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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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Keywords:	Adolescent Health, Child Psychiatry, Epidemiology, Psychology, Obesity

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Title: 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 foetus, often termed as 'Developmental Origins of Health and Disease'(DOHaD) resulting in smaller size at birth, greater NCD (Non Communicable Diseases) risk factors during childhood and adolescence, and cardiometabolic disorders in adulthood. Nevertheless, very few studies have examined relationship between DOHaD programming and Mental Health. This study aims to examine if impaired prenatal growth (directly related to maternal factors), indicated by birth weight is associated with depression scores and cognition among adolescents in *Kisalaya* cohort, a rural birth cohort in south India, thus providing newer insights into DOHaD programming for adolescent mental health in a Low 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 reduce adverse birth outcomes and pediatric HIV infections. 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* program are available for this study. Presently, children born to women who received care through *Kisalaya* are adolescents between 10 to 12 years. In the current study, information would be collected on sociodemographic data and assessments of mental health, stressful life events, cognition, vision, speech, language, hearing and anthropometric measures, blood pressure and correlated with birth weight adjusted to gestational age and other relevant parameters. We plan to retrace as many adolescents as possible out of 1,544 adolescents who are currently available for study excluding twins, abortions, stillbirths and post-delivery deaths. Analyses will be extended to construct life course pathway for mental health using structural equation modelling.

Keywords: Birth weight, Adolescence, Mental Health, Cohort, Rural, India

Introduction:

Globally, an estimated 16% of newborns have low birthweight[1] and this burden is particularly high among low- and middle-income countries (LMIC).[2] Studies from both high-income and LMICs have established maternal health as an important determinant of growth, development, mental health and social outcomes of the offspring. During the 1980's, Prof David Barker[7] proposed that adverse intrauterine environment resulted in 'the early life programming' - alterations in metabolism and physiological development of the foetus, (often termed as the DOHaD-Developmental Origins of Health and Disease hypothesis) resulting in smaller size at birth, greater NCD risk factors during childhood and adolescence, and cardiometabolic disorders (obesity, cardiovascular disease, diabetes, stroke, hypertension and dyslipidaemia) in adulthood.[4-7]

The reported rates of adolescent depression are much higher in India when compared to higher income settings. Depression during adolescence is related to long term adverse outcomes including but not limited to poorer physical health including stunting, behavioral difficulties and

poor social functioning, lower cognition, higher rates of substance abuse, poor quality of life and higher suicide rates.[8] Similar to other NCD risk factors, depression is thought to have its origins in early life. While substantial epidemiological evidence exists for the DOHaD hypotheses related to chronic physical health conditions, little is known about the relationship with mental health outcomes. The developmental mechanism of depression is known to have both genetic and environmental components, but genetic studies show that major depressive disorder has a lower heritability than other neuropsychiatric disorders like bipolar disorder and schizophrenia, indicating that environmental factors like foetal exposures may play a considerable role in its aetiology.[9]

Previous studies examining the associations of birthweight with depression among adolescents, were mostly conducted in High Income Countries, and have showed mixed results, with a majority reporting a possible but weak inverse relationship, while others showing no relationship. A meta-analysis of 26 cohort studies showed a weak association between low birthweight and depression during adulthood, but with limitations including publication and reporting bias.[7,9,10] Some previous studies in this direction are older, and thus might not reflect the impact of recent advances in obstetrics and neonatal care on infant health outcomes.[9-11] Overall, previous literature shows modest measures of association, indicating that while there may indeed exist an evidence for foetal origins of depression, several other biological, social and environmental factors across the life course may have a cumulative effect on the development of this condition.

As the world's second largest country with a growing incidence of mental disorders and suicides among young adults, whilst still having high burden of low birthweight, India represents a critical site for studying the early life influences on adolescent mental health.[12-17] Hence, this study aims to examine if impaired prenatal growth (directly related to maternal factors), indicated by birthweight is associated with depression scores and 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 a LMIC setting.

Kisalaya **Cohort**

Kisalaya Birth Cohort was set up between 2008-2012 to explore the acceptability and effectiveness of an integrated HIV testing and antenatal care delivered through mobile clinics to improve maternal and child health outcomes in rural Mysuru, Karnataka, India. In brief, the cohort comprises of 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 post-delivery [Figure 1]. A total of 141 offsprings deaths and losses to follow-up during postnatal follow-up period (Abortions/Stillbirths: n =76; Infant deaths: n = 65 singletons and Twins: n=04) will be excluded in the current study. Data obtained from the *Kisalaya* cohort includes information on sociodemographic status of the woman and her family, details of present and previous pregnancies, reports of all routine antenatal investigations and information on birthweight of the child, breastfeeding practices, birth preparedness, details of delivery and health of the mother and the child during immediate postnatal period. [Table 1]

The offspring of these mothers (born between 2008-2012) are now adolescents aged 10 to 11 years. The study team has kept in touch with all the mother-infant dyads informally between 2012

and 2019 though no data was collected during this period. We will retrace and examine the surviving members of this cohort for this study between 2020 and 2021.

