Size at birth: an examination of meaning and usefulness

A prospective study of a cohort of infants born in Nepal

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Declaration

I, Anjana Vaidya, declare that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Abstract

Background: Low birth weight (LBW) remains a major public health problem in developing countries, but is only one measure of size at birth. Others include small-for-gestational-age (SGA) and low ponderal index (PI). The objectives of the thesis were: to estimate the prevalence of LBW, SGA and low PI in a cohort of Nepalese infants; to identify risk factors for small size, and to investigate whether prediction models were useful for screening; and to assess the effects of size at birth on subsequent outcomes.

Methods: Mothers enrolled in a prospective trial were followed through pregnancy and delivery. Child anthropometry was collected at birth and at two years of age. A range of indices of size at birth were described. Multivariable regression models were developed to predict them, and their associations with subsequent outcomes.

Results: There was a high prevalence of LBW (25%), SGA (55%) and low PI (70%) at birth. None of the prediction models for size at birth was particularly good, the strongest being for birth weight (R^2=33%). Common predictors were parity, pre-pregnancy weight, gestational weight gain, gestational duration and infant sex. LBW was associated with neonatal (OR 3.5, 95% CI 1.4-8.9), infant (3.6, 1.6-7.9) and young child (3.7, 1.7-7.8) mortality, and stunting (3.4, 2.2-5.3), wasting (2.9, 1.5-5.6) and underweight (3.7, 2.5-5.5) at two years of age.

Discussion: In southern Nepal, many newborn infants were classified as small, and most were disproportionate. The modifiable risks for small size at birth were few, even though it was associated with mortality and size in childhood.

Conclusion: The previously undescribed disproportionate majority of Nepalese infants is worrying for public health. However, measurement of birth weight is not yet routine and it

seems better to recommend LBW as a single risk measure than to add new and more complicated activities.

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Acknowledgments

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Abbreviations and acronyms

AGA	Appropriate for Gestational Age
AHW	Auxiliary Health Worker
AIDS	Acquired Immune Deficiency Syndrome
ANM	Auxiliary Nurse Midwife
API	Appropriate Ponderal Index
BINP	Bangladesh Integrated Nutrition Project
BMI	Body Mass Index
CI	Confidence Interval
DALY	Disability-Adjusted Life Years
DHS	Demographic and Health Survey
HSD	Health Systems Development
HAZ	Height-for-age Z Score
HIV	Human Immunodeficiency Virus
IUGR	Intrauterine Growth Retardation/Restriction
LGA	Large for Gestational Age
LBW	Low Birth Weight
LMP	Last Menstrual Period
LPI	Low Ponderal Index
MICS	Multiple Indicator Cluster Survey
MOH	Ministry of Health
NBW	Normal Birth Weight
NDHS	Nepal Demographic Health Survey
NFHS	National Family Health Survey
OR	Odds Ratio
PCA	Principal Component Analysis
PI	Ponderal Index
SD	Standard Deviation
SES	Socioeconomic Status
SGA	Small for Gestational Age
SPSS	Statistical Package for the Social Sciences
U5MR	Under Five Mortality Rate
UN	United Nations
UNICEF	United Nations Children's Fund
WAZ	Weight-for-age Z Score
WHO	World Health Organization
WHZ	Weight-for-height Z Score

Definitions

Low birth weight	Birth weight of an infant less than 2500 g irrespective of gestation
Very Low Birth Weight	Birth weight of an infant less than 1500 g irrespective of gestation
Extremely Low Birth Weight	Birth weight of an infant less than 1000 g irrespective of gestation
Intrauterine Growth Retardation	Fetus fails to fulfill inherent growth potential
Small for Gestational Age	Birth weight for gestational age below 10^{th} percentile
Appropriate for Gestational Age	Birth weight between 10^{th} and 90^{th} percentile for gestational age
Large for gestational Age	Birth weight above 90^{th} percentile for gestational age
Appropriate Ponderal Index	Ponderal index above 10^{th} percentile
Low Ponderal Index	Ponderal index below 10^{th} percentile
Preterm	Infant born before 37 completed weeks of gestation
Term	Infant born between 37 and 42 completed weeks of gestation
Post term	Infant born after 42 completed weeks of gestation
Miscarriage	Cessation of confirmed pregnancy before 23 weeks' gestation
Stillbirth	Delivery of an infant showing no signs of life after 23 weeks' gestation
Neonatal	Period from birth to 28 complete days
Early Neonatal	Period from birth to 7 complete days
Late Neonatal	Period from 7 to 28 complete days
Infant	Period from birth to 1 year of age
Neonatal Mortality	Death of a live born infant within 28 complete days of life
Early Neonatal mortality	Death of a live born infant within the first 7 complete days of life
Late Neonatal mortality	Death of a live born infant from 7 to 28 complete days of life
Infant Mortality	Death of an infant in the first year of life
Post Neonatal Mortality	Death of an infant between 28 days and one year of life
Child under-five Mortality	Death of a child in the first 5 years of life
Z Score	Application of transformation rules: how far and in what direction, that item deviates from its distribution mean, expressed in units of its distribution's standard deviation. The transformed scores will have a mean of zero and a standard deviation of 1
Stunting	Height-for-age <-2SD below the reference median (WHO standard)
Mild Stunting	More than one and up to two z scores below the median (>1 – 2 SD)
Moderate Stunting	More than two and up to three z scores below the median (>2-3 SD)
Severe Stunting	More than three below the median (> -3 SD)
Wasting	Weight-for-height <-2SD below the reference median
Mild Wasting	More than one and up to two z scores below the median
Moderate Wasting	More than two and up to three z scores below the median
Severe Wasting	More than three below the median
Underweight	Weight-for-age <-2SD below the reference median
Mild Underweight	More than one and up to two z scores below the median
Moderate Underweight	More than two and up to three z scores below the median
Severe Underweight	More than three below the median
LMP	First day of the last menstrual period
DALY	Measure of a future stream of healthy life lost as a result of disease or injuries

Chapter 1. Introduction and objectives

1.1. Scope of the thesis

"*The category of low birth weight in particular is uninformative and seldom justified."*[1]

Size at birth is a multidimensional entity determined by the sizes of different constituents of the body: bone, muscle, other tissues and fluid spaces. Its dimensions include birth weight, birth length, head circumference, chest circumference, mid-upper arm circumference and abdominal circumference. Size can also be expressed by combining these primary measures into composite indices, of which body mass index is the most familiar. Both gestational age and rate of fetal growth contribute to size at birth, which is also determined by the interaction between genetic characteristics (maternal and paternal) and environmental factors (nutritional). Optimal fetal growth is achieved if the infant has achieved optimum size at birth for gestational age, sex and ethnicity.

Birth size is the result of prenatal growth and the intrauterine environment. It has important implications for mortality, morbidity, growth and development, cognitive outcomes and academic achievement. Associations have also been demonstrated between small size at birth and coronary heart disease and its risk factors, hypertension, non-insulin dependent diabetes mellitus and abnormalities in lipid metabolism and blood coagulation. At the opposite end of the spectrum of size at birth, bigger infants are more prone to obesity, an increasing public health problem in developed countries and an emerging one in developing countries.

The usual measure of size is birth weight, an easily and precisely measurable anthropometric parameter. Birth weight is often the only anthropometric parameter used, and has been the most studied. Epidemiological studies have shown it to be a determinant of infant mortality. Because infant mortality rates in developing countries are high, there has been a large amount of work on low birth weight and studies of risk factors for low birth weight and intrauterine growth

retardation were a natural step forward. Low birth weight is linked adversely with morbidity, mortality, growth and development. A strong association of *birth length* with development at 12 months has been demonstrated. Low birth length has also been related to mortality and hospitalization. Small *head circumference* indicates poor development of brain - as seen in symmetrically growth-retarded infants – and is associated with compromised cognitive development.

Although birth weight has been used as a standard measure of size at birth, it is only one dimension of size and is a crude marker of fetal growth. Each dimension of size has different implications and should be measured at birth, but the existing literature is dominated by discussions of weight alone. Moreover, birth weight is the only birth parameter measured in many hospitals as a proxy for birth size and as an indicator of health. The patterns, associations and implications of the various dimensions are the subject of the thesis.

The expression low birth weight was used interchangeably with prematurity for four decades between the 1920s and 1960s. In the 1970s, prematurity and intrauterine growth retardation were understood as two separate concepts, as were differences in mortality between them. This evolution of concepts over time, and the arbitrary cut-off point set on the basis of mortality rates and ease of measurement should make us wonder about the credibility of low birth weight as an entity[1]. Even today, risk factor studies for low birth weight are popular among researchers. Because the studies conducted in different settings showed different results, the causal relationship between important risk factors and low birth weight is difficult to establish. However, the extensive previous work on risk factors can be used for better understanding and documentation of their usefulness.

This thesis brings together evidence from past and current research. It will address important issues with regard to current work on size at birth - particularly the meaning of size at birth and its risk factors - and discuss its relevance. The thesis discusses the identification of research on birth size: past and current. It assesses the usefulness of the current pool of knowledge on size

at birth. The idea is to address, in a semi-rural setting in Nepal, an important public health problem in relation to what is already known.

The scope of the thesis includes:

(a) Describing the distribution of different indicators of size at birth in a cohort of infants in Nepal, which has not been done before,

(b) Development of prediction models for different indicators of size at birth, and assessment of how useful they might be.

(c) Looking at the outcomes in infants and young children of different classifications of size at birth.

1.2. Objectives

1.2.1. General objectives

The general objectives of the work carried out for the thesis were:

1. To understand size at birth in order to improve child survival and prevent adverse outcomes in Nepal.

2. To understand the implications of measuring different parameters of size at birth – weight, length and head circumference - and using derived indices such as size for gestational age, body mass index and ponderal index.

1.2.2. Specific Objectives

The specific objectives were:

Describing size at birth

1. To describe the distribution of size at birth in a cohort in southern Nepal: birth weight, length, head circumference, body mass index and ponderal index.

2. To estimate the prevalence of low birth weight, small for gestational age and low ponderal index in the cohort.

Risk factors for size at birth

1. To examine the independent effects of maternal demographic factors, nutritional status and health status on size at birth.

2. To identify important risk factors for abnormal size at birth.

3. To generate models for prediction of abnormal size at birth and to investigate whether known risk factors can predict size at birth adequately.

Effects of size at birth

1. To assess the effects of size at birth on mortality at 1 month and in early childhood.

2. To assess the effects of size at birth on malnutrition at two years of age.

3. To assess the effects of size at birth on morbidity at two years of age.

1.3. Role of the investigator

I was the clinical trial coordinator for a double blind randomized controlled trial of antenatal multiple micronutrient supplementation in southern Nepal from 2001 to 2007.[2;3] I was based in Janakpur, Dhanusha for most of the research period. For the trial, I was trained in obstetric ultrasonography and worked from a base at Janakpur Zonal Hospital. I supervised enrollment of participants, follow-up in pregnancy, measurement of infants at birth and follow-up of children at two years of age. I was trained in and performed the obstetric ultrasonography for the trial. I

was responsible for maintaining the database, entering and cleaning data. I co-ordinated the follow-up study, designing the questionnaire and database and supervising piloting and field work. In summary, I am answerable for the data used in the thesis, from collection to analysis.

1.4. Sequence of the thesis

The thesis is organized as follows. It includes 7 Chapters:

The second and third chapters describe the literature review. Chapter two summarizes the Millennium Development Goals and gives a snapshot of the UN declaration of the responsibility of the world as a whole for human equality, equity and dignity. The thesis is particularly focused on the 4th goal: reduction of child mortality. The chapter provides a general idea of the gravity of childhood health problems, and particularly neonatal mortality. It discusses low birth weight as an important public health problem in developing countries and an underlying factor in neonatal mortality, and therefore a major contributor to deaths of children under five. A number of anthropometric parameters at birth are described as a background to using them in later work. Gestational age and Z score are also described. This is followed by a detailed consideration of the classification of abnormal birth sizes and the identification of abnormal size. The next chapter covers the subject of what is already known about risk factors for low birth weight in low income countries and high income countries. This draws upon work on risk factors and provides a critical review of the methodological approaches to the research work. It gives a perspective on the risk factors relevant to the context of the thesis.

The fourth chapter discusses the study design, setting and methods for the field research. It provides a detailed description of the setting in which the study was carried out, and the procedures that were followed. The stages of the studies are summarized from selection of participants to follow-up, and the tools used and data management are described. Ethical considerations and maintenance of data quality are also covered.

Chapter five generally describes the data available for the study.

Chapter six presents the basic results of an analysis of size at birth. It begins with maternal demographic characteristics followed by the prevalence of small size at birth using a population sample who did not receive multiple micronutrient supplementation.

Chapter seven summarizes risk factor analysis, specially focusing on prediction models to draw on the determinants of size at birth.

Chapter eight summarizes the investigation of the effects of size at birth on immediate and longer term outcome. It describes neonatal, infant and childhood mortality, morbidity and malnutrition represented by stunting, wasting and underweight.

Chapter nine summarizes the key findings, discusses the limitations of the studies and goes on to discuss the implications of the findings. It particularly considers their generalisability.

The final chapter attempts to draw clear and simple conclusions in this complex field.

Chapter 2. Background to the consideration of size at birth

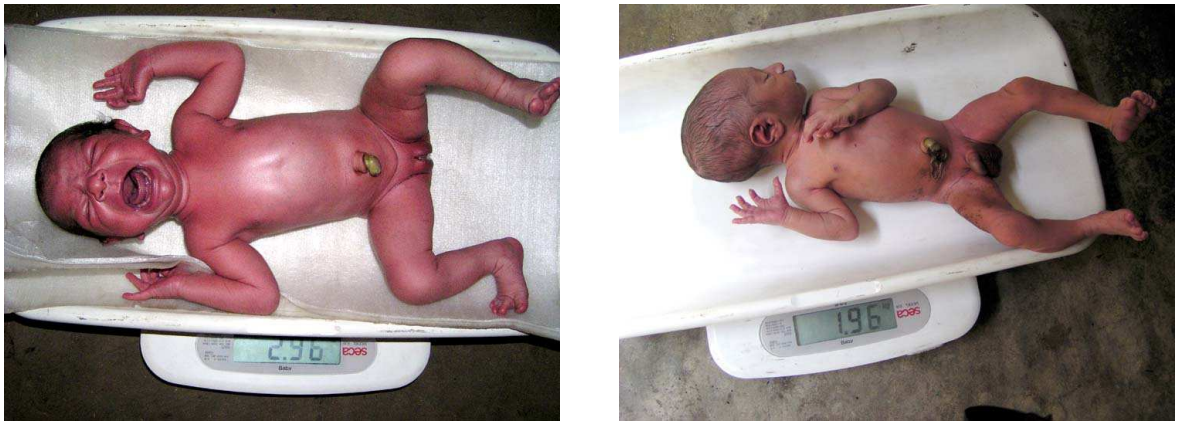


Figure 2.1. Normal birth weight and Low birth weight infant born at >37 weeks of gestation

2.1. The Millennium Development Goals

In September 2000, heads of state of 189 countries approved the UN Millennium Declaration. Many member countries are committed to the Millennium Development Goals (MDGs) to reduce poverty and hunger, and to tackle ill health, gender inequality, lack of education, lack of access to clean water and environmental degradation. The goals are set to be achieved by 2015. Table 2.1 presents the MDGs, targets and indicators. There are eight goals, 16 targets and 48 indicators, out of which one goal, one target and 3 indicators are related to child health. The fourth goal is to reduce child mortality. The target is to reduce under-five mortality by two-thirds between 1990 and 2015. There are three health indicators to measure the progress towards the target: under-five mortality rate, infant mortality rate and the proportion of one-year children immunized against measles.

The measurement of achievement of MDG 4 over the period of 25 years will be reported by the degree of reduction in child mortality across countries. To review progress, an interim analysis was carried out. It showed an asymmetrical reduction in mortality: in urban Sub-Saharan Africa, only five out of 22 countries studied met the targeted reduction of 4% per year between 1990 and 2000, and the rest of the countries showed either an increase or a nominal decline in

mortality.[4] Similarly, another analysis for the year 1990 and 2004 in 60 countries with the highest mortality showed only 7 countries to be on track, 39 making nominal progress and 14 off-track (serious concern category).[5] This analysis gave an overview of the progress and recommended country-specific and time-specific changes in efforts and coverage of interventions in those countries which were lagging behind. It included equitable coverage of interventions to all economic strata in poor countries.

Table 2.1. Millennium development goals, targets and indicators related to health

Goal 1	**Eradicate extreme poverty and hunger**
Target 1	Halve, between 1990 and 2015, the proportion of people whose income is less than one dollar a day
Indicators	Proportion of population below one dollar a day Poverty gap ratio (Incidence * depth of poverty) Share of poorest quintile in national consumption
Target 2	Halve, between 1990 and 2015, the proportion of people who suffer from hunger
Indicators	Prevalence of underweight children under five years of age Proportion of population below minimum level of dietary energy consumption
Goal 2	**Achieve universal primary education**
Target 3	Ensure that, by 2015, children everywhere, boys and girls alike, will be able to complete a full course of primary schooling
Indicators	Net enrolment ratio in primary education Proportion of pupils starting grade 1 who reach grade 5 Literacy rate of 15-24 year-olds
Goal 3	**Promote gender equality and empower women**
Target 4	Eliminate gender disparity in primary and secondary education, preferably by 2005, and at all levels of education no later than 2005
Indicators	Ratio of girls to boys in primary, secondary and tertiary education Ratio of literate women to men, 15–24 years old Share of women in wage employment in the non-agricultural sector Proportion of seats held by women in national parliament
Goal 4	**Reduce child mortality**
Target 5	Reduce by two-thirds, between 1990 and 2015, the under –five mortality rate
Indicators	Under-five mortality rate Infant mortality rate Proportion of one-year –old children immunized against measles
Goal 5	**Improve maternal health**
Target 6	Reduce by three-quarters, between 1990 and 2015, the maternal mortality ratio
Indicators	Maternal mortality ratio Proportion of births attended by skilled health personnel
Goal 6	**Combat HIV/AIDS, Malaria and other diseases**
Target 7	Have halted by 2015 and begun to reverse the spread of HIV/AIDS
Indicators	HIV prevalence among pregnant women aged 15-24 years Condom use rate of the contraceptive prevalence rate Condom use at last high-risk sex Proportion of population aged 15–24 years with comprehensive correct knowledge of HIV/AIDS Contraceptive prevalence rate Ratio of school attendance of orphans to school attendance of non-orphans aged 10-14 years
Target 8	Halve halted by 2015 and begun to reverse the incidence of malaria and other major diseases

Indicators	Prevalence and death rates associated with malaria Proportion of population in malaria-risk areas using effective malaria prevention and treatment measures Prevalence and death rates associated with tuberculosis Proportion of tuberculosis cases detected and cured under DOTS (Directly observed short-course)
Goal 7	**Ensure environmental sustainability**
Target 9	Integrate the principles of sustainable development into country policies and programs and reverse the loss of environmental resources
Indicators	Proportion of land area covered by forest Ratio of area protected to maintain biological diversity to surface area Energy use (kg oil equivalent) per US$1 GDP (PPP) Carbon dioxide emissions per capita and consumption of ozone-depleting CFCs (ODP tons) Proportion of population using solid fuels
Target 10	Halve by 2015 the proportion of people without sustainable access to safe drinking-water and sanitation Proportion of population with sustainable access to an improved water source, urban and rural Proportion of population with access to improved sanitation, urban and rural
Target 11	By 2020 to have achieved a significant improvement in the lives of at least 100 million slum dwellers Proportion of households with access to secure tenure.
Goal 8	**Develop a global partnership for development**
Target 12	Develop further an open, rule-based, predictable, non discriminatory trading and financial system
Target 13	Address the special needs of the least developed countries
Target 14	Address the special needs of landlocked countries and small island developing states
Target 15	Deal comprehensively with the debt problems of developing countries through national and international measures in order to make debt sustainable in the long term
Target 16	In cooperation with developing countries, develop and implement strategies for decent and productive work for youth Unemployment rate of young people aged 15–24 years, each sex and total
Target 17	In cooperation with pharmaceutical companies provide access to affordable, essential drugs in developing countries Proportion of population with access to affordable essential drugs on a sustainable basis
Target 18	In cooperation with the private sector, make available the benefits of new technologies, especially information and communications
Indicators	Telephone lines and cellular subscribers per 100 people Personal computers in use per 100 people Internet users per 100 people

Adapted from United Nations declaration: http://www.undp.org/mdg/basics.shtml accessed on 18 September 2008[6]

2.2. Status of the world's children

Almost 130 million children are born every year. Approximately 11 million die before attaining the age of five years, out of which more than four million children die in the Asia and Pacific region alone.[7] Most of these deaths are in low and middle-income countries. Table 2.2 shows that developing countries fall into low, lower-middle and upper-middle income categories, and that these account for quite a range of possible incomes. 90% of the child deaths occur in just 42 countries of the world and 50 % in just five countries.[8]

Table 2.2. World Bank classification of the economies of member countries

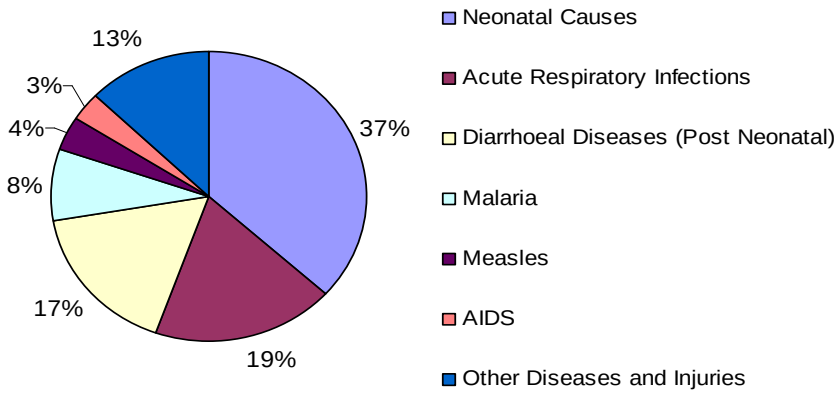
Categories		Gross National Income per capita (2007) in US$
Low Income	Developing countries *Most child deaths*	935 or less
Lower middle income		936 - 3,705
Upper Middle income		3,706 – 11,455
High Income		11,456 or more

Adapted from World Bank figures[9]

2.2.1. Causes of Child Mortality

The World Health Organization (WHO) presented estimates of medical causes of under-five deaths in geopolitical regions for the years 2000 to 2003. The estimates are shown in Figure 2.2. The figure shows that a considerable percentage of under-five deaths (37%) occur during the first 28 days of life – the neonatal period.[10] The next most important categories of mortality are acute respiratory infections (19%), diarrhoea (17%), malaria (8%), measles (4%), and HIV/AIDS (3%). The majority of listed causes are preventable and treatable, such as malaria, measles, diarrhoea and acute respiratory infections.

Figure 2.2. Causes of deaths in children under five, 2002 - 2003



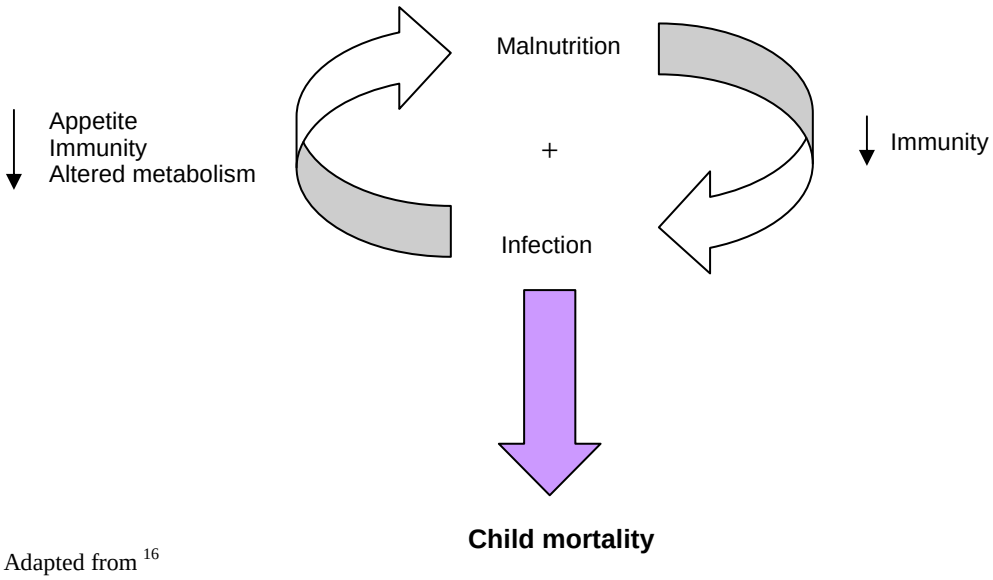
Adapted from[11]

2.2.2. Child Survival and Malnutrition

Malnutrition among children still causes major public health problems in many countries.[12] In South Central Asia alone, 40% of preschool children were stunted (71.5 million), 41%

underweight (73.4 million) in the year 2000 and 15% wasted in the year 1995.[13],[14] In 1968, Scrimshaw described a synergistic effect between malnutrition and infection (Figure 2.3).[15] Poor nutritional status makes children more susceptible to infections by lowering immune status. Infections in turn lower the nutritional status of the children by lowering appetite and gut absorption of nutrients (reduced protein absorption by 20 to 30% in diarrhoea, vitamin A malabsorption in systemic febrile illness); and by increasing metabolic rate (catabolism of musle protein for gluconeogenesis, participation of hormones regulating carbohydrate metabolism in host defence, anabolism of amino acids for synthesis of immunoglobulin and lymphokines) and by changing nutrient levels in the body - lipids, vitamin A (reduced in acute respiratory infection, , measles, gastroenteritis), riboflavin (reduced in sandfly fever), iron (in malaria) and ascorbic acid, for example.[16] Malnourished children are more likely to die from infectious disease[17] and undernutrition (low weight-for-age) is a leading underlying cause for more than half of under-five mortality among children in developing countries. Mild to moderate malnutrition is responsible for as much as 87% of child deaths, in comparison to severe malnutrition.[18]

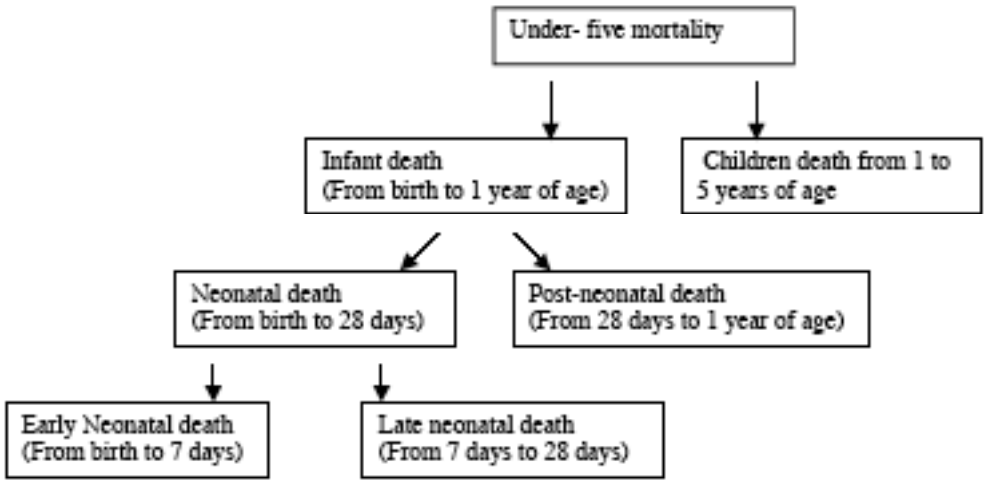
Figure 2.3. Pathways of malnutrition and child mortality



Adapted from [16]

Figure 2.4 shows how under-five mortality has been categorized into age groups. Since there has been a considerable decline in post-neonatal mortality due to vaccines, treatment of infections and oral rehydration therapy, there is a pressing need to address the problem of neonatal mortality.[19] The first seven days of life- the early neonatal period - is a crucial period. Three-quarters of neonatal deaths occur in this period, mainly within 24 hours of birth. A meta-analysis from six developing countries showed preterm delivery as the leading cause of early neonatal death, followed by asphyxia and birth trauma, congenital anomalies, unknown causes and infections respectively.[20]

Figure 2.4. Categorization of under-five mortality

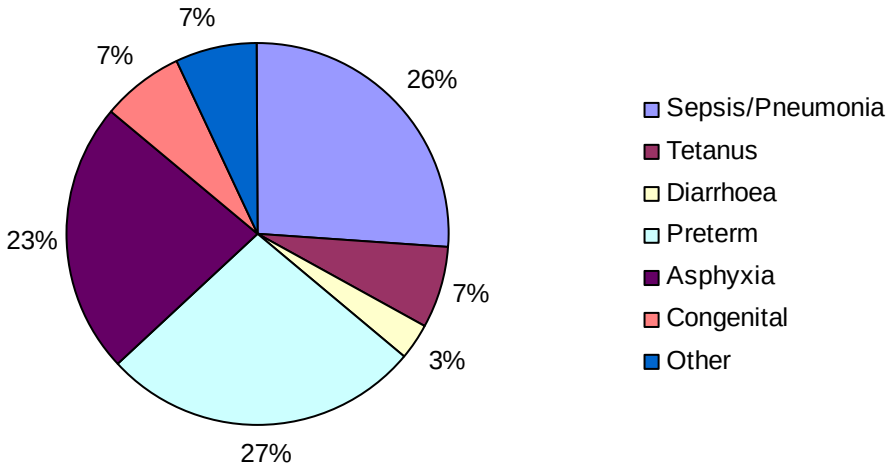


The inclusion of stillbirths with early neonatal deaths constitutes perinatal death. It is estimated that for every neonatal death there is one stillbirth. Perinatal death alone is responsible for 7% of the total global burden of disease.[21] It is ranked third after lower respiratory tract infections and diarrhoeal diseases. (Table 2.3)

Neonatal deaths account for two-thirds (64%) of infant mortality.[1;22] The main causes of death in the neonatal period have been identified and are depicted in Figure 2.5, which shows that prematurity presents the greatest risk for neonatal deaths (28%). Sepsis contributes the second most to neonatal death (26%), followed by asphyxia (23%). Congenital anomalies, tetanus and

diarrhoea contribute a small part to the overall causes of deaths, just 16% when combined together.[19]

Figure 2.5. Causes of neonatal deaths



Adapted from[19]

In summary, neonatal mortality is mainly due to perinatal events, whereas post-neonatal mortality is mainly due to environmental factors. Early neonatal death is mainly due to asphyxia, preterm birth and congenital defects and late neonatal death is predominantly due to infections.

Table 2.3. Leading global burden of disease, 1990

Disease/Injury	DALYs (thousands)	% of total
Lower Respiratory Infection	112898	8.2
Diarrhoeal Disease	99633	7.2
Perinatal condition	92313	6.7
Depression	50810	3.7
Ischemic Heart Disease	46699	3.4
Cerebrovascular Disease	38523	2.8
Tuberculosis	38426	2.8
Measles	36520	2.7
Road Traffic Accident	34317	2.5
Congenital Anomaly	32921	2.4

Adapted from Lopez 2005[21]

2.2.3. Child survival and low birth weight

Approximately 130 million infants are born every year. Usually, the only birth size indicator measured at birth is weight. Of the babies born, 14% weigh less than 2500 g – low birth weight. Back in 1985, McCormick and colleagues noted that low birth weight was one of the major causes of neonatal mortality[23]. Low birth weight was responsible for 60-80% of neonatal deaths. It has been shown to have a strong relationship with infant mortality: the cut-off point of 2500 g was mortality-based.[24]

Birth weight has been demonstrated to be a sensitive indicator of neonatal and post-neonatal mortality as shown by birth weight specific mortality (Table 2.4). Low birth weight infants are more prone to sepsis due to altered immunity[25], asphyxia, hypothermia and feeding problems.[26] Term low birth weight infants weighing 2000 – 2499 g have 4 and 2 times higher risk respectively of neonatal and post-neonatal mortality than infants weighing 2500 - 3000 g. Likewise, they have 10 times and 4 times higher neonatal and post-neonatal mortality than infants in the weight group 3000-3499 g.[27]

Low birth weight is a result of preterm birth, retarded intrauterine growth or a combination of both. The majority of low birth weight in developing countries is due to growth retardation. Preterm delivery is directly causal in 28% of neonatal deaths and term intrauterine growth retardation in 1-2% of neonatal deaths.[19] Growth retarded infants not only suffer intrapartum asphyxia, low apgar scores and meconium aspiration during late pregnancy, they are also prone to hypothermia due to reduced body fat mass, polycythemia secondary to hypoxia, hypocalcemia and hypoglycemia in the early neonatal period. Term growth retarded infants are born with low weight and less fat. They lack insulation and energy thus making them prone to hypothermia and poor growth. They may show catch-up growth during early infancy and attain a normal growth curve by one year of age. However, term growth retardation is linked with increased mortality, morbidity, disability, poor growth, cognitive development in children and morbidity in adults.

Table 2.4. Relative risks of neonatal and post-neonatal mortality

Term birth weight (g)	Relative Risks	
	Neonatal mortality (death within 28 days)	Post-neonatal mortality (death between 28 days and 364 days)
2000-2499	4	2
2500-2999	1	1
3000-3499	0.4	0.5
3500-3999	0.3	0.5

Adapted from [27]

2.2.4. Childhood morbidity and low birth weight

The important consequences of low birth weight on childhood morbidity include disabilities, hospitalization.[28] poorer language development[29], diarrhoeal disease[30] and acute respiratory infections.[30] Cognitive, psychological, behavioural and educational deficits may also be seen[31].

2.2.5. Size is important

The above evidence confirms the importance of birth weight to childhood and adult health and survival. However, there is more to birth size than just low birth weight. Very few studies have gone beyond low birth weight to investigate the importance of other dimensions of birth size, especially in developing countries, where fetal growth retardation and child mortality is common. Little is known about the association of other dimensions of size at birth with childhood and adult outcomes.

The importance of size at birth has increased with the advent of the fetal origins hypothesis (now known as the Developmental Origins of Health and Adult Disease, DOHAD), which states that adult disease is programmed in utero through influences which alter fetal growth. Programming is the process of adaptation of the fetus to nutrition by altering the metabolic, physiological and structural parameters of the body.[32] Fetal malnutrition (adverse intrauterine environment) may occur in any phase of fetal development and for variable duration and severity (acute and chronic malnutrition). Each fetus has its own genetic potential and intrauterine environment, which influences fetal growth pathways. Infants with similar weights at birth could have other different birth dimensions - length, head circumference, body mass index, ponderal index, abdominal circumference, gestational duration and so on. Birth weight is

the most studied anthropometric parameter among many that could describe fetal size, prenatal growth and birth size. It is used as a marker of the intrauterine environment. However, it is just a crude marker of fetal growth.

Different anthropometric measurements have different implications. For instance, head circumference reflects brain size and growth.[33] Small head circumference indicates poor development of the brain - as seen in symmetrically growth-retarded infants – and is associated with compromised cognitive development and poor intellectual performance.[34] A strong association of birth length with development at 12 months has been demonstrated, and there appears to be an association with blood pressure in adulthood.[35-37]

Duration of exposure to intrauterine malnutrition manifests as proportionate growth retardation and disproportionate growth retardation, a feature of adaptation. Chronically malnourished fetuses present with proportionate growth retardation. This is manifested as visually appreciable change in birth size parameters especially smaller head circumference, shorter length and reduced weight and altered tissue mass. Similarly, acutely malnourished fetuses present with disproportionate growth retardation: normal birth weight and length, with wasting.

The importance of the opposite end of the spectrum of birth weight has also been recently recognized. Infants who are bigger at birth are more prone to obesity[38], an increasing public health problem in developed countries and an emerging one in developing countries.

2.3. Cost of abnormal birth size

Cost of providing care for low birth weight infants is high not only for families, but also for health services and communities. Because of its array of short term and long term complications, LBW imposes an enormous economic and emotional burden on the family throughout life. In developing countries where the problem is epidemic, health services and systems face functional difficulties. Modern technology for management of affected infants is next to impossible for the time being. Setting up whole health systems is a major challenge in

itself. Preventive care and intervention might be more cost effective than the management of the problem and its complications. For example, Borghi et al recommended a participatory intervention with a women's group in the rural setting of Nepal where supply side interventions are probably not feasible on a large scale because of the vast resource requirements.[39] The intervention offers an affordable means of reducing neonatal mortality and could benefit from expansion. Mass production of interventions like prenatal iron and folate supplements cost an estimated less than $1 per person throughout pregnancy, and might improve birth outcomes among women in developing countries.

2.4. Measurements of size at birth

Anthropometry is the external measurement of the human body and is used to assess nutritional status, growth and development. Anthropometric measurements at birth are the easiest, quickest and most inexpensive method of estimating body size and identification of newborn infants at risk for adverse outcomes. Anthropometric measurements in common use are birth weight, length and head circumference, but mid-upper arm circumference, abdominal circumference and chest circumference are sometimes used. These anthropometric measurements can be assessed against gestation at birth, but this is not always done. Although it is not anthropometric, since gestation at birth is one of the important determinants of birth size, a section on it is included.

2.4.1. Birth weight

Birth weight is the first weight of an infant measured after delivery. It does not take account of gestation, but is one of the most important and widely used anthropometric measurements. Weight is used for assessment of fetal growth and also to imply the maturity attained by birth. The newborn infant loses 10% of birth weight in the first week and, if all remains well, regains it in the next few days. Therefore, it is important to weigh the infant within the first hour of birth, preferably before significant postnatal weight loss occurs. It is essential to note the age and time at which birth weight is measured. Current intervention studies accept measurements

of birth weight made within the first 72 hours. This is a compromise between accuracy and feasibility.

2.4.1.1 Measurement

Birth weight can be measured with a spring or beam balance or precision electronic scales. It is measured in grams. The measurement of birth weight is not consistent and tends to show inter-observer and intra-observer variation. The reliability and validity of weighing scales should be checked and calibrated from time to time. It is problematic if the weighing scale does not have an infant pan. In this event, the mother is weighed with and without the infant and the difference is equated with the weight of the infant.

Depending on the birth weight, newborn infants are categorized into 5 groups, low birth weight (<2500 g), very low birth weight (<1500 g), extremely low birth weight (<1000 g), normal birth weight (>2500 - <4000 g) and high birth weight (>4000 g). These strata have different survival rates and require different levels of care.

2.4.1.2 Practical problems

In developing countries, it is often not possible to achieve consistency in birth weight data for the following reasons. Firstly, the weighing scale used may not be up to international standards. Secondly, the weighing scale may not be reliable and valid because of lack of calibration at intervals and lack of durability. Thirdly, it may not feasible to weigh the infant within the first hour of birth because most deliveries occur at home. Table 2.5 shows how uncommon birth in hospital with a skilled attendant is in some Asian countries. In Nepal, the figure for home birth is 92%.[40]

As can be noted from the classification, the cut-off point used for the definition of normal and low birth weight infants is a fine line. Infants with birth weight of 2499 g are termed low birth weight while those of 2500 g are not. This is complicated by observation error and digit

preference while recording birth weight. Digit preference is the tendency of the observer to prefer terminal digits such as 0 or 5, so that infants of fractionally less than 2.5 Kg are classified as 2.5 Kg. This hides the real picture of the incidence of low birth weight and should be avoided or corrected when analyzing data and interpreting results.[41]

Table 2.5. Place of birth

Country	Home delivery	Skilled Birth Attendant	Traditional Birth Attendant	Source
Nepal	92%	19%	-	NFHS 1996[40]
India	65%	42%	35%	NFHS-2[42]
Bangladesh	92%	12%	64%	WHO[43] *
Pakistan	>89%	_	80%	National health survey of Pakistan 1990-94[44]
Indonesia	90%	37%	_	Ronsmans 2001[45]

* http://www.whoban.org/skill_birth_training.html accessed on 19th September 2008

2.4.2. Gestation

2.4.2.1 Definition

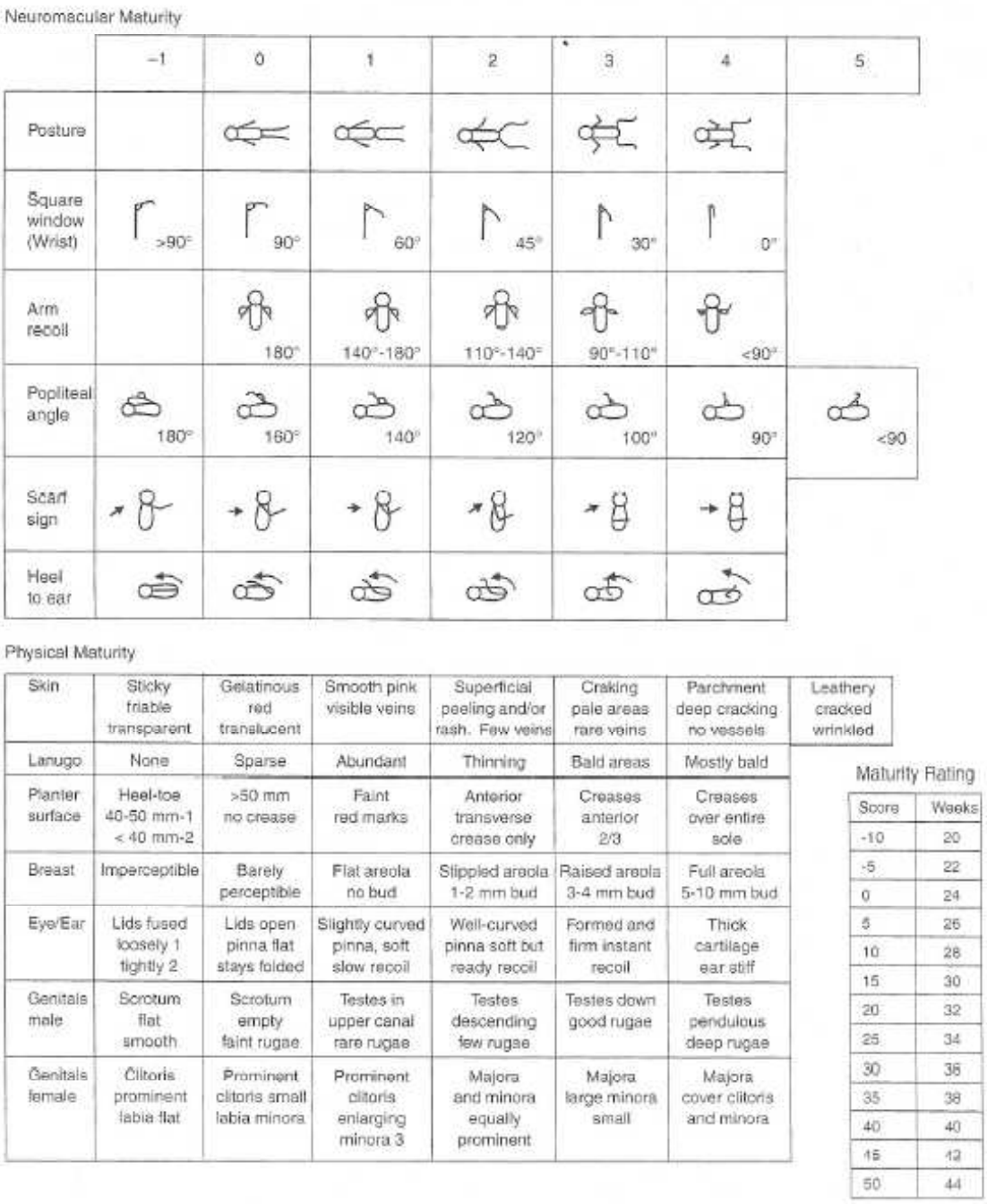
Gestation is the period of development from conception to birth. The average duration of gestation is 280 days or 40 weeks. Gestational age and rate of fetal growth determine the size of an infant at birth. Clinical decisions for management and resource allocation largely depend upon gestational age at birth and birth weight. The importance of correct estimation of gestational age has been recognized for a long time and studies have been carried out to test methods of assessing it.[46;47] In recent years, because of the necessity to differentiate small-for-dates infants from appropriate-for-dates infants who are born prematurely (Dubowitz), assessment has gained more value as small-for-dates infants are at risk from different conditions than appropriate-for-gestational-age infants. Furthermore, neurological behaviour in the neonatal period depends on gestational age and assessment helps to interpret it and the subsequent development of the infant.[48]

2.4.2.2 Measurement of gestational age

Many parameters have been used to estimate gestational age, but none of them is error free. Of interest are: biological methods using basal body temperature; last normal menstrual period; ultrasound scan using fetal crown-rump length, biparietal diameter, femur length and abdominal circumference; clinical methods such as measurement of the height of the uterus per abdomen from the symphysis pubis (symphysio-fundal height), asking about the first movement of the fetus felt by the mother (quickening), fetal heart sound detection and immunological methods such as urine luteinizing hormone (LH) and human chorionic gonadotropin (hCG).[49,50] The commonest method is a combination of reliable recall of last normal menstrual period and early ultrasound scans.[51-53]

In the postnatal period, gestational age can be estimated by a scoring system depending on physical and nervous system maturation. In practice, such systems are too time consuming and cumbersome to use routinely. The methods of Parkin, Ballard, Dubowitz and Robinson are all options which can be used if the gestational age by menstrual dates is not compatible with the physical and neurological appearance of the newborn infant[54-56] . Figure 2.6 gives Ballard score for newborn maturity rating. Gestational assessment of this type, which is usually based on a summary score, is presumed to be accurate to within ± 2 weeks.[48]

Figure 2.6. Ballard score for the assessment of gestational age in infants after birth



Neuromuscular Maturity

	-1	0	1	2	3	4	5
Posture							
Square window (Wrist)		>90°	90°	60°	45°	30°	0°
Arm recoil			180°	140°-180°	110°-140°	90°-110°	<90°
Popliteal angle		180°	160°	140°	120°	100°	90° <90
Scarf sign							
Heel to ear							

Physical Maturity

Skin	Sticky friable transparent	Gelatinous red translucent	Smooth pink visible veins	Superficial peeling and/or rash. Few veins	Cracking pale areas rare veins	Parchment deep cracking no vessels	Leathery cracked wrinkled
Lanugo	None	Sparse	Abundant	Thinning	Bald areas	Mostly bald	
Plantar surface	Heel-toe 40-50 mm-1 < 40 mm-2	>50 mm no crease	Faint red marks	Anterior transverse crease only	Creases anterior 2/3	Creases over entire sole	
Breast	Imperceptible	Barely perceptible	Flat areola no bud	Slipped areola 1-2 mm bud	Raised areola 3-4 mm bud	Full areola 5-10 mm bud	
Eye/Ear	Lids fused loosely 1 tightly 2	Lids open pinna flat stays folded	Slightly curved pinna, soft slow recoil	Well-curved pinna soft but ready recoil	Formed and firm instant recoil	Thick cartilage ear stiff	
Genitals male	Scrotum flat smooth	Scrotum empty faint rugae	Testes in upper canal rare rugae	Testes descending few rugae	Testes down good rugae	Testes pendulous deep rugae	
Genitals female	Clitoris prominent labia flat	Prominent clitoris small labia minora	Prominent clitoris enlarging minora 3	Majora and minora equally prominent	Majora large minora small	Majora cover clitoris and minora	

Maturity Rating

Score	Weeks
-10	20
-5	22
0	24
5	26
10	28
15	30
20	32
25	34
30	36
35	38
40	40
45	42
50	44

Extracted from[57]

2.4.2.3 Classification

Depending on gestation, the newborn infant is classified into one of three categories: preterm, term and post-term (See Table 2.6).

Table 2.6. Classification of newborn infants depending on gestation

Preterm	Infants born at < 37 completed weeks (up to 36 weeks + 6 days or < 259 days)
Term	Infants born between 37 and 41 weeks of gestation (259–293 days)
Post-term	Infants born at term: > 42 weeks or > 294 days

2.4.2.4 Practical problems associated with gestational age assessment

Accurate estimation of gestational age is essential for the diagnosis of abnormal birth size like small-for-gestational-age. Gestational age estimation by last normal menstrual period is based on maternal recall which depends on the memory, guess-work and intention of the respondent. In 1988 Kramer demonstrated a systematic underestimation of gestation up to 37 weeks and progressive overestimation after 40 weeks.[47] Furthermore, estimation is complicated by other factors: use of oral contraceptives, irregular periods, bleeding in early pregnancy, ovulation bleeding, delayed ovulation and use of lunar months. Ultrasound estimation of gestational age in the early period of gestation is correct to within 7 days, but in developing countries where most of the population are poor estimation by ultrasound is an expensive, non-affordable, sophisticated and undesirable method.

2.4.3. Head circumference

Occipito-frontal head circumference is routinely measured in many countries. It provides a clinical indication of head growth in utero, brain volume[58] and cerebrospinal fluid space. Although it has no simple relationship with brain growth, deviation from normal head circumference suggests intracranial pathology and may be related to intelligence, growth and development. It is an easy, reliable and reproducible means of assessing fetal growth which can be measured with a simple measuring tape.

2.4.3.1 Measurement

Head circumference is measured at the level of maximum circumference over the supra-orbital ridge anteriorly (glabella) and the occipital protuberance posteriorly. At birth, the term head circumference measures 31–38 cm.

2.4.3.2 Classification

Depending on head circumference, head size is classified in three categories: microcephalic, normal and macrocephalic. Microcepaly describes a head circumference which lies below the 10^{th} percentile, more than 3 SD below the mean or less than the 5^{th} centile for age, sex and gestation. It may imply dysmorphic syndromes, isolated microcephaly, congenital infections, or intrauterine growth retardation. Macrocephaly describes a head circumference above the 90^{th} centile for age, sex and gestation. (see Table 2.7). It may imply hydrocephalus or macrosomia

Table 2.7. Cut-offs used for classification of infant head size

	Cut-offs for age, sex and gestation
Microcephaly	<10th percentile >3SD below the mean <5th percentile <2SD
Macrocephaly	>90th percentile

2.4.3.3 Practical problems

Although measurement of head circumference with a measuring tape seems like a simple procedure, it needs practice to get the right position. Special care should be taken while reading the decimals on measuring tapes. Bartram claims that the old worn out tape tends to stretch, which may not be clinically significant but is statistically significant.[59] It is especially important in developing countries where the measuring tape may not be replaced frequently.

2.4.4. Mid-upper arm circumference

MUAC is a standard anthropometric measurement of nutritional status. It can be used as a proxy for birth weight[60;61], for which it has been described as a reliable predictor.[62;63] Some studies have shown that there is a direct association of mid-upper arm circumference with both birth weight and gestational age.[64;65] It is a useful tool especially for developing countries where women are illiterate and recall of last normal menstrual period is difficult, and where most deliveries are conducted at home and reliable weighing scales are not available. It is an easy, quick and reproducible anthropometric measurement. Curves for MUAC have been developed for newborn infants.[66;67]

2.4.4.1 Measurement

MUAC is measured at the midpoint between the acromion process and the tip of the olecranon process. It is measured to the nearest 1 mm.

2.4.4.2 Classification

MUAC can be used to classify infants as normal birth weight and low birth weight, for which a cut-off point of 9 cm has the best combination of sensitivity and specificity.[63;68] (see Table 2.8) MUAC reference data are available for ages between 6 and 60 months.[69] For children between 2 and 20 years old, percentiles are generally used. Those less than the 5^{th} percentile are underweight while those above the 95^{th} percentile are overweight. Children between the 85^{th} and 95^{th} percentiles are at risk of becoming overweight.[70]

Table 2.8. Classification of newborn infant based on mid upper arm circumference

Mid upper arm circumference	Classification
<9 cm	Low birth weight
>9 cm	Normal birth weight

2.4.4.3 Practical problems

Although it is suggested as a useful tool for developing countries, MUAC is almost never measured at birth. Like other anthropometric measurements, there are chances of intra-observer and inter-observer variation. MUAC should be measured when the infant is relaxed. The observer should be careful not to squeeze the soft tissue but place the tape firmly on the arm. The measurement should be taken three times. Therefore, the observer should have enough practice before actually starting to take measurements.

2.4.5. Chest circumference

Chest circumference is measured at the time of birth in some institutions, and is a pointer to intrauterine fetal growth. In a normal newborn infant, chest circumference is smaller than head circumference by about 2.5 cm, but becomes roughly equal to head circumference by the end of the first year and greater thereafter.

A 1993 WHO collaborative study conducted in 22 centers of the world on 400 consecutive samples found that chest circumference could be used as a proxy to identify infants at risk of low birth weight. It could be used in communities where the accurate early weighing of neonates is not feasible.[71] A cut-off point of $\leq$ 29 cm could be used with high predictive value, sensitivity (91%) and specificity (94.7%) for the identification of intrauterine growth retarded infants.[72]

2.4.5.1 Measurement

Chest circumference is measured at the level of the nipples. It is simple, easy to measure and does not require expensive equipment.

2.4.5.2 Classification

Chest circumference is one of the parameters used to distinguish between proportionate and disproportionate intrauterine growth retardation, which will be discussed later.

2.4.5.3 Practical problems

The chest moves with inspiration and expiration, which can make a difference to measurements if the observer is not careful enough. Circumference should be measured at maximum inspiration.

2.4.6. Crown-heel length

Crown-heel length is a good measure of skeletal growth. Measurement of length is a routine part of the clinical examination of the newborn infant in many countries and is of importance in detecting abnormal skeletal growth. Crown-heel length is measured for infants and children of length ≤ 85cm.[73] Body height is measured for children with length > 85 cm.

2.4.6.1 Measurement

Length can be measured on a bespoke length meter with the infant in extended position. The heels should be placed against the foot piece with the head touching the base of the board and knees in an extended position. The measurement should be accurate to 1 mm. At birth, length is approximately 50 cm.[48]

2.4.6.2 Classification

Length has been used to classify growth-retarded infants into proportionate and disproportionate intrauterine growth retardation, of which more later.

2.4.6.3 Practical problems

Two observers are required to do the measurements. It may be difficult to find a flat surface to place the length measurer in rural areas of developing countries.

2.4.7. Waist circumference

Waist circumference is a measure of abdominal fat distribution (abdominal obesity), and has been related to increased risk of cardiovascular disease[74] and type II diabetes.[75] Obesity is an emerging public health problem in developed and developing counties. Waist circumference has recently been demonstrated to have a closer correlation with obesity-related risk factors for health than BMI.[76]

2.4.7.1 Measurement

Waist circumference is an easy, non-invasive method of measuring abdominal obesity and does not require sophisticated equipment. It is measured at the level of the narrowest part of the abdomen or midway between the iliac crest and lower level of the ribs in the mid-axillary line.

2.4.7.2 Classification

Studies have chosen various cut-off points for defining obesity-linked health risk in terms of waist circumference. For instance, Wildman in 2004 found that the Chinese population was at lower risk of developing cardiovascular disease than western populations.[77] The WHO recommended cut-off point is ≥94 cm for men and ≥80 cm for women.[78] This is based on a western population. Deurenberg demonstrated that Asian populations were at risk at lower levels of waist circumference and should not use the cut-off based on data from western subjects.[79] Cut-off points should be sex specific and ethnicity specific. A recent retrospective study on 2746 people aged 18-72 years with body mass index 18–60 kg/m^2 and waist

circumference 65–150 cm showed that waist circumference was an independent risk factor for insulin resistance. Waist circumference <100 cm excluded insulin resistance.[78]

Table 2.9. Cut-off points for waist circumference

	Increased risk	Substantially increased risk
Men	94 cm or more	102 cm or more
Women	80 cm or more	88 cm or more

Adapted from[78]

2.4.7.3 Practical problems

Different studies have used different methods of measurement. Some have used the natural waistline while some have used the mid-point between the highest point of the hip and lower ribs in the mid-axillary line. We have been unable to find internationally recommended cut-offs for waist circumference in newborn infants.

2.5. Composite indices of size at birth

The most commonly used indices for measurements of nutritional status and growth in children are weight-for-age, weight-for-height, and height-for-age. However, these indices are not generally used for newborn infants. The commonest indices in use are body mass index and ponderal index.

2.5.1. Body Mass Index

BMI (Quetelet's index) is an anthropometric measurement of nutritional status based on ideal weight-for-height. It was first described by Adolphe Quetelet, between 1830 and 1850. BMI is defined as weight (in Kg) / height squared (in m^2). BMI is a validated measurement of adiposity in adults and probably in children and adolescents (5-20yrs)[80;81], and is a marker of cardiovascular risk: blood pressure, lipids and serum insulin[81;82], diabetes and heart disease and asthma in children.[83]

Although it attempts to describe size, BMI does not take into account the percentage of fat, muscle or bone. Again, although it is a well-known index, BMI is little used in young children. Different ultrasonically derived growth standards for fetal size parameters for different gestational ages are available to determine the optimum growth achieved: biparietal diameter[84], head circumference, abdominal circumference[85], femur length[86] and different growth standards for newborn infants are also available for gestational age, sex, and ethnic groups. It has not been possible to find literature that has used BMI standards or reference data for the fetus and newborn infant, apart from a paper by Odland, which used body mass index in newborn infants to compare the effects of essential trace elements in maternal serum on birth size.[87]

2.5.2. Ponderal Index

PI has been used as an indicator of fetal growth. It was described by Lubchenco in 1966 for the detection of intrauterine growth retardation.[88;89] The index is calculated by dividing birth weight in grams by the cube of crown-heel length in centimetres (and therefore is expressed in g/cm^3). PI is a gender- and gestation-independent neonatal variable which is an important indicator of fetal malnutrition.

2.5.2.1 Normal values

In general terms, a value of 2.5 g/cm^3 is considered normal in neonates[90], while a value of less than 2 g/cm^3 is considered low for a child. Morris has classified infants with values <2.6 as low PI, 2.6-2.8 as average and ≥2.8 as high.[91]

2.5.2.2 Classification of infants

PI has been used to categorize small-for-gestational-age infants with intrauterine growth retardation into proportionate and disproportionate groups.[92] IUGR infants with low PI - below the 10^{th} percentile - are disproportionate or asymmetrically growth retarded and wasted. Only the weight of the infant is compromised. This is presumed to be due to acute or subacute

intrauterine malnourishment. Basically, infants are 'longer and thinner'. It seems that this type of IUGR is more likely to be seen in developed countries.[93 93] IUGR infants with PI above the 10th percentile are proportionate. Proportionate growth retarded infants have appropriate PI and are assumed to have been chronically malnourished in utero. Weight and length are both compromised. This type is seen mostly in developing countries. Infants with PI above the 90th percentile have high PI. They are 'shorter and fatter'. Therefore, PI is also referred to as a measure of fatness.

2.5.2.3 Ponderal index and outcome

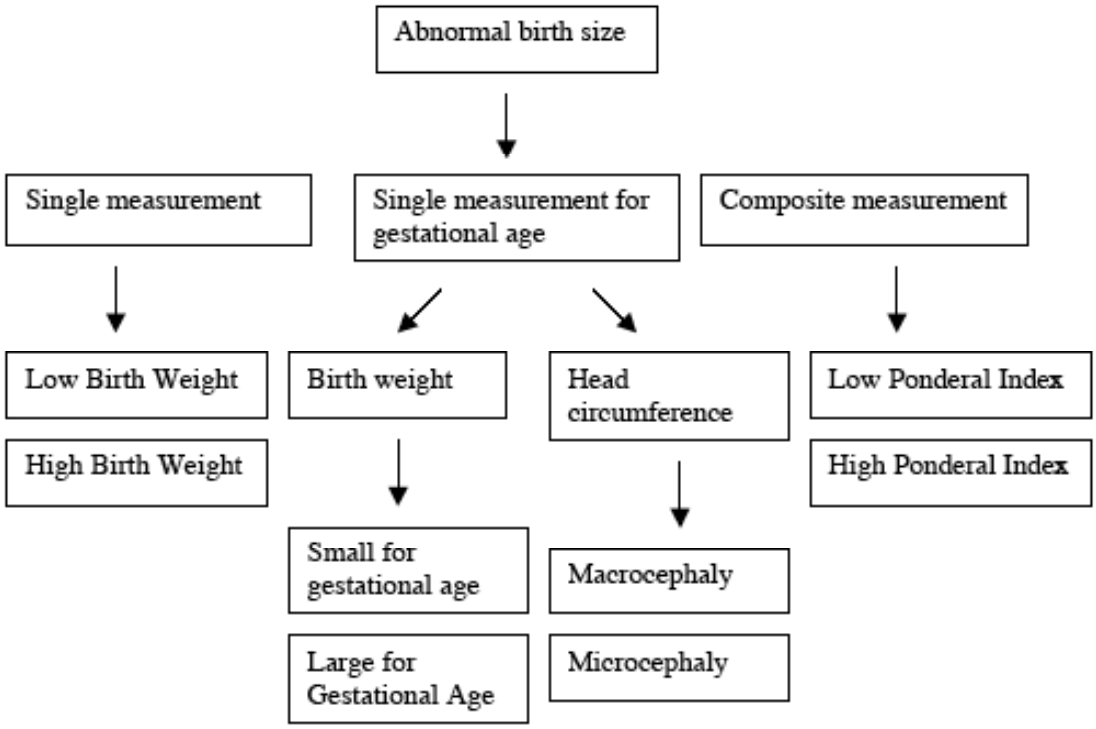
Studies have described the effect of PI on neonatal outcome. Although birth weight-for-gestational-age and birth weight percentile are used for diagnosis of growth retardation, Walther and Fay's studies found PI to be equally or more useful to predict neonatal problems and intrauterine growth problems respectively.[94;95] A Guatemalan study[96] showed that term IUGR classified by PI for gestational age (low, intermediate, high and appropriate) had different neonatal outcomes. Infants with low PI (below 10th percentile) had the highest morbidity and those with high PI (above 90th percentile) the lowest. There is evidence that body proportionality is itself related to morbidity, as shown by the higher morbidity in normal birth weight infants with low PI.[96;97]

2.6. Classification of size at birth

Birth anthropometric measurements are usually aimed at detecting an abnormality in birth size, especially LBW and IUGR. This section will deal with the basic concepts and causal factors of entities such as LBW, macrosomia, small-for-gestational-age, large-for-gestational-age, microcephaly, macrocephaly, proportionate and disproportionate IUGR (low PI). For the purposes of the thesis, we have developed the framework summarized in Figure 2.7. The framework allows us to classify abnormal birth size in three ways: based on a single

measurement, a relation between a single measurement and gestational age, and a composite index based on more than one measurement.

Figure 2.7. Classification of abnormal size at birth



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2.6.1. Single measurement: birth weight

An anthropometric parameter may be used to describe infant size at birth, irrespective of gestational age, sex and ethnicity. The obvious example is birth weight, which is often classified into three groups: low, normal and high. High birth weight is defined as a birth weight of more than 4000 g. Risk factors for high birth weight include maternal obesity, prolonged gestational duration and gestational diabetes. High birth weight infants are prone to low blood glucose in the early neonatal period, shoulder dystocia, cerebral palsy, obesity and type 2 diabetes in later life. Low birth weight is defined as a birth weight of less than 2500 g. There are two main causes: prematurity and intrauterine growth retardation. Infants born before 37 weeks of gestation are termed preterm or premature, and those born after 37 weeks of

gestation are term. Most preterm infants are LBW. IUGR infants are those whose weight for gestational age is below the 10th percentile.

2.6.2. Relation between single measurement and gestational age

Birth size for gestational age adds the time dimension, and is therefore more meaningful than a measurement of size alone. Separate reference standards are available for infant sex and ethnicity. Birth weight for gestational age is one of the most commonly used parameters to describe size at birth. Authors have used different cut-off points in studies to classify the newborn infant. These are summarized in Table 2.10.

Table 2.10. Cut-offs used for classification of newborn infant size for gestational age

Classification	Cut-offs used	Authors
Small-for-gestational-age (Small-for-dates)	<10th percentile for gestational age	Usher et al., 1969 [98] Goldernberg et al., 1989 [99]
	<3rd percentile for gestational age	Starfield et al., 1982[100]
	<5th percentile for gestational age	Fitzhardinge et al., 1972[101] Michaleis et al., 1970[102]
Appropriate-for-gestational-age (Appropriate-for-dates)	Between 10th and 90th percentile	Most authors
Large-for-gestational-age (Large-for-dates)	>90th percentile for gestational age	Most authors

AGA infants are 'normal' size for gestational age. Most studies have used a cut-off of between the 10th and 90th percentiles for gestational age. SGA is a function of birth size and gestational age, not a diagnosis of a pathological condition.[103] It may describe a constitutionally small infant as well as an infant with growth retardation. Statistically, SGA also includes 10% of infants with normal growth if a cut off point of the 10th percentile is used for definition. This means that infants can be classified as normal SGA, abnormal SGA and growth restricted.[103] Normal SGA infants are SGA infants with no growth restriction and no fetal abnormality. Abnormal SGA infants are SGA infants with fetal causes - chromosomal, structural or infective. SGA infants who are small due to placental dysfunction are categorized as having fetal growth restriction. Since they represent one end of the spectrum, it is thought that normal SGA infants are no different neurodevelopmentally from AGA infants.[104]

There is no uniformity in the use of parameters and cut-off points across studies. Different cut-off points for different fetal parameters have been used to define SGA, including birth weight, length and abdominal circumference.[105],[103] This brings more confusion to the detection of SGA and to comparison between studies. WHO has recommended the use of the sex-specific, single or twin-specific 10th percentile of birth weight for the classification of SGA.[69;106]

Most studies have used a cut-off point of <10th percentile for gestational age to define SGA. Some have used <3rd percentile or >2SD below the mean or 5th centile as the cut-off point. Similarly, the most commonly used parameter is birth weight below the 10th percentile on a gestational age chart. Smith and Colleagues have used fetal abdominal circumference for the prediction of small-for-dates infants, since it is the best predictor of fetal weight. The cut-off used is 2 SD below the mean for gestational age, which corresponds with the 2.5th percentile.[107]

2.6.2.1.1 Large-for-gestational-age

Infants with birth weight > 90th percentile for gestational age are categorised as large-for-gestational-age (large-for-dates). Both ends of the spectrum of the size of newborn infants are associated with problems. Small-for-dates and large-for-dates infants have increased mortality and morbidity and more chance of developmental problems. Large-for-gestational-age infants are at risk of obesity and subsequent cardiovascular disease[108;109] and type 2 diabetes mellitus.[110]

2.6.2.2 Head circumference for gestational age

Normally, an infant's head circumference is about 2 cm larger than her chest circumference. There are two abnormal head size categories for gestational age: microcephaly and macrocephaly, both of which are associated with abnormal brain growth. Brain growth occurs during the intrauterine phase and the first 2 years of life, so that micro- and macrocephaly may be present at birth or develop during the early years of life.

Microcephalic infants have head circumference below 2 SDs of the mean for gender, age and race. Microcephaly, as mentioned above, is either congenital or develops in the first few years after birth. Common causes include genetic problems, syndromes, chemical exposures, radiation, alcohol, drugs, and intrauterine infections. Later in life, microcephalic children may present with neurological problems such as convulsions, developmental delay, hyperactivity and spastic quadriplegia.

Head circumference above 2 SDs of the mean for gender, age and race is termed macrocephaly. It may present at birth or develop later in life, and is often due to abnormal brain growth. Some infants' heads may be constitutionally large. Macrocephaly may also be genetic (osteogenesis imperfecta, agenesis of corpus callosum, achondroplasia), or due to hydrocephalus or intracranial bleeding. There are important associations with low intelligence and learning difficulties.

2.6.3. Intrauterine growth retardation

Intrauterine growth is a complex dynamic process determined by the interaction of maternal, uterine, placental and fetal factors. Each fetus has its own growth potential, which is both genetically determined and influenced by environmental factors such as maternal height and nutritional status. An infant is said to be growth retarded if she fails to reach or follow the genetically determined growth trajectory for a given gestational age. This may be due to intrauterine insult by single or multiple etiological factors, but the mechanics of the effect are poorly understood. Since growth is dynamic, at least two intrauterine assessments of fetal size are required to trace the course of growth and to diagnose IUGR.[111] It is recommended that fetal size be assessed at four-to-six week intervals for the correct diagnosis of IUGR.[112]

The prenatal detection of abnormal fetal growth is important. Growth retardation has been related to perinatal morbidity[113] and mortality[114;115] and clear distinction of growth-retarded infants is necessary. However, small-for-gestational-age and IUGR have been used

interchangeably although they are not identical.[116] Small-for-gestational-age is simply a description of the size of an infant at a particular gestational age. Small-for-gestational-age infants may be small but not necessarily growth retarded. They may also be constitutionally small on the basis of ethnicity, parity, maternal weight and height. This distinction can avoid unnecessary intervention during pregnancy, which is directly linked to the safety of the mother as well as appropriate use of resources. Furthermore, the issue of small-for-gestational-age versus IUGR has confused clinicians as well as researchers and hampered them from a clear vision of the causes, consequences and clinical management of growth retarded small-for-gestational-age infants.

2.6.3.1 Diagnosis of intrauterine growth retardation

In developing countries where ultrasonography is expensive and is not a routine investigation, diagnosis is based on clinical suspicion when there is low maternal weight gain, lag in fundal height by 4 cm or greater, or when there is an incidental finding on ultrasound of fetal measurements smaller than expected for gestational age.

As mentioned above, the diagnosis of intrauterine growth retardation should not be based on a single estimate of fetal size. Customized and non-customized fetal biometric charts have been produced by researchers for the screening of fetuses.[117;118] Non-customized fetal growth charts have been used conventionally. They allow assessment of fetal size against gestational age for males and females. Customized charts are adapted for individual pregnancies and take into account physiological variables that are documented to have a significant effect on intrauterine growth: maternal ethnicity, parity, height, and weight at first visit. Their use reduces false positive diagnosis of IUGR. There are also other methods for detection of intrauterine growth retarded infants, such as uterine artery Doppler abnormalities, cardiotocography, and fetal venous Doppler, but all of these require sophisticated equipment.

Chapter 3. Knowledge of size at birth

3.1. Chapter summary

This chapter describes what is already known on this area of study and reviews global and regional status of low birth weight. It tells us how most studies are focused on birth weight and underscores the dubiousness of its role in understanding adverse consequences like neonatal and infant mortality. It highlights the lack of investigation of other parameters of birth size.

3.2. Low birth weight

Low birth weight is a major problem and a challenge to most developing countries because of its high prevalence (16.5%)[119], its multiple and complex associated factors (maternal, placental, fetal or combination)[120], and its major contribution to the mortality and morbidity of neonates, infants and adults. The influence of intrauterine growth on adult health has recently developed into a field of study in its own right: the Developmental Origins of Health and Adult Disease (DOHAD).

Table 3.1 summarizes a number of factors that have been assumed to have a causal association with premature low birth weight and low birth weight with growth retardation.

Table 3.1. Causes of low birth weight in newborn infants born preterm and growth retarded

Causes of Low Birth weight Prematurity	Intrauterine growth retardation
Maternal	
Pre-eclampsia, pregnancy-induced hypertension[121]	Chronic maternal illnesses: diabetes, hypertension, heart disease
Chronic illnesses: heart, kidney	Infections - Cytomegalovirus, Rubella, Toxoplasmosis, Herpes [129]
Acute illnesses: Urinary tract infections[122], vaginal infections (Group B streptococcus) [123-125]	Abuse: smoking, alcohol, drugs
Drug use: cocaine, alcohol, smoking	Immunologic: Anti-phospholipid syndrome[130]
Uterine abnormality: unicornuate, bicornuate uterus	Metabolic: Phenylketonuria[131], Poor maternal nutrition
Cervical incompetence [126;127]	Low socioeconomic status
Previous preterm delivery[128]	
Polyhydramnios	
Premature rupture of membrane [124]	
Fetal	
Infections	Multiple pregnancies
Multiple pregnancies	Genetic disorders: Triploidy, Trisomy 13[132]
Congenital defects	
Placental	
Infections	Placental insufficiency: Pre-eclampsia, Idiopathic elevated maternal alpha-feto-protein
Structural malformation: Placenta praevia[133;134], Placental abruption[135]	Structural malformation of placenta-Placental abruption[135], Placental praevia[136;137], Circumvallate placenta[138], Placenta accrete[138]

Low birth weight infants have 20 times more odds of dying than heavier infants.[119] It is generally believed that timely prevention, detection and intervention may improve the outcome of LBW. However, definite measures have not been well understood. It is the intricate nature of LBW that has led researchers and governments to spend much energy, resources and research on finding the most effective solution. It is not only a problem of poor countries but also a problem of the poorest groups in wealthier countries. However, differences lie in the cause of LBW in poor and well-off countries.

