

Size at birth and cognitive function among rural adolescents: a life course epidemiology study protocol of the Kisalaya cohort in Mysuru, South India

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ABSTRACT

Introduction It is proven that adverse intrauterine environment results in ‘early life programming,’ alterations in metabolism and physiological development of the fetus, often termed as ‘Developmental Origins of Health and Disease’ (DOHaD) resulting in a smaller size at birth, greater non-communicable diseases (NCD) risk factors during childhood and adolescence, and cardiometabolic disorders in adulthood. Nevertheless, very few studies have examined the relationship between DOHaD programming and cognition. This study aims to examine if impaired prenatal growth indicated by birth weight is associated with cognition among adolescents in the Kisalaya cohort, a rural birth cohort in South India, thus providing newer insights into DOHaD programming for adolescent mental health in a low-income and middle-income country setting.

Methods and analysis Kisalaya cohort was established in 2008, to provide integrated antenatal care and HIV testing using mobile clinics to improve maternal and child health outcomes. This cohort included pregnant women residing in 144 villages of Mysuru Taluk (rural) who received antenatal care through mobile clinics and delivered their children between 2008 and 2011. Data related to mother–infant dyads for all pregnant women who received care in the Kisalaya programme are available for this study. Presently, children born to women who received care through Kisalaya are adolescents between 10 and 12 years. At this point, information would be collected on sociodemographic data and assessments of mental health, stressful life events, cognition, vision, speech, language, hearing and anthropometric measures would be done and relevant maternal data and child data, available from the cohort would be retracted for analysis. We plan to retrace as many adolescents as possible out of 1544 adolescents who are currently available for study excluding twins, abortions, stillbirths and postdelivery deaths. Analyses will be extended to construct a life course pathway for cognition using structural equation modelling.

INTRODUCTION

Globally, an estimated 16% of newborns have low birth weight¹ and this burden is particularly high among low-income and

What is already known on this topic?

- ▶ Many studies conducted in high-income countries and Indian settings have shown a direct correlation of low birth weight with cognition. However, these findings were from the urban population and additionally, none of these studies have considered the influence of maternal health during the antenatal period on cognitive outcomes of the child.

What this study hopes to add?

- ▶ This study is unique in comparison with previous studies conducted in this direction as it would be conducted in the rural adolescent population of a well-established cohort, which has data of mothers collected during the antenatal period and hence would contribute in understanding the correlation of not only the birth weight, but also the influence of maternal factors and various life course events on cognition in rural population.

middle-income countries (LMIC).² Studies from both high-income countries and LMICs have established maternal health as an important determinant of growth, development, mental health and social outcomes of the offspring. During the 1980s, Professor David Barker³ proposed that adverse intrauterine environment resulted in ‘the early life programming’—alterations in metabolism and physiological development of the fetus, (often termed as the Developmental Origins of Health and Disease (DOHaD) hypothesis) results in a smaller size at birth, greater non-communicable disease (NCD) risk factors during childhood and adolescence, and cardiometabolic disorders (obesity, cardiovascular disease, diabetes, stroke, hypertension and dyslipidaemia) in adulthood.^{4–7}



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While substantial epidemiological evidence exists for the DOHaD hypotheses related to chronic physical health conditions, little is known about the relationship of low birth weight with brain health including cognition. Similar to other NCD risk factors, several studies conducted before have indicated that cognitive development is influenced by both genetic and environmental components, with environmental factors like fetal exposures also playing a major role in its aetiology. Studies examining the associations of birth weight with cognition among adolescents were mostly conducted in high-income countries, and have shown mixed results, with a majority reporting a possible relationship, while others showing no relationship.^{8–15} Overall, previous literature shows modest measures of association, indicating that while there may indeed exist evidence for fetal origins for the cognitive outcome, several other biological, social and environmental factors across the life course may have a cumulative effect on the development.