Objectives of the study:

The primary objective of this study is to examine the life course determinants of mental health among rural adolescents in South India. We will examine a specific hypothesis that low birthweight, after adjusting for gestational age would be inversely related to depression, and directly related to other indicators of brain health such as cognitive function, vision, hearing, speech and language abilities, and head circumference (proxy indicator for brain reserve) in this cohort. In addition, we will report the prevalence of depression and its associations with additional exposures across the life course.

a. *Current factors:* age, gender, current socioeconomic position, nutritional status (indicators from anthropometric measurements: BMI (Body Mass Index), height, leg length and head circumference), violence at home, life events and stress, and blood pressure. [Table 1]

b. *Childhood factors*: immunization status, exposure to domestic violence and physical abuse, behavioral difficulties at school.

c. other indicators of adversity in early life: socioeconomic status of parents, parental education, maternal anemia, domestic violence, maternal stress during prenatal period.

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 off springs born to mothers enrolled and followed up in the *Kisalaya* cohort between 2008-12 (n=1496, excluding the abortions, stillbirths, infant deaths and twins) and invite them to participate in an assessment [Table 2] that will last approximately 1.5 to 2 hours.

Interviews and measures:

1. *Information from the database:* Data collected between 2008-2011 for the cohort of relevance to this project has been extracted from the *Kisalaya* cohort database [Table1].

2. *Interviews and questionnaires:* The following assessments will be conducted for the adolescents in the current study. [Table 2]
   a. Mental Health Assessments: Severity of Depression will be measured as a continuous variable by administration of Patient Health Questionnaire- Adolescents (PHQ-A)[18], a 9-item questionnaire that has been validated and adapted for use among south Indians. The instrument measures symptoms of depression related to mood, behavior, sleep and cognition. Cognition would be measured by administration of the following battery of tests derived from Weschler's Intelligence scale for Children (WISC)[19] 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. Adolescent life events stress

scale (ALESS) will be administered for assessing effects of stressful life events[20]. 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.

b. Assessment of Speech Language and Hearing:
   i. *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 (SSI), Consensus of auditory-perceptual evaluation of voice (CAPE-V). [22]
   ii. *Assessment of Language* by profiling language comprehension and production in terms of syntax, semantics, phonology using Linguistic profile test (LPT).[23]
   iii. *Assessment of Hearing* using screening audiometer at speech frequencies such as 500 Hz, 1kHz, 2 kHz.[24]
   iv. Screening of *Vision* will be done using Snellen's Chart: The chart will be placed ensuring bright light. Participant will be placed about 6 meters 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.

c. Physical assessments
   i. *Height* and *Weight* will be recorded with the help of a wall mount tape and mechanical weighing scale respectively by standardized procedures. Please provide more details here in terms of units and how the measurements will be done.

   ii. *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.

   iii. *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.

   iv. *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.

   v. *Hip circumference* will be measured at the widest part of the hip in centimetres.

Statistical Analysis:

Data obtained will be entered in MS Excel, coded, anonymized and analyzed. Descriptive and inferential statistics (parametric/non-parametric tests based on distribution of depression and cognitive function scores) will be used to report differences between the groups (for e.g., between the sexes and BMI groups). Associations of exposures from early life, childhood and from the

current study (listed in Table 1 and 2) with depression and cognition will be examined by conducting simple linear regression analysis. Additional analyses will be conducted to examine the interaction between these exposures and potential confounders or mediating variables (e.g., paternal education, socioeconomic position etc.,). The above analyses will help us identify important variables of interest that need to be sequentially adjusted for in the regression models examining the associations of birth weight with scores of depression. Analyses will be extended to construct life course pathway for mental health using structural equational modelling.

Ethics and Dissemination: Since the study participants are adolescents between the age group of 10-12 years, an oral consent as well as written assent will be taken from them, and a written consent from their parents/guardian in accordance with 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. The findings from this study will be disseminated locally and at international meetings and will be published in a peer reviewed journal.