In developed countries, prematurity of unknown cause makes a major contribution to LBW, while in developing countries IUGR is the most important cause.[139] This statement is supported by Table 3.2, published by Belizan and colleagues.[140] The information is clearly depicted by Figure 3.1 and Figure 3.2. This shows that both developed and developing countries have almost the same proportion of premature infants, but different prevalence of LBW. This implies that the higher percentage of LBW in less affluent societies is due to term LBW, and presumed IUGR. As the prevalence of LBW increases, the percentage of term LBW increases. For instance, in developing countries like Guatemala, especially in the less affluent areas, the

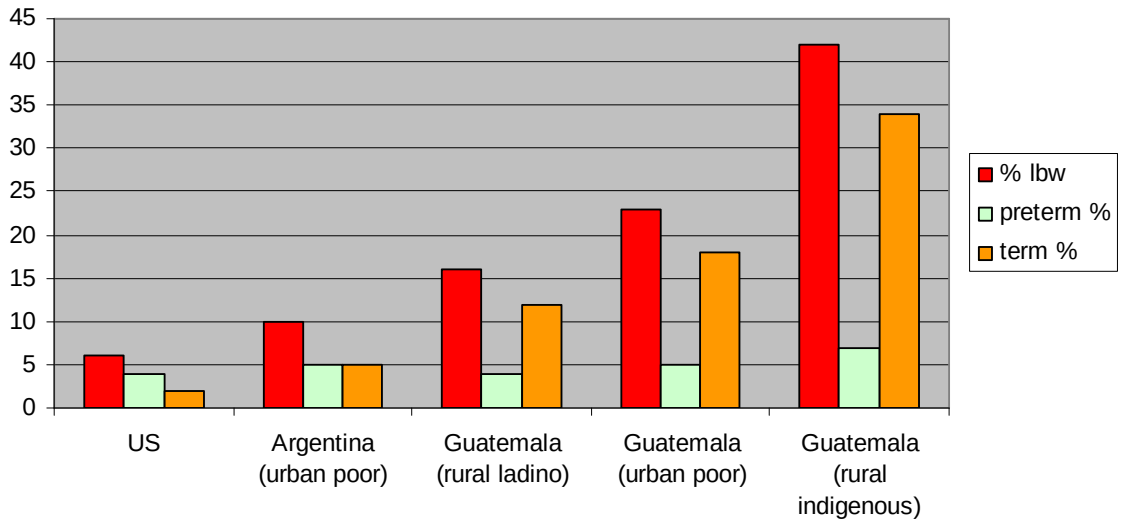
percentage of LBW is high. There are higher numbers of LBW infants born at term, compared with preterm infants. The number of preterm infants contributing to the total prevalence of LBW is almost the same in developed and developing countries, supporting the fact that the high incidence of LBW in less affluent societies is due to term LBW, which is not the case in the affluent societies.

Table 3.2. Contribution of preterm and term to LBW, by proportion of infants born LBW

		Proportion of LBW infants		Proportion of all infants	
	Proportion of infants born LBW	Preterm (%)	Term (%)	Preterm (%)	Term ` (%)
United States	6%[a]	69.5	30.5	4.2	1.8
Argentina (Urban Poor)	10%[b]	50.0	50	5.0	5
Guatemala (Rural Ladino)	16%[C]	27	73	4.0	12
Guratemala (Urban Poor)	23% [d]	23	77	5.0	18
Guatemala (Rural indigenous)	41.6%[e]	17	83	7.2	34.4

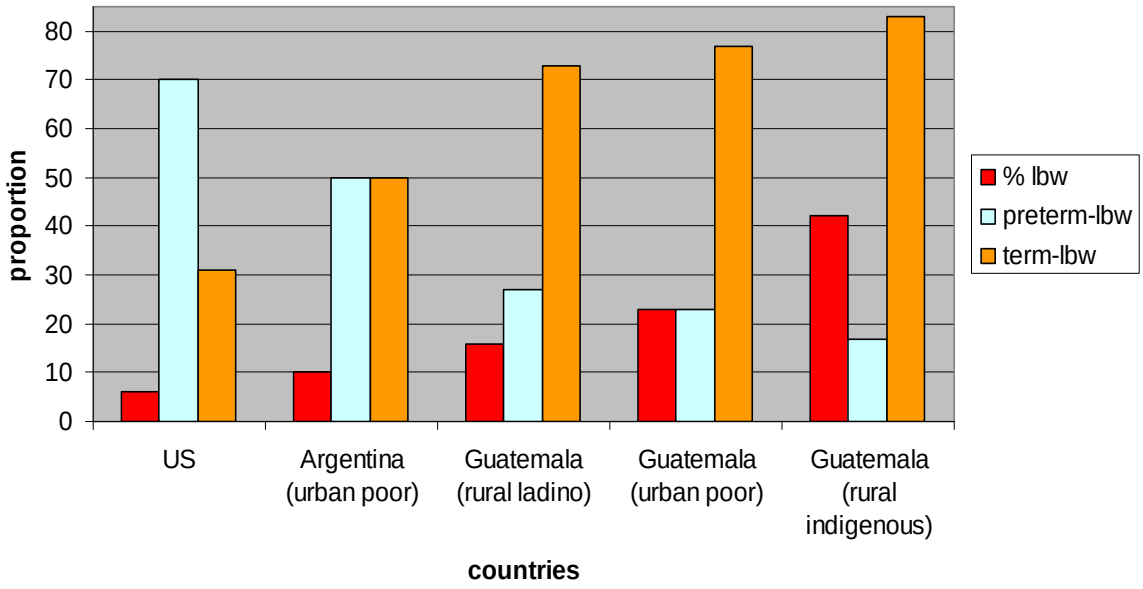
a: National figures from United States, b: Urban poor population, Argentina (Belizan, J.M,: unpublished data, 1975), c: Rural Ladino population, Guatemala (Delgado, G.: unpublished data, 1977), d: Urban poor population, Guatemala (Belizan, J. M., and Berganza, E.R.: unpublished data), (e) Rural indigenous population, Guatemala.
Source: Belizan 1978[140]

Figure 3.1. Incidence of LBW and proportion of term and preterm infants in all infants



Adapted from[140]

Figure 3.2. Incidence of LBW and proportion of preterm and term in LBW infants



Adapted from [140]

3.2.1. Epidemiology of low birth weight: a global picture

A UNICEF and WHO report on LBW published in 2004 gives the overall picture of the prevalence of LBW in the world for the years 1997-2001.[119] The report, although not without drawbacks, claims to give a better picture of LBW than previously because of improved reporting systems. Table 3.3 shows that every year around 130 million infants are born in the world, of which more than 20 million are LBW (15.5%). The majority of LBW infants are born in less developed countries. Of the United Nations regions, Asia has the highest number of births - about 77 million - out of which approximately 40 million occur in South-central Asia, the world's most populous region. Around 27% of births in South-central Asia are LBW. It is therefore fair to say that the global burden of LBW lies in South-central Asia.

LBW estimates are based on the data obtained from national household surveys and routine reporting systems in developing countries and from service based data and national birth registration in developed countries. It is common knowledge, verified by studies in developing countries (Nepal NFHS 1996[40], India NFHS-2 1998 – 99[42]), that most deliveries occur at home.

They are generally not attended by skilled health personnel (doctors, nurses, midwives) and infants are not weighed at birth. Therefore, LBW has often been classified on the basis of mothers' subjective assessments of infant size. National and regional estimates have also been derived using a range of data sources and methods for all the countries and territories with >300,000 population.

The estimates of LBW prevalence by UNICEF and WHO are derived from surveys. Survey data are less reliable than birth registration especially when there is no weighing of infants at birth. In developing countries more than half of the infants (58%) are not weighed at birth. In South-central Asia, where most of the births take place, approximately 74% of infants are not weighed at birth. Also, there are 44 developing countries where routine service reporting is used as the source of information, but there is a lack of information about the completeness of reports. Furthermore, this analysis does not contain recent information from 18 countries. For the global and regional estimates, the main weakness is the low percentage of newborn infants weighed in populous countries with high prevalence of LBW. For example, only about 1in 3 births in DHS surveys in India are weighed.

Table 3.3. Percentage and number of low birth weight infants

Regions 2000	% Low birth weight infants	Number of low birth weight infants (1000s)	Number of live births (1000s)
World	15.5	20,629	132,882
More developed	7.0	916	13,160
Less developed	16.5	19,713	119,721
Least developed	18.6	4,968	26,639
Africa	14.3	4,320	30,305
Asia*	18.3	14,195	77,490
South central Asia	27.1	10,819	39,937
South east Asia	26.2	10,069	38,452
Europe	6.4	460	2,709
Latin America and Caribbean	10.0	1,171	11,671
Northern America	7	343	4,479
Oceania	10.5	27	255

Adapted from[119]

3.2.2. Status of Low birth weight in South Asia

Table 3.4 shows LBW prevalence in South Asia, and how it differs between countries. The table uses figures from majaor national initiatives such as Demographic and Health Surveys. The prevalence ranges from 15% in Bhutan to 30% in Bangladesh and India. All the South Asian countries have higher LBW prevalence than developed countries. For instance, the United Kingdom had a prevalence rate of 8% for the year 2000 (National Report on follow-up to World Summit for Children) and Sweden had a low birth weight prevalence as low as 4% in 1994 (WHO database for Europe).

Table 3.4. Prevalence of low birth weight in South Asia

Country	Year	Low birth weight %	Method of collection
Bangladesh	1998	30	BINP, MOH, family welfare 1998
India	1999	30	DHS 1999
Maldives	2001	22	MICS 2001
Srilanka	2000	20	DHS
Nepal	2001	21	DHS 2001
Pakistan	1991	19	DHS 1991
Afghanistan	NA		
Bhutan	1999	15	WHO 1998-2000

Adapted from[119], http://www.childinfo.org/areas/birthweight/database.php
Accessed on 18th April 08

Table 3.5 presents a summary of studies of the prevalence of LBW in South Asian countries. It includes all published studies with data from which population estimates might be made. The variation of prevalence within countries is striking. For instance, in Nepal the incidence was estimated to be 17% in 2001 at Patan missionary hospital, an urban hospital[141], while it was 25% in Janakpur zonal hospital, a secondary referral hospital.[3] Christian in 2003 estimated the incidence of low birth weight as high as 43% in a rural setting in southern Nepal.[142] Likewise, Bangladesh had a low birth weight percentage ranging from 24% to 36% for the year 2004.[143;144] This wide range could be attributed to different factors: type of population, socioeconomic status, settings, timings and methodology of collecting data. However, the internationally recommended cut-off point for public health action is a LBW proportion >15%, and the prevalence of LBW in all the South Asian studies exceeds this.

Table 3.5. Studies of the Prevalence of low birth weight in South Asian countries

	Country	Year	Setting	Sample	Study design	LBW Prevalence	Mean birth weight (gram) (sd)
Deshmukh	India	1994	Urban community	210 pregnant	Survey	30.3%	NA
Hirve	India	1994	Rural community	1922 pregnant	Prospective	29%	NA
Unicef	Nepal	1999	Urban Hospitals	2700 births	Prospective	27%	2800
Bondevik	Nepal	2000	Urban Hospital	1400	Case control Prospective	17%	NA
Christian	Nepal	2003	Rural community	1037 control	Prospective	43.4%	NA
Osrin	Nepal	2005	Semi-rural Hospital	600 control	Case control Prospective	25%	2733 (422) BW <72h
Goodburn	Bangladesh	1994	Rural community	255 mothers	Prospective	51%	2420 83% weighed <72 h
Salam	Bangladesh	2003 – 04	National	3843 live births	National survey	36% Rural 37% Urban 29%	2632 (433) BW <72 hours
Hosain	Bangladesh	2005	Rural	350 women	Prospective	24%	2961 BW <48 hours
Najimi	Pakistan	2000	Hospital		Prospective	19%, 70% preterm 16% growth retarded 14% premature and growth retarded	2910

Adapted from [3;141-147]

3.2.3. Underlying causes of low birth weight

The maternal, fetal and placental unit should work in harmony for the fetus to reach her inherent growth potential. One of the underlying causes of LBW is inadequate supply of nutrients and oxygen to the fetus. The defect may be in the placenta, in the mother or in the fetus. Low blood flow to the fetus caused by vasoconstriction is seen in pre-eclampsia, use of alcohol and drugs, and smoking. Low levels of nutrients in the blood are seen in maternal undernutrition, anemia, and infections. In developing countries, maternal nutritional status is the major determinant of LBW.[120]

3.2.3.1 Studies of risk factors for low birth weight in developing countries

Table 3.7 presents a summary of studies of risk factors for LBW in developing countries. The literature search included PubMed, recommendations from colleagues and hand searching of the literature cited in individual articles. Search terms included 'low birth weight', 'risk factors' and specific risk factors such as 'weight gain' and 'maternal prepregnancy weight'. As the thesis will discuss later, there are many studies that try to examine risk factors for LBW. There have been many such studies, possibly because the methodology requires a number of LBW infants, a number of non-LBW infants and a questionnaire (or hospital records) which provides demographic and anthropometric information on mothers. For this reason, the studies in the table were chosen systematically. The reasons for including particular studies were (a) to report research from countries similar to Nepal, such as India and Pakistan; (b) to report key risk factors documented as important in large studies of multiple factors; (c) to highlight evidence based on studies with robust methodology; and (d) to include the major studies cited by in the literature.

It includes studies that categorized cases by weight <2500 g irrespective of age and sex. 13 articles that looked into risk factors associated with LBW were identified from developing (Guatemala, India, Mexico, Brazil and Pakistan) and developed countries (United Kingdom, United States, Sweden, Latin America and Greece). Out of these, three studies looked into a number of risk factors and 10 looked into a single risk factor: smoking, alcohol (1), teenage pregnancy (2), maternal anaemia (1), inter-pregnancy interval (3), ethnicity (1), maternal weight (2), hard work (1) and socioeconomic status (1).

A study from India[145] assessed maternal risk factors in 210 pregnant women from a house-to-house survey in an urban community between January and May 1994. The data showed a significant association of LBW with maternal anemia, (OR 4.8; 95% CI: 1.7-12.4), low socioeconomic status (4.0; 2.1-6.5), short birth interval (3.8; 2.1-8.4), tobacco use (3.1; 2.1-4.9), maternal height (2.8; 1.9-3.9), maternal age (2.7; 1.7-3.8), maternal body mass index (2.0;

1.3-3.1) and primiparity (1.6; 1.2-2.1). Since this was not a hospital-based study and the LBW prevalence in the community was high - 30% - it is likely to be representative of the population. Unfortunately, the study does not give definitions and cut-off points used for anemia, birth interval, maternal age, weight gain, or height, for comparison with other studies.

Neel and colleagues[148] described maternal risk factors for LBW and IUGR in 306 hospital births between July and November 1988 in a regional hospital in Guatemala. Their data demonstrated that pregnancy related variables (parity, birth interval and prenatal care), nutrition related variables (maternal height, maternal triceps skinfold thickness, maternal weight) and sociodemographic indicators (maternal education, race and socioeconomic status) were significantly associated with birth weight. It is striking that the study did not show any association of LBW with infant sex, since this is the usual case.

There is one recent Pakistani study that attempted to assess the influence of maternal anaemia on the outcome of pregnancy.[149] Comparable groups of 313 anaemic and 316 non-anaemic pregnant women in terms of race, language, education, economic status and family structure were enrolled at a tertiary hospital between Oct 2001 and 2002. There was a four-times increased odds of preterm delivery (95% CI: 2.5-6.3) and two-times increased odds of LBW (95% CI 1.0-3.4) in the anaemic compared to non-anaemic cohort. Moreover, there was two-times more odds of low Apgar score of $\leq$5 at 1 minute (95% CI: 1.2-3.7) and four-times more odds of intrauterine death (95% CI: 0.9-14.6) in the infants of anaemic than non-anaemic pregnant women. Since the investigators did not mention the method of determination of gestational age, the reliability of the preterm delivery outcome could not be assessed.

In a hospital-based case-control study[150] of the effect of socioeconomic factors on the incidence of LBW in pregnant Mexican women, the socioeconomic factors of 158 LBW infants and 474 normal controls were adjusted for reproductive (parity, prior preterm delivery, prior LBW), nutritional (calcium and iron supplementation), pre-gestational weight, prenatal care, morbidity during pregnancy, tobacco exposure and demographic factors. The data demonstrated

socioeconomic factors as the main risk factors for LBW. Women of low socioeconomic status were 2.7 times more likely to give birth to LBW infants, independently of other confounding factors.

Lima and colleagues reported a retrospective cohort study of the influence of hard work during pregnancy on birth weight conducted in two maternity hospitals in a palmers district in Brazil, where most of the population (72%) was engaged in sugarcane production.[151] This hospital based study of 250 cases and 708 controls claimed that there was a significant fall in the mean birth weight of infants among women who worked in agriculture throughout pregnancy compared to housewives, by 190 g. The proportion of LBW was significantly higher among women who worked throughout pregnancy (10.4%) than housewives (7.1%).

There are 4 different studies that assessed the effect of interpregnancy interval as an independent risk factor on pregnancy outcome. Out of them, one was conducted in Latin America[152] and three in developed countries. Conde-Agudelo and colleagues examined the perinatal outcomes of interpregnancy interval from a large sample of 1,125,430 derived from the database of the Latin American Centre for Perinatology (Uruguay, Peru, Argentina, Colombia, Honduras, Paraguay, El Salvador, Chile, Bolivia, Costa Rica, Panama, Dominican Republic, Nicaragua, Brazil, Ecuador, Mexico, Bahamas, Belize and Venezuela) between 1985 and 2000.[152] Women with interpregnancy interval of > 59 months or < 12 months had independent risks of giving birth to LBW, SGA infants, preterm delivery and increased infant mortality during the intranatal and neonatal periods. Women with an interpregnancy interval of < 6 months had almost 100% odds of giving birth to LBW infants even after adjustment for other confounding factors.

Risk factors for LBW in developing countries are summarized in Table 3.6. The risk factors listed are categorized as important based on positive results in previous studies, showing a causal relationship with birth outcome. Of all the risk factors reviewed, 15 have shown significant associations with LBW. They are categorized under three subheadings.

Table 3.6. Summary of risk factors for low birth weight in developing countries

Based on positive findings in studies discussed above		
Nutrition related	Pregnancy related	Socio-demographic
Maternal height	Parity	Maternal education
Maternal weight	Birth interval: short and very long	Race
Maternal BMI	Prenatal care	Socioeconomic status
Maternal triceps skin-fold thickness	Fetal sex	Maternal hard work
Anemia		Tobacco
		Maternal age
		Fuel

Table 3.7. Studies of risk factors for low birth weight in developing countries

Site and date	Case definition	Sample	Methods	Results	Comment
India, 1994[145]	LBW: birth weight <2500 gram Maternal weight gain: weight gained from 12 weeks till delivery	Urban community Prospective N 210 pregnancies 61 LBW and 140 normal birth weight newborn infants	House to house survey SES Kuppuswamy's scale Birth anthropometric measurement in <1h for hospital delivery and 24h for home delivery	LBW 30.3% Anaemia OR: 4.81 Low SES OR: 3.96 Short Birth interval OR: 3.84 Tobacco OR: 3.14 Height OR: 2.78 Maternal age OR: 2.68 BMI OR: 2.02 Primi parity OR: 1.58	Reason and number of exclusion given Definition of anaemia, classification of birth interval, BMI, Height, age not mentioned Positive association with anemia, low SES, short birth interval, tobacco, height, age, BMI and prim parity
Guatemala 1988[148]	LBW Premature: birth < 37 gestational weeks IUGR: term birth weight < 10th percentile for gestational age Type I IUGR : proportionate Type II UUGR: disproportionate Ponderal Index Gestational Age: A Ballard method	Hospital July – Nov 1988 N 306 Exclusion Premature Congenital anomalies Twins Maternal illness Refusal	Interview Birth anthropometric measurement in <36h of birth Nutritional, demographic, obstetric, socioeconomic data	Prevalence: Type I IUGR: 27%, Type II IUGR: 7% of Newborn Sex: Non significant for BW and IUGR Race: significantly lower BW in Indians than Ladino even after controlling for SES, height Parity: Positive correlation up to 4th pregnancy; significantly higher type I & II IUGR from 1st pregnancy Maternal age: association with birth weight; incidence of IUGR & type I IUGR higher in teenager Anthropometry: Postpartum weight <107 pound > IUGR & small infants; height <143 cm- more IUGR, type I & II Education: NS (SES controlled) SES: Significant (controlled for race); > IUGR in low SES Running water: > IUGR & type I compared to no running water Prenatal care: direct relationship; NS trends towards higher BW who had an early 1st visit; NS difference in private & public physician Birth interval: BW increased up to 48m interval but declined after 48m	Sex: Non significant Parity: significantly more IUGR in primiparous mothers Age: direct relationship with increasing age Race: Significant Private Physician: 113 g heavier than public health providers Birth interval: Heavier in longer birth interval, Uneducated receiving adequate prenatal care deliver significantly heavier babies than uneducated

Site and date	Case definition	Sample	Methods	Results	Comment
Pakistan 2001-02[153]	Anemia (WHO) Hb≤11g/L Anemia (Exposure) Hb< 11g/L in labor and on 2 previous occasions in the current pregnancy	Hospital based N 629 pregnant women Anemic 313 Not anemic 316 Inclusion criteria (<16 gestational weeks, >16yrs, singleton pregnancy, complete medical records) Exclusion criteria Past history of preterm birth, obstetric complication, medical illness	Interview 2nd day and at 1 month of delivery Questionnaires Hb 28-32 (1st antenatal visit, 33-37 weeks, labour) Confounding factors: Age, Education. Employment status, family structure, monthly income,	Most Muslims, urban, speak Urdu Risk of preterm is 4 times and low birth weight is 2.2 times and IUGR is 1.9 times with Anemia	Gestational age estimation method not mentioned Well matched confounding factors
Zimbabwe 1994-99 [154]	Fuel: wood, dung, straw, LPG, natural gas and electricity BW to the nearest 10g Health card BWto the nearest 100g	3559 child births Confounders: sex, birth order, education, nutritional status, prenatal care, household living standard, other potential confounders like residence,	Demographic health survey (5 years preceding 1999) 2 stage cluster sample : first area selection by equal probability and second by probability proportional to size Questionnaire field tested BW recorded by trained workers in clinics, health cards at home or maternal recall	Birth weight was 175g [95% CI:-300 - -50] lighter for those using wood, dung or straw fuel than LPG, gas and electricity	Fuel may be associated with birth weight Nationally representative sample Response rate 97.8% Taken account into important confounders except for history of smoking by household members
Guatemala 2002 [155]	Fuel LBW <2500g Gestational age: LMP corroborated by postnatal grading of somatic characteristics of newborn Socioeconomic status: house construction, floor material, literacy, marital status	N 1717 women and newborn Rural and urban Home births 572 Public hospital 1 145 Household fuel Fire Socioeconomic	Confounding factors:economic, social and maternal BW to the nearest 50g (home) and 25g (hospital) Maternal anthropometry to the nearest 0.1cm: height, calf circumference,	Cooking on open fires 861, lowest mean birth weight 2819g [95% CI: 2 790 – 2 848] Chimney intermediate BW 2 863 [2824 – 2902] Cleanest fuel 2948 [2898 – 2998] LBW%: 18.8 (hospital), 17.1 (home), LBW % : 19.9 (open fire), 16.8 (chimney), 16 (electricity), Wood users birth weight 63g lower P=0.05	Wood fuel (carbon monoxide exposure) use reduced birth weight

Site and date	Case definition	Sample	Methods	Results	Comment
Mexico 1996[150]	LBW <2500 g	Case control study Hospital study LBW n= 158 Control n= 474	Interview at delivery Questionnaires Review of newborn records Data Socioeconomic: Age, education, civil status, occupation, income, owning certain goods Reproductive: Parity, prior preterm, low birth weight infant Nutritional: Calcium, Iron pregestational weight, prenatal care, morbidity, tobacco	Low socioeconomic status: significant OR 2.19 (CI) than medium and high socioeconomic status Hypertension, Calcium: marginally significant OR 1.53(CI) and 1.86 (CI)	Low socioeconomic status: most important risk factor for LBW independent of other factors: reproductive, nutrition, smoking, morbidity, accessibility of health facilities and prenatal care
Brazil 1992 [151]	GA Capurro method	Retrospective study Hospital based N 958 [Housewives 708 2nd and 3rd trimester work for 3 months 250] Inclusion No congenital anomaly No chromosomal No congenital infection Low income Singleton pregnancy	Interview 12-48h after delivery Anthropometry and gestation within 24h of delivery	Exposed women: poorer, older, grandmulti, poor antenatal care, lighter, shorter with similar BMI, birth interval and prior LBW and fetal loss Mean BW 190 g lower in women who worked in field for 9 months compared to housewives Mean BW 117g lower (significant) after confounding factors are controlled Heavy work on 6, 7 or 8 months: no significant effect	Hard work throughout pregnancy significantly reduces BW in low income population
Latin America 1985-2004[152]	GA: LMP and birth date interval Inter-pregnancy interval: time between last delivery and LMP for index pregnancy	N: 1 125 430 Inclusion: Parous, Singleton, Previous delivery >19w Exclusion: Multiple pregnancy	Hospital data Records	Prevalence: 7.9% LBW, 13.9% SGA, 9.3% preterm <12 month interval: younger mothers with late and less prenatal care, prior miscarriage, LBW, fetal deaths, early neonatal deaths >59 months interval: older mothers with adequate prenatal care, greater BMI, heavier previous baby No difference: parity, education, smoking and marital status <6 months: 80-100% increase in LBW than 18-23 months interval, very LBW,	<12 and >59 months birth interval has significant greater risk for LBW

Site and date	Case definition	Sample	Methods	Results	Comment
				preterm and very preterm, 30% increase in SGA risk >60 months: 20% increase risk in LBW Maternal characteristics or infant birth weight and gestational age controlled: not much of the difference	

BW: Birth weight; GA: Gestational age; H: hour; Hb: Haemoglobin; IUGR: Intrauterine Growth Retardation; LBW: Low Birth Weight; LMP: Last Menstrual Period; NS: Non significant; OR: Odds Ratio; SES: Socioeconomic status; SGA: Small for Gestational Age; W: weeks; WHO: World Health Organization; Yr: Year;

3.2.3.2 Studies of risk factors for low birth weight in developed countries

There have been a number of studies from industrialized countries. Some of their findings are relevant to a consideration of size at birth in developing countries. For the sake of clarity, only the larger studies, systematic reviews and meta-analyses will be discussed here. A large retrospective study of 134,088 births in Utah between 1970 and 1990 looked for an association of pregnancy at younger age with infant outcomes.[156] The risk of LBW, SGA and preterm delivery was examined in a limited cohort of white, educated, married primigravidae with healthy lifestyles (less prevalence of smoking, use of alcohol and drugs) and adequate prenatal care. The relative risk of low birth weight in teenage pregnancy (< 17 years of age) was 1.7 (95% CI: 1.5-2.0) compared to the 20-24 years age group. Regarding premature delivery and SGA in younger teenage pregnancies, there was a relative risk of 1.9 (1.7-2.1) and 1.3 (1.2-1.4) compared with older mothers (20-24 years). The investigators related these adverse effects on outcome to young gynaecologic age and ongoing maternal growth. The data also showed that inadequate prenatal care doubled the odds of having a LBW infant.

Another retrospective hospital-based case-control study conducted in the United States compared the incidence of LBW in 1102 teenagers and 1250 older women delivering between 1996 and 1999.[157] The study showed a negative relationship between maternal age and LBW. Younger teenagers were more likely to give birth to LBW (8.6%) and growth restricted infants (2.6%) than older teenage (5.1% and 2.2% respectively) and older mothers (7.5% and 2.3% respectively). However, the published study does not present data on potential pregnancy related and socioeconomic confounding factors. The authors reported that teenagers were more likely to be nulliparous (88%), Hispanic (80%), unmarried (96%) and not having prenatal care than older women in the cohort. Furthermore, the study was limited by drawing its sample from a teenage care programme.

Table 3.10 presents two studies on interpregnancy interval conducted in affluent countries: Greece [51] and the USA[158]. Dafopolous and colleagues used a six-month pregnancy interval as the cut-off point for looking at the incidence of preterm birth in a sample of 652 urban Christian and 578 rural Romany Muslims of Greece, who were socio-economically and racially different. In comparison with urban Christians, prevalence of preterm birth was significantly higher in rural Muslims and only rural Muslims demonstrated interpregnancy birth interval as an independent risk factor for preterm births. The prevalence of preterm birth was 16% versus 7% for birth interval <6 months and >6 months respectively.

Murphy and colleagues in 2000 performed a systematic review (14 studies) and metanalysis (8 studies) to determine the association between abuse and low birth weight.[159] They showed increased odds of low birth weight infants for mothers who reported physical, emotional or sexual abuse. The major limitation of the studies involved was the definition of the variable used to describe abuse. The review concluded that abuse may be interacting with other factors in the causation of LBW.

Flynn and colleagues published a metaanalysis of 19 studies (all except two from industrialized countries) on bacterial vaginosis and risk of prematurity published between 1966 and 1999.[160] It showed significant associations between bacterial vaginosis and several outcomes: preterm delivery, LBW, preterm premature rupture of membrane and preterm labor. There was an almost two-fold increased risk for all outcomes.

The study by Zhu and colleagues[158] considered seven birth interval categories, 0-5, 6-11, 12-17, 18-23, 24-5, 60-119 and >/=120 months, in Utah, United States. The authors confessed that the drawback was use of retrospective data with estimation of gestational age based on different methods: last menstrual period and date of birth interval, clinical methods and ultrasound scans and low prevalence of reproductive risk factors. Interestingly, the study found that shorter

interpregnancy interval of <6 months was not riskier compared to birth interval of >120 months. The safest interval was 18-23 months for this hospital based population.

Brooke and colleagues in 1989 carried out a prospective hospital-based study of the effect of smoking, alcohol, caffeine, socioeconomic factors and psychological stress on LBW in 513 women in London ([161]). Although smoking showed a significant association with LBW, passive smoking showed no effect. The study reported an equal risk of LBW in infants of ex-smokers and non-smokers. There was no independent risk of alcohol, caffeine, socioeconomic status or psychological stress in the non-smoking population.

A study from California[162] compared the incidence of LBW in a large sample of 203,815 black and white residents of California. Race was a significant independent risk factor for LBW and black infants had 1.7 times greater odds of being very low birth weight and 1.6 times greater odds of being moderately low birth weight (1500-2499 g). It is unclear whether the authors included both term and preterm LBW infants. They do not report the method of gestational age estimation. Moreover, the researchers mentioned that there could be a bias due to differences in missing data in black and white groups. Other independent risk factors included education, maternal age, prior history of LBW or premature baby, primigravidity, complications during pregnancy, labour and delivery, no insurance for prenatal care and median household income.

Cnattingius and colleagues carried out a large retrospective study in Sweden of 167,750 singleton pregnancies from medical birth records registered between 1992 and 1993 and paediatric records, to look for an association between prepregnancy BMI and adverse pregnancy outcome (late fetal death, preterm delivery and small-for-gestational-age).[163] This study demonstrated that underweight mothers (BMI <20 kg/m2) were likely to have less late fetal death, more SGA infants compared to heavier mothers and less consistent association with preterm delivery. However, the findings were

weakened by recall bias (maternal recall of pre-pregnancy weight) and case definition of SGA was not mentioned.

Table 3.8 summarises reviewed studies of LBW in developed countries. It is possible to categorize them under three general headings- nutrition, pregnancy and sociodemographic. The modifiable and non-modifiable possible risk factors are summarized in Table 3.9. The table does not include the effects of sanitation and diet on birth weight. These have been suggested as potential risk factors, but the literature does not provide sufficient evidence for their inclusion

Table 3.8. Summary of risk factors for low birth weight in developed countries

Based on positive findings in studies discussed above

Nutrition related	Pregnancy related	Socio-demographic
Pre-pregnancy BMI	Birth interval	Smoking
	Prior LBW or preterm	Race
	Primigravida	Maternal education
	Complications during pregnancy, labour or delivery	Insurance for prenatal care
	Bacterial vaginosis	Maternal age
		Abuse

Table 3.9. Summary of risk factors in terms of modifiability

	Modifiable risk factors	**Non modifiable risk factors**	**Uncertain**
Pregnancy related	Birth interval Complications during pregnancy, labor or delivery Bacterial vaginosis	Prior LBW	Preterm delivery
Nutrition related	Pre-pregnancy BMI Maternal anemia		
Socio-demographic	Smoking Teenage pregnancy Maternal education Abuse Fuel	Race Primiparity	Insurance for prenatal care Abuse

Table 3.10. Studies of risk factors for low birth weight in developed countries

Site and date	Case definition	Sample	Methods	Result	Comment
Utah 1970-90[156]	LBW: <2500 g Prematurity: <37 weeks SGA- birth weight <10th percentile for gestational age and sex Maternal age groups- 13-17y 18-19y 20-24y	N 134 088 Inclusion: White, singleton, first born infants, 13-24 years of age, complete data	Records Confounders controlled: Socio-demographic covariates analysis with comparable mothers	13-17y: unmarried, poor perinatal care 18-19y: age inappropriate education level Prevalence in <17y, 18-19y and >20 LBW: 7%: 5% and 4% Preterm: 10%,8% and 5% SGA: 14%, 12% and 10% <17y mother compared to >20y mother (reference category) LBW [OR:1.7 (95% CI: 1.5-2)] Preterm [OR: 1.9 (1.7-2.1)] SGA [OR:1.3 (1.2-1.4)] Poor prenatal care: strongly associated with LBW, preterm, SGA No prenatal care: twice more likely to be LBW than adequate care	Younger age is at increased risk of adverse pregnancy outcome- LBW, preterm, SGA, independent of sociodemographic factors younger age, Unmarried inappropriate education, inadequate prenatal care increase the risk of LBW, preterm, SGA
US 1996-99[157]	Teenage: <20y SGA: <10th percentile for Gestational age Macrosomic: >4000g at term or >90th percentile for Gestational age Maternal age: years completed at the time of delivery <16, 16-19, >20	Retrospective Case control study Hospital based N 1102 teenagers delivered between 1996-99 < 16 y (n=116) 16-19y (n=986) >20y (control): 1250	Records: prenatal and hospital	Comparable demographic, marital status, mostly non-private patient More Hispanic, fewer Caucasians, more nulliparous, weighed less and gained less weight in the youngest group Birth weight increased with advancing maternal age Younger the gravida the more likely for her to give birth to very LBW- not significant Relatively high incidence of LBW among young gravida, not preterm but relatively higher IUGR Lower rate for macrosomia in <16y and significantly fewer postterm births	Younger the teenager more likely to give birth to LBW or very LBW or IUGR infants but few post-term infants

Site and date	Case definition	Sample	Methods	Result	Comment
Greece 2002[51]	Inter-pregnancy interval: Interval between 2 consecutive deliveries minus gestational age of the 2nd neonate (13w=3months) Cutoffs: 6 months Gestational age: LMP if regular cycles and Ultrasound scan in 1st and 2nd trimester Preterm <37w	Retrospective study Singleton pregnancy with prior single term pregnancy with no abortion Urban Christian n=652 Rural Muslim n= 578 ≤6mo inter-pregnancy interval Urban n= 46 Rural n= 87 Preterm prevalence 5.9% (primi) 8.4% (multi)	Confounders controlled: Age at delivery, smoking during pregnancy (>5/d), prenatal care after 1st trimester, few antenatal care visits (<8)	Prevalence of preterm births was 16% and 7% for short and long interpregnancy interval in rural Muslim community respectively Since no significant difference in the risk factor among women in <6 and >6month pregnancy interval in both Rural and Urban population, it could not be causing preterm birth	Pregnancy interval an independent risk factor and significantly more in <6 months interpregnancy interval in rural Muslims than Urban Christian Strengths: Potential confounders assessed Limitation Small sample size in women with <6month pregnancy interval so should be cautious while interpreting results
2001[159]	Abuse: physical, sexual, emotional LBW: <2500g	Case control and cohort studies 178 to 1897 Consecutive or selective participants interviewed at prenatal or postnatal period	Metaanalysis: 2 investigators Medline, Cochrane library, CINAHL (1966-99) Bracken's guidelines for observational studies to analyse methodological quality OR using fixed effects models	14 studies reviewed 8 studies selected OR: 1.4 (95% CI:1.1 – 1.8)	Significant association Strengths: methodological quality assessed; Limitation: variation in the definition of exposure and outcome; reporting bias; low socioeconomic status women mostly so not generalisable;
1999[160]	Bacterial vaginosis Premature delivery Preterm birth: delivery <37 weeks of gestation Low birth weight Preterm PROM Preterm labour	Inclusion Case control and cohort studies Risk factor: bacterial vaginosis Outcomes: gestational age or birth weight Excluded: non english	Metaanalysis 2 investigators Mediline (1966-96), bibliographies, personal contact with leading researchers OR using fixed and random effects models	19 studies selected (all except 2 were from developed countries) OR for preterm delivery: 1.85 (95% CI: 1.62-2.11) OR for LBW 1.57 (1.32-1.87) OR for preterm PROM: 1.83 (1.39 – 2.44) OR for preterm labor: 2.19(1.73-2.76)	Significant risk factor for prematurity Limitation Publication bias:absence of studies finding that BV protects from delivery of LBW infant (funnel plot) Appropriateness of combining different studies

Site and date	Case definition	Sample	Methods	Result	Comment
Utah 1989-96[158]	LBW <2500 g Preterm <37 weeks SGA Birth weight <10th percentile for gestational age and sex GA: LMP and date of birth interval or ultrasound scans or physical or neurological assessment Interpregnancy interval: period between delivery and conception- Interval between 2 consecutive deliveries minus GA of 2nd infant	N 173 205 Hospital based Inclusion: Singleton, live, at least one live infant, multigravida, information on birth weight, sex, gestational age, date of previous delivery of a live infant Birth interval <6month, >120 month	Birth certificates 16 maternal reproductive risk factors Short interval: Young unmarried, Hispanic or non white, less educated, tobacco, poor prenatal care, prior infant death Long interval: Old unmarried, tobacco or alcohol, recent stillbirth or abortion No association: maternal height, pre-pregnant weight, pregnancy weight gain, prior SB, abortion, pregnancies, area of residence	Prevalence : (LBW: 4.3%, Preterm:5.7%, SGA:8.6%, <6 months interpregnancy interval: Risk (reference groups 18-23 mo) <6 months LBW: [OR:1.4 Preterm: [OR:1.4 SGA [OR:1.3] >120 months longer LBW: [OR:2] Preterm: [OR:1.5] SGA [OR:1.8] 18-23 months interval Lowest risk	<3month: risk highest 18-23month: risk lowest >23month: risk increased Strengths: Potential confounding factors assessed except for number of losses of pregnancy, Larger sample size Limitation: Different methods of assessment of GA, use of records, prevalence of reproductive risk factor relatively low (author confessed)
California 1992[162]	LBW: <2500g Very LBW: 500-1499g Moderately LBW 1500-2499g Race: Black and white mothers	N 203 815 Exclusion Missing birth certificate Missing variables Multiple births		Parental, infant, community risk factors controlled- OR reduced from 3.37 to 1.73 in very LBW and 2.5 to 1.6 in moderate LBW for black parents Independent risk factors: parental education <13y, Primi parity, previous preterm or LBW, pregnancy, labour and delivery complications and no insurance for prenatal care and gestational age <259d Independent risk factors for moderately LBW: maternal and paternal age >34, education, unmarried, no previous births, >3 previous births, previous premature or LBW babies, tobacco during	Black race had increased risk of LBW Strength Large sample size Proxy for data on the SES of individuals validated Limitation Selection bias: racial differences in the proportion of cases excluded due to missing data. It may not be representative Underreporting of

Site and date	Case definition	Sample	Methods	Result	Comment
				pregnancy, pregnancy complications, labor and delivery complications, no insurance for prenatal care, no medical care, median household income < $20 000 per year, younger gestational age, female infant	information
Sweden 1992-93 [163]	Pre-pregnancy BMI: weight(kg) divided by square of height(m) Categories of BMI: Lean <20 Normal 20-24.9 Overweight 25-29.9 Obese ≥30 Very preterm ≤32w Preterm ≤37w Still birth ≥28w ENND: death during the first week after birth	N 167 750 singleton	Medical birth register Pediatric record Pre-pregnancy weight recall	Preterm delivery: In primi, obese women had significantly higher risk of preterm delivery than lean mothers OR:1.6 (95% CI:1.1-2.3) In Parous women, risk highest among lean mothers Small-for-gestational-age: Risk less with increasing BMI among multigravida than Primi Low weight gain is positively associated with small-for-gestational-age but lots of missing data so should be interpreted with caution	Higher pregnancy weight protects against SGA and underweight mothers have higher risk for SGA Association between low BMI and preterm delivery is less consistent Lean women had lower risk of adverse outcome Strength Large population based sample
London 1989[161]	GA: LMP or early USS Smokers >15 cigarettes per day <14 cigarettes per day	Hospital Prospective N 1860 white mothers at booking for delivery Exclusion: insufficient English, booked after 24w, insulin dependent diabetes, multiple pregnancy Estimated BW Births in Sheffield	Interview and Structured antenatal and obstetric record At booking, 17, 28, 36 weeks General health questionnaire Modified Paykel's interview Eysenck personality questionnaire at 17w 40 indicators of socioeconomic status and Psychosocial stress	Smokers: strong relationship Passive smoking: not significant Ex smokers and non smokers: no difference Non smokers and smokers >15 cigarette per day: 241g difference at 40w, smokers <14cig/d: 140g at 40w Alcohol: significant decrease in BW Non smokers- no effect of alcohol smokers: effects women consuming 100g/w 0.069 or 7% between non drinkers and drinkers (≥) Caffeine: significant No significant dose response trend Smoking controlled: non significant	Smoking significantly associated but not passive smoking No independent effect of alcohol, caffeine, few socioeconomic and stress in non smokers No independent effect of 4 socioeconomic factors after smoking is controlle Social and psychological factors : little or no effect on birth weight

Site and date	Case definition	Sample	Methods	Result	Comment
			BW for GA adjusted for height, parity and Baby's sex	Smoking-BW relationship remained with alcohol and caffeine controlled Psychological stress: Missed antenatal care reduced bw But disappeared when smoking is controlled Bad neighbours increased bw but effect remained with smoking controlled Socioeconomic factors: reduce BW	

BW: Birth weight; EBW: Estimated birth weight; GA: Gestational age; IUGR: intrauterine growth retardation; LBW: Low birth weight; LMP; Last Menstrual Period; SGA: Small-for-gestational-age, SES socioeconomic status, S significant, NS Non significant, CI: Confidence interval; ENND: Early neonatal death; OR: Odds ratio

3.3. Studies of size at birth in South Asia

A number of studies have been carried out on size at birth other than LBW. Table 3.11 shows the different indicators of size considered in studies in South Asia. There are studies on prevalence[164], risk factors[141;165;166], consequences[36;167;168], interventions[3;142] and growth[169;170]. In all the published studies of birth size, birth weight is the only outcome that was measured consistently. Some studies present data on length and head circumference[3;164;167]. Interestingly, there are also studies that have not calculated ponderal index in spite of available data on birth weight and length[3;167;171] except for studies by Kumaran et al, Arifeen et al and Cheung et al.[36;169;172] A zinc supplementation study conducted in Bangladesh by Osendarp and colleagues measured its effects on weight, length and circumference - head, chest and MUAC - at birth. The authors investigated almost all except for abdominal circumference and skinfold thickness. The supplementation showed no effects on birth size. However, similar type of zinc supplementation study chose only 3 birth parameters-birth weight, length and head circumference.[173] The study showed that 20 g of zinc supplementation had no effect on size at birth.

Anderson and colleagues' investigation of the prevalence of early neonatal hypoglycaemia in uncomplicated pregnancies was stratified by birth weight (<2.5 kg, 2.5-3 kg and >3 kg). Attempts to consider other birth parameters as risk factors for hypoglycaemia were not seen, despite the evidence of strong association between birth weight and hypoglycaemia. The study suggested that 55% of LBW infants suffered hypoglycaemia compared to 32% of normal birth weight infants. Christian and colleagues investigated the role of multiple micronutrient supplementation on birth size: weight, length, head circumference and chest circumference.[142] Multiple micronutrient supplementation during pregnancy was shown to reduce LBW compared to placebo, but not compared to government recommended supplementation with folic acid and iron. The study also demonstrated an effect on head and chest circumference, but not on length. Another study published by the same team did not investigate the effect of anthelmintic on parameters of size at

birth other than birth weight[174] in the same sample frame of 4130 live birth infants in Sarlahi, Nepal. Anthelmintic increased birth weight by 59 g and reduced infant mortality at six months by 41%. In the same cohort, Katz and colleagues investigated the hypothesis that the treatment effects actually varied by birth weight percentiles.[175] The authors chose only one birth weight to investigate the hypothesis and dropped other significant birth anthropometry, specifically chest and head circumference.

Bondevik and colleagues investigated the associations of maternal characteristics with LBW and preterm delivery.[141] Severe maternal anemia was associated with both LBW and preterm birth. Karim and colleagues[170] chose weight and length at birth to measure growth in the first year of life at monthly intervals. The authors compared growth of infants against NCHS reference data for height-for-age, weight-for-age and weight-for-height. They found that the first six months of life involved catch-up and catch-down growth, followed by growth influenced by genetic and earlier intrauterine effects in the later half of infancy. Arifeen et al examined the infant growth patterns in relation to birth weight, SGA, proportionate SGA, disproportionate SGA, prematurity and length, from birth to one year of age.[169] They concluded that weight at 12 months was a function of weight at birth. Finally, a multicentre hospital-based study conducted in Nepal measured weight, length and head circumference at birth.[164] The authors reported the prevalence of LBW.

As expected, birth weight tended to get particular attention for research over other measurements of size. Given that it is such a major public health problem, it is surprising to see how few studies have focused on size at birth, even LBW. The exceptions are a growing number of investigations on the effect of size on outcomes (mortality, morbidity, growth and development). This is mainly due to the recently developed area of study of DOHAD. For example, Yajnik and colleagues recorded six birth size parameters in addition to birth weight.[176] The authors believe that birth weight alone does not represent intrauterine growth and body composition, which may be relevant to morbidity and mortality later in life. Younger, lighter, shorter Indian mothers with lower BMI

gave birth to lighter infants with smaller abdominal circumference and mid-arm circumference compared to infants in Southampton, UK. Interestingly, Indian babies were longer and had more adipose tissue in the 2800-3300g birth weight category. The proposition was that other birth anthropometric parameters should be investigated along with birth weight.

Rao and colleagues explored six birth size anthropometric parameters, including birth weight.[166] Excessive maternal activity during pregnancy was an independent risk factor for size at birth. The effect was reflected in weight, head circumference and MUAC. In the Pune Maternal Nutrition Study, 631 term live births were investigated to look at the influence of parity on birth size.[165] Seven neonatal anthropometric parameters were measured, out of which three were shown to have an association with parity: birth weight, abdominal circumference and skinfold thickness. One may argue that if the effects of risk factors are observed on different parameters of size at birth, why should other birth size parameters be given less importance than birth weight. These findings urge us to take our studies of size at birth beyond birth weight alone.

Table 3.11. Studies of size at birth in South Asia

Study and date	Sample frame	BW	BL	HC	CC	AC	MUAC	PI	SFT	Birth gestation	Sample size	Comment
Nepal												
Anderson 1993[177] Kathmandu	Urban Hospital	+								Capurro method	226 infants	Hypoglycemia study LBW as risk factor
Unicef 2000[164] Kathmandu	Urban Hospital	+	+	+							2700 infants	Prevalence study
Bondevik 2001[141] Patan	Urban Hospital	+								LMP	1400 infants	Risk factor study Maternal characteristics and LBW and preterm delivery
Christian 2003[142] Sarlahi district	Rural Community	+	+	+	+					LMP	4130 infants	Supplementation study Birth size, infant mortality
Christian 2004[174] Sarlahi district	Rural Community	+								LMP	4130 infants	Anthelmintic study Birth size, infant mortality
Katz 2006[175] Sarlahi district	Rural Community	+								LMP or urine test	4096 pregnancies	Supplementation study Birth weight, infant mortality
Osrin 2005[3] Dhanusha district	Semi-rural Hospital	+	+	+						Ultrasound	1200 infants	Supplementation study Birth weight
India												
Stein 1996,[167] Mysore	Hospital	+	+	+						No gestational age in records	517 infants	Outcome study Coronary heart disease
Kumaran 2000[36] Mysore	Hospital 1934-53	+	+	+				+		Maternal weight	435 infants	Outcome study Small size at birth and Blood pressure
Tripathy 2002[178] India	Hospital 1998-2000	+				+				Ballard score + LMP	11223 infants	Outcome study Neonatal mortality
Rao 2003[166] Pune	Rural Community	+	+	+		+	+		+	LMP + Ultrasound	797 pregnancies	Effect of maternal activity Birth size, placental weight
Yajnik 2003[176] Maharashtra	Community 1994-96	+	+	+		+	+		+	LMP	631 infants	Consequence study Placental weight
Yajnik 2003 [110] Maharashtra	Hospital 1998	+	+	+	+	+	+		+	LMP + Ultrasound	157 infants	DOHAD Diabetes
Muthayya 2006[179] Bangalore	Hospital	+	+				+		+		712 pregnancies	Descriptive study Arm fat index, arm muscle index, Birth weight and MUAC

Study and date	Sample frame	BW	BL	HC	CC	AC	MUAC	PI	SFT	Birth gestation	Sample size	Comment
Bangladesh												
Arifeen 2000[169] Dhaka	Urban community	+	+					+		LMP + Capurro method	1654 infants	Outcome study Growth
Osendarp 2000[171]	Hospital 1996	+	+	+	+		+			LMP	559 women	Supplementation study Zinc
Matlab												
Karim 2001[170] Dhaka,	Poor Urban 1993-95	+	+							_	91 infants	Outcome study Growth
Pakistan												
Cheung 2001[172] Lahore	Community 1984-87	+	+					+		Dubowitz method LMP	1476 live born	Outcome study Diarrhoea
Joshi 2005[165] Pune	Community 1994-96	+	+	+		+	+	+	+	LMP	814 pregnancies	Effect of Parity on birth size
Hafeez 2005[173] Pakistan	Community Hospital 2003-04	+	+	+						_	242 women	Supplementation study Zinc

BW: Birth weight; BL: Birth length; HC: Head circumference; CC: Chest circumference; AC: Abdominal circumference; LMP: Last menstrual period; MUAC: Mid-upper arm circumference; PI: Ponderal Index; SFT: Skinfold thickness (triceps, sub-scapular).

Chapter 4. Study design, setting and methods

4.1. Chapter summary

The thesis describes a prospective study of size at birth in a cohort of 600 infants, and predictors and outcomes of size at birth in a cohort of 1200 infants. This chapter describes the methods and processes used in the data collection of the study. The main aim was collection of information on birth size, its determinants and outcomes. This involved collection of information and measurements in sequential stages. The methods employed were short structured interviews, physical examination, laboratory examinations and anthropometric measurements.

The study had five stages:

1. Enrolment of pregnant women.

2. Follow-up of pregnancies.

3. Measurement of birth size.

4. Assessment of neonatal morbidity and mortality.

5. Anthropometry, morbidity and mortality assessment at two years of age.

4.2. The antenatal multiple micronutrient supplementation trial

The study was conducted within a double blind randomized controlled trial conducted in southern Nepal. The trial ran for 2 years from August 2002 to July 2004. 1200 pregnant women were randomised to receive monthly supplementation with either iron and folic acid (control group) or multiple micronutrients (intervention group), and followed up until delivery and one month post delivery.[3] The trial showed that antenatal multiple micronutrient supplementation

was associated with a mean increase in birth weight of 77 g. We did not observe any association with gestational duration. At a mean 2.5 years of age, children in the intervention group were also 204 g heavier.[2] Publications from the trial are available in annex A and B.

4.3. Setting

4.3.1. Nepal

Nepal is a small landlocked country in the South Asian region. It covers an area of 140,800 square km. It is bordered by India on three sides (east, west and south) and by Tibet to the North. It has a varied altitude ranging from 100 m to above 8000 m above sea level, which contributes to large climatic variation.

Nepal is roughly rectangular in shape, about 650 km in length from east to west and 200 km in width from north to south (see Figure 4.1). It is divided administratively into five development regions: eastern, central, western, mid-western and far western, and three distinctive regions topographically: mountain, hill and *terai* (plain). It is further divided into 14 zones and 75 districts. The study covered the population of two districts, Dhanusha and Mahottari. These are part of the central development region in the plain region.

In Nepal, there are 92 mother tongues and 103 ethnic goups based on the census of 2001.[180] The national language is Nepali, which is spoken and understood by most of the population. The other main languages are Maithili, Bhojpuri, Tharu, Tamang, Nepal Bhasa, Magar, Awadhi, Bantawa Rai, Limbu and Bajjika. The 11 largest ethnic groups are Chhetri, Hill Brahmin, Magar, Tharu, Tamang, Newar, Muslim, Kami, Rai, Gurung and Damain. Nepal has three main religions: Hindu, Buddhist and Muslim.

Nepal had a population of about 23.2 million in 2001 based on the report published by the Central Bureau of Statistics in 2006. The population is growing at a rate of 2.25 % per year (1991-2001). Nepal has a population density of 157 per square km.[181] The sex ratio was 997

males per thousand females in 2001. Nepal has a gross domestic product of US$ 39 billion, a per capita income of US $ 1402 and a human development index of 0.527. Life expectancy at birth is 60.4 yrs – 60.1 yrs for males and 60.7 yrs for females in 2001.

Figure 4.1. Map of Nepal

The total literacy rate was 54% in 2001 (66% for males and 43% for females). There are gender, household wealth and ethnic disparities in school attendance rates, though this disparity has narrowed over the past few years because of government scholarships for females, *dalits* (untouchables), disabled children and needy children. Females residing in rural areas, *dalits* and the poorest are less likely to go to school.

Based on the 2006 NDHS report, which provides estimates over the five years 2001-2005, the neonatal mortality rate was 33 deaths per 1000 live births, post-neonatal mortality 15, infant

mortality 48, child mortality 14 and under-five mortality 61 per 1000, and the perinatal mortality rate was 45 per 1000 births respectively.[182] Mortality rates have declined over the last 10 years. More deaths are likely to occur in poor families with no education residing in the rural hills of the eastern region.

4.3.2. Dhanusha and Mahottari

The caste system used by the locals in these areas is traditionally defined based on occupation and religion. There are Brahmins (priests and scholars), Kshatriya, (rulers and warriors), Vaishya (merchants) and Sudra (peasants and manual laborers, the untouchables). Dhanusha, a place of great cultural and historic value, covers an area of 1180 sq. km in the *terai* at a sea level of 61-610 m. It is bordered by India in the south, Mahottari district to the west, Sindhuli to the north and Siraha to the east, and is 400 km south east of Kathmandu. It has one municipality where Janakpur Zonal hospital is located. Dhanusha is mainly the home of the traditional Maithili ethnic group. The results of the 2001 census revealed that it is the 5th most populous district in Nepal, with 671,364 residents. The adult literacy rate is 49 % and human development index 0.534 (2005).[183]

Mahottari, a district adjoining Dhanusha, is 1002 sq. km in area at a sea level of 61-808 m. It has one municipality and 76 Village Development Committees (VDCs). The district headquarters is Jaleswor (named after the presence of the god Mahadeva in a water source), another spot of religious value. Mahottari has a population of 553,481 (2001 population census). The literacy rate of 34% is lower than that of Dhanusha and the human development index is 0.322. Mahottari is bounded by Dhanusha to the east, Sarlahi to the west, Sindhuli to the north, and the Indian state of Bihar to the south.

Figure 4.2. Janaki temple

4.3.3. Janakpur Zonal Hospital

The study was conducted in collaboration with the maternity and paediatric units of Janakpur Zonal hospital. This is a government hospital established in 1973, situated in Janakpur municipality of Dhanusha district. It is a secondary referral centre providing services to people from Dhanusha, Mahottari, and Sarlahi districts, those referred from lower level health institutions and also to people from the adjoining area of India. The sanctioned number of beds is 100, but the bed availability at the time of the study was 170, out of which 20 beds were in the maternity department and 20 beds in the paediatric department. Among 72 sanctioned staff (32 doctors and 40 nurses), most of the posts were filled. The hospital provides specialist care – paediatrics, obstetrics and gynecology, medicine, surgery, laboratory services, radiology, dermatology, ear, nose and throat, dental and emergency care. It is managed by a development committee and funded mainly by government, self-generation of income and donations.

The obstetrics and gynaecology department has general, private and semi-private rooms. There are no separate rooms for maternity and gynaecological cases. It has one labour ward with three beds and two neonatal resuscitaires, There are one consultant, three medical officers, staff

nurses, auxiliary nurse midwives and student nurses. The unit has a fairly good maternity recording system, supported regularly by training by the Nepal Safe Motherhood Programme.

The total number of hospital outpatients including emergencies was 14,629 for the fiscal year 2002/2003. There were 9930 surgical admissions. Of 1172 deliveries, no maternal deaths were recorded. 25% of women delivering at the hospital had made four antenatal clinic visits.

At the beginning of the study, antenatal services existed but were provided in mixed clinics. There was no designated antenatal clinic. The study contributed to the setting up and support of an antenatal clinic, in partnership with the District Public Health Office and the hospital. The clinic was staffed by two auxiliary nurse midwives (ANMs) supervised by one staff nurse. Auxiliary nurse midwives are trained in specific obstetric care. Their qualifications and responsibilities are summarised in Table 4.1, along with those of Auxiliary Health Workers. The new antenatal clinic provided free care to pregnant mothers, distributed free iron and folic acid tablets, and referred to the hospital obstetricians in case of risk and complications.

Table 4.1. Qualifications and responsibilities of health workers in the community

	Maternal health	Child Health	Training
Auxiliary Nurse Midwife	Antenatal care Postnatal care Delivery Manual removal of placenta Emergency Obstetric First Aid Family planning	Immunizations Acute respiratory infection Diarrhoeal disease (treatment and referral)	10 years of school 18 months of training
Auxiliary Health worker	Family planning Treatment of minor illnesses related to maternal health Referral	Treatment of minor illnesses related to child health Referral	10 years of school 18 months of training

Adapted from[184]

4.4. Participants

The cohort constituted pregnancies in the MIRA Janakpur Antenatal Multiple Micronutrient Supplementation Study.[3] Women were eligible to enter the cohort if they attended the hospital antenatal clinic.

4.5. Eligibility and inclusion criteria

All women who attended the antenatal clinic were screened for eligibility for the study. Women were eligible to participate in the study if (1) their last menstrual period corroborated by physical examination showed a gestational age less than 20 completed weeks, and (2) they lived not too far away from Janakpur Zonal Hospital for monthly antenatal and home follow-up. Inclusion criteria (assessed after basic eligibility) were:

1. Viable fetus.

2. Gestational age of up to 20 completed weeks.

3. Singleton pregnancy.

4. No gross fetal anomaly detected on ultrasound examination.

5. No chronic maternal medical illnesses that could potentially affect birth weight.

4.6. Procedures

4.6.1. Enrolment

In the antenatal clinic, ANMs took a short medical, obstetric, and gynaecological history and the date of the last menstrual period. They performed physical examination to confirm the pregnancy, physical health and to detect pregnancies at risk. Blood and urine were also sent for laboratory examination. Detailed addresses were taken to pick up those pregnant women residing in the area covered by the study. Eligible women were referred to a special study room for further discussion.

In the study room, participants who fulfilled the eligibility criteria were screened by ultrasound scan for confirmation of gestational age, viability, fetal number and detection of gross congenital anomalies. If the ultrasound confirmed that a pregnant woman was suitable for the

study, she was explained the objectives and process of the trial and provided an information sheet, which was available in Maithili, Nepali and English.

A written consent form was prepared in English and translated into Nepali and Maithili. (see annex C and annex F) This was read to participants before enrollment. Participants were encouraged to clear all their doubts regarding the study and to take the opinion of their family members, especially heads of family. Well-informed written consent, preferably in the presence of family members, was taken. Written consent was taken by staff who were fluent in Maithili, Nepali and English.

A series of detailed questionnaires were filled during antenatal clinic visits. The first questionnaire, (enrolment questionnaire) was filled after the participants give formal consent for inclusion (see enrolment form in annex C). It contained the participant's identification information, socio-demographic details, dating of pregnancy, family and personal medical information, current general illnesses, birthing plans, clinical obstetric and anthropometric examination details and details of previous births.

4.6.2. Ultrasound screening and gestational assessment

In order to confirm gestational age at enrolment, we obtained history of last menstrual period and performed ultrasound scans for dating of pregnancy. We used only ultrasound-based dating of pregnancy for the trial. All scans were performed with an Aloka SSD 900 ultrasound unit with a 5 MHz obstetric transducer probe (Aloka, Tokyo). Eligible participants were explained the process and purpose prior to the scan (See Annex E). It was conducted in the presence of the woman's partner or mother-in-law in a quiet and private room. Verbal report of the scan was provided to the women in an understandable way. Hard copies of scan-reports were kept for evidence. The measurements were also recorded manually into the participants' record files. Pregnancies with non-viable fetus or congenital anomaly were referred to the hospital gynaecologist or radiologist for further investigation and management.

Most women had a single scan at enrolment. An anomaly scan was arranged at approximately 20 weeks of gestation if the first scan was undertaken before 16–18 weeks or if gestational age estimation was not reliable due to fetal position. The anomaly scan involved a series of checks, including inspection of spine, head shape and structure, nuchal pad translucency, abdominal shape and content at the level of stomach, kidneys and umbilicus, thorax at the level of cardiac four chamber view, arms and legs numbers and bones (humerus, radius, ulna, tibia, fibula and femur) and face and lips. All measurements were taken by a single observer (AV) to minimize observational error, except nine scans (taken by another doctor).

Crown-rump length (CRL) was used for dating of pregnancies for fetuses up to 12-14 weeks of gestation (Robinson and Fleming charts)[185], and biparietal diameter (BPD) for fetuses of 14-16 weeks gestation (Chitty chart).[186] If it was difficult to measure these parameters due to unusual positioning of the fetus, either repeat ultrasound was performed one month later or femur length (FL) [187]or abdominal circumference (AC)[188] was used. CRL was measured at the longest length along the longitudinal axis of the fetus. BPD measurement was made from the outer margin of the proximal to the inner margin of the distal skull table using internal electronic calipers, at the level where the cross section appeared oval with a clear outline of the calvaria, and the cavum septum pellucidum and falx cerebri lying anteriorly and posteriorly in the midline respectively. Head circumference was measured along the outer margin of the calvaria at the same level as BPD. FL was measured from the greater trochanter to the distal metaphysis at the level where the longest image of the femur with sharp ends appeared. AC was measured in the axial plane at the level of the umbilical vein-ductus venosus complex. Measurements were taken at the outer perimeter of the abdomen.

Ultrasound training and quality control were provided by the Superintendent Ultrasonographer of University College London Hospitals. Scan stills were printed and stored in the participant file, and scan videotapes were sent to the UK for regular quality control examination.

4.6.3. Follow-up

We developed a system to follow participants up every two weeks: monthly at the antenatal clinic and monthly at home on an alternate basis. At every antenatal clinic visit, participants were provided with iron and folic acid and monthly physical examination as recommended by His Majesty's Government, Nepal: maternal weight, blood pressure, urine stick test for pH and albumin, and blood tests for hemoglobin concentration, blood group, rhesus and rapid plasma reagin test for syphilis were taken at enrolment and 32 weeks. Blood haemoglobin was assayed spectrophotometrically with a HemoCue system, with daily calibration checks (HemoCue, Switzerland). Other tests were performed by the hospital pathology department. Participants were referred for any pregnancy related complications to the obstetric or medical department of the hospital.

Every month, participants received a home visit. A home-visit team of four was trained to take birth anthropometry. The team visited participants every four weeks at home and encouraged them to have regular antenatal check-ups, to take the recommended iron and folic acid tablets regularly, and to visit the antenatal clinic for any complications.

We defined loss to follow-up as failure to attend the antenatal clinic for three months and failure to meet the participant after three home visits. We defined miscarriage as the cessation of confirmed pregnancy before 23 weeks gestation, stillbirth as the delivery of an infant exhibiting no signs of life – movement, breathing or heartbeat - after 23 weeks gestation, early neonatal death as the death of a liveborn infant in the first seven days after birth, and late neonatal death as the death of a liveborn infant after seven but within 28 days.

In the event of significant illness, we arranged for the participant to be seen by a consultant obstetrician or physician. There were two pre-specified deviations from protocol. If a participant's enrollment blood haemoglobin level was below 7 g/dl, she was given an extra 60 mg of iron daily, antihelminthic medication, and her blood haemoglobin was rechecked after

one month. If a participant described night blindness at any time, she was given 2000 μg of vitamin A daily and referred for medical follow-up.

4.6.4. Measurement of birth size

Participants were encouraged to have their delivery at the hospital or to inform the home visit team in case of home delivery as soon as possible. The main aim was to measure size within 72 hours of birth. If the participant delivered in hospital, she was recognized by the study midwives in the obstetric ward or contacted the study midwives in case of hospital delivery. This was aided by a coloured enrolment card. Midwives were well trained to measure birth anthropometry: birth weight, birth length and head circumference were taken and a form containing details of the birth was completed. Measurements were taken as soon as possible after delivery. If the participant delivered at home, their family informed the home visit team (all except one AHWs). Trained team members completed birth detail forms and birth anthropometry as soon as they were informed and able to reach the home.

Birth weight was measured on Seca 835 electronic scales accurate to 10 g, tared before each measurement (Seca, Germany). We attempted to do this as soon after birth as possible, but defined late birth weight as a measurement recorded after 72 hours. Infant length was measured on a Kiddimetre board accurate to 1 mm (Raven Equipment Ltd, UK) in hospital and at home births where vehicular access was possible. Some infant lengths were measured on a Rollametre (Raven Equipment Ltd, UK) when severe monsoon conditions made transport of the large, heavy Kiddimetre to the home impractical. Occipitofrontal head circumference was measured with a plastic length tape accurate to 1 mm, taking the central value of three consecutive measurements.

4.6.5. Follow-up at one month

Participants were asked to come for a postnatal check-up one month after delivery (see one month check form in Annex C. Information was gathered on their infant's feeding and illnesses

(cough, fever, diarrhoea, breathlessness) and on their own postnatal illnesses. Information on deaths was also recorded. In the event of illness, infants were referred to the hospital paediatrician. In the event of death, neonatal verbal autopsies were conducted[189].

4.6.6. Follow-up at two years of age

All infants were followed up at home at 2–3 years of age. A new home visit team of five was set up after training them in anthropometric measurements and filling forms for infant illness and verbal autopsy. One of them was appointed as a coordinator. The quality of measurements and observer variation was assessed in a sample size of 300 schoolchildren and women not involved in the original trial. Repeatability of the measurements was tested within observer and between observers. We were particularly concerned to minimise inter-observer variation since, for example, it accounted for 23% of the variation in head circumference, while intra-observer variation accounted for 8%.[2] Because of these variations, the measurement of the anthropometry was assigned to two members of the team with minimum inter-observer and intra-observer variation, and filling of forms to another two team members to keep the measurement bias to a minimum. Each team consisted of one measurer and one form-filler. Visiting schedules were set according to the ages of individual children and the need to cover flood-prone areas outside the monsoon season. All participants who had not relocated beyond the possibility of follow-up were visited at home, a process that required up to five visits. Participants were categorized as lost to follow-up if they could not be found after three attempts. The main reasons were that they moved out of the study area, moved to a new address which could not be traced, or withdrew from the trial. The field workers were unaware of the initial supplement allocation as access to the codes was restricted to principal investigators. They took informed verbal consent from heads of household and mothers after explaining the purpose of study. At first, forms were filled in to allay the child's anxiety and to gain the child's confidence by taking time to be friendly and playful. The parent was then asked to lay the child on her lap and measurements were carried out.

Weight was measured with Seca 835 electronic scales (Hamburg, Germany) accurate to 10 g. Standing height was measured with a portable Leicester stadiometer accurate to 1 mm, barefoot and with the head in the Frankfurt plane. Head and mid-upper arm circumferences were measured with disposable insertion tapes accurate to 1 mm (Harlow Printing Ltd, South Shields, Tyne and Wear). Head circumference was taken at the maximum occipito-frontal measurement. Mid-upper arm circumference was measured at a level midway between the tip of the olecranon process and the acromion process. Chest, waist and hip circumferences were measured with a plastic measuring tape accurate to 1 mm. Chest circumference was measured at the level of the nipples, midway between inspiration and expiration during quiet breathing. Waist circumference was measured at the level of the natural waist, and hip circumference at the level of maximum circumference over the buttocks. Triceps skinfold thickness was measured with Harpenden callipers accurate to 1 mm (CEO 120, UK). The measurement was taken midway between the tip of the olecranon process and the acromion process, in the midline of the posterior surface of the extended dominant arm. All measurements except weight and height were made three times and the middle value recorded for analysis.

We collected information about the number of illnesses in the first year of life and about specific illnesses in the 14 days preceding the interview (Annex D). Medical reports were examined where available and verbal autopsy questionnaires were completed in the event of mortality. These were analyzed for cause of death by two paediatricians, one of whom was the author.

All data were entered in a relational database management system in Filemaker Pro 5.5. Data were rechecked manually for accuracy, with reference to the hard copy forms..

4.7. Ethical considerations and funding

The trial was funded by a project grant from The Wellcome Trust. The follow-up study was conducted under a grant from an anonymous charitable donor. The trial was approved by the Nepal Health Research Council and the ethics committee of the Institute of Child Health and

Great Ormond Street Hospital for Children, and was conducted in collaboration with His Majesty's Government Ministry of Health, Nepal. It was also approved by the Medical Superintendent of Janakpur Zonal Hospital and the District Public Health Officer. The approval covered all the data collection involved in the thesis study. Benefits to participants included the supply of supplements, free health care, and expedited referral in the event of complications.

Participants were numerically coded and only the researcher and research assistants knew their names. Participants' names did not appear on any documentation, analyses or outputs. All study documents were kept confidential and will be destroyed five years after the completion of the study.

Chapter 5. Data available for analysis and analytical methods

5.1. Data available for analysis

The first participant joined the trial on 11th August 2002 and the 1200th on 22nd October 2003. As a result of the process described in Chapter 4, a number of questionnaires and tools were available for examination. They are summarized in Table 5.1. Data were collected at four points: during pregnancy, at birth, at one month and at two years of age. As mentioned above, the women invited to participate were selected from a pool that included all those who attended the antenatal clinic.

Table 5.1. Questionnaires providing data for analysis

During pregnancy
Enrolment questionnaire
Monthly follow-up questionnaires
At birth
Birth questionnaire and anthropometry
At one month
Follow-up questionnaire
At two years
Maternal and child anthropometry
Infant and child morbidity questionnaire
Infant or child verbal autopsy (when required)

Table 5.2 summarises the data available from all the tools combined. Of the 1985 women who came to the antenatal clinic, 785 were not enrolled. Inclusion was based mainly on the possibility of tracking the healthy woman and fetus from early pregnancy (at less than 20 weeks gestation) until delivery. Most of the exclusions at initial screening occurred for two reasons. Either participants lived outside the study area, which made it impossible to achieve monthly visits - at the hospital or at home - or their gestation was more than 20 completed weeks according to estimates based on the date of the last menstrual period, corroborated by symphysis-fundal height measurement. The second stage of screening involved obstetric ultrasound. Exclusions at this stage resulted from either a gestation confirmed to be over 20 weeks, or from the identification of a congenital abnormality that might interfere with fetal growth. The third stage of screening involved medical examination. Medical conditions that could interfere with fetal growth were barred from the study.

