The American Journal of Clinical Nutrition

Association of linear growth velocities between 0 and 6 years with kidney function and size at 10 years: a birth cohort study in Ethiopia.

--Manuscript Draft--

Manuscript Number:	AJCN-D-23-00413R2
Full Title:	Association of linear growth velocities between 0 and 6 years with kidney function and size at 10 years: a birth cohort study in Ethiopia.
Short Title:	linear growth velocities and kidney function
Article Type:	Original Research Article
Section/Category:	Growth, development, and pediatrics
Keywords:	linear growth velocities, Kidney function, Kidney size, cohort study, Ethiopia.
Corresponding Author:	Beakal Zinab Zinab, MSc Jimma University College of Public Health and Medical Sciences Jimma, ETHIOPIA
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	Jimma University College of Public Health and Medical Sciences
Corresponding Author's Secondary Institution:	
First Author:	Beakal Zinab Zinab, MSc
First Author Secondary Information:	
Order of Authors:	Beakal Zinab Zinab, MSc
	Rahma Ali, MPH
	Bikila Megersa
	Tefera Belachew
	Elias Kedir
	Tsinuel Girma
	Alemseged Abdisa
	Melkamu Berhane
	Bitiya Admasu
	Henrik Friis
	Mubarek Abera
	Mette F Olsen
	Gregers S Andersen
	Jonathan CK Wells
	Suzanne Filteau
	Rasmus Wibaek
	Dorothea Nitsch
	Daniel Yilma
Order of Authors Secondary Information:	
Abstract:	Background: The risk of non-communicable diseases accrues from fetal life, with early childhood growth having an important role for the risk of adult disease. There is a need

	to understand how early life growth relates to kidney function and size. Objectives: This study aimed to assess the association of linear growth velocities among children between 0 and 6 years with kidney function and size among children aged 10 years. Methods: The Ethiopian Anthropometric and Body Composition (iABC) birth cohort participants were followed up with 13 measurements between birth and 6 years of age. The latest follow-up was at ages 7-12 years with measurement of serum cystatin C as a marker of kidney function, and ultrasound assessment of kidney dimensions. Kidney volume was computed using an ellipsoid formula. Linear spline multi-level modelling was used to compute linear growth velocities between 0-6 years. Multiple linear regression modelling was used to examine the associations of linear growth velocities in selected age periods with cystatin C and kidney size. Results: Data were captured from 355 children, at a mean age of 10 (range 7-12) years. The linear growth velocity was high between 0-3 months and then decreased with age. There was no evidence of an association of growth velocity up to 24 months with cystatin C at 10 years. Between 24-48 and 48-76 months, serum cystatin C was higher by 2.3% (95% CI 0.6, 4.2) and 2.1 % (95% CI 0.3, 4.0) for one SD higher linear growth velocity, respectively. We found a positive association between linear growth velocities at all intervals between 0-6 years and kidney volume. Conclusion: Greater growth between 0-6 years of development was positively associated with kidney size, however greater growth velocity after 2 years is associated with higher serum cystatin C level.
Additional Information:	
Question	**Response**
Number of words:	5654
AJCN publishes systematic reviews with or without meta-analyses as original research articles. Other reviews involving reanalysis of published data such as scoping or umbrella reviews also will be considered. Systematic reviews must be pre-registered in PROSPERO. Authors must provide the exact URL and unique identification number for the trial registration at the time of submission. This information will be published in the article and authors should include the URL and identification number in the abstract of their manuscript.	
Has this manuscript been posted to a preprint server?	No
REGISTRATION OF CLINICAL TRIALS In accordance with the Clinical Trial Registration Statement from the International Committee of Medical Journal Editors (ICMJE) all clinical trials published in ASN journals must be registered in a public trials registry at or before the onset of participant enrollment. For any clinical trials beginning before 2008, retrospective registration will be	Trial registration number: URL of registration:

accepted. Authors must provide the exact URL and unique identification number for the trial registration at the time of submission. This information will be published in the article and authors should include the URL and identification number on the title page of their manuscript. See https://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html for additional information.	
Please select a collection option from the list below:	Maternal, Perinatal and Pediatric Nutrition

Declaration of interests

☐The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Daniel Yilma reports financial support was provided by GSK Africa Non-Communicable Disease Open Lab.