Discussion: Mental illnesses are the leading causes of disability adjusted life years (DALYs) worldwide, accounting for 37% of healthy years lost from NCD's[26]. Worldwide, the first main cause of YLDs (Years lived with Disability) for 10–24-year-olds are neuropsychiatric disorders (45%)[27]. Many epidemiological studies conducted in India on mental and behavioral disorders in adolescent age group have reported varying prevalence, ranging from 9.5-16.5 pecent[28]. Developmental Origins of Health and Disease i.e., fetal programming for chronic diseases in adulthood is among one of several explanations put forth to fill the gap in the knowledge on etiopathogenesis for noncommunicable diseases. While substantial epidemiological evidence exists for DOHaD in relation to chronic physical health conditions, little is known about the early life influences on the mental health and cognitive outcomes of the child.

Much remains unknown about the developmental mechanism of depression and other mental health disorders. Investigating the potential fetal origins of mental health disorders will be key to improving our knowledge of the causal mechanism and intergenerational effects of the condition. Considering the growing global burden of mental health disorders, it is critical now more than ever to understand the etiology of mental health disorders, along with means of preventing its initial onset.

In exploring the potential fetal origins of depression, this study will help scientists and clinicians better understand developmental mechanisms of adolescent depression, allowing them to devise methods of preventing and mitigating the initial onset of depression, starting even before conception. Thus, this research will be critical to the work of healthcare providers in improving health outcomes for women and children throughout their lifetimes.

Competing interests: The authors declare that they have no competing interests.

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DECLARATION SECTION:

Author Contribution:

Dr. Smitha Chandrashekarappa has full access to all data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis.

Study concept and design: Chandrashekarappa S, Krishna M, Madhivanan P, Krupp K, Dawes P, Newall J

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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

Disclaimer: The funding bodies had no influence on the conduct of the study or interpretation of the results.

Availability of data and materials: The study data are not 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. For further information contact: Dr Smitha Chandrashekarappa at JSS Medical college, JSS Academy of Higher Education and Research, Mysuru, Karnataka, India (smithu.mc@gmail.com)

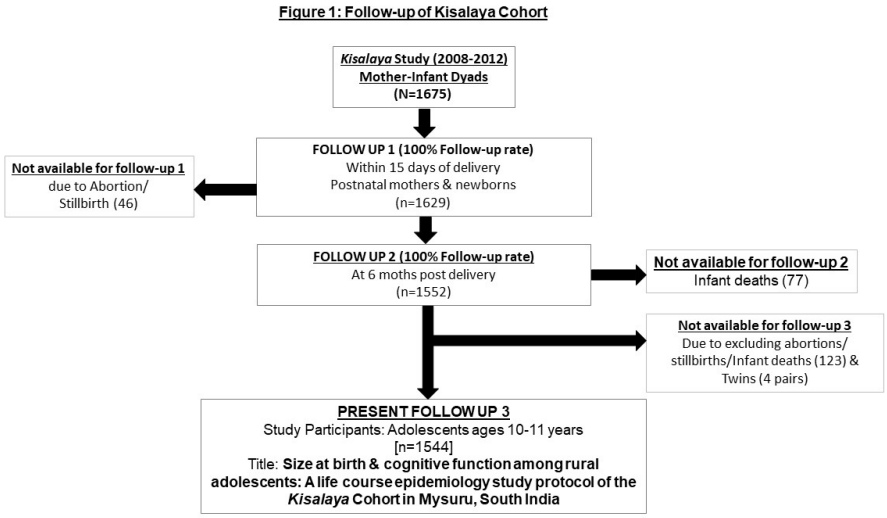

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Table 1: Data collected in 2008-2012 of the *Kisalaya* Cohort database, of relevance to the current study

Data collected previously (2008-2012 onwards)	
Data for	**Variables available for analysis**
Parents	• Socio-demographic variables including socio-economic status by Standard of living Index[18] • Literacy • Occupation • Family structure and composition • Data related to maternal stress • Data related to domestic violence • Data related to maternal health profile during antenatal period
Child	• Birth weight • Gestational age at birth

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Table 2: Instruments, Assessments and Investigations in the Study Protocol

Data to be collected now (2010 onwards)	
Data of	**Variables**
Parents	Socio-demographic variables including socio-economic status by Standard of living Index[18], Literacy, Occupation, Family Structure and composition.
Adolescent Children	*Anthropometry (by standardised procedures)* • Height in cms • Weight in Kgs • Waist Circumference in cms • Hip Circumference in cms • Head Circumference in cms • Leg length in cms
	Assessment of Mental Health • Child Trauma Questionnaire • Adolescent Life Events Stress Scale to assess the stressful life events[20] • Patient Health Questionnaire – Adolescents (PHQ-A) to assess the depression scores[19]
	Assessment of Cognition • Digit span, Matrix reasoning, Picture completion, Block design from Wechsler's Intelligence scale for Children IV Indian adaptation[21] • Assessment of Immediate and delayed recall by Word list recall test • Assessment of semantic perception • Assessment of Verbal Fluency
	Vision • Snellen's Chart
	Audio logical Evaluation: • Otoscopic evaluation • Pure tone audiometry • Immittance: Tympanometry and relaxometry
	Speech Evaluation • 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