Table 5.2. Data available for analysis

	Antenatal		Birth	1 month	2 years	
	Mothers	Fetuses	Infants	Infants	Children	Mothers
Measurements	Age	BPD			Weight,	Weight
	Height	HC			Height	Height
	Weight at 1st visit	AC			HC	BP
	Weight gain	FL			CC	WC
	Parity	EFW			WC	HC
	BMI	Gestation			Hip Circumference	MUAC
	Blood pressure				MUAC	Triceps skinfold
	Morbidity				Triceps skin-fold thickness	thickness
	Urine protein				Blood pressure	
	Urine sugar				Mortality and Morbidity	
Outcomes			LBW	Neonatal deaths	Stunting	
			SGA	Morbidity	Wasting	
			Low PI		Underweight	
					Infant death	
					Child death	
					Morbidity	

BPD: Biparietal diameter; HC: Head circumference; AC: Abdominal circumference; FL: Femur length; EFW: Estimated fetal weight; BW: Birth weight; BL: Birth length; HC: Head circumference; CC: Chest circumference, WC: Waist circumference; MUAC: Mid upper arm circumference; BP: Blood Pressure

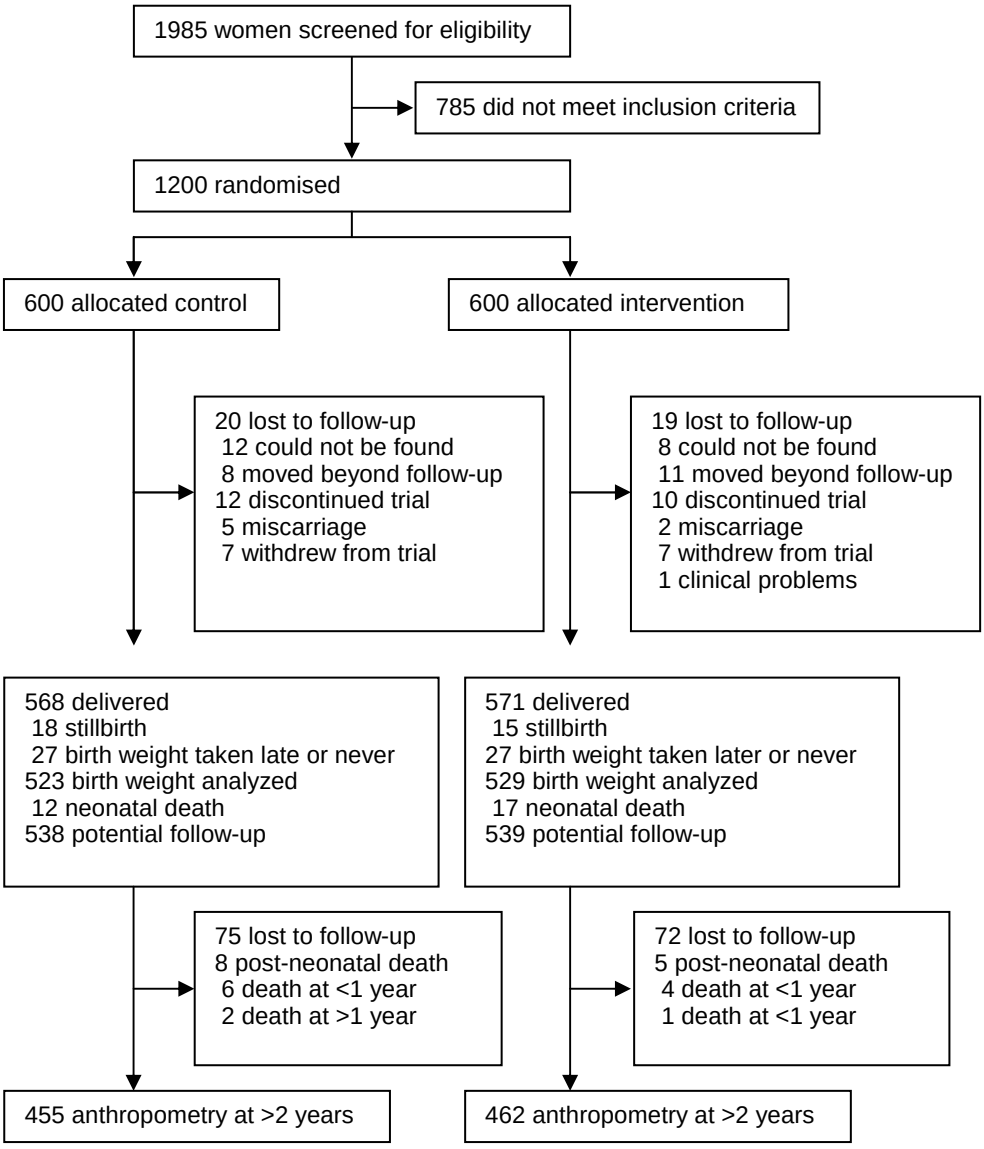
Most exclusions at enrollment were for gestations greater than 20 weeks. Maternal illnesses that led to exclusion were: recently treated recurrent cysticercosis (1), chlorpromazine (1) or anticoagulant (1) medication with changing doses, and symptomatic mitral stenosis (1) or multivalvular heart disease (1). Fetal exclusions were: twin pregnancies (6), anencephaly (1), occipital meningocoele (1), encephalocoele (1), duodenal atresia (1) and a grossly dilated pelvicalyceal system (1).

Figure 5.1 is the study profile for the MIRA Janakpur Multiple Micronutrient Supplementation Trial. 20 participants enrolled in the trial but were never seen again, even after a thorough search in the areas they had given as their addresses. 19 participants moved out of the areas in which they could be tracked and we did not know their birth outcomes. Seven participants suffered spontaneous abortion. 14 participants withdrew from the trial because they felt it would not benefit them. One participant withdrew after developing generalized itching. In deviations from protocol, four participants received treatment for severe anaemia and three for night blindness. Information about 1139 deliveries was available for the analysis of gestational duration. Because most of the stillborn infants were not weighed, we included only liveborn infants in the analysis of birth weight. The birth weight outcome was available for 523 (87·2%) infants in the control group and 529 (88·2%) in the intervention group.

In the childhood follow-up phase, we located and visited 917 mothers and children from December 2005 to December 2006: 455 in the control group and 462 in the intervention group. Retention rates from enrolment (after discontinuation, fetal loss, stillbirths, infant deaths, post-infancy deaths and loss to follow-up) were 76% and 77% respectively. Retention rates of children who could potentially have been followed up after the neonatal period were 85% in the control and 86% in the intervention group.

The following sections describe the data handling for the three studies covered in the thesis: characteristics of mothers and infants, including size at birth, predictors of size at birth and associations of size at birth with mortality, morbidity and malnutrition in childhood.

Figure 5.1. Study profile for the MIRA Janakpur Trial



5.2. Characteristics of mothers and infants, including size at birth

Table 5.3 presents summaries of size at birth for all infants born in the MIRA Janakpur trial. 51% of infants were male.

Table 5.3. Size of infants at birth

	Available	Mean	(SD)		Frequency	(%)
Gestational age at birth (w)	1048	39.46	(1.71)			
Weight (Kg)	1048	2.777	(0.429)	LBW	231	(22.0)
				SGA	542	(51.9)
Length (cm)	1035	48.89	(2.56)			
Ponderal index (g/cm^3)	1035	2.38	(0.34)	LPI	701	(67.7)
Body mass index (Kg/m^2)	1035	11.60	(1.50)			
Head circumference (cm)	1039	33.59	(1.49)			

SGA: small for gestational age (< -1.28 z score ~ <10th percentile); LPI: low ponderal index (<2.5 g/cm^3); LBW: low birth weight (<2.500 Kg)

Because we wanted to describe size at birth in the general population, the overall study presented us with a problem. The effects of antenatal multiple micronutrient supplementation, though not large, could make the analysis unrepresentative of the usual situation. For this reason, we described size at birth for only infants in the control group. In later chapters, we included all the infants because we could control for the intervention in multivariable regression analysis.

5.2.1. Outcomes used in the analysis

The primary outcome of interest was birth weight. The other measurements taken at birth were length and head circumference. Body mass index and ponderal index were calculated and small-for-gestational-age was computed using an appropriate reference. A cut-off of <2500 g was used to define low birth weight (29th World health Assembly, 1976), <2.5 g/cm^3 for low ponderal index[190], and birth weight below the 10th percentile of the British population (British reference LMSGrowth software) for SGA. The cut-off to define small for gestational age in this population was < -1.28 z score, which is equivalent to <10th percentile.

5.2.2. Statistical methods

Preliminary analysis involved baseline maternal socio-demographic, nutritional, health and reproductive characteristics. Infant size at birth was described in terms of mean, standard deviation and as a percentage of all infants measured within 72 hours of birth. The Datadesk program was used for the detection of outliers and all analyses were performed in SPSS.

5.3. Predictors of size at birth

We included infants born in both arms of the trial in this analysis. The database was restricted to cases with available primary outcome.

5.3.1. Outcomes used in the analysis

We examined the associations of potential risk factors with a range of indicators of size at birth. These included weight, length, head circumference; BMI and PI; and LBW, SGA, and low PI. Cases without the outcomes in question were removed from the analysis. For the analysis of each birth size indicator, the cases without anthropometric measurements were not included in the analysis. Therefore, the total number of cases available for analysis varied across the birth size indicators analyzed.

5.3.1.1 Statistical methods

Based on the literature review, potential predictors of size at birth were chosen from the database that had been developed.[24] There were 21 variables of interest. They were categorized under two main headings, maternal and fetal. Maternal factors included socioeconomic status, illness during pregnancy, obstetric history, anthropometry and nutritional status. Fetal factors included infant sex and gestational age at birth.

To describe socioeconomic status, we used an asset scoring system that was recommended for similar work and had been used before in Nepal.[191] It was divided into 4 categories: 0 (did not

own any household durables), 1 (possessing a clock, radio, iron, or bicycle), 2 (possessing a sewing machine, cassette player, camera, fan or bullock) and 3 (possessing a motor vehicle, television or refrigerator). However, since that time it has become more usual to use lists of assets collected in Demographic and Health Surveys. The assets are listed independently and then a composite score is generated using the technique of principal components analysis. Socioeconomic status was assessed based on land ownership, possession of household durables and husband's occupation. There were eight factors and the score was generated from the first component of the principal components analysis according to published guidelines.[192]

For maternal morbidity, common complaints during pregnancy were abdominal pain, itching, dysuria, vaginal bleeding, constipation, parasite infestation, pneumonia, fever, perineal problems, nausea, backache, abdominal bloating, excessive vaginal discharge, weakness or cramp, urinary tract infection, visual problems, diarrhoea, and cough. Table 5.4 presents the categories of maternal morbidity during pregnancy based on time, number and nature of complaints. Maternal morbidities were divided into two groups based on which trimester the complaints were made. Second and third trimester maternal health complaints were again grouped under four categories: 0 (no complaints at all), 1 (abdominal complaints), 2 (infections) and 3 (other complaints).

Table 5.4. Categories of maternal morbidity during pregnancy based on time, number and nature of complaint

Time of morbidity	Complaints	Categories of complaints	
First trimester morbidity	First complaints (I)	No complaints at all	(0)
Second trimester morbidity	Second complaints (II)	Abdominal complaints	(1)
		Infections	(2)
		Other complaints	(3)

Data patterns were examined through two-way scatterplots. A two-step statistical analysis was carried out to identify independent factors predictive of size at birth. First, univariable analysis was carried out to determine the association between each independent factor and the dependent variable. Second, multivariable analysis of all significant factors (at $p < 0.05$) in the

univariable analysis was run to develop a prediction model. Some important predictors (maternal weight, maternal height, previous history of small birth, parity, gestational age at birth, infant sex, socioeconomic status and micronutrient supplementation) were included in the multivariable regression irrespective of significance level in the univariable analysis. R^2, the coefficient of determination, was used to measure the size of contribution of variables to outcome. We used logistic regression for dichotomous dependent variables (LBW, SGA and PI) and linear regression for continuous dependent variables (birth weight, length, head circumference). A factor was considered significant at $p < 0.05$. All the variables that were significant in the univariable analysis were entered first in continuous form into the model, after which they were tested in categorical versions. We looked particularly at their effects on the coefficients of determination and regression coefficients. The models were tested to see if the addition of variables previously not significantly associated made a difference, since a lack of association in univariable analysis may hide an association after adjustment. Third, the adequacy of each model was ascertained using a graph of residual values plotted against predicted values. The distribution of errors was examined by histogram and normal probability plot.

5.4. Associations of size at birth with mortality, morbidity and malnutrition in childhood

Once again, we included infants born in both arms of the trial in this analysis. The database was restricted to cases with indicators of size at birth. Cases without birth size indicators were removed from the analysis. Therefore, the total number of cases available for analysis varied across the birth size indicators analyzed.

5.4.1.1 Outcomes used in the analysis

We examined the associations of different classifications of size at birth on the following outcomes: mortality (neonatal death, infant death, child death before follow-up), illness in infancy (cough and fever, diarrhoea and fever, rash and fever, frequency of illness), and illness

in the preceding two weeks (fever, cough, difficulty breathing, diarrhoea), and malnutrition (stunting, underweight, wasting). The definitions and cut-offs for the factors used in this chapter were as follows.

Weaning was defined as the introduction of solid food to infants who were not fed something other than breast-milk and water. The rate of exclusive breastfeeding was defined as the proportion of infants who were not fed something other than breast milk. A cut-off of 2 SD below the median weight-for-age, height-for-age and weight-for-height in the WHO reference data was used for defining children as underweight, stunted or wasted.

We asked mothers about the illnesses in the first year of life at follow-up at 2-3 years of age. The illnesses were classified as cough and fever (respiratory infections), diarrhoea and fever (gastroenteritis), rash and fever and frequency of illness. Diarrhoea was defined as passage of 3 or more loose watery stools daily. Frequency of illness was categorized into five groups: 0-2, 3-4, 5-7, 8-10 and >10 times. These were further coded as a dummy variable in which <4 times took a value of 0 and >5 times a value of 1.

5.4.1.2 Statistical methods

Cox proportional hazards modeling was used to explore the role of measurements at birth in the prediction of death from birth to the end of follow-up. The predictor variables explored were weight, weight z-score, ponderal index and gestational age at birth. The time from birth until deaths at one month, one year and at the end of follow-up were explored. We also used logistic regression to examine the effects of categories of size at birth on subsequent outcomes. The predictors evaluated represented the permutations of LBW, SGA and low PI. They are presented in Table 5.5.

Table 5.5. Newborn classification based on anthropometric parameters

Single index	Combination of 2 indices	Combination of 3 indices
LBW	Birth weight and ponderal index	LBW-LPI-AGA
LPI	LBW-LPI	LBW-API-SGA
SGA	LBW-API	LBW-LPI-SGA
	NBW-LPI	LBW-API-AGA
	NBW-API	NBW-LPI-AGA
		NBW-API-SGA
	Birth weight and weight for gestational age	NBW-LPI-SGA
	LBW-SGA	NBW-API-AGA
	LBW-AGA	
	NBW-SGA	
	NBW-AGA	
	Ponderal index and weight for gestational age	
	LPI-SGA	
	LPI-AGA	
	API-SGA	
	API-AGA	

There was a range of possible confounders for the effect of size at birth on health outcomes. These were dealt with as follows. First, univariable associations were examined between each outcome and possible confounders. Second, three models were developed for each outcome. Model I was an unadjusted logistic or linear regression of outcome on parameter of size at birth. Model II was an adjusted multivariable regression using only variables that showed significant association and that demonstrated almost significant association with the outcome in the first step. The confounder adjusted for neonatal death was weight at enrolment and for child death was gestational age at birth. Infant death has no significant confounders. Similarly, the significant confounders that were adjusted for stunting were parity, education, socioeconomic status, weight at enrolment, gestational age at birth, age at weaning, age at follow up and frequency of illness. Underweight had same significant confounders. The exceptional factor was age at follow up. Wasting was adjusted for only two significant factors- education and weight at enrolment. For illness during infancy the confounders adjusted were as follows. Cough and fever was adjusted for maternal age and education. Diarrhoea and fever was adjusted for ethnicity, supplementation and age at follow up. Rash and fever was adjusted for maternal age and education. Frequency of illness was adjusted for parity, education, socioeconomic status and infants gender. Similarly, illness in the last fortnight before follow up

was adjusted for the following factors. Fever was adjusted for four significant factors. They were parity, education, socioeconomic status, weight at enrolment and age at weaning. Cough was adjusted for seven factors- parity, education, socioeconomic status, weight at enrolment, infants gender, age at weaning and age at follow up. Difficulty breathing was adjusted for parity, education, age at weaning and age at follow up. Diarrhoea had six significant confounders- parity, education, socioeconomic status, weight at enrolment, age at weaning and age at follow up. Systolic blood pressure was adjusted for parity and maternal age and diastolic blood pressure was adjusted for parity, ethnicity and education.

Model III was an adjusted multivariable regression using all possible confounders. They were maternal age, parity, ethnicity, education, socioeconomic status, supplements, weight at enrolment, gestation at birth, infant sex and age at weaning for neonatal, infant and child deaths. For malnutrition, the factors adjusted were same. We also adjusted for one more factor - frequency of illness. For illness during infancy and in the fortnight before follow up, it is also same as deaths. The extra factor adjusted was age of child at follow up.

Chapter 6. Results: characteristics of mothers and infants, including size at birth

6.1. Chapter summary

This chapter describes size at birth in the infants of an initial sample of 600 pregnant women recruited into the control group of the MIRA Dhanusha Antenatal Multiple Micronutrient Supplementation Trial. The previous chapter summarized the study profile for participants and infants in both arms of the trial. The whole dataset was used for the analysis of predictors and outcomes of size at birth (described Chapters 7 and 8). However, a reduced dataset was used in this chapter because the objective was to describe the distribution of size at birth in Nepalese infants. Since the maternal multiple micronutrient supplements were associated with greater size at birth, it was felt that including infants whose mothers had taken them would reduce the external validity of the findings. After describing losses to enrollment and follow-up, the chapter summarises the final dataset available for analysis. It describes baseline characteristics of the study participants, anthropometry of newborn infants, composite indices (BMI and PI), and then a detailed presentation and comparison of indices of small size (LBW, low PI and SGA).

6.2. Exclusions from analysis

Table 6.1 summarises the reasons for exclusion of participants from the main analysis. From the 600 women enrolled, 523 infant birth weights were analyzed. The analysis was restricted to mothers who completed the study and gave birth to a live infant whose anthropometry was taken within 72 hours of birth. Participants were defined as lost to follow-up if they failed to visit the antenatal clinic for three consecutive months, and if the home visit team failed to meet them at home after three visits in spite of rigorous attempts.

Table 6.1. Exclusions from analysis

Dropped out during pregnancy	
Lost to follow-up	
12 Never found	Wrong address provided at enrolment
8 Participants moved	Beyond study follow-up area
	Across the country
Ceased trial	
5 Miscarriages	4 Spontaneous
	1 Induced
7 Withdrew from trial	Generalized itching
	Not doing her any good
	No reason given
Problems with birth weight ascertainment	
18 Stillbirths	Unknown reason
27 Birth weight measured at >72 hours	Lack of easy communication: telephone facility, transport facility
	Weakness in convincing participants

In general, early losses were due to miscarriage or unwillingness to take part in the study, and later losses were due to movement out of the study area. It is a tradition for women in Dhanusha to go to their maternal homes for later pregnancy and delivery. Overall, the birth weights available for analysis were 87% of the initial group. The mean gestation at loss to follow-up was 26.8 weeks (SD 7.9), equivalent to 80 days (SD 47).

6.3. Characteristics of mothers

Table 6.2 summarises maternal characteristics at enrolment. It allows comparison of the women in the trial control group with women who were lost to follow-up. The mean gestation at enrollment was 16 weeks (SD 2.6). 44% of the women were in their first pregnancy. Approximately 86% of the cohort was of Maithili ethnic origin and the rest belonged to ethnic groups from Nepal's hills (6%). Most of the participants were Hindu (95%), with half of them dwelling in town (53%). As expected, all the mothers were married. Mothers tended to be young and in their second pregnancy, with a mean age of 21.5 years (range: 15–38) and median parity of 1 (range: 0–6). Less than one third of the pregnant women were teenagers (171, 29%). More than half of the participants had some education.

No participant said that she smoked, but the data may not be reliable due to social stigma. One third of participants had mild to moderate anaemia at enrollment (35%). There were no mothers

with severe anaemia. The mean weight at enrolment was 45.1 kg (SD 6.0) and the mean height was 151.0 cm (SD 5.7). Mean BMI was low (19.8, SD 2.4). 28% of pregnant women had a BMI lower than 18.5 Kg/m^2.

Table 6.2. Maternal characteristics at enrollment

	Cohort (n=523)	(%)	Lost to follow-up (n=77)	(%)
Residence				
Urban	273	(52.2)	43	(55.8)
Rural	250	(47.8)	34	(44.2)
Religion				
Hindu	497	(95)	71	(92.2)
Muslim	25	(4.8)	6	(7.8)
Buddhist	1	(0.2)		
Ethnicity				
Terai Brahmin	69	(13.2)	14	(18.2)
Terai Chhetri	15	(2.9)	2	(2.6)
Terai Vaishya	360	(68.8)	46	(59.7)
Terai Sudra	11	(2.1)	1	(1.3)
Hindu Brahmin	16	(3.1)	4	(5.2)
Hindu Chhetri	14	(2.7)	2	(2.6)
Muslim	26	(5)	6	(7.8)
Newar, Tibeto-Burman and others	12	(2.3)	2	(2.6)
Age (y)	21.54	(3.54)	22.39	(4.54)
<19	153	(29.3)	18	(23.4)
20-29	346	(66.2)	52	(67.5)
≥30	24	(4.6)	7	(9.1)
Education				
None	238	(45.5)	33	(42.9)
Primary, class 1-5	52	(9.9)	15	(19.5)
Secondary, class 6 or higher	233	(44.6)	29	(37.7)
Anthropometry				
Weight (Kg) [mean, SD]	45.19	(6.00)	44.70	(5.85)
Height (cm) [mean, SD]	151.13	(5.77)	150.04	(4.85)
BMI (Kg/m^2) [mean, SD]	19.79	(2.41)	19.84	(2.27)
Low BMI (<18.5)	148	(28.4)		
Medical Status				
Blood haemoglobin at enrolment (g/dL) [mean, SD]	11.55	(1.56)	11.38	(1.48)
<110 g/L	177	(34.2)	24	(36.4)
<70 g/L	0	(0.0)	0	(0.0)
Blood haemoglobin at 32 w gestation (g/dL) [mean, SD]	11.79	(1.35)	11.88	(1.53)
Systolic blood pressure (mmHg) [mean, SD]	103.43	(9.66)	101.56	(10.0)
Diastolic blood pressure (mmHg) [mean, SD]	63.18	(7.92)	61.95	(8.28)
Obstetric Status				
Parity at birth of index child [median, range]	1	(0–6)	1	(0 - 6)
0	231	(44.2)	35	(45.5)
1	162	(31.0)	14	(18.2)
2	70	(13.4)	15	(19.5)
3+	60	(11.5)	13	(16.9)
Gestation at booking (wk) [mean, SD]	15.96	(2.55)	16	(2.51)

Data are frequency (%) unless otherwise indicated

Table 6.3 presents indicators of socioeconomic status. Most of the participants had some land, with off-farm employment to supplement low farm income: small-scale shops (19%), waged employment (11%) and migration for labour (1%). Half of the participants' families were ranked as having a good economic condition based on the household ownership of a set of consumer durables. This could be misleading because of inclusion of television ownership in the first rank. A small television could be procured for as little as 1000–1500 Nepalese Rupees (£9-14).

Table 6.3. Indicators of socioeconomic status

	Cohort (n=523)	(%)	Lost to follow-up (n=77)	(%)
Land owned				
None	33	(6.3)	6	(7.8)
≤10 kattha	277	(53.2)	35	(45.5)
>10 kattha	211	(40.5)	36	(46.8)
Husband's occupation				
No work	59	(11.3)	2	(2.6)
Farming	78	(14.9)	14	(18.2)
Salaried	217	(41.5)	35	(45.5)
Small business	97	(18.5)	17	(22.1)
Waged labour	57	(10.9)	9	(11.7)
Student	8	(1.5)		
Out of country	7	(1.3)		
Ownership of Consumer durables				
Motor vehicle, television, refrigerator	277	(53)	24	(31.6)
Sewing machine, cassette player, camera, fan, bullock cart	27	(5.2)	7	(9.2)
Clock, radio, iron, bicycle	137	(26.2)	30	(39.5)
None of the above	82	(15.7)	15	(19.7)

10 kattha is about 0.3 hectares

6.4. Characteristics of infants

Table 6.4 presents figures on birth characteristics. 53% of deliveries were conducted at the hospital. Most had no signs of birth asphyxia at five minutes after birth, and only 7% required resuscitation. Less than one percent suffered severe asphyxia on assessment at five minutes after delivery. 7% of infants were born with congenital anomalies. The physical state of a newborn is recorded at one minute and five minutes as a score -Apgar score- based on respiratory rate, heart beat, skin colour, muscle tone and reflexes. The total score is 10. Newborn with severe birth asphyxia has a score of three or below; moderate birth asphyxia has a score of four to six and mild birth asphyxia or normal newborn has a score of seven or more.

Table 6.4. Infant status at birth

	Frequency	(%)
Delivery [n=566]		
Hospital	300	(53)
Home	246	(43.5)
Other	20	(3.5)
Apgar Score at 1 minute [n=295]		
Severe Asphyxia	5	(1.7)
Moderate Asphyxia	21	(7.1)
Mild Asphyxia/ Normal	269	(91.2)
Apgar Score at 5 minutes [n=546]		
Severe Asphyxia	4	(0.7%)
Moderate Asphyxia	21	(7.1%)
Mild Asphyxia/ Normal	269	(91.2%)
Resuscitation [n = 555]	38	(6.8%)
Congenital Anomaly [n =591]	38	(6.8%)

6.5. Infant size at birth

6.5.1. Distributions

Birth anthropometry was analysed for 523 infants. One newborn, an extreme outlier in the birth weight distribution, due to extreme preterm delivery (900g at 28.14 weeks gestation), was removed from the dataset. Other anthropometric measurements which were outliers were not analyzed. There were four birth length outliers and one head circumference outliers. Figure 6.1, Figure 6.2 and Figure 6.3 illustrate the distributions of birth weight, length and head circumference. All were normally distributed.

Figure 6.1. Distribution of birth weight

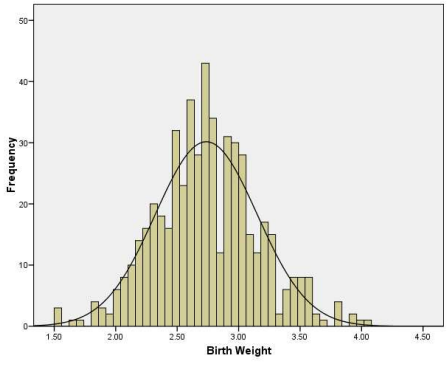


Figure 6.2. Distribution of birth length

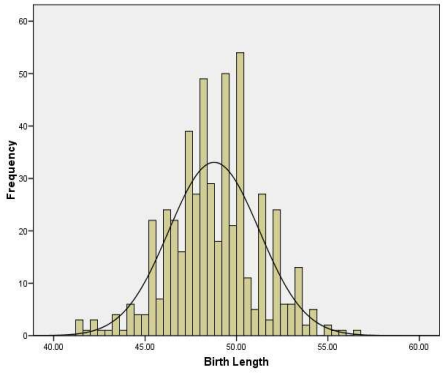
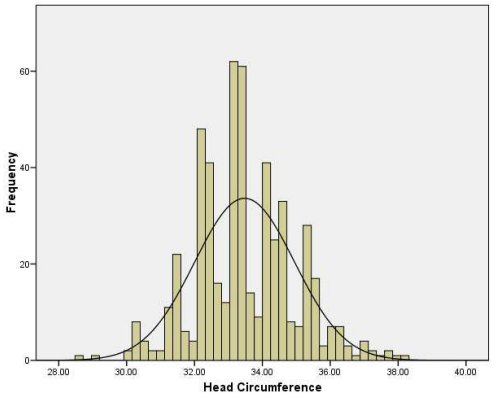


Figure 6.3. Distribution of birth head circumference



6.5.2. Measures of central tendency

Measures of central tendency and spread for major anthropometric indicators are shown in Table 6.5. Mean birth weight of live-born singleton infants was 2736 g, mean length was 48.8 cm, and mean head circumference was 33.5 cm. The mean gestational age at delivery was 39 weeks and 2 days. Two composite indices are presented: PI, with a mean of 2.4 g/cm^3, and BMI, with a mean of 11.5 kg/m^2.

Table 6.5. Birth anthropometry

Birth Size	Mean (SD) [n]	95% CI	Range
Birth Weight (g)	2736 (414) [522]	(2701–2772)	1500-4040
Birth Length (cm)	48.77 (2.47) [513]	(48.56–48.99)	41.2-56.8
Birth Head Circumference (cm)	33.48 (1.47) [517]	(33.35–33.60)	28.5-38.2
Gestational Age (weeks)	39.34 (1.76) [522]	(39.19–39.50)	31.58-45.14
Ponderal Index (g/cm^3)	2.37 (0.33) [513]	(2.34–2.39)	1.48-3.68
Body mass index (kg/m^2)	11.50 (1.46) [513]	(11.37–11.63)	7.74-17.45

6.5.3. Birth size by gestation: term and preterm

Table 6.6 presents the prevalence of "abnormal" size at birth: LBW, low PI and SGA. 133 (25%) infants met the WHO definition of LBW. Out of these, 77% were born at term. The ratio of term to preterm LBW was 3.4:1 (77:23). 70% (358) of infants were born with low PI, and 287 (55%) were classified as SGA, most being born at term (97%).

Table 6.6. Figures for abnormal size at birth

Abnormal size category	Frequency	(%,	95% CI)
LBW	132/522	(25.3,	21.6–29.2)
Term LBW	104/522	(19.9,	16.6–23.6)
Preterm LBW	30/522	(5.7,	3.9–8.1)
Low PI	358/513	(69.8,	65.6–73.7)
Term low PI	328/513	(63.9,	59.6–68.1)
Preterm low PI	30 /513	(5.8,	4.0–8.2)
SGA	287/520	(55.2,	50.8–59.5)
Term SGA	274/520	(52.7,	48.3–57.1)
Preterm SGA	13/520	(2.5,	1.3–4.2)

6.5.4. Size at birth by infant sex

Table 6.7 summarizes size at birth stratified by infant sex. As expected, male infants had higher birth weight, length and head size compared to females. The mean gender differences were 128 g, 0.76 cm and 0.59 cm, respectively. All these differences in birth anthropometry reached statistical significance. In spite of this, there was only a small difference in mean PI. Though marginally larger in males than females, this did not reach statistical significance. Male and female infants were both wasted at birth (PI <2.5), as shown by mean PIs of 2.37 (SD 0.36) and 2.36 (SD 0.32) respectively. In contrast, there was a difference in BMI of 0.25 g/cm^3 between males and females. This was closer to statistical significance (p = 0.06).

The table also presents the odds ratios for abnormal birth size in females compared with males. 81 girls (31%**)** and 51 boys (20%**)** were born with LBW, irrespective of gestational age. Boys had almost half the odds of being born LBW than girls (OR 0.54; 95% CI 0.35–0.84). This was highly significant (p = 0.006). 70% of newborn infants were wasted at birth (low PI). Boys had 14% lower odds of being born with low ponderal index than girls, but as mentioned above this was not significant (OR 0.86; 95% CI 0.58 – 1.29). Similarly, boys had 5% lower odds of being SGA than girls but the difference was not significant.

Table 6.7. Birth size stratified by infant sex

Birth Sizes	Males Mean (SD) [n]	Females Mean (SD) [n]	Difference (95% CI)
Birth weight (Kg)	2.800 (0.419) [262]	2.672 (0.399) [260]	0.128 (0.06–0.20)
Length (cm)	49.15 (2.51) [256]	48.40 (2.38) [257]	0.76 (0.33–1.18)
Head circumference (cm)	33.77 (1.44) [260]	33.18 (1.45) [257]	0.59 (0.34–0.84)
Composite birth indices			
PI (g/cm^3)	2.37 (0.36) [256]	2.36 (0.32) [257]	0.02 (-0.04–0.07)
BMI (Kg/m^2)	11.62 (1.50) [256]	11.38 (1.41) [257]	0.25 (-0.01–0.50)
Abnormal birth sizes			
LBW	51 (19.5%)	81 (31.2%)	OR = 0.54 (0.35–0.84)
Low PI	171 (66.8%)	187 (72.8%)	OR = 0.86 (0.58–1.29)
SGA	134 (51.5%)	153 (58.8%)	OR = 0.95 (0.64–1.39)

6.5.5. Comparison of categorizations of size at birth: birth weight and ponderal index

Table 6.8 shows the results of combining LBW and PI classifications. The prevalence of low PI was 70% (n = 358) and of LBW was 25% (n = 129). A large proportion had low PI: 64% in normal birth weight and 88% in LBW infants.

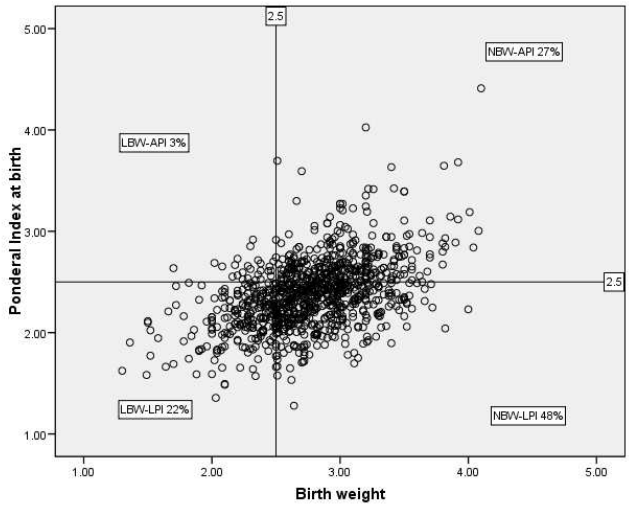
Table 6.8. Proportion of newborn infants based on birth weight and ponderal index classification

	Normal birth weight	LBW	Total
API Proportionate	139 (36%)	16 (12%)	155 (100%)
LPI Disproportionate	245 (64%)	113 (88%)	358 (100%)
Total	384 (75%)	129 (25%)	513 (100%)

API: Appropriate Ponderal Index (normal or stunted); LPI: Low Ponderal Index (wasted)

Figure 6.4 shows a scatterplot of ponderal index at birth against birth weight, with quadrants representing different categories of newborns. Each dot represents a single newborn. Two lines pass through the cut-off points of 2.5 for ponderal index and birth weight in their respective units. The right upper quadrant represents newborns with normal birth weight and appropriate PI. Out of 513 infants with available data, only 27% were normal in terms of both weight and PI. 22% were abnormal on both classifications (LBW-LPI). Only 3% of infants were proportionate but LBW. Almost half of infants were normal birth weight for their gestational age but had abnormal PI. If the purpose of the study was to identify normal infants in terms of both birth weight and PI, then only 27% of infants would be classified as normal

Figure 6.4. Scatterplot of Ponderal Index at birth against Birth Weight



6.5.6. Comparison of categorizations of size at birth: birth weight and weight-for-gestation

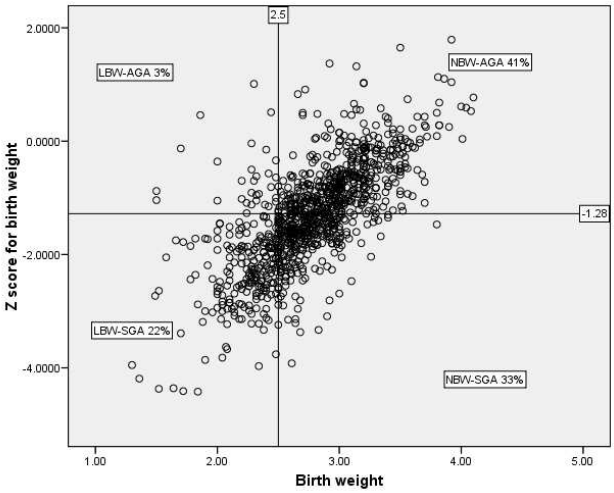
Table 6.9 shows the results of combining birth weight and weight-for-gestational-age classifications. The sample available for analysis was 520. The prevalence of SGA was 55% and of LBW was 25%. SGA accounted for 45% of normal birth weight (173/388) and 86% of LBW infants. It is striking that almost 60% of SGA infants had normal birth weights.

Table 6.9. Proportion of newborn infants based on birth weight and weight-for-gestational-age classification

	Normal birth weight	LBW	Total
AGA	215 (55%)	18 (14%)	233 (100%)
SGA	173 (45%)	114 (86 %)	287 (100%)
Total	388 (75%)	132 (25%)	520 (100%)

Figure 6.5 shows a scatterplot of birth weight Z-score against birth weight. As in Figure 6.4, the quadrants are defined by lines passing through the cut-off points for small for gestational age (-1.28) and low birth weight. The right upper quadrant represents newborns with normal birth weight and appropriate weight-for-gestational-age. 22% of infants were small in terms of birth weight and weight for their gestational age (LBW-SGA), whereas only 41% had appropriate weight for their gestational age at birth and weight >2500g (AGA-NBW). In spite of having weight appropriate for their gestational age, around 4% of infants had birth weight <2500 g (LBW-AGA). 33% of infants had normal birth weight but were SGA (NBW-SGA).

Figure 6.5. Scatterplot of Birth Weight Z score against Birth Weight



6.5.7. Comparison of categorizations of size at birth: weight-for-gestation and ponderal index

Table 6.10 stratifies SGA and AGA infants into subgroups based on PI. The number of cases available was 511. The numbers differ from previous sections because of some missing data for birth length. The overall incidence of SGA was 56% (n=284) and of low PI was 70% (n=356). Most SGA infants were disproportionate (82%) and more than half of infants of normal weight-for-gestational-age were actually wasted (n = 124, 54%) The ratio of proportionate to disproportionate SGA was almost 1:4.5.

Table 6.10. Proportion of newborn infants based on weight-for-gestational-age and ponderal index classification

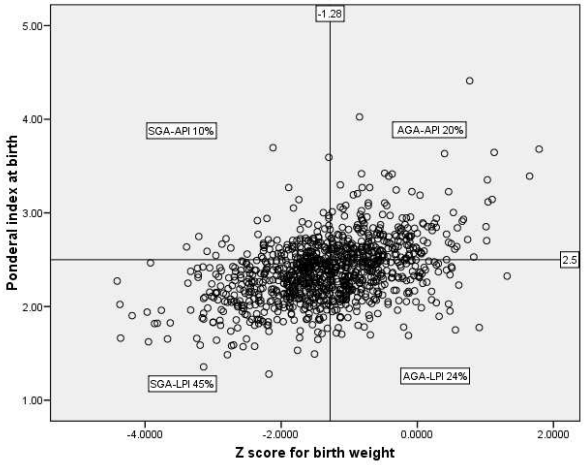
	AGA	SGA	Total
API Proportionate	103 (20.2%)	52 (10.2%)	155 (100%)
LPI Disproportionate	124 (24.3%)	232 (45.4%)	356 (100%)
Total	227 (44%)	284 (56%)	511 (100%)

API: Appropriate Ponderal Index (normal or stunted); LPI: Low Ponderal Index (wasted)
AGA: Appropriate for gestational age; SGA: Small for gestational age

Figure 6.6 shows a scatterplot of ponderal index against birth weight Z-score. Two intersecting lines pass through the cut-off point of 2.5 for ponderal index and -1.28 for weight for gestational age. The left upper quadrant represents proportionate SGA (SGA-API), the right upper quadrant proportionate AGA (AGA-API), the left lower quadrant disproportionate SGA

(SGA-LPI) and the right lower quadrant disproportionate AGA (AGA-LPI). Only one fifth of infants (103) were normal for both weight-for-gestational-age and PI (AGA-API), and one tenth were stunted SGA (SGA-API). 45% and 24% of newborns were disproportionate SGA (SGA-LPI) and disproportionate AGA respectively.

Figure 6.6. Scatterplot of Ponderal Index at birth against Birth Weigh Z score



6.5.8. Comparison of categorizations of size at birth: birth weight, ponderal index and weight for gestation

Table 6.11 presents categories of size based on a combination of all three classifications: birth weight, weight-for-gestational-age and PI. The total number of infants with data available for all three classifications was 513. The prevalence of LBW was 26%, of SGA 56%, and of low PI was 70%. The table includes a 'composite classification'. Because the combinations of categories are hard to visualize, we have tried to signpost them in terms of what sort of baby they represent. The descriptions are not always true for each infant, but they give an idea. For example, an infant who is AGA-LPI-NBW is of generally of normal size but has some wasting. This would tend to apply to term infants with some acute growth restriction. An infant who is SGA-API-LBW is of generally small size, is small for gestation but is proportionate. This would tend to apply to preterm infants with chronic growth restriction, or to term infants with chronic growth restriction.

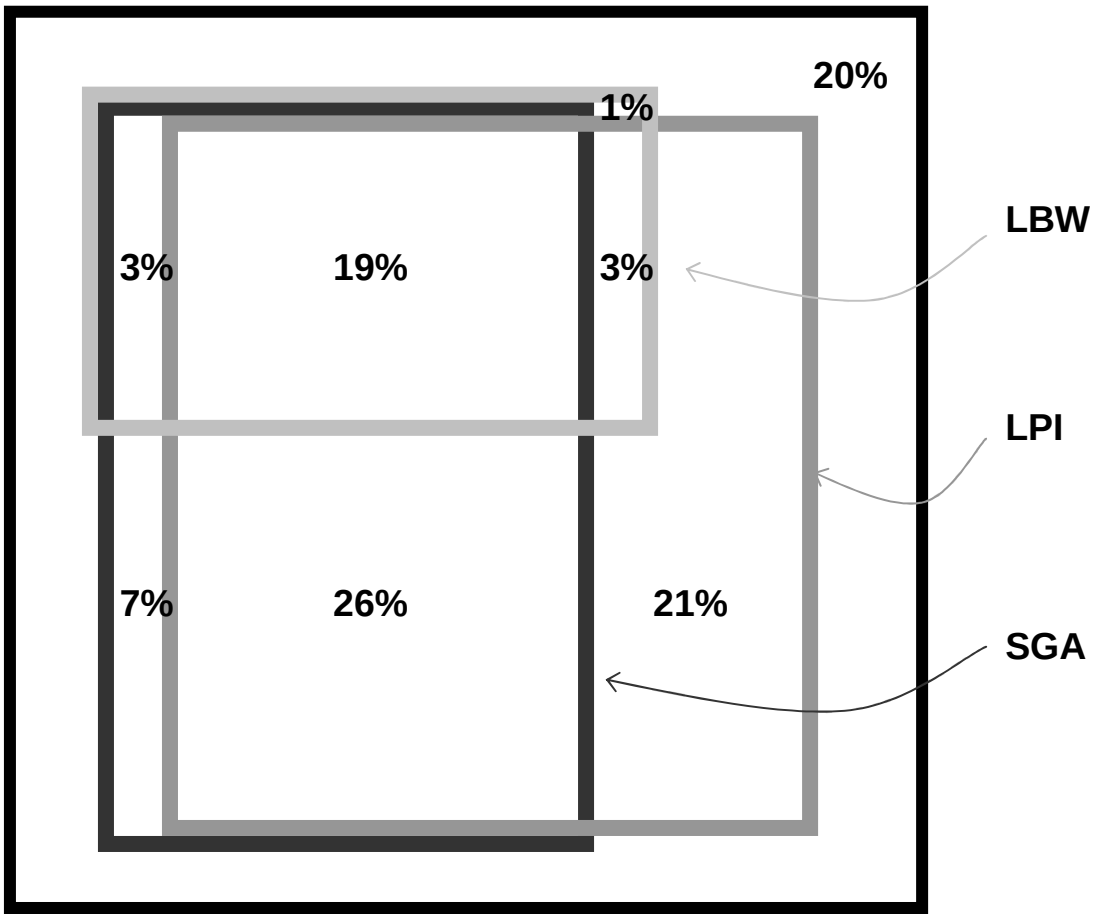
Table 6.11. Proportion of newborn infants based on birth weight, weight-for-gestational-age and ponderal index classification

Newborn Classification					
Weight for GA	**PI**	**Birth weight**	**Composite classification**	**Frequency**	**%**
AGA	API	NBW	Term	103	20.1
		LBW	Preterm (chronic GR)	2	0.4
	LPI	NBW	Term (acute GR)	109	21.2
		LBW	Preterm (acute GR)	15	2.9
SGA	API	NBW	Term (chronic GR)	38	7.4
		LBW	Preterm/term (chronic GR)	14	2.7
	LPI	NBW	Term (acute GR)	134	26.1
		LBW	Preterm/term (acute GR)	98	19.1
Total				513	100

GR: growth retardation; AGA: Appropriate for gestational age; SGA: Small for gestational age; API: Appropriate Ponderal Index (normal or stunted); LPI: Low Ponderal Index (wasted); NBW: Normal birth weight; LBW: low birth weight

To visualize the relationship between classifications based on three anthropometric parameters, we have presented a venn diagram (see Figure 6.7). The figure shows three small rectangles representing LBW, SGA and LPI and a large rectangle outside them representing infants with all normal features in every respect (AGA-API-NBW). The figure shows all the possible combinations of birth anthropometric categories. One fifth of infants were born with normal birth anthropometry in all three classifications (AGA-API-NBW: 20%). One fifth were abnormal in all three classifications (SGA-LPI-LBW: 19 %). One fifth had normal birth weight and were appropriate for gestational age, but were wasted (AGA-LPI-NBW: 20 %). One fourth had normal weight but were SGA and disproportionate (SGA-LPI-NBW: 26 %). Finally, 3% of infants had normal weight for gestational age, but were wasted and LBW (AGA-LBW-LPI).

Figure 6.7. Venn diagram of newborn size based on birth weight, ponderal index and weight for dates



Chapter 7. Results: Predictors of size at birth

7.1. Chapter summary

It is evident from the results in Chapter 6 that the problem of small size at birth is large from a public health perspective in Dhanusha district. Literature review suggests that size at birth has a strong association with infant morbidity and mortality and the aetiology of LBW has been well studied over decades. However, addressing the problem of small size at birth has not been successful. The study provided an ideal sample for testing a series of risk factors that are believed to affect size at birth. This chapter describes an extensive investigation of associations - maternal and fetal - of size at birth.

The objectives of the investigation were: 1) to examine the effects of known predictive factors of size at birth; 2) to develop models for prediction of abnormal size at birth; and 3) to investigate whether known risk factors predict size at birth adequately. However, the analysis had an ulterior motive. As suggested in the introductory chapters of the thesis, there is a feeling that the studies of risk factors are more about carrying out a study than achieving a public health change. Part of the reason for the analysis – its proposition before being carried out – was that we felt that it was unlikely to yield results that were either unpredictable or particularly useful, and that we were keen to make a statement about the redundancy of such approaches.

7.2. Relationship between variables

The Figure 7.1, Figure 7.2 and Figure 7.3 show scatterplots of birth weight, length and head circumference against independent variables used for the prediction of birth size. An examination of the relationship between independent variables showed a few outliers in maternal height and weight at booking.

Figure 7.1. Scatterplots of outcome (birth weight) against independent variables

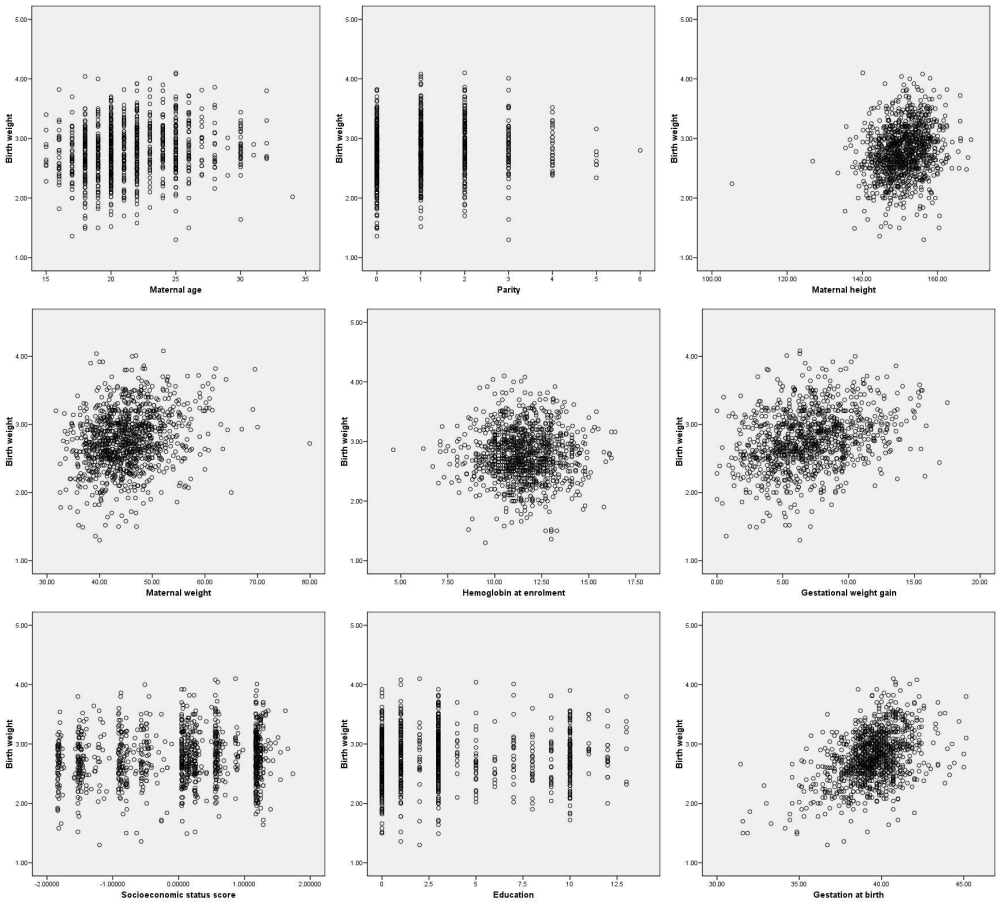


Figure 7.2. Scatterplot of birth length against independent variables

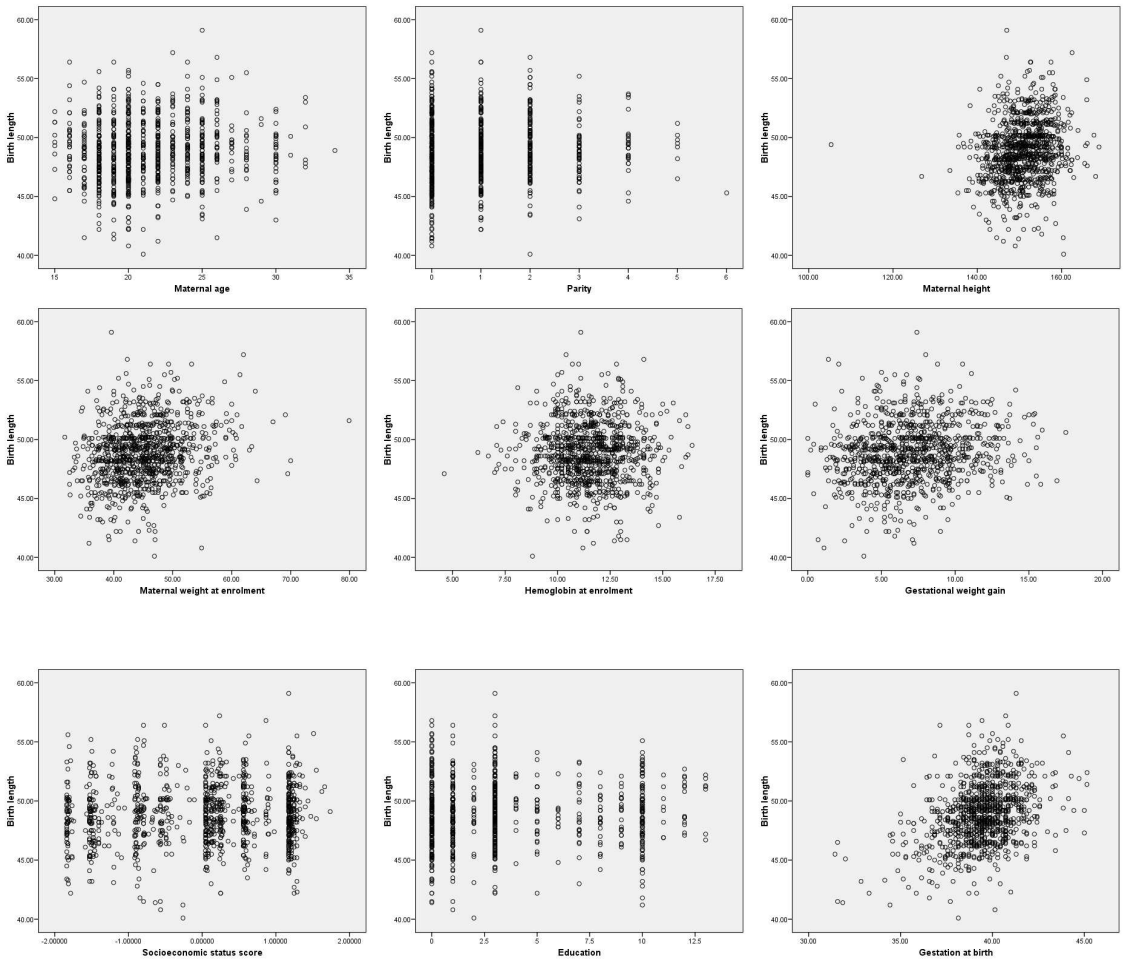
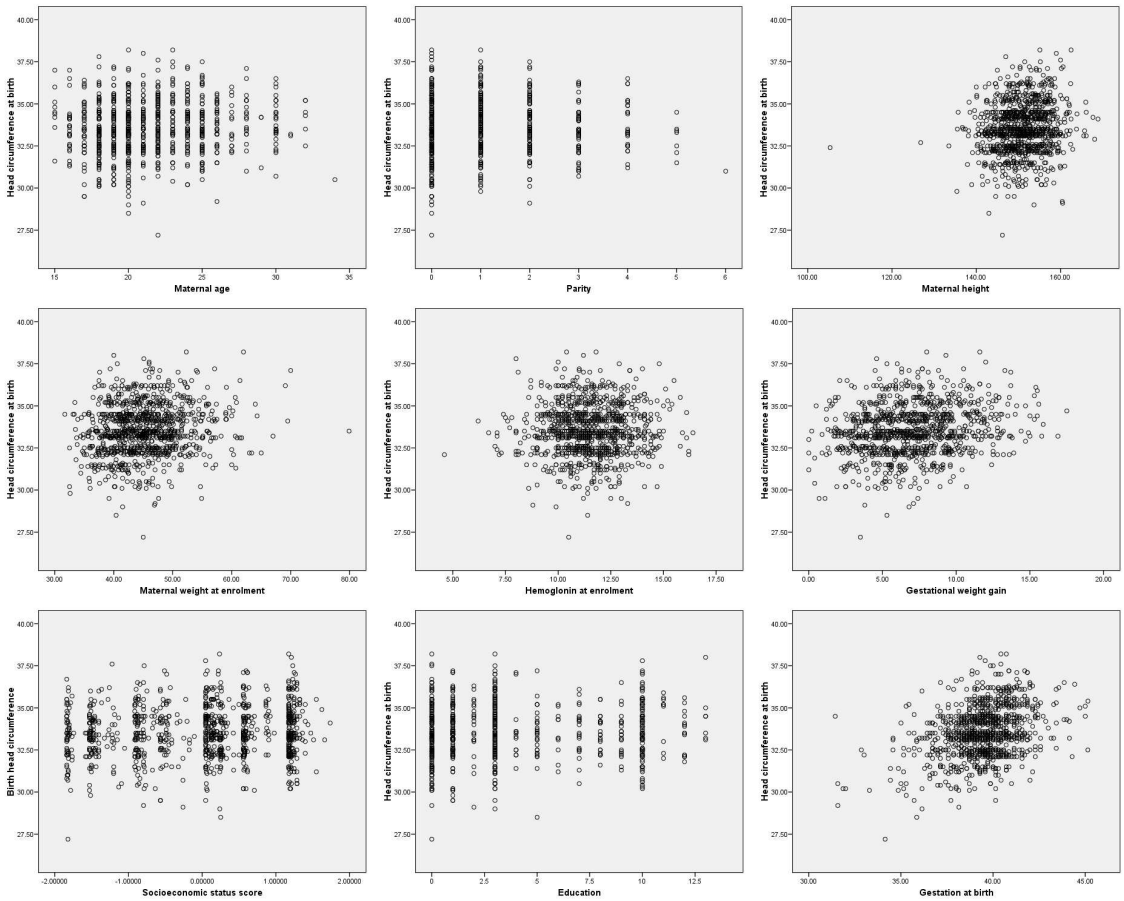


Figure 7.3. Scatterplot of head circumference at birth against independent variables



7.3. Characteristics of mothers

Of 1200 subjects enrolled in the randomized controlled trial, 1052 newborn infants were available for weighing within 72 hours of birth. Four preterm infants, extreme outliers for birth weight, were removed from the data. The number of participants available for analysis was 1048. The sample size was 1048 for birth weight and LBW, 1045 for SGA, 1035 for BMI, PI and low PI, and 1039 for head circumference. Participants' characteristics at enrolment for 1048 women are shown in Table 7.1. As mentioned in the previous section (which considered a sub-cohort of 600), most participants were middle-income Hindu Maithili women in their twenties, in their second pregnancy, with monthly antenatal visits, low mean BMI and some education. Around 1% said they had suffered eclampsia (as convulsions associated with pregnancy).

Table 7.1. Participants with valid infant anthropometry: characteristics at enrolment

Variables	Frequency [n = 1048]	(%)
Residence		
Urban	546	(52.1)
Rural	502	(47.9)
Education [mean (SD)]	4.7	(4.7)
None	474	(45.2)
Primary	101	(9.6)
Secondary	473	(45)
Age (y) [mean (SD)]	21.45	(3.42)
Ethnicity		
Terai Brahmin-Chhetri	172	(16.4)
Terai Vaishya	693	(66.1)
Terai Sudra	25	(2.4)
Hindu Brahmin-Chhetri	62	(5.9)
Muslim	65	(6.2)
Newar, Tibetoburman or others	31	(2.9)
Religion		
Hindu	978	(93.3)
Muslim	64	(6.1)
Buddhist	6	(0.6)
Land Owned (kattha) [mean (SD)]	21.9	(44.9)
Husband's occupation		
No work	122	(11.6)
Farming	153	(14.5)
Salaried	450	(42.9)
Small business	192	(18.3)
Waged labour	104	(9.9)
Student	13	(1.2)
Out of country	14	(1.3)
Ownership of consumer durables		
(3) Motor vehicle, television, refrigerator	554	(52.9)
(2) Sewing machine, cassette player, camera, fan, bullock cart	48	(4.6)
(1) Clock, radio, iron, bicycle	289	(27.6)
(0) None of the above	157	(15)
Anthropometry		
Weight (kg) [mean (SD)]	45.26	(5.95)
Height (cm) [mean (SD)]	150.9	(5.6)
BMI (kg/m^2) [mean (SD)]	19.9	(2.3)
Nutritional status		
Blood haemoglobin (g/dl) [mean (SD)]	11.53	(1.57)
Anaemia (<11 g/dl)	362	(34.9)
Weight gain between 15.9 wks and last visit before delivery (Kg) [mean (SD)]	7.06	(3.04)
Multiple micronutrient supplements	526	(50.2)
Health Status		
Systolic Blood pressure (mmhg) [mean (SD)]	103.56	(9.60)
Diastolic Blood Pressure (mmhg) [mean (SD)]	63.11	(7.65)
Eclampsia	7	(0.7)
Obstetric History		
Primigravida	472	(45)
Prior miscarriage [n = 1046]	86	(9.2)
Prior history of LBW infant [n = 1044]	22	(2.1)
Prior Still Birth [n 1046]	64	(6.1)

Data are n (%) unless otherwise indicated.

7.4. Predictors of birth weight

The corresponding results of the univariable and multivariable analysis for all the outcomes are presented. The final prediction models present the variables based on significance level. Among the likely determinants of birth weight listed in Table 7.2, the univariable analysis showed that the significant predictors were: ethnic group, maternal age and education; maternal parity; maternal height and weight; maternal weight gain and antenatal supplementation; and sex and gestation at birth.

Table 7.2. Univariable analysis of associations with birth weight

Parameters n = 1048	β	(95% CI)	P value
Maternal factors			
Ethnicity	0.027	(0.012 – 0.043)	0.001
Terai Brahmin	Reference		
Terai Chhetri	0.028	(-0.127 – 0.184)	0.7
Terai Vaishya	-0.077	(-0.155 – 0.001)	0.05
Terai Sudra	-0.176	(-0.352 - 0.003)	0.06
Hindu Brahmin	0.061	(-0.095 – 0.216)	0.4
Hindu Chhetri	0.028	(-0.150 – 0.206)	0.8
Muslim	0.102	(-0.023 – 0.227)	0.1
Newar	-0.038	(-0.288 – 0.212)	0.8
Other small ethnic groups	0.379	(-0.175 – 0.582)	0.001
Demographic			
Education level in years	0.012	(0.006 – 0.017)	0.001
Residence urban or rural	0.017	(-0.035 – 0.069)	0.5
Socioeconomic status in scores	-0.013	(-0.039 – 0.013)	0.3
Age	0.019	(0.011 – 0.026)	0.001
Morbidity			
Systolic Blood Pressure at enrolment	0.001	(-0.001 – 0.004)	0.3
Diastolic Blood Pressure at enrolment	0.002	(-0.001 – 0.006)	0.2
2nd trimester morbidity I ‡	0.002	(-0.024 – 0.028)	0.9
None	Reference		
Abdominal complaints	0.050	(-0.022 – 0.122)	0.2
Infections	0.081	(-0.047 – 0.209)	0.2
Other	-0.021	(-0.103 – 0.062)	0.7
2nd trimester morbidity II †	0.009	(-0.020 – 0.039)	0.5
None	Reference		
Abdominal complaints	-0.061	(-0.177 – 0.055)	0.3
Infections	0.027	(-0.159 – 0.213)	0.8
Other	0.037	(-0.056 – 0.131)	0.4
3rd trimester morbidity I ‡	0.003	(-0.022 – 0.028)	0.8
None	Reference		
Abdominal complaints	0.025	(-0.044 – 0.094)	0.4
Infections	0.153	(0.013 – 0.293)	0.03
Other	-0.019	(-0.098 – 0.061)	0.6
3rd trimester morbidity II †	0.015	(-0.017 – 0.048)	0.4
None	Reference		
Abdominal complaints	-0.071	(-0.212 - 0.071)	0.3
Infections	0.168	(0.001 – 0.336)	0.05
Other	0.026	(-0.080 – 0.132)	0.6
Eclampsia at birth	-0.118	(-0.437 – 0.202)	0.5
Obstetric history			
Parity	0.054	(0.0031 – 0.078)	0.001
Prior small infant [193;194]	-0.016	(-0.186 – 0.153)	0.9
Prior miscarriage [195;196]	0.063	(-0.006 – 0.131)	0.07
Prior stillbirth[197]	-0.042	(-0.124 – 0.041)	0.3
Prior child death[197]	-0.004	(-0.052 – 0.044)	0.9
Anthropometry			
Height	0.017	(0.012 – 0.021)	0.001
Weight[198;199]	0.018	(0.014 – 0.022)	0.001
Nutrition			
Gestational weight gain	0.042	(0.034 – 0.051)	0.001
Hemoglobin status	0.001	(-0.017 – 0.016)	0.9
Supplements[3]	0.081	(0.029 – 0.133)	0.002
Fetal factors			
Sex	0.101	(0.049 – 0.153)	0.001
Gestational duration	0.111	(0.098 – 0.125)	0.001

‡: First complaints of antenatal illness in the specified trimester †: Second complaints of antenatal illness in the specified trimester

Table 7.3 presents the final prediction model and adjusted R^2 in multivariable analysis for birth weight. The strongest predictors of birth weight were gestation, gestational weight gain, infant sex, maternal weight at enrolment and parity (p = 0.001), followed by antenatal supplementation, maternal height and education level. 33 % of the variance in the birth weight was explained by these variables.

Each Kilogram increase in gestational weight gain predicted a 27 g increase in birth weight, and every centimetre increase in maternal height increased birth weight by 5 g. Taking supplements during pregnancy translated into an increase of 58 g in birth weight. Maternal education had small positive effects on birth weight. A woman who had a unit more education gave birth to a heavier infant by 6 g. The effect of gestational duration on birth weight was the strongest. For every week increase in gestation a 89 g increase in birth weight was predicted. Male infants were a mean 118 g heavier than females. A mother who had children was more likely to give birth to a heavier infant than a mother who never had children before; the difference was a mean 109 g.

Table 7.3. Multivariable analysis of associations with birth weight

Predictors of birth weight (kg) n=1048	β (95% CI)	T	P value	R^2
Gestation (wks)	0.089 (0.076 – 0.102)	13.19	0.001	0.327
Maternal weight gain (kg)	0.027 (0.020 – 0.035)	7.144	0.001	
Male sex	0.118 (0.075 – 0.162)	5.353	0.001	
Maternal weight at enrolment (kg)	0.012 (0.007 – 0.016)	5.241	0.001	
Multiparity	0.109 (0.055 – 0.164)	3.928	0.001	
Supplement	0.058 (0.014 – 0.101)	2.596	0.01	
Maternal height (cm)	0.005 (0.001 – 0.009)	2.053	0.04	
Education	0.006 (0.001 – 0.011)	1.973	0.05	

Figure 7.4, Figure 7.5 and Figure 7.6 show the histograms of residuals, normal probability plot and residual plot, respectively. The histogram of residuals produced by the model confirms a fairly normal distribution. The normal probability plot shows residuals lying around the diagonal line. The residual plot shows points scattered randomly around 0, showing no obvious patterns in the residual distribution. The plots indicate that the normality assumption is satisfied.

Figure 7.4. Histogram of residuals for birth weight

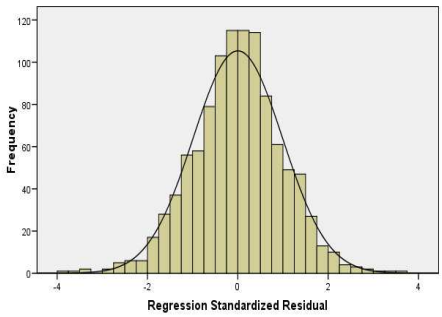


Figure 7.5. Normal probability plot for birth weight

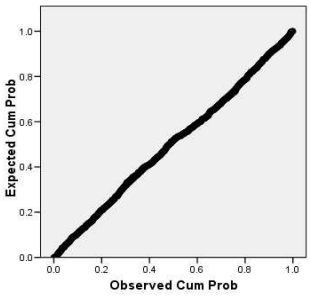
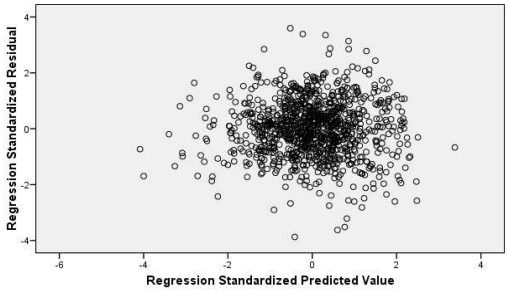


Figure 7.6. Residual plot for birth weight



7.5. Predictors of low birth weight

The univariable associations between LBW and the independent variables are shown in Table 7.4. LBW showed a positive association with maternal education, age, parity, weight, height, weight gain, antenatal supplementation, gestational age at birth and infant sex. Maternal age, education and parity explored as categorical variables also showed positive associations with LBW. There was no association with ethnicity, residence, socioeconomic status, antenatal morbidity and previous adverse obstetric history (death of children, miscarriage and birth of a LBW infant).

Table 7.4. Univariable analysis of associations with low birth weight

Parameters n=1048	β	(95% CI)	P value
Maternal factors			
Ethnicity	0.96	(0.87 – 1.05)	0.3
Terai Brahmin	reference		
Terai Chhetri	0.42	(0.14 – 1.29)	0.1
Terai Vaishya	1	(0.65 – 1.55)	0.9
Terai Sudra	2.1	(0.87 – 5.13)	0.1
Hindu Brahmin	0.97	(0.40 – 2.34)	0.9
Hindu Chhetri	0.62	(0.20 – 1.92)	0.4
Muslim	0.69	(0.32 – 1.48)	0.3
Newar	0.68	(0.14 – 3.26)	0.6
Other small ethnic groups	0.64	(0.17 – 2.32)	0.5
Demographic factors			
Education	0.96	(0.93 – 0.99)	0.007
Residence	0.96	(0.72 – 1.29)	0.8
Socioeconomic status	1.07	(0.93 – 1.24)	0.4
Age (category)	0.91	(0.86 – 0.95)	0.001
Morbidity			
Eclampsia	2.67	(0.59 – 12.04)	0.2
Systolic Blood Pressure at enrolment	0.99	(0.98 – 1.01)	0.5
Diastolic Blood Pressure at enrolment	0.99	(0.97 – 1.01)	0.2
2nd trimester morbidity I	1	(0.86 – 1.15)	1
None	Reference		
Abdominal complaints	0.77	(0.50 – 1.18)	0.2
Infections	0.61	(0.27 – 1.38)	0.2
Other complaints	1.12	(0.71 – 1.17)	0.6
2nd trimester morbidity II	0.91	(0.76 – 1.09)	0.3
None	Reference		
Abdominal complaints	0.94	(0.49 – 1.81)	0.9
Infections	0.57	(0.17 – 1.97)	0.4
Other complaints	0.81	(0.47 – 1.41)	0.5
3rd trimester morbidity I	0.99	(0.86 - 1.14)	0.9
None	Reference		
Abdominal complaints	0.72	(0.48 – 1.09)	0.1
Infections	0.50	(0.19 – 1.31)	0.2
Other complaints	1.09	(0.70 – 1.67)	0.7
3rd trimester morbidity II	0.86	(0.70 – 1.05)	0.1
None	Reference		
Abdominal complaints	0.97	(0.44 – 2.16)	0.9
Infections	0.28	(0.07 – 1.21)	0.09
Other complaints	0.73	(0.38 – 1.38)	0.3
Obstetric history			
Parity (category)	0.76	(0.65 – 9.88)	0.001
Prior small infant	1.81	(0.79 – 4.17)	0.2
Prior miscarriage	0.65	(0.40 – 1.05)	0.08
Prior stillbirth	1.35	(0.90 – 2.05)	0.2
Prior death of child	1.04	(0.80 – 1.35)	0.8
Anthropometry			
Height	0.93	(0.91 – 0.96)	0.001
Weight	0.94	(0.91 – 0.96)	0.001
Nutrition			
Weight gain	0.82	(0.77 – 0.86)	0.001
Blood haemoglobin	1.02	(0.93 – 1.12)	0.6
Supplements	0.69	(0.51 – 0.92)	0.01
Fetal factors			
Sex	0.55	(0.41 – 0.74)	0.001
Gestation at birth	0.62	(0.56 – 0.69)	0.001

Table 7.5 shows significant predictors of LBW derived from multivariable logistic regression analysis of significant variables from univariable analysis. The final model identified six statistically significant predictors. Among the predictors, there was a strong negative association between LBW and gestation at birth, maternal weight gain and infant sex.