Indian being a country with the second-largest population, still has a high burden of low birth weight, India represents a critical site for studying the early life influences on cognition.² Hence, with this background, the study aims to examine if impaired prenatal condition, indicated by birth weight is associated with cognition among adolescents in the Kisalya cohort, a rural birth cohort in South India, thus providing newer insights into the DOHaD programming for adolescent mental health in an LMIC setting.

KISALAYA COHORT

Kisalya birth cohort was set up between 2008 and 2012 to explore the acceptability and effectiveness of integrated HIV testing and antenatal care delivered through mobile clinics to improve maternal and child health outcomes in rural Mysuru, Karnataka, India. The cohort profile has been published elsewhere.¹⁶ In brief, the cohort comprises 1675 pregnant women who received antenatal care from 144 villages in rural Mysuru and

their offspring who were followed up at 2 weeks and 6 months following postdelivery (figure 1). A total of 141 offspring deaths and lost to follow-up during the postnatal follow-up period (abortions/stillbirths: n=76; infant deaths: n=65 singletons and twins: n=04) will be excluded in the current study. Hence a sample size of 1544 adolescents would be eligible to participate in the current study. Data of the Kisalya cohort collected during 2008–2012, includes information on the sociodemographic status of the woman and her family, details of present and previous pregnancies, reports of all routine antenatal investigations and information on birth weight of the child, breastfeeding practices, birth preparedness, details of delivery and health of the mother and the child during the immediate postnatal period.

The offspring of these mothers (born between 2008 and 2012) are now adolescents aged 10–11 years. The study team has kept in touch with all the mother–infant dyads informally from 2012 to the present though no data were collected during this period. We will retrace and examine the surviving members of this cohort for the study.

Objectives of the study

The primary objective is to assess the relationship between birth weight and cognitive outcome.

The secondary objective is to assess the influence of other confounders and covariate across life course on cognitive outcome.

Primary and secondary outcome

Primary outcome: The effect of birth weight on composite cognitive outcome.

Secondary outcome: The effect of confounders/covariates which include, depression scores, vision, hearing, speech, language abilities, head circumference (proxy indicator for brain reserve), and maternal factors during the antenatal period on the composite cognitive outcome.

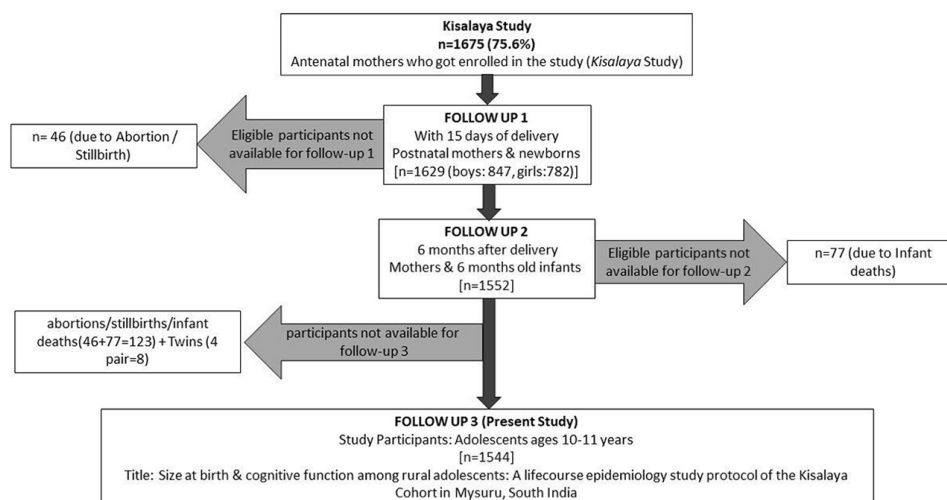


Figure 1 Follow-up of Kisalya cohort.