Language Evaluation

- Linguistic profile by phonology
- Morphology, Syntax and semantics
- Reception
- Expression
- Reading and Writing

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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 foetus, often termed as 'Developmental Origins of Health and Disease'(DOHaD) resulting in smaller size at birth, greater NCD (Non Communicable Diseases) risk factors during childhood and adolescence, and cardiometabolic disorders in adulthood. Nevertheless, very few studies have examined 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 *Kisalaya* cohort, a rural birth cohort in south India, thus providing newer insights into DOHaD programming for adolescent mental health in a Low 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 *Kisalaya* program are available for this study. Presently, children born to women who received care through *Kisalaya* are adolescents between 10 to 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 1,544 adolescents who are currently available for study excluding twins, abortions, stillbirths and post-delivery deaths. Analyses will be extended to construct life course pathway for cognition using structural equation modelling.

Keywords: Birth weight, Adolescence, Mental Health, Cohort, Rural, India

Introduction:

Globally, an estimated 16% of newborns have low birthweight[1] and this burden is particularly high among low- and middle-income countries (LMIC).[2] Studies from both high-income and LMICs have established maternal health as an important determinant of growth, development, mental health and social outcomes of the offspring. During the 1980's, Prof David Barker[3] proposed that adverse intrauterine environment resulted in 'the early life programming' - alterations in metabolism and physiological development of the foetus, (often termed as the DOHaD-Developmental Origins of Health and Disease hypothesis) results in smaller size at birth, greater NCD risk factors during childhood and adolescence, and cardiometabolic disorders (obesity, cardiovascular disease, diabetes, stroke, hypertension and dyslipidaemia) in adulthood.[4-7]

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 foetal exposures also playing a major role in its aetiology. Studies examining the associations of birthweight with cognition among adolescents, were mostly conducted in High Income Countries, and have showed 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 an evidence for foetal origins for 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 having high burden of low birthweight, 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 birthweight 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 a LMIC setting.

Kisalaya **Cohort**

Kisalaya Birth Cohort was set up between 2008-2012 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 of 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 post-delivery [Figure 1]. A total of 141 offspring deaths and losses to follow-up during 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 *Kisalaya* cohort collected during 2008-2012, includes information on sociodemographic status of the woman and her family, details of present and previous pregnancies, reports of all routine antenatal investigations and information on birthweight of the child, breastfeeding practices, birth preparedness, details of delivery and health of the mother and the child during immediate postnatal period.

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

Objectives of the study:

Primary objective is to assess the relationship between birthweight and cognitive outcome.

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/co-variates which include, depression scores, vision, hearing, speech, language abilities, head circumference (proxy indicator for brain reserve) and maternal factors during antenatal period on the composite cognitive outcome.

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 off springs born to mothers enrolled and followed up in the *Kisalaya* cohort between 2008-12 (n=1496, excluding the abortions, stillbirths, infant deaths and twins) and invite them to participate in an assessment that will last approximately 1.5 to 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:

1. *Information from the database:* Data collected between 2008-2011 for the cohort of relevance to this project will be extracted from the *Kisalaya* cohort database [Table1].

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	• Socio-demographic 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 antenatal period
Child	• Birth weight • Gestational age at birth

2. *Interviews and questionnaires:* The following assessments will be conducted for the adolescents 2019 onwards. [Table 2]

I. Mental Health Assessments:

i. Severity of Depression will be measured as a continuous variable by administration of *Patient Health Questionnaire- Adolescents* (PHQ-A)[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, behavior, sleep and cognition.

ii. Cognition would be measured by administration of the following battery of tests derived from *Weschler's Intelligence scale for Children* (WISC)[18] 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.

iii. *Adolescent life events stress scale* (ALESS) will be administered for assessing 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.

iv. The *Child Trauma Questionnaire (CTQ)*[20] used would measures the severity of emotional abuse and neglect, physical abuse and neglect and sexual abuse while growing up as a child or a teenager.