Table 7.5. Multivariable analysis of associations with low birth weight, with odds ratios

Predictors of low birth weight N = 1048	Odds ratio	(95% CI)	Wald	P value
Birth gestation (wks)	0.65	(0.58 – 0.72)	61.4	0.001
Maternal weight gain (Kg)	0.85	(0.80 – 0.91)	24.8	0.001
Male sex	0.45	(0.32 – 0.64)	20.5	0.001
Maternal Weight at enrolment (Kg)	0.96	(0.92 – 0.99)	5.8	0.02
Supplementation	0.71	(0.51 – 0.99)	3.96	0.05
Multiparity	0.66	(0.44 – 1.00)	3.87	0.05

The odds of giving birth to an infant with LBW for a mother who was 1 Kg heavier at enrolment and who gained 1 extra Kg of weight during pregnancy were 4% (OR 0.96; 95% CI 0.92 - 0.99) and 15% (0.85; 0.80 -0.91) lower respectively. Increasing gestational duration by 1 week lowered the odds by 35%. Similarly, multigravid mothers had a lower odds of giving birth to a LBW infant (0.66; 0.44 – 0.99) compared to mothers in their first pregnancy. Antenatal supplementation lowered the odds of LBW by 30%. A mother bearing a male fetus had 55% lower odds of delivering a LBW infant. Positive associations between LBW and maternal age, height and education disappeared when other variables were taken into consideration.

7.6. Predictors of small for gestational age

The sample available for analysis was 1044. Four cases were removed due to missing data. The results of univariable analysis with regression coefficients and 95% confidence interval are shown in Table 7.6. Significant variables that were entered into the multivariable logistic regression were socioeconomic status, maternal age, parity, prior history of miscarriage, weight, height, weight-gain, supplementation during pregnancy and gestation at birth.

Table 7.6. Univariable analysis of associations with small for gestational age

Parameters N = 1044	β	(95% CI)	P value
Ethnicity			0.1
Terai Brahmin	reference		
Terai Chhetri	0.84	(0.40 – 1.76)	0.7
Terai Vaishya	1.12	(0.77 – 1.61)	0.6
Terai Sudra	1.10	(0.47 – 2.55)	0.8
Hindu Brahmin	0.84	(0.40 – 1.76)	0.7
Hindu Chhetri	1.10	(0.47 – 2.55)	0.8
Muslim	0.67	(0.37 – 1.22)	0.2
Newar	0.94	(0.29 – 3.07)	0.9
Other small ethnic groups	0.25	(0.08 – 0.80)	0.02
Demographic			
Education	0.99	(0.96 – 1.03)	0.6
Residence (urban or rural)	0.98	(0.77 – 1.25)	0.9
Socioeconomic status	0.85	(0.75 – 0.96)	0.01
Age	0.96	(0.93 – 1.0)	0.04
Morbidity			
Eclampsia	2.33	(0.45 – 12.05)	0.3
Systolic Blood Pressure at enrolment	1.00	(0.99 – 1.02)	0.6
Diastolic Blood Pressure at enrolment	1.00	(0.99 – 1.02)	0.9
2^{nd} trimester morbidity I	0.99	(0.88 – 1.12)	0.8
0 Reference category	0.86	(0.62 – 1.21)	
1 Abdominal complaints	0.83	(0.46 – 1.50)	
2 Infections	1.05	(0.46 – 1.50)	
3 Other complaints	1.11	(0.71 – 1.54)	
2^{nd} trimester morbidity II	0.97	(0.85 – 1.12)	0.7
0 Reference category			
1 Abdominal complaints	0.85	(0.50 – 1.46)	
2 Infections	1.49	(0.61 – 3.62)	
3 Other complaints	0.88	(0.57 – 1.35)	
3^{rd} trimester illness I	0.96	(0.85 – 1.08)	0.5
0 Reference category			
1 Abdominal complaints	0.83	(0.60 – 1.14)	
2 Infections	0.84	(0.43 – 1.62)	
3 Other complaints	0.92	(0.64 – 1.33)	
3^{rd} trimester illness II	0.87	(0.74 – 1.01)	0.06
0 Reference category			
1 Abdominal complaints	0.75	(0.39 – 1.45)	
2 Infections	0.47	(0.21 – 1.06)	
3 Other complaints	0.74	(0.45 – 1.21)	
Obstetric history			
Parity	0.88	(0.79 – 0.98)	0.02
Prior LBW infant	1.20	(0.54 – 2.67)	0.7
Prior miscarriage	0.67	(0.48 – 0.94)	0.02
Prior stillbirth	1.11	(0.75 – 1.63)	0.6
Prior child death	0.97	(0.77 – 1.21)	0.8
Anthropometry			
Height	0.94	(0.92 – 0.96)	0.001
Weight	0.93	(0.91 – 0.95)	0.001
Nutrition			
Weight gain (Kg)	0.92	(0.89 – 0.96)	0.001
Blood haemoglobin (g/dL)	1.03	(0.95 – 1.11)	0.5
Supplements	0.77	(0.60 – 0.98)	0.04
Fetal factors			
Sex	0.84	(0.66 – 1.06)	0.1
Gestation at birth	1.27	(1.18 – 1.38)	0.001

Table 7.7 shows the results of the multivariable regression analysis. The strongest predictors of SGA were maternal weight at enrolment, gestational weight gain and parity. Another predictor was antenatal supplementation. A woman who was 1 Kg heavier at enrolment and who gained 1 Kg more weight during pregnancy had 6% lower odds of giving birth to a SGA infant (OR 0.94; 95% CI 0.92 – 0.97 and 0.94; 0.92 – 0.98, respectively) when maternal education, parity, prior history of miscarriage, height, antenatal supplementation and infant sex were taken into consideration. With a unit increase in parity, mothers had 0.19 times lower odds of giving birth to a SGA infant when other factors were taken into consideration. Women who received supplementation had 0.29 times lower odds of giving birth to a SGA infant when other factors entered in the model were controlled for.

Table 7.7. Multivariable analysis of associations with small for gestational age, with odds ratios

Predictors of Small for Gestational Age N = 1044	Odds ratio	(95% CI)	Wald	P value
Maternal weight at enrolment (Kg)	0.94	(0.92 – 0.97)	18.22	0.001
Maternal weight gain (Kg)	0.94	(0.92 – 0.98)	7.32	0.007
Parity	0.81	(0.69 – 0.95)	6.81	0.009
Antenatal supplementation	0.71	(0.55 – 0.92)	6.6	0.01

7.7. Predictors of birth length

The sample available for analysis was 1033. Six participants did not have measurements of birth length and nine implausible outliers were removed from the dataset. The univariable associations of independent variables with birth length are shown in Table 7.8. Birth length showed an association with systolic blood pressure at enrolment (p=0.02). An association with diastolic blood pressure was possible but not significant (p=0.07). No associations were significant in the obstetric history category except prior history of death of a child. For maternal anthropometry, maternal height and weight at enrolment showed strong associations. Gestational weight also had a significant association with birth length. Other significant variables were maternal age, fetal sex and gestation at birth. There was no association with socioeconomic status (p=0.06) but it was almost significant.

Table 7.8. Univariable analysis of associations with birth length

Parameters N = 1033	β	(95% CI)	P value
Maternal factors			
Ethnicity	0.094	(0.001 – 0.186)	0.001
Terai Brahmin	Reference		
Terai Chhetri	-0.173	(-1.108 – 0.762)	0.7
Terai Vishya	-0.386	(-0.852 – 0.080)	0.1
Terai Sudra	-1.284	(-2.339 - -0.229)	0.02
Hindu Brahmin	0.141	(-0.794 – 1.076)	0.8
Hindu Chhetri	0.265	(-0.807 – 1.338)	0.6
Muslim	0.265	(-0.487 – 1.018)	0.5
Newar	-0.635	(-2.119 – 0.848)	0.4
Other small ethnic groups	1.498	(0.262 – 2.736)	0.02
Demographic			
Education	0.030	(-0.012 – 0.073)	0.2
Residence	0.108	(-0.200 – 0.417)	0.5
Socioeconomic status	0.148	(-0.006 – 0.302)	0.06
Age	0.058	(0.013 – 0.103)	0.01
Morbidity			
Eclampsia	0.018	(-3.286 - 0.469)	0.1
Systolic blood pressure at enrolment	0.018	(0.003 – 0.034)	0.02
Diastolic blood pressure at enrolment	0.019	(-0.001 – 0.039)	0.07
2nd trimester morbidity	0.076	(-0.077 – 0.228)	0.3
None	Reference		
Abdominal problem	0.031	(-0.394 – 0.456)	0.9
Infection	0.728	(-0.034 - 1.489)	0.06
Other	0.127	(-0.362 – 0.616)	0.6
2nd trimester morbidity	-0.009	(0.090)	0.9
None	Reference		
Abdominal problem	-0.403	(-1.098 – 0.292)	0.3
Infection	0.638	(-0.455 – 1.732)	0.3
Other	-0.025	(-0.574 – 0.523)	0.9
3rd trimester general illness	0.027	(-0.122 – 0.177)	0.7
None	Reference		
Abdominal problem	0.285	(-0.122 – 0.692)	0.2
Infection	-0.097	(-0.945 – 0.750)	0.8
Other	0.058	(-0.415 – 0.531)	0.8
3rd trimester general illness	0.031	(-0.161 – 0.222)	0.8
None	Reference		
Abdominal problem	0.350	(-0.482 – 1.181)	0.4
Infection	0.005	(-0.982 – 0.991)	1
Other	0.072	(-0.551 – 0.695)	0.8
Obstetric history			
Parity	0.121	(-0.018 – 0.260)	0.09
Prior small infant	-0.375	(-1.396 – 0.647)	0.5
Prior miscarriage	0.061	(-0.349 - 0.472)	0.8
Prior still birth	-0.306	(-0.793 – 0.181)	0.2
Prior death of child	-0.297	(-0.581 - -0.013)	0.04
Anthropometry			
Height	0.086	(0.059 – 0.113)	0.001
Weight	0.093	(0.067 – 0.118)	0.001
Nutrition			
Weight gain	0.141	(0.090 – 0.193)	0.001
Blood haemoglobin	0.016	(-0.083 – 0.114)	0.8
Supplements	0.190	(-0.118 – 0.498)	0.2**
Fetal factors			
Sex	0.583	(0.277 – 0.890)	0.001
Gestation at birth	0.538	(0.453 – 0.622)	0.001

The coefficients and standard errors of the significant variables in the multivariable linear regression model for this population are presented in Table 7.9. The results indicate that the strongest predictor of infant birth length was gestational duration. The other predictors were infant sex, maternal weight at enrolment and antenatal weight gain, followed by maternal height. Among the variables that were significant in the univariable analysis, maternal ethnicity, education, age, systolic and diastolic blood pressure did not remain significant when other variables were accounted for.

Each week increase in gestational duration was associated with a 4.7 mm increase in infant birth length. Being male was likely to increase birth length by 6.6 mm. Each cm increase in maternal height and each Kg increase in maternal weight at enrolment was likely to increase birth length by 3 mm and 5 mm, respectively. Every kilogram increase in maternal weight gain was associated with an increase in birth length by 7 mm. Similarly, a mother with a unit increase in the number of children who died was associated with a decrease in the length of the index newborn by 2.9 mm.

This optimal model for birth length had a low adjusted R^2 of 0.19. The model was able to explain about 19% of the variance in the length of an infant at birth. The tolerances for variables in the regression model were not close to zero and the variance inflation factors (VIF) were below 10 for all variables.

Table 7.9. Multivariable analysis of associations with birth length, with odds ratios

Predictors of birth length in cm N = 1033	β	(95% CI)	t	P	R^2
Birth gestation (weeks)	0.47	(0.38 -0.55)	10.79	0.001	0.19
Male sex	0.66	(0.38 – 0.94)	4.64	0.001	
Maternal weight at enrolment (Kg)	0.05	(0.02 – 0.08)	3.59	0.001	
Maternal weight gain (Kg)	0.07	(0.03 – 0.12)	2.95	0.003	
Maternal height (cm)	0.03	(0.00 – 0.06)	2.20	0.028	
Prior death of child	-0.29	(-0.57 - -0.02)	-2.07	0.039	

Figure 7.7 shows a roughly normal distribution of residuals for birth length. The standardized normal probability plot shows residuals falling randomly across the diagonal line (Figure 7.9) The standardized residuals plotted against the standardized predicted values show no obvious patterns (Figure 7.8). All these indicate that the model is adequate.

Figure 7.7. Histogram of residuals for birth length

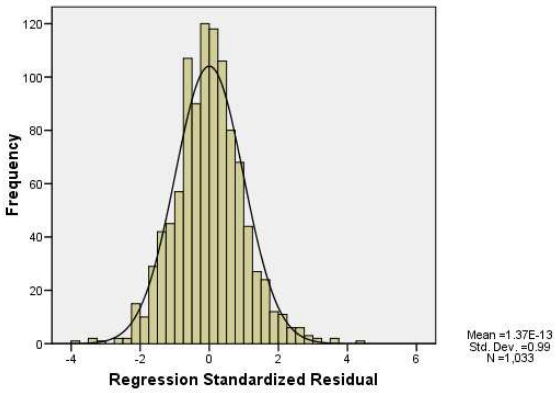


Figure 7.9. Normal probability plot for birth length

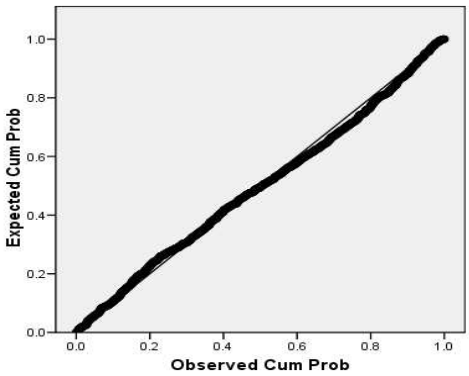
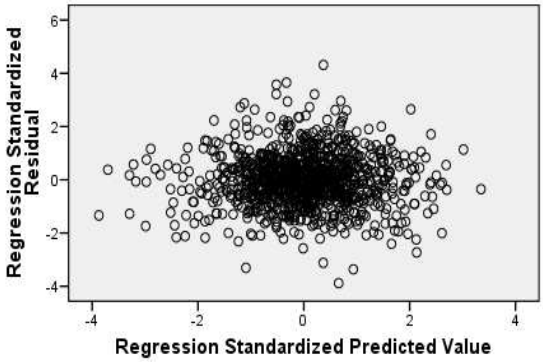


Figure 7.8. Residual plot for birth length



7.8. Predictors of body mass index at birth

The sample available for analysis was 1034. The univariable associations of BMI at birth and possible determinants of size at birth are shown in Table 7.10. The analysis showed that ten variables were significantly associated with BMI at birth: ethnicity, socioeconomic status, age, parity, height, weight, antenatal weight gain, antenatal supplementation, age, infant sex and gestational age at birth.

Table 7.10. Univariable analysis of associations of body mass index

Parameters n = 1033	β	(95% CI)	P value
Maternal factors			
Ethnicity	0.071	(0.016 – 0.126)	0.01
Terai Brahmin	Reference		
Terai Chhetri	0.201	(-0.355 – 0.758)	0.5
Terai Vishya	-0.110	(-0.388 – 0.167)	0.4
Terai Sudra	-0.093	(-0.721 – 0.535)	0.8
Hindu Brahmin	0.154	(-0.402 – 0.711)	0.6
Hindu Chhetri	0.076	(-0.562 – 0.715)	0.8
Muslim	0.345	(-0.103 – 0.793)	0.1
Newar	0.158	(-0.725 – 1.041)	0.7
Other small ethnic groups	0.840	(0.104 – 1.576)	0.03
Demographic			
Education	0.014	(-0.012 – 0.039)	0.3
Residence	-0.002	(-0.185 – 0.182)	0.9
Socioeconomic status	0.135	(0.044 – 0.226)	0.004
Age	0.050	(0.023 – 0.076)	0.001
Morbidity			
Eclampsia	0.177	(-0.938 – 1.291)	0.8
Systolic Blood Pressure at enrolment	-0.002	(-0.012 – 0.007)	0.7
Diastolic Blood Pressure at enrolment	0.001	(-0.011 – 0.013)	0.9
2nd trimester illness I	-0.011	(-0.101 – 0.079)	0.8
None	Reference		
Abdominal complaints	0.194	(-0.059 – 0.446)	0.1
Infections	-0.031	(-0.483 – 0.421)	0.9
Other	-0.086	(-0.376 – 0.204)	0.6
2nd trimester illness II	0.041	(-0.062 – 0.144))	0.4
None	Reference		
Abdominal complaints	-0.007	(-0.419 – 0.405)	1
Infections	-0.198	(-0.847 - 0.451)	0.6
Other	0.166	(-0.160 – 0.491)	0.3
3rd trimester illness I	0.015	(-0.073 – 0.104)	0.7
None	Reference		
Abdominal complaints	-0.015	(-0.256 – 0.225)	0.9
Infections	0.629	(0.127 – 1.130)	0.01
Other	-0.045	(-0.325 – 0.235)	0.8
3rd trimester illness II	0.045	(-0.068 – 0.159)	0.4
None	Reference		
Abdominal complaints	-0.451	(-0.943 – 0.040)	0.07
Infections	0.706	(0.123 – 1.289)	0.02
Other	0.052	(-0.317 – 0.420)	0.8
Obstetric			
Multiparity	0.455	(0.273 – 0.636)	0.001
Prior LBW infant	0.045	(-0.561 – 0.651)	0.9
Prior miscarriage	0.189	(-0.054 – 0.432)	0.1
Prior stillbirth	-0.022	(-0.311 – 0.267)	0.9
Prior death of child	0.088	(-0.081 – 0.257)	0.3
Anthropometry			
Height	0.031	(0.051 – 0.047)	0.001
Weight	0.036	(0.020 – 0.051)	0.001
Nutrition			
Weight gain	0.111	(0.081 – 0.141)	0.001
Blood haemoglobin	-0.012	(-0.071 – 0.046)	0.7
Supplements	0.216	(0.034 – 0.398)	0.02
Fetal factors			
Sex	0.189	(0.007 – 0.372)	0.04
Gestation at birth	0.222	(0.171 – 0.274)	0.001

All the variables with significant associations were entered in the multivariable linear regression. The effect of prior history of giving birth to a small infant was also explored for their effect on the model. These variables did not change the coefficients significantly. Table 7.11 displays the results of the multivariable regression analysis for newborn BMI. The final model contained six variables, which explained 12% of the variation in BMI. The variables which were strongly associated with BMI at birth were gestational age at birth, gestational weight gain and parity. Other predictors in the model were maternal weight at enrolment, infant sex and antenatal supplementation. The variables that were insignificant when other variables were taken into account were maternal age, ethnicity and socioeconomic status.

Each week increase in gestational duration increased BMI at birth by 0.162 Kg/m^2. Similarly, a unit increase in maternal weight gain translated into an increase in infant BMI by 0.082 kg/m^2. Multigravid mothers were more likely to give birth to bigger babies than women in their first pregnancy: there was an increase in infant BMI by 0.375 kg/m^2. Male infants tended to be bigger than female infants by 0.220 kg/m^2. Supplementation of mothers increased infant BMI by 0.189 kg/m^2. Similarly, heavier mothers were likely to give birth to bigger infants. A gram increase in maternal weight increased infant BMI by 0.022 kg/m^2.

Table 7.11. Multivariable analysis of associations of body mass index

Predictors of BMI (Kg/m^2) N = 1033	β (95%CI)	t-value	P-value	Adjusted R^2
Birth Gestation (w)	0.162 (0.110 – 0.215)	6.05	0.001	0.124
Maternal weight gain (Kg)	0.082 (0.051 – 0.112)	4.99	0.001	
Multigravida	0.375 (0.159 – 0.590)	3.42	0.001	
Maternal weight at enrolment (Kg)	0.022 (0.005 – 0.039)	2.49	0.01	
Male sex	0.220 (0.049 – 0.392)	2.52	0.01	
Antenatal supplements	0.189 (0.001 – 0.379)	1.96	0.05	

The tolerances were not close to 0 and Variance Inflation Factors were less than 10. Figure 7.10 demonstrates the distribution of the residuals. It shows that the residuals were somewhat normally distributed. Figure 7.11 is the normal probability plot which shows no obvious outliers. Similarly, Figure 7.12, a plot of predicted values against residuals, shows that the residuals were roughly normally distributed. In summary, the residual analysis showed that the residuals followed the normality assumption

Figure 7.10. Histogram of residuals for body mass index

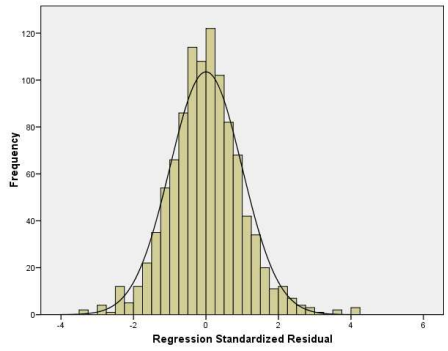


Figure 7.11. Normal probability plot for body mass index at birth

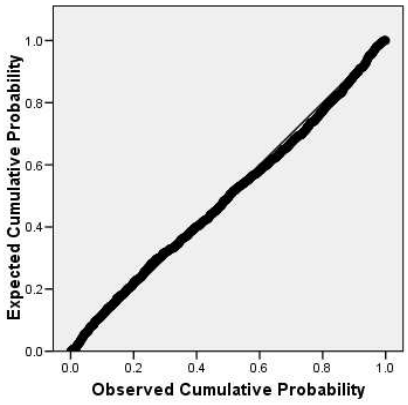
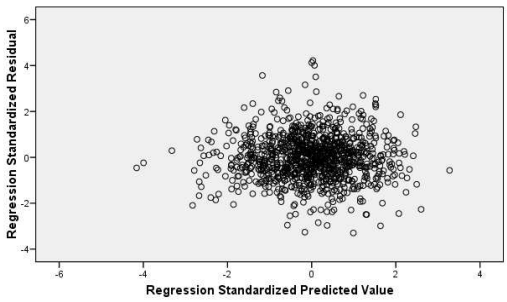


Figure 7.12. Residual plot for body mass index at birth



7.9. Predictors of ponderal index at birth

The univariable associations of variables with PI are presented in Table 7.12. The factors significantly related to PI at birth in the linear regression analysis were parity, age, gestational age at birth and antenatal weight gain.

Table 7.12: Univariable analysis of associations of ponderal index

Parameters N = 1033	β	(95% CI)	P value
Maternal factors			
Ethnicity	0.011	(-0.002 – 0.023)	0.1
Terai Brahmin	reference		
Terai Chhetri	0.044	(-0.083 – 0.172)	0.5
Terai Vaishya	-0.006	(-0.069 – 0.058)	0.9
Terai Sudra	0.045	(-0.099 – 0.189)	0.9
Hindu Brahmin	0.020	(-0.108 – 0.147)	0.8
Hindu Chhetri	0.011	(-0.136 – 0.157)	0.9
Muslim	0.056	(-0.047 – 0.159)	0.3
Newar	0.060	(-0.143 – 0.263)	0.6
Other	0.113	(-0.056 – 0.282)	0.2
Demographic			
Education	0.001	(-0.005 – 0.007)	0.7
Residence	-0.006	(-0.048 – 0.036)	0.8
Socioeconomic status	0.020	(-0.001 – 0.041)	0.06
Age	0.007	(0.001 – 0.013)	0.02
Morbidity			
Eclampsia	0.106	(-0.149 – 0.361)	0.4
Systolic Blood Pressure at enrolment	-0.001	(-0.003 – 0.001)	0.2
Diastolic Blood Pressure at enrolment	-0.001	(-0.003 – 0.002)	0.7
2nd trimester morbidity I	-0.006	(-0.027 – 0.014)	0.6
None	Reference		
Abdominal problems	0.039	(-0.018 – 0.097)	0.2
Infections	-0.043	(-0.146 – 0.060)	0.4
Other	-0.025	(-0.091 – 0.041)	0.5
2nd trimester morbidity II	0.009	(-0.015 – 0.032)	0.5
None	Reference		
Abdominal complaints	0.021	(-0.073 – 0.116)	0.7
Infections	-0.072	(-0.221 – 0.076)	0.3
Other	0.035	(-0.039 – 0.110)	0.4
3rd trimester morbidity I	0.003	(-0.017 – 0.023)	0.8
None	Reference		
Abdominal complaints	-0.017	(-0.072 – 0.038)	0.5
Infections	0.141	(0.027 – 0.256)	0.01
Other	-0.009	(-0.073 – 0.055)	0.8
3rd trimester morbidity II	0.008	(-0.018 – 0.034)	0.5
None	Reference		
Abdominal complaints	-0.104	(-0.217 – 0.281)	0.07
Infections	0.148	(0.015 – 0.281)	0.03
Other	0.006	(-0.078 – 0.091)	0.9
Obstetric			
Parity (category)	0.026	(0.008 – 0.045)**	0.006
Prior LBW infant	0.025	(-0.113 – 0.164)	0.7
Prior miscarriage	0.035	(-0.021 – 0.091)	0.2
Prior stillbirth	0.010	(-0.056 – 0.076)	0.8
Prior death of child	0.031	(-0.007 – 0.070)	0.1
Anthropometry			
Height	0.002	(-0.002 – 0.006)	0.3
Weight	0.003	(-0.001 – 0.007)*	0.1
Nutrition			
Weight gain	0.016	(0.009 – 0.023)	0.001
Blood haemoglobin (g/dL)	-0.003	(-0.017 – 0.010)	0.6
Supplements	0.035	(-0.007 – 0.077)	0.1
Fetal factors			
Sex	0.012	(-0.029 – 0.054)	0.6
Gestation at birth	0.020	(0.008 – 0.033)	0.001

The significant factors were entered in the multivariable linear regression, which left three variables significant (see Table 7.13): maternal parity (p=0.02), antenatal weight gain (p=0.001) and gestational age at birth (p=0.05).

Each unit increase in gestational weight gain was translated as an increase in PI by 0.014 g/cm^3. Multiparity increased PI by 0.062 g/cm3 compared to primiparous mothers. Longer gestational duration was associated with increased PI. A week longer gestational duration increased PI by 0.012g/cm^3.

Socioeconomic status, education level, and prior history of small birth were entered into the model, but showed no significant associations. The model explained 3.2% of the variability in the PI at birth. The best predictor was gestational weight gain. There was no evidence of collinearity: variance inflation factors were all below 10 and tolerances for all the variables were not close to 0. Standardized residuals were normally distributed (see Figure 7.13)

Figure 7.14 shows the normal probability plot for standardized residuals. It shows that the residuals lie close to the line and no outliers are evident. Figure 7.15 shows that the residuals were randomly distributed around the zero line. In summary, no outliers were detected on examination of the residual diagnostics.

Table 7.13: Multivariable analysis of associations of ponderal index

PI at birth (g/cm^3) n = 1033	β (95% CI)	t	P	R square
Maternal weight gain (kg)	0.014 (0.007 – 0.021)	3.78	0.001	0.032
Primiparity	0.062 (0.011 – 0.112)	2.40	0.02	
Gestational age at birth	0.012 (0.000 – 0.025)	1.95	0.05	

Figure 7.13. Histogram for residuals for ponderal index

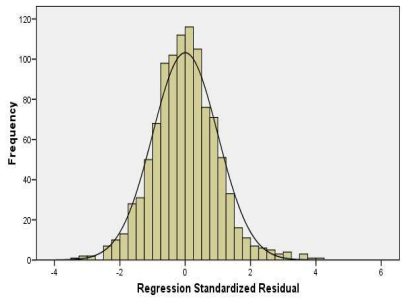


Figure 7.14. Normal probability plot for ponderal index

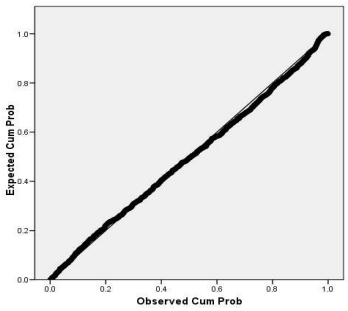
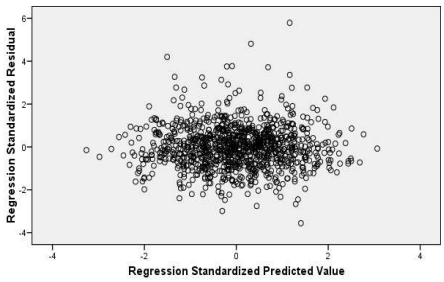


Figure 7.15. Residual plot for ponderal index at birth



7.10. Predictors of low ponderal index at birth

The univariable regression coefficients and 95% confidence interval for coefficients of the potential determinants of low PI are given in Table 7.14. The variables that showed significant association with low PI were: parity as a categorical variable, antenatal weight gain, socioeconomic status and gestational age at birth.

Table 7.14. Univariable analysis of associations of low ponderal index

Parameters N = 1033	β	(95% CI)	P value
Maternal factors			
Ethnicity	0.93	(0.86 – 1.01)	0.08
Terai Brahmin	Reference		
Terai Chhetri	0.64	(0.30 – 1.36)	0.3
Terai Vaishya	1.10	(0.74 – 1.64)	0.7
Terai Sudra	0.76	(0.32 – 1.82)	0.6
Hindu Brahmin	1.04	(0.47 – 2.32)	0.9
Hindu Chhetri	1.02	(0.41 – 2.54)	0.9
Muslim	0.73	(0.39 – 1.35)	0.7
Newar	0.34	(0.10 – 1.14)	0.08
Other	0.60	(0.22 – 1.62)	0.3
Demographic			
Education	0.99	(0.95 – 1.02)	0.5
Residence	1.22	(0.94 – 1.58)	0.1
Socioeconomic status	0.85	(0.75 – 0.97)	0.02
Age	0.98	(0.94 – 1.02)	0.3
Morbidity			
Eclampsia	0.64	(0.14 – 2.87)	0.6
Systolic Blood Pressure at enrolment	1.01	(0.99 – 1.02)	0.4
Diastolic Blood Pressure at enrolment	1	(0.98 – 1.02)	0.9
2nd trimester illness I	1.04	(0.91 – 1.19)	0.6
None	Reference		
Abdominal complaints	0.78	(0.55 – 1.10)	0.2
Infections	1.04	(0.54 – 2.00)	0.9
Other	1.23	(0.80 – 1.89)	0.4
2nd trimester illness II	0.90	(0.78 – 1.04)	0.1
None	Reference		
Abdominal complaints	0.93	(0.52 – 1.66)	0.8
Infections	1.16	(0.45 – 3.02)	0.7
Other	0.68	(0.44 – 1.07)	0.09
3rd trimester illness I	0.98	(0.86 – 1.11)	0.7
None	Reference		
Abdominal complaints	1.02	(0.72 – 1.44)	0.9
Infections	0.38	(0.19 – 0.74)	0.005
Other	1.10	(0.73 – 1.66)	0.7
3rd trimester illness II	0.89	(0.76 – 1.04)	0.1
None	Reference		
Abdominal complaints	1.2	(0.57 – 2.53)	0.6
Infections	0.40	(0.18 – 0.87)	0.02
Other	0.80	(0.48 – 1.33)	0.4
Obstetric history			
Parity (category)	0.71	(0.55 – 0.93)	0.01
Prior small infant	1.27	(0.51 – 3.15)	0.6
Prior miscarriage	0.88	(0.63 – 1.23)	0.5
Prior stillbirth	0.93	(0.62 – 1.40)	0.7
Prior death of child	0.90	(0.71 – 1.14)	0.4
Anthropometry			
Height	1	(0.98 – 1.03)	0.8
Weight	0.99	(0.97 – 1.01)	0.3
Nutrition			
Weight gain	0.93	(0.89 – 0.97)	0.01
Blood haemoglobin	1.03	(0.95 – 1.12)	0.5
Supplements	0.82	(0.63 – 0.99)	0.1
Fetal factors			
Sex	0.88	(0.68 – 1.45)	0.4
Gestation at birth	0.92	(0.85 – 0.99)	0.03

Table 7.15 shows the final model of predictors of low PI at birth. Introducing prior history of giving birth to a small infant into the regression did not change the model. Only two variables were significant: maternal weight gain during pregnancy (p = 0.005) and gestational age at birth (p = 0.04).

The model showed that a unit increase in parity or in gestational weight gain decreased the probability of giving birth to an infant with low PI. The odds of giving birth to a low PI infant for a woman of higher parity were 26% lower than for lower parity mothers (OR 0.74; 95% CI 0.57–0.98). The predicted odds for giving birth to an infant with low PI for a mother who gained 1 kg more during pregnancy were 6 % lower (0.94; 0.90 – 0.98).

Table 7.15. Multivariable analysis of associations with low ponderal index, with odds ratios

Factors N = 1033	Odds ratio	95% CI for OR	Wald	P value
Maternal weight gain (Kg)	0.94	0.90 – 0.98	7.89	0.005
Multiparity	0.74	0.57 – 0.99	4.27	0.04

7.11. Predictors of birth head circumference

The univariable associations between head circumference at birth and independent variables are shown in Table 7.16. Variables that showed associations with head circumference at birth were maternal height (p=0.001), weight (p=0.001), antenatal weight gain (p=0.001), socioeconomic status (p=0.002), education level (p=0.01), infant sex (p=0.001), gestational age at birth (p=0.001), parity (p=0.04), age (p=0.02) and prior history of giving birth to small infant. The variable showing almost an association was antenatal supplementation (p=0.08)

Table 7.16 Univariable analysis of associations of head circumference

Parameters N = 1038	β	(Std. Error)	P value
Maternal factors			
Ethnicity	0.008	(-0.047 – 0.064)	0.8
Terai Brahmin	reference		
Terai chhetri	-0.050	(0.600 – 0.500)	0.9
Terai Vaishya|	-0.193	(-0.468 – 0.083)	0.1
Terai sudra	-0.117	(-0.745 – 0.511)	0.7
Hindu Brahmin	-0.016	(-0.566 – 0.534)	1
Hindu chhetri	0.314	(0.325 – 0.953)	0.4
Muslim	-0.180	(-0.623 – 0.262)	0.4
Newar	-0.627	(-1.511 – 0.256)	0.2
Other	0.476	(-0.279 – 1.232)	0.2
Demographic			
Education	0.032	(0.007 – 0.057)	0.01
Residence	-0.101	(-0.280 – 0.080)	0.3
Socioeconomic status	0.147	(0.056 – 0.238)	0.002
Age	0.033	(0.006 – 0.059)	0.02
Morbidity			
Eclampsia	-0.102	(-1.216 – 1.012)	0.9
Systolic Blood Pressure at enrolment	0.002	(-0.007 – 0.012)	0.6
Diastolic Blood Pressure at enrolment	0.004	(-0.008 – 0.016)	0.5
2nd trimester morbidity I	0.074	(-0.015 – 0.164)	0.1
None	Reference		
Abdominal complaints	-0.052	(-0.304 – 0.201)	0.7
Infections	0.423	(-0.023 – 0.869)	0.1
Other	0.192	(-0.097 – 0.480)	0.2
2nd trimester illness II	-0.026	(-0.129 – 0.076)	0.6
None	Reference		
Abdominal complaints	-0.335	(-0.740 – 0.069)	0.1
Infections	-0.034	(-0.682 – 0.614)	0.9
Other	-0.035	(-0.361 – 0.292)	0.8
3rd trimester illness I	0.008	(-0.080 – 0.096)	0.9
None	Reference		
Abdominal complaints	0.056	(-0.185 – 0.296)	0.7
Infections	0.119	(-0.371 – 0.608)	0.6
Other	-0.002	(-0.280 – 0.276)	1
3rd trimester illness II	-0.022	(-0.135 – 0.092)	0.7
None	Reference		
Abdominal complaints	-0.496	(-0.995 – 0.002)	0.1
Infections	0.131	(-0.453 – 0.714)	0.7
Other	-0.042	(-0.410 – 0.327)	0.8
Obstetric history			
Parity (category)	0.195	(0.013 – 0.378)	0.04
Prior small infant	-0.545	(-1.149 – 0.058)*	0.08
Prior miscarriage	-0.015	(-0.259 – 0.228)	0.9
Prior still birth	-0.099	(-0.389 – 0.191)	0.5
Prior death of child	-0.148	(-0.317 – 0.021)	0.1
Anthropometry			
Height	0.039	(0.023 – 0.055)	0.001
Weight	0.036	(0.021 – 0.052)	0.001
Nutrition			
Weight gain	0.102	(0.072 – 0.132)	0.001
Blood haemoglobin	0.017	(-0.041 – 0.075)	0.6
Supplements	0.165	(-0.020 – 0.350)	0.08
Fetal factors			
Sex	0.469	(0.289 – 0.650)	0.001
Gestation at birth	0.305	(0.256 – 0.355)	0.001

Table 7.17 shows the final contributors to the prediction model for head circumference at birth. The multivariable analysis demonstrated gestational duration, infant sex and maternal weight gain as independent determinants of head circumference. The univariable analysis suggested an effect of maternal height, parity, education, maternal weight at enrolment, but this was eliminated in the multivariable analysis. Similarly, maternal age, parity and previous history of giving birth to a small infant did not contribute to the prediction model. The model explained only 19% of the variability in head circumference at birth.

A plot of standardized residuals revealed no specific patterns; points were evenly distributed around a horizontal line centred on zero (see Figure 7.18). Figure 7.16 shows the histogram of the residuals. It revealed normal distribution of residuals with no outliers. The normal probability plot showed residuals distributed around a diagonal line, as seen in Figure 7.17.

Table 7.17. Multivariable analysis of associations of head circumference

Head circumference (cm) N = 1038	β	(95% CI)	t-value	P-value	R^2
					18.8
Birth gestation (wks)	0.28	(9.23 – 0.33)	11.0	0.001	
Male sex	0.51	(0.35 – 0.68)	6.11	0.001	
Maternal weight gain (kg)	0.06	(0.03 – 0.09)	4.11	0.001	

Figure 7.16. Histogram of residuals for head circumference

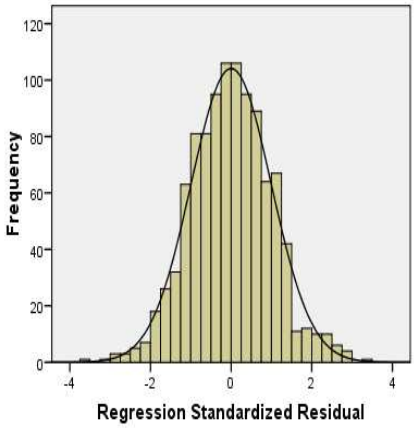


Figure 7.17. Normal probability plot for head circumference at birth

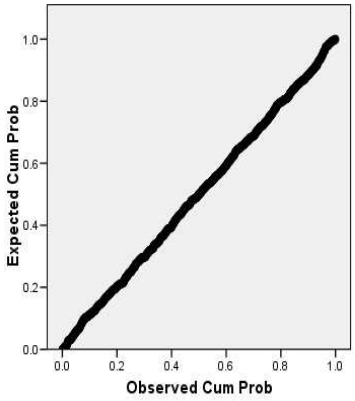
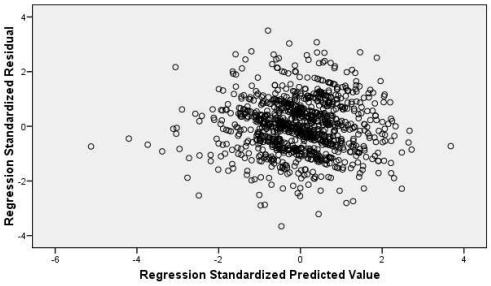


Figure 7.18. Residual plot for head circumference at birth



7.12. Summary

The coefficients of determination (adjusted R^2) for all prediction models for size at birth outcomes were not high, ranging from 2.8% to 32.7%. The highest of them was for birth weight (32.7%), followed by birth length (19%), head circumference (18.8%), body mass index

(12.4%) and PI (3.2%). Nevertheless, the residual analyses confirmed that the models were adequate and did not violate the assumption of normality.

The number of parameters in the prediction models ranged from two to eight. The results of the multivariable regression analysis showed that most of the models contained gestation at birth, maternal weight at enrolment and parity as the important determinants of size at birth. Antenatal maternal weight gain was the strongest determinant present in the final regression models for all birth outcomes. Similarly, gestational age, infant sex and maternal weight at enrolment were present in all models except for PI and low PI. The same goes for parity, which was present in all models except that for head circumference and length. Prior history of child mortality was significant in the final regression for length at birth.

Birth weight, LBW and SGA had generally common predictors in the final regression models. Birth weight had two more predictors than LBW - maternal height and education - although their contributions were limited in the model. The model for LBW contained six factors and their rank order of contribution was the same as for birth weight. Since SGA is sex and gestation specific, sex and gestation do not figure in its final model. Otherwise, all the predictors of LBW were the same as for SGA. In the prediction of birth length, parity, education and antenatal supplementation were not elements of the model. Head circumference had similar predictors as birth weight, although parity, height, weight and antenatal supplementation did not feature in the model.

The contribution of known risk factors in explaining the variability in birth indices was as low as 3-12%, the least explained being PI. The common predictors were parity and gestational weight gain. The multivariable logistic regression identified only two variables as significant predictors of low PI - parity and maternal weight gain during pregnancy - and three variables for PI (parity, gestational weight gain and gestational age). Table 7.18 summarises the results of the various multivariable prediction models for interpretation in subsequent discussion.

Table 7.18. Main risk factors in the analyses

Variable	Predicts to some degree in multivariable analyses
Gestation (wks)	Birth weight, LBW, length, BMI, PI, head circumference
Maternal weight at enrolment (kg)	Birth weight, LBW, SGA, length, BMI
Maternal height (cm)	Birth weight, length
Maternal weight gain (kg)	Birth weight, LBW, SGA, length, BMI, PI, LPI, head circumference
Parity	Birth weight, LBW, SGA, BMI, PI, LPI
Infant sex	Birth weight, LBW, length, BMI, head circumference
Supplement	Birth weight, LBW, SGA, BMI
Education	Birth weight

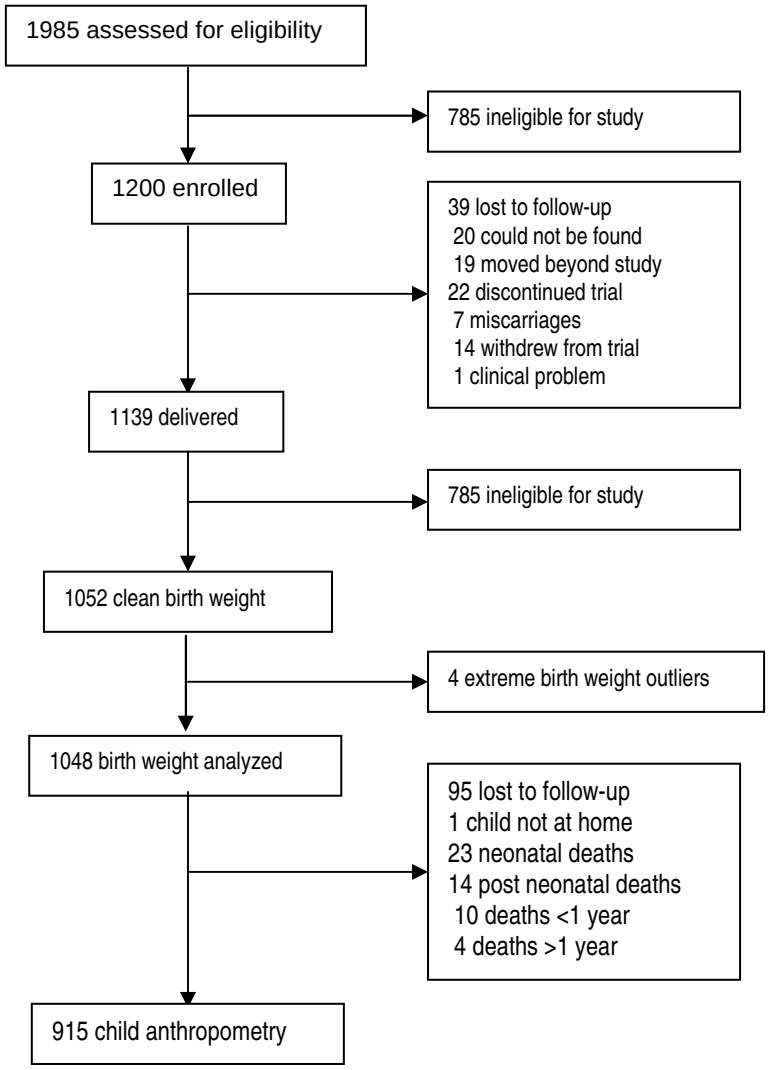
Chapter 8. Results: Associations of size at birth with mortality, morbidity and malnutrition in childhood

8.1. Chapter summary

Previous chapters used a range of birth anthropometric parameters and indices to define size at birth. They demonstrated overlaps between classifications of size which put different proportions of infants into risk categories. This chapter describes an investigation of the associations between different measures of size at birth and short and longer term health outcomes in a sample of 1048 children born to women in the antenatal multiple micronutrient supplementation trial. Information on outcomes was collected at two points: about 1 month after birth, and 2-3 years of age.

The study profile was presented in Chapter 5, but a simplified version for this analysis is shown in Figure 8.1. The number of children with information available varied across different indices of size at birth. We included children whose birth weight was measured within 72 hours of birth. The sample available for the analysis of neonatal deaths was 1048. The sample available for analysis of infant and child deaths was 953 after losses to follow-up. Child anthropometry was available for 915 children after losses to follow-up, infant deaths and child deaths.

Figure 8.1. Study profile for outcome analysis



Child characteristics

Table 8.1 presents infant nutritional and immunization status, child anthropometry and blood pressure of children at follow-up. 99% of mothers breastfed their infants. Infants were exclusively breastfed for a mean duration of six months and were given solid food at a mean age of eight months. The immunisation rate for measles was 97%. BCG and DPT Vaccination rates exceeded 98%. Around 94% of children received the hepatitis B vaccination.

Table 8.1. Infant feeding, Immunization status, child anthropometry and blood pressure of children at follow-up

Nutrition	Frequency	(%)
Breastfed [n=926]	913	(98.6)
Duration of exclusive breastfeeding in months [n=916] (mean [SD])	6.44	(3.24)
Age at introduction of solids in months [n=919] (mean [SD])	8.46	(3.41)
Immunization status [n=925]		
BCG	919	(99.4)
DPT1	917	(99.1)
DPT2	914	(98.8)
DPT3	911	(98.5)
Measles	902	(97.5)
HBV1	868	(93.8)
HBV2	865	(93.5)
HBV3	858	(92.9)
Child anthropometry and blood pressure [n=915]	*Mean*	*(95% CI)*
Weight (Kg)	10.80	(10.70 – 10.89)
Height (cm)	83.90	(83.59 – 84.21)
BMI (Kg/m^2)	15.31	(15.21 – 15.40)
Systolic blood pressure (mmHg) [n=903]	99.79	(98.90 – 100.68)
Diastolic blood pressure (mmHg) [n=904]	62.40	(61.53 – 63.28)
MUAC (cm)	14.30	(14.23 – 14.37)
Head circumference (cm)	46.52	(46.43 – 46.62)
Chest circumference (cm)	48.12	(47.96 – 48.27)
Waist circumference (cm)	46.64	(46.46 – 46.83)
Hip circumference (cm)	46.14	(46.00 – 46.33)
Waist hip ratio	1.01	(1.00 - 1.02)
Triceps skinfold thickness (mm)	7.05	(6.95 – 7.16)

The mean age at follow-up of children was 2.56 years (SD 0.35) and half of them were male (51%). The age ranged from 1.98 to 3.85 years. Figure 8.2, 8.3 and 8.4 show scatterplots of weight, height and head circumference against age of children at follow-up. The association of age with weight was not as strong ($R^2 = 0.134$) as with height. ($R^2 = 0.321$). There was little association of age with head circumference ($R^2 = 0.055$).

Figure 8.2. Scatterplot of weight by age of child at follow up

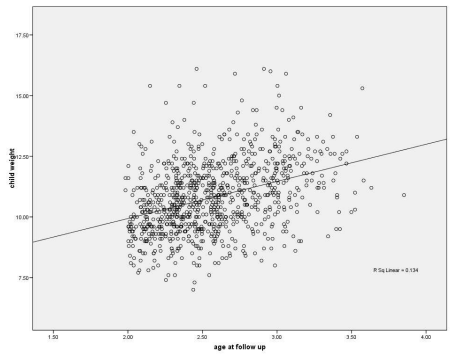


Figure 8.3. Scatterplot of height by age of child at follow up

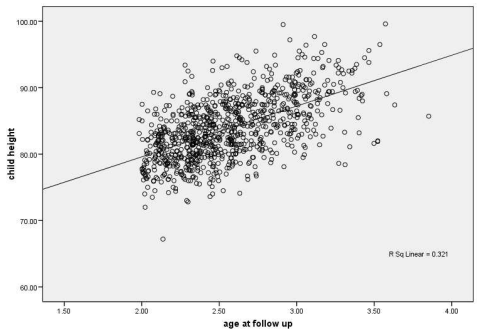
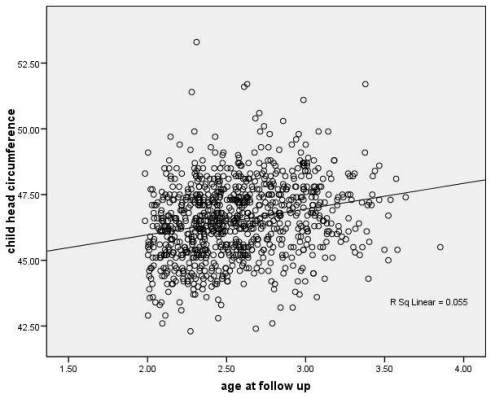


Figure 8.4. Scatterplot of head circumference by age of child at follow up



The mean weight was 10.80 kg (SD: 1.47; range 7.00 to 16.10 kg) and mean height was 83.90 cm (4.75; 67.2 – 99.6). The mean systolic blood pressure and diastolic blood pressure were 99.79 (SD 13.61) and 62.40 (SD 13.38) respectively.

Figure 8.5, Figure 8.6 and Figure 8.7 show the average annual gain in weight, height and head circumference agaist weight of infants at birth. These averages were derived from the difference between the initial and follow-up measurements, divided by the age at follow-up. In fact, the true growth pattern will vary from year to year and these figures are simple summaries based on only two measures. The average annual weight gain was around 3 kg for all levels of birth weight: this absolute weight gain was quite similar irrespective of actual birth weight. Figure 8.6 and Figure 8.7 illustrate that the absolute annual gain in head circumference and length varied across the ranges of head circumference and length at birth. The annual gain in

length ranged from 12.5 to 15.5 cm. The annual gain in head size ranged from 7.5 cm when the head size was 27 cm at birth, to 3.5 cm for a head size of 38 cm at birth.

Figure 8.5. . Mean annual weight gain by birth weight

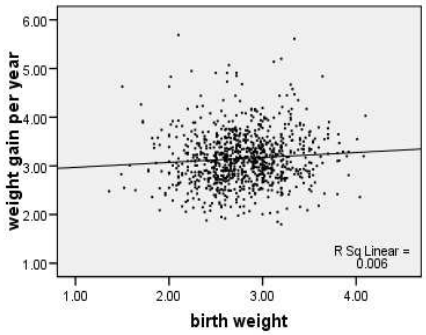


Figure 8.6. . Mean annual height gain by length at birth

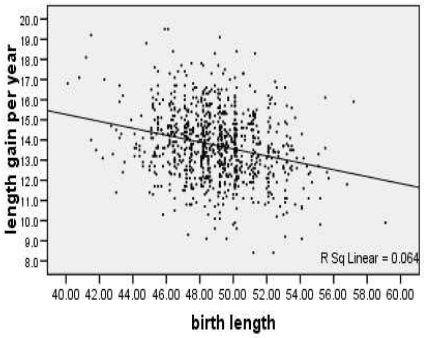
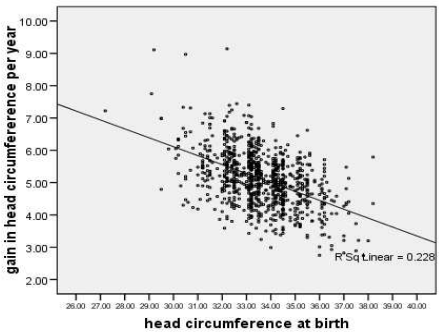


Figure 8.7. Mean annual gain in head circumference by head circumference at birth



These charts have expressed growth in terms of absolute measurements. Figure 8.8, Figure 8.9 and Figure 8.10 show the mean change in z-scores of weight, height and head circumference for age, relative to the WHO reference. Mean changes in z scores per year were -0.209 (SD 0.459), -0.770 (0.579) and -0.358 (0.501) for weight, height and head circumference respectively. The negative signs show that children became relatively more underweight, stunted and smaller in head size relative to WHO reference groups. In all the figures, the annual changes in z-score were greater for infants with lower z-scores at birth. The annual change in weight z-scores

decreased with increasing z-scores of birth weight: infants with lower size at birth gained relatively more weight, height and head circumference than larger infants. For most infants and young children, the change in z-score was negative. However, the graphs show that at the lower end of the distribution the change was positive. The general pattern was for a downward movement in z-score with time, but smaller infants tended to 'catch up' and larger infants tended to 'catch down'.

Figure 8.8. Mean annual change in z-score for weight for age, by z-score at birth

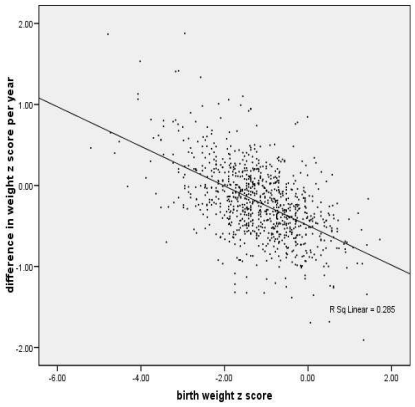


Figure 8.9. Mean annual change in z-score for height for age, by z-score at birth

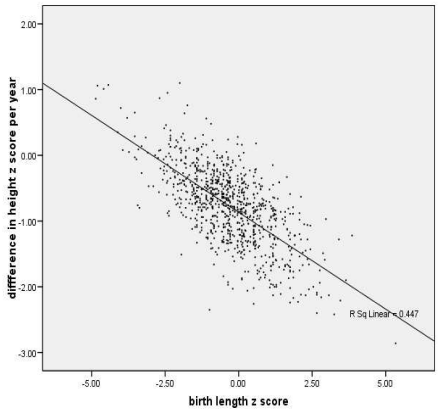
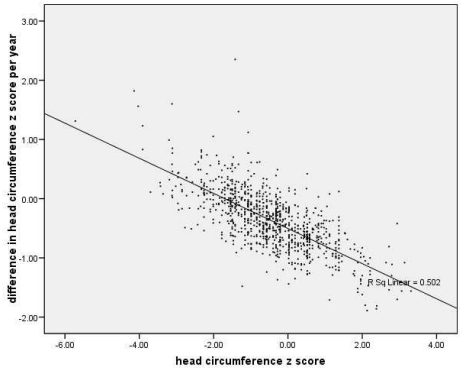


Figure 8.10. Mean annual change in z-score for head circumference for age, by z-score at birth



8.2. Adjustment for possible confounding

We used an intuitive approach and the findings of previous studies to select confounders from the pool of data available. The potential confounders assessed were: maternal age at enrolment,[200] parity,[200] ethnicity, education level, socioeconomic status, antenatal supplementation status, weight at enrolment, gestational age at birth, infant sex, age of weaning, age of child at follow-up and frequency of illnesses. Some confounders did not apply to all the outcomes that were assessed. In the case of neonatal death as an outcome: age at weaning, age of child at follow-up and frequency of illnesses. In the case of infant and child deaths: age at follow-up and frequency of illnesses. In the case of morbidity outcomes: frequency of illnesses. Age at weaning was preferred to frequency of breastfeeding as a possible confounder because almost all women breastfed their newborns (99%). The month of introduction of solid food varied across the participants, ranging from 1 to 24 months.

All the above mentioned confounders were assessed for univariable associations with birth outcomes. Table 8.2 shows the results of univariable logistic regressions of mortality from birth to 2.5 years of age on all confounders. Out of nine possible confounders, only maternal weight at enrolment showed a significant univariable association with neonatal death. Infant and child deaths demonstrated no association with any confounder. However, gestation at birth was closer to significance in its association with child death ($p=0.08$).

Morbidity factors assessed during infancy were cough and fever, rash and fever, and diarrhoea and fever. The results of the univariable logistic regression are shown in Table 8.3. Cough and fever, and rash and fever showed no significant association with any of the possible confounders. However, maternal age and education level were closer to significant association ($p <0.09$). Diarrhoea and fever showed significant associations with ethnicity, antenatal supplementation and children's age at follow-up. Frequency of illnesses was significantly related to maternal parity, education, socioeconomic status and age of weaning.

Illness during 14 days before follow-up was also assessed for its association with possible confounders (see Table 8.4). The particular symptoms asked were fever, cough, difficulty breathing and diarrhoea. Fever, difficulty breathing and diarrhoea were shown to have an association with maternal parity, education and age at weaning. Apart from that, fever was also related to socioeconomic status and weight at enrolment. Cough was also associated with socioeconomic status, infant sex, weight at enrolment and age at follow-up. Difficulty breathing was associated with age at follow-up. Diarrhoea was associated with socioeconomic status, weight at enrolment and age at follow-up. Systolic blood pressure was univariably associated with maternal age and parity. Diastolic blood pressure was associated with parity, ethnicity and education (SeeTable 8.5).

Table 8.6 shows univariable associations between malnutrition and possible confounders. For malnutrition, all 12 confounders were examined. Stunting and underweight in children showed significant associations with all confounders except for maternal age, ethnicity, antenatal supplementation and infant sex. There was an almost significant association with age of children at follow-up ($p=0.09$) for stunting. Wasting was associated with only two factors: maternal education and maternal weight at enrolment.

As described in Chapter 5, we developed three models for each outcome. The model was developed following identification of possible confounders for deaths, illnesses and malnutrition. Model I was an unadjusted logistic or linear regression of outcome on parameter of size at birth. Model II adjusted for confounders that were associated with the outcome in univariable analysis. Model III adjusted for all possible confounders by including variables that may not have shown univariable association, but were felt to be important.

Table 8.2. Univariable association between possible confounders and neonatal, infant and child mortality up to 2.5 years of age

Possible confounders	Neonatal death (n=1048) OR (95% CI)	Infant death (n=953) OR (95% CI)	Child death (n=953) OR (95% CI)
Maternal age	0.89 (0.77–1.02) P = 0.1	0.98 (0.89–1.09) P =0.7	0.97 (0.88–1.07) P = 0.5
Maternal parity	0.86 (0.57–1.3) P = 0.5	1.10 (0.82–1.48) P = 0.5	1.10 (0.83–1.45) P = 0.5
Ethnicity	1.07 (0.85–1.34) P = 0.6	0.96 (0.77–1.19) P = 0.7	1.09 (0.91–1.3) P = 0.4
Maternal education	0.97 (0.86–1.1) P = 0.6	0.93 (0.83–1.04) P = 0.2	0.93 (0.83–1.03) P = 0.2
Socioeconomic status	0.88 (0.59–1.33) P = 0.5	0.84 (0.60–1.18) P = 0.3	0.83 (0.60–1.14) P = 0.2
Supplements	1.56 (0.07–3.6) P = 0.3	1.19 (0.59–2.39) P = 0.6	1.04 (0.54–2.01) P = 0.9
Weight at enrolment	0.9 (0.85–0.99) P = 0.04	0.95 (0.89–1.01) P = 0.1	0.97 (0.91–1.03) P = 0.3
Gestation at birth	0.88 (0.7–1.1) P = 0.2	0.87 (0.72–1.01) P = 0.1	0.86 (0.72–1.02) P = 0.08
Infant sex	0.74 (0.3–1.7) P = 0.5	0.62 (0.31–1.26) P = 0.2	0.65 (0.33–1.27) P = 0.2
Age at weaning	-	0.83 (0.62-1.11) P = 0.2	0.96 (0.77–1.18) P= 0.7

Table 8.3. Univariable association between possible confounders and illnesses during infancy

Possible confounders n=953	Cough and fever OR (95% CI)	Diarrhoea and fever OR (95% CI)	Rash and fever OR (95% CI)	Frequency of illness OR (95% CI)
Maternal age	0.94 (0.81–1.01) P = 0.08	0.96 (0.93–1.00) P = 1.00	0.95 (0.89-1.01) P = 0.08	0.99 (0.95–1.03) P = 0.5
Maternal parity	0.99 (0.78–1.27) P = 0.9	1.07 (0.94–1.22) P = 0.3	0.98 (0.82–1.18) P = 0.8	1.13 (1.00–1.30) P = 0.04
Ethnicity	0.99 (0.85–1.20) P = 0.9	0.92 (0.85–0.99) P = 0.04	1.07 (0.96–1.20) P = 0.2	1.05 (0.97–1.13) P = 0.3
Maternal education	0.94 (0.88–1.01) P = 0.06	0.98 (0.94–1.02)P = 0.3	0.95 (0.89–1.01) P = 0.09	0.94 (0.90–0.97) P = 0.001
Socioeconomic status	0.81 (0.61–1.10) P = 0.1	0.95 (0.83–1.09) P = 0.5	0.90 (0.74–1.09) P = 0.3	0.85 (0.75–0.97) P = 0.02
Supplements	1.28 (0.73–2.22) P = 0.4	0.75 (0.57–1.00) P = 0.05	1.06 (0.71–1.58) P = 0.8	0.93 (0.71–1.21) P = 0.6
Weight at enrolment	1.03 (0.98-1.08) P = 0.3	0.99 (0.96–1.01) P = 0.3	0.99 (0.97–1.03) P = 0.97	0.99 (0.98–1.02) P = 0.8
Gestation at birth	0.94 (0.79–1.11) P = 0.5	1.00 (0.92–1.09) P = 0.9	1.07 (0.95–1.22) P = 0.3	0.98 (0.91–1.06) P = 0.6
Infant sex	0.89 (0.51–1.55) P = 0.7	0.84 (0.64–1.12) P = 0.2	0.97 (0.65–1.46) P = 0.9	1.32 (1.01–1.72) P = 0.04
Age at weaning	1.05 (0.96–1.19) P = 0.3	1.04 (0.99–1.09) P = 0.1	0.99 (0.93–1.05) P = 0.7	1.03 (0.99–1.08) P = 0.1
Age at follow up	1.11 (0.50–2.45) P = 0.8	0.61 (0.41–0.91) P = 0.02	1.05 (0.59–1.85) P = 0.9	0.83 (0.51–1.20) P = 0.8

Table 8.4. Univariable association between possible confounders and illnesses in the 14 days before follow up

Possible confounders n=915	Fever OR (95% CI)	Cough OR (95% CI)	Difficulty breathing OR (95% CI)	Diarrhoea OR (95% CI)
Maternal age	1.01 (0.97–1.05) P = 0.5	1.01 (0.99–1.07) P =0.2	1.03 (0.96–1.10) P = 0.4	0.98 (0.92–1.03) P = 0.39
Maternal parity	1.18 (1.05–1.33) P = 0.007	1.20 (1.06–1.35) P = 0.003	1.30 (1.07–1.60) P = 0.008	1.18 (1.01–1.38) P = 0.04
Ethnicity	1.02 (0.94–1.11) P = 0.6	0.99 (0.92–1.08) P = 0.9	0.93 (0.80–1.09) P = 0.4	1.0 (0.89–1.12) P = 1.00
Maternal education	0.91 (0.87–0.95) P = 0.001	0.91 (0.88–0.95) P = 0.001	0.86 (0.79–0.94) P = 0.001	0.94 (0.89–0.99) P = 0.04
Socioeconomic status	0.82 (0.72–0.94) P = 0.004	0.81 (0.71–0.92) P = 0.002	0.85 (0.67–1.08) P = 0.2	0.85 (0.71–1.02) P = 0.08
Supplements	0.99 (0.76–1.31) P = 9	1.02 (0.78–1.33) P = 1	1.26 (0.77–2.06) P = 0.4	0.87 (0.59–1.26) P = 0.5
Weight at enrolment	0.95 (0.93-0.98) P = 0.001	0.97 (0.95-0.99) P = 0.01	0.98 (0.93–1.02) P = 0.3	0.95 (0.92–0.98) P = 0.003
Gestation at birth	0.96 (0.89–1.04) P = 0.9	0.94 (0.87–1.02) P = 0.1	1.05 (0.90–1.21) P = 0.6	1.01 (0.90-1.13) P = 0.9
Infant sex	1.18 (0.90–1.55) P = 0.2	1.32 (1.00–1.73) P = 0.05	1.15 (0.70–1.87) P = 0.6	1.21 (0.83–1.77) P = 0.3
Age at weaning	1.05 (1.01–1.10) P = 0.02	1.07 (1.03–1.12) P = 0.001	1.09 (1.01-1.17) P = 0.02	1.07 (1.01–1.13) P = 0.02
Age at follow up	1.03 (0.70–1.52) P = 0.9	0.69 (0.47–1.03) P = 0.06	1.93 (0.99–3.75) P = 0.05	0.50 (0.28–0.88) P = 0.02

Table 8.5. Univariable association between possible confounders and blood pressure in children at 2.5 years of age

Possible confounders n=915	Systolic Blood Pressure OR (95% CI)		Diastolic Blood Pressure OR (95% CI)	
Maternal age	-0.30 (-0.51 - 0.01)	P = 0.05	-0.16 (-0.41 – 0.09)	P = 0.2
Maternal parity	-1.29 (-2.09 - 0.50)	P = 0.001	-0.83 (-1.62 - 0.52)	P = 0.04
Ethnicity	-0.32 (0.85 – 0.21)	P = 0.2	-0.54 (-1.06 – 0.02)	P = 0.04
Maternal education	0.09 (-0.15 – 0.34)	P = 0.8	0.276 (0.04 – 0.52)	P = 0.02
Socioeconomic status	-0.02 (-0.89 – 0.86)	P = 0.9	0.23 (-0.63 – 1.1)	P = 0.6
Supplements	-1.05 (2.83 – 0.73)	P = 0.3	-0.86 (-2.6 – 0.89)	P = 0.3
Weight at enrolment	0.01 (-0.14 – 0.16)	P = 0.9	0.07 (-0.08 – 0.2)	P = 0.4
Gestation at birth	-0.06 (-0.59 – 0.47)	P = 0.8	-0.4 (-0.9 – 1.12)	P = 0.1
Infant sex	0.40 (-1.38 – 2.18)	P = 0.7	-0.89 (-2.63 – 0.86)	P = 0.3
Age at weaning	-0.08 (-0.36 – 0.19)	P = 0.6	-0.16 (-0.43– 0.11)	P = 0.3
Age at follow up	-0.07 (-2.61 – 2.47)	P = 1.0	1.31 (-1.18 – 3.80)	P = 0.3

Table 8.6. Univariable association between possible confounders and malnutrition in children at 2.5 years of age

Possible confounders n=915	Stunting OR (95% CI)	Wasting OR (95% CI)	Underweight OR (95% CI)
Maternal age	0.99 (0.96–1.03) P = 0.7	1.03 (0.95–1.11) P = 0.5	1.02 (0.98–1.06) P = 0.2
Maternal parity	1.33 (1.17–1.51) P = 0.001	1.17 (0.94–1.47) P = 0.2	1.35 (1.19–1.52) P = 0.001
Ethnicity	0.98 (0.91–1.06) P = 0.6	0.89 (0.74–1.07) P = 0.3	1.03 (0.95–1.11) P = 0.5
Maternal education	0.89 (0.85–0.92) P = 0.001	0.93 (0.85–1.01) P = 0.09	0.89 (0.85–0.93) P = 0.001
Socioeconomic status	0.68 (0.59–0.77) P = 0.001	0.93 (0.71–1.21) P = 0.6	0.69 (0.60-0.79) P = 0.001
Supplements	0.90 (0.68–1.16) P = 0.4	1.11 (0.64–1.92) P = 0.1	0.93 (0.71–1.21) P = 0.6
Weight at enrolment	0.91 (0.88–0.93) P = 0.001	0.89 (0.84–0.94) P = 0.001	0.89 (0.86–0.91)P = 0.001
Gestation at birth	0.01 (0.84–0.99) P = 0.03	0.90 (0.77–1.05) P = 0.2	0.88 (0.82–0.96) P = 0.003
Infant sex	0.82 (0.63–1.06) P = 0.1	1.25 (0.72–2.17) P = 0.4	1.00 (0.77–1.31) P = 0.9
Age at weaning	1.07 (1.03-1.12) P = 0.002	1.05 (0.97–1.14) P = 0.4	1.06 (1.02–1.11) P = 0.008
Age at follow up	0.73 (0.50-1.05) P = 0.09	1.04 (0.48–2.25) P = 0.9	1.20 (0.82–1.75) P = 0.4
Frequency of illness	1.21 (1.08–1.35) P = 0.001	1.17 (0.94–1.45) P = 0.2	1.22 (1.09–1.36) P = 0.001

8.3. Effects of birth size on outcomes

Annex M shows associations between size at birth and morbidity, mortality and growth from birth to 2.5 years of age. It includes results for all the models (I, II and III). Understanding the relationships between 16 outcomes and 23 birth size categories in 3 models was difficult. An adjusted model was preferable, and model III was chosen for presentation because it did not differ substantially from model II and represented maximal adjustment.

8.4. Size at birth and mortality

We investigated the effect of various classifications of size at birth on mortality. The numbers of deaths identified are shown in Table 8.7. Mortality rates were high. The neonatal mortality rate was 21 per 1000 live births, the infant mortality rate was 33 per 1000 live births and the child mortality rate was 39 per 1000 live births (denominators adjusted for losses to follow-up).

Table 8.7. Numbers of deaths

	Denominator	Frequency	Rate/1000
Neonatal death <28 d	1048	22	21.0
Early neonatal death <7d	1048	14	13.4
Late neonatal death >7 to <28 d	1048	8	7.6
Post-neonatal infant death >/=28 d - <1 y	953	9	9.4
Infant death <1 year	953	31	32.5
Child death <2.5 years	953	37	38.8

Most deaths took place in the neonatal period (n=22). Of the neonatal deaths, nearly two-thirds occurred in the first seven days of life. Neonatal deaths were due to preterm birth (two), infection (seven), birth asphyxia (five), congenital anomaly (one), sudden unexplained death overnight (six) and aspiration during feeding (one). Post-neonatal deaths less than one year of age were due to pneumonia (two), meningitis (one), measles (one), infection (one), a hepatic syndrome (one), complications of cleft palate (one), and sudden unexplained death overnight (two). Child deaths below 2.5 years of age were due to measles followed by tuberculosis (one), a bleeding disorder (one), convulsion (two) and diarrhoea (two).

Table 8.8 shows the number of deaths and death rates per 1000 live births by gestation of infants at birth. Infant mortality was highest at the very low gestational age at birth, 250 deaths per 1000 live births at 31 weeks of gestation and 125 deaths per 1000 live births at 34 weeks of gestation. Mortality rate decreased until 40 weeks of gestation (18 deaths per 1000 live births) but rose again in infants born post-term (77 per 1000 live births)

Table 8.8. Live births and child deaths by gestational age

		Numbers				Rates per 1000 live births				
Gestation at Birth (Week)	Live Birth	Early Neonatal Deaths	Late Neonatal Deaths	Post Neonatal Deaths	Post Infancy Deaths	Early Neonatal (<7d)	Late Neonatal (>7 – 28d)	Post Neonatal (>28d - <1y)	Infant (<1y)	Post Infancy (>1 y – 2.5 y)
31	4	0	1	0	0	0	250	0	250	0
32	2	0	0	0	0	0	0	0	0	0
33	2	0	0	0	0	0	0	0	0	0
34	8	1	0	0	0	125	0	0	125	0
35	21	1	1	0	0	47.6	47.6	0	95.2	0
36	39	1	1	1	1	25.6	25.6	25.6	76.8	25.6
37	83	0	0	2	1	0	0	24.1	24.1	12.0
38	195	3	0	2	2	15.4	0	10.3	25.7	10.3
39	313	3	2	2	0	9.6	6.4	6.4	21.4	0
40	228	2	1	1	2	8.8	4.4	4.4	17.6	8.8
41	101	1	1	0	0	9.9	9.9	0	19.8	0
42 and over	52	2	1	1	0	38.5	19.2	19.2	76.9	0

The mean follow up age was 2.26 years and the minimum and maximum follow up time was from 0 years to 3.85 years. Cox proportional hazards modeling was used to explore the role of measurements at birth in the prediction of death from birth to the end of follow-up. Figure 8.11 illustrates graphically the survival rate from birth to an average 2.5 years of age. It shows that there were more deaths in the first two weeks after which there was a sharp decline. This is entirely predictable from known patterns of neonatal and infant mortality. The overall survival rates at 1 year and at the end of follow-up were 97% and 96% respectively.