Title

Association of linear growth velocities between 0 and 6 years with kidney function and size at 10 years: a birth cohort study in Ethiopia.

Name of authors

Beakal Zinab[1,3], Rahma Ali[2,3], Bikila S Megersa[3],Tefera Belachew[1,] Elias Kedir[4], Tsinuel Girma[5], Alemseged Abdisa[6], Melkamu Berhane[5], Bitiya Admasu[2], Henrik Friis[3], Mubarek Abera[7], Mette F Olsen[3,8], Gregers S Andersen[9], Jonathan CK Wells[10], Suzanne Filteau[11], Rasmus Wibaek[9], Dorothea Nitsch[11] * and Daniel Yilma[12] *.

[1] Department of Nutrition and Dietetics; and [2]Department of Population and Family Health, Faculty of Public Health, Jimma University, Jimma, Ethiopia.

[3] Department of Nutrition, Exercise, and Sports, University of Copenhagen, Copenhagen, Denmark.

[4] Department of Radiology; and [5]Department of Pediatrics and Child Health Faculty of Medical Sciences, Jimma University, Jimma, Ethiopia.

[6] Armauer Hansen Research Institute, Addis Ababa, Ethiopia.

[7] Department of Psychiatry, Faculty of Medical Sciences, Jimma University, Jimma, Ethiopia.

[8] Department of Infectious Diseases, Rigshospitalet, Copenhagen, Denmark

[9] Steno Diabetes Center Copenhagen, Herlev,Denmark.

[10] Childhood Nutrition Research Center, UCL Great Ormond Street Institute of Child Health, London, United Kingdom.

[11] Faculty of Epidemiology and Population Health, London School of Hygiene & Tropical Medicine, London, United Kingdom.

[12] Department of Internal Medicine, Faculty of Medical Sciences, Jimma University, Jimma, Ethiopia.

* These authors contributed equally to this work.

Corresponding author: Beakal Zinab (beakalzinab1@gmail.com)

Conflict of Interest

All authors declare no conflicting interests.

Funding statement

The study was funded by a project grant from the GSK Africa Non-Communicable Disease Open Lab (Project number: 8658). The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Data sharing

Data described in the manuscript, code book, and analytic code will be made available upon request pending application and approval.

Abbreviations

iABC, infant Anthropometric and Body Composition; ADP, air displacement plethysmograph; DOHaD, Developmental Origins of Health and Disease; Glomerular Filtration Rate; LMICs, Low and Middle Income Countries; LBW, Low Birth Weight.

Abstract

Background: The risk of non-communicable diseases accrues from fetal life, with early childhood growth having an important role for the risk of adult disease. There is a need to understand how early life growth relates to kidney function and size.

Objectives: This study aimed to assess the association of linear growth velocities among children between 0 and 6 years with kidney function and size among children aged 10 years.

Methods: The Ethiopian Anthropometric and Body Composition (iABC) birth cohort recruited infants born at term to mothers living in Jimma, with a birth weight of ≥1500 grams, and without congenital malformations. Participants were followed up with 13 measurements between birth and 6 years of age. The latest follow-up was at ages 7-12 years with measurement of serum cystatin C as a marker of kidney function, and ultrasound assessment of kidney dimensions. Kidney volume was computed using an ellipsoid formula. Linear spline multi-level modelling was used to compute linear growth velocities between 0-6 years. Multiple linear regression modelling was used to examine the associations of linear growth velocities in selected age periods with cystatin C and kidney size.

Results: Data were captured from 355 children, at a mean age of 10 (range 7-12) years. The linear growth velocity was high between 0-3 months and then decreased with age. There was no evidence of an association of growth velocity up to 24 months with cystatin C at 10 years. Between 24-48 and 48-76 months, serum cystatin C was higher by 2.3% (95% CI 0.6, 4.2) and 2.1 % (95% CI 0.3, 4.0) for one SD higher linear growth velocity, respectively. We found a positive association between linear growth velocities at all intervals between 0-6 years and kidney volume.