II. Assessment of Speech Language and Hearing*:*

i. *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 (SSI), Consensus of auditory-perceptual evaluation of voice (CAPE-V). [22]

ii. Assessment of Language by profiling language comprehension and production in terms of syntax, semantics, phonology using Linguistic profile test (LPT).[23]

iii. Assessment of Hearing using screening audiometer at speech frequencies such as 500 Hz, 1kHz, 2 kHz.

iv. Screening of *Vision* will be done using Snellen's Chart: The chart will be placed ensuring bright light. Participant will be placed about 6 meters 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.

III. Physical assessments

a. Anthropometric measures:

i. *Height* and *Weight* will be recorded with the help of a wall mount tape and mechanical weighing scale respectively by standardized procedures. Please provide more details here in terms of units and how the measurements will be done.

ii. *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.

iii. *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.

iv. *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.

v. *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 both the description and picture depiction that would help in better self-reporting of pubertal stage[24]

Table 2: Instruments, Assessments and Investigations in the Study Protocol

Data to be collected now (2019 onwards)	
Data of	Variables
Parents	Socio-demographic variables including socio-economic status, Education, Occupation, Family Structure and composition (Type of family, family size, place of residence etc)
Adolescent Children	Anthropometry (by standardised procedures) • Height in cms • Weight in Kgs • Waist Circumference in cms • Hip Circumference in cms • Head Circumference in cms • Leg length in cms
	Assessment of Mental Health • Child Trauma Questionnaire • Patient Health Questionnaire – Adolescents (PHQ-A) to assess the depression scores • Adolescent Life Events Stress Scale to assess the stressful life events
	Assessment of Cognition • Digit span, Matrix reasoning, Picture completion, Block design from Wechsler's Intelligence scale for Children IV Indian adaptation[21] • Assessment of Immediate and delayed recall by Word list recall test • Assessment of semantic perception • Assessment of Verbal Fluency
	Vision • Snellen's Chart
	Audio logical Evaluation: • Otoscopic evaluation • Pure tone audiometry • Immittance: Tympanometry and relaxometry
	Speech Evaluation • 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
	Language Evaluation • Linguistic profile by phonology • Morphology, Syntax and semantics • Reception • Expression • Reading and Writing
	Staging of Puberty • Self-administered questionnaire based on tanner staging

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 standard deviations of a continuous outcome (cognitive score) per SD of a continuous exposure (birth weight).

The analysis will be done in two steps: [Figure 2]

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 is not normally distributed) to derive composite cognitive scores (in SD), which is the primary outcome variable of interest. The relationship between birthweight 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 composite cognitive score is different between the groups of interest (eg: between gender, between lower and higher socio economic position groups etc).

In the second step: Based on the range of composite cognitive score, a score less than 0.5 SD adjusted to gender will be considered as lower cognitive function (a binary outcome). The relationship between the birth weight and binary cognitive outcomes will be examined by conducting logistic regression analyses. Further we will construct multivariate logit models by making serial adjustments for potential confounders and covariates (as listed in Figure 2). That is, we will extend the analyses by employing structural equation modeling, a multivariate statistical analysis technique for analyzing structural relationships. This includes factor analysis and multiple regression analysis to explore structural relationship between measured variables and latent constructs (cognition) to build a lifecourse model for cognitive development in this cohort.

Ethics and Dissemination: Since the study participants are adolescents between the age group of 10-12 years, an oral consent as well as written assent will be taken from them, and a written consent from their parents/guardian in accordance with 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 course of 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 course of 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 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: Developmental Origins of Health and Disease i.e., fetal programming for chronic diseases in adulthood is among one of several explanations put forth to fill the gap in the knowledge on etiopathogenesis for noncommunicable diseases. While substantial epidemiological evidence exists for DOHaD in relation to chronic physical health conditions, little is known about the early life influences on cognitive outcomes of the child.

Much remains unknown about the developmental mechanism of Cognition and Investigating the potential fetal origins in relation to 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.

What is known and What this study Hopes to add

Many studies conducted in High Income countries and in Indian setting have shown direct correlation of Low Birth Weight with Cognition. However, these findings were from the Urban population and additionally none of these studies have considered influence of maternal health during Antenatal period on Cognitive outcomes of the Child. Hence, this study is unique with respect to both these aspects as it would be conducted in the rural adolescent population of a well-established cohort, which has data pertaining to mothers collected during the antenatal period and hence would contribute in the direction of understanding the correlation of birthweight and influence of maternal factors and various life course events on cognition in rural population.

Competing interests: The authors declare that they have no competing interests.