Figure 8.11. Predicted survival for children born in the study from birth to 2.5 years of age

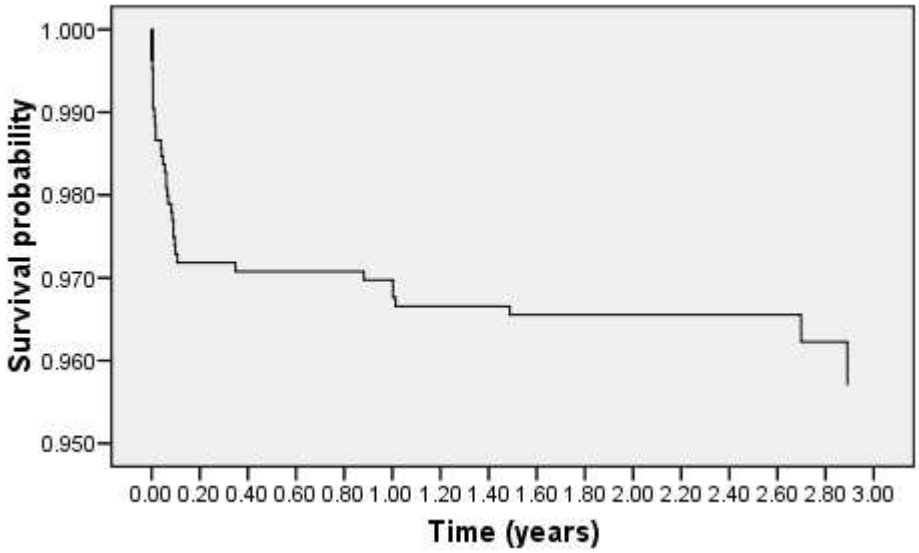


Table 8.9 shows estimates of hazard ratio for neonatal, infant and child deaths, with 95% confidence intervals calculated for different anthropometric parameters measured at birth. None of the anthropometric measurements was a significant determinant of survival.

Table 8.9. Estimates of hazard ratio for anthropometric measurements at birth

	Predicted 1 mo survival			Predicted 1 yr survival			Predicted 2.5 yr survival		
	HR	(95% CI)	P value	HR	(95% CI)	P value	HR	(95% CI)	P value
G	0.87	(0.43 – 2.05)	0.9	0.84	(0.45 – 1.57)	0.6	0.82	(0.47 – 1.43)	0.5
BW	0.40	(0.00- 35.00)	0.7	0.91	(0.03 – 32.45)	1.0	1.10	(0.05 – 26.90)	0.9
BWZ	0.82	(0.13 – 5.38)	0.8	0.66	(0.15 – 3.00)	0.6	0.56	(0.17 – 2.56)	0.6
PI	1.19	(0.28 – 5.12)	0.8	0.76	(0.21 – 2.73)	0.7	0.67	(0.17 – 1.83)	0.3

BW: Birth weight; BWZ: Birth weight Z score; G: Gestation; HR: Hazard ration; mo: month; PI: Ponderal Index; yr: year

Table 8.10 shows associations between different classifications of size at birth and mortality. Three groups of findings are shown: predictors comprising a single index (LBW, SGA or LPI), predictors based on a combination of two indices, and predictors based on a combination of three indices

8.4.1. One anthropometric index as a predictor of mortality

In a model adjusted for the potential confounding factors, LBW was strongly associated with neonatal, infant and child mortality (Table 8.10). The prevalence of LBW was 22%. 5% of

LBW infants died in the first month, compared with 1% of normal birth weight infants. Similarly, 7% of LBW infants died in the first year, compared with 2% of normal birth weight infants. 8% of LBW infants died before their 3rd birthday, compared with 2% of normal birth weight infants. The odds of dying during the neonatal period for a LBW infant were 3.5 times higher than for an infant with normal birth weight. The odds of infant death and childhood death were also higher (3.6 and 3.7, respectively). In contrast with LBW, LPI and SGA were not by themselves associated with increased risk of mortality at any of the three time points.

8.4.2. Two anthropometric indices as a predictor of mortality

When LBW was combined with PI, proportionate LBW infants were at highest risk of neonatal, infant and childhood mortality (API-LBW) but none were significant. As a group, disproportionate LBW infants were only marginally more likely to die in the neonatal period than other infants. When LBW was combined with weight-for-gestational-age, appropriately grown LBW infants were at highest risk of neonatal mortality (LBW-AGA), but not at increased risk of later death. LBW infants who were SGA were at increased risk of mortality in all three age bands, although the association was not significant in the neonatal period. When PI was combined with weight-for-gestational-age, no significant increases in odds were seen.

8.4.3. Three anthropometric indices as a predictor of mortality

Two combinations were not analysed as no deaths were seen, a limitation of the sample size. There were no deaths in LBW infants who were appropriate for their gestational age and had normal PI and normal birth weight infant who were small for their gestational age and had appropriate PI. Three combinations of indices appeared to increase the risk of mortality, although none achieved significance in all three age bands. The highest risk appeared to be to infants who were LBW, proportionate and SGA (LBW-API-SGA) but association was only significant for infant deaths. Infants who were LBW, disproportionate and AGA (LBW-LPI-AGA) had significant risk for neonatal deaths.

Table 8.10. Mortality in children of different birth sizes

Adjusted models	Neonatal death OR (95% CI)	Infant death OR (95% CI)	Child death OR (95% CI)
Single index			
LBW	3.46 (1.36 – 8.85)*	3.60 (1.63 – 7.93)*	3.66 (1.73 – 7.75)*
SGA	1.11 (0.45 – 2.73)	1.34 (0.63 -2.85)	1.67 (0.81 – 3.45)
LPI	1.26 (0.48 – 3.32)	0.98 (0.45 – 2.12)	1.03 (0.49 – 2..16)
2 index combination			
LBW-LPI	2.65 (1.03 – 6.79)*	2.26 (0.90 – 1.03)*	2.13 (0.98 – 4.59)*
LBW-API	6.95 (2.45 – 19.70)	5.98 (2.06 – 17.41)	7.04 (2.31 – 21.44)
NBW-LPI	0.55 (0.22 – 1.40)	0.51 (0.24 – 1.12)	0.57 (0.28 – 1.19)
NBW-API	0.53 (0.17 – 1.61)	0.60 (0.24 – 1.51)	0.50 (0.20 – 1.24)
LBW-SGA	2.15 (0.86 – 5.38)	2.79 (1.31 – 5.96)	3.07 (1.50 – 6.30)
LBW-AGA	5.69 (1.02 – 31.83)*	2.30 (0.47 – 11.24)	1.64 (0.35 – 7.85)
NBW-SGA	0.45 (0.14 – 1.44)	0.40 (0.14 – 1.10)	0.49 (0.19 – 1.25)
NBW-AGA	0.60 (0.23 – 1.53)	0.63 (0.29 – 1.37)	0.54 (0.26 – 1.14)
LPI_SGA	1.15 (0.48 – 2.75)	1.15 (0.55 – 2.38)	1.29 (0.64 - 2.58)
LPI_AGA	1.1 (0.40 – 2.98)	0.86 (0.36 – 2.06)	0.79 (0.35 – 1.80)
API_SGA	0.92 (0.20 – 4.17)	1.46 (0.48 – 4.43)	1.87 (0.67 – 5.16)
API_AGA	0.76 (0.25 – 2.37)	0.85 (0.34 – 2.17)	0.67 (0.27 – 1.70)
3 index combination			
LBW-LPI-AGA	6.55 (1.16 – 37.06)*	2.52 (0.51 – 12.38)	1.82 (0.38 – 8.75)
LBW-API-SGA	4.08 (0.82 – 20.19)	6.46 (1.93 – 21.60)*	8.09 (2.64 – 24.78)
LBW-LPI-SGA	1.66 (0.63 – 4.36)	1.82 (0.81 – 4.08)	1.87 (0.87 – 4.03)
LBW-API-AGA	-	-	-
NBW-LPI-AGA	0.58 (0.17 – 2.02)	0.61 (0.23 – 1.63)	0.62 (0.25 – 1.55)
NBW-API-SGA	-	-	-
NBW-LPI-SGA	0.70 (0.22 – 2.23)	0.62 (0.26 – 1.68)	0.72 (0.28 – 1.83)
NBW-API-AGA	0.78 (0.25 – 2.44)	0.87 (0.34 – 2.22)	0.69 (0.27 – 1.75)

***** Significant at $p<0.05$

8.5. Size at birth and morbidity

8.5.1. Size at birth and morbidity in the first year of life

The association of categories of size at birth with illness in the first year of life is shown in Table 8.11. More than 90% (860) of infants were reported as having had an episode of cough and fever during infancy. 70% (636) suffered diarrhoea and fever. Only 11% had a bout of illness with rashes and fever. Around 28% (307) of infants had more than five episodes of illness. In the 14 days before follow-up at 2.5 years of age, 14% were reported as having diarrhoea, 36% had cough and <1% had measles. The table does not suggest any associations between different classifications of size at birth and illness in infancy. The exceptions were LPI, LBW-AGA and LBW-LPI-AGA. It reduced the risk of cough and fever.

Table 8.11. Summary of association between size at birth and illnesses in infancy

Adjusted models	Cough and fever OR (95% CI)	Diarrhoea and fever OR (95% CI)	Rash and fever OR (95% CI)	Frequency of illness OR (95% CI)
Single index				
LBW	0.83 (0.40 – 1.72)	0.88 (0.60 – 1.29)	0.65 (0.36 – 1.17)	1.31 (0.92 – 1.87)
LPI	0.42 (0.20 – 0.88)*	0.96 (0.70 – 1.32)	1.10 (0.70 – 1.72)	1.18 (0.88 – 1.59)
SGA	1.10 (0.61 – 2.00)	0.94 (0.69 – 1.29)	1.23 (0.79 – 1.93)	1.31 (0.98 – 1.75)
2 index combination				
LBW-LPI	0.69 (0.34 – 1.42)	0.93 (0.63 – 1.38)	0.58 (0.31 – 1.07)	1.35 (0.93 – 1.95)
LBW-API	-	0.68 (0.26 – 1.79)	1.63 (0.45 – 5.89)	0.92 (0.36 – 2.36)
NBW-LPI	0.65 (0.36 – 1.17)	1.01 (0.75 – 1.36)	1.45 (0.95 – 2.21)	0.96 (0.74 – 1.29)
NBW-API	2.18 (1.03 – 4.62)	1.06 (0.76 – 1.48)	0.90 (0.56 – 1.44)	0.86 (0.63 – 1.16)
LBW-SGA	1.14 (0.52 – 2.47)	0.99 (0.67 – 1.47)	0.80 (0.45 – 1.41)	1.39 (0.97 – 1.99)
LBW-AGA	0.18 (0.04 – 0.79)*	0.45 (0.17 – 1.19)	-----	0.66 (0.25 – 1.73)
NBW-SGA	1.02 (0.54 – 1.93)	0.94 (0.67 – 1.31)	1.48 (0.93 – 2.35)	1.07 (0.78 – 1.46)
NBW-AGA	1.10 (0.61 – 1.99)	1.14 (0.84 – 1.56)	0.92 (0.59 – 1.43)	0.80 (0.60 – 1.07)
LPI-SGA	0.85 (0.47 – 1.52)	0.96 (0.70 – 1.30)	0.95 (0.61 – 1.46)	1.30 (0.97 – 1.73)
LPI-AGA	0.53 (0.28 – 1.00)	1.05 (0.74 – 1.48)	1.12 (0.69 – 1.82)	0.85 (0.62 – 1.18)
API-SGA	3.18 (0.75 – 13.52)	0.99 (0.59 – 1.65)	1.81 (0.97 – 3.39)	1.05 (0.66 – 1.68)
API-AGA	1.86 (0.81 – 4.29)	1.02 (0.71 – 1.47)	0.64 (0.36 – 1.12)	0.81 (0.57 – 1.13)
3 index combination				
LBW-LPI-AGA	0.15 (0.03 – 0.68)*	0.48 (0.18 – 1.31)	-	0.66 (0.24 – 1.81)
LBW-API-SGA	-	0.73 (0.26 – 2.06)	1.88 (0.51 – 6.89)	0.93 (0.35 – 2.50)
LBW-LPI-SGA	0.97 (0.45 – 2.10)	1.02 (0.68 – 1.54)	0.70 (0.38 – 1.29)	1.44 (0.99 – 2.09)
LBW-API-AGA	-	0.34 (0.02 – 5.88)	-	0.87 (0.05 – 14.93)
NBW-LPI-SGA	0.86 (0.45 – 1.64)	0.90 (0.63 – 1.27)	1.18 (0.73 – 1.91)	1.06 (0.76 – 1.47)
NBW-LPI-AGA	0.68 (0.36 – 1.29)	1.08 (0.76 – 1.54)	1.34 (0.84 – 2.16)	0.90 (0.65 – 1.25)
NBW-API-SGA	2.55 (0.59 – 10.97)	1.06 (0.60 – 1.89)	1.73 (0.87 – 3.46)	1.08 (0.64 – 1.82)
NBW-API-AGA	1.83 (0.79 – 4.23)	1.04 (0.72 – 1.50)	0.65 (0.37 – 1.14)	0.81 (0.57 – 1.14)

* Significant at $p<0.05$

8.5.2. Size at birth and morbidity in the fortnight before follow-up

Mothers were asked about illness in the 14 days before follow-up. No association was seen between size at birth and diarrhoea, cough or difficulty in breathing. The exception was disproportionate NBW (NBW-LPI), normal birth weight AGA (NBW-AGA) and disproportionate AGA (LPI-AGA). They have significant reduced risk. Table 8.12 gives the impression that LBW might have been associated with an increased likelihood of fever in the last fortnight, since the association appears to recur in several categorisations.

Table 8.12. Summary of associations between size at birth and illnesses in last 14 days before follow-up at 2.5 years of age

Adjusted models	Fever OR (95% CI)	Diarrhoea OR (95% CI)	Cough OR (95% CI)	Difficult breathing OR (95% CI)
LBW	1.57 (1.09 – 2.25)*	1.05 (0.64 – 1.73)	1.43 (0.99 – 2.05)	1.29 (0.68 – 2.46)
LPI	0.88 (0.65 – 1.20)	0.82 (0.54 – 1.24)	0.83 (0.61 – 1.13)	0.97 (0.56 – 1.66)
SGA	1.10 (0.61 – 2.00)	0.94 (0.69 – 1.29)	1.23 (0.79 – 1.93)	1.31 (0.98 – 1.75)
2 index combination				
LBW-LPI	1.46 (1.01 – 2.12)*	1.00 (0.60 – 1.68)	1.34 (0.92 – 1.94)	1.38 (0.71 – 2.65)
LBW-API	1.62 (0.62 – 4.19)	1.07 (0.29 – 3.93)	1.55 (0.60 – 3.99)	-
NBW-LPI	0.71 (0.53 – 0.95)*	0.72 (0.54 – 0.96)*	0.81 (0.48 – 1.35)	0.84 (0.56 – 1.25)
NBW-API	1.09 (0.79 – 1.49)	1.16 (0.85 – 1.59	1.22 (0.80 – 1.86)	1.13 (0.66 – 1.96)
LBW-SGA	1.73 (1.20 – 2.49)*	1.12 (0.68 – 1.85)	1.43 (0.99 – 2.06)	1.36 (0.72 – 2.58)
LBW-AGA	0.51 (0.18 – 1.44)	1.02 (0.39 – 2.66)	0.61 (0.07 – 5.18)	0.56 (0.12 – 2.70)
NBW-SGA	1.10 (0.80 – 1.52)	1.00 (0.72 – 1.39)	1.62 (0.93 – 2.82)	1.12 (0.72 – 1.74)
NBW-AGA	0.69 (0.51 – 0.92)*	0.88 (0.59 – 1.33)	0.80 (0.59 – 1.07)	0.54 (0.31 – 0.94)*
LPI-SGA	1.37 (1.02 – 1.84)*	1.05 (0.70 – 1.57)	1.11 (0.83 – 1.50)	1.46 (0.87 – 2.46)
LPI-AGA	0.57 (0.40 – 0.81)	0.54 (0.27 – 1.06)	0.71 (0.50 – 1.00)*	0.71 (0.43 – 1.18)
API-SGA	1.31 (0.81 – 2.11)	1.25 (0.67 – 2.32)	1.31 (0.81 – 2.11)	1.49 (0.71 – 3.15)
API-AGA	1.01 (0.71 – 1.44)	1.16 (0.72 – 1.86)	1.09 (0.77 – 1.55)	0.80 (0.41 – 1.57)
3 index combination				
LBW-LPI-AGA	0.44 (0.15 – 1.34)	0.67 (0.14 – 3.27)	1.25 (0.46 – 3.38)	0.63 (0.07 – 5.43)
LBW-API-SGA	1.59 (0.58 – 4.31)	1.98 (0.73 – 5.37)	1.26 (0.34 – 4.70)	---
LBW-LPI-SGA	1.66 (1.14 – 2.42)*	1.05 (0.62 – 1.77)	1.31 (0.90 – 1.93)	1.43 (0.74 – 2.76)
LBW-API-AGA	1.94 (0.12 – 32.87)	-	-	-
NBW-LPI-SGA	1.02 (0.73 – 1.43)	1.03 (0.65 – 1.62)	0.94 (0.67 – 1.32)	1.23 (0.70 – 2.18)
NBW-LPI-AGA	0.61 (0.43 – 0.88)*	0.72 (0.43 – 1.20)	0.68 (0.48 – 0.96)	0.54 (0.27 – 1.08)
NBW-API-SGA	1.23 (0.73 – 2.10)	1.24 (0.62 – 2.48)	1.16 (0.68 – 1.98)	1.92 (0.89 – 4.16)
NBW-API-AGA	1 (0.70 – 1.42)	1.11 (0.78 – 1.58)	1.18 (0.73 – 1.90)	0.81 (0.41 – 1.58)

* Significant at $p<0.05$

8.6. Size at birth and malnutrition

Table 8.13 shows the associations of different classifications of size at birth with malnutrition at 2.5 years of age. The prevalence of malnutrition was high. 538 children (58.8%) were stunted (chronic malnutrition), 55 (6%) were wasted (acute malnutrition) and 344 (37.6%) were underweight (stunted, wasted or both).

Table 8.13. Summary of associations between size at birth and malnutrition at 2.5 years of age

All confounders	Stunting OR (95% CI)	Wasting OR (95% CI)	Underweight OR (95% CI)
Single index			
LBW	3.40 (2.19 – 5.30)*	2.93 (1.53 – 5.59)*	3.69 (2.47 – 5.50)*
SGA	2.42 (1.75 – 3.36)*	1.56 (0.83 – 2.92)	3.05 (2.18 – 4.27)*
LPI	1.05 (0.76 – 1.45)	2.16 (1.05 – 4.44)*	1.30 (0.94 – 1.82)
2 index combination			
LBW-LPI	2.95 (1.89 – 4.63)*	2.63 (1.37 – 5.07)*	3.15 (2.09 – 4.75)*
LBW-API	5.29 (1.11 – 25.34)*	2.10 (0.54 – 8.17)	5.72 (1.70 – 19.21)*
NBW-LPI	0.59 (0.43 – 0.80)*	0.91 (0.50 – 1.65)	0.64 (0.47 – 0.88)*
NBW-API	0.85 (0.61 – 1.18)	0.35 (0.15 – 0.79)	0.64 (0.45 – 0.90)
LBW-SGA	3.01 (1.92 – 4.70)*	2.63 (1.39 – 4.97)*	4.08 (2.71 – 6.15)*
LBW-AGA	3.28 (0.85 – 12.69)	2.18 (0.49 – 9.72)	0.65 (0.23 – 1.81)
NBW-SGA	1.31 (0.93– 1.85)	0.65 (0.32 – 1.28)	1.20 (0.85 – 1.69)
NBW-AGA	0.39 (0.28 – 0.54)	0.57 (0.30 – 1.08)	0.35 (0.25 – 0.49)
LPI-SGA	1.92 (1.39 – 2.66)*	1.99 (1.10 – 3.61)*	2.13 (1.54 – 2.93)*
LPI-AGA	0.47 (0.33 – 0.67)	0.89 (0.44 – 1.79)	0.49 (0.34 – 0.72)
API-SGA	1.85 (1.05 – 3.24)*	0.41 (0.12 – 1.40)	2.27 (1.34 – 3.82)*
API-AGA	0.72 (0.50 – 1.03)	0.58 (0.25-1.34)	0.45 (0.30 – 0.68)
3 index combination			
LBW-LPI-AGA	5.17 (1.06 – 25.16)*	1.25 (0.23 – 6.73)	0.63 (0.21 – 1.85)
LBW-API-SGA	11.26 (1.35 – 93.71)*	1.47 (0.30 – 7.11)	7.82 (1.99 – 30.74)*
LBW-LPI-SGA	2.58 (1.64 – 4.07)*	2.56 (1.34 – 4.90)*	3.59 (2.35 – 5.48)*
LBW-API-AGA	0.36 (0.02 – 6.14)	10.27 (0.49 – 215.12)	0.92 (0.05 – 15.99)*
NBW-LPI-AGA	0.42 (0.29 – 0.60)*	0.81 (0.39 – 1.69)	0.53 (0.36 – 0.78)*
NBW-API-SGA	1.40 (0.77 – 2.56)	0.17 (0.02 – 1.25)	1.65 (0.92 – 2.95)
NBW-LPI-SGA	1.22 (0.85 – 1.75)	0.99 (0.50 – 1.96)	1.00 (0.70 – 1.44)
NBW-API-AGA	0.73 (0.51 – 1.05)	0.49 (0.20 – 1.19)	0.45 (0.30 – 0.68)

***** Significant

8.6.1. One anthropometric index as a predictor of malnutrition

There was a significantly increased odds of malnutrition among children who were born with LBW. The odds was highest for underweight (OR 3.7), followed by stunting (3.40) and wasting (2.93) at 2.5 years of age. Low PI in newborn infants by itself had no significant association with stunting or underweight in children. However, low PI was associated with wasting (OR 2.2). SGA infants had increased odds of being stunted and underweight in childhood. The odds was 3-fold for underweight (OR 3.05) and 2-fold for stunting (2.42). Children who were born SGA were not more at risk for wasting.

8.6.2. Two anthropometric indices as a predictor of malnutrition

The greatest risk of subsequent malnutrition was in children born LBW. Proportionate LBW infants had a five-fold increased odds of stunting and underweight at 2.5 years of age. Disproportionate LBW carried significant risks of stunting, wasting and underweight during

childhood, although the odds ratios were in the region of 2. LBW infants born SGA were more likely to be malnourished in all three categories at 2.5 years of age. There was not much effect of combining PI with weight-for-gestational-age: SGA infants were more likely to be malnourished at 2.5 years of age, and this association was not modified much by proportionality for stunting and underweight.

8.6.3. Three anthropometric indices as a predictor of malnutrition

The most striking risk groups were the combination of LBW with SGA (LBW-API-SGA or LBW-LPI-SGA), which was significantly associated with stunting and underweight at 2.5 years of age. Proportionality did not seem to play a major part in the risk. LBW with AGA and low PI showed increased risk for stunting (LBW-LPI-AGA).

The sensitivity, specificity and positive predictive value of different categories of size at birth in predicting the outcomes is given in Table 8.14. It shows the results only for those categories which had a significant association with mortality and malnutrition.

Table 8.14. Sensitivity, specificity and positive predictive value for a range of possible risk groups and outcomes

	Risk + Outcome +	Risk + Outcome -	Risk - Outcome +	Risk – Outcome -	Sensitivity (%)	Specificity (%)	Positive predictive value (%)
Neonatal mortality							
LBW	12	219	11	806	52.2	78.6	5.2
LBW-LPI	10	191	13	819	43.5	81.1	5.0
LBW-AGA	3	27	20	994	13.0	97.4	10.0
LBW-LPI-AGA	3	24	20	986	13.0	97.6	11.1
Mortality under 2.5 y							
LBW	19	212	18	799	51.4	79.0	8.2
LBW-LPI	14	187	22	810	38.9	81.2	7.0
LBW-API	4	21	32	976	11.1	97.9	16.0
LBW-SGA	16	185	21	822	43.2	81.6	8.0
LBW-API-SGA	4	19	32	978	11.1	98.1	17.4
Stunting							
LBW	151	43	387	334	28.1	88.6	77.8
SGA	321	147	216	228	59.8	60.8	68.6
LBW-LPI	132	40	401	331	24.8	89.2	76.7
LBW-API	17	3	516	368	3.2	99.2	85.0
LBW-SGA	133	38	404	337	24.8	89.9	77.8
LPI-SGA	258	119	274	250	48.5	67.8	68.4
API-SGA	61	27	471	342	11.5	92.7	69.3
LBW-LPI-SGA	115	36	418	335	21.6	90.3	76.2
LBW-API-SGA	16	2	517	369	3.0	99.5	88.9
LBW-LPI-AGA	17	4	516	367	3.2	98.9	81.0
Wasting							
LBW	23	171	32	689	41.8	80.1	11.9
LPI	44	572	11	277	80.0	32.6	7.1
LBW-LPI	20	152	35	697	36.4	82.1	11.6
LBW-SGA	20	151	34	707	37.0	82.4	11.7
LPI-SGA	31	346	23	501	57.4	59.1	8.2
LBW-LPI-SGA	18	133	37	716	32.7	84.3	11.9
Underweight							
LBW	118	76	226	495	34.3	86.7	60.8
SGA	227	241	115	329	66.4	57.7	48.5
LBW-LPI	102	70	240	492	29.8	87.5	59.3
LBW-API	15	5	327	557	4.4	99.1	75.0
LBW-SGA	109	62	34	707	76.2	91.9	63.7
LPI-SGA	179	198	161	363	52.6	64.7	47.5
API-SGA	47	41	293	520	13.8	92.7	53.4
LBW-LPI-SGA	94	57	248	505	27.5	89.9	62.3
LBW-API-SGA	14	4	328	558	4.1	99.3	77.8

Chapter 9. Discussion

9.1. Key findings

Examination of size at birth showed that there was a high prevalence of LBW (25%), SGA (55%) and LPI (70%) in the infants of women from Dhanusha and Mahottari districts involved in the trial. Low PI was particularly common.

As expected, none of the prediction models for size at birth was particularly strong. The most common predictors of size at birth were gestational duration, infant sex, maternal pre-pregnancy weight, gestational weight gain, and parity. PI and low PI were the least explained by potential risk factors.

LBW and LBW-LPI were associated with neonatal, infant and young child mortality and indicators of malnutrition. LBW had higher odds ratios than LBW-LPI. LBW-SGA was the category with highest sensitivity and specificity as a predictor across the board.

9.2. General limitations

As mentioned earlier, the study was based on a cohort of pregnant women enrolled in a trial of antenatal multiple micronutrient supplementation. The intervention group showed effects on size at birth that could have made the overall findings unrepresentative of the population. We tried to reduce bias by using only the control group for quantification of the size at birth and prevalence, whereas we adjusted for the supplementation in risk factor and outcome analysis. However, the effects of multiple micronutrients on size at birth cannot be ruled out completely.

The sample size was calculated to evaluate the birth weight difference for the multiple micronutrient supplementation trial. We did not have independent sample size estimation for other birth size indicators. The sample size was slightly reduced for subsequent analysis because of some missing measurements.

Although participants came from both rural and urban areas in two districts, the core activities of the study were hospital-based and, although the findings are likely to be generalizable, we cannot be sure of this. National figures suggest that 26% of pregnant women do not make antenatal care visits (NDHS 2006).[182] Conversely, though hospital-based, the study did not exactly reflect the obstetric case-mix of the hospital because many pregnant women came to the hospital specifically to be enrolled in the study. This was because the study provided free antenatal care and ultrasound evaluation, which attracted a wide range of women from better-off to poor, 'higher' ethnic groups to untouchables, and students to business families.

Another potential limitation could be measurement error. Although we trained, randomly visited and checked the measurement technique, measurement error cannot be ruled out completely, especially for the measurement of size at birth because of involvement of a number of observers for hospital and home delivery cases.

Other factors that might limit the generalisability of the findings were the characteristics of the study population. In general, the area is inhabited by maithili ethnic groups and some other groups who have migrated from other regions of Nepal. The relative proportions of ethnic groups were not 'representative' of Nepal, although it is hard to see how this could be possible without a national sample. The national figure for 2006 reported female education in the reproductive age group (15-49 years) as 29% for secondary schooling or higher. The nutrition statuses documented were: a mean BMI of 20.6 Kg/m^2, a prevalence of low BMI of 24%, and an anemia level (<110g/L) of 36%. The prevalence of LBW was 14.3%. Comparison with this study gives the impression that our sample consisted of relatively privileged groups with more schooling (44%). It was felt that this was a result of the case-mix of urban and rural women with easy access to health facilities, and a moderately poor population, rather than extremely poor or wealthy groups. However, women in the study were more likely to be thin (mean BMI 19.79 Kg/m^2) and anaemic (35%), and more likely to give birth to LBW infants.

9.3. Limitations of the individual studies

9.3.1. Characteristics of mothers and infants, including size at birth

Most of the limitations of this part of the study fell under the general heading. The other limitations were sample size and the cut-offs used to define abnormal size. The sample available for describing size at birth was limited. We omitted newborns born to mothers who had taken multiple micronutrient supplements to avoid possible contamination of the data. Another drawback was the lack of a gold standard cut-off point to assess the proportionality of infants based on PI. Different studies have used different cut-offs to define proportionality in the newborn infant. We used a cut-off of 2.5 g/cm^3 to categorize infants into proportionate and disproportionate groups.[90;201] This makes comparison with other studies difficult in some cases.

Similarly, another weakness of the methodology was the use of British reference standards to define SGA due to lack of a reference standard for the Nepalese population. SGA was defined as birth weight below the 10^{th} percentile of the British population (British reference LMSgrowth programme; T Cole, personal communication). We used a cut-off of < -1.28 z scores, which is equivalent to < 10^{th} percentile. A further limitation was the classification of SGA rather than IUGR, because of lack of diagnosis antenatally through continuous monitoring of growth trajectory. Although we did track some pregnancies with serial ultrasound, continuous monitoring of intrauterine growth was not feasible in the study setting. Individual identification, clinical case management and prevention of complications do not tend to be a priority in this population.[202] Bakketeig's approach is to identify each and every growth retarded infant in a clinical setting, but this applies in high-income countries. Finally, we were unable to investigate low BMI in newborns, because we could not find studies that have used low BMI to define abnormal size at birth.

9.3.2. Predictors of size at birth

The variables used to build the models included documented potential risk factors in low-income countries. This may mean that relevant variables found to be risk factors in developed

countries were omitted. However, these would not have been significant in our population. For example, health insurance is rare in Nepal. Psychological stress and hard work during pregnancy might have an influence, but were not measured. Regarding the investigation of an independent relationship with the outcome, one might argue that our failure to adjust for maternal smoking was problematic, since maternal smoking has been shown to have an independent effect on fetal growth and infant mortality.[1;203] No participants reported smoking, but we have the impression that this was not the case.

We used an ethnic group classification that was used locally rather than nationally. The locally prevalent ethnic groups were based on Hinduism, with Brahmins highest and Sudras lowest. The NDHS survey used a broad classification and put most of the ethnic groups in the region under two categories: Yadav and other Terai origin. This would have been simpler, but we feel that it might not have much real meaning.

The obstetric history obtained from mothers was based on maternal recall, which might not be accurate. Reports of miscarriages could be unreliable due to the prevalent practice of female feticide.[204] Mothers' recall of giving birth to a small infant was used as a surrogate for previous infants with LBW.

Generally, gestational age is determined based on date of last menstrual period (LMP). Estimation of gestational age by ultrasound does not reflect the usual practice in the general population. Analysis of the difference in the mean gestational age by LMP and ultrasound showed underestimation of gestational age by 0.43 weeks in LMP-based gestational age (16.30 versus 15.87), which is equivalent to less than one day. However, 29% of the mothers could not recall the date of their LMP. Accurate estimation was especially important to quantify the proportion of SGA and to classify size at birth for gestational age.

Another limitation might be our description of socioeconomic status. This is difficult in a context where more than one family member's income sources (farming and off-farming

income like small business and labour) are involved and the government tax system is not properly established. The indicators collected were not comprehensive because they failed to quantify the total household wealth and cash income and expenditure. The asset score that we used for the study was rough, and we have already pointed out that the inclusion of a television in the top group was probably unwise. Socioeconomic status score was based on principal components methods used by the World Bank, which used only the first component as an indicator.

9.3.3. Associations of size at birth with mortality, morbidity and malnutrition in childhood

The age of children at follow-up ranged from 1.98 years to 3.85 years. There were a number of reasons for this: follow-up was started late due to funding pressures; duration of follow up was limited for the same reason and follow-up was dictated by the age of children and necessity of covering flood-prone areas ahead of the monsoon season.

A question of particular interest is whether the outputs investigated were comparable to international norms. We considered all outcomes in the context of international acceptability, except for child mortality. The norm is to report under-five child mortality rates, but the study reported for children under about 2.5 years of age. This was an unavoidable result of the follow-up timing.

The morbidity data were entirely dependent on maternal reporting of illnesses. We failed to compare the maternal reports with physician reports. The bias in the result depends on the time span that had elapsed between recall and illness. Based on this, morbidity data for the first year of life was probably less reliable than that of illness in the last 14 days before the interview. We did collect information on physicians' prescriptions for recent morbidity if available, but we could not rely on them because of haphazard use of medicines (including antibiotics) for the illness. The major limitation of morbidity data in the first year of life was that it was based on retrospective maternal interviews at 2-3 years of age. The possibility of misdiagnosis was high.

Firstly, data were collected using closed-questions. Secondly, the illnesses were not properly defined. No rigorous attempts were made to differentiate between upper and lower respiratory tract infections or severity of illness. Lower respiratory tract infections are usually of a more serious nature than upper respiratory tract infections. Cough and fever due to the common cold is common in children and estimates are up to 6-10 illnesses per year. No attempts were made to exclude other causes like allergies. Although symptoms were recalled better for the last 14 days, collection of only specific symptoms of illness made it difficult to diagnose cases with certainty. Physician's prescription was not utilized for the diagnosis for the reasons mentioned above. For these reasons, we find the models with morbidity outcomes unconvincing. There were some possible associations, but they could have arisen from a 'fishing expedition', as a many associations were tested. We do not make much of the morbidity findings in either the results or discussion chapters.

We compared our cohort with international WHO references for describing child malnutrition using z-scores (standard deviation scores). How appropriate the international reference was to the study setting is a matter for investigation.

9.4. Strengths

The study was based in a population where small size at birth is a public health problem. The major strength of the study was its use of prospective data. National birth data are based on the DHS[182], which uses maternal reports of small size at birth. Blanc and colleagues reported pitfalls in DHS data such as digit preference and the influence of cultural preferences on maternal reporting of size at birth.[205]

I am not aware of any prospective studies in Nepal that have followed up pregnancies from early gestation to delivery, and have then followed up children. The study was novel in investigating anthropometric indices at birth - PI, BMI and SGA - and in examining newborn classification using combined anthropometric parameters and indices. We have found only two studies which have reported similar indices (Pal et al and manandhar et al).[206;207] To our

knowledge, this is the first time that the prevalence of SGA has been derived using reliable estimates of gestational age. Furthermore, the retention rate of the participants was high (94%). The sample available for follow-up of children was 953 out of 1200.

The study used ultrasound based gestational age estimates. This is more appropriate than LMP in this context for the following reasons. First, recall of LMP was confusing because it was based on recall of important events like festivals and full moon days. Second, since the study was aimed at size at birth, it was important to use ultrasound-based gestational age for consistency across the study participants and for reliability. Since it was performed by a single observer except for nine cases, this reduced the possible inter-observer error. Another clear advantage was that it allowed the quantification of SGA and the accurate assessment of term LBW.

Data on birth anthropometry were available within 72 hours of birth. This timing of evaluation of size at birth is internationally accepted. Another strength of the study was that anthropometric measurements were made by trained observers using accurate scales: electronic weighing scales accurate to 10 g, rollameters accurate to 1 mm and measuring tapes accurate to 1 mm. One of the major strengths of the outcome study is the use of the median of three anthropometric measurements. The observers were trained in child and maternal anthropometry at follow-up. A pilot study was conducted to train the field workers, to assess the inter-observer and intra-observer variability among eligible observers, and for practice. We employed only two observers for measurements to reduce intra-observer and inter-observer variation, and two for interviews.[2] Morbidity data were collected by ANMs and CMAs from the local community, who had been trained in IMCI. We believe that they had a better understanding of local communities, health perceptions and medical knowledge. We did not offer free medical treatment which could have prevented mothers from over-reporting illnesses.

The prediction study was able to take account of most of the well-known determinants of size at birth applicable to Nepal. Apart from gestational age, maternal characteristics used were readily available and measurable at the time of booking in the antenatal clinic.

9.5. Characteristics of mothers and infants, including size at birth

The purpose of this part of the study was to investigate the distribution of normal and abnormal size at birth in a southern Nepalese population and to evaluate the implications of using different classifications to define size at birth. The special interest lay in what birth weight really means in the prevention of morbidity and mortality, and in its implications for adult health. The sample of women involved in the study mainly constituted middle-income, multigravid Maithili women in their twenties with some education. Substantial percentages of women were undernourished with low BMI at enrolment and anaemia (28% and 35% respectively). For the derivation of mean birth anthropometric parameters for this population, the analysis was restricted to healthy mothers who were on government recommended iron and folic acid supplements. Conditions which were likely to affect fetal growth were excluded at the time of enrolment. The data were therefore fairly representative of healthy mothers in this population.

9.5.1. General findings

As expected, the size of infants at birth was small compared to infants in high-income countries.[208;209] It is striking to note that the mean PI was low for the population, indicating that most infants born in the area have disproportionate body size at birth. This probably means that the majority suffer acute or sub-acute malnutrition in utero. Table 9.1 provides a comparison of studies that have reported results on birth size distribution for Nepal. The evidence from these studies confirms the smallness of infants at birth. Standard deviations were similar across all studies.

Table 9.1. Studies reporting the distribution of infant size at birth in Nepal

Study (year)	Place	N	Sex	Weight (kg)	Length (cm)	HC (cm)	PI (g/cm^3)	BMI (kg/m^2)	Comment
Present study 2002 - 03	Hospital Janakpur Prospective	522		2.736 (0.414)	48.7 (2.47)	33.48 (1.47)	2.37 (0.33)	11.50 (1.46)	Strengths: scale accurate to 1g; anthropometry measured within 72 h; abnormal conditions that affect pregnancy not included; included term and preterm, singleton; ultrasound based gestation
			M	2.800 (0.419)	49.15 (2.51)	33.77 (1.44)	2.37 (0.36)	11.62 (1.49)	
			F	2.672 (0.399)	48.40 (2.38)	33.18 (1.45)	2.36 (0.32)	11.37 (1.41)	Limitations: hospital based
			P value	0.001	0.001	0.001	0.6	0.06	
Christian et al. 1998-01 [142]	Community Sarlahi Prospective	685		2.587 (0.445)	47.2 (2.32)	32.5 (0.46)			Strengths: Community based; included term and preterm; scale accurate to 1g; anthropometry obtained within 72 h; LMP checked against week of positive pregnancy test Limitations: inclusion of twins; all mothers (healthy, unhealthy) included
UNICEF 1998[164]	Hospital Biratnagar, Pokhara, Nepalgunj, Kathmandu Cross-sectional	3636		2.810 (0.4)					Strengths: more diverse hospital population; scale accurate to 10g; gestation by LMP; included term and preterm singletons Limitations: inclusion criteria not mentioned for mothers and time of measurement
			M	2.850 (0.47)					
			F	2.770 (0.44)					
			P value	< 0.05					
Manandhar et al. 1997 [210]	Hospital Kathmandu Cross-sectional	1499		2.800 (0.400)					Strength: Live singleton healthy newborns; gestation by Ballard method; healthy mothers; weighed within 24 h; Limitations: Scale accurate to 100g; only term infants
			M	2.800 (0.200)					
			F	2.700 (0.100)					
			P value	0.001					
Manandhar et al. 1993-94[207] and Pal 2000 [206]	Hospital Kathmandu Cross-sectional	578		2.690 (0.390)	47.2 (2.1)	32.6 (1.3)	2.5 (0.29)	12 (1.3)	Hypoglycemia study 1993-94 Strengths: Live singleton healthy newborns; healthy mothers; scale accurate to 10g; weighed within 24 h; gestation by Capurro method Limitations: Only term infants
			M	2.710 (0.390)	47.5 (2.1)	32.8 (1.4)		12 (1.3)	
			F	2.660 (0.390)	46.9 (2.0)	32.4 (1.2)		12.1 (1.4)	
			P value	>0.05	0.001	0.001		> 0.05	

Data presented are mean (SD)
M: Male; F: Female, S: Significance, +: significant difference between male and female infant ($p < 0.05$);
HC: Head circumference; PI: Ponderal index, BMI: Body mass index

Out of five studies, only one study by Christian and colleagues was based in the community.[142] The others were from zonal, regional or urban hospitals located in different parts of Nepal. As expected, the community-based study showed lower mean birth size than the present study: 149 g lower for birth weight, 1.57 cm for birth length and 0.98 cm for head circumference. Given the expense involved in hospital care, including transport expenditure, users of public hospitals are not necessarily representative of the general population. The poorest and richest groups tend to be less represented in hospital samples. As observed in our study, richer people prefer to use the private sector over government hospitals, and poor families tend to access less antenatal and delivery care.

Comparison of maternal anthropometric parameters at enrolment showed that despite having a similar mean height of 150.1 cm, mothers from the study in Sarlahi were 2.23 kg lighter and 0.79 kg/m^2 lower in BMI than mothers in our study.[142] This could be a truer representation of the general population, and the lower mean birth size in Sarlahi could be partly explained by maternal nutritional status. On the other hand, the methodology used in Sarlahi for the selection of participants was different from our study: twins and all mothers were included, irrespective of their health status. This may have brought down mean estimates of birth size.

The four studies that investigated birth size in hospitals had a range of findings. The methodologies used differed in terms of sample size, inclusion and exclusion criteria and scales used for measurement. Hence, they are not directly comparable. The figures from the urban maternity hospital in 1999 had a mean birth weight for males similar to our study, but 28 g lower for females.[210] Mean birth weight was 64 g greater. The drawback of the urban hospital study is that birth weight was reported to one decimal place, making comparison difficult. Moreover, exclusion of preterm births from the study made comparison difficult and presumably inflated mean birth size.

The 1993 maternity hospital data showed lower birth size.[206;207] The findings were derived from an urban hospital population of healthy infants with uncomplicated deliveries. The mean values are of interest in that male infants were 90 g lighter than in our study, and female infants 12 g lighter. Overall mean birth weight was 46 grams lower. The study did not show a significant difference in mean birth weight between sexes. Similarly, mean length and head circumference at birth were lower than the current study: 1.5 cm lower for birth length and 0.8 cm lower for head circumference. There were significant sex differences in length and head circumference, as in our study, but the study demonstrated insignificant sex difference, in contrast to our study. The differences in the two populations are that our study sample was not purely hospital-based, and that the Kathmandu statistics did not include preterm infants. The data are also a decade old. Birth anthropometry for the same urban maternity hospital with the same study design showed higher birth size in 1997 than 1993. However, comparison was made difficult by the reporting of measurements to one decimal place. It is possible that during the intervening four years there had been an improvement in birth anthropometric status. This finding may reflect a trend towards increasing birth weight over time due to improvement in nutrition and intergenerational effects. In the larger multicentre study,[164] however, infants were larger despite the fact that the data were collected five years earlier than ours. The methods were quite similar to our study, but involved diverse hospital samples across the country.

None of the studies discussed above reported mean PI, except that of Pal and colleagues, [206]or BMI, except that of Manandhar and colleagues.[207] Both of these studies reported data for a tertiary hospital sample with a sample size similar to ours, but without preterm infants. The mean BMI was also lower in our study. All the studies reported similar smaller mean birth lengths (47.2 cm) and head circumferences (32.5 to 32.6 cm). Interestingly, the infants born in our study were heavier, longer and had larger head circumferences. Possible reasons for this include differences in methodology, the years of study and the inclusion criteria.

Overall, the existing studies had a number of weaknesses. They tended to exclude preterm infants, and were therefore documenting birth size at term; they tended to be drawn from

hospital deliveries, and included women with illnesses; they tended to measure birth size to the nearest hundred grams, which causes problems when trying to classify infants measured as 2.5 Kg as normal or LBW; and few studies reported PI or size for gestational age.

We still lack representative studies that document the prevalence of LBW country-wide. Our study reported a prevalence of LBW (25%) similar to other Nepalese studies.[164] The estimate reported by the DHS was 21% for 2001, but this was based on maternal recall of rough infant size.[182] The best existing estimate was probably 27%, based on the multi-hospital study of 1998.[164] There is a similarity in the prevalence in spite of the different methodologies used. The prevalence is well above the cut-off for public health intervention (>15 %).

9.5.2. Specific findings

The high incidence of LBW in Nepal is mainly due to intrauterine growth retardation.[92] As expected, the ratio of term to preterm LBW showed that most of the infants born in this part of the country were smaller due to intrauterine insult and not due to shorter gestational duration. The UNICEF study also demonstrated similar larger proportions of term LBW contributing to the total LBW incidence.[164]

Having mentioned that SGA was based on a British reference, the actual prevalence might be lower than observed in our study. The study classified 55% of infants as SGA. Table 9.2 summarises previous breakdowns of birth dimensions along these lines. As observed previously among Nepalese infants, the incidence of SGA was considerably higher than in high-income countries.[211] However, the previous calculation was based on indirect methods and the observations seem unrealistic. Evidence is that the incidence was relatively lower. We have calculated the prevalence of SGA for the first time in southern Nepal, with precise dating. As documented, most infants suffered SGA at term.

Table 9.2. Studies describing abnormal birth sizes in Nepal

Study (year)	Birth anthropometry	Site	Mean (SD) [n]
de Onis (1988) [211]	LBW	Rural	14.3 %
	LBW	Urban	22.3 %
	IUGR-LBW	Rural	11.8 %
	IUGR-LBW	Urban	18.2 %
Pal 2000 [206]	LBW	Urban	32 % [577]

The fact that so many infants had low PI merits more discussion. The pattern of compromised growth was seen in most infants, including those of normal birth weight and appropriate for gestational age. It is difficult to interpret this large discrepancy between PI and birth weight and weight-for-gestational-age. There are four possibilities.. First, this is perhaps just the use of the wrong index for defining size at birth. Second, it could be due to selection of an arbitrary cut-off point. It is possible that the cut-off should be set higher for this population. To my knowledge, there is no standard cut-off available to define low PI. The only reason for our choice was that it has been used in India, a country similar to ours,[90] and that the cut-off used in other countries is not that different. For instance, Morris used a cut-off of <2.6 g/cm^3 for a population in Brazil.[91] Third, the observation may be just a fluke and incorrect. In my opinion, this is unlikely because the anthropometric measurements are the main outcome of our study, and were carried out within 72 hours of birth after rigorous training with constant checking throughout the study using accurate scales. Finally, the estimation may be a true picture of newborn size. I believe that this is the most likely possibility because of the quality of the study. It is quite possible that most Nepalese infants are disproportionate as a result of some growth restriction.

9.5.3. Wider implications

What is the likely implication if most Nepalese infants are disproportionate? If most infants are born after suffering fetal under-nutrition, the rapidly increasing epidemic of diabetes and coronary heart disease in developing countries might be partially accounted for. The fetal

origins hypothesis states that disproportionate fetal growth programmes later adult onset diseases.[32;212] Low PI alone has been demonstrated to have an independent association with adult coronary heart disease[213;214], diabetes[215] and microalbuminuria, in turn related to insulin resistance and cardiovascular disease[216]. If our hypothesis is correct, the previously undiagnosed wasting in newborns would be a time bomb set to explode in the near future. Furthermore, a positive association with later morbidity has also been described.[96;97] These ideas raise questions regarding the use of PI in hospitals as a standard practice and regarding what can be done towards minimizing the risk of adult disease.

Different methods of classifying newborn infants based on anthropometry might allow us to develop a new classification. Small (LBW) infants are at substantial risk of morbidity and mortality whether due to preterm or to intrauterine growth retardation (represented by SGA). Studies have shown that sub-categories of birth size may be associated with mortality, morbidity and size in later life. For example, disproportionate SGA infants are more at risk of mortality than AGA infants compared to proportionate SGA infants.[217]

Most LBW infants in our study were SGA. This is an important public health problem. The prevalence of LBW was as high as 25% and of SGA as high as 55%. If so many infants are judged to be at risk on the basis of simple classification, it might be useful to sub-classify infants to focus on particular groups at greatest risk. Wasted SGA infants constituted nearly 80% of total SGA. Cuttini reported a considerable increase in neonatal deaths among stunted SGA infants compared with wasted SGA infants[218],but disproportionate SGA infants have been shown to have more early postnatal morbidity than proportionate SGA infants.[96;97;219] Our results support the previous findings of low mean birth weight in wasted infants.[219]

There is a tendency to underestimate the proportion of infants at risk when a single method is used. Only one fifth of infants were normal in terms of weight, PI and weight-for-gestational-age. It is noteworthy that a considerable proportion of SGA infants had normal weight at birth (>= 2500 g), and that a substantial proportion of LBW infants suffered SGA, the majority of

them being wasted. The importance of this finding is at the clinical level where the use of growth charts and serial ultrasound scans for detecting intrauterine growth retardation is not the usual practice, and where weight at birth is the only indicator available. For instance, the most popular category in use in developing countries is LBW. Table 9.3 demonstrates how other abnormal categories are hidden in this single anthropometric category. Only 27% of NBW infants have normal PI and weight adequate for their gestational age

Table 9.3 Subcategories of LBW and NBW

	LBW (%)	NBW (%)
SGA-LPI	76	35
SGA-API	10	11
AGA-LPI	12	29
AGA-API	2	27

In summary, we found levels of LBW similar to those described in previous studies, but added to this a clear understanding that many more infants were small for their gestational ages, and still more were disproportionate. These findings have implications for both early survival and long term health.

9.6. Predictors of size at birth

The purpose of this study was to deepen existing knowledge of factors associated with size at birth and to provide information on how well the potential risk factors found in previous studies explain size at birth. The hypothesis was that known risk factors for LBW could be used to predict size at birth in other dimensions. As mentioned earlier in the thesis, although this hypothesis was reasonable, I had a second reason for asking the question. There have been many risk factor studies, but I was not convinced that they could be translated into actual practice in low-income countries. Not many of the risk factors seemed modifiable and, because small size at birth is so common, I wondered if a careful analysis could argue that we have reached the limit of usefulness. Of particular interest was the question ‘do we need more risk factor studies?’

9.6.1. General findings

In this cohort of healthy mothers, we found that known risk factors did not seem to explain size at birth outcomes convincingly. The hypothesis was tested through a prospective cohort with normal pregnancy outcomes (live, singleton newborn infants with no gross congenital anomalies). The cohort of mothers was of low-to-middle income, in their twenties and mostly in their second pregnancies. They had low mean BMI and no chronic illnesses. The study was conducted in a semi-rural setting in Nepal with a high prevalence of LBW, low PI, SGA and malnutrition in children, as illustrated in the preceding chapter. In short, the situation was a good one for addressing the question. Table 9.4 summarises the findings of all of the analyses in schematic form.

Table 9.4. Summary of significant associations of size at birth in the study

Birth Size	Ethnicity	Education	Rural or urban	SES	Poor obstetric history	Maternal age	Parity	Maternal height	Maternal weight	Weight gain	Maternal illness	Blood haemoglobin	Supplement	Gestation at birth	Infant sex
W	+	+ +			‡ miscarriage	+	+ +	+ +	+ +	+ +			+ +	+ +	+ +
LBW		+				+	+ +	+	+ +	+ +			+ +	+ +	+ +
SGA				+	+ miscarriage	+	+ +	+	+ +	+ +			+ +	NA	
L	+			‡	++ death	+	‡	+ +	+ +	+ +	+ SBP ‡ DBP			+ +	+ +
BMI	+			+		+	+ +	+	+ +	+ +			+ +	+ +	+ +
PI				‡		+	+ +			+ +				+ +	
LPI				+			+ +			+ +				+	
HC		+		+		+	+	+	+	+ +				+ +	+ +

W: weight; L: length; LBW: Low birth weight; SGA: Small for gestational age; BMI: Body mass index; PI: Ponderal index; LPI: Low ponderal index; SES: socioeconomic status; Poor obstetric history: prior history of stillbirth, LBW or dead child; NA: Not applicable- small for gestational age is sex and gestation specific.
+ significant in univariable analysis ++ significant in univariable and multivariable analysis ‡ almost significant in univariable analysis but not significant in multiivariable analysis

9.6.2. Specific findings

Table 9.5 is presented again here, since it summarises the same findings as Table 7.18 but in a different way.

Table 9.5. Main risk factors identified in the analyses

Variable	Predicts to some degree in multivariable analyses
Gestation (wks)	Birth weight, LBW, length, BMI, PI, head circumference
Maternal weight at enrolment (kg)	Birth weight, LBW, SGA, length, BMI
Maternal height (cm)	Birth weight, length
Maternal weight gain (kg)	Birth weight, LBW, SGA, length, BMI, PI, LPI, head circumference
Parity	Birth weight, LBW, SGA, BMI, PI, LPI
Infant sex	Birth weight, LBW, length, BMI, head circumference
Supplement	Birth weight, LBW, SGA, BMI
Education	Birth weight

Evaluation of associations with 21 potential determinants of size at birth showed that only a few had an independent and significant association in our sample (see Table 9.4). Maternal characteristics that had no significant influence on various dimensions of size at birth included rural/urban residence, antenatal general illness and blood haemoglobin level. When these potential factors were forced into the regression, none of them demonstrated any effect in the final model. There was no effect of maternal residence on birth size parameters in this population univariably or multivariably. This goes against the general perception that the urban population are a more economically stable, more advantaged group and are more likely to give birth to bigger infants. None of the birth size indicators had any association with maternal general illness except for birth length. Systolic and diastolic blood pressure showed a univariable association but showed no independent association. Surprisingly, blood haemoglobin status of women at enrolment showed no association. The lack of effect of maternal illness, blood pressure and blood haemoglobin level on size at birth is difficult to interpret. Compromise in blood pressure or haemoglobin level during pregnancy could affect the supply of nutrients and oxygen to the fetus. The fact that maternal eclampsia also had no significant effect could be explained by the limited sample size.

Despite significant univariable association, some risk factors lost significance in the multiple regression analysis. These were categorized as having doubtful association, and included maternal socioeconomic status, age, education, obstetric history and ethnicity. It is interesting to note that maternal socioeconomic status appeared to have no effect on size at birth in our sample. It showed significant univariable association with almost all birth size indicators except for weight and LBW, but no independent association. For length and PI, the univariable association was almost significant. Similarly, no association was observed between socioeconomic status and maternal nutritional status. Mothers residing in urban areas were better off than those from rural areas. The socioeconomic status of the urban population is boosted by the availability of non-agricultural work. To our surprise, despite mothers from Janakpur municipality having significantly higher socioeconomic status, maternal nutritional status (anthropometry and hemoglobin level) remained the same. The only reason for this (and here I speculate) is the possibility that women had similar dietary patterns driven by culture and religion. Perhaps fasting, the hierarchy of food distribution in the family, and readily available and affordable foods are driven more by culture than by socioeconomic status.

With the exception of low PI, maternal age showed univariable associations with all parameters of size at birth, but the significance was not sustained when other risk factors were adjusted for. This suggests that maternal age does not have an independent effect on size at birth. It is consistent with the findings of the systematic review by Kramer[24]: high quality studies based on criteria set out by the author showed no effect of age on size at birth [220-222] (except one by Yudkin[223]). Teenage pregnancy has been linked with size at birth, but our study did not support this argument. It is possible that maternal age affects size at birth by affecting maternal height. There was no significant difference in maternal height (<150 cm versus >150.1cm) between teenage and older mothers (<19 years versus ≥ 20 years). There were also few mothers of extreme ages at either end of the distribution: there were no participants with age >35 years and only 38 (0.9 %) with age <16 years. It is interesting that extreme teens (<16 years) were taller than older mothers (>16years) (151.58 versus 150.87cm). Two possible explanations could be

that maturity occurs earlier in this sample of extreme teenagers, or that teenagers are becoming taller than older women due to a reduction in stunting. Since height has a positive effect on birth weight, teenage mothers may end up more likely to give birth to heavier and longer infants. It is possible that the next generation may have less LBW problems.

An issue that might have affected the findings is that information on past obstetric history was based on maternal self-report. This may be subject to recall bias. Furthermore, it is likely that reports of previous miscarriages were under-represented due to preference for male over female children. Deep interrogation on this subject was not attempted, especially for previous history of stillbirth, miscarriage and total number of child deaths. Similar findings were observed for maternal education level. It had no significant univariable association with all birth outcomes except for birth weight, LBW and head circumference. The effect became insignificant in all cases when confounding factors were adjusted for, except for birth weight. The effect of maternal education on birth weight could operate in two ways. Firstly, maternal education might improve health care seeking behavior. However, all the participants experienced similar free monthly antenatal care facilities and monthly home visits and consultation on health problems. Secondly, education might improve understanding and support within the family, with a more liberal and healthy psychosocial environment. This is reflected in the parity and significantly higher antenatal weight gain in educated mothers. For instance, Terai Vaishya, Sudra and Muslim women were less likely to be literate and tended to have significantly more children than literate mothers. These ethnic groups generally occupy lower social classes and are more conservative. Thirdly, education might reflect socioeconomic status. However, socioeconomic status itself did not have an independent relationship with size at birth (including birth weight). There are a number of possible reasons for this. The socioeconomic status score based on land and asset ownership and husband's occupation may not be a true indicator of socioeconomic differences in our sample. Maternal education may be a better indicator of the socioeconomic status in a woman's maternal home, which would in turn affect her nutritional status. Although it is fair to say that marriage usually takes place between

couples of similar socioeconomic status, educated women had husbands with higher occupational status. The majority of farmers, laborers or those who were working abroad had wives with no education. Similarly, most salaried workers, students, and businessmen had wives with secondary or higher education. This supports the idea of a healthier family environment, compared to women with no education.

In our sample, ethnicity showed significant univariable associations with birth weight, length and BMI, but this association disappeared when other potential risk factors were taken into consideration. The absence of effect of ethnic groups residing in this area on size at birth implies that there is no significant independent effect of ethnicity in this sample.

With few exceptions, the risk factors that had independent associations with most measures of size at birth were maternal weight at enrolment, infant sex, parity, weight gain over pregnancy and gestation at birth. Birth weight, length and BMI were independently associated with all these risk factors. The exceptional variables were as follows: length and head circumference had no independent association with parity; PI had no association with infant sex and pre-pregnancy weight; and low PI had no association with infant sex, maternal weight at enrolment and gestational age at birth. Similarly, parity was associated with all birth size parameters except for PI and low PI. Maternal weight gain was the single risk factor which had a significant association with all birth outcomes. Pre-pregnancy weight and maternal weight gain during pregnancy represent the nutrition of a growing fetus.[24] In this study, mean maternal weight gain was around 7.1 kg. The optimal weight gain required over pregnancy is 11 kg.[224]

Some potential risk factors showed an independent association with fewer birth sizes. They were maternal height, antenatal supplementation, prior history of child death and maternal education. Maternal education has been discussed under potential risk factors with no association. Apart from birth weight, it showed no association with other birth sizes. The exception is for birth length for which it showed only a univariable association.

Maternal height was an independent risk factor for only weight and length at birth. Kramer described it as the reflection of genetic potential, environmental influence and maturity.[24] Although significant univariably with LBW, SGA, BMI and head circumference, it showed no independent association. It was not related PI and low PI univariably or multivariably. Antenatal supplementation showed an independent association with weight, BMI, LBW and SGA. It did not show any effects on length, head circumference, PI and low PI. Since the sample was derived from the antenatal multiple micronutrient supplementation trial, half of the participants received iron and folic acid and half of them received multiple micronutrients. Surprisingly, of all the adverse obstetric history variables, death of previous offspring showed an independent effect on the size of the newborn. The rest showed no association.

Factors that were not investigated included paternal height and weight, maternal psychological factors, pregnancy interval, caloric intake and energy expenditure. Other factors like antenatal care, number of antenatal care visits, quality of care, smoking, caffeine and drug intake, other toxic exposures, malaria, urinary tract infection, genital tract infection, and prior infertility were not thought to be important features of the sample. The women involved were healthy and received monthly antenatal care and health check-ups, with no self-reporting of smoking, caffeine or drug use.

Prediction of size at birth is important from the management point of view at delivery and postnatally. A number of studies have considered the prediction of birth weight. The methods used can be categorized into three groups: (1) abdominal palpation, (2) ultrasound biometry, and (3) maternal characteristics. The most common method in developing countries has been palpation, the most sophisticated method is ultrasound and a promising method is the use of maternal risk factors. The abdominal palpation method involves estimation of fetal weight by clinicians by measurement of fundal height and integrating the clinician's experience with obstetric histories. Maternal characteristics-based prediction uses routine antenatal measurements like height, weight, parity and age.

Prediction of size at birth, especially through equations to estimate birth weight, has been central to the development of obstetric ultrasonography. Fetal biometric parameters have been used to develop prediction models for birth weight, particularly using biparietal diameter, head circumference, abdominal circumference, femur length, and fractional limb volume.[225] Several equations have been published, and are used in ultrasound machines worldwide to estimate fetal weight, but all are based on data from high-income countries. Common examples are the Hadlock formula for biparietal diameter and the Robinson formula for crown-rump length. Nahum demonstrated that most of the equations were equally accurate (except Warsof's equation)[226], but the most accurate of all was an equation that used only abdominal circumference, developed by Campbell and Wilkin in 1975.[227] Moreover, the prediction of fetal weight is of limited value because 20–44% of estimates lie outside the band of 10% on either side of the actual birth weight.[228;229]

In the setting of semi-rural Nepal, ultrasonographic screening remains a sophisticated procedure inaccessible to the majority of the population. Ultrasound machines are expensive to procure and maintain, and require skilled operators and maintenance teams. Ultrasound-based prediction is further challenged by intra-observer and inter-observer variation in fetal measurement. In this situation, the best solution is to develop an inexpensive method of prediction. Annex L summarizes a comparison of predictability based on birth weight estimation methods. It shows that maternal characteristic methods are comparable to ultrasound methods, and that clinical methods of estimation at term are more accurate than ultrasound. If one has to choose one method over another despite its poor predictability, it is economical and practical to use maternal characteristics-based birth weight prediction.

9.6.3. Wider implications

Although their effects were limited, key potential risk factors identified in the study were maternal weight at enrolment, infant sex, parity, weight gain over pregnancy and gestation at birth. Individuals with modifiable risk factors are the targets of public health action. (see Table

9.6). Only two factors in our list are easily and ethically modifiable: maternal pre-pregnancy weight and weight gain during pregnancy.

Table 9.6. Risk factors established in the study, according to potential for modification

Birth anthropometry assessed	Modifiable determinants	Determinants that would be difficult or unethical to modify
Weight	Education Pre-pregnancy weight Antenatal weight gain Supplementation	Infant sex Gestational age at birth (uncertain) Parity Maternal height (possibly in the long term)
LBW	Pre-pregnancy weight Maternal weight gain Supplementation	Parity Infant sex Gestational age at birth (uncertain)
SGA	Pre-pregnancy weight Maternal weight gain Supplementation	Parity
Length	Pre-pregnancy weight Maternal weight gain	Maternal height (possibly in the long term) Infant sex Gestational age at birth (uncertain)
BMI	Pre-pregnancy weight Maternal weight gain Supplementation	Parity Infant sex Gestational age at birth (uncertain)
PI	Maternal weight gain	Parity Gestational age at birth (uncertain)
LPI	Maternal weight gain	Parity
HC	Maternal weight gain	Infant sex Gestational age at birth (uncertain)

LBW: low birth weight; SGA: small for gestational age; BMI: body mass index; PI: ponderal index; LPI: low ponderal index; HC: head circumference

Gestational duration was associated with most indicators of size at birth, but what predicts gestational duration and whether it can be successfully modified is governed by multiple factors. Maternal height is classified as a non-modifiable risk factor, although 30% of the participants were teenagers. Although extreme teenagers (<16 years) were taller than older counterparts, I observed that, although not significant, teenagers (<19 years) were shorter than older mothers. Maternal height had an independent association with birth weight and birth length. Delaying pregnancy could reduce the risk to some extent. All of the factors examined were easily obtainable at the time of antenatal visit except for gestational age. The estimate of gestational age used in the study was ultrasound-based and would not be available and accessible to all in Nepal. The other drawback is that the measurement of these variables has its

own inherent errors, especially gestational age and maternal anthropometry. The net effect is a reduction in the predictive accuracy.

Table 9.7 summarizes studies of prediction models for size at birth based on known maternal determinants. I have compared eight studies which examined potential risk factors for abnormal birth weight and reported their predictive ability. The present study confirms earlier reports[230-233] that size at birth is only partly explainable. Prospective hospital-based studies from 1966 in Baltimore to 2007 in Bangladesh reported that potential risk factors provided little explanatory power in prediction models for birth outcomes. The range of coefficients of determination was 2.5-33% (except in a study by Etikan et al conducted in Turkey, which claimed to have a coefficient of determination of 59.8%. It included an extra variable, blood glucose level before and after ingestion of glucose load).

A preliminary report of a study from India reported a low coefficient of determination of 13.2% for birth weight.[232] The final model for birth weight and LBW consisted of maternal weight on the third day after delivery, prematurity, birth order and maternal height. The model applied to both term and preterm infants. In contrast to our study, maternal weight gain was not included in the final prediction model. Considering the fact that our study used ultrasound-based gestation, it is not surprising to find the prediction power low in the Indian study. Our study could not confirm previous reports that low socioeconomic status and previous history of giving birth to a small infant were likely to affect infant size.[230]

One important and plausible prediction model for birth weight has an R^2 value of 33%.[233] This finding is consistent with ours despite the fact that the other study was conducted in term infants in a European population. It was similar in that the pregnancies were uncomplicated, but it involved a sample of only 262. Unlike the present study, Nahum examined the role of blood glucose screening in the third trimester, but did not consider maternal education. Glucose screening was not helpful in the prediction. Nahum's equation claimed the prediction of birth weight to within 10.8% of actual birth weight.

I am unaware of previous analyses that have examined the prediction of other parameters of size using potential risk factors. In our study, the predictive accuracies were all lower than that for birth weight.

Table 9.7. Studies of predictors of size at birth based on maternal characteristics

Study, date and location	Maternal characteristics assessed	Design	N	Significant predictors in final model	Size at birth	R^2	Inference
Present study, Nepal	Ethnicity, education, residence, socioeconomic status, systolic blood pressure, diastolic blood pressure, general antenatal illnesses, parity, prior history of giving birth to small infant, miscarriage, still birth, child death, maternal height, maternal weight, antenatal weight gain, hemoglobin status at enrolment, antenatal supplementation, maternal age, gestational duration, infant sex. Interaction: maternal age*parity.	Hospital Prospective	1048	Gestational age, maternal weight gain, infant sex, pre-pregnancy weight, parity, antenatal supplementation, maternal height, maternal education,	Weight	32.7	Healthy population, singleton pregnancy, no gross congenital anomaly, no chronic maternal medical illness, 19 variables explored, all measurable at booking Limitation Ultrasound based gestational age, factors not explored-psychological stress, work load, caloric intake and expenditure
				Gestational duration, Infants gender, antenatal weight gain, maternal height, prior death of child	Length	19	
				Gestational duration, antenatal weight gain, parity, pre-pregnancy weight, infant sex, antenatal supplementation	BMI	12.4	
				Antenatal weight gain, parity, gestational duration	PI	3.2	
				Gestational duration, infants gender, antenatal weight gain	HC	18.6	
				Gestation, infant sex, antenatal weight gain, maternal weight at enrolment, antenatal micronutrient supplementation, Parity	LBW		
				Antenatal weight gain, parity,	LPI		
				Prepregnancy weight, antenatal weight gain, parity, antenatal supplementation	SGA		
Nahar 2007[231] Bangladesh	Maternal weight, antenatal weight gain and body mass index at 3, 4, 5 ad 6 months of pregnancy, maternal height	Community, longitudinal	1104 singleton healthy	Maternal Weight at registration (3-5 months) and at 9 months	Weight	2.5 to 20	Only 4 maternal anthropometric parameters explored

Study, date and location	Maternal characteristics assessed	Design	N	Significant predictors in final model	Size at birth	R^2	Inference
Kutty 2004[232] India	Maternal age, height, weight, weight gain, hemoglobin, blood pressure, weight post delivery	Hospital, prospective	1894	Maternal weight on 3rd day after delivery, height, parity, gestational duration <38 w	Weight LBW	13.7	Only 7 variables explored Important variables not explored: education, socioeconomic status, parity, infant sex
Etikan 2005[234] Turkey	Blood glucose level before and after ingestion of glucose load, age, body mass index, %of change in weight during pregnancy, height, gestational age, parity, fetal sex	Hospital, retrospective	300 term singleton healthy	Gestational age, infant sex, body mass index, maternal height, blood glucose level	Weight	59.8	Different: blood glucose level after glucose loading Limitation: Important variables not explored: maternal age, education, socioeconomic status
Nahum 1998[233] California	Maternal weight at 26 w, height, age, parity, third trimester glucose screening test value, obesity (body mass index at the start of the 3rd trimester), and gestational duration	Hospital	262	Gestational age which affects male and female separately, maternal height*weight at 26w, parity*the rate of maternal 3rd trimester pregnancy weight gain	Weight	33	Important variables not explored: maternal socioeconomic status, education
Breschi[235] Ohio	maternal height, BMI before pregnancy and at delivery, parity, week of delivery, fasting and 2-h plasma glucose concentrations, and male gender, maternal age, Smoking	Hospital	503 normal	maternal height, BMI at baseline and delivery, parity, week of delivery, fasting and 2-h plasma glucose concentrations, and male gender	Weight	26	Limitation: height and body mass index explored together, education and socioeconomic status not explored fasting and 2- hour plasma glucose concentration also explored
Abernathy 1966[230] Baltimore	Race, marital status, hospital type, socioeconomic status, height, parity, prior fetal and neonatal death, pre-pregnancy weight, hemoglobin, SBP, DBP, obstetric complications, placenta and cord condition, congenital anomaly, **Interaction**: maternal age*parity, (maternal age)^2*parity, age*illness, age*illness*socioeconomic status, sex, paternal age, maternal age, (age)^2, inter-current illness	Hospital prospective	10000	**Common to birth weight and length**: race, hospital type, maternal height, prior fetal and neonatal death, maternal weight, Systolic blood pressure, obstetric complications, congenital anomaly, placental and cord condition, infant sex			Limitation: infants with congenital anomaly included Other variables explored: placental and cord condition included **Different form current study:** Maternal age, obstetric complications, maternal illness, hemoglobin status formed the final prediction model
				Age*illness*social class, hemoglobin	Weight	16	
				Parity, age^2*parity, age*illness, paternal age, maternal age*SES	Length	7	

Study, date and location	Maternal characteristics assessed	Design	N	Significant predictors in final model	Size at birth	R^2	Inference
Abernathy 1966[236] Baltimore	Gestation, maternal weight, parity, smoking, psychosomatic score, work, marital status, blood group, hemoglobin, hypertension, eclampsia, education, infant sex **Interaction**: sex*parity, sex*parity*maternal age, sex*maternal age, maternal age*parity, PSS*parity, PSS*smoking, PSS*gestation, PSS*parity*age, PSS*gestation; PSS*age, smoking*parity, smoking*age, smoking*age*parity	Hospital prospective	2700	gestation, gestation^2, smoking, parity, parity^2, sex, hemoglobin III, Hypertension II, eclampsia I, II, sex*parity	Weight	24.03	Other variables explored: Psychosomatic score and blood group, **Different form current study:** hypertension, eclampsia, hemoglobin and smoking in the final model; pre-pregnancy weight and maternal education not in the final model

PSS: Psychosomatic score; LBW: low birth weight; BMI: body mass index; PI: ponderal index; LPI: low ponderal index; SGA: Small for gestational age;

9.7. Associations of size at birth with mortality, morbidity and malnutrition in childhood

9.7.1. General findings

In a study where information on confounders was available, we investigated the association of size at birth with death, malnutrition and illness from birth to 2.5 years of age. We found that newborns of different sizes had varied risks for the outcomes investigated. Risks for mortality, morbidity and malnutrition were assessed against a range of classifications of size at birth. Newborn infants were classified using a) a single anthropometric index, b) a combination of two anthropometric indices, and c) a combination of three anthropometric indices. A simplified summary of the findings is presented in Table 9.8 and Table 9.9.

