, regional, and national morbidity, mortality, and aetiologies of diarrhoeal diseases: A systematic analysis for the global burden of disease study 2015. The Lancet Infectious Diseases, 2017. 17(9): p. 909-948.
28. Ministry of Health and Population (MOHP) [Nepal], New ERA, and Macro International Inc. 2007. Nepal Demographic and Health Survey 2006. Kathmandu, Nepal: Ministry of Health and Population, New ERA, and Macro International Inc.
29. Kalipeni, E. Determinants of infant mortality in malawi: A spatial perspective. Social Science and Medicine, 1993. 37: p. 183-183.
30. Ezeh, O.K., Agho, K.E., Dibley, M.J., Hall, J.J., Page, A.N. Risk factors for postneonatal, infant, child and under-5 mortality in nigeria: A pooled cross-sectional analysis. BMJ open, 2015. 5(3): p. e006779.
31. Chowdhury, A.H. Determinants of under-five mortality in bangladesh. Open Journal of Statistics, 2013. 3(03): p. 213.
32. Van De Poel, E., O'Donnell, O., Van Doorslaer, E. What explains the rural-urban gap in infant mortality: Household or community characteristics? Demography, 2009. 46(4): p. 827-850.
33. Nisar, Y.B., Dibley, M.J., Mebrahtu, S., Paudyal, N., Devkota, M. Antenatal iron-folic acid supplementation reduces neonatal and under-5 mortality in nepal1–4. The Journal of nutrition, 2015. 145(8): p. 1873-1883.
34. Jehan, K., Sidney, K., Smith, H., de Costa, A. Improving access to maternity services: An overview of cash transfer and voucher schemes in south asia. Reprod Health Matters, 2012. 20(39): p. 142-54.
35. Montgomery, M.R., Gragnolati, M., Burke, K.A., Paredes, E. Measuring living standards with proxy variables. Demography, 2000. 37(2): p. 155-174.

36. Filmer, D., Pritchett, L. Estimating wealth effects without income of expenditure data— or tears: Educational enrollment in india. World Bank Policy Working Paper, 1998(1994).
37. Ezeh, O.K. Trends and population-attributable risk estimates for predictors of early neonatal mortality in nigeria, 2003-2013: A cross-sectional analysis. BMJ Open, 2017. 7(5): p. e013350.
38. Ezeh, O.K., Agho, K.E., Dibley, M.J., Hall, J., Page, A.N. The impact of water and sanitation on childhood mortality in nigeria: Evidence from demographic and health surveys, 2003-2013. Int J Environ Res Public Health, 2014. 11(9): p. 9256-72.
39. Ezeh, O.K., Agho, K.E., Dibley, M.J., Hall, J., Page, A.N. Determinants of neonatal mortality in nigeria: Evidence from the 2008 demographic and health survey. BMC Public Health, 2014. 14: p. 521.
40. Ezeh, O.K., Agho, K.E., Dibley, M.J., Hall, J.J., Page, A.N. The effect of solid fuel use on childhood mortality in nigeria: Evidence from the 2013 cross-sectional household survey. Environ Health, 2014. 13: p. 113.
41. Abir, T., Agho, K.E., Page, A.N., Milton, A.H., Dibley, M.J. Risk factors for under-5 mortality: Evidence from bangladesh demographic and health survey, 2004–2011. BMJ open, 2015. 5(8): p. e006722.
42. Agha, S. The determinants of infant mortality in pakistan. Social science & medicine, 2000. 51(2): p. 199-208.
43. Rodgers, G.B. Income and inequality as determinants of mortality: An international cross-section analysis. Population studies, 1979. 33(2): p. 343-351.
44. Abir, T., Agho, K.E., Ogbo, F.A., Stevens, G.J., Page, A., Hasnat, M.A., Dibley, M.J., Raynes-Greenow, C. Predictors of stillbirths in bangladesh: Evidence from the 2004–2014 nation-wide household surveys. Global health action, 2017. 10(1): p. 1410048.
45. Sharma, V., Katz, J., Mullany, L.C., Khatry, S.K., LeClerq, S.C., Shrestha, S.R., Darmstadt, G.L., Tielsch, J.M. Young maternal age and the risk of neonatal mortality in rural nepal. Archives of pediatrics & adolescent medicine, 2008. 162(9): p. 828-835.
46. Ghimire, P.R., Agho, K.E., Ezeh, O.K., Renzaho, M.N., Dibley, M., Raynes-Greenow, C. Under-5 mortality and associated factors: Evidence from the nepal demographic and health survey (2001-2016). International Journal of Environmental and Public Health, 2019.