Table 1 Data collected in 2008–2012 of the Kisalaya cohort database, of relevance to the current study

Data collected previously (2008–2012)

Data of	Variables available for analysis
Mother	<ul style="list-style-type: none"> ▶ Sociodemographic variables ▶ Education ▶ Occupation ▶ Family structure and composition ▶ Parity ▶ Marital status ▶ Data related to maternal stress ▶ Data related to domestic violence ▶ Data related to maternal health profile during the antenatal period
Child	<ul style="list-style-type: none"> ▶ Birth weight ▶ Gestational age at birth

METHODS AND ANALYSIS

Study design and setting

This is a longitudinal follow-up of a well-established birth cohort in rural Mysuru, South India. We will retrace all the singleton offsprings born to mothers enrolled and followed up in the Kisalaya cohort between 2008 and 2012 (n=1544, excluding the abortions, stillbirths, infant deaths and twins) and invite them to participate in an assessment that will last approximately 1.5–2 hours. Maternal and child data, relevant to the current study would also be retracted from the database of the Kisalaya cohort

Interviews and measures at present

Information from the database

Data collected between 2008 and 2011 for the cohort of relevance to this project will be extracted from the Kisalaya cohort database (table 1).

Interviews and questionnaires

The following assessments will be conducted for adolescents from 2019 onwards (table 2).

Mental Health Assessments

1. The severity of depression will be measured as a continuous variable by the administration of Patient Health Questionnaire-Adolescents,¹⁷ a 9-item questionnaire that has been validated and adapted for use among south Indians. The instrument measures symptoms of depression related to mood, behaviour, sleep and cognition.
2. Cognition would be measured by administration of the following battery of tests derived from Weschler's Intelligence Scale for Children¹⁸ IV Indian adaptation by a trained clinical psychologist for digit span, matrix reasoning, picture completion, block design and assessment of Immediate and delayed recall by Word list recall test. Semantic perception and Verbal Fluency would also be assessed.

3. Adolescent Life Events Stress Scale will be administered for assessing the effects of stressful life events.¹⁹ The scale consists of 41 items and provides life change unit scores for important stressful life events in the child's life including changes in the family and the school environment.
4. The Child Trauma Questionnaire²⁰ used would measure the severity of emotional abuse and neglect, physical abuse and neglect while growing up as a child or a teenager.

Assessment of speech language and hearing

1. Assessment of speech by evaluating the speech functions such as articulation, fluency and voice using screening tools such Kannada articulation test,²¹ Stuttering severity instrument, consensus of auditory-perceptual evaluation of voice.²²
2. Assessment of language by profiling language comprehension and production in terms of syntax, semantics, phonology using Linguistic profile test.²³
3. Assessment of hearing using screening audiometer at speech frequencies such as 500 Hz, 1 kHz, 2 kHz.
4. Screening of vision will be done using Snellen's Chart: The chart will be placed ensuring bright light. The participant will be placed about six m from the chart and asked to read the letters on the Snellen's chart (either English/ local language) from below covering one eye at a time. If the participant is wearing spectacles, he/she will be asked to read the chart with and without wearing spectacles and visual acuity of each eye would be recorded.

Physical assessments

a. Anthropometric measures:

1. Height and weight will be recorded with the help of a wall mount tape and mechanical weighing scale, respectively, by standardised procedures. Please provide more details here in terms of units and how the measurements will be done.
 2. Head circumference will be measured using a non-stretchable tape by wrapping it around the widest possible circumference—from the most prominent part of the forehead (often 1–2 fingers above the eyebrow) and around to the widest part of the back of the head. The largest measurement after taking three measurements would be considered.
 3. Leg length which is the measurement between the Anterior Superior Iliac Spine to the medial malleolus will be measured using a non-stretchable tape in centimetres.
 4. Waist circumference will be measured at the standing position by measuring the circumference of the waist just above the hip bone at the end of expiration in centimetres.
 5. Hip circumference will be measured at the widest part of the hip in centimetres.
- ##### b. Staging of puberty: By self-administered questionnaire based on the Tanner staging. This questionnaire has