Table 9.8. Summary of significant increased odds ratios for mortality and childhood malnutrition on the basis of potential risk groups for size at birth

	Proportion	Neonatal death		Infant death		Young child death		Stunting		Wasting		Underweight	
LBW	22%	3.5	(1.4 – 8.9)	3.6	(1.6 – 7.9)	3.7	(1.7 – 7.8)	3.4	(2.2 – 5.3)	2.9	(1.5 – 5.6)	3.7	(2.5 – 5.5)
LPI	68%									2.2	(1.1 – 4.4)		
SGA	52%							2.4	(1.8 – 3.4)			3.1	(2.2 – 4.3)
LBW-LPI	20%	2.7	(1.0 – 6.8)	2.3	(0.9 – 1.0)	2.1	(1 – 4.6)	3.0	(1.9 – 4.6)	2.6	(1.4 – 5.1)	3.2	(2.1 – 4.8)
LBW-API	2%					7.0	(2.3 – 21.4)	5.3	(1.1 – 25)			5.7	(1.7 – 19.2)
LBW-SGA	19%			2.8	(1.3 – 6)	3.1	(1.5 – 6.3)	3.0	(1.9 – 4.7)	2.6	(1.4 – 5.0)	4.1	(2.7 – 6.2)
LBW-AGA	3%	5.7	(1.0 – 31.8)										
LPI-SGA	41%							1.9	(1.4 – 2.7)	2.0	(1.1 – 3.6)	2.1	(1.5 – 2.9)
API-SGA	10%							1.9	(1.0 – 3.2)			2.3	(1.3 – 3.8)
LBW-LPI-SGA	11%							2.6	(1.6 – 4.1)	2.6	(1.3 – 4.9)	3.6	(2.4 – 5.5)
LBW-API-SGA	2%			6.5	(1.9 – 22)	8.1	(2.6 – 25)	11.3	(1.4 – 93)			7.8	(2.0 – 30.7)
LBW-LPI-AGA	3%	6.6	(1.2 – 37.1)					5.2	(1.1 – 25)				

Values are OR (95% CI)

Table 9.9 Summary of significant lowered odd ratios for mortality and childhood malnutrition on the basis of potential risk groups for size at birth

	Proportion	Neonatal death	Infant death	Young child death	Stunting		Wasting		Underweight	
NBW-LPI					0.6	(0.4 – 0.8)			0.6	(0.5 – 0.9)
NBW-API							0.4	(0.2 – 1.2)	0.6	(0.5 – 0.9)
NBW-AGA					0.4	(0.3 – 0.5)			0.4	(0.3 – 0.5)
LPI_AGA					0.5	(0.3 – 0.7)			0.5	(0.3 – 0.7)
API-AGA									0.5	(0.3 – 0.7)
NBW-LPI-AGA					0.4	(0.3 – 1.6)			0.5	(0.4 – 0.8)
NBW-API-AGA									0.5	(0.3 – 0.7)

Values are OR (95% CI)

The chief findings for the effects of birth size on mortality were: (a) that LBW was a stronger single predictor than SGA and LPI, (b) that proportionate LBW infants were at greater risk of childhood death, (c) that appropriate for gestational age LBW infants were at greater risk of neonatal death, and (d) that proportionate LBW infants who were SGA were at greater risk of infant and childhood death. The most powerful predictors of neonatal mortality were LBW-AGA and LBW-LPI-AGA. For infant mortality, the most powerful predictor was LBW-API-SGA, and for childhood mortality it was LBW-API, with or without SGA. These associations were not explained by gestational duration, socioeconomic status, education level, maternal weight, antenatal supplementation, ethnicity, infant sex, maternal age, birth order or age of weaning.

The incidences of neonatal, infant and young child deaths were high in the partly hospital-based study sample. The rates were 22, 35 and 39 per thousand for neonatal, infant and young child mortality respectively. The national mortality rates were 33, 48 and 61 for neonatal, infant and under five child mortality in the five years preceding the 2006 DHS[237]. Our mortality rates were lower than national figures, possibly as a result of the care and attention that women and children received in the study. The previous finding that early neonatal deaths constitute the majority of neonatal deaths (and 75% of infant deaths) is supported by our study.

A model that examined the relation between birth anthropometric parameters and survival showed no significant associations (see Figure 8.11). There are several possible reasons for this. As mentioned earlier, the sample size was small for mortality data. Sample size was calculated only for the antenatal multiple micronutrient supplementation study, whose main outcome was not mortality. Secondly, there are chances of data overlap. For example, birth weight, birth weight z-score and ponderal index all involve birth weight and the chance of collinearity is increased. Thirdly, it could be true that the parameters we studied are actually not predictors of mortality. This warrants further study on the use of size at birth as a measure of survival.

A LBW classification put newborn infants into a mortality risk group better than SGA or LPI. More infants were categorized as SGA (52%) or LPI (68%) than LBW (22%). The benefits of this finding are that birth weight is already in use and adopting a single birth anthropometric category is practical in poor countries. The combinations of two anthropometric indices that were useful to define risk groups were proportionate LBW (child mortality), disproportionate LBW (neonatal, infant and child mortality), LBW-SGA (infant and child mortality) and LBW-AGA (neonatal mortality).

The study suggested that if more than one anthropometric parameter was used, three groups were categorised as high risk, the most striking being the LBW-API group. This group had the highest risk for child mortality, as high as a 7-fold increase in deaths. The group made up 2% of infants. The other two groups which showed highest risk for mortality were LBW-SGA and LBW-LPI, for which the odds of mortality in infants and young children were 2-3 times higher. These groups each made up about 19% of infants. If one had to choose two anthropometric parameters for a risk category, the first choice would be PI and birth weight, not an SGA-based category. There are a number of reasons for this. First, PI is easier to calculate than SGA. It only requires measurements of birth weight and length. SGA requires more than just measurements, particularly the comparison of measurements against reference data or charts. This is next to impossible at the moment due to lack of trained human resources. Second, LBW-SGA (20%) and LBW-LPI (19%) had the same prevalence and conferred similar risks for infant and young child mortality. Third, given the low prevalence and highest risk for mortality in young children, it might be economical to follow-up infants who are just LBW-API (2% and OR 7).

The analysis of combinations of three anthropometric indices put two groups at highest risk: LBW-API-SGA (prevalence 2%) and LBW-LPI-AGA (prevalence 3%). LBW-LPI-AGA infants had 7 times higher odds of neonatal death and LBW-API-SGA had 7-8 times higher odds of infant or

young child death. The important finding here was that only 5% of newborn infants were in high risk groups, compared to 22% in a system based on LBW alone.

In our study, size at birth conferred no higher risk for recalled illness in the first year of life. We have already discussed the lack of conviction behind these findings. A report from the Family Health Division documented the nationally representative prevalences of stunting, wasting and underweight as 48%, 11% and 47% respectively in children under three years of age for the year 1996.[238] We found prevalences of 59%, 6% and 38% for stunting, wasting and underweight at 2.5 years of age for 2005-06. Children in our study suffered more stunting, less wasting and less underweight compared to a national survey in 1996. The comparison shows that malnutrition among children is still markedly high ten years later.

All the categories based on single anthropometric indices were associated with malnutrition. LBW infants were significantly stunted, wasted and underweight as young children. LPI infants were significantly wasted, and SGA infants were significantly stunted and underweight. It is difficult to identify the best predictor of stunting, wasting or underweight. However, it is worth using LBW because the prevalence is substantially lower and the risk of stunting, wasting and underweight was higher in the LBW group. This means that from a management point of view it is more administrable in the context of a poor country. The sensitivity, specificity and positive predictive value for LBW was 28%, 89% and 78% respectively for stunting; 42%, 80% and 12% for wasting; and 34%, 87% and 61% for underweight. The risk groups based on two anthropometric indices which had higher risk of all three types of malnutrition were LBW-LPI (19%), LPI-SGA (42%) and LBW-SGA (19%). The odds were highest for the LBW-SGA group (OR 3-4).

It is interesting to note that with a classification based on birth weight and weight-for-gestational-age, only one category, LBW-SGA, was at risk of later malnutrition. The prevalence of LBW-SGA was 19% and it had an odds ratio of 3-4 for stunting, wasting and underweight. As a predictor,

LBW-SGA had sensitivity, specificity and positive predictive value of 25%, 90% and 78% respectively for stunting, 37%, 82% and 12% for wasting and 77%, 92% and 64% for underweight respectively.

With classifications based on birth weight and PI, two groups were high risk: LBW-API and LBW-LPI. But LBW-API and LBW-LPI together are just LBW. Newborns who were LBW-API had the highest risk for stunting and underweight in childhood. The risk was 5 to 6 times higher than other newborns, but it had a very low sensitivity despite good specificity (3% and 92% respectively for stunting and 4% and 99% for underweight). The positive predictive values were 85%, and 75% respectively. The other category, LBW-LPI, had a 3-times higher risk for all forms of malnutrition. The sensitivity and specificity were 25% and 89% respectively for stunting, 36% and 82% for wasting and 30% and 88% for underweight. The positive predictive values were 77%, 11% and 60% respectively for stunting, wasting and underweight. A classification based on PI and weight-for-gestational-age had two groups at higher risk, API-SGA and LPI-SGA. But these are just equivalent to SGA. LPI-SGA newborns were more likely to be stunted, wasted and underweight and the risk was 2-fold. As a predictor, LPI-SGA had sensitivity, specificity and positive predictive values of 49%, 68% and 68% respectively for stunting, 57%, 59% and 8% for wasting and 53%, 65% and 48% for underweight. Similarly, API-SGA had higher risk for stunting and underweight and the risk was 2-fold. The prevalence was 10%. The sensitivity, specificity and predictive value for stunting were 12%, 93% and 69% and for underweight were 14%, 93% and 53% respectively.

When we examined combinations of three indices, three groups were at risk: LBW-LPI-SGA, LBW-API-SGA and LBW-LPI-AGA. Children born LBW-LPI-AGA (2%) were more likely to be stunted. The sensitivity, specificity and positive predictive value were 3%, 99% and 81%, respectively. LBW-API-SGA newborns (2%) were more likely to be stunted (OR 11) and underweight (OR 8). The sensitivity, specificity and positive predictive value were 3%, 100% and 89% respectively for stunting and 4%, 99% and 78% for underweight. LBW-LPI-SGA children

(17%) had 3-4 times higher risk of becoming stunted, wasted and underweight. The sensitivity, specificity and positive predictive value were 22%, 90% and 76% respectively for stunting, 33%, 84% and 12% for wasting and 28%, 90% and 62% for underweight.

The findings suggest that groups based on LBW and LBW-SGA are a better choice than groups based on other combinations. The reasons for this are that (1) only one category is a high risk group for all forms of malnutrition and therefore easier for health workers to understand and apply in daily practice, (2) the sensitivity, specificity and positive predictive values were comparatively better, even if not ideal for screening purposes. Groups based on two indices were better predictors than groups based on three. They had higher sensitivity and specificity, the numbers of children falling into a risk group were similar, and the odds ratios for later malnutrition were higher.

9.7.2. Wider implications

The risks of malnutrition and mortality varied across different categorisations of size at birth. The relationship between size at birth and later morbidity was not clarified by our analysis. Being LBW alone conferred higher risk for morality and malnutrition than LPI or SGA. However, SGA infants were at increased risk for stunting and underweight and LPI for childhood wasting. The most powerful predictors of neonatal mortality were LBW-AGA and LBW-LPI-AGA. For infant mortality, the most powerful predictor was LBW-API-SGA, and for childhood mortality it was LBW-API, with or without SGA. We will attempt to generalize in rough terms about these categories.

The key protective factor was to be born with normal birth weight. All categories with weight >2500g had significantly lower odds of malnutrition and mortality. LBW-AGA were mostly preterm.Most of them were immature fetuses who had grown normally so it is understandable that the initial months were the high risk period of survival. LBW-LPI-AGA infants were also mostly

preterm, but were the disproportionate subgroup. They had the highest odds of all for neonatal mortality.

LBW-SGA infants were mostly term infants with IUGR. Their growth was compromised and they had a higher risk of subsequent malnutrition and death in childhood. On top of this, whether they were proportionate or disproportionate did not seem to affect their mortality (LBW-SGA with either LPI or API). So many of them were disproportionate, however, that this is easy to understand and highlights the need for studies with larger sample size.

Size at birth independently predicted size in childhood. Most of the abnormal categories conferred higher odds of malnutrition in childhood. For example, newborn infants with disproportionate SGA, disproportionate LBW and LBW-SGA had similar significantly higher odds of stunting, wasting and underweight. The key factor here was SGA: small babies end up small. Proportionate SGA and proportionate LBW infants had higher odds of stunting. Preterm acutely malnourished infants (LBW-LPI-AGA) were more likely to be stunted in childhood if they survived the neonatal period. Proportionate LBW infants who were SGA (chronically malnourished term or preterm infants) were at greater risk of infant death, childhood death, stunting and underweight.

The study confirms that LBW is a reasonable predictor of later mortality and malnutrition. Would there be a benefit in adding more indices? After extensive analysis, candidate categories include, for mortality, LBW-API, LBW-API-SGA and LBW-LPI-AGA; and, for malnutrition, LBW-SGA. Who are the infants represented by these categories? LBW-API infants are term or preterm, LBW-API-SGA infants are symmetrically small (chronically growth restricted preterm or term), LBW-LPI-AGA are acutely growth restricted preterm, and LBW-SGA are chronically growth restricted preterm or term. These categories are diverse, apart from the fact that they all include LBW. Introducing either PI or weight-for-gestational-age is likely to be a difficult task for Nepal's health system, and we would require a simpler idea of risk groups to even consider it.

Chapter 10. Conclusions

This thesis began with three general obectives, which are presented once again.

1) Describing the distribution of different indicators of size at birth in a cohort of infants in Nepal.

2) Development of prediction models for different indicators of size at birth, and assessment of how useful they might be.

3) Looking at the outcomes in infants and young children of different classifications of size at birth.

To our knowledge, none of these had been done well in Nepalese infants. In spite of studies of risk factors for size at birth, the usefulness of different potential predictors for prevention and public health intervention remained questionable. Likewise, the usefulness of different classifications of size at birth in predicting outcomes had not been investigated in depth and had not been used in practice. The quality of the data and the need for investigation enabled this in-depth study of size at birth.

In our study of measurements of size at birth in semi-rural communities in Nepal, we found that the proportion of infants classified as having abnormal size was high (LBW, SGA, Low PI). Although LBW was common, the striking finding was the degree to which infants who would usually be classified as normal appeared to be small and disproportionate. This probably indicates that the majority of infants suffered intrauterine growth retardation due to acute or subacute malnutrition. If the hypothesis of association of wasting with adult onset disease is correct, this is an emergency situation that needs immediate action. We need to follow the infants born in the study into later

childhood if we are to answer the questions that arise. Will the excess of disproportionality be associated with physiological tendencies to insulin resistance, hyperlipidaemia and hypertension? The next step is to track the children as they go to school, and to add more complex measurements – body composition, blood tests – to the protocol.

Our understanding of the etiology of abnormal size at birth is limited. Importantly, previously reported risk factors did not explain size at birth adequately. Only a few risk factors were shown to have independent associations with size at birth. We were unable to unravel the risk factors that are important but omitted from usual analyses, indicating that maybe we have reached the limit of usefulness for these sort of studies. This is especially important as research on risk factors for abnormal size at birth still seems to be prioritized, and it is possible that further work could be a waste of resources. Moreover, such studies may be of limited importance in terms of explaining observed size at birth and in the prevention and management of the problem.

Given the fact that the potential risk factors explained a limited proportion of size at birth, reduction in the problem of abnormal size remains a difficult proposition. There are two ways to address the problem. The first approach is prevention of abnormal size at birth. Our findings suggest that most of the underlying determinants are not clear and known determinants explain only a small proportion of size at birth. This may explain why preventive measures have not led to remarkable improvement.[239;240] Furthermore, most of the risk factors are non-modifiable. The major modifiable determinants of size at birth are factors like maternal nutritional status: under-nutrition during childhood (maternal height), poor pre-conception nutritional status (pre-pregnancy weight), poor nutrition during pregnancy (gestational weight gain and antenatal supplementation). Nutritional status is compromised in situations of poverty and illiteracy, and these modifiable determinants should be the targets for public health intervention. However, the problem is likely to be preventable only to some extent through measures such as antenatal supplementation, nutrition improvement and behavior change.

A second approach is the management of abnormal size at birth to prevent adverse outcomes. Prediction of size at birth is only possible with a robust prediction model with high predictive accuracy. As discussed above, the predictive accuracy of maternal characteristic-based equations and ultrasound based equations were almost similar. However, in a situation where most pregnancies fall into the high-risk group and most of the population are poor, the management options are limited. Recent studies on risk factors have added little information to our understanding of causes or intervention and prevention efforts, and it is possible that the model is unlikely to improve. In the absence of a significant improvement in the model, it might be better to change the priority from risk factor studies to a focus on intervention measures. The failure to develop a robust prediction model using major determinants of abnormal size requires attention. Indeed, it warrants rethinking the necessity of further work on risk factors. Furthermore, It might be prudent to take a holistic view of known risk factors, focusing on modifiable factors like nutrition and education, all of which are linked with poverty. Addressing this single factor could be the best strategy to reduce the incidence of small size at birth.

The third study confirmed associations of size at birth with neonatal, infant and child mortality. It also showed clear associations with malnutrition in childhood. The detailed analysis of the anthropometric parameters to correlate with adverse outcome showed that different combinations have different odds, making it difficult to choose the best group. From a public health intervention point of view in a poor country like Nepal, one might choose a few high risk groups based on applicability in a situation with limited human, time and financial resources. The implication is that we could prioritize intervention for a small group of infants, thus saving effort and cost and achieving important public health change. If one of the objectives of the study was to derive screening categories for either mortality or malnutrition, further studies with larger sample size are recommended. However, we feel it is unlikely that a combination of parameters will prove more useful than simple birth weight. We found that both ponderal index and weight-for-gestational age

showed particular associations with later outcomes in certain cases, but it is not clear that adding their assessment to current practice would help mothers and health workers to guard against future risk.

The paradox of the thesis in this sense is that it set out to explain that size at birth is so much more than birth weight, but – after extensive analysis of good data – found that birth weight was probably the most useful predictor after all. Measurement of birth weight is by no means routine across Nepal, and it seems better to recommend efforts to improve routine weighing and classification of infants as low birth weight, than to recommend new activities which might dilute the likely impact.

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Annex A. Research article 1

Effects of antenatal multiple micronutrient supplementation on birth weight and gestational duration in Nepal: double-blind, randomized controlled trial. Lancet 2005; 365-62

Effects of antenatal multiple micronutrient supplementation on birthweight and gestational duration in Nepal: double-blind, randomised controlled trial

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Summary

Background Neonatal mortality is the biggest contributor to global mortality of children younger than 5 years, and low birthweight is a crucial underlying factor. We tested the hypotheses that antenatal multiple micronutrient supplementation would increase infant birthweight and gestational duration.

Methods We did a double-blind, randomised controlled trial in Dhanusha district, Nepal. Women attending for antenatal care with singleton pregnancies at up to 20 weeks' gestation were invited to participate. Participants were randomly allocated either routine iron and folic acid supplements (control; n=600) or a multiple micronutrient supplement providing a recommended daily allowance of 15 vitamins and minerals (intervention; n=600). Supplementation began at a minimum of 12 weeks' gestation and continued until delivery. Primary outcome measures were birthweight and gestational duration. Analysis was by intention to treat. The study is registered as an International Standard Randomised Controlled Trial, number ISRCTN88625934.

Findings Birthweight was available for 523/600 infants in the control group and 529/600 in the intervention group. Mean birthweight was 2733 g (SD 422) in the control group and 2810 g (453) in the intervention group, representing a mean difference of 77 g (95% CI 24–130; p=0·004) and a relative fall in the proportion of low birthweight by 25%. No difference was recorded in the duration of gestation (0·2 weeks [–0·1 to 0·4]; p=0·12), infant length (0·3 cm [–0·1 to 0·6]; p=0·16), or head circumference (0·2 cm [–0·1 to 0·4]; p=0·18).

Interpretation In a poor community in Nepal, consumption of a daily supplement containing a recommended daily allowance of 15 micronutrients in the second and third trimesters of pregnancy was associated with increased birthweight when compared with a standard iron and folic acid preparation. The effects on perinatal morbidity and mortality need further comparisons between studies.

Introduction

A third of global deaths happen in children younger than 5 years,[1] most in the neonatal period.[2] Low birthweight (<2500 g, irrespective of gestation) underlies many of these deaths. 25 million low-birthweight infants are born every year, and associations with neonatal mortality have been well described.[3–6] Low birthweight is also associated with diminished childhood growth,[7] morbidity,[8] compromised cognitive and behavioural development,[9,10] and disease in adulthood.[11] It is, however, rather a blunt indicator of fetal history and infant health: low-birthweight infants can be small for gestational age, preterm, or both. Most birthweight data from poor countries do not discriminate between these factors, a dilemma that has led to several approaches to classification and uncertainty about disease burden.[12,13] Although the epidemiology and associations of low birthweight have been examined closely,[14] approaches to alleviate the burden have met with limited success.[15,16]

Maternal nutritional status is linked with fetal weight, particularly small-for-gestational-age birth, as a result of presumptive intrauterine growth restriction. Increases in macronutrient consumption during pregnancy do lead to increased birthweight,[17,18] but control of fetal growth is complex,[19] and the effectiveness of interventions remains patchy.[20,21] The possibility that improvements in vitamin and mineral status might lead to reductions in low birthweight is attractive in terms of policy planning. A wealth of descriptive epidemiology has drawn links between deficiencies of such micronutrients—particularly several at the same time[22]—and birth outcomes.[23] Many women in wealthy and poor countries already take multiple micronutrient supplements before and during pregnancy, and iron and folic acid supplements are generally recommended. If multiple micronutrient supplement tablets were shown to be helpful, only minor adjustments to policy would be needed.

Repletion might improve birth outcomes,[24] a proposal lent support by findings of a study of infants of women infected with HIV.[25] An expert group has formulated a combination of ten vitamins and five minerals at levels of about one recommended daily allowance for this reason.[26] However, the evidence base for policy change is insufficient.[27,28] We undertook a trial with the aim of establishing whether second and third trimester supplementation with a multiple micronutrient regimen at one recommended daily allowance would increase birthweight and prolong gestational duration.

Participants and methods

Study location and population

Nepal is a south Asian country challenged by geography, poverty, and a violent insurrection. The most recent estimates of neonatal and perinatal mortality rates are 39 per 1000 livebirths and 47 per 1000 births, respectively.[29] More than half of women cannot read.[30] About a third have low body-mass index (<18·5 kg/m²)[31] and a quarter report limiting their own food consumption to provide food for their children;[32] half of children have stunted growth.[33] Deficiencies of several micronutrients have been well described in individual studies[33–36] and in a national sample.[37] Hospital-based figures for low birthweight suggest a prevalence of 27%;[38] this number is certainly an underestimate—a level of 40% has been reported in a southern rural population.[39]

The fifth most populous of Nepal's districts, Dhanusha, lies in the southern plains of the central zone. It has a population of about 670 000, 13% of whom are younger than 5 years. The human development index is 0·329, the population per doctor about 19 000, and the population per hospital bed 6700.[40] Two-thirds of households have access to safe drinking water. The urban population forms 11% of the district. Janakpur, the district municipality and former capital of the Mithila kingdom, is a town of great cultural and historic significance.

The sampling frame for potential participants included all women attending a designated antenatal clinic at Janakpur zonal hospital. The clinic was supervised by a senior nurse (YS) and run by auxiliary nurse midwives. It was open six mornings a week on a walk-in basis and provided all the routine services specified in Nepal's national maternity care guidelines and antenatal care protocol.[41,42]

Women were eligible for enrolment at up to 20 completed weeks of gestation. After screening on the basis of history, dates, and examination, we invited potential participants to a room serving as the study centre. We made a firm offer of enrolment if further history, examination, and ultrasound screening confirmed: (1) a gestation of up to 20 completed weeks; (2) a singleton pregnancy; (3) no notable fetal abnormality; (4) no existing maternal illness of a severity that could compromise the outcome of pregnancy; and (5) that the participant lived in an area of Dhanusha or the adjoining district of Mahottari accessible for home visits. If preliminary ultrasound examination suggested a congenital anomaly, we referred participants for repeat ultrasound by a consultant radiologist and management by obstetric specialists. We covered the costs of such unexpected procedures on their behalf.

We explained the nature and process of the trial to potential participants if they met the inclusion criteria. Oral and written information was available in English, Nepali, and Maithili. We deferred consent until women had discussed the trial with their families, and we encouraged them to bring senior family members to the study centre for the consent process. Literate participants provided signed consent and those unable to write provided witnessed thumbprints.

The trial was approved by the Nepal Health Research Council and the ethics committee of the Institute of Child Health and Great Ormond Street Hospital for Children, London, UK, and was undertaken in collaboration with His Majesty's Government Ministry of Health, Nepal. Benefits to participants included the supply of supplements, free health care, and expedited referral in the event of complications. Information provided by participants remained confidential. Access was restricted to supervisory and research staff at the analytical level. No analyses or outputs included the names of participants.

Procedures

We did randomisation in advance of recruitment. One of us (DO) randomly allocated 1200 participant identification numbers by computer into two groups in permuted blocks of 50. The allocation code was kept on file in Kathmandu and London. We allocated every identification number a supplement container to last throughout the trial. Containers were filled with either intervention or control tablets in Kathmandu by a team member who was otherwise uninvolved in the trial; these containers were then marked only with identification numbers and transported to the study centre in Janakpur. Intervention and control supplements were manufactured by Danish Pharmaceutical Industries (Ballerup, Denmark) to look, smell, and taste identical.

After screening, consent, and enrolment, one of us (YS) allocated participants sequential identification numbers and the corresponding supplement containers. Supplements were provided in a take-home bottle at monthly visits to the study centre. Bottles were labelled with the participants' names and identification numbers only. The allocation code was broken on two occasions: (1) for the first 500 participants to inform the interim data monitoring committee (by DO: the committee were not told which group represented the intervention); and (2) for this analysis.

In accordance with recommendations for trial design,[43] controls received current nationally advised tablets containing iron 60 mg and folic acid 400 μg.[41] The intervention group received tablets containing vitamin A 800 μg, vitamin E 10 mg, vitamin D 5 μg, vitamin B1 1·4 mg, vitamin B2 1·4 mg, niacin 18 mg, vitamin B6 1·9 mg, vitamin B12 2·6 μg, folic acid 400 μg, vitamin C 70 mg, iron 30 mg, zinc 15 mg, copper 2 mg, selenium 65 μg, and iodine 150 μg. These amounts adhere to the suggested composition of multiple micronutrient supplements for antenatal use recommended by UNICEF, WHO, and the United Nations University.[26] We sent a sample of tablets from participants' allocations for composition analysis midway through the trial. Vitamin E concentrations were 25% higher than expected, a surplus added by the manufacturer in view of probable

degradation. Retinol, iron, and vitamin C concentrations were about 10% lower than expected.

Participants received supplements from enrolment (at no earlier than 12 weeks' gestation) to delivery. We advised women to take one tablet daily, preferably after food and at the same time, and to avoid other supplements and drugs unless recommended by a study obstetrician. The follow-up plan included a contact visit every 2 weeks—a combination of monthly clinic visits and monthly home visits. At every contact visit, we asked the participant about morbidity, questions about the trial, her plans for delivery, and her consumption of supplements. We encouraged all women to make plans for delivery and advised them to consider hospital birth.

We offered the following blood tests to all participants at enrolment: haemoglobin concentration; blood group; rhesus status; and rapid plasma reagin test for syphilis. We prepared blood samples and stored them for micronutrient assays with the woman's permission. We undertook urine dipstick testing for protein and sugar at every antenatal care visit, and we offered repeat testing for blood haemoglobin concentration and amounts of selected micronutrients at about 32 weeks' gestation.

We assayed blood haemoglobin spectrophotometrically with a HemoCue system (Dronfield, UK), with daily calibration checks. Blood samples were spun in a centrifuge and plasma was stored at –20°C until transport to the UK in liquid nitrogen, after which samples were stored at –80°C. We measured vitamins A and E in a randomly selected 10% subsample of specimens taken at enrolment and 32 weeks' gestation. Plasma retinol and α tocopherol concentrations were assayed simultaneously by high performance liquid chromatography.[44] We standardised the method with control serum purchased from the National Institute of Standards and Technology (Gaithersburg, MD, USA) and quality control samples were run within every batch. The interassay coefficient of variation for the quality control plasma was 6% for both retinol and α tocopherol. α tocopherol was expressed as a ratio to plasma triglycerides, measured on a COBAS Fara autoanalyser with a commercial kit (Roche Diagnostics, Basel, Switzerland). The interassay coefficient of variation for triglycerides was 4·6%.

In the event of significant illness, we arranged for the participant to be seen by a consultant obstetrician or doctor. We prespecified two deviations from protocol: (1) if a participant's enrolment blood haemoglobin concentration was less than 70 g/L, she was given an extra 60 mg of iron daily, anthelmintic treatment, and her blood haemoglobin was rechecked after 1 month; and (2) if a participant described night blindness at any time, she was given 2000 μg of vitamin A daily and referred for medical follow-up.

For hospital births, study team midwives identified participants presenting at the maternity unit and obtained birth details and infant anthropometric measurements. For home births, we encouraged participants' families to contact the study team, after which a field supervisor visited as soon as possible to collect birth details and undertake infant anthropometry. Babies who became unwell were referred for management at the hospital paediatric unit. Women exited the study when their babies reached 1 month of age, at which time mother and child attended for postnatal checks. We met the cost of any medical care needed during pregnancy, delivery, or postpartum and transport for deliveries or emergencies.

Primary outcomes were birthweight and gestational duration. We measured birthweight on Seca 835 electronic scales (Hamburg, Germany) accurate to 10 g, tared before every measurement. We attempted to establish birthweight as soon after birth as possible, but defined late birthweight as a measurement recorded after 72 h. We estimated gestational age on the basis of transabdominal ultrasound fetal biometry with an Aloka SSD 900 with obstetric probe (Tokyo, Japan). In pregnancies less than 13 weeks and 6 days, we used crown-rump length and the chart of Robinson.[45] Between 14 and 20 weeks, we used biparietal diameter and head circumference and the charts of Chitty.[46] We added in measurements of femur length if necessary. One of us (AV) did the scans, with the exception of 30 women scanned by DO. Ultrasound training and quality control were provided by the superintendent ultrasonographer of University College London Hospitals. Scan stills were printed and stored in the participant's file, and scan videotapes were sent to the UK for regular quality control examination.

Secondary outcomes included infant length and head circumference. We measured infant length on a Kiddimetre board accurate to 1 mm (Raven Equipment, Castlemead, UK) for hospital and home births where vehicular access was possible. When severe monsoon conditions made transport of the large, heavy Kiddimetre to homes impractical, we measured some infant lengths on a Rollametre (Raven Equipment). We assessed occipitofrontal head circumference with a plastic length tape accurate to 1 mm, taking the middle value of three consecutive measurements.

We defined loss to follow-up as failure to attend the antenatal clinic for 3 months and failure to meet the participant after three home visits. We identified miscarriage as cessation of confirmed pregnancy before 23 weeks' gestation; stillbirth as delivery of an infant showing no signs of life—movement, breathing, or heartbeat—after 23 weeks' gestation; early neonatal death as death of a liveborn infant in the first 7 days after birth; and late neonatal death as death of a liveborn infant after 7 but within 28 days.

We assessed adherence by the discrepancy estimate method.[47] Supplements were provided every month in a varying (but known) quantity in excess of requirements. Team members were aware of the numbers of tablets remaining and added to take-home bottles, but did not imply to participants that they were important. We told

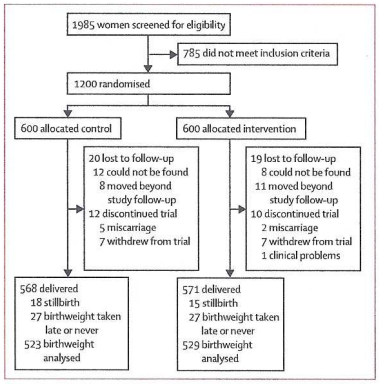

Figure: Trial profile

participants that the bottles contained more than enough tablets to last a month, but that they were formulated for pregnancy and should not be given to other family members.

Statistical analysis

We calculated the sample size at a power of 90% and a two-sided significance level of 5%. We allowed for the possibility of 30% loss to follow-up, a figure that seemed pessimistic but reasonable in view of the logistic difficulties of such trials. At 600 participants per arm, the study would attribute significance to a change in mean birthweight of 100 g (assuming a control mean of 2800 g [SD 450]) and a change in mean gestational duration of 3 days (assuming a control mean of 275 days [12·4]). Analysis was by intention to treat.

An independent data monitoring committee met in November, 2003, to consider interim data from 500 participants. The committee reported that there had been high adherence to the study protocol, that randomisation had resulted in comparable groups, that no evidence of harm could be attributed to either supplement, that there was no evidence of substantial mortality differences, and that the sample size should remain as projected.

We obtained information about participants, their progress, and outcomes in individual files that we checked manually for completeness. Data were entered into a relational database management system (FileMaker Pro 5.5), which incorporated validation constraints. We subjected the data to range checks and case-by-case examination for completeness and accuracy after export to SPSS version 11. Birthweight and gestational duration were normally distributed and were assessed with independent sample *t* tests assuming equal variances. We assessed categorical outcomes (low birthweight and preterm birth) with logistic regression. The distribution of plasma retinol conformed to normality. Data for α tocopherol/triglycerides needed natural logarithmic transformation, and geometric means were calculated.

Role of the funding source

The sponsor had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The first participant joined the trial on Aug 11, 2002, and the last on Oct 22, 2003; all women had exited the trial by July, 2004. The figure shows the trial profile. Most exclusions from enrolment were for gestations of more than 20 weeks. Maternal illnesses that led to exclusion were: recently treated recurrent cysticercosis (1); need for chlorpromazine (1) or anticoagulant (1) drugs with changing doses; and symptomatic mitral stenosis (1) or multivalvular heart disease (1). Fetal exclusions were: twin pregnancies (6); anencephaly (1); occipital meningocele (1); encephalocele (1); duodenal atresia (1); and a grossly dilated pelvicalyceal system (1). All participants received their allocated supplements, irrespective of whether they took any. 20 participants enrolled in the trial but were never seen again, even after a thorough search in the areas they had given as their addresses. 19 moved out of the areas in which they could be tracked and we do not know their birth outcomes. Seven participants had spontaneous abortion. 14 women withdrew from the trial because they felt it would not benefit them. One withdrew after developing generalised itching. In deviations from protocol, four participants received treatment for severe anaemia and three for night blindness.

Data for 1139 deliveries were available for the analysis of gestational duration. Because most stillborn infants were not weighed, we included only liveborn infants in the analysis of birthweight. The birthweight outcome was available for 523 (87%) infants in the control group and 529 (88%) in the intervention group.

Table 1 shows baseline characteristics. Both arms were comparable. Most participants belonged to the Maithil group, traditional residents of the area: 518/599 (86%) in the control group and 499/599 (83%) in the intervention group. The remaining women were mainly from Muslim and hill Indo-Aryan groups. Half the participants came from Janakpur municipality and most came from families who owned some land and were supported by non-agricultural income from shops and small-scale manufacture. About half of participants had been to school, at least at primary level. 540 (45%) were in their first pregnancies. Enrolment weight was measured at mean 16·0 weeks (SD 3·1) in the control group and 15·7 weeks (3·7) in the intervention group. Although

	Control (n=600)	Intervention (n=600)
Residence		
Urban	316 (53%)	314 (52%)
Rural	284 (47%)	286 (48%)
Land owned		
None	39 (7%)	29 (5%)
≤10 kattha*	312 (52%)	337 (56%)
>10 kattha*	247 (41%)	227 (38%)
Husband's occupation		
No work	61 (10%)	69 (12%)
Farming	92 (15%)	89 (15%)
Salaried	252 (42%)	261 (44%)
Small business	114 (19%)	109 (18%)
Waged labour	66 (11%)	53 (9%)
Student	8 (1%)	9 (2%)
Out of country	7 (1%)	10 (2%)
Age		
<20 years	171 (29%)	190 (32%)
20–29 years	398 (66%)	387 (65%)
≥30 years	31 (5%)	23 (4%)
Schooling		
None	271 (45%)	273 (46%)
Primary	67 (11%)	56 (9%)
Lower secondary or higher	262 (44%)	271 (45%)
Parity		
0	266 (44%)	274 (46%)
1–2	261 (44%)	276 (46%)
≥3	73 (12%)	50 (8%)
Enrolment weight (kg)	45·1 (6·0)	45·1 (6·2)
Height (cm)†	151·0 (5·7)	150·5 (5·4)
Enrolment body-mass index (kg/m²)	19·8 (2·4)	19·9 (2·4)
<18·5 kg/m²	170 (28%)	172 (29%)

Data are number of participants (%) or mean (SD). *10 kattha is about 0·3 hectares. †Control, n=598; intervention n=599.

Table 1: **Baseline household and participant characteristics**

mean height was not strikingly short, mean weight at enrolment was low at 45 kg, and 342 (29%) women had a low body-mass index. Participants who were lost to follow-up or withdrew from the trial were less likely to be Maithil and were wealthier than those who remained.

The mean period of potential supplementation was 158 days (SD 30) in the control group and 161 days (29) in the intervention group. Discrepancy estimates of adherence included all enrolled participants: if they withdrew from the trial or were lost to follow-up, we calculated their days of involvement and assumed that they had taken no supplements. We assessed adherence in terms of the number of tablets used over the period of participation, which relies on the assumption that they had been consumed by the participant. The distribution of adherence was J-shaped with clustering towards 100%. Consumption accounted for a median 98% of days of participation in the control group (IQR 91–100) and 97% in the intervention group (91–100).

Blood haemoglobin samples were available for 1054 women at enrolment and for 1050 in the third trimester (table 2). Enrolment blood samples were taken at a mean gestation of 16·3 weeks (SD 3·0) in the control group and 16·1 weeks (2·9) in the intervention group; third trimester samples were taken at 31·4 weeks (2·0) and 31·6 weeks (2·2), respectively. Blood haemoglobin concentrations did not differ between arms at enrolment. 401 (38%) women were anaemic at enrolment (<110 g/L) but severe anaemia was rare (one participant in the control group and three in the intervention group had haemoglobin concentrations <70 g/L). Allocation to either supplement was associated with a fall in the prevalence of anaemia. At enrolment, plasma retinol concentration was assayed in 127 participants and vitamin E in 108; respective numbers for the third trimester were 101 and 91. Micronutrient supplementation resulted in significantly higher retinol (p=0·01) and vitamin E (p=0·03) concentrations at around 32 weeks' gestation.

Of 568 deliveries in the control group, 300 (53%) took place in hospital and 43 (8%) were caesarean sections. In the intervention group, 346 (61%) of 571 deliveries were hospital births and 46 (8%) were caesarean sections. Table 3 presents the analysis of primary and secondary outcomes. 1052 birthweights were available for analysis; 832 (79%) were taken on the first day, 184 (17%) on the second, and 36 (3%) on the third. Birthweight was greater in the intervention group than in the control group; this difference barely changed when restricted to infants born at term. The intervention was associated with a 25% relative reduction in the prevalence of low birthweight. Although gestational duration was 1·5 days longer in the intervention group than in the control group, the difference was not significant. Birth length and infant head circumference did not differ between arms.

Mean birthweight was 91 g higher in male than in female infants (2817 g *vs* 2726 g; [95% CI for the difference 38–144]), 150 g greater in infants of multiparous than primiparous women (2839 g *vs* 2689 g; [97–202]), and 116 g higher in infants of participants whose body-mass index was 18·5 kg/m² or more compared with less than 18·5 kg/m² (2804 g *vs* 2688 g; [57–175]). Table 3 also summarises the birthweight outcome after stratification for these factors.

The study was not powered to detect differences in mortality, and none of the differences shown in table 4 is

	Control group	Intervention group
Haemoglobin		
Enrolment sample (n)	517	537
Mean (SD) concentration (g/L)	115 (16)	115 (16)
<110 g/L (n [%])	200 (39%)	201 (37%)
Third trimester sample (n)	517	533
Mean (SD) concentration (g/L)	118 (14)	118 (12)
<110 g/L (n [%])	148 (29%)	133 (25%)
Retinol		
Enrolment sample (n)	67	60
Mean (SD) concentration (μmol/L)	1·11 (0·32)	1·17 (0·39)
Third trimester sample (n)	56	45
Mean (SD) concentration (μmol/L)	1·20 (0·39)	1·39 (0·33)
α tocopherol/triglycerides		
Enrolment sample (n)	56	52
Geometric mean (95% CI) ratio (μmol/mmol)	12·9 (11·7–14·2)	13·3 (11·8–14·8)
Third trimester sample (n)	52	39
Geometric mean (95% CI) ratio (μmol/mmol)	10·7 (9·8–11·6)	12·6 (11·1–14·4)

Table 2: **Maternal nutritional biochemistry**

	Control	Intervention	Difference (95% CI)	p
Primary and secondary outcomes				
Birthweight (g)	2733 (422) [n=523]	2810 (453) [n=529]	77 (24 to 130)	0·004
Gestation at birth (weeks)	39·2 (2·0) [n=568]	39·4 (1·9) [n=571]	0·2 (−0·1 to 0·4)	0·12
Birth length (cm)	48·6 (3·2) [n=517]	48·9 (2·9) [n=526]	0·3 (−0·1 to 0·6)	0·16
Head circumference (cm)	33·6 (2·2) [n=519]	33·8 (2·2) [n=526]	0·2 (−0·1 to 0·4)	0·18
Stratified birthweight outcomes				
Infant sex				
Female	2672 (399) [n=260]	2780 (429) [n=256]	108 (36 to 179)	0·003
Male	2794 (437) [n=261]	2838 (474) [n=273]	44 (−33 to 122)	0·261
Mother's parity				
Primigravid	2664 (404) [n=231]	2714 (418) [n=242]	50 (−24 to 124)	0·189
Multigravid	2787 (428) [n=292]	2891 (467) [n=287]	104 (31 to 177)	0·005
Mother's body-mass index				
<18·5 kg/m²	2661 (443) [n=148]	2715 (402) [n=145]	54 (−43 to 152)	0·274
≥18·5 kg/m²	2762 (410) [n=374]	2845 (467) [n=383]	83 (20 to 146)	0·010
Categorical outcomes				
Low birthweight	133/523 (25%)	101/529 (19%)	0·69 (0·52 to 0·93)*	0·014
Preterm	54/568 (10%)	47/571 (8%)	0·85 (0·57 to 1·29)*	0·45

Data are mean (SD) [n] unless otherwise indicated. *Odds ratio (95% CI).

Table 3: Primary, secondary, and stratified outcomes

significant. More stillbirths were reported in the control group and more early neonatal deaths in the intervention group. Overall perinatal mortality rates were, therefore, similar. A combination of verbal autopsy and clinical assessment suggested that the commonest causes of death were infection, preterm birth, and birth asphyxia. No obvious imbalance was noted between the groups with respect to these factors.

Morbidity was both a potential outcome and a potential adverse effect. Typical antenatal problems were gastrointestinal symptoms (nausea, dyspepsia, abdominal pain) and backache. We recorded no differences between the groups in morbidity or reported problems during pregnancy or in incidence of complications such as failure to progress, retained placenta, and postpartum haemorrhage. Seven participants in the control group and two in the intervention group were treated for clinical eclampsia. No differences were seen between the groups in postpartum morbidity reports. Likewise, in infants we recorded no differences in modified Apgar scores, cough, breathing difficulties, diarrhoea, feeding problems, or fever. Two infants in the control group had identifiable congenital anomalies (talipes equinovarus; cleft lip and palate), as did two in the intervention group (acyanotic congenital heart disease; tracheo-oesophageal fistula, imperforate anus, and preterm birth). Both infants in the intervention group died in the neonatal period.

	Control group	Intervention group
Births	568	571
Stillbirths	18	15
Livebirths	550	556
Neonatal deaths	11	17
Early neonatal deaths	5	13
Late neonatal deaths	6	4
Perinatal deaths	23	28
Neonatal mortality rate (per 1000 livebirths)	20·0	30·6
Early neonatal mortality rate (per 1000 livebirths)	9·1	23·4
Late neonatal mortality rate (per 1000 livebirths)	10·9	7·2
Stillbirth rate (per 1000 births)	31·7	26·3
Perinatal mortality rate (per 1000 births)	40·5	49·0

Table 4: Mortality outcomes

Discussion

We have shown that antenatal supplementation with a multiple micronutrient preparation was associated with increased birthweight when compared with a standard iron and folic acid preparation. Gestational duration was not affected by supplementation. We achieved high retention rates, and imprecision was restricted to tolerances implied by use of electronic scales for weighing, a 72-h window for measurement of birthweight, and ultrasound biometry for gestational assessment.

A trial of this type was undertaken in Tanzania and included 1067 women infected with HIV-1.[25] Supplementation with multivitamins at 2–20 times the recommended daily allowance in the third trimester was associated with a 44% fall in low birthweight and reductions in preterm deliveries (39%), small-for-gestational age infants, and fetal death. In a double-blind randomised controlled trial in Mexico,[48] a supplement containing 1–1·5 times the recommended daily allowance of ten vitamins and three minerals was compared with iron alone. No effects were reported on birthweight, gestational age, or proportion of low birthweight infants. Although the design maximised compliance, loss to follow-up was appreciable (229/874) and—more importantly—a third of participants were overweight and the rate of low birthweight was less than 9%.

In a double-blind cluster randomised controlled trial from a district in southern Nepal, 426 villages received one of five supplement regimens.[19] The researchers noted that folic acid and iron supplementation were associated with a non-significant 60 g increase in birthweight over control or folic acid alone. This effect was not seen when zinc was added to folic acid and iron. Multiple micronutrient supplements (in a generally similar formulation to our study that also contained 100 mg of magnesium, 30 mg of zinc, 60 mg of iron, but no selenium) were associated with a significant 64 g rise in birthweight over control. The interpretation of this trial[19] has been that multiple micronutrients confer no added benefit over that of iron and folic acid supplements alone.

A double-blind placebo-controlled randomised trial has been reported from Harare, Zimbabwe.[49] Participants were enrolled at 22–35 weeks' gestation and outcomes were available for only 66%, but the trial is valuable for having included many women with HIV infection. A 50 g increase in birthweight in the supplemented group (in a slightly different tablet composition from our study) was not significant, but birthweights in this population were higher than in south Asia, and the rate of low birthweight was only 10·5%. The concentration of low birthweight in south Asia, with higher birthweights in general in sub-Saharan

Africa, does have implications for roll-out of potential programmes.

How far can our findings be generalised? Micronutrient supplementation has its adherents and its critics. Supplementation began at about 4 months' gestation and lasted until delivery. This strategy seems feasible in settings where antenatal care uptake is high, and continuation into the postpartum period is also a possibility. In settings like rural Nepal where uptake is low, the effectiveness of supplementation programmes has been limited. The discrepancy estimate method probably overestimated adherence, but the changes in plasma vitamin concentrations, the outcome of the study, and our own impression during implementation, all suggest that participants did take substantial numbers of tablets. Incidentally, it is noteworthy that even with regular support and encouragement and an assurance of exemption from fees, only 50–60% of participants availed themselves of hospital delivery.

The external validity of the findings would also be limited if the participants were an unusual group. Census figures suggest that the level of female literacy in Dhanusha district is about 36%; 37% of children attend primary and 18% lower secondary school. In a previous Nepalese trial,[19] 20% of participants were literate and 90% delivered at home. Comparison of these figures with those of our study confirms our impression that the sample was a mix of urban and rural women and favoured the moderately poor population rather than the extreme rural poor or the wealthy: participants had somewhat more schooling and were more literate, were usually from families involved in small-scale urban and periurban businesses, and were less likely to be anaemic than average survey figures suggest.[17] Likewise, birthweights and low birthweight rates accord with estimates that probably under-represent the rural poor.[18]

Research is justified if the populations in which it is done are likely to benefit from the results.[43] Does an improvement in birthweight of this size translate into reduced mortality or morbidity? Is the improvement associated with better developmental indices? Does it have long-term health benefits? These questions remain open. In common with some other investigators,[50] we suggest that changes in birthweight at term might not have resounding effects. Modest changes in rates of preterm birth or increases in gestational duration could have stronger effects on mortality,[13] but large studies would be necessary to describe them. We did not record significant effects on morbidity or mortality and agree with other authors that multiple micronutrient supplementation needs more evaluation before we consider large-scale programmes.[27,51] We draw attention to the high early neonatal mortality in the intervention group, which—although not significant—is similar to a finding reported by Christian and colleagues.[52] Our study did not address the particular issue of multiple micronutrient supplements for women living with HIV, in whom impressive effects of high doses of selected micronutrients have been described in Tanzania.[25]

Our tentative finding of a differential effect of the supplement is interesting. The effect of multiple micronutrients on fetal weight seems to have been enhanced in female infants, in births of higher order, and in babies of women with a greater body-mass index. The growth potential for fetuses of larger, parous women is high, but female fetuses are usually smaller than males, and the finding of a greater increment in females is somewhat counterintuitive. We look forward to further work and opinions on our findings.

The public-health implications of our findings await confirmation by the results of other studies currently underway in Bangladesh, Burkina Faso, China, Guinea Bissau, Indonesia, and Pakistan.

Contributors

The investigators are members of an international study group, which met in 2002 (http://www.ich.ucl.ac.uk/ich/html/academicunits/cich/pdfs/micronutrientmi.pdf [accessed Feb 15, 2005]) and 2004. All authors contributed to implementation of the study and criticised drafts of the paper. D Osrin was responsible for study protocols, methods, and electronic database, advised on implementation, did the analysis, and wrote the first draft of the paper. A Vaidya was the clinical coordinator of the study, undertook ultrasound and medical assessment, entered data, and did the analysis. Y Shrestha supervised all nursing and maternity aspects of the study and undertook data collection and allocation. R B Baniya supervised field activities and was the programme manager in Dhanusha. D S Manandhar and R K Adhikari were principal investigators and took overall responsibility for the study in Nepal. S Filteau, A Tomkins, and A M de L Costello were principal investigators in the UK and contributed to study design and writing of the report.

Conflict of interest statement

In the planning phase of the study, DO, SF, and AT attended an international principal investigators' meeting funded by the Micronutrient Initiative. After study completion, but before this paper was written, AV, DSM, and AT attended a second meeting funded by UNICEF. The other authors declare that they have no conflict of interest.

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its conclusion. This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN88625934.

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Annex B. Research article 2

Effects of antenatal multiple micronutrient supplementation on children's weight and size at 2 years of age in Nepal; follow-up of a double blind randomized controlled trial. Lancet 2008; 371:492

Effects of antenatal multiple micronutrient supplementation on children's weight and size at 2 years of age in Nepal: follow-up of a double-blind randomised controlled trial

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Summary

Background The negative effects of low birthweight on the later health of children in developing countries have been well studied. However, undertaking programmes to address this issue can be difficult since there is no simple correlation between increasing birthweight and improving child health. In 2005, we published results of a randomised controlled trial in Nepal, in which 1200 women received either iron and folic acid or a supplement that provided the recommended daily allowance of 15 vitamins and minerals, over the second and third trimesters of pregnancy. Here, we report on 2–3 years' follow-up of children born during the trial.

Methods We visited children at home and obtained data for the primary outcomes of weight and height, for childhood illnesses, and maternal blood haemoglobin. The study is registered as an International Standard Randomised Controlled Trial, number ISRCTN88625934.

Findings Between December, 2005, and December, 2006, we assessed 917 children (455 controls, 462 intervention) at a mean age of 2·5 years. Mean birthweight had been 77 g (95% CI 24–130) greater in the micronutrient group than in controls. At 2·5 years old, controls weighed a mean of 10·7 kg (SD 1·38), and those in the intervention group 10·9 kg (SD 1·54). Children of women who had taken multiple micronutrient supplements during pregnancy were a mean 204 g (95% CI 27–381) heavier than controls. They also had greater measurements than controls in the circumference of the head (2·4 mm [95% CI 0·6–4·3]), chest (3·2 mm [0·4–6·0]), and mid-upper arm (2·4 mm [1·1–3·7]), and in triceps skinfold thickness (2·0 mm [0·0–0·4]). Systolic blood pressure was slightly lower in the intervention group (2·5 mm Hg [0·5–4·6]).

Interpretation In a poor population, the effects of maternal multiple micronutrient supplementation on the fetus persisted into childhood, with increases in both weight and body size. These increases were small, however, since those exposed to micronutrients had an average of 2% higher weight than controls. The public-health implications of changes in weight and blood pressure need to be clarified through further follow-up.

Introduction

The negative effects of a birthweight of less than 2500 g on child morbidity and survival in developing countries have been well described.[1–3] What is less clear is what effect interventions to raise birthweight might have on child health. Health strategies have generally been based on the observation that in poor countries, low birthweight is more common in babies who are born at full term than in those born prematurely,[4] and that low birthweight might lead to childhood malnutrition.

Creating public-health programmes to tackle this issue has been difficult, however, for three reasons. First, we have not yet managed to get potential interventions to women at risk, at a time of life when they might be helpful, and at a population level.[5] Second, increased birthweight is not necessarily followed by increased survival and reductions in morbidity in either newborn babies or children—children with similar weights could differ in mortality rates between populations.[6] Third, possible associations between fetal and infant growth and adult disease have made us cautious about increasing infant weight.[7]

In 2005, we published the results of an individually randomised, double-blind controlled trial in Dhanusha district, Nepal.[8] 1200 women received either routine iron and folic acid supplements or a multiple micronutrient supplement providing the recommended daily allowance of 15 vitamins and minerals, over the second and third trimesters of pregnancy. Mean birthweights were 2733 g (SD 422) in the control group and 2810 g (SD 453) in the intervention group, representing a difference of 77 g (95% CI 24–130) and a 25% fall in the proportion of low birthweight infants. The groups did not differ in the duration of gestation, infant length, or head circumference.

Nine trials of similar supplementation approaches are being systematically reviewed.[6–18] Antenatal multiple micronutrient supplementation probably does increase birthweight, but whether this translates into short-term or long-term health benefits remains uncertain. Important questions include whether the effects of antepartum intervention are sustained, and whether micronutrient repletion improves early childhood growth in a way that

could confer lasting benefit. To answer these questions, we undertook a follow-up of children born in the original trial, at the age of 2–3 years.

Methods

Participants

In the original trial, we enrolled 1200 participants from an antenatal clinic at Janakpur zonal hospital, in Nepal's Dhanusha district. The inclusion criteria were gestation of up to 20 completed weeks, based on dates and ultrasound biometry; singleton pregnancy; no notable fetal abnormality on obstetric ultrasound; no existing maternal illness of a severity that could compromise the outcome of the pregnancy; and accessibility for follow-up at home.

After providing signed consent, participants received supplements from enrolment (at no earlier than 12 weeks' gestation) to delivery. The daily micronutrient supplements were provided in monthly allocations. Participants were followed up every 2 weeks, at birth, and at 1 month postpartum. Anthropometric measures were recorded within 72 h of birth. Allocation was double-blind and randomised to two groups of 600 participants. The control group received tablets containing iron (60 mg) and folic acid (400 µg). The intervention group received tablets containing vitamin A (800 µg), vitamin E (10 mg), vitamin D (5 µg), vitamin B_1 (1·4 mg), vitamin B_2 (1·4 mg), niacin (18 mg), vitamin B_6 (1·9 mg), vitamin B_{12} (2·6 µg), folic acid (400 µg), vitamin C (70 mg), iron (30 mg), zinc (15 mg), copper (2 mg), selenium (65 µg), and iodine (150 µg).[19] All supplements were manufactured by Danish Pharmaceutical Industries Ltd (Ballerup, Denmark).

The trial was approved by the Nepal Health Research Council, and by the ethics committee of the Institute of Child Health and Great Ormond Street Hospital for Children, UK, and was undertaken in collaboration with the Nepal Government Ministry of Health. Benefits to participants included the supply of supplements, free healthcare, and expedited referral in the event of complications. Information provided by participants remained confidential. Access was restricted to supervisory and research staff at the analytical level. No analyses or outputs included the names of participants.

Procedures

Children born in the trial were followed-up at 2·5 years of age by five field workers, one of whom acted as coordinator. Training in anthropometric techniques included taking test measurements of 300 children who were not in the trial. We were particularly keen to keep variation between observers to a minimum since, for example, it accounted for 23% of the variation in head circumference, whereas intra-observer variation accounted for 8%. Final study measurements were therefore restricted to two field workers.

Visiting schedules were set according to the ages of individual children and the need to cover flood-prone areas outside the monsoon season. All participants who had not moved home too far for us to travel to were visited at home up to five times. The field workers were unaware of the initial supplement allocation since access to the codes was restricted to principal investigators. We obtained additional informed verbal consent from mothers and family members to collect follow-up information and measurements. Participants received a towel and a sweet as a token of appreciation.

Primary outcomes were weight and height. Weight was measured with Seca 835 electronic scales (Hamburg, Germany) accurate to 10 g. Standing height was measured with a portable Leicester stadiometer accurate to 1 mm, barefoot and with the head in the auriculo-orbital plane. Secondary outcomes included circumferences of the head, chest, waist, hip, and mid-upper arm, triceps skinfold thickness, and blood pressure.

We also obtained information on childhood illnesses and measured maternal blood haemoglobin. Head and mid-upper arm circumferences were measured with disposable insertion tapes accurate to 1 mm (Harlow

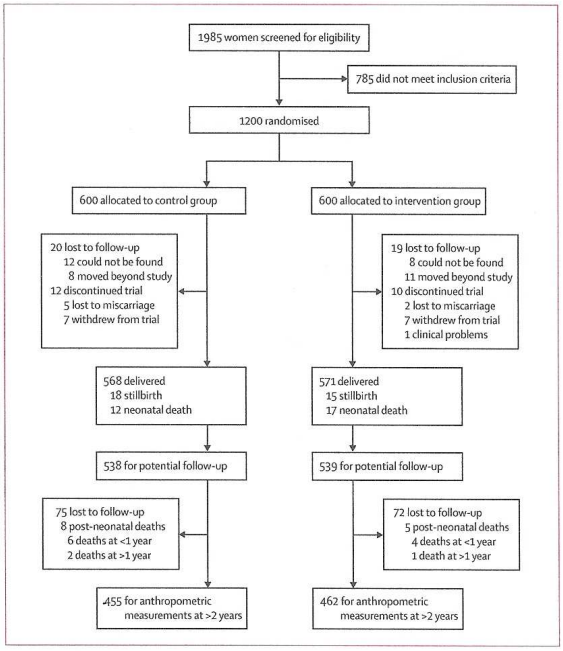

Figure: Trial profile

	Control (n=455)	Intervention (n=462)	Lost-to-follow up (n=147)
Location			
Urban	227 (49·9%)	231 (50·0%)	96 (65·3%)
Rural	228 (50·1%)	231 (50·0%)	51 (34·7%)
Land owned			
None	22 (4·8%)	23 (5·0%)	11 (7·5%)
<10 kattha (0·3 hectares)	241 (53·0%)	267 (57·8%)	81 (55·1%)
>10 kattha	192 (42·2%)	172 (37·2%)	55 (37·4%)
Husband's occupation			
No work	53 (11·7%)	51 (11·0%)	16 (10·9%)
Farming	71 (15·6%)	68 (14·7%)	19 (12·9%)
Salaried	181 (39·8%)	203 (43·9%)	71 (48·3%)
Small business	83 (18·2%)	84 (18·2%)	32 (21·7%)
Waged labour	53 (11·7%)	45 (9·8%)	5 (3·4%)
Student	7 (1·5%)	5 (1·1%)	2 (1·4%)
Out of country	7 (1·5%)	6 (1·3%)	2 (1·4%)
Consumer durables			
Motor vehicle, television, or refrigerator	243 (53·4%)	239 (51·5%)	78 (53·1%)
Sewing machine, cassette player, camera, fan, or bullock cart	26 (5·7%)	18 (3·9%)	5 (3·4%)
Clock, radio, iron, or bicycle	122 (26·8%)	133 (28·8%)	42 (28·5%)
None of the above	64 (14·1%)	73 (15·8%)	22 (15·0%)
Schooling			
None	212 (46·6%)	219 (47·4%)	45 (30·6%)
Primary	40 (8·8%)	39 (8·4%)	21 (14·3%)
Lower secondary or higher	203 (44·6%)	204 (44·2%)	81 (55·1%)
Parity at birth of index child			
0	217 (47·7%)	223 (48·3%)	71 (48·3%)
1	135 (29·7%)	130 (28·1%)	41 (27·9%)
2	65 (14·3%)	63 (13·6%)	23 (15·6%)
3	26 (5·7%)	32 (6·9%)	9 (6·1%)
4	10 (2·2%)	9 (2·0%)	1 (0·7%)
≥5	2 (0·4%)	5 (1·1%)	2 (1·4%)

Table 1: **Household and participant characteristics at enrolment**

Printing Ltd, South Shields, Tyne and Wear, UK). Head circumference was taken at the maximum occipito-frontal measurement. Upper arm circumference was measured midway between the tip of the olecranon process and the acromion process. Chest, waist, and hip circumferences were measured with a plastic measuring tape accurate to 1 mm. The chest was measured at the level of the nipples, midway between inspiration and expiration during quiet breathing. Waist circumference was measured at the level of the natural waist, and the hip at the level of maximum circumference over the buttocks. Triceps skinfold thickness was measured with Harpenden callipers accurate to 1 mm (Assist Creative Resource, Wrexham, UK). The measurement was taken midway between the tip of the olecranon process and the acromion process, in the midline of the posterior surface of the extended dominant arm. All measurements except weight and height were made three times and the middle value recorded for analysis.

Blood pressure was measured with the child on her mother's lap, with a portable CE0 197 Omron electronic sphygmomanometer (Japan). We measured maternal haemoglobin with a spectrophotometer on finger-prick blood samples using a portable HemoCue AB CE201 (Dronfield, UK), with daily calibration checks. We collected information about the number of illnesses in the first year of life and about specific illnesses in the 14 days preceding the interview. Medical reports were examined where available and verbal autopsy questionnaires were completed in the event of death. We defined loss-to-follow-up as confirmed information that a participant had moved beyond the possibility of visiting, usually to India. Information about participants, their progress, and outcomes, was collected in individual files which were manually checked for completeness. Data were entered into a relational database management system with field validity rules (FileMaker Pro 5.5, USA).

Statistical analysis

The original trial sample size was computed to detect a difference in mean birthweight of 100 g at a power of 90% and a two-sided significance level of 0·05, allowing for 30% loss-to-follow-up. The power of the study would be 81% if the true difference were equal to the 77 g difference observed. We assessed outliers in Data Desk 6.2.1 (Ithaca, NY). The rest of the analysis was done in the Statistical Program for the Social Sciences version 11 (SPSS Inc, USA). Baseline confounders were assessed by inspecting proportions for categorical variables and means for continuous variables. Continuous anthropometric outcomes were compared first through *t* tests and univariate regression, and then adjusted for potential confounding with multivariate linear regression models. Total upper arm area was estimated as the square of the circumference divided by 4π.[20] Upper-arm fat area was calculated as circumference multiplied by triceps skinfold thickness, and then divided by two, a model reported as consistent with magnetic resonance images.[21]

Role of the funding source

The original study was funded by The Wellcome Trust. The follow-up study was funded by a grant from an anonymous charitable donor. Neither played a part in the study design; the collection, analysis, or interpretation of data; the writing of the report; or the decision to submit the paper for publication.

Results

The figure shows the trial profile. We visited 917 mothers and children from December, 2005, to December, 2006: 455 in the control group and 462 in the intervention group. Retention rates in the control and intervention groups (taking into account discontinuation in the study, fetal loss, stillbirths, infant deaths, post-infancy deaths

and losses-to-follow-up) were 76% and 77%, respectively. Retention rates in children who could potentially have been followed up after the neonatal period were 85% and 86%, respectively.

At follow-up, we identified a neonatal death in the control group that we could not have noted in the first phase. This changed the neonatal mortality rate in the control group (quoted in the original paper as 20·0)[8,22] to 21·8 (95% CI 11·3–37·8) per 1000 livebirths. The rate in the intervention group remains the same as the initial report, at 30·6 (17·9–48·5). We identified six post-neonatal infant deaths in the control group and four in the intervention group. Infant mortality rates (deaths at younger than 1 year, with a denominator of livebirths minus losses-to-follow-up) were 37·9 (22·6–59·2) per thousand livebirths in the control and 43·4 (27·1–65·6) in the intervention group. Post-neonatal deaths were ascribed to pneumonia (two), diarrhoea (two), meningitis (one), convulsion (two), measles followed by confirmed tuberculosis (one), a hepatic syndrome (one), complications of cleft palate (one), a bleeding disorder (one), and sudden unexplained death overnight (two). Four mothers had died between the postnatal period and follow-up, of burns, pesticide ingestion, head injury after a fall, and a possible haematological malignancy.

Table 1 compares household and participant characteristics at enrolment in the two groups, and in the 147 participants who were lost-to-follow-up at 2 years. Investigation suggests that potential confounders were evenly allocated. Compared with the retained individuals, women lost-to-follow-up were more likely to be urban, have husbands who were salaried or ran small businesses, and have gone to school. They were less likely to own land and have husbands who worked in agriculture or as waged labourers.

Table 2 compares maternal and child characteristics between the groups at follow-up. 43% of women were anaemic. 42% had blood haemoglobin levels below 6·8 mmol/L and 1% below 4·3 mmol/L. Just under half of participants had been primigravid in the trial and there were no significant differences between maternal anthropometric findings. 94% of infants had been breastfed. The mean ages of introduction of other liquids, cow's milk, or regular solids did not differ between the allocation groups. Reported morbidity was common: 35% of children were described as having had fever, and 36% as having had a cough, in the fortnight before the interview. We identified no difference between the groups in reports of illness in either the previous 14 days or the first year of life. Immunisation levels were equivalent and high, with reporting of over 90% for BCG (Bacille Calmette Guérin) vaccine, 99% for oral polio vaccine and DPT (diphtheria, pertussis, and tetanus) 1-3, and 98% for measles. The most recent inclusion in the schedule—hepatitis B immunisation—was reported at rates of over 93% for all three doses.

	Control	Intervention
Mothers		
Age (years)	24·5 (3·4) [n=455]	24·6 (3·5) [n=452]
Weight (kg)	45·8 (7·3) [n=452]	45·8 (7·4) [n=457]
Height (m)	1·51 (0·54) [n=452]	1·50 (0·57) [n=455]
Body-mass index (kg/m²)	20·4 (5·0) [n=452]	20·4 (2·9) [n=455]
Haemoglobin (mmol/L)	6·98 (0·79) [n=452]	6·96 (0·83) [n=456]
Had another pregnancy since the trial pregnancy	159 (34·9%) [n=455]	155 (33·5%) [n=462]
Age of infant from subsequent pregnancy in weeks	29·1 (18·4) [n=455]	31·7 (21·3) [n=462]
Children		
Breastfed	432 (94·9%) [n=455]	433 (93·7%) [n=462]
Age at introduction of other liquids (months)	4·04 (2·62) [n=455]	4·04 (2·71) [n=462]
Age at introduction of other milk (months)	8·6 (5·0) [n=455]	8·4 (4·9) [n=462]
Age at introduction of regular solids (months)	8·4 (3·5) [n=455]	8·5 (3·3) [n=462]
Reported illnesses in previous 2 weeks		
Fever	160 (35·2%) [n=454]	162 (35·1%) [n=462]
Cough	162 (35·7%) [n=454]	166 (35·9%) [n=462]
Diarrhoea	66 (14·5%) [n=454]	59 (12·8)% [n=462]
Difficulty breathing	31 (6·8%) [n=453]	39 (8·4%) [n=462]
Illness in first year		
Fewer than five episodes of illness	223 (50·5%) [n=442]	237 (52·4%) [n=452]
Five or more episodes	219 (49·5%) [n=442]	215 (47·6%) [n=452]

Data are number (%) or mean (SD) unless otherwise indicated.

Table 2: **Maternal and child characteristics at follow-up**

For children who were followed up, mean gestation at birth was 39·38 (SD 1·70) weeks in the control group and 39·58 (1·57) in the intervention group. 468 (51·0%) were boys and 449 (49·0%) girls. This distribution did not differ between either allocation or loss-to-follow-up. Mean age at follow-up was 2·56 (SD 0·35; range 1·98–3·63) years in the control group and 2·56 (0·35, 1·98–3·85) in the intervention group. Table 3 shows the anthropometric findings and summarises four analyses: (1) unadjusted analysis comparing mean measures between the groups; (2) analysis adjusted for the ages of children when the measurements were made; (3) analysis adjusted for age, and also for sex, maternal parity, and gestation at birth—this is an intuitive approach similar to that used in a study from India;[23] and (4) analysis based on a parsimonious model adjusted for age, sex, gestation at birth, maternal weight at enrolment, and maternal education. We used single variables to describe maternal size and social status, on the basis of significance and greatest explanatory effect in univariate analysis. The model accounts for 28% of the variance in child weight at follow-up. Tables 1 and 2 suggest that randomisation dealt with potentially uneven distribution of confounders, and the outcomes appear robust to adjustment. Thus, we will discuss the findings as they are presented after adjustment for age at follow-up.

The mean weight was 10·7 kg (SD 1·38) in the control group and 10·9 kg (SD 1·54) in the intervention group. Children of women who had taken multiple micronutrient

supplements during pregnancy were a mean 204 g (95% CI 27–381) heavier than controls at 2·5 years of age. Their mean heights did not differ, but their head circumferences were a mean 2·4 mm (0·6–4·3) larger, their chest circumferences a mean 3·2 mm (0·4–6·0) larger, and their hip circumferences a mean 4·0 mm (0·5–7·4) larger. A mean 3·3 mm difference in waist circumference was not significant at the 5% level, and waist-to-hip ratios were no different. Mid-upper arm circumference was a mean 2·4 mm (1·1–3·7) larger, and triceps skinfold thickness a mean 2·0 mm (0·0–0·4) greater. Table 4 shows prenatal and postnatal differences between the groups by comparing unadjusted mean weight, height, and head circumference at birth and at follow-up. Of the 203 g difference in weight between the groups at follow-up, 126 g was accrued in early childhood. The incremental differences in height and head circumference were small: 0·6 mm and 0·7 mm, respectively, in early childhood.