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DECLARATION SECTION:

Author Contribution:

Study concept and design: Chandrashekarappa S, Krishna M, Madhivanan P, Krupp K, Dawes P, Newall J

Drafting of the manuscript: Chandrashekarappa S, Krishna M, Madhivanan P, Krupp K, Veeraraje Ura C, Sathyapal Puri G, Dawes P, Newall J, Ravi K, Khan A, Arun A,

Acquisition of data: Chandrashekarappa S, Veeraraje Urs C, Jay P, Sathyapal Puri G, Ravi K, Khan A, Arun A

Critical revision of the manuscript for important intellectual content: Chandrashekarappa S, Krishna M, Madhivanan P, Krupp K, Veeraraje Urs C, Jay P, Sathyapal Puri G, Dawes P, Newall J

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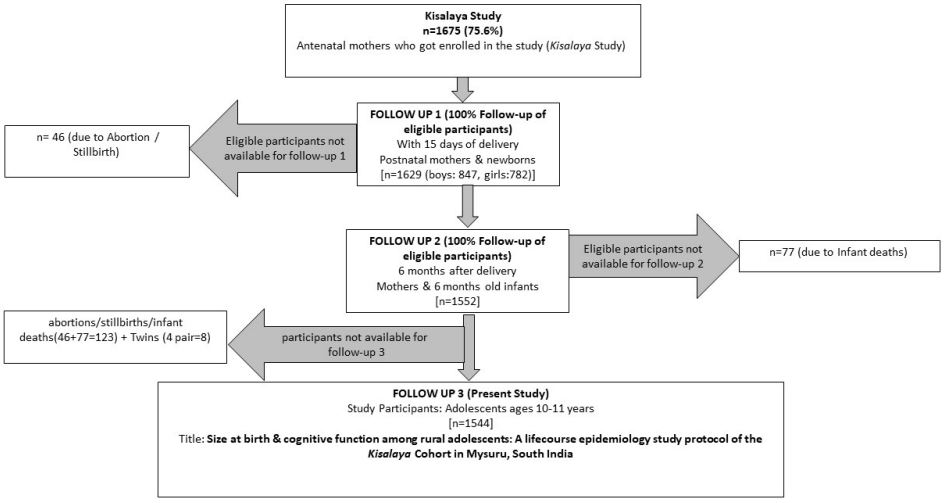
Patient and Public Involvement:

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

Disclaimer: The funding bodies had no influence on the conduct of the study or interpretation of the results.

Availability of data and materials: The study data are not 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. For further information contact: Dr Smitha Chandrashekarappa at JSS Medical college, JSS Academy of Higher Education and Research, Mysuru, Karnataka, India (smithu.mc@gmail.com)

Figure 1: follow-up of Kisalaya Cohort



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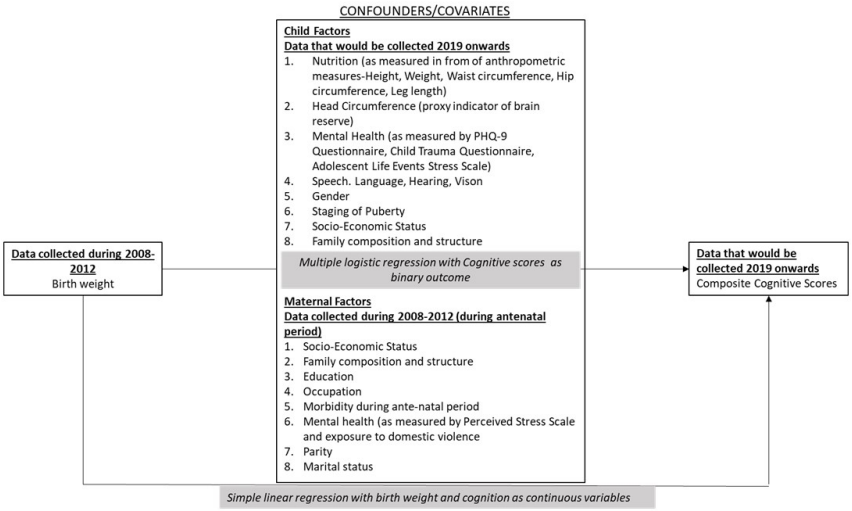

FIGURE 2: VARIABLES INCLUDED FOR STATISTICAL ANALYSIS

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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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Keywords:	Adolescent Health, Child Psychiatry, Epidemiology, Psychology, Obesity

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Title: 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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Introduction:

Globally, an estimated 16% of newborns have low birthweight[1] and this burden is particularly high among low- and middle-income countries (LMIC).[2] Studies from both high-income and LMICs have established maternal health as an important determinant of growth, development, mental health, and social outcomes of the offspring. During the 1980s, Prof David Barker[7] proposed that adverse intrauterine environment resulted in 'the early life programming' - alterations in metabolism and physiological development of the fetus, (often termed as the DOHaD-Developmental Origins of Health and Disease hypothesis) results in a smaller size at birth, greater NCD risk factors during childhood and adolescence, and cardiometabolic disorders (obesity, cardiovascular disease, diabetes, stroke, hypertension, and dyslipidemia) in adulthood.[4-7]

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 etiology. 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**

Kisalaya Birth Cohort was set up between 2008-2012 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 post-delivery [Figure 1]. A total of 141 offspring deaths and losses 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 *Kisalaya* 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 2008-2012) are now adolescents aged 10 to 11 years. The study team has kept in touch with all the mother-infant dyads informally from 2012 to the present though no data was 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/co-variates 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.

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 2008-12 (n=1496, excluding the abortions, stillbirths, infant deaths, and twins) and invite them to participate in an assessment that will last approximately 1.5 to 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:

1. *Information from the database:* Data collected between 2008-2011 for the cohort of relevance to this project will be extracted from the *Kisalaya* cohort database [Table1].

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	• Socio-demographic 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	• Birth weight • Gestational age at birth

2. *Interviews and questionnaires:* The following assessments will be conducted for adolescents from 2019 onwards. [Table 2]

I. Mental Health Assessments:

i. The severity of depression will be measured as a continuous variable by the administration of *Patient Health Questionnaire- Adolescents* (PHQ-A)[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, behavior, sleep, and cognition.

ii. Cognition would be measured by administration of the following battery of tests derived from *Weschler's Intelligence Scale for Children* (WISC)[18] 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.

iii. *Adolescent life events stress scale* (ALESS) 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.

iv. The *Child Trauma Questionnaire (CTQ)*[20] used would measure the severity of emotional abuse and neglect, physical abuse and neglect, and sexual abuse while growing up as a child or a teenager.

II. Assessment of Speech-Language and Hearing*:*

i. *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 (SSI), Consensus of auditory-perceptual evaluation of voice (CAPE-V). [22]

ii. Assessment of Language by profiling language comprehension and production in terms of syntax, semantics, phonology using Linguistic profile test (LPT).[23]

iii. Assessment of Hearing using screening audiometer at speech frequencies such as 500 Hz, 1kHz, 2 kHz.

iv. Screening of *Vision* will be done using Snellen's Chart: The chart will be placed ensuring bright light. The participant will be placed about 6 meters 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.

III. Physical assessments

a. Anthropometric measures:

i. *Height* and *Weight* will be recorded with the help of a wall mount tape and mechanical weighing scale respectively by standardized procedures. Please provide more details here in terms of units and how the measurements will be done.

ii. *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.

iii. *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 centimeters.

iv. *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 centimeters.

v. *Hip circumference* will be measured at the widest part of the hip in centimeters.

b. *Staging of Puberty*: By Self-administered questionnaire based on the Tanner staging. This questionnaire has both the description and picture depiction that would help in better self-reporting of pubertal stage[24]

Table 2: Instruments, Assessments, and Investigations in the Study Protocol

Data to be collected now (2019 onwards)	
Data of	Variables
Parents	Socio-demographic variables including socioeconomic status, Education, Occupation, Family Structure and composition (Type of family, family size, place of residence, etc)
Adolescent Children	Anthropometry (by standardized procedures) • Height in cms • Weight in Kgs • Waist Circumference in cms • Hip Circumference in cms • Head Circumference in cms • Leg length in cms
	Assessment of Mental Health • Child Trauma Questionnaire • Patient Health Questionnaire – Adolescents (PHQ-A) to assess the depression scores • Adolescent Life Events Stress Scale to assess the stressful life events
	Assessment of Cognition • Digit span, Matrix Reasoning, Picture completion, Block design from Wechsler's Intelligence Scale for Children IV Indian adaptation[21] • Assessment of Immediate and delayed recall by Word list recall test • Assessment of semantic perception • Assessment of Verbal Fluency
	Vision • Snellen's Chart
	Audiological Evaluation: • Otoscopic evaluation • Pure tone audiometry • Immittance: Tympanometry and relaxometry
	Speech Evaluation • 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
	Language Evaluation • Linguistic profile by phonology • Morphology, Syntax, and semantics • Reception • Expression • Reading and Writing
	Staging of Puberty • A self-administered questionnaire based on tanner staging

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 standard deviations 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 is not normally distributed) to derive composite cognitive scores (in SD), which is the primary outcome variable of interest. The relationship between birthweight 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 by employing structural equation modeling, a multivariable statistical analysis technique for analyzing 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.