Table 2 Instruments, assessments and investigations in the study protocol**Data to be collected now (2019 onwards)**

Data of	Variables
Parents	Sociodemographic variables including socioeconomic status, education, occupation, family structure and composition (type of family, family size, place of residence, etc)
Adolescent Children	<p><u>Anthropometry (by standardised procedures)</u></p> <ul style="list-style-type: none"> ▶ Height in cms ▶ Weight in kilo gram ▶ Waist circumference in centimetre ▶ Hip circumference in centimetre ▶ Head circumference in centimetre ▶ Leg length in centimetre <p><u>Assessment of mental health</u></p> <ul style="list-style-type: none"> ▶ Child Trauma Questionnaire ▶ Patient Health Questionnaire-Adolescents to assess the depression scores ▶ Adolescent Life Events Stress Scale to assess the stressful life events <p><u>Assessment of Cognition</u></p> <ul style="list-style-type: none"> ▶ Digit span, Matrix Reasoning, Picture completion, Block design from Wechsler's Intelligence Scale for Children IV Indian adaptation²¹ ▶ Assessment of Immediate and delayed recall by Word list recall test ▶ Assessment of semantic perception ▶ Assessment of verbal fluency <p><u>Vision</u></p> <ul style="list-style-type: none"> ▶ Snellen's Chart <p><u>Audiological Evaluation:</u></p> <ul style="list-style-type: none"> ▶ Otoscopic evaluation ▶ Pure tone audiometry ▶ Immittance: Tympanometry and relaxometry <p><u>Speech evaluation</u></p> <ul style="list-style-type: none"> ▶ Oral peripheral mechanism ▶ Examination of structure and functions of oral structures ▶ Assessment of voice by maximum phonation duration and s/z ratio ▶ Assessment of fluency by stuttering severity ▶ Assessment of articulation by diadochokinetic rate <p><u>Language evaluation</u></p> <ul style="list-style-type: none"> ▶ Linguistic profile by phonology ▶ Morphology, syntax and semantics ▶ Reception ▶ Expression ▶ Reading and writing <p><u>Staging of puberty</u></p> <ul style="list-style-type: none"> ▶ A self-administered questionnaire based on tanner staging

both the description and picture depiction that would help in better self-reporting of pubertal stage²⁴

Power calculation and statistical analysis

The sample size from the kisalaya birth cohort available for this study, after accounting for the 20% estimated losses to follow and non-participation of participation is 1235 including both boys and girls. Using a test at the 5% significance level, the study will have 80% power to detect an association of 0.105 SD of a continuous outcome (cognitive score) per SD of continuous exposure (birth weight).

The analysis will be done in two steps:

In the first step: Scores from each of five domains of Cognition will be subjected to data reduction techniques like principal component analysis (after log transformation of the scores in case the data are not normally distributed) to derive composite cognitive scores (in SD), which

is the primary outcome variable of interest. The relationship between birth weight and composite cognitive scores will be examined with simple linear regression initially. Also, sensitivity analysis will be done to examine if the relationship between the birth weight and the composite cognitive score is different between the groups of interest (eg, between gender, between lower and higher socioeconomic position groups, etc).

In the second step: Based on the range of composite cognitive score, a score of less than 0.5 SD adjusted to gender will be considered as a lower cognitive function (a binary outcome). The relationship between birth weight and binary cognitive outcomes will be examined by conducting logistic regression analyses. Further, we will construct multivariable logit models by making serial adjustments for potential confounders and covariates (as listed in figure 2). That is, we will extend the analyses