Mean systolic blood pressure was 101·9 mm Hg (SD 17·54, n=454) in the control group and 99·4 mm Hg (SD 13·68, n=460) in the intervention group. Mean diastolic blood pressure was 63·4 mm Hg (SD 14·71) in the control group and 62·05 (12·80) in the intervention group. Children of women who had taken multiple micronutrient supplements during pregnancy had systolic blood pressures a mean 2·5 mm Hg (95% CI 0·47–4·55) lower than controls, but there was no difference in mean diastolic blood pressure (-1·5 mm Hg [95% CI -3·1–0·4]).

Table 5 compares weight and height with WHO standards.[24,25] Overall, the mean weight-for-age was 1·70, the mean height-for-age 2·24, and the mean weight-for-height 0·34 *Z* scores below the median. The intervention group showed a slightly significant increase in weight-for-age (p=0·048) and a non-significant increase in height-for-age (p=0·281), which also resulted in a non-significant difference in weight-for-height (p=0·097). Defining the cut-offs for underweight, stunting, and wasting as two *Z* scores below the medians for weight-for-age, height-for-age, and weight-for-height respectively, the overall numbers of those underweight were 340 (37·2%), of stunting 534 (58·4%), and of wasting 54 (5·9%). None of these rates were significantly different between the groups. Table 5 presents a detailed categorical breakdown of these indices, which gives the

	Control (n=455)	Intervention (n=462)	Unadjusted (95% CI)	Adjusted for age at follow-up (95% CI)	Adjusted for age at follow-up, sex, maternal parity, gestation at birth (95% CI)	Adjusted for age at follow-up, sex, gestation at birth, maternal weight at enrolment, maternal education (95% CI)
Weight (kg)	10·697 (1·383)	10·900(1·544)	0·203 (0·013 to 0·393)*	0·204 (0·027 to 0·381)*	0·199 (0·027 to 0·370)*	0·194 (0·038 to 0·350)*
Height (cm)	83·76 (4·68)	84·07 (4·83)	0·30 (–0·31 to 0·92)	0·31 (–0·20 to 0·82)	0·29 (–0·21 to 0·79)	0·28 (–0·17 to 0·73)
BMI (kg/m^2)	15·22 (1·32)	15·39 (1·47)	0·17 (–0·01 to 0·35)	0·17 (–0·01 to 0·35)	0·17 (–0·01 to 0·34)	0·16 (–0·01 to 0·34)
Head circumference (cm)	46·40 (1·43)	46·64 (1·49)	0·24 (0·06 to 0·43)*	0·24 (0·06 to 0·43)*	0·23 (0·07 to 0·40)*	0·23 (0·07 to 0·39)*
Chest circumference (cm)	47·96 (2·26)	48·28 (2·45)	0·32 (0·01 to 0·66)*	0·32 (0·04 to 0·60)*	0·31 (0·03 to 0·58)*	0·30 (0·04 to 0·56)*
Waist circumference (cm)	46·48 (2·75)	46·81 (2·84)	0·33 (–0·03 to 0·69)	0·33 (–0·01 to 0·68)	0·33 (–0·01 to 0·67)	0·32 (–0·01 to 0·65)
Hip circumference (cm)	45·95 (2·68)	46·34 (2·94)†	0·39 (0·03 to 0·76)*	0·40 (0·05 to 0·74)*	0·39 (0·05 to 0·74)*	0·39 (0·06 to 0·71)*
Mid-upper arm circumference (cm)	14·18 (0·99)	14·42 (1·07)	0·24 (0·11 to 0·37)*	0·24 (0·11 to 0·37)*	0·24 (0·11 to 0·37)*	0·24 (0·11 to 0·36)*
Triceps skinfold thickness (mm)	6·95 (1·45)	7·15 (1·61)†	0·20 (0·00 to 0·40)*	0·20 (0·00 to 0·40)*	0·20 (–0·005 to 0·40)	0·20 (–0·004 to 0·40)

Data are mean (SD) unless otherwise indicated. BMI=body-mass index. *p<0·05 †n=461.

Table 3: **Child anthropometry by allocation group, with four analytic models for differences between group means**

	Control (n=455)			Intervention (n=462)			Difference between groups (95% CI)			Proportional increase over control group at follow-up
	At birth	At follow-up	Increment	At birth	At follow-up	Increment	At birth	At follow-up	Increment	
Weight (kg)	2·75 (0·41)	10·70 (1·38)	7·95 (1·28)	2·82 (0·43)	10·90 (1·54)	8·08 (1·47)	0·077 (0·02 to 0·13)	0·203 (0·01 to 0·39)	0·126 (0·05 to 0·30)	1·9%
Length/height (cm)	48·79 (3·23)	83·76 (4·68)	34·98 (5·07)	49·03 (3·14)	84·07 (4·83)	35·04 (5·14)	0·24 (–0·17 to 0·65)	0·30 (–0·31 to 0·92)	0·06 (–0·60 to 0·73)	0·4%
Head circumference (cm)	33·65 (2·21)	46·40 (1·43)	12·75 (2·35)	33·82 (2·24)	46·64 (1·49)	12·82 (2·38)	0·18 (–0·11 to 0·47)	0·24 (0·06 to 0·43)	0·07 (–0·23 to 0·38)	0·5%

Data are mean (SD) unless otherwise indicated.

Table 4: **Mean measurements at birth and at follow-up, with mean and proportional increments**

	Control group (n=453)	Intervention group (n=462)	Difference (95% CI)	p value
Weight-for-age Z score†	−1·76 (0·98)*	−1·63 (1·08)*	0·14 (0·001 to 0·27)	0·048
Height-for-age Z score†	−2·28 (1·06)*	−2·20 (1·12)*	0·08 (−0·06 to 0·22)	0·048
Weight-for-height Z score†	−0·40 (1·05)*	−0·28 (1·12)*	0·12 (−0·02 to 0·26)	0·097
Underweight†				
Normal‡	98 (21·6)	124 (26·8)	..	..
Mild underweight§	184 (40·6)	169 (36·6)	..	..
Moderate underweight¶	125 (27·6)	125 (27·1)	..	..
Severe weight||	46 (10·2)	44 (9·5)	..	..
Stunting†				
Normal‡	52 (11·5)	61 (13·2)	..	..
Mild stunting§	129 (28·5)	139 (30·1)	..	..
Moderate stunting¶	162 (35·7)	150 (32·5)	..	..
Severe stunting||	110 (24·3)	112 (24·2)	..	..
Wasting†				
Normal‡	331 (73·1)	354 (76·6)	..	..
Mild wasting§	97 (21·4)	79 (17·1)	..	..
Moderate wasting¶	19 (4·2)	25 (5·4)	..	..
Severe wasting||	6 (1·3)	4 (0·9)	..	..
Total upper arm area (cm^2)**	16·07 (2·24)	16·63 (2·50)	0·56 (0·25 to 0·87)	0·0004
Upper arm fat area estimate (cm^2)††	4·96 (1·23)	5·20 (1·43)	0·24 (0·07 to 0·41)	0·007

*Mean (SD); all other data are n (%). †Comparisons with WHO standards.[24,25] ‡One Z score below the median or above. §More than one and up to two Z scores below the median. ¶More than two and up to three Z scores below the median. || More than three Z scores below the median. **Calculated according to equations in reference 20. ††Calculated according to equations in reference 21.

Table 5: **Underweight, stunting, and wasting according to WHO standards, and estimates of mean upper arm total and fat areas**

impression that differences between the groups might indicate a reduction in mild degrees of underweight, stunting and wasting in the intervention group. None of the differences was significant. Table 5 also shows estimates of mean total upper arm area (TUA)[20] and mean upper arm fat area estimate (UFE),[21] both of which were greater in the intervention group. The upper arm fat percentages (UFE/TUA) were 30·1% in the control and 31·3% in the intervention group, a difference of 1·2%.

Discussion

In our study, children aged 2·5 years whose mothers were given multiple micronutrients during pregnancy were 204 g heavier than children in the control group (iron and folate). Although the difference in height was not significant, circumferences of the head, chest, hip, and mid-upper arm in children exposed to micronutrients were larger and their triceps skinfolds thicker than controls.[4] Children in the micronutrient group were also less likely to be underweight, stunted, or wasted, although these findings were not significant.

We think that the only limitations of the study were that the sample size was insufficient to detect small changes in anthropometric categories against international standards, and that field and budgetary constraints precluded more sophisticated assessments of body composition. Retention was satisfactory. Participants lost-to-follow-up were disproportionately likely to come from a mobile, urban group who had moved out of the study area. The balance between potential confounders and the robustness of the findings to adjustment confirmed the value of blinding and random allocation. Anthropometrical assessments were done by only two observers, and systematic error should also have been distributed by randomisation.

One issue that might have affected the results is that supplement compositions differed in this non-placebo-controlled trial. The supplement doses were chosen to match those used in other trials to optimise comparability and to avoid micronutrient interaction. The iron content of the supplements differed (60 mg in the control and 30 mg in the intervention group) in line with expert opinion,[19] to avoid a possible negative influence on zinc absorption (although this concern might not apply in practice[26]). Possibly, the effects we noted were the result not of the addition of vitamins and minerals, but of a reduction in the dose of iron. The question of potential adverse effects of iron supplementation in general remains unanswered.[27]

Our findings suggested that the gains in size at birth because of multiple micronutrient supplementation during pregnancy were maintained into childhood. They should, however, be kept in perspective, particularly with respect to childhood growth. The adjusted difference of 204 g in mean weight between control and intervention groups represented an increment of 127 g over the 77 g difference that already existed at birth—an overall

1·9% gain over the mean control group weight. Likewise, the postnatal increments in height and head circumference were only 0·6 mm and 0·7 mm, respectively (0·4% and 0·5% gains over the control group measures).

We think that the findings raise two key questions. First, were the children in the intervention group more healthy? Mothers' recall of their children's illnesses during infancy and the 2 weeks before the interview did not support this hypothesis, but it is quite possible that health had been affected in more subtle ways. We are particularly keen to assess the children's development in further follow-up studies. The increment in head circumference in the micronutrient group could indicate a difference in brain growth and the potential for improved cognitive performance.[28] Equally, it might be explained by extracranial adiposity. A second question is whether the sustained gain in size is associated with physiological changes. This possibility is intriguing given the rapid increase in research into the developmental origins of health and adult disease.[29] The small but significant decrease in systolic blood pressure in the multiple micronutrient group suggests it might have implications for the development of adult hypertension. Again, we do not want to over-interpret a single finding and need to follow up trial cohorts.

Previously, our awareness of the burden of low birthweight and childhood malnutrition would have made us optimistic about the effects of greater fetal, infant, and childhood growth on subsequent illness and mortality. Research over the past decade, however, raises questions about this assumption. We lack evidence to show that increasing weight at birth—and the subsequent tracking shown in this study—will translate into substantial improvements in child survival. We have raised the possibility of an imbalance in stillbirths and neonatal deaths between the allocation groups.[22] The slight alteration to our original neonatal mortality findings is mildly reassuring, as is the similarity of aggregate infant mortality rates between the allocation groups. However, neonatal mortality remained 40% higher in the intervention group and mortality needs to be examined in larger datasets.

Children such as those in our trial might show a predictive adaptive physiological phenotype that turns out to be mismatched with their later nutritional experience.[30] In simple terms, South Asian children, though apparently small and thin, may have an intrinsic susceptibility to harmful patterns of fat deposition in situations of nutritional plenty.[31] The children born in our study are generally lighter, shorter, and more wasted than children in affluent populations. Has fetal multiple micronutrient supply had generalised effects on growth, with potentially beneficial increments in lean body mass, or has it translated into increased adiposity? The biggest difference between the two groups was in weight for age, and the estimates of upper arm composition suggest a small but significant increase in adiposity.

We are only beginning to unravel the longer-term effects of increasing body mass. Its distal effects on health—cognitive performance, childhood illness and mortality, and later blood pressure—might be beneficial, but we need further follow-up and larger studies to confirm our findings.

Contributors

AV coordinated the study and data entry, cleaned the data, did the analysis, and produced the first draft of the paper. NS advised on design and implementation and co-coordinated field and data management. BPS supervised field activities and was the programme manager in Dhanusha. DSM, AMC, and DO were principal investigators. DSM had overall responsibility for the study in Nepal. AMC had overall responsibility for UK partner contributions to the research programme. DO conceived the study and supervised the analysis. All authors contributed to critique and modification of the manuscript.

Conflict of interest statement

None of the authors has a conflict of interest. DO had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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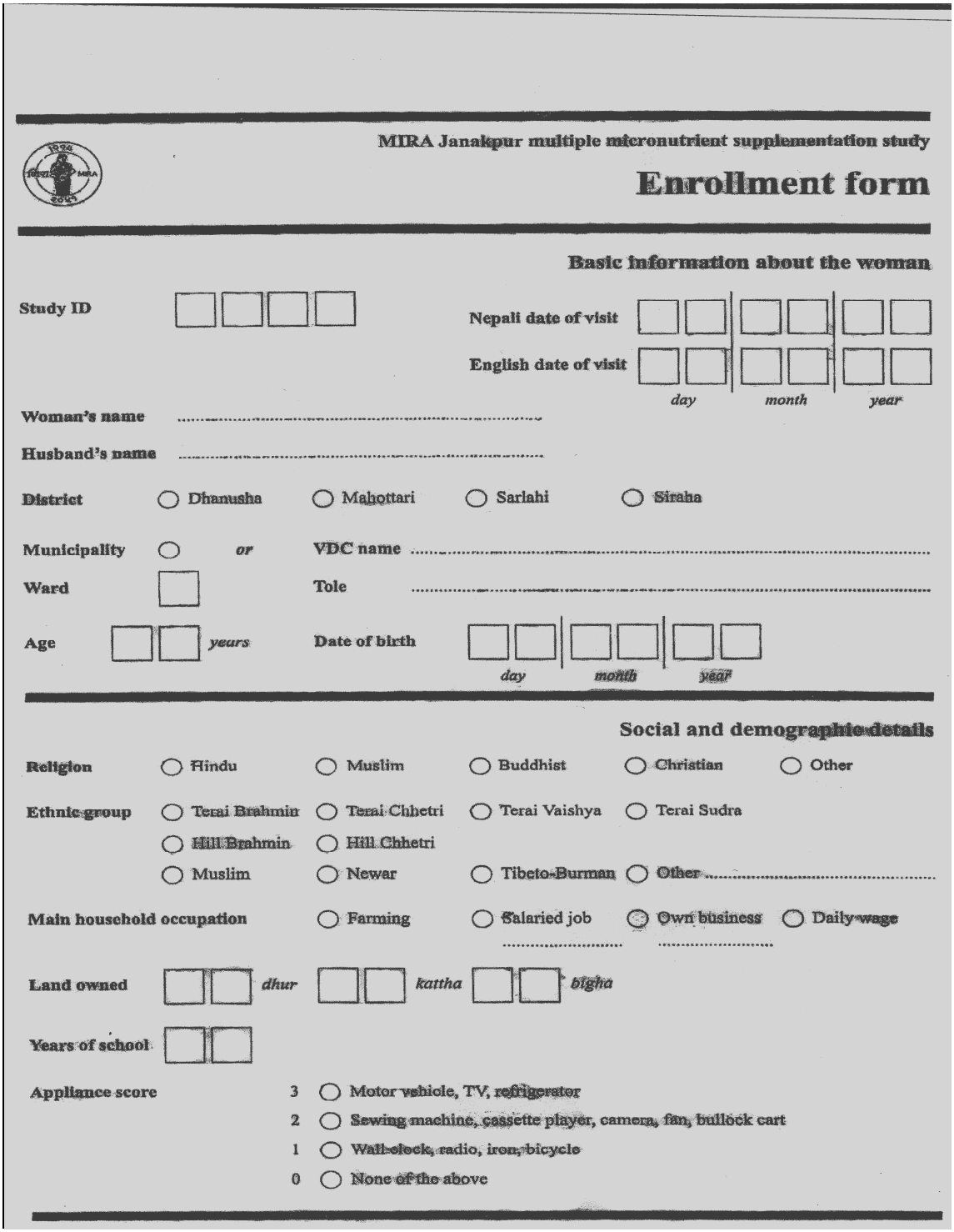
31 Yajnik C, Fall C, Coyaji K, et al. Neonatal anthropometry: the thin-fat Indian baby. The Pune Maternal Nutrition Study. *Int J Obes Relat Metab Disord* 2003; **27:** 173–80.

Annex C. Study form



MIRA Janakpur multiple micronutrient supplementation study

Enrollment form

Basic information about the woman

Study ID ☐☐☐☐

Nepali date of visit ☐☐ ☐☐ ☐☐ (day / month / year)

English date of visit ☐☐ ☐☐ ☐☐ (day / month / year)

Woman's name .....

Husband's name .....

District ○ Dhanusha ○ Mahottari ○ Sarlahi ○ Siraha

Municipality ○ *or* VDC name .....

Ward ☐ Tole .....

Age ☐☐ *years* Date of birth ☐☐ ☐☐ ☐☐ (day / month / year)

Social and demographic details

Religion ○ Hindu ○ Muslim ○ Buddhist ○ Christian ○ Other

Ethnic group ○ Terai Brahmin ○ Terai Chhetri ○ Terai Vaishya ○ Terai Sudra
○ Hill Brahmin ○ Hill Chhetri
○ Muslim ○ Newar ○ Tibeto-Burman ○ Other .....

Main household occupation ○ Farming ○ Salaried job ○ Own business ○ Daily wage
....

Land owned ☐☐ *dhur* ☐☐ *kattha* ☐☐ *bigha*

Years of school ☐☐

Appliance score
3 ○ Motor vehicle, TV, refrigerator
2 ○ Sewing machine, cassette player, camera, fan, bullock cart
1 ○ Wall clock, radio, iron, bicycle
0 ○ None of the above

Para ☐☐ Gravida ☐☐

Gestational dating

Nepali LMP ☐☐ ☐☐ ☐☐

English LMP ☐☐ ☐☐ ☐☐

day *month* *year*

Gestation (uss) ☐☐ *weeks* ☐ *days*

EDD (uss) ☐☐ ☐☐ ☐☐

day *month* *year*

CRL	☐☐.☐ *mm*	Gestation by CRL	☐☐ *weeks* ☐ *days*
BPD	☐☐.☐ *mm*	Gestation by BPD	☐☐ *weeks* ☐ *days*
HC	☐☐☐ *mm*	Gestation by HC	☐☐ *weeks* ☐ *days*
FL	☐☐.☐ *mm*	Gestation by FL	☐☐ *weeks* ☐ *days*
AC	☐☐☐ *mm*	Gestation by AC	☐☐ *weeks* ☐ *days*

Placental position	◯ Posterior	◯ Anterior	◯ Fundal	
Placental maturity	◯ Grade 0	◯ Grade 1	◯ Grade 2	◯ Grade 3
Fetal position	◯ OA	◯ OP	◯ OT	

Comment .....

.....

Family history

Hypertension	◯ Yes	◯ No
Diabetes	◯ Yes	◯ No
Tuberculosis	◯ Yes	◯ No

Medical history

Hypertension	◯ Yes	◯ No			
Diabetes	◯ Yes	◯ No	Blood transfusion	◯ Yes	◯ No
Tuberculosis	◯ Yes	◯ No	Smoking	◯ Yes	◯ No
Heart disease	◯ Yes	◯ No	Alcohol	◯ Yes	◯ No
Epilepsy	◯ Yes	◯ No	Other drugs	◯ Yes	◯ No
Chest disease	◯ Yes	◯ No	Drug allergy	◯ No	◯ Yes .....
Renal disease	◯ Yes	◯ No	Abdominal surgery	◯ Yes	◯ No

Problems in this pregnancy

Vaginal bleeding	◯ Yes	◯ No			
Facial swelling	◯ Yes	◯ No	**Breathlessness**	◯ Yes	◯ No
Severe headache	◯ Yes	◯ No	**Night blindness**	◯ Yes	◯ No
Dysuria	◯ Yes	◯ No	**Fever**	◯ Yes	◯ No
Vaginal discharge	◯ Yes	◯ No	**Fetal movements**	◯ ? ◯ OK	◯ Less ◯ None

Previous TT doses *1st* *2nd* *3rd* *4th* *5th* — **TT given** ◯ Yes ◯ No

Plans for this birth

Place of delivery ◯ Hospital ◯ Pvt Clinic ◯ PHC ◯ Home

Intended family planning ◯ No ◯ Depo ◯ Norplant ◯ Minilap ◯ Yes: method?
◯ Vasectomy ◯ Pill ◯ Condom ◯ IUCD ◯ Undecided

Examination

Blood pressure ☐☐☐/☐☐ *mmHg*

Weight ☐☐☐.☐ *Kg*

Height ☐☐☐.☐ *cm*

Urine protein ◯ Neg ◯ Trace ◯ + ◯ ++ ◯ +++ ◯ ++++

Urine sugar ◯ Neg ◯ Trace ◯ + ◯ ++ ◯ +++ ◯ ++++

Pallor ◯ No ◯ Yes

Oedema ◯ No ◯ + ◯ ++ ◯ +++

Fundal height ☐☐ *weeks*

Caesarian scar ◯ No ◯ Yes

Lie ◯ Longitudinal ◯ Oblique ◯ Transverse

Presentation ◯ Vertex ◯ Breech

Fetal movements ◯ Yes ◯ No

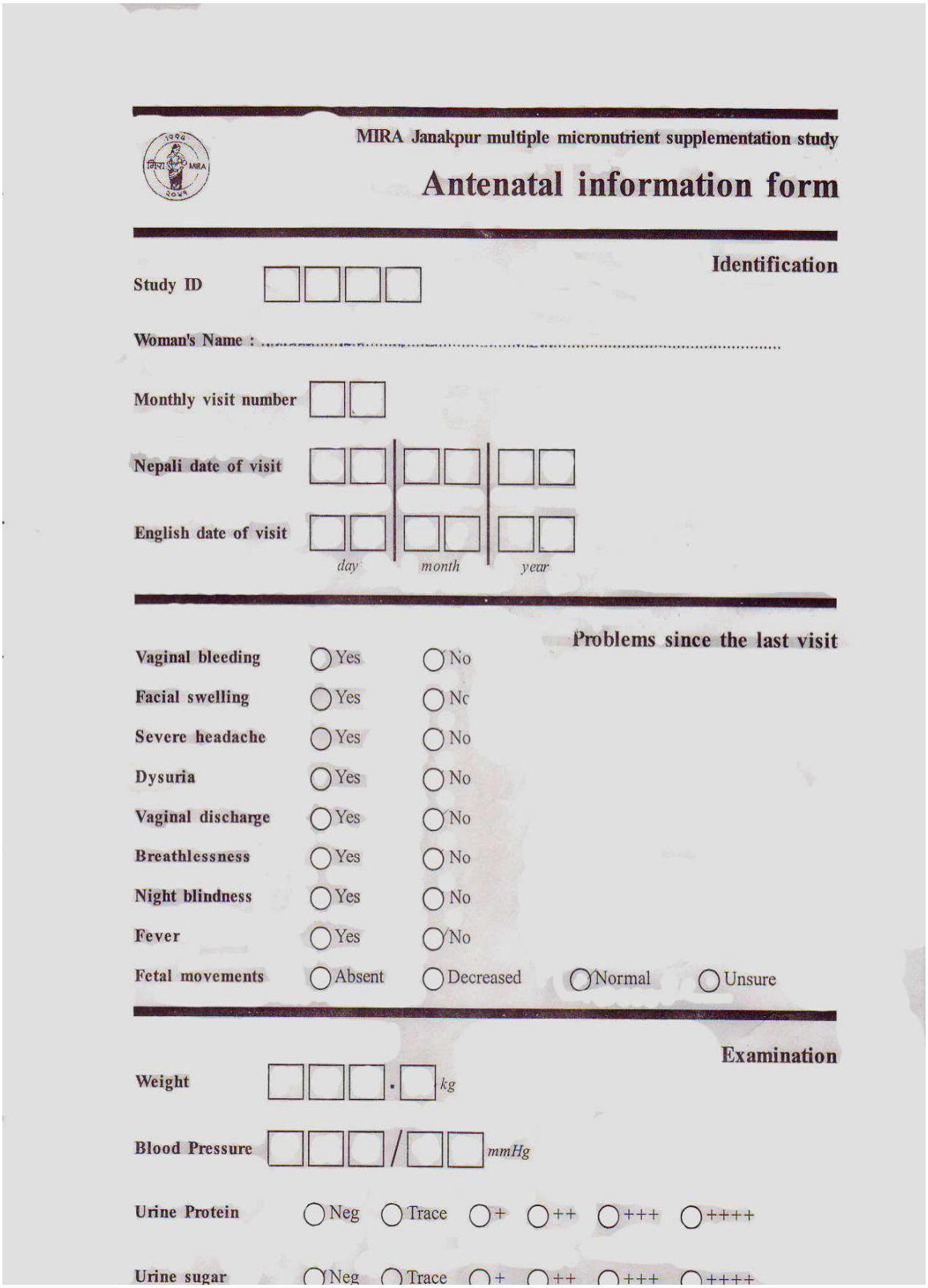
Fetal heart beat ◯ Yes ◯ No

Obstetric history

Pregnancy	Age	Place of birth	Type of delivery	State of baby	Sex	Baby problems	Current state	Mother problems
1	years or months	Home / Institution	SVD / Vacuum / Forceps / LSCS / Breech	Livebirth / Stillbirth / Abortion	M / F	Normal / Preterm / Anomaly / Very small / Twin	Alive / Died / Age at death years or months	Normal / Prolonged labour / Retained placenta / PPH
2	years or months	Home / Institution	SVD / Vacuum / Forceps / LSCS / Breech	Livebirth / Stillbirth / Abortion	M / F	Normal / Preterm / Anomaly / Very small / Twin	Alive / Died / Age at death years or months	Normal / Prolonged labour / Retained placenta / PPH
3	years or months	Home / Institution	SVD / Vacuum / Forceps / LSCS / Breech	Livebirth / Stillbirth / Abortion	M / F	Normal / Preterm / Anomaly / Very small / Twin	Alive / Died / Age at death years or months	Normal / Prolonged labour / Retained placenta / PPH
4	years or months	Home / Institution	SVD / Vacuum / Forceps / LSCS / Breech	Livebirth / Stillbirth / Abortion	M / F	Normal / Preterm / Anomaly / Very small / Twin	Alive / Died / Age at death years or months	Normal / Prolonged labour / Retained placenta / PPH
5	years or months	Home / Institution	SVD / Vacuum / Forceps / LSCS / Breech	Livebirth / Stillbirth / Abortion	M / F	Normal / Preterm / Anomaly / Very small / Twin	Alive / Died / Age at death years or months	Normal / Prolonged labour / Retained placenta / PPH
6	years or months	Home / Institution	SVE / Vacuum / Forceps / LSCS / Breech	Livebirth / Stillbirth / Abortion	M / F	Normal / Preterm / Anomaly / Very small / Twin	Alive / Died / Age at death years or months	Normal / Prolonged labour / Retained placenta / PPH

You may need to add in another page here if she has had more than six babies

Antenatal information form (1 of 2)



MIRA Janakpur multiple micronutrient supplementation study

Antenatal information form

Identification

Study ID ☐☐☐☐

Woman's Name : .....

Monthly visit number ☐☐

Nepali date of visit ☐☐ / ☐☐ / ☐☐

English date of visit ☐☐ / ☐☐ / ☐☐

day / month / year

Problems since the last visit

Vaginal bleeding	◯ Yes	◯ No		
Facial swelling	◯ Yes	◯ Nc		
Severe headache	◯ Yes	◯ No		
Dysuria	◯ Yes	◯ No		
Vaginal discharge	◯ Yes	◯ No		
Breathlessness	◯ Yes	◯ No		
Night blindness	◯ Yes	◯ No		
Fever	◯ Yes	◯ No		
Fetal movements	◯ Absent	◯ Decreased	◯ Normal	◯ Unsure

Examination

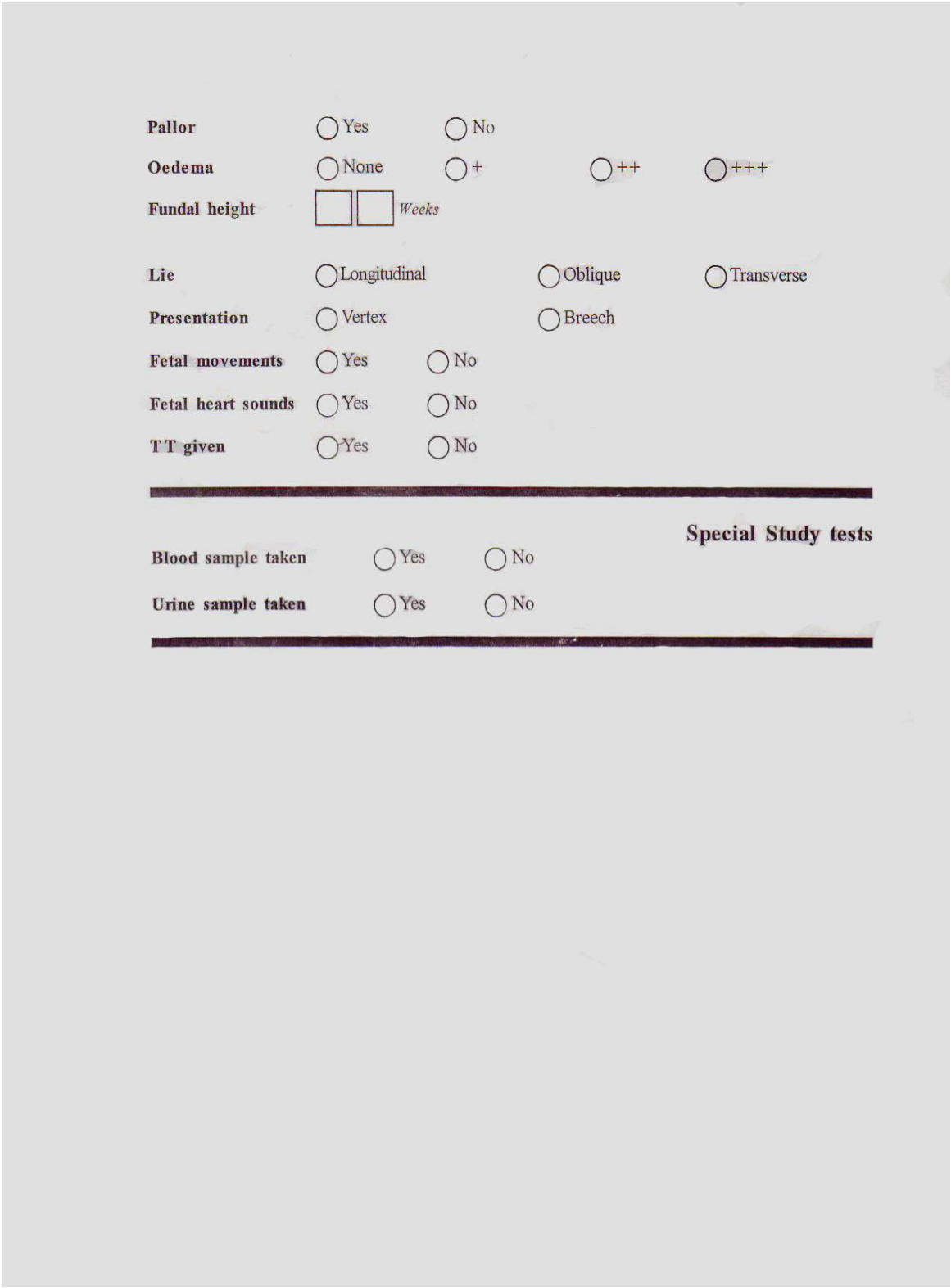
Weight ☐☐☐.☐ kg

Blood Pressure ☐☐☐/☐☐ mmHg

Urine Protein ◯ Neg ◯ Trace ◯ + ◯ ++ ◯ +++ ◯ ++++

Urine sugar ◯ Neg ◯ Trace ◯ + ◯ ++ ◯ +++ ◯ ++++

Antenatal information form (2 of 2)



Pallor ◯ Yes ◯ No

Oedema ◯ None ◯ + ◯ ++ ◯ +++

Fundal height ☐☐ *Weeks*

Lie ◯ Longitudinal ◯ Oblique ◯ Transverse

Presentation ◯ Vertex ◯ Breech

Fetal movements ◯ Yes ◯ No

Fetal heart sounds ◯ Yes ◯ No

TT given ◯ Yes ◯ No

Special Study tests

Blood sample taken ◯ Yes ◯ No

Urine sample taken ◯ Yes ◯ No

MIRA Janakpur multiple micronutrient supplementation study

Laboratory form

Identification

Study ID ☐☐☐☐

Woman's name .....

Early lab tests

English date of test ☐☐ | ☐☐ | ☐☐ (day | month | year)

Blood haemoglobin ☐☐.☐ g/dl

Group and Rhesus ☐ ○ + ○ -

RPR ○ + ○ -

Other sample preparation

	Tick if prepared
PLASMA	○ *prepared*
VITAMIN C	○ *prepared*
EDTA	○ *prepared*

Later lab tests

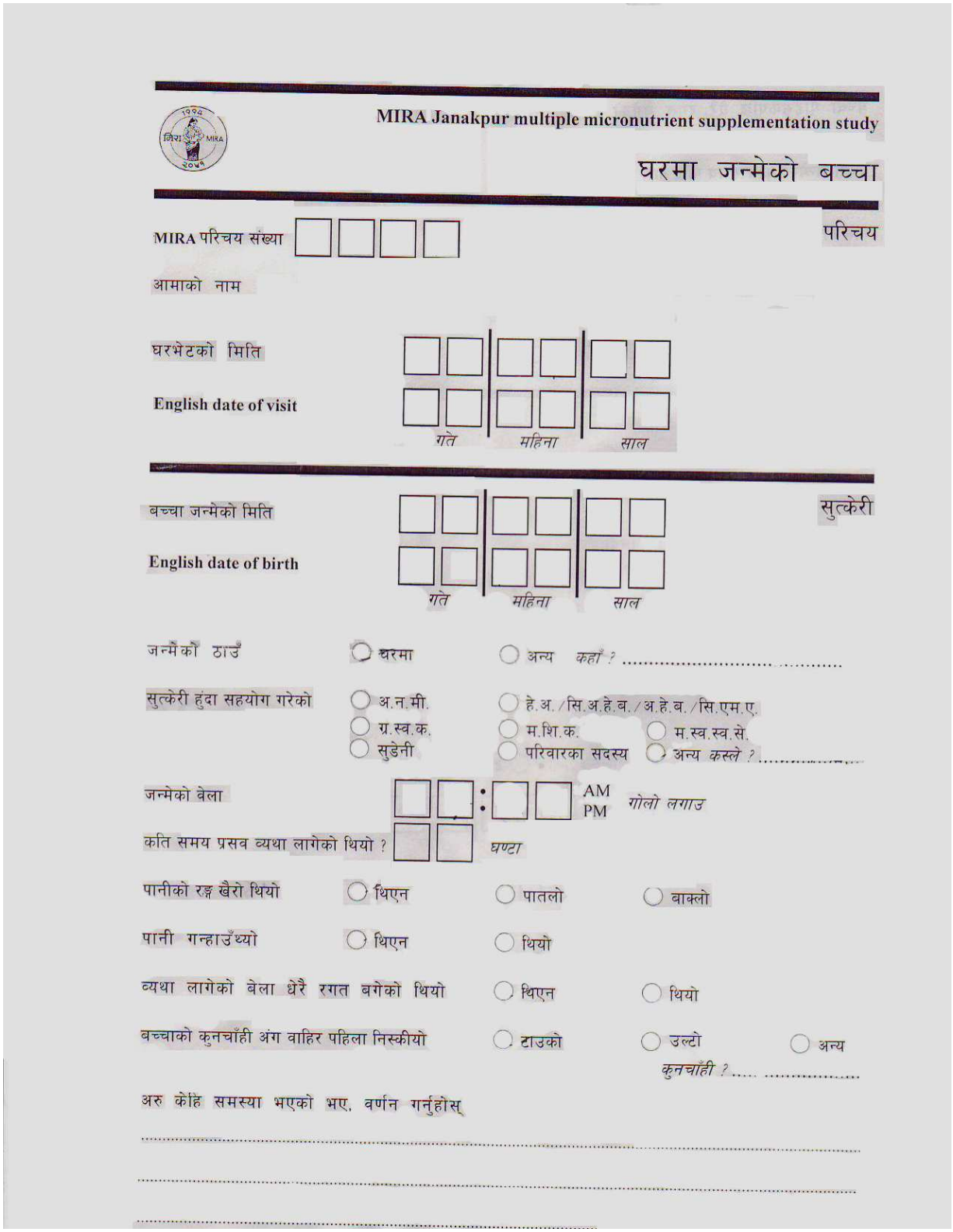
English date of test ☐☐ | ☐☐ | ☐☐ (day | month | year)

Blood haemoglobin ☐☐.☐ g/dl

Other sample preparation

	Tick if prepared
PLASMA	○ *prepared*
VITAMIN C	○ *prepared*
EDTA	○ *prepared*
URINE SAMPLE	○ *taken*

Home delivery form (1 of 2)



MIRA Janakpur multiple micronutrient supplementation study

घरमा जन्मेको बच्चा

MIRA परिचय संख्या ☐☐☐☐ परिचय

आमाको नाम

घरभेटको मिति ☐☐/☐☐/☐☐

English date of visit ☐☐/☐☐/☐☐

गते महिना साल

बच्चा जन्मेको मिति ☐☐/☐☐/☐☐ सुत्केरी

English date of birth ☐☐/☐☐/☐☐

गते महिना साल

जन्मेको ठाउँ ○ घरमा ○ अन्य कहाँ ? .....

सुत्केरी हुंदा सहयोग गरेको ○ अ.न.मी. ○ हे.अ./सि.अ.हे.ब./अ.हे.ब./सि.एम.ए. ○ ग्र.स्व.क. ○ म.शि.क. ○ म.स्व.स्व.से. ○ सुडेनी ○ परिवारका सदस्य ○ अन्य कस्ले ? .....

जन्मेको बेला ☐☐:☐☐ AM PM गोलो लगाउ

कति समय प्रसव व्यथा लागेको थियो ? ☐☐ घण्टा

पानीको रङ्ग खैरो थियो ○ थिएन ○ पातलो ○ बाक्लो

पानी गन्हाउँथ्यो ○ थिएन ○ थियो

व्यथा लागेको बेला धेरै रगत बगेको थियो ○ थिएन ○ थियो

बच्चाको कुनचाँही अंग बाहिर पहिला निस्कीयो ○ टाउको ○ उल्टो ○ अन्य कुनचाँही ? ....

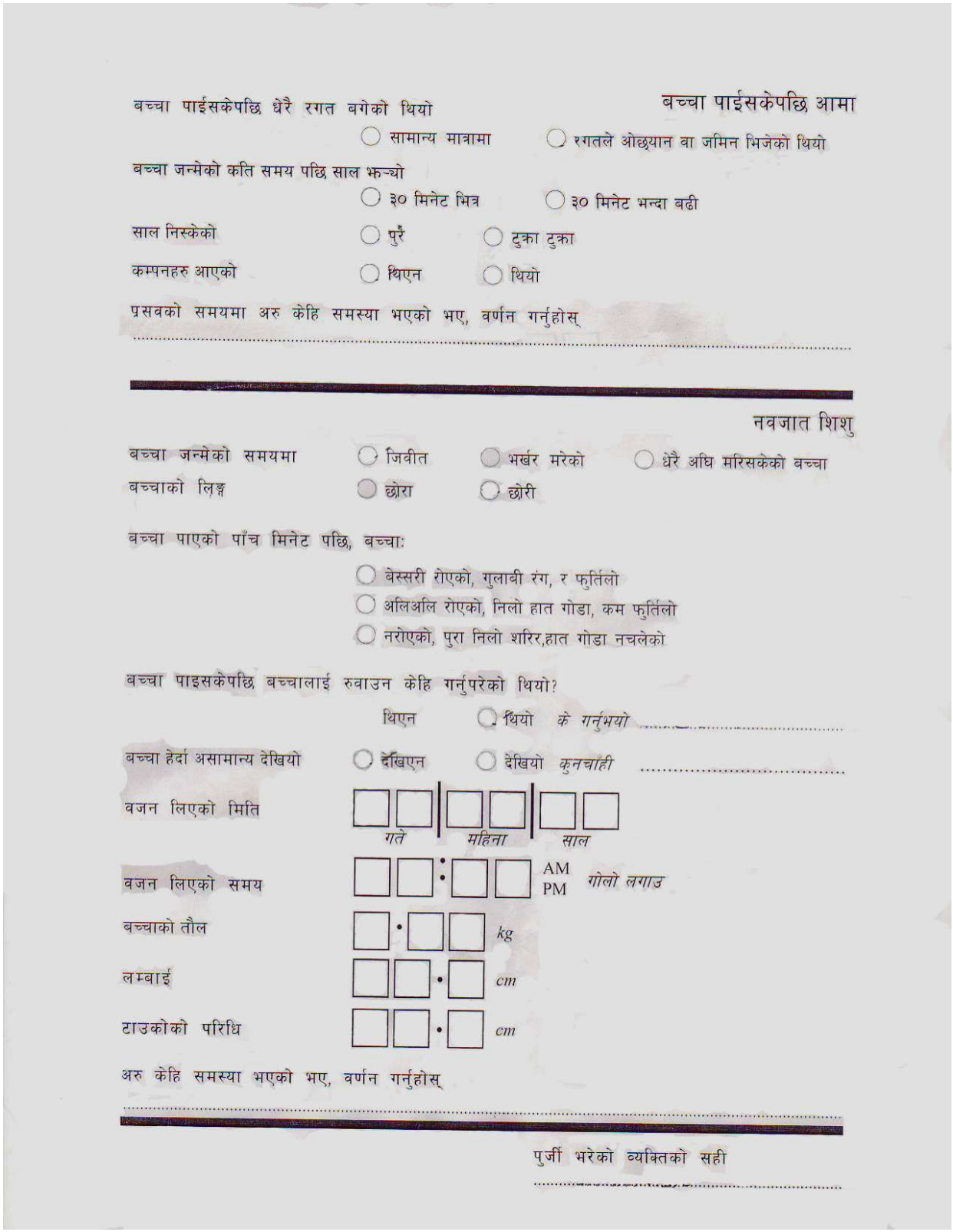
अरु केहि समस्या भएको भए, वर्णन गर्नुहोस्

.....

.....

.....

Home delivery form (2 of 2)



बच्चा पाईसकेपछि धेरै रगत बगेको थियो — बच्चा पाईसकेपछि आमा

○ सामान्य मात्रामा ○ रगतले ओछ्यान वा जमिन भिजेको थियो

बच्चा जन्मेको कति समय पछि साल झर्‍यो

○ ३० मिनेट भित्र ○ ३० मिनेट भन्दा बढी

साल निस्केको ○ पुरै ○ टुक्रा टुक्रा

कम्पनहरु आएको ○ थिएन ○ थियो

प्रसवको समयमा अरु केहि समस्या भएको भए, वर्णन गर्नुहोस्

.....

नवजात शिशु

बच्चा जन्मेको समयमा ○ जिवीत ○ भर्खर मरेको ○ धेरै अघि मरिसकेको बच्चा

बच्चाको लिङ्ग ○ छोरा ○ छोरी

बच्चा पाएको पाँच मिनेट पछि, बच्चा:

○ बेस्सरी रोएको, गुलाबी रंग, र फुर्तिलो

○ अलिअलि रोएको, निलो हात गोडा, कम फुर्तिलो

○ नरोएको, पुरा निलो शरिर,हात गोडा नचलेको

बच्चा पाइसकेपछि बच्चालाई रुवाउन केहि गर्नुपरेको थियो?

थिएन ○ थियो *के गर्नुभयो* .....

बच्चा हेर्दा असामान्य देखियो ○ देखिएन ○ देखियो *कुनचाहीं* .....

वजन लिएको मिति ☐☐/☐☐/☐☐ *गते / महिना / साल*

वजन लिएको समय ☐☐:☐☐ AM PM *गोलो लगाउ*

बच्चाको तौल ☐.☐☐ *kg*

लम्बाई ☐☐.☐ *cm*

टाउकोको परिधि ☐☐.☐ *cm*

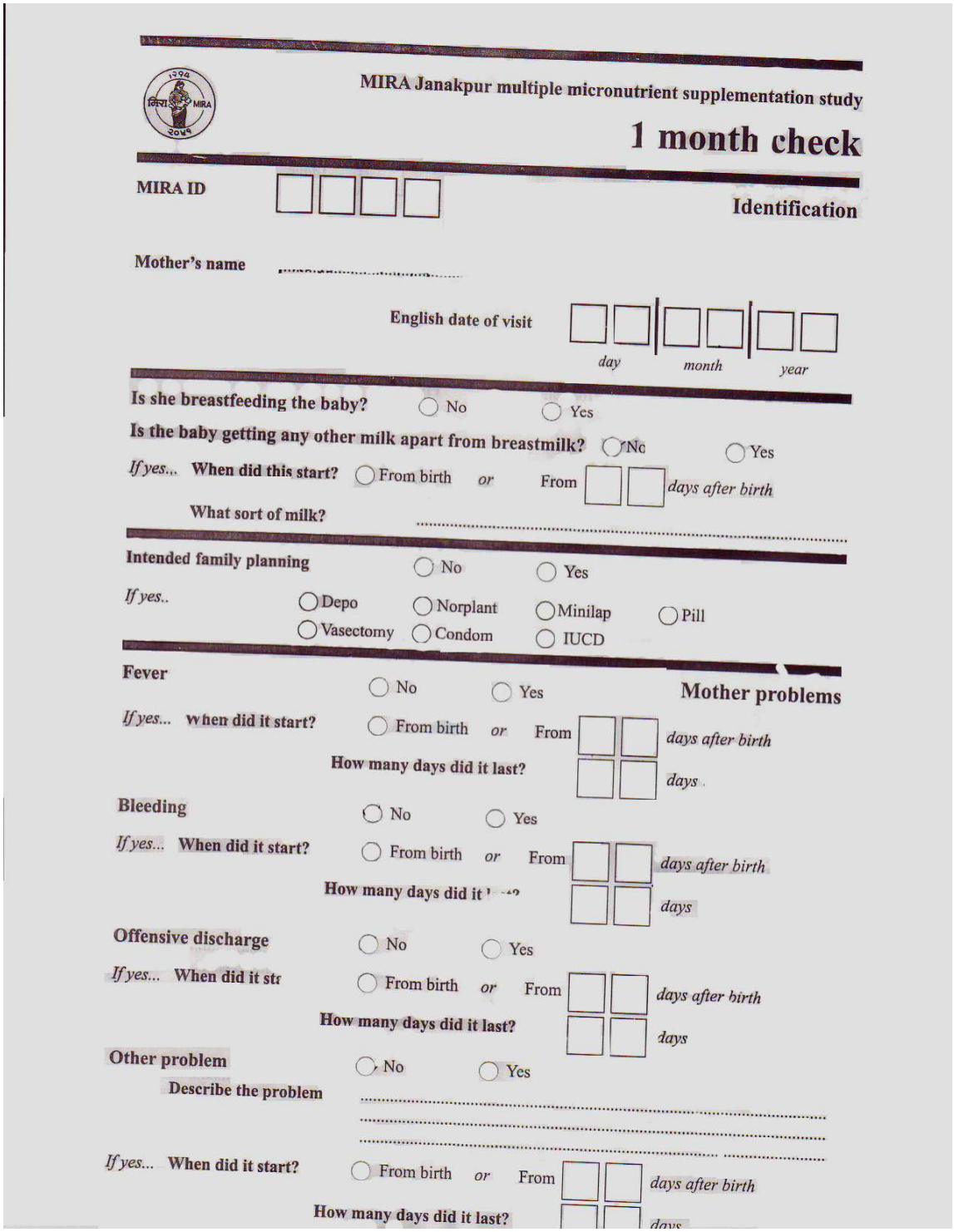
अरु केहि समस्या भएको भए, वर्णन गर्नुहोस्

.....

पुर्जी भरेको व्यक्तिको सही

.....

One month form (1 of 2)



MIRA Janakpur multiple micronutrient supplementation study

1 month check

MIRA ID ☐☐☐☐ **Identification**

Mother's name .....

English date of visit ☐☐ day ☐☐ month ☐☐ year

Is she breastfeeding the baby? ○ No ○ Yes

Is the baby getting any other milk apart from breastmilk? ○ No ○ Yes

If yes... When did this start? ○ From birth *or* From ☐☐ *days after birth*

What sort of milk? .....

Intended family planning ○ No ○ Yes

If yes.. ○ Depo ○ Norplant ○ Minilap ○ Pill ○ Vasectomy ○ Condom ○ IUCD

Mother problems

Fever ○ No ○ Yes

If yes... when did it start? ○ From birth *or* From ☐☐ *days after birth*

How many days did it last? ☐☐ *days*

Bleeding ○ No ○ Yes

If yes... When did it start? ○ From birth *or* From ☐☐ *days after birth*

How many days did it [illegible] ☐☐ *days*

Offensive discharge ○ No ○ Yes

If yes... When did it str ○ From birth *or* From ☐☐ *days after birth*

How many days did it last? ☐☐ *days*

Other problem ○ No ○ Yes

Describe the problem .....

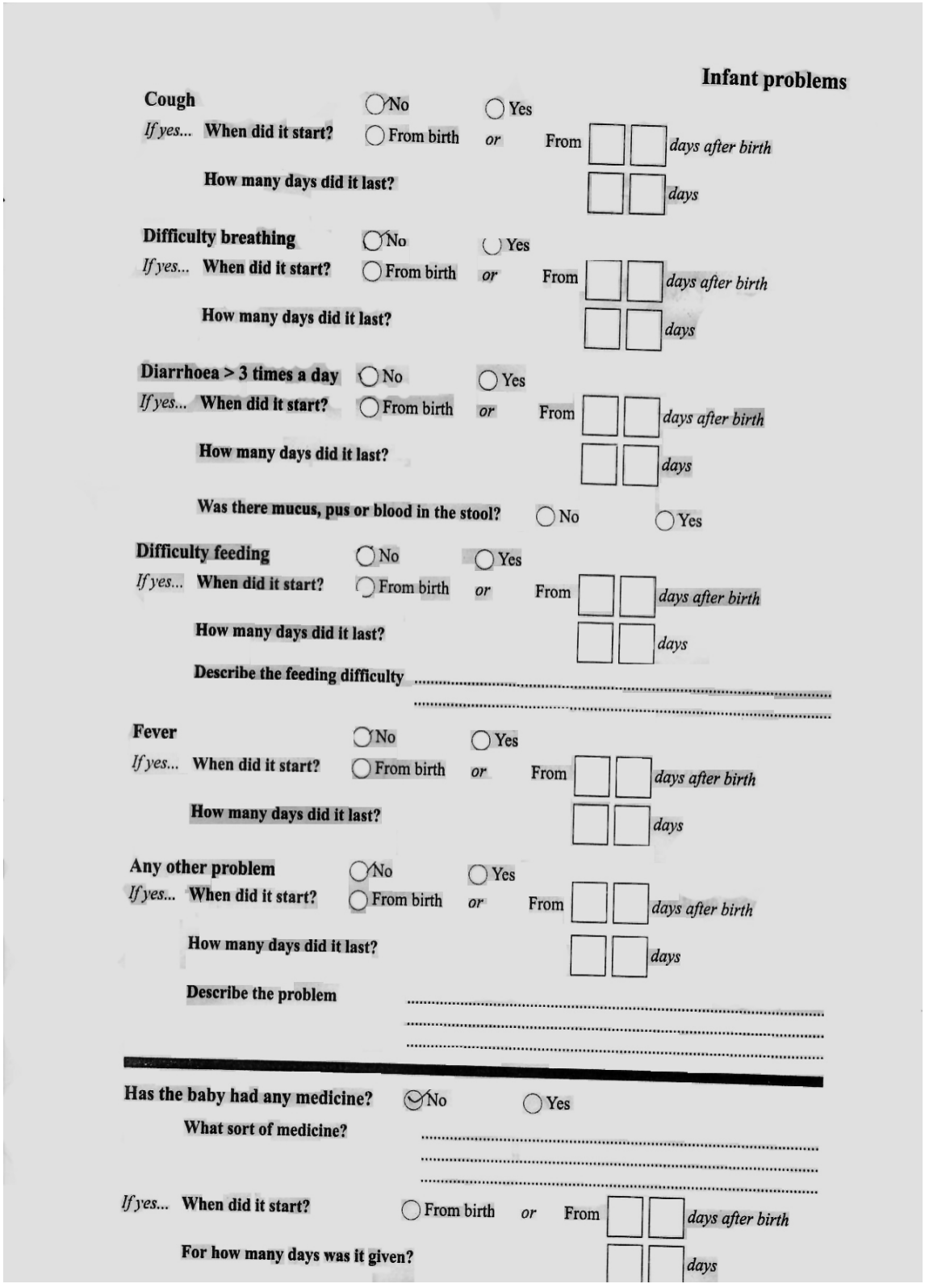
.....

.....

If yes... When did it start? ○ From birth *or* From ☐☐ *days after birth*

How many days did it last? ☐☐ *days*

One month form (2 of 2)



Infant problems

Cough ◯ No ◯ Yes

If yes... **When did it start?** ◯ From birth *or* From ☐☐ *days after birth*

How many days did it last? ☐☐ *days*

Difficulty breathing ◯ No ◯ Yes

If yes... **When did it start?** ◯ From birth *or* From ☐☐ *days after birth*

How many days did it last? ☐☐ *days*

Diarrhoea > 3 times a day ◯ No ◯ Yes

If yes... **When did it start?** ◯ From birth *or* From ☐☐ *days after birth*

How many days did it last? ☐☐ *days*

Was there mucus, pus or blood in the stool? ◯ No ◯ Yes

Difficulty feeding ◯ No ◯ Yes

If yes... **When did it start?** ◯ From birth *or* From ☐☐ *days after birth*

How many days did it last? ☐☐ *days*

Describe the feeding difficulty .....

.....

Fever ◯ No ◯ Yes

If yes... **When did it start?** ◯ From birth *or* From ☐☐ *days after birth*

How many days did it last? ☐☐ *days*

Any other problem ◯ No ◯ Yes

If yes... **When did it start?** ◯ From birth *or* From ☐☐ *days after birth*

How many days did it last? ☐☐ *days*

Describe the problem .....

.....

.....

Has the baby had any medicine? ◯ No ◯ Yes

What sort of medicine? .....

.....

.....

If yes... **When did it start?** ◯ From birth *or* From ☐☐ *days after birth*

For how many days was it given? ☐☐ *days*

Nepali consent form

मन्जुरीनामा

मातृ शिशु अनुसन्धान क्रियाकलाप (Mother Infant Research Activities) ले धेरै वर्ष देखि नेपालका विभिन्न जिल्लामा आमा र नवजात शिशुको स्वास्थ्य राम्रो बनाउने साथै रोग र मृत्युदर घटाउन अध्ययन अनुसन्धान गर्दै आएको छ र हाल जनकपुर अस्पतालमा आउने गर्भवती आमा र नवजात शिशुको स्वास्थ्य तन्दुरुस्त राख्नमा सुक्ष्म पौष्टिक तत्वको भूमिका बारे अध्ययन गर्न लागेको छ । कुपोषित आमाबाट जन्मेको बच्चा कम वजनको हुनु र विभिन्न रोगले ग्रसित हुन सक्दछ । त्यसैले अस्पतालमा आउने गर्भवती महिलालाई रक्त अल्पता र पौष्टिक तत्वको कमी हुन नदिन आइरन र फोलिक एसिड चक्की दिने गरेको र केही महिलालाई अन्य भिटामिन साथै आइरन फोलिक एसिड दिने गरेको विदितै छ । हाल नेपाल स्वास्थ्य अनुसन्धान परिषद एवं स्वास्थ्य मन्त्रालयको स्वीकृतिमा आइरन फोलिक एसिड चक्की खाएको गर्भवती महिला र आइरन फोलिक एसिड साथै अन्य भिटामिन खनिज पदार्थ भएको चक्की खाएको महिला तथा शिशुको स्वास्थ्यमा के कति फरक पार्छ भन्ने बारे अध्ययन गर्न लागेका छौं । तपाईहरु सबैले आइरन फोलिक एसिड पाउनु हुने छ र तपाईहरु मध्ये आधाले आइरन फोलिक साथै अन्य भिटामिन तथा खनिज मिश्रित चक्की पाउनु हुने छ । तर कुनमा के छ हामीलाई थाहा छैन । यसको लागि १२ सय जना गर्भवती महिलाले भाग लिने छन् । यस कार्यक्रममा भाग लिने सहभागी लाई निम्न सेवा पनि निःशुल्क प्रदान गरिने छ ।

१. प्रत्येक महिना क्लिनिकमा जाँच तथा स्वास्थ्य स्थिति बारे छलफल गर्न घर भेट ।
२. बच्चा जन्मनु अघि पूर्व प्रसुती सेवा
३. बच्चाको उमेर हेर्न अल्ट्रा साउण्ड सेवा
४. श्री ५ को सरकारले सिफारिस गरेको रगत र पिसाब जाँच सेवा
५. अस्पतालमा बच्चा जन्माउन र जन्मे पछिको आमाको स्वास्थ्य जाँच
६. रगतमा भिटामिन र खनिजको जाँच
७. गर्भवती तथा प्रसुती सम्बन्धी कुनै समस्या भएमा सोको उपचार
८. बच्चा जन्मे पछि दूधको जाँच

➢ यो अध्ययनमा भाग लिने वा नलिने तपाईको खुशीको कुरा हो र चाहेमा छाडन् सक्नु हुनेछ ।
➢ भाग लिने महिलाको बारेमा सबै कुरा गोप्य राखिने छ ।
➢ यो वाहेक तपाईलाई कुनै किसिमको प्रश्न वा समस्या भएमा निम्न ठेगानामा सम्पर्क राख्नु होस ।

मिरा जनकपुर, सुक्ष्म पोषण वितरण कार्यक्रम अध्ययन,
रामानन्द चौक, फोन नं. २४०३२

यस मन्जुरी नामामा लेखेको सबै कुरा जानकारी लिएँ ।
यस अध्ययनमा भाग लिन मेरो मन्जुर छ ।

दस्तखत : .....

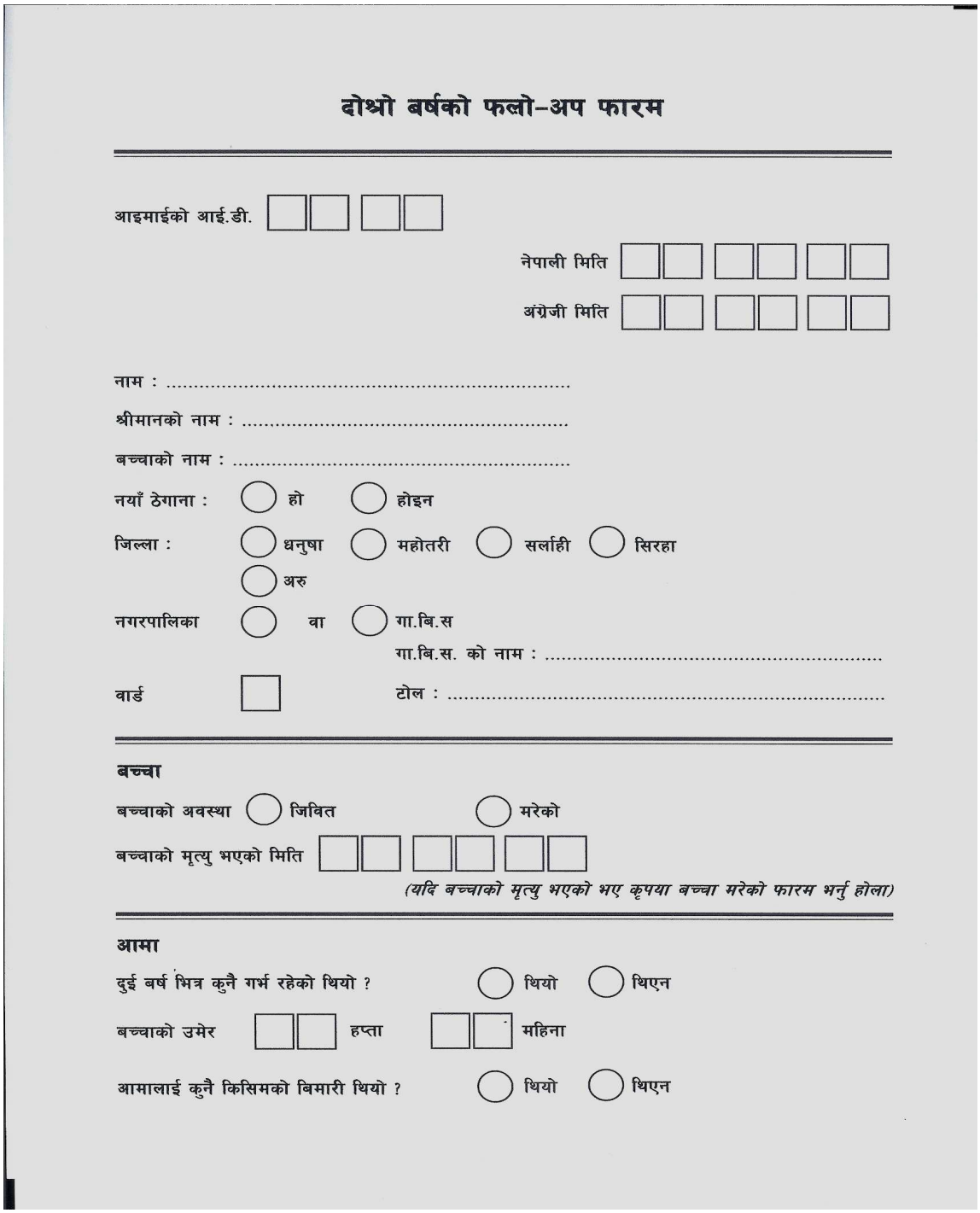
नाम : .....
ठेगाना : .....
मिति : २०

यस अनुसन्धानमा परेको सहभागी आफैले सहि गर्न नसकेको खण्डमा साक्षीको मात्र सही गरे पनि हुन्छ ।

यो जानकारी मेरो सामुन्ने पढेर सुनाएको हो । (महिला लाई बुझाएको हो ।) सो अनुसार गर्न श्रीमती .....
बाट मञ्जुर जनाएको कुरा साँचो हो ।

साक्षीको नाम .....
सही .....
मिति .....

Annex D. Two year follow up form



दोश्रो बर्षको फलो-अप फारम

आइमाईको आई.डी. ☐☐ ☐☐

नेपाली मिति ☐☐ ☐☐ ☐☐

अंग्रेजी मिति ☐☐ ☐☐ ☐☐

नाम : .....

श्रीमानको नाम : .....

बच्चाको नाम : .....

नयाँ ठेगाना : ◯ हो ◯ होइन

जिल्ला : ◯ धनुषा ◯ महोतरी ◯ सर्लाही ◯ सिरहा ◯ अरु

नगरपालिका ◯ वा ◯ गा.बि.स

गा.बि.स. को नाम : .....

वार्ड ☐ टोल : .....

बच्चा

बच्चाको अवस्था ◯ जिवित ◯ मरेको

बच्चाको मृत्यु भएको मिति ☐☐ ☐☐ ☐☐

(यदि बच्चाको मृत्यु भएको भए कृपया बच्चा मरेको फारम भर्नु होला)

आमा

दुई बर्ष भित्र कुनै गर्भ रहेको थियो ? ◯ थियो ◯ थिएन

बच्चाको उमेर ☐☐ हप्ता ☐☐ महिना

आमालाई कुनै किसिमको बिमारी थियो ? ◯ थियो ◯ थिएन

स्तनपान

स्तनपान गराईएको थियो ? ◯ थियो ◯ थिएन

बिगौती दूध खुवाइएको थियो ? ◯ थियो ◯ थिएन

सघन स्तनपान कति उमेर सम्म गराईएको थियो ? ☐☐ हप्ता ☐☐ महिना

कति उमेर देखि पानी अथवा अरु झोल पढार्थ खुवाइयो ? ☐☐ हप्ता ☐☐ महिना

कति उमेर देखि पाउडरको दूध खुवाइयो ? ☐☐ हप्ता ☐☐ महिना

कति उमेर देखि अन्य दूध खुवाइयो ? ☐☐ हप्ता ☐☐ महिना

कति उमेर देखि ठोस पढार्थ खुवाइयो ? ☐☐ हप्ता ☐☐ महिना

बच्चालाई के ठोस खाना खुवाइयो ?

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स्तनपान सम्बन्धि कुनै समस्या थियो ?

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खोप

बि.सि.जि.	◯ थियो	◯ थिएन
डि.पि.टी. १, ओ.पि.भि. १	◯ थियो	◯ थिएन
डि.पि.टी. २, ओ.पि.भि. २	◯ थियो	◯ थिएन
डि.पि.टी. ३, ओ.पि.भि. ३	◯ थियो	◯ थिएन
दादुरा	◯ थियो	◯ थिएन
एच.बि.भि. १	◯ थियो	◯ थिएन
एच.बि.भि. २	◯ थियो	◯ थिएन
एच.बि.भि. ३	◯ थियो	◯ थिएन

The Child's Anthropometry

Weight	☐☐.☐ *Kg*		
Height	☐☐☐.☐ *cm*		
Blood pressure	☐☐☐/☐☐ *mm of Hg*		
Sitting height	☐☐☐.☐ *cm*		
Midupper arm circumference	☐☐☐ *cm*	☐☐☐ *cm*	☐☐☐ *cm*
Head circumference	☐☐☐ *cm*	☐☐☐ *cm*	☐☐☐ *cm*
Chest circumference	☐☐☐ *cm*	☐☐☐ *cm*	☐☐☐ *cm*
Waist	☐☐☐ *cm*	☐☐☐ *cm*	☐☐☐ *cm*
Hip	☐☐☐ *cm*	☐☐☐ *cm*	☐☐☐ *cm*
Skinfold triceps	☐☐☐ *mm*	☐☐☐ *mm*	☐☐☐ *mm*

बच्चालाई गत दुई हप्तामा निम्न लिखित समस्याहरु भएको थियो ? यदि समस्या छ भने गोलो चिन्हमा ✓ लगाउने अन्यथा × लगाउनुहोस् ।

ज्वरो	◯	☐☐ दिन
पातलो दिसा	◯	☐☐ दिन
दिसामा रगत	◯	☐☐ दिन
खोकी	◯	☐☐ दिन
छिटो छिटो श्वास फेर्ने	◯	☐☐ दिन
छाती घ्यार घ्यार	◯	☐☐ दिन
काँपेको	◯	☐☐ दिन
घाँटी अररो हुने	◯	☐☐ दिन
छालामा डाबर	◯	☐☐ दिन
पूरा शरीरमा	◯	☐☐ दिन
मुखमा	◯	☐☐ दिन
पानी भरेको फोका	◯	
के यो दादुरा हो ?	◯	
रतन्धो	◯	☐☐ दिन
अरु कुनै बिमारी	◯	लेख्नुहोस् .....

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घरमै उपचार ◯ को द्वारा उपचार गराईयो ?

स्वास्थ्य संस्था ◯ .....

अरु ठाउँ ◯ .....

हस्पिटलमा भर्ना गरिएको समय ☐ दिन

कुनै औषधी १. .....
२. .....
३. .....

तपाईको बिचारमा बच्चा जन्मेको १ वर्ष भित्र कति पटक बच्चा बिमारी भयो ?

◯ ० - २ ◯ ३ - ४ ◯ ५ - ७ ◯ ८ - १० ◯ >१०

के बच्चालाई

१. खोकी र ज्वरो आएको थियो ? ◯ छ भने सालाखाला कति उमेरमा भएको थियो .....

२. झाडा पखाला लागेको थियो (> ३ पटक दिसा प्रति दिन लागेमा) ? ◯ छ भने सालाखाला कति उमेरमा भएको थियो .....

३. छालामा डाबर र ज्वरो आएको थियो ? ◯ छ भने सालाखाला कति उमेरमा भएको थियो .....

४. अरु कुनै बिमारी लागेको थियो ? ◯ थियो भने बर्णन गर्नुहोस्

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Annex E. Information given for ultrasound scan to eligible participants

This scan allows to see inside the uterus. It is done to check how many weeks pregnant you are, the well being of the baby and how many babies you are pregnant with. It is painless and does not involve use of needles. It is harmless to the baby and your health. It uses sound. It does not use rays like in x-rays so can be done repeatedly.

No strangers will be allowed to be in the room during the scan for privacy reason. It will be done in presence of your partner or mother in law or somebody you want to be present like a friend or sister.

You should have a full bladder (6 glasses of water). You should loosen your cloth and expose your lower part of the abdomen. Gel will be applied to the abdomen. It is a sticky material. You might sometime feel discomfort when applying pressure to get the better and closer view. It might take 10 minutes to 20 minutes. It involves taking measurements, Once the process is done, gel will be wiped off your skin. I will share the results with you after finishing the procedure.

Sometime you might need a second scan if the baby is very small or the baby is lying in awkward position. It will be arranged in your next antenatal visit.

It is not always easy and possible to detect all congenital problems. We cannot be sure that the baby is 100 % free of congenital anomaly. There are still chances of missing some congenital anomalies. If we are not sure of the condition, we will refer you to the hospital radiologist for specialist scan. The cost of the scan will be refunded.

Annex F. Consent form for antenatal multiple micronutrient supplementation trial

Consent Form

Mother Infant Research Activities has for many years been conducting research in various districts of Nepal to improve the health of mothers and newborn babies, as well as to reduce illness and deaths, and is now starting a study with pregnant women who come to Janakpur Hospital, on the role of micronutrients in improving newborn infant health. The newborn babies of malnourished mothers are of low birth weight and diseased. Therefore, at the hospital, we are supplying iron and folic acid to prevent anaemia and micronutrient deficiency, and some women are supplied with other micronutrients as well as iron and folic acid. The Nepal Health Research Council and the Ministry of Health have given permission for us to conduct research comparing the role of multiple micronutrient supplementation for pregnant women with iron and folic acid tablet supplementation. Of the tablets we are giving you, some contain iron and folic acid, and the others contain iron and folic acid as well as some other minerals and vitamins, although we cannot tell which is which. For this 1200 pregnant women will be enrolled. This programme will also provide free services:

1. Antenatal care examination every month and discussion of your state of health at home.
2. Full predelivery care services
3. Ultrasound scan to assess the age of the baby.
4. Blood and urine examination as recommended by His Majesty's Government.
5. Maternity care during and after the birth of the baby.
6. Measurement of blood vitamin and mineral levels.
7. Treatment for any problems arising from pregnancy or childbirth.
8. Milk test after the baby is born.

Whether or not to take part in this study is up to you and you may leave if you like.
All information about participants will remain confidential.

Besides this, if you have any problems or questions you can contact the following address.
MIRA Janakpur Multiple Micronutrient Supplementation Study, Ramanand Chowk. Telephone 24032.
I have understood all the information written on this consent form.
I give my consent to take part in the study.

Signature
Name
Address
Date

If the participant is unable to sign for herself, a witness may sign for her.
The consent form has been read out in front of me (the woman has understood it) and it is true that she is willing to take part.
Name of witness
Date

Annex G. Verbal consent form

Verbal consent form

Mother Infant Research Activities has for many years been conducting research in various districts of Nepal to improve the health of mothers and newborn babies, as well as to reduce illness and deaths. It is now following up children at 2 years of age born to mothers of antenatal micronutrient supplementation study conducted in Janakpur Hospital. This will include

1. short medical history of the children
2. nutritional and immunization history
3. history on developmental mile-stones
4. anthropometric measurements of children
5. anthropometric measurements of mothers
6. examination of mother's blood

It is your wish to choose not to participate. Everything will be confidential, and all the information will not be disclosed to anyone. You can ask any questions regarding this study.