Ethics and Dissemination: Since the study participants are adolescents between the age group of 10-12 years, oral consent, as well as written assent, will be taken from them, and written consent from their parents/guardian by 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: Developmental Origins of Health and Disease i.e., 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 noncommunicable diseases. 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.

What is known

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 birthweight, but also the influence of maternal factors and various life-course events on cognition in rural population.

Competing interests: The authors declare that they have no competing interests.

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DECLARATION SECTION:

Author Contribution:

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Drafting of the manuscript: Chandrashekarappa S, Krishna M, Madhivanan P, Krupp K, Veeraraje Ura C, Sathyapal Puri G, Dawes P, Newall J, Ravi K, Khan A, Arun A,

Acquisition of data: Chandrashekarappa S, Veeraraje Urs C, Jay P, Sathyapal Puri G, Ravi K, Khan A, Arun A

Critical revision of the manuscript for important intellectual content: Chandrashekarappa S, Krishna M, Madhivanan P, Krupp K, Veeraraje Urs C, Jay P, Sathyapal Puri G, Dawes P, Newall J

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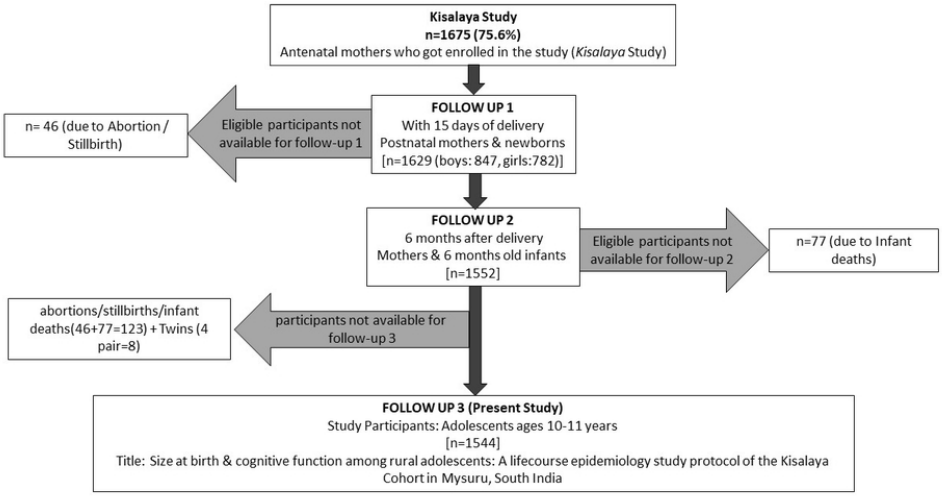
Patient and Public Involvement:

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

Disclaimer: The funding bodies did not influence the conduct of the study or interpretation of the results.

Availability of data and materials: The study data are not 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. For further information contact: Dr. Smitha Chandrashekarappa at JSS Medical College, JSS Academy of Higher Education and Research, Mysuru, Karnataka, India (smithu.mc@gmail.com)

Figure 1: follow-up of Kisalaya Cohort



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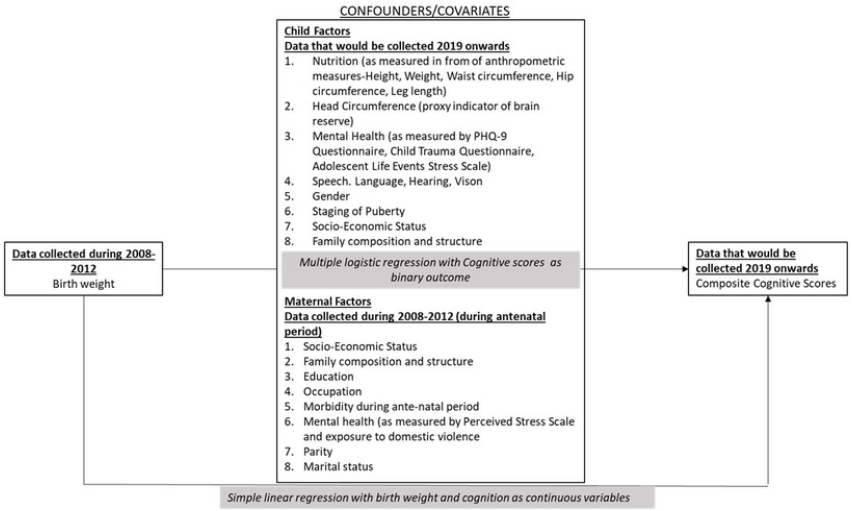

FIGURE 2: VARIABLES INCLUDED FOR STATISTICAL ANALYSIS

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