47. Zwane, E., Masango, S. Factors influencing neonatal mortality: An analysis using the swaziland demographic health survey 2007. Journal of Public Health in Africa, 2012. 3(2): p. 18.
48. Ajaari, J., Masanja, H., Weiner, R., Abokyi, S.A..Owusu-Agyei, S., Impact of place of delivery on neonatal mortality in rural tanzania. International Journal of MCH and AIDS, 2012. 1(1): p. 49.
49. Guillot, M..Allendorf, K., Hindu-muslim differentials in child mortality in india. Genus, 2010. 66(2).
50. Thind, A., Mohani, A., Banerjee, K..Hagigi, F., Where to deliver? Analysis of choice of delivery location from a national survey in india. BMC public health, 2008. 8(1): p. 29.
51. Caldwell, J.C. Education as a factor in mortality decline an examination of nigerian data. Population studies, 1979: p. 395-413.
52. Cleland, J.G.Van Ginneken, J.K., Maternal education and child survival in developing countries: The search for pathways of influence. Social science & medicine, 1988. 27(12): p. 1357-1368.
53. Buor, D. Mothers' education and childhood mortality in ghana. Health policy, 2003. 64(3): p. 297-309.

54. Joshi, C., Torvaldsen, S., Hodgson, R., Hayen, A. Factors associated with the use and quality of antenatal care in nepal: A population-based study using the demographic and health survey data. BMC pregnancy and childbirth, 2014. 14(1): p. 94.
55. Shaikh, B.T., Hatcher, J. Health seeking behaviour and health service utilization in pakistan: Challenging the policy makers. Journal of public health, 2004. 27(1): p. 49-54.
56. Chakraborty, N., Islam, M.A., Chowdhury, R.I., Bari, W., Akhter, H.H. Determinants of the use of maternal health services in rural bangladesh. Health promotion international, 2003. 18(4): p. 327-337.
57. Mustafa, H. Socioeconomic determinants of infant mortality in kenya. 2008.
58. Hobcraft, J.N., McDonald, J.W..Rutstein, S.O., Demographic determinants of infant and early child mortality: A comparative analysis. Population studies, 1985. 39(3): p. 363-385.
59. Rutstein, S.O. Factors associated with trends in infant and child mortality in developing countries during the 1990s. Bulletin of the World Health Organization, 2000. 78: p. 1256-1270.
60. Gubhaju, B.B. Effect of birth spacing on infant and child mortality in rural nepal. Journal of Biosocial Science, 1986. 18(4): p. 435-447.
61. Oyefara, J.L. Maternal age at first birth and childhood mortality in yoruba society: The case of osun state, nigeria. Res Humanities Soc Sci, 2013. 3: p. 246-254.
62. DaVanzo, J., Hale, L., Razzaque, A., Rahman, M. The effects of pregnancy spacing on infant and child mortality in matlab, bangladesh: How they vary by the type of pregnancy outcome that began the interval. Population studies, 2008. 62(2): p. 131-154.
63. Chola, L., McGee, S. Tugendhaft, A., Buchmann, E..Hofman, K., Scaling up family planning to reduce maternal and child mortality: The potential costs and benefits of modern contraceptive use in south africa. PLoS One, 2015. 10(6): p. e0130077.
64. Boerma, J.T., Bicego, G.T. Preceding birth intervals and child survival: Searching for pathways of influence. Studies in family planning, 1992. 23(4): p. 243-256.
65. Chen, L.C., Huq, E., d'Souza, S. Sex bias in the family allocation of food and health care in rural bangladesh. Population and development review, 1981: p. 55-70.
66. Bhuiya, A., Streatfield, K. Mothers' education and survival of female children in a rural area of bangladesh. Population Studies, 1991. 45(2): p. 253-264.
67. Arokiasamy, P. Regional patterns of sex bias and excess female child mortality in india. Population, 2004. 59(6): p. 831-863.
68. Quamrul, H., Islam, R., Hossain, K. Effects of demographic characteristics on neonatal, post neonatal, infant and child mortality. J Biol Sci, 2010. 2: p. 132-138.
69. Krell, R., Rabkin, L. The effects of sibling death on the surviving child: A family perspective. Family Process, 1979. 18(4): p. 471-477.
70. Prendergast, A.J., Humphrey, J.H. The stunting syndrome in developing countries. Paediatrics and international child health, 2014. 34(4): p. 250-265.
71. World Health Organization. The world health report 2002: Reducing risks, promoting healthy life. 2002: World Health Organization.