Annex H. Team members

Main study	
Hospital based staffs	
ANC	Yagya kumari Shrestha
	Durna Kumari Thapa
	Pushpa Baniya
Laboratory	Gunanand Sah
	Shyam Jha
	Birendra Kumar Yadav
Obstetric and Gynaecology department	Sunita yadav
	Sushila Karki
	Chandra MayaThapa
	Nayan Tara Sah
Study room	Anjana Vaidya
Field team	
	Mahottry team
	Bechan Chaudhary
	Dhanusha VDC
	Shiv Shanker Chave
	Dhanusha and Municipality team
	Binaya Karki
Follow up staffs	
Data	Anupa Regmi
Filed team	Team 1
	Durna kumari Thapa (Anthropometric)
	Shiv Shanker Chauve (Consent and Forms)
	Team 2
	Chandra Maya Thapa (Anthropometric)
	Gagan Kumar Chauve (Consent and Forms)

Annex I. Methods of data collection

On booking in the antenatal clinic	Ultrasound room	Delivery room	1 month postnatal interview	2 year follow-up
Introduction Address Menstrual history	1st scan at <20 weeks	Newborn Apgar Score	Infant morbidity	Maternal anthropometry
Details of the study	Enrolment after consent if inclusion criteria fulfilled	Newborn anthropometry	Infant mortality	Child anthropometry
Brief obstetric and gynaecological history	Medical, Obstetric and Gynaecological history	Congenital anomaly check	Maternal morbidity	Child morbidity
	Maternal anthropometry	Delivery events	Maternal mortality	Child mortality

Annex J. Composition of supplements

Supplement 1		Supplement 2	
Iron	(60 mg)	Vitamin A	(800 mcg)
Folic acid	(400 mcg)	Vitamin B1	(1.4 mg)
		Vitamin B2	(1.4 mg)
		Vitamin B6	(1.9 mg)
		Vitamin B12	(2.6 mcg)
		Vitamin C	(70 mg)
		Vitamin D	(5 mcg)
		Vitamin E	(10 mg)
		Niacin	(18 mg)
		Folic acid	(400 mcg)
		Iron	(30 mg)
		Zinc	(15 mg)
		Copper	(2 mg)
		Selenium	(65 mcg)
		Iodine	(150 mcg)

Annex K. Principal components analysis

The study used a score derived from the first component.

Component loading of socioeconomic factors					
Variable	Principal component 1	Principal component 2	Principal component 3	Principal component 4	Principal component 5
Farming	.020	-.919	.177	-.025	-.055
Salary	-.812	.444	.195	-.184	-.077
Business	.841	.298	.189	-.157	-.023
Daily wage	.160	-.004	-.803	.114	-.174
Student	-.019	.043	.041	.966	.017
Out of country	.031	.007	-.009	.019	.974
Land ownership	.118	-.168	.573	.093	-.111
Consumables	.156	.465	.529	.154	-.184
Eigenvalue	1.534	1.445	1.211	1.032	1.022
% of variation explained	19.181	18.062	15.134	12.897	12.772
Cumulative % of variation explained	19.181	37.243	52.377	65.274	78.046

Extraction method: Principal Components Analysis.
Rotation: Varimax with Kaiser Normalization.

Annex L. Studies comparing predictive accuracy of different estimation methods for birth weight

Study and date	Methods	Accuracy of estimation	Inference
Chauhan 1998[228]	Clinical/USS	**Lower simple error and mean standardized absolute error for USS EFW than Clinical EFW [mean (+/- Standard error)]** Clinical simple error of (48.2 +/- 411 g) and standardized absolute error (130 +/- 122g/kg) USSl simple error for EFW (-6.6 +/- 381g) and standardized absolute error of (104 +/- 89g/kg) **% of EFW that was predicted correctly within 10% of ABW** <2500 g (40% for clinical and 56% for USS) 2500-3999 g (60% for clinical and 58% for USS) >4000 g (53% for clinical and 62% for USS)	USS EFW is superior to clinical EFW in preterms Both methods have limited value in the estimation of actual birth weight and lie outside useful bandwidth (±10% of ABW)
Chauhan 2000[241]	USS biometric/clinical/USS soft tissue	**Areas under ROC curves (Area ± Standard error)** Clinical (0.72 ± 0.06) USS biometric (0.73 ± 0.06) USS soft tissues – 0.52 ±0.06 to 0.58 6 0.07	USS soft tissue not superior to clinical or USS biometric methods
Hendrix 2000[242]	Clinical/USS (RCT)	Clinical significantly more likely to be within 10% of actual weight (58%) than estimates derived from ultrasound examination	At term clinical more predictive ROC curve showed similar predictive ability
Nahum 2003 [227]	Maternal/USS	USS 7.5 – 18.8% Maternal characteristics 10.4%	Ultrasound no more accurate than maternal characteristics
Halaska 2006[229]	Maternal/ USS	**% of birth weight predicted within 10% of ABW** Maternal [243]- 63% Hadlock equation [244] 79% Halaska equation 75% Shepherd equation[245]- 58%	Nahum (maternal) comparable to shepherd Hadlock comparable to Halaska and more accurate

ABW: Actual birth wight; EFW: Estimated Fetal Weight; RCT: Randomized controlled trial; ROC: Receiver operating characteristics; USS: Ultrasound scan

Annex M Prediction models

The tables present odds ratios and 95% confidence interval
Model I: Unadjusted
Model II: Adjusted for significant confounders:
Neonatal death: weight at enrolment
Infant death: no significant confounders
Child death: gestation at birth
Stunting: parity, education, socioeconomic status, weight at enrolment, gestation at birth, age at weaning, age at follow up and frequency of illness
Wasting: education and weight at enrolment
Underweight: parity, education, socioeconomic status, weight at enrolment, gestation at birth, age at weaning and frequency of illness
Illness during infancy
Cough and fever: maternal age and education
Diarrhoea and fever: ethnicity, supplementation and age at follow up
Rash and fever: maternal age and education
Frequency of illness: parity, education, socioeconomic status and infants gender
Illness in the last fortnight
Fever: parity, education, socioeconomic status, weight at enrolment and age at weaning
Cough: parity, education, socioeconomic status, weight at enrolment, infants gender, age at weaning and age a follow up
Difficulty breathing: parity, education, age at weaning and age at follow up
Diarrhoea: parity, education, socioeconomic status, weight at enrolment, age at weaning and age at follow up
Systolic Blood Pressure: maternal age and parity,
Diastolic Blood Pressure: parity, ethnicity and education
Model III: Adjusted for all possible confounders
For neonatal deaths: Maternal age, parity, ethnicity, education, socioeconomic status, supplements, weight at enrolment, gestation at birth and infant sex
For infant deaths and child deaths: All confounders for neonatal deaths plus age at weaning
For malnutrition: All confounders for deaths plus age at weaning and frequency of illness
For illness: All confounders for deaths plus age at follow up

LBW	**Model I**	**Model II**	**Model III**
Neonatal death	4.02 (1.75 – 9.22) p = 0.001	3.54 (1.53 – 8.24) p = 0.003	3.46 (1.36 – 8.85) p = 0.009
Infant death	3.93 (1.95 – 7.91) p = 0.001	-	3.60 (1.63 – 7.93) p = 0.001
Child death	3.93 (2.02 – 7.63) p = 0.001	3.75 (1.85 – 7.57) p = 0.001	3.66 (1.73 – 7.75) p = 0.001
Stunting	3.03 (2.10 – 4.38) p = 0.001	3.53(2.28 – 5.44) p = 0.001	3.40 (2.19 – 5.30) p = 0.001
Wasting	2.90 (1.65 – 5.10) p = 0.001	2.43 (1.37 – 4.31) p = 0.002	2.93 (1.53 – 5.59) p = 0.001
Underweight	3.40 (2.45 – 4.72) p = 0.001	3.39 (2.31 – 4.98) p = 0.001	3.69 (2.47 – 5.50) p = 0.001
Cough and fever during infancy	0.84 (0.48 – 1.81) p = 0.8	0.85 (0.44 – 1.67) p = 0.6	0.83 (0.40 – 1.72) p = 0.6
Diarrhoea and fever during infancy	0.97 (0.68 – 1.36) p = 0.8	0.93 (0.38 – 2.19) p = 0.7	0.88 (0.60 – 1.29) p = 0.9
Rash and fever during infancy	0.68 (0.39 – 1.17) p = 0.2	0.63 (0.36 – 1.09) p = 0.1	0.65 (0.36 – 1.17) p = 0.1
Frequency of illness in the first year of life	1.23 (0.89 – 1.70) p = 0.2	1.25 (0.90 – 1.73) p = 0.2	1.31 (0.92 – 1.87) p = 0.1
Fever in last 14 days	1.56 (1.13 – 2.16)) p = 0.007	1.48 (1.06 – 2.09) p = 0.02	1.57 (1.09 – 2.25) p = 0.02
Diarrhoea in last 14 days	1.09 (0.69 – 1.72) p = 0.7	1.06 (0.66 – 1.70) p = 0.8	1.05 (0.64 – 1.73) p = 0.8
Cough in last 14 days	1.39 (1.00 – 1.92) p = 0.05	1.47 (1.04 – 2.08) p = 0.03	1.43 (0.99 – 2.05) p = 0.06
Difficult breathing in 14 days	1.12 (0.62 – 1.20) p = 0.7	1.17 (0.64 – 2.13) p = 0.6	1.29 (0.68 – 2.46) p = 0.4
Child systolic blood pressure	0.350 (-1.797 – 2.497) p = 0.8	-0.308 (-2.469 – 1.854) p = 0.8	-0.346 (-2.654 – 1.962) p = 0.8

Child diastolic blood pressure	2.004 (-0.104 – 4.112) p = 0.06	1.649 (-0.460 – 3.758) p = 0.1	1.246 (-1.004 – 3.497) p = 0.3

SGA	**Model I**	**Model II**	**Model III**
Neonatal death	1.21 (0.53 – 2.78) p = 0.7	1.00 (0.43 – 2.35) p = 1	1.11 (0.45 – 2.73) p = 0.8
Infant death	1.28 (0.63 – 2.58) p = 0.5		1.34 (0.63 -2.85) p = 0.5
Child death	1.39 (0.71 – 2.71) p = 0.4	1.57 (0.79 – 3.12) p = 0.2	1.67 (0.81 – 3.45) p = 0.2
Stunting	2.31 (1.76 – 3.02) p = 0.001	2.50 (1.81 – 3.48) p = 0.001	2.42 (1.75 – 3.36) p = 0.001
Wasting	1.81 (1.02 – 3.21) p = 0.04	1.43 (0.79 – 2.58) p = 0.2	1.56 (0.83 – 2.92) p = 0.2
Underweight	2.70 (2.04 – 3.56) p = 0.001	2.98 (2.14 – 4.14) p = 0.001	3.05 (2.18 – 4.27) p = 0.001
Cough and fever during infancy	0.97 (0.56 – 1.69) p = 0.9	0.93 (0.53 – 1.62) p = 0.8	1.10 (0.61 – 2.00) p = 0.8
Diarrhoea and fever during infancy	1.01 (0.76 – 1.34) p = 0.9	0.96 (0.72 – 1.29) p = 0.8	0.94 (0.69 – 1.29) p = 0.7
Rash and fever during infancy	1.22 (0.82 – 1.84) p = 0.3	1.18 (0.79 – 1.78) p = 0.4	1.23 (0.79 – 1.93) p = 0.4
Frequency of illness in the first year of life	1.22 (0.94 – 1.59) p = 0.1	1.23 (0.94 – 1.60) p = 0.1	1.31 (0.98 – 1.75) p = 0.07
Fever in last 14days	1.56 (1.19 – 2.06) p = 0.001	1.44 (1.08 – 1.93) p = 0.01	1.57 (1.16 – 2.13) p = 0.004
Diarrhoea in last 14 days	1.32 (0.90 – 1.94) p = 0.2	1.17 (0.79 – 1.74) p = 0.4	1.19 (0.79 – 1.80) p = 0.4
Cough in last 14 days	1.26 (0.96 – 1.65) p = 0.1	1.18 (0.89 – 1.58) p = 0.3	1.26 (0.94 – 1.71) p = 0.1
Difficult breathing in 14 days	1.92 (1.15 – 3.20) p = 0.01	1.93 (1.15 – 3.26) p = 0.01	1.94 (1.11 – 3.37) p = 0.02
Child systolic blood pressure	-0.140 (-1.898 – 1.619) p = 0.9	-0.412 (-2.177 – 1.352) p = 0.7	-0.584 (-2.456 – 1.288) p = 0.5
Child diastolic blood pressure	-0.380 (-2.110 – 1.350) p = 0.7	-0.471 (-2.195 – 1.253) p = 0.6	-0.180 (-2.006– 1.647) p = 0.8

LPI	**Model I**	**Model II**	**Model III**
Neonatal death	1.38 (0.54 – 3.53) p = 0.5	1.31 (0.51 – 3.37) p = 0.6	1.26 (0.48 – 3.32) p = 0.6
Infant death	1.07 (0.51 – 2.29) p = 0.9		0.98 (0.45 – 2.12) p = 1
Child death	1.11 (0.54 – 2.27) p = 0.8	1.06 (0.51 – 2.17) p = 0.9	1.03 (0.49 – 2.16) p = 0.9
Stunting	1.16 (0.87 – 1.54) p = 0.3	1.06 (0.77 – 1.46) p = 0.7	1.05 (0.76 – 1.45) p = 0.8
Wasting	1.94 (0.98 – 3.82) p = 0.06	1.86 (0.94 – 3.69) p = 0.07	2.16 (1.05 – 4.44) p = 0.04
Underweight	1.32 (0.99 – 1.77) p = 0.06	1.29 (0.93 – 1.79) p = 0.1	1.30 (0.94 – 1.82) p = 0.1
Cough and fever during infancy	0.42 (0.20 – 0.88) p = 0.02	0.41 (0.20 – 0.86) p = 0.02	0.42 (0.20 – 0.88) p = 0.02
Diarrhoea and fever during infancy	0.96 (0.71 – 1.30) p = 0.8	0.94 (0.69 – 1.28) p = 0.7	0.96 (0.70 – 1.32) p = 0.8
Rash and fever during infancy	1.10 (0.71 – 1.71) p = 0.7	1.08 (0.69 – 1.67) p = 0.7	1.10 (0.70 – 1.72) p = 0.7
Frequency of illness in the first year of life	1.18 (0.89 – 1.57) p = 0.2	1.19 (0.90 – 1.59) p = 0.2	1.18 (0.88 – 1.59) p = 0.3
Fever in last 14days	0.94 (0.70 – 1.26) p = 0.7	0.90 (0.67 – 1.22) p = 0.5	0.88 (0.65 – 1.20) p = 0.4
Diarrhoea in last 14 days	0.83 (0.55 – 1.23) p = 4	0.79 (0.53 – 1.19) p = 0.3	0.82 (0.54 – 1.24) p = 0.4
Cough in last 14 days	0.88 (0.66 – 1.17) p = 0.4	0.84 (0.63 – 1.14) p = 0.3	0.83 (0.61 – 1.13) p = 0.2
Difficult breathing in 14 days	1.0 (0.59 – 1.69) p = 1	1.01 (0.59 – 1.73) p = 1	0.97 (0.56 – 1.66) p = 0.9
Child systolic blood pressure	-0.041 (-1.930 – 1.848) P = 1.0	-0.369 (-2.265 – 21.527) P = 0.7	-0.405 (-2.317 – 1.506) P = 0.7
Child diastolic blood pressure	0.466 (-1.392 – 2.324) P = 0.6	0.348 (-1.504 – 2.200) P = 0.7	0.283 (-1.582 – 2.149) P = 0.8

LBW_LPI	Model I	Model II	Model III
Neonatal death	3.31 (1.43 – 7.65) p = 0.005	2.93 (1.26 – 6.86) p = 0.01	2.65 (1.03 – 6.79) p = 0.04
Infant death	2.76 (1.35 – 5.67) p = 0.005	-	2.26 (0.90 – 1.03) p = 0.05
Child death	2.60 (1.31 – 5.14) p = 0.006	2.33 (1.13 – 4.81) p = 0.02	2.13 (0.98 – 4.59) p = 0.06
Stunting	2.75 (1.88 – 4.03) p = 0.001	3.08 (1.98 – 4.79) p = 0.001	2.95 (1.89 – 4.63) p = 0.001
Wasting	2.62 (1.47 – 4.66) p = 0.001	2.24 (1.24 – 4.01) p = 0.008	2.63 (1.37 – 5.07) p = 0.004
Underweight	3.02 (2.15 – 4.25) p = 0.001	2.95 (1.99 – 4.37) p = 0.001	3.15 (2.09 – 4.75) p = 0.001
Cough and fever during infancy	0.79 (0.41 – 1.54) p = 0.5	0.72 (0.37 – 1.41) p = 0.4	0.69 (0.34 – 1.42) p = 0.7
Diarrhoea and fever during infancy	1.01 (0.70 – 1.45) p = 1	0.97 (0.67 – 1.40) p = 0.9	0.93 (0.63 – 1.38) p = 0.7
Rash and fever during infancy	0.61 (0.34 – 1.10) p = 0.01	0.57 (0.31 – 1.02) p = 0.06	0.58 (0.31 – 1.07) p = 0.08
Frequency of illness in the first year of life	1.25 (0.89 – 1.75) p = 0.2	1.27 (0.90 – 1.79) p = 0.2	1.35 (0.93 – 1.95) p = 0.1
Fever in last 14days	1.48 (1.05 – 2.07) p = 0.02	1.41 (0.99 – 2.01) p = 0.06	1.46 (1.01 – 2.12) p = 0.05
Diarrhoea in last 14 days	1.02 (0.63 – 1.65) p = 0.9	1.00 (0.61 – 1.65) p = 1	1.00 (0.60 – 1.68) p = 1
Cough in last 14 days	1.30 (0.93 – 1.83) p = 0.1	1.38 (0.96 – 1.98) p = 0.08	1.34 (0.92 – 1.94) p =0.1
Difficult breathing in 14 days	1.20 (0.66 – 2.17) p = 0.6	1.27 (0.69 – 2.34) p = 0.5	1.38 (0.71 – 2.65) p = 0.3
Child systolic blood pressure	0.94 (-1.30 – 3.18) p = 0.4	0.24 (-2.02 – 2.50) p = 0.9	0.27 (-2.10 – 2.65) p = 0.8
Child diastolic blood pressure	2.33 (0.13 – 4.53) p = 0.04	1.89 (-0.31 – 4.09) p = 0.09	1.51 (-0.80 – 3.83) p = 0.2

LBW_API	Model I	Model II	Model III
Neonatal death	3.78 (0.84 – 17.00) p = 0.08	3.17 (0.70 – 14.45) p = 0.1	3.46 (0.71 – 17.00) p = 0.1
Infant death	5.87 (1.89 – 18. 18) p = 0.002		5.71 (0.90 – 1.03) p = 0.3
Child death	6.95 (2.45 – 19.70) p = 0.001	5.98 (2.06 – 17.41) p = 0.001	7.04 (2.31 – 21.44) p = 0.001
Stunting	4.04 (1.18- 13.89) p = 0.03	5.4 (1.13 – 25.89) p = 0.04	5.29 (1.11 – 25.34) p = 0.04
Wasting	2.84 (0.81 – 10.00) p = 0.1	2.28 (0.63 – 8.24) p = 0.2	2.10 (0.54 – 8.17) p = 0.3
Underweight	5.11 (1.84 – 14.18) p = 0.002	5.17 (1.58 – 16.93) p = 0.007	5.72 (1.70 – 19.21) p = 0.005
Cough and fever during infancy	38927109 P=1	-	
Diarrhoea and fever during infancy	0.74 (0.29 – 1.91) p = 0.5	0.71 (0.27 – 1.86) p = 0.5	0.68 (0.26 – 1.79) p = 0.4
Rash and fever during infancy	1.41 (0.40 – 4.91) p = 0.6	1.38 (0.39 – 4.83) p = 0.6	1.63 (0.45 – 5.89) p = 0.5
Frequency of illness in the first year of life	0.96 (0.39 – 2.38) p = 0.9	0.95 (0.38 – 2.39) p = 0.9	0.92 (0.36 – 2.36) p = 0.9
Fever in last 14days	1.66 (0.67 – 4.14) p = 0.3	1.54 (0.61 – 3.91) p = 0.4	1.62 (0.62 – 4.19) p = 0.3
Diarrhoea in last 14 days	1.19 (0.34 – 4.14) p = 0.8	1.07 (0.30 – 3.79) p = 0.9	1.07 (0.29 – 3.93) p = 0.9
Cough in last 14 days	1.62 (0.65 – 4.02) p = 0.3	1.62 (0.63 – 4.12) p = 0.3	1.55 (0.60 – 3.99) p = 0.4
Difficult breathing in 14 days	0.00 (0.00 – 00) p = 0.1	-	-
Child systolic blood pressure	-4.00 (-9.99 – 1.99) p =0.2	-4.17 (-10.14 – 1.81) p = 0.2	-4.30 (-10.36 – 1.76) p = 0.2
Child diastolic blood pressure	-0.16 (-6.07 – 5.74) p = 1	-0.11 (-5.96 – 5.74) p = 1	-0.67 (-6.59 – 5.26) p = 0.8

NBW_LPI	Model I	Model II	Model III
Neonatal death	0.47 (0.19 – 1.14) p = 0.1	0.49 (0.19 – 1.19) p = 0.1	0.55 (0.22 – 1.40) p = 0.2
Infant death	0.45 (0.21 – 0.96) p = 0.04		0.51 (0.24 – 1.12) p = 0.09
Child death	0.50 (0.25 – 1.00) p = 0.05	0.54 (0.26 – 1.09) p = 0.08	0.57 (0.28 – 1.19) p = 0.1
Stunting	0.65 (0.50 – 0.84) p = 0.001	0.58 (0.43 – 0.79) p = 0.001	0.59 (0.43 – 0.80) p = 0.001
Wasting	0.79 (0.46 – 1.37) p = 0.4	0.86 (0.49 – 1.49) p = 0.6	0.91 (0.50 – 1.65) p = 0.8
Underweight	0.63 (0.48 – 0.82) p = 0.001	0.65 (0.48 – 0.88) p = 0.005	0.64 (0.47 – 0.88) p = 0.005
Cough and fever during infancy	0.62 (0.35 – 1.09) p = 0.1	0.64 (0.36 – 1.13) p = 0.1	0.65 (0.36 – 1.17) p = 0.1
Diarrhoea and fever during infancy	0.96 (0.72 – 1.27) p = 0.8	0.96 (0.72 – 1.29) p = 0.8	1.01 (0.75 – 1.36) p = 1
Rash and fever during infancy	1.42 (0.95 – 2.14) p = 0.09	1.46 (0.97 – 2.19) p = 0.07	1.45 (0.95 – 2.21) p = 0.09
Frequency of illness in the first year of life	1.01 (0.8 – 1.32) p = 0.9	1.01 (0.77 – 1.32) p = 1	0.96 (0.74 – 1.29) p = 0.9
Fever in last 14days	0.74 (0.56 – 0.97) p = 0.03	0.74 (0.58 – 0.98) p = 0.04	0.71 (0.53 – 0.95) p = 0.02
Diarrhoea in last 14 days	0.76 (0.58 – 0.99) p = 0.04	0.71 (0.53 – 0.94) p = 0.02	0.72 (0.54 – 0.96) p = 0.02
Cough in last 14 days	0.89 (0.54 – 1.46) p = 0.6	0.87 (0.53 – 1.44) p = 0.6	0.81 (0.48 – 1.35) p = 0.8
Difficult breathing in 14 days	0.83 (0.57 – 1.22) p = 0.3	0.81 (0.55 – 1.20) p = 0.3	0.84 (0.56 – 1.25) p = 0.4
Child systolic blood pressure	-0.615 (-2.376 – 1.145) p = 0.5	-0.463 (-2.222 – 1.1296) p = 0.6	-0.514 (-2.312 – 1.284) p = 0.6
Child diastolic blood pressure	-1.031 (-2.762 – 0.700) p = 0.2	-0.853 (-2.570 – 0.865) p = 0.3	-0.616 (-2.371 – 1.138) p = 0.5

NBW_API	Model I	Model II	Model III
Neonatal death	0.48 (0.16 – 1.44) p = 0.2	0.52 (0.18 – 1.55) p = 0.2	0.53 (0.17 – 1.61) p = 0.3
Infant death	0.55 (0.23 – 1.36) p = 0.2	-	0.60 (0.24 – 1.51) p = 0.3
Child death	0.48 (0.20 – 1.16) p = 0.1	0.51 (0.21 – 1.24) p = 0.1	0.50 (0.20 – 1.24) p = 0.1
Stunting	0.77 (0.58 – 1.03) p = 0.08	0.83 (0.60 – 1.16) p = 0.3	0.85 (0.61 – 1.18) p = 0.3
Wasting	0.39 (0.18 – 0.83) p = 0.01	0.41 (0.19 – 0.89) p = 0.02	0.35 (0.15 – 0.79) p = 0.01
Underweight	0.64 (0.47 – 0.86) p = 0.004	0.65 (0.46 – 0.92) p = 0.01	0.64 (0.45 – 0.90) p = 0.01
Cough and fever during infancy	2.13 (1.02 – 4.42) p = 0.04	2.19 (1.05 – 4.57) p = 0.04	2.18 (1.03 – 4.62) p = 0.04
Diarrhoea and fever during infancy	1.05 (0.77 – 1.44) p = 0.8	1.08 (0.79 – 1.49) p = 0.6	1.06 (0.76 – 1.48) p = 0.7
Rash and fever during infancy	0.90 (0.57 – 1.42) p = 0.7	0.92 (0.59 – 1.46) p = 0.7	0.90 (0.56 – 1.44) p = 0.7
Frequency of illness in the first year of life	0.85 (0.64 – 1.14) p = 0.3	0.85 (0.63 - 1.14) p = 0.3	0.86 (0.63 – 1.16) p = 0.3
Fever in last 14 days	1.02 (0.76 – 1.37) p = 0.9	1.07 (0.79 – 1.46) p = 0.7	1.09 (0.79 – 1.49) p = 0.6
Diarrhoea in last 14 days	1.10 (0.81 – 1.47) p = 0.6	1.14 (0.84 – 1.55) p = 0.4	1.16 (0.85 – 1.59) p = 0.4
Cough in last 14 days	1.20 (0.80 – 1.80) p = 0.4	1.27 (0.84 – 1.92) p = 0.3	1.22 (0.80 – 1.86) p = 0.4
Difficult breathing in 14 days	1.12 (0.66 – 1.89) p = 0.7	1.10 (0.65 – 1.89) p = 0.7	1.13 (0.66 – 1.96) p = 0.7
Child systolic blood pressure	0.497 (-1.436 – 2.430) p = 0.6	0.884 (-1.057 – 2.825) p = 0.4	0.937 (-1.028 – 2.903) p = 0.4
Child diastolic blood pressure	-0.414 (-2.316 – 1.487) p = 0.7	-0.272 (-2..169 – 1.625) p = 0.8	-0.142 (-2.060 – 1.777) p = 0.9

LBW_SGA	Model I	Model II	Model III
Neonatal death	2.78 (1.18 – 6.51) p = 0.02	2.40 (1.01 – 5.71) p = 0.05	2.15 (0.86 – 5.38) p = 0.1
Infant death	3.17 (1.56 – 6.45) p = 0.001		2.79 (1.31 – 5.96) p = 0.008
Child death	3.31 (1.69 – 6.47) p = 0.001	3.08 (1.56 – 6.08) p = 0.001	3.07 (1.50 – 6.30) p = 0.002
Stunting	2.92 (1.98 – 4.31) p = 0.001	3.25 (2.09 – 5.07) p = 0.001	3.01 (1.92 – 4.70) P = 0.001
Wasting	2.75 (1.54 – 4.92) p = 0.001	2.31 (1.27 – 4.17) p = 0.006	2.63 (1.39 – 4.97) p = 0.003
Underweight	3.83 (2.71 – 5.43) p = 0.001	3.80 (2.56 – 5.63) p = 0.001	4.08 (2.71 – 6.15) p = 0.001
Cough and fever during infancy	1.16 (0.55 – 2.41) p = 0.7	1.08 (0.52 – 2.28) p = 0.8	1.14 (0.52 – 2.47) p = 0.8
Diarrhoea and fever during infancy	1.04 (0.72 – 1.50) p = 0.8	1.02 (0.70 – 1.47) p = 0.9	0.99 (0.67 – 1.47) p = 0.9
Rash and fever during infancy	0.81 (0.47 – 1.41) p = 0.5	0.77 (0.44 – 1.34) p = 0.4	0.80 (0.45 – 1.41) p = 0.4
Frequency of illness in the first year of life	1.28 (0.91 – 1.79) p = 0.2	1.31 (0.93 – 1.84) p = 0.1	1.39 (0.97 – 1.99) p = 0.08
Fever in last 14days	1.70 (1.21 – 2.38) p = 0.002	1.64 (1.15 – 2.33) p = 0.006	1.73 (1.20 – 2.49) p = 0.003
Diarrhoea in last 14 days	1.19 (0.74 – 1.89) p = 0.5	1.13 (0.70 – 1.82) p = 0.6	1.12 (0.68 – 1.85) p = 0.7
Cough in last 14 days	1.37 (0.97 – 1.92) p = 0.07	1.44 (1.00 – 2.06) p =0.05	1.43 (0.99 – 2.06) p = 0.06
Difficult breathing in 14 days	1.21 (0.66 – 2.19) p = 0.5	1.26 (0.68 – 2.32) p = 0.5	1.36 (0.72 – 2.58) p = 0.4
Child systolic blood pressure	0.338 (-1.914 – 2.590) p = 0.8	-0.004 (-2.260 – 2.251) p = 1	-0.26 (-2.59 – 2.08) p = 0.8
Child diastolic blood pressure	1.631 (-0.582 – 3.844) p = 0.2	1.293 (-0.910 – 3.497) p = 0.3	1.032 (-1.243 – 3.308) p = 0.4

LBW_AGA	Model I	Model II	Model III
Neonatal death	5.52 (1.55 – 10.71) p = 0.008	5.43 (1.51 – 10.57) p = 0.01	5.69 (1.02 – 31.83) p = 0.05
Infant death	3.89 (1.11- 13.66) p = 0.03		2.30 (0.47 – 11.24) p = 0.3
Child death	3.41 (0.98 – 11.93) p = 0.05	2.20 (0.48 – 10.10) p = 0.3	1.64 (0.35 – 7.85) p = 0.5
Stunting	2.57 (0.94 – 6.98) p = 0.07	2.33 (0.69 – 7.84) p = 0.2	3.28 (0.85 – 12.69) p = 0.09
Wasting	2.47 (0.71 – 8.57) p = 0.2	2.32 (0.66 – 8.19) p = 0.2	2.18 (0.49 – 9.72) p = 0.3
Underweight	1.07 (0.46 – 2.51) p = 0.9	0.65 (0.23 – 1.78) p = 0.4	0.65 (0.23 – 1.81) p = 0.4
Cough and fever during infancy	0.41 (0.12 – 1.42) p = 0.2	0.33 (0.09 – 1.18) p = 0.09	0.18 (0.04 – 0.79) p = 0.02
Diarrhoea and fever during infancy	0.67 (0.29 – 1.56) p = 0.4	0.60 (0.25 – 1.41) p = 0.2	0.45 (0.17 – 1.19) p = 0.1
Rash and fever during infancy	----	---	-----
Frequency of illness in the first year of life	0.88 (0.38 – 2.05) p = 0.7	0.84 (0.35 – 1.98) p = 0.7	0.66 (0.25 – 1.73) p = 0.4
Fever in last 14days	0.80 (0.33 – 1.97) p = 0.6	0.66 (0.25 – 1.74) p = 0.4	0.51 (0.18 – 1.44) p = 0.2
Cough in last 14 days	1.39 (0.60 – 3.21) p = 0.4	1.39 (0.57 – 3.93) p = 0.5	1.02 (0.39 – 2.66) p = 1
Difficult breathing in 14 days	0.54 (0.07 – 4.06) p = 0.6	0.57 (0.07 – 4.37) p = 0.6	0.61 (0.07 – 5.18) p = 0.6
Diarrhoea in last 14 days	0.60 (0.14 – 2.58) p = 0.5	0.65 (0.15 – 2.89) p = 0.7	0.56 (0.12 – 2.70) p = 0.5
Child systolic blood pressure	-0.051 (-5.657 – 5.556) p = 1	-0.626 (-6.224 – 4.973) p = 0.8	-1.088 (-7.176 – 4.999) p = 0.7
Child diastolic blood pressure	3.353 (-2.158 – 8.864) p = 0.2	2.900 (-2.570 – 8.371) p = 0.3	1.418 (-4.521 – 7.358) p = 0.6

NBW_AGA	Model I	Model II	Model III
Neonatal death	0.52 (0.21 – 1.28) p = 0.2	0.62 (0.25 – 1.55) p = 0.3	0.60 (0.23 – 1.53) p = 0.3
Infant death	0.59 (0.28 - 1.22) p = 0.2		0.63 (0.29 – 1.37) p = 0.2
Child death	0.56 (0.28 – 1.13) p = 0.1	0.55 (0.27 – 1.12) p = 0.1	0.54 (0.26 – 1.14) p = 0.1
Stunting	0.39 (0.30 – 0.52) p = 0.001	0.39 (0.28 – 0.53) p = 0.001	0.39 (0.28 – 0.54) p = 0.001
Wasting	0.47 (0.26 – 0.86) p = 0.01	0.60 (0.32 – 1.10) p = 0.1	0.57 (0.30 – 1.08) p = 0.08
Underweight	0.36 (0.27 -0.48) p = 0.001	0.36 (0.26 – 0.50) p = 0.001	0.35 (0.25 – 0.49) p = 0.001
Cough and fever during infancy	1.17 (0.67 – 2.04) p = 0.6	1.25 (0.71 – 2.2) p = 0.4	1.10 (0.61 – 1.99) p = 0.8
Diarrhoea and fever during infancy	1.04 (0.78 – 1.38) p = 0.8	1.1 (0.82 – 1.47) p = 0.5	1.14 (0.84 – 1.56) p = 0.4
Rash and fever during infancy	0.92 (0.61 – 1.38) p = 0.7	0.96 (0.64 – 1.45) p = 0.8	0.92 (0.59 – 1.43) p = 0.7
Frequency of illness in the first year of life	0.83 (0.64 – 1.08) p = 0.2	0.83 (0.63 – 1.08) p = 0.2	0.80 (0.60 – 1.07) p = 0.1
Fever in last 14 days	0.65 (0.49 – 0.86) p = 0.002	0.72 (0.54 – 0.96) p=0.03	0.69 (0.51 – 0.92) p = 0.01
Diarrhoea in last 14 days	0.79 (0.54 – 1.16) p = 0.2	0.88 (0.59 – 1.32) p = 0.6	0.88 (0.59 – 1.33) p = 0.6
Cough in last 14 days	0.77 (0.59 – 1.01) p = 0.06	0.82 (0.61 – 1.09) p = 0.2	0.80 (0.59 – 1.07) p = 0.1
Difficult breathing in 14 days	0.54 (0.32 – 0.91) p =0.02	0.54 (0.32 – 0.91) p = 0.02	0.54 (0.31 – 0.94) p = 0.03
Child systolic blood pressure (n=902)	0.145 (-1.618 – 1.909) p = 0.9	0.526 (-1.251 – 2.304) p = 0.6	0.670 (-1.178 – 2.518) p = 0.5
Child diastolic blood pressure	0.050 (-1.684 – 1.785) p = 1	0.186 (-1.551 – 1.923) p = 0.8	0.044 (-1.760 – 1.848) p = 1

NBW_SGA	Model I	Model II	Model III
Neonatal death	0.43 (0.14 – 1.27) p =0.1	0.39 (0.13 – 1.16) p = 0.09	0.45 (0.14 – 1.44) p = 0.2
Infant death	0.37 (0.14 – 0.97) p = 0.04	-	0.40 (0.14 – 1.10) p = 0.07
Child death	0.40 (0.17 – 0.97) p = 0.04	0.46 (0.18 – 1.14) p = 0.09	0.49 (0.19 – 1.25) p = 0.1
Stunting	1.32 (0.99 – 1.75) p = 0.06	1.28 (0.91 – 1.80) p = 0.2	1.31(0.93– 1.85 p = 0.1
Wasting	0.79 (0.43 – 1.45) p = 0.4	0.69 (0.37 – 1.27) p = 0.2	0.65 (0.32 – 1.28) p = 0.2
Underweight	1.15 (0.87 – 1.53) p = 0.3	1.20 (0.86 – 1.68) p = 0.3	1.20 (0.85 – 1.69) p = 0.3
Cough and fever during infancy	0.88 (0.50 – 1.57) p = 0.7	0.88 (0.49 – 1.56) p = 0.7	1.02 (0.54 – 1.93) p = 1
Diarrhoea and fever during infancy	0.98 (0.73 – 1.33) p = 0.9	0.95 (0.70 – 1.29) p = 0.7	0.94 (0.67 – 1.31) p = 0.7
Rash and fever during infancy	1.42 (0.94 – 2.15) p = 0.1	1.42 (0.93 – 2.15) p = 0.1	1.48 (0.93 – 2.35) p = 0.09
Frequency of illness in the first year of life	1.06 (0.80 – 1.41) p = 0.7	1.05 (0.79 – 1.39) p =0.8	1.07 (0.78 – 1.46) p = 0.7
Fever in last 14days	1.13 (0.85 – 1.51) p = 0.4	1.05 (0.78 – 1.41) p = 0.8	1.10 (0.80 – 1.52) p = 0.6
Cough in last 14 days	1.04 (0.78 – 1.39) p = 0.8	0.93 (0.69 – 1.26) p = 0.7	1.00 (0.72 – 1.39) p = 0.1
Difficult breathing in last 14 days	1.73 (1.05 – 2.83) p = 0.03	1.68 (1.02 – 2.78) p = 0.04	1.62 (0.93 – 2.82) p = 0.09
Cough in 14 days	1.21 (0.81 – 1.80) p = 0.4	1.09 (0.73 – 1.63) p = 0.7	1.12 (0.72 – 1.74) p = 0.6
Child systolic blood pressure	-0.39 (-2.27 – 1.48) p = 0.7	-0.38 (-2.25 – 1.49) p = 0.7	-0.49 (-2.53 – 1.54) p = 0.6
Child diastolic blood pressure	-1.56 (-3.41 – 0.28) P = 0.1	-1.42 (-0.33 – 0.41) P = 0.1	-0.99 (-2.98 – 0.99) P = 0.3

LPI_SGA	Model I	Model II	Model III
Neonatal death	1.29 (0.57 – 2.96) p = 0.5	1.14 (0.49 – 2.62) p = 0.8	1.15 (0.48 – 2.75) p = 0.8
Infant death	1.16 (0.58 – 2.33) p = 0.7	-	1.15 (0.55 – 2.38) p = 0.7
Child death	1.18 (0.61 – 2.29) p = 0.6	1.28 (0.66 – 2.50) p = 0.5	1.29 (0.64 -2.58) p = 0.5
Stunting	1.99 (1.51 – 2.62) p = 0.001	2.01 (1.46 – 2.77) p = 0.001	1.92 (1.39 – 2.66) p = 0.001
Wasting	1.96 (1.12 – 3.42) p = 0.02	1.68 (0.95 – 3.00) p = 0.07	1.99 (1.10 – 3.61) p = 0.02
Underweight	2.05 (1.56 – 2.70) p = 0.001	2.14 (1.56 – 2.94) p = 0.001	2.13 (1.54 – 2.93) p = 0.001
Cough and fever during infancy	0.80 (0.46 – 1.39) p = 0.4	0.76 (0.44 – 1.34) p = 0.3	0.85 (0.47 – 1.52) p = 0.6
Diarrhoea and fever during infancy	1.00 (0.75 – 1.33) p = 0.9	0.95 (0.71 – 1.28) p = 0.9	0.96 (0.70 – 1.30) p = 0.8
Rash and fever during infancy	0.98 (0.65 – 1.48) p = 0.9	0.95 (0.63 – 1.44) p = 0.8	0.95 (0.61 – 1.46) p = 1
Frequency of illness in the first year of life	1.23 (0.94 – 1.60) p = 0.1	1.25 (0.95 – 1.64) p = 0.1	1.30 (0.97 – 1.73) p = 0.08
Fever in last 14days	1.39 (1.06 – 1.84) p = 0.02	1.33 (0.99 – 1.77) p = 0.06	1.37 (1.02 – 1.84) p = 0.04
Diarrhoea in last 14 days	1.15 (0.78 – 1.69) p = 0.5	1.06 (0.72 – 1.57) p = 0.8	1.05 (0.70 – 1.57) p = 0.8
Cough in last 14 days	1.11 (0.84 – 1.46) p = 0.5	1.09 (0.82 – 1.45) p = 0.6	1.11 (0.83 – 1.50) p = 0.4
Difficult breathing in 14 days	1.48 (0.91 – 2.43) p = 0.1	1.54 (0.93 – 2.54) p = 0.09	1.46 (0.87 – 2.46) p = 0.2
Child systolic blood pressure	0.12 (-1.67 – 1.67) p = 0.9	-0.21 (-2.00 – 1.59) p = 0.8	-0.32 (-2.17 – 1.53) p = 0.7
Child diastolic blood pressure	0.19 (-1.57 – 1.95) p = 0.8	0.04 (-1.71 – 1.79) p = 1.0	0.24 (-1.57 – 2.05) p = 0.8

LPI_AGA	Model I	Model II	Model III
Neonatal death	1.01 (0.40 – 2.60) p = 1	1.15 (0.44 – 3.0) p = 0.8	1.1 (0.40 – 2.98) p = 0.9
Infant death	0.94 (0.42 – 2.11) p = 0.9	-	0.86 (0.36 – 2.06) p = 0.7
Child death	o.94 (0.43 – 2.02) p = 0.9	0.80 (0.37 – 1.77) p = 0.6	0.79 (0.35 – 1.80) p = 0.6
Stunting	0.51 (0.38 – 0.69) p = 0.001	0.45 (0.32 – 0.64) p = 0.001	0.47 (0.33 – 0.67) p = 0.001
Wasting	0.79 (0.41 – 1.53) p = 0.5	0.94 (0.48 – 1.84) p = 0.9	0.89 (0.44 – 1.79) p = 0.7
Underweight	0.52 (0.38 – 0.72) p = 0.001	0.48 (0.33 – 0.70) p = 0.001	0.49 (0.34 – 0.72) p = 0.001
Cough and fever during infancy	0.62 (0.35 – 1.1) p = 0.1	0.63 (0.35 – 1.14) p = 0.1	0.53 (0.28 – 1.00) p = 0.05
Diarrhoea and fever during infancy	0.99 (0.71 – 1.36) p = 0.8	1.01 (0.73 – 1.41) p = 0.9	1.05 (0.74 – 1.48) p = 0.8
Rash and fever during infancy	1.09 (0.69 – 1.72) p = 0.7	1.10 (0.70 – 1.75) p = 0.7	1.12 (0.69 – 1.82) p = 0.7
Frequency of illness in the first year of life	0.92 (0.68 – 1.25) p = 0.6	0.91 (0.67 – 1.23) p = 0.6	0.85 (0.62 – 1.18) p = 0.3
Fever in last 14 days	0.61 (0.44 – 0.84)) p = 0.003	0.62 (0.45 – 0.87) p = 0.006	0.57 (0.40 – 0.81) p = 0.002
Diarrhoea in last 14 days	0.57 (0.30 – 1.08) p = 0.08	0.55 (0.29 – 1.05) p = 0.07	0.54 (0.27 – 1.06) p = 0.07
Cough in last 14 days	0.77 (0.56 – 1.05) p = 0.1	0.75 (0.54 – 1.04) p = 0.09	0.71 (0.50 – 1.00) p = 0.05
Difficult breathing in 14 days	0.64 (0.40 – 1.03) p = 0.07	0.68 (0.42 – 1.10) p = 0.1	0.71 (0.43 – 1.18) p = 0.2
Child systolic blood pressure	-0.043 (-2.051 – 1.966) p = 1	-0.022 (-2.033 – 1.989) p = 1	0.070 (-2.031 – 2.171) p = 1
Child diastolic blood pressure	0.288 (-1.688 – 2.264) p = 0.8	0.313 (-1.651 – 2.277) p = 0.8	0.001 (-2.048 – 2.051) p = 1

API_SGA	Model I	Model II	Model III
Neonatal death	0.82 (0.19 – 2.53) p = 0.8	0.71 (0.16 – 3.07) p = 0.6	0.92 (0.20 – 4.17) p = 0.9
Infant death	1.27 (0.44 – 3.71) p = 0.7	-	1.46 (0.48 – 4.43) p = 0.5
Child death	1.45 (0.55 – 3.83) p = 0.5	1.63 (0.61 – 4.33) p = 0.3	1.87 (0.67 – 5.16) p = 0.2
Stunting	1.64 (1.02 – 2.633) p = 0.04	1.78 (1.02 - 3.09) p = 0.04	1.85 (1.05 – 3.24) p = 0.03
Wasting	0.73 (0.26 – 2.08) p = 0.6	0.58 (0.20 – 1.68 p = 0.6	0.41 (0.12 – 1.40) p = 0.2
Underweight	2.03 (1.31 – 3.16) p = 0.002	2.06 (1.24 – 3.42) p = 0.005	2.27 (1.34 – 3.82) p = 0.002
Cough and fever during infancy	2.77 (0.66 – 11.59) p = 0.2	2.75 (0.66 – 11.54) p = 0.2	3.18 (0.75 – 13.52) p = 0.2
Diarrhoea and fever during infancy	1.06 (0.65 – 1.72) p = 0.8	1.05 (0.64 – 1.72) p = 0.9	0.99 (0.59 – 1.65) p = 1
Rash and fever during infancy	1.71 (0.94 – 3.10) p = 0.08	1.69 (0.92 – 3.08) p = 0.09	1.81 (0.97 – 3.39) p = 0.06
Frequency of illness in the first year of life	1.04 (0.67 – 1.63) p = 0.9	1.00 (0.64 – 1.57) p = 1.0	1.05 (0.66 – 1.68) p = 0.8
Fever in last 14days	1.33 (0.85 – 2.09) p = 0.2	1.20 (0.74 – 1.91) p = 0.4	1.31 (0.81 – 2.11) p = 0.3
Diarrhoea in last 14 days	1.37 (0.76 – 2.47) p = 0.3	1.21 (0.66 – 2.21) p = 0.5	1.25 (0.67 – 2.32) p = 0.5
Cough in last 14 days	1.36 (0.87 – 2.13) p = 0.2	1.19 (0.75 – 1.90) p = 0.5	1.31 (0.81 – 2.11) p = 0.3
Difficult breathing in 14 days	1.67 (0.82 – 3.39) p = 0.2	1.57 (0.76 – 3.23) p = 0.2	1.49 (0.71 – 3.15) p = 0.3
Child systolic blood pressure	-0.76 (-3.74 – 2.22) p = 0.6	-0.63 (-3.61 – 2.34) p = 0.7	-0.70 (-3.72 – 2.33) p =0.7
Child diastolic blood pressure	-1.49 (-4.42 – 1.43) p = 0.4	-1.40 (-4.30 – 1.51) p = 0.4	-1.06 (-4.01 - 1.90) p = 0.5

API_AGA	Model I	Model II	Model III
Neonatal death	0.74 (0.25 – 2.21) p = 0.6	0.85 (0.28 – 2.55) p = 0.8	0.76 (0.25 – 2.37) p = 0.6
Infant death	0.82 (0.33 – 2.02) p = 0.7		0.85 (0.34 – 2.17) p = 0.7
Child death	0.71 (0.29 – 1.72) p = 0.4	0.71 (0.29 – 1.73) p = 0.45	0.67 (0.27 – 1.70) p = 0.4
Stunting	0.67 (0.49 0 – 0.91) p = 0.01	0.71 (0.50 – 1.02) p = 0.07	0.72 (0.50 – 1.03) p = 0.07
Wasting	0.51 (0.23-1.14) p = 0.1	0.60 (0.26-1.36) p = 0.2	0.58 (0.25-1.34) p = 0.2
Underweight	0.48 (0.34 – 0.68) p = 0.001	0.49 (0.33 – 0.72) p = 0.001	0.45 (0.30 – 0.68) p = 0.001
Cough and fever during infancy	1.93 (0.86 – 4.34) p = 0.1	2.00 (0.89 – 4.53) p = 0.09	1.86 (0.81 – 4.29) p =0.1
Diarrhoea and fever during infancy	1 (0.71- 1.41) p = 1	1.03 (0.72 – 1.46) p = 0.9	1.02 (0.71 – 1.47) p = 0.9
Rash and fever during infancy	0.66 (0.38 – 1.14) p = 0.1	0.68 (0.39 – 1.18) p = 0.2	0.64 (0.36 – 1.12) p = 0.1
Frequency of illness in the first year of life	0.81 (0.59 – 1.12) p = 0.2	0.82 (0.60 – 1.14) p = 0.2	0.81 (0.57 – 1.13) p = 0.2
Fever in last 14 days	0.93 (0.67 – 1.30) p = 0.7	1.03 (0.73 – 1.46) p = 0.9	1.01 (0.71 – 1.44) p = 1
Diarrhoea in last 14 days	1.10 (0.70 – 1.73) p = 0.7	1.24 (0.78 – 1.96) p = 0.4	1.16 (0.72 – 1.86) p = 0.6
Cough in last 14 days	1.00 (0.72 – 1.39) p = 1	1.12 (0.80 – 1.59) p = 0.5	1.09 (0.77 – 1.55) p = 0.7
Difficult breathing in 14 days	0.72 (0.38 – 1.38) p = 0.3	0.74 (0.38 – 1.42) p = 0.4	0.80 (0.41 – 1.57) p = 0.5
Child systolic blood pressure	0.469 (-1.663 – 2.600) p = 0.6	0.861 (-1.289 – 3.011) p = 0.4	0.941 (-1.238 – 3.120) p = 0.4
Child diastolic blood pressure	0.305 (-1.792 – 2.402) p = 0.8	0.453 (-1.648 – 2.553) p = 0.7	0.359 (-1.768 – 2.486) p = 0.7

LBW_LPI_AGA	Model I	Model II	Model III
Neonatal death	6.26 (1.74 – 22.48) p = 0.005	6.09 (1.68 – 22.08) p = 0.006	6.55 (1.16 – 37.06) p = 0.03
Infant death	4.28 (1.21 – 15.14) p = 0.02		2.52 (0.51 – 12.38) p = 0.3
Child death	3.76 (1.07 – 13.22) p = 0.04	2.50 (0.55 – 11.33) p = 0.2	1.82 (0.38 – 8.75) p = 0.5
Stunting	3.02 (1.0 – 9.6) p = 0.05	3.27 (0.85 – 12.57) p = 0.08	5.17 (1.06 – 25.16) p = 0.04
Wasting	1.67 (0.38 – 7.36) p = 0.5	1.56 (0.35 – 7.01) p= 0.6	1.25 (2.32 – 6.73) p = 0.8
Underweight	1.02 (0.42 – 2.49) p = 1	0.62 (0.22 – 1.80) p = 0.4	0.63 (0.21 – 1.85) p = 0.4
Cough and fever during infancy	0.37 (0.10 – 1.28) p = 0.1	0.29 (0.08 – 1.03) p = 0.06	0.15 (0.03 – 0.68) p = 0.01
Diarrhoea and fever during infancy	0.70 (0.29 – 1.70) p = 0.4	0.63 (0.26 – 1.56) p = 0.3	0.48 (0.18 – 1.31) p = 0.2
Rash and fever during infancy	0.00 (0.00 - .) p = 1	-	-
Frequency of illness in the first year of life	0.86 (0.35 – 2.10) p = 0.8	0.80 (0.32 – 1.96) p = 0.6	0.66 (0.24 – 1.81) p = 0.4
Fever in last 14days	0.73 (0.28 – 1.90) p = 0.5	0.56 (0.20 – 1.60) p = 0.3	0.44 (0.15 – 1.34) p = 0.2
Diarrhoea in last 14 days	0.66 (0.15 – 2.86) p = 0.6	0.73 (0.16 – 3.26) p = 0.7	0.67 (0.14 – 3.27) p = 0.6
Cough in last 14 days	1.64 (0.69 – 3.91) p = 0.3	1.64 (0.65 – 4.14) p = 0.3	1.25 (0.46 – 3.38) p = 0.7
Difficult breathing in 14 days	0.62 (0.60 – 4.51) p = 0.6	0.58 (0.07 – 4.51) p = 0.6	0.63 (0.07 – 5.43) p = 0.7
Child systolic blood pressure	0.457 (-5.404 – 6.317) p = 0.9	-0.555 (-6.417 – 5.307) p = 0.9	-0.430 (-6.743 – 5.882) p = 0.9
Child diastolic blood pressure	4.509 (-1.248 – 10.267) p = 0.1	4.145 (-1.575 – 9.865) p = 0.2	2.775 (-3.38 – 8.932) p = 0.4

LBW_API_SGA	Model I	Model II	Model III
Neonatal death	4.34 (0.96 – 19.67) p = 0.06	3.55 (0.77 – 16.30) p = 0.1	4.08 (0.82 – 20. 19) p = 0.09
Infant death	6.54 (2.09 – 20.45) p = 0.03		6.46 (1.93 – 21.60) p = 0.002
Child death	7.80 (2.72 – 22.31) p = 0.001	6.89 (2.38 – 19.98) p = 0.001	8.09 (2.64 – 24.78) p = 0.001
Stunting	5.75 (1.31 – 25.15) p = 0.02	11.60 (1.39 – 96.77) p = 0.02	11.26 (1.35 – 93.71) p = 0.03
Wasting	1.99 (0.45 – 8.89) p = 0.4	1.55 (0.34 – 7.10) p = 0.6	1.47 (0.30 – 7.11) p = 0.6
Underweight	6.01 (1.96 – 18.42) p = 0.002	6.82 (1.80 – 25.91) p = 0.005	7.82 (1.99 – 30.74) p = 0.003
Cough and fever during infancy	-		
Diarrhoea and fever during infancy	0.79 (0.29 – 2.15) p = 0.6	0.79 (0.28 – 2.19) p = 0.6	0.73 (0.26 – 2.06) p = 0.6
Rash and fever during infancy	1.62 (0.46 – 5.75) p = 0.5	1.57 (0.44 – 5.59) p = 0.5	1.88 (0.51 – 6.89) p = 0.3
Frequency of illness in the first year of life	0.94 (0.36 – 2.46) p = 0.9	0.90 (0.34 – 2.38) p = 0.8	0.93 (0.35 – 2.50) p = 0.9
Fever in last 14days	1.65 (0.63 – 4.32) p = 0.3	1.45 (0.54 – 3.88) p = 0.5	1.59 (0.58 – 4.31) p = 0.4
Diarrhoea in last 14 days	2.04 (0.78 – 5.34) p = 0.1	1.99 (0.74 – 5.36) p = 0.2	1.98 (0.73 – 5.37) p = 0.2
Cough in last 14 days	1.36 (0.39 – 4.81) p = 0.6	1.21 (0.34 – 4.35) p = 0.8	1.26 (0.34 – 4.70) p = 0.7
Difficult breathing in 14 days	-	-	-
Child systolic blood pressure	-3.868 (-10.183 – 2.446) p = 0.2	-3.944 (-10.241 – 2.352) p = 0.2	-4.011 (-10.368 – 2.346) p = 0.2
Child diastolic blood pressure	0.835 (-5.381 – 7.051) p = 0.8	1.036 (-5.119 – 7.191) p = 0.7	0.578 (-5.630 – 6.786) p = 0.9

LBW_API_AGA	Model I	Model II	Model III
Neonatal death 1048	-	-	-
Infant death 953 (totalfup)	-	-	-
Child death 953	-	-	-
Stunting 915	0.70 (0.04 – 11.23) p = 0.8	0.34 (0.02 – 5.69) p = 0.5	0.36 (0.02 – 6.14) p = 0.5
Wasting 915	15.91 (0.98 – 257.81) p = 0.05	15.58 (0.92 – 264.63) p = 0.06	10.27 (0.49 – 215.12) p = 0.1
Underweight 915	1.66 (0.10 – 26.65) p = 0.7	0.99 (0.06 – 16.98) p = 1	0.92 (0.05 – 15.99) p = 1
Cough and fever during infancy	1E+008 (0.00 - .) p = 1	-	-
Diarrhoea and fever during infancy	0.43 (0.03 – 6.01) p = 0.6	0.31 (0.02 – 5.04) p = 0.4	0.34 (0.02 – 5.88) p = 0.5
Rash and fever during infancy	-	-	-
Frequency of illness in the first year of life	1.06 (0.07 – 16.96) p = 1	1.41 (0.09 – 22.97) p = 0.8	0.87 (0.05 – 14.93) p = 0.9
Fever in last 14days	1.84 (0.12 – 29.53) p = 0.7	2.66 (0.16 – 43.90) p = 0.5	1.94 (0.12 – 32.87) p = 0.7
Diarrhoea in last 14 days	-	-	-
Cough in last 14 days	-	-	-
Difficult breathing in 14 days	-	-	-
Child systolic blood pressure (n=902)	-4.80 (-23.59 – 13.99) p = 0.6	-5.798 (-24.52 – 12.92) p = 0.5	-6.21 (-25.22 – 12.80) p = 0.5
Child diastolic blood pressure	-8.42 (-26.90 – 10.06) p = 0.4	-9.632 (-27.91 – 8.65) p = 0.3	-11.1 (-29.61 – 7.45) p = 0.2

LBW_LPI_SGA	Model I	Model II	Model III
Neonatal death	2.23 (0.90 – 5.51) p = 0.08	1.95 (0.78 – 4.86) p = 0.2	1.66 (0.63 – 4.36) p = 0.3
Infant death	2.18 (1.02 – 4.67) p = 0.05		1.82 (0.81 – 4.08) p = 0.2
Child death	2.13 (1.03 – 4.40) p = 0.04	1.98 (0.95 – 4.12) p = 0.07	1.87 (0.87 – 4.03) p = 0.1
Stunting	2.60 (1.75 – 3.89) p = 0.001	2.82 (1.79 – 4.42) p = 0.001	2.58 (1.64 – 4.07) p = 0.001
Wasting	2.64 (1.46 – 4.77) p = 0.001	2.23 (1.22 – 4.09) p = 0.01	2.56 (1.34 – 4.90) p = 0.004
Underweight	3.44 (2.40 – 4.94) p = 0.001	3.40 (2.26 – 5.11) p = 0.001	3.59 (2.35 – 5.48) p = 0.001
Cough and fever during infancy	1 (0.48 – 2.08) p = 1	0.93 (0.44 – 1.96) p = 0.9	0.97 (0.45 – 2.10) p = 0.9
Diarrhoea and fever during infancy	1.06 (0.72 – 1.56) p = 0.8	1.03 (0.70 – 1.53) p = 0.9	1.02 (0.68 – 1.54) p = 0.9
Rash and fever during infancy	0.73 (0.41 – 1.32) p = 0.3	0.69 (0.38 – 1.26) p = 0.3	0.70 (0.38 – 1.29) p = 0.3
Frequency of illness in the first year of life	1.30 (0.91 – 1.85) p = 0.2	1.34 (0.94 – 1.92) p = 0.1	1.44 (0.99 – 2.09) p = 0.06
Fever in last 14days	1.62 (1.14 – 2.31) p = 0.008	1.59 (1.10 – 2.29) p = 0.01	1.66 (1.14 – 2.42) p = 0.009
Diarrhoea in last 14 days	1.08 (0.66 – 1.78) p = 0.8	1.05 (0.63 – 1.75) p = 0.9	1.05 (0.62 – 1.77) p = 0.9
Cough in last 14 days	1.24 (0.87 – 1.78) p = 0.2	1.33 (0.91 – 1.93) p = 0.1	1.31 (0.90 – 1.93) p = 0.2
Difficult breathing in 14 days	1.28 (0.69 – 2.36) p = 0.4	1.37 (0.73 – 2.57) p = 0.3	1.43 (0.74 – 2.76) p = 0.3
Child systolic blood pressure	0.992 (-1.365 -3.349) p = 0.4	0.373 (-1.989 – 2.735) p = 0.8	0.368 (-2.056 – 2.793) p = 0.8
Child diastolic blood pressure	1.919 (-0.397 – 4.235) p = 0.1	1.486 (-0.819 – 3.791) p = 0.2	1.251 (-1.113 – 3.616) p = 0.3

NBW_LPI_AGA	Model I	Model II	Model III
Neonatal death	0.50 (0.15 – 1.68) p = 0.3	0.56 (0.16 – 1.92) p = 0.4	0.58 (0.17 – 2.02) p = 0.4
Infant death	0.57 (0.22 – 1.50) p = 0.3		0.61 (0.23 – 1.63) p = 0.3
Child death	0.62 (0.26 – 1.51) p = 0.3	0.60 (0.25 – 1.45) p = 0.3	0.62 (0.25 – 1.55) p = 0.3
Stunting	0.44 (0.33 – 0.60) p = 0.001	0.41 (0.29 – 0.59) p = 0.001	0.42 (0.29 – 0.60) p = 0.001
Wasting	0.70 (0.35 – 1.41) p = 0.70	0.85 (0.41 – 1.73) p = 0.7	0.81 (0.39 – 1.69) p = 0.6
Underweight	0.51 (0.36 – 0.71) p = 0.001	0.52 (0.36 – 0.76) p = 0.001	0.53 (0.36 – 0.78) p = 0.001
Cough and fever during infancy	0.73 (0.40 – 1.38) p = 0.3	0.76 (0.42 – 1.40) p = 0.4	0.68 (0.36 – 1.29) p = 0.2
Diarrhoea and fever during infancy	0.98 (0.71 – 1.37) p = 0.9	1.03 (0.73 – 1.45) p = 0.9	1.08 (0.76 – 1.54) p = 0.7
Rash and fever during infancy	1.28 (0.82 – 2.02) p = 0.3	1.33 (0.84 – 2.09) p = 0.2	1.34 (0.84 – 2.16) p = 0.2
Frequency of illness in the first year of life	0.94 (0.69 – 1.28) p = 0.7	0.94 (0.69 – 1.28) p = 0.7	0.90 (0.65 – 1.25) p = 0.9
Fever in last 14days	0.61 (0.44 – 0.86) p = 0.004	0.64 (0.46 – 0.91) p = 0.01	0.61 (0.43 – 0.88) p = 0.007
Diarrhoea in last 14 days	0.65 (0.40 – 1.05) p = 0.08	0.68 (0.41 – 1.11) p = 0.1	0.72 (0.43 – 1.20) p = 0.7
Cough in last 14 days	0.70 (0.50 – 0.97) p = 0.03	0.69 (0.49 – 0.97) p = 0.03	0.68 (0.48 – 0.96) p = 0.03
Difficult breathing in 14 days	0.57 (0.30 – 1.11) p = 0.09	0.56 (0.29 – 1.09) p = 0.09	0.54 (0.27 – 1.08) p = 0.08
Child systolic blood pressure	-0.18 (-2.24 – 1.89) p = 0.9	-0.009 (-2.075 – 2.057) p = 0.9	0.065 (-2.052 – 2.182) p = 1
Child diastolic blood pressure	-0.206 (-2.232 – 1.820) p = 0.8	-0.104 (-2.122 – 1.913) p = 0.9	-0.232 (-2.297 – 1.833) p = 0.8

NBW_API_SGA	Model I	Model II	Model III
Neonatal death	-	-	-
Infant death	-	-	-
Child death	-	-	-
Stunting	1.29 (0.77 – 2.14) p = 1.29	1.34 (0.74 – 2.42) p = 0.3	1.40 (0.77 – 2.56) p = 0.3
Wasting	0.44 (0.11 – 1.84) p = 0.44	0.35 (0.08 – 1.50) p = 0.4	0.17 (0.02 – 1.25) p = 0.08
Underweight	1.53 (0.94 – 2.50) p = 0.09	1.54 (0.88 – 2.72) p = 0.1	1.65 (0.92 – 2.95) p = 0.09
Cough and fever during infancy	2.18 (0.52 – 9.13) p = 0.3	2.15 (0.51 – 9.07) p = 0.3	2.55 (0.59 – 10.97) p = 0.2
Diarrhoea and fever during infancy	1.12 (0.65 – 1.95) p = 0.7	1.11 (0.64 – 1.95) p = 0.7	1.06 (0.60 – 1.89) p = 0.8
Rash and fever during infancy	1.68 (0.87 – 3.25) p = 0.1	1.68 (0.87 – 3.26) p = 0.1	1.73 (0.87 – 3.46) p = 0.1
Frequency of illness in the first year of life	1.06 (0.65 – 1.74) p = 0.8	1.02 (0.62 – 1.69) p = 0.9	1.08 (0.64 – 1.82) p = 0.8
Fever in last 14days	1.25 (0.76 – 2.05) p = 0.4	1.13 (0.68 – 1.89) p = 0.6	1.23 (0.73 – 2.10) p = 0.4
Diarrhoea in last 14 days	1.34 (0.70 – 2.57) p = 0.4	1.18 (0.61 – 2.30) p = 0.6	1.24 (0.62 – 2.48) p = 0.6
Cough in last 14 days	1.21 (0.73 – 1.99) p = 0.5	1.03 (0.61 – 1.74) p = 0.9	1.16 (0.68 – 1.98) p = 0.6
Difficult breathing in 14 days	2.18 (1.06 – 4.46) p = 0.03	2.03 (0.97 – 4.22) p = 0.06	1.92 (0.89 – 4.16) p = 0.1
Child systolic blood pressure	0.206 (-3.095 – 3.508) p = 0.9	0.381 (-2.915 – 3.676) p = 0.8	0.345 (-3.040 – 3.729) p = 0.8
Child diastolic blood pressure	-1.956 (-5.202 – 1.289) p = 0.2	-1.884 (-5.101 – 1.333) p = 0.3	-1.368 (-4.669 – 1.934) p = 0.4

NBW_LPI_SGA	Model I	Model II	Model III
Neonatal death	0.65 (0.22 – 1.92) p = 0.4	0.61 (0.21 – 1.81) p = 0.4	0.70 (0.22 – 2.23) p = 0.6
Infant death	0.54 (0.21 – 1.42) p = 0.2		0.62 (0.26 – 1.68) p = 0.3
Child death	0.59 (0.24 – 1.43) p = 0.24	0.68 (0.27 – 1.69) p = 0.4	0.72 (0.28 – 1.83) p = 0.5
Stunting	1.28 (0.94 – 1.75) p = 0.1	1.20 (0.84 – 1.72) p = 0.3	1.22 (0.85 – 1.75) p = 0.3
Wasting	0.94 (0.50 – 1.79) p = 0.9	0.87 (0.46 – 1.66) p = 0.7	0.99 (0.50 – 1.96) p = 1
Underweight	1.00 (0.73 – 1.37) p = 1	1.03 (0.73 – 1.47) p = 0.9	1.00 (0.70 – 1.44) p = 0.9
Cough and fever during infancy	0.77 (0.42 – 1.42) p = 0.4	0.77 (0.42 – 1.41) p = 0.4	0.86 (0.45 – 1.64) p = 0.6
Diarrhoea and fever during infancy	0.92 (0.67 – 1.28) p = 0.6	0.89 (0.64 – 1.24) p = 0.5	0.90 (0.63 – 1.27) p = 0.5
Rash and fever during infancy	1.21 (0.77 – 1.89) p = 0.4	1.20 (0.76 – 1.89) p = 0.4	1.18 (0.73 – 1.91) p = 0.5
Frequency of illness in the first year of life	1.06 (0.78 – 1.44) p = 0.7	1.06 (0.78 – 1.44) p = 0.7	1.06 (0.76 – 1.47) p = 0.7
Fever in last 14days	1.06 (0.77 – 1.45) p = 0.7	1.01 (0.73 – 1.39) p = 1	1.02 (0.73 – 1.43) p = 0.9
Diarrhoea in last 14 days	1.11 (0.72 – 1.70) p = 0.6	1.03 (0.67 – 1.59) p = 0.9	1.03 (0.65 – 1.62) p = 0.9
Cough in last 14 days	0.97 (0.72 – 1.33) p = 0.9	0.91 (0.66 – 1.26) p = 0.6	0.94 (0.67 – 1.32) p = 0.7
Difficult breathing in 14 days	1.34 (0.79 – 2.29) p = 0.3	1.33 (0.77 – 2.30) p = 0.3	1.23 (0.70 – 2.18) p = 0.5
Child systolic blood pressure	-0.449 (-2.484 – 1.586) p = 0.7	0.411 (-2.445 – 1.624) p = 0.7	-0.568 (-2.696 – 1.560) p = 0.6
Child diastolic blood pressure	-1.013 (-3.014 – 0.987) p = 0.3	-0.862 (-2.848 – 1.125) p = 0.4	-0.449 (-2.526 – 1.627) p = 0.7

NBW_API_AGA	Model I	Model II	Model III
Neonatal death	0.76 (0.26 – 2.25) p = 0.6	0.87 (0.29 – 2.60) p = 0.8	0.78 (0.25 – 2.44) p = 0.7
Infant death	0.83 (0.34 – 2.06) p = 0.7		0.87 (0.34 – 2.22) p = 0.8
Child death	0.72 (0.30 – 1.75) p = 0.5	0.73 (0.30 – 1.79) p = 0.5	0.69 (0.27 – 1.75) p = 0.4
Stunting	0.67 (0.49 – 0.92) p = 0.01	0.73 (0.51 – 1.05) p = 0.08	0.73 (0.51 – 1.05) p = 0.09
Wasting	0.42 (0.18 – 1.0) p = 0.05	0.50 (0.21 – 1.20) p = 0.1	0.49 (0.20 – 1.19) p = 0.1
Underweight	0.47 (0.33 – 0.67) p = 0.001	0.48 (0.32 – 0.71) p = 0.001	0.45 (0.30 – 0.68) p = 0.001
Cough and fever during infancy	1.89 (0.84 – 4.26) p = 0.1	1.97 (0.87 – 4.44) p = 0.1	1.83 (0.79 – 4.23) p = 0.1
Diarrhoea and fever during infancy	1.00 (0.71 – 1.42) p = 1	1.04 (0.73 – 1.49) p = 0.8	1.04 (0.72 – 1.50) p = 0.8
Rash and fever during infancy	0.66 (0.38 – 1.14) p = 0.1	0.68 (0.40 – 1.18) p = 0.2	0.65 (0.37 – 1.14) p = 0.1
Frequency of illness in the first year of life	0.81 (0.59 – 1.12) p = 0.2	0.82 (0.59 – 1.13) p = 0.2	0.81 (0.57 – 1.14) p = 0.2
Fever in last 14 days	0.92 (0.66 – 1.28) p = 0.6	1.01 (0.72 – 1.43) p = 0.9	1 (0.70 – 1.42) p = 1
Diarrhoea in last 14 days	1.02 (0.73 – 1.41) p = 0.9	1.14 (0.81 – 1.61) p = 0.5	1.11 (0.78 – 1.58) p = 0.6
Cough in last 14 days	1.11 (0.71 – 1.74) p = 0.7	1.25 (0.79 – 1.99) p = 0.3	1.18 (0.73 – 1.90) p = 0.5
Difficult breathing in 14 days	0.74 (0.39 – 1.40) p = 0.4	0.74 (0.38 – 1.43) p = 0.4	0.81 (0.41 – 1.58) p = 0.5
Child systolic blood pressure	0.586 (-1.553 – 2.724) p = 0.6	1.002 (-1.156 – 3.159) p = 0.4	1.088 (-1.099 – 3.274) p = 0.3
Child diastolic blood pressure	0.477 (-1.657 – 2.551) p = 0.7	0.617 (-1.490 – 2.725) p = 0.6	0.538 (-1.596 – 2.673) p = 0.6