Conclusion: Greater growth between 0-6 years of development was positively associated with kidney size~~, however~~ and greater growth velocity after 2 years ~~is~~ was associated with higher serum cystatin C level.

Key words: linear growth velocities, Kidney function, Kidney size**,** cohort study, Ethiopia.

Introduction

The developmental origins of health and disease (DOHaD) hypothesis states that adverse environmental factors acting early in life increase the risk of later-life disease vulnerability (1). For example, stressors in early life may result in structural and functional changes in the developing kidney, increasing individuals' vulnerability to kidney, and cardiovascular disease in later life (2,3).

In humans, kidney development begins during the ninth week of pregnancy and continues until the 36th week (4). Except for extremely preterm neonates, there is no evidence of nephrogenesis in humans after birth (4). The normal human kidney has an average of 1 million nephrons, which consisting of a glomerulus (filter unit) and a tubule~~s~~ (controlling urinary composition). Multiple studies have shown that the total glomerular number may vary by thirteen ~~13~~-fold between individuals (5–7). The number of nephrons during adulthood reflects the difference between the number of nephrons at birth and the number of nephrons lost (8–10).

Trajectories of growth reflect the complex interplay of biological and environmental processes that influence life course health and development (11,12). Linear growth retardation in early~~-~~ life is a good indicator of a poor ~~early~~ early-life environment and is associated with increased risk of morbidity later in life (13). Previous studies have shown that children with short stature exhibit reduced kidney size and a lower nephron number (14,15).

Linear growth failure manifested as stunting is a major public health problem in developing countries in general and in sub-Saharan Africa in particular (16)(17). Therefore, in this setting, there may be subclinical differences in kidney function and volume that~~which~~ may already be detectable in childhood and may explain the susceptibility of individuals to kidney disease in adulthood (18). Understanding ~~of~~ the natural history of kidney function, including subclinical differences and modifiable risk factors, is pivotal to designing and implementing efficient preventive strategies at the population level. Studies have described a high burden of acute and chronic pediatric kidney disease in low- and middle-income countries (19–21), but many of the existing studies on childhood predictors of adult kidney function were conducted in high-income countries (22–24). Evidence from high-income settings suggests that birth characteristics, fetal growth, and early childhood growth influence kidney function throughout one's life course (25). ~~Thus, t~~The current study was intended to fill current research ~~paucity~~ gaps by investigating the association of early-life linear growth with a marker of kidney function and kidney size at 10 years using an Ethiopian birth cohort.

Methods

Study setting and participants

The study included children from the Ethiopian iABC birth cohort, which has been described earlier (26,27). Briefly, infants of mothers who lived in Jimma Town, born at term (gestational age at birth ≥37 completed weeks) with a birth weight of ≥1500 gram and without congenital malformations were included in the cohort. The mother-child pairs were invited to attend a total of 13 study visits at birth, at 1.5, 2.5, 3.5, 4.5, 6 months, and 1, 1.5, 2, 3, 4, 5, and 6 years. A total of 644 mother-newborn dyads were recruited for the study between December 2008 and October 2012.

The current follow-up visits, hereafter referred to as 10-year follow-up, were conducted from June 2019 to December 2020~~,~~ and included 355 children aged 7-12 years~~, hereafter referred to as 10-year follow-up~~. Families of all children were traced by previously provided phone number or residential location and invited to bring their children after receiving clear information about the study. In ~~the event~~cases ~~when~~ where phone numbers were not working, a study nurse visited the family's last known address.

Data collection tools and procedures

Experienced research nurses and laboratory technicians collected the data. For the 10-year follow-up, families were requested to bring their children fasting in early morning; samples were taken in the morning because of postprandial changes in plasma (28). Maternal and childhood characteristics were collected using questionnaires. Body dimensions, body composition, and renal size were measured using anthropometry, air displacement plethysmography, and ultrasound, respectively. Serum cystatin C was analyzed from blood samples as described below.