72. Günther, I., Fink, G. Water and sanitation to reduce child mortality: The impact and cost of water and sanitation infrastructure. 2011: The World Bank.
73. World Health Organization and United Nations Children's Fund. Progress on sanitation and drinking water: update and Millennium Development Goal Assessment. 2015: World Health Organization.
74. Smith, K.R., Samet, J.M., Romieu, I., Bruce, N. Indoor air pollution in developing countries and acute lower respiratory infections in children. Thorax, 2000. 55(6): p. 518-532.

75. Gajate-Garrido, G. The impact of indoor air pollution on the incidence of life threatening respiratory illnesses: Evidence from young children in peru. The Journal of Development Studies, 2013. 49(4): p. 500-515.
76. Lehtonen, L., Gimeno, A., Parra-Llorca, A., Vento, M. Early neonatal death: A challenge worldwide. in Seminars in Fetal and Neonatal Medicine. 2017. Elsevier.
77. Mason, E., McDougall, L., Lawn, J.E., Gupta, A., Claeson, M., Pillay, Y., Presern, C., Lukong, M.B., Mann, G., Wijnroks, M., Azad, K., Taylor, K., Beattie, A., Bhutta, Z.A., Chopra, M. From evidence to action to deliver a healthy start for the next generation. The Lancet, 2014. 384(9941): p. 455-467.
78. Shah, R., Sharma, B., Khanal, V., Pandey, U.K., Vishwokarma, A., Malla, D.K. Factors associated with neonatal deaths in chitwan district of nepal. BMC Res Notes, 2015. 8: p. 818.
79. Lawn, J.E., Cousens, S., Zupan, J., Team, L.N.S.S. 4 million neonatal deaths: When? Where? Why? The lancet, 2005. 365(9462): p. 891-900.
80. World Health Organization. Every newborn: An action plan to end preventable deaths. 2014.
81. Blencowe, H., Lawn, J., Vandelaer, J., Roper, M., Cousens, S. Tetanus toxoid immunization to reduce mortality from neonatal tetanus. International journal of epidemiology, 2010. 39(suppl_1): p. i102-i109.
82. Titaley, C.R., Dibley, M.J., Roberts, C.L., Hall, J., Agho, K. Iron and folic acid supplements and reduced early neonatal deaths in indonesia. Bulletin of the World Health Organization, 2010. 88: p. 500-508.
83. Haider, B.A., Olofin, I., Wang, M., Spiegelman, D., Ezzati, M., Fawzi, W.W. Anaemia, prenatal iron use, and risk of adverse pregnancy outcomes: Systematic review and meta-analysis. Bmj, 2013. 346: p. f3443.
84. Imdad, A., Bhutta, Z.A. Routine iron/folate supplementation during pregnancy: Effect on maternal anaemia and birth outcomes. Paediatric and perinatal epidemiology, 2012. 26: p. 168-177.
85. Rabe-Hesketh, S., Skrondal, A. Generalized latent variable modeling: Multilevel, longitudinal, and structural equation models. 2004: Chapman and Hall/CRC.
86. Cox, D.R. Regression models and life-tables, in Breakthroughs in statistics. 1992, Springer. p. 527-541.
87. Christou, A., Dibley, M.J., Raynes-Greenow, C. Beyond counting stillbirths to understanding their determinants in low- and middle-income countries: A systematic assessment of stillbirth data availability in household surveys. Trop Med Int Health, 2017. 22(3): p. 294-311.
88. Ghimire P.R., Agho K.E., Renzaho A.M., Nisha M.K., Dibley M., Raynes-Greenow C. Factors associated with perinatal mortality in Nepal: evidence from Nepal demographic and health survey 2001–2016. BMC pregnancy and childbirth. 2019 Dec;19(1):88..
89. Manandhar, D.S., Osrin, D., Shrestha, B.P., Mesko, N., Morrison, J., Tumbahangphe, K.M., Tamang, S., Thapa, S., Shrestha, D., Thapa, B., Shrestha, J.R., Wade, A., Borghi, J., Standing, H., Manandhar, M., Costello, A.M. Effect of a participatory intervention with women's groups on birth outcomes in nepal: Cluster-randomised controlled trial. Lancet, 2004. 364(9438): p. 970-9.
90. Manandhar, S.R., Ojha, A., Manandhar, D.S., Shrestha, B., Shrestha, D., Saville, N., Costello, A.M., Osrin, D. Causes of stillbirths and neonatal deaths in dhanusha district, nepal: A verbal autopsy study. Kathmandu Univ Med J (KUMJ), 2010. 8(29): p. 62-72.