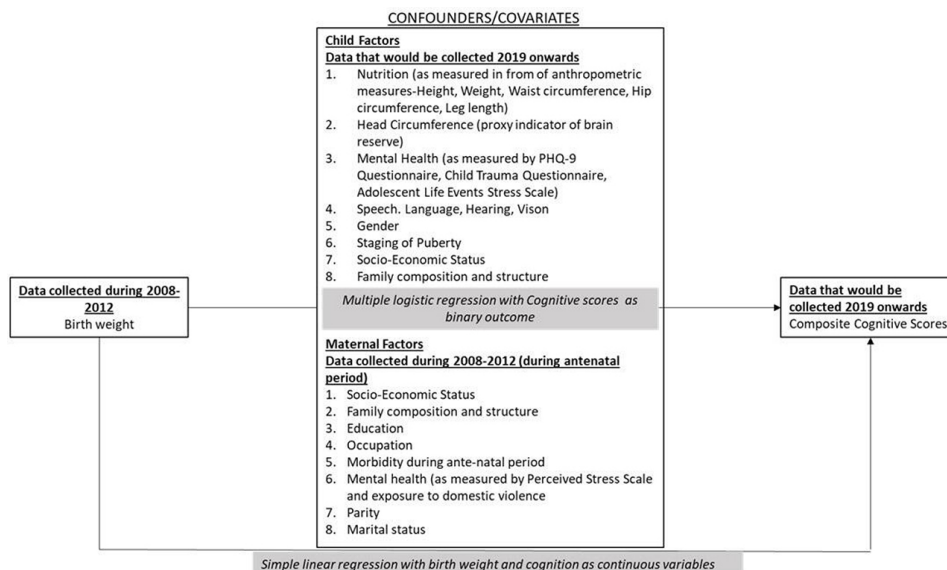


Figure 2 Variables included for statistical analysis.

by employing structural equation modelling, a multivariable statistical analysis technique for analysing structural relationships. This includes factor analysis and multiple regression analysis to explore the structural relationship between measured variables and latent constructs (cognition) to build a life course model for cognitive development in this cohort.

Patient and public involvement

It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research

ETHICS AND DISSEMINATION

Since the study participants are adolescents between the age group of 10 and 12 years, oral consent, as well as written assent, will be taken from them, and written consent from their parents/guardian will be obtained as per the Indian Council of Medical Research guidelines 2018.²⁵ The ethical clearance for the study has been taken from the Public Health Research Institute of India, Mysuru, India. Adolescents requiring counselling or any other therapy/ management for the ailments discovered during the project are provided with appropriate referrals. The research team has been well trained with standard operating procedures to deal with any such issues. The research team also consists of psychiatrist, psychologist and speech pathologists who are from Mysuru (The place where the project will be conducted). In the event of even the slightest clue of distress to the child during the interview, the research team is instructed to stop the interview. Also to mention the Public health Research Institute of India, where the project is being conducted holds a great connection with this rural population since 2008.

The findings from this study will be disseminated locally and at international meetings and will be published in a peer-reviewed journal.

DISCUSSION

DOHaD, that is, fetal programming for chronic diseases in adulthood is among the of several explanations put forth to fill the gap in the knowledge on etiopathogenesis for NCDs. While substantial epidemiological evidence exists for DOHaD concerning chronic physical health conditions, little is known about the early life influences on the cognitive outcomes of the child.

Much remains unknown about the developmental mechanism of cognition and investigating the potential fetal origins concerning cognitive outcomes, would be key to improving our knowledge of the causal mechanism and intergenerational effects on brain health and would be critical to the work of healthcare providers in improving health outcomes for women and children throughout their lifetimes.

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Contributors Study concept and design: SMC, MK, PM, KK, PD and JN. Drafting of the manuscript: SMC, MK, PM, KK, CVU, SPG, PD, JN, KR, AK and AA; Acquisition of data: SMC, CVU, P.J, SPG, AK and AA; Critical revision of the manuscript for important intellectual content: SMC, MK, PM, KK, CVU, P.J, SPG, PD and JN.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement The study data would not be freely available, but the team would welcome collaborations with other researchers. Data set (in Table 2) will be made available for those participating in the ongoing study.

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