Questionnaire data

A pre-tested interviewer interviewer-administered structured questionnaire was used to collect information concerning socio-demographic and economic characteristics of the family. The tool includes questions intended to capture family and child socio-demographic characteristics, status of the house they live, and ownership of properties. Additional relevant previous maternal and child characteristics were abstracted from iABC data.

Anthropometric and body composition measurements

Weight from birth to six months was measured to the nearest 1 gram using a PEA POD, an infant air displacement plethysmograph (ADP; COSMED, Rome, Italy); for the follow-up visits starting from 12 months, it weight was measured to the nearest 0.1 kg using an electronic UNICEF scale (SECA, Hamburg, Germany). Length was measured in a recumbent position for infants below 24 months to the nearest 0.1 cm using a SECA 416 Infantometer. In children 24 months and above, standing height was measured to the nearest 0.1 cm using a SECA 213 portable stadiometer (SECA, Hamburg, Germany). More detailed information on specific measurements at different follow-up visits is published elsewhere (29).

For the current visit at 10 years, the participants' weight was measured to the nearest 0.1 g by the BOD POD, a child/adult version of ADP, after removing heavy clothes. Height was measured to the nearest 0.1 cm using a stadiometer, according to the standard procedure without shoes. All anthropometric measurements were taken twice, and the average values were used.

Body composition assessment

Body composition was assessed at birth at 1.5, 2.5, 3.5, 4.5, and 6 months of age with the PEA- POD, designed to measure infants between birth and 6 months of age (COSMED, Rome, Italy). BOD- POD, a child/adult version of ADP, was used to assess body composition at the 4, 5, 6, and 10 years follow-ups. Children were fasting and wearing close-fitting underwear and a swimming cap during measurement. Both the PEA-POD and BOD-POD have high accuracy and precision and are feasible and safe for assessing body composition in infants and children, respectively (30,31)

Ultrasound measurement

Kidney size was measured by ultrasonography using a C1-5-D 2D convex probe (GE P6) (General electronics Co.Ltd Boston, USA). The kidney was identified in the sagittal plane along its longitudinal axis. ~~A m~~Measures of maximal bipolar kidney length, width, and thickness were obtained for both kidneys. Renal width and thickness were measured at the level of the kidney hilum. All dimensions were measured to nearest 0.1 cm~~ in both kidneys~~. All children were examined by the same certified radiologist. Kidney volume was calculated in cubic centimeters using the formula of an ellipsoid: length × width × depth × 0.523 (32,33). Total kidney volume was calculated as the sum of the right and left kidney volumes.

Blood sample collection and analysis

Families were asked ahead of the visit to bring their children fasted overnight for 8 hours. Lab technicians collected blood samples (4 ml) after confirming that the child had fasted. The study nurses provided the children with a meal immediately after sample collection. ~~Initially there were more children without outcome measurements due to children were in non-fasting state and failure of the ultrasound machine. In that.~~In cases where children came non-fasting or where the ultrasound machine was not working, participants were ~~reappointed and~~ given new appointments for outcome measurements~~ taken~~.

Samples were stored ~~briefly~~ in the lab fridge for a maximum of 4 hours in K2-EDTA tubes. Blood samples underwent centrifugation for 10 minutes and were stored at -80°C until further lab analysis ~~was done~~. Serum cystatin C was determined using an enhanced immune turbidimetric assay on a Cobas c 702 analyser (Roche Diagnostic, Germany). Cystatin C is a low molecular weight protein, produced at a relatively constant rate. The concentration of serum cystatin C is highly correlated with directly measured Glomerular Filtration Rate (GFR) values, and small reductions in GFR can be detected more readily with serum cystatin C (34,35). The estimated glomerular filtration rate was calculated using Zappitelli's formula eGFRCyst = 75.94 / $[CysC^{1.17}]$ (36). ~~However, b~~Because this formula is not validated for the target population, the results are unlikely to reflect true eGFR in these children; further analyses were carried out only using cystatin C as the ~~primary~~ outcome.

Statistical analyses

Data were double-entered ~~in double~~ in Epi Data version 4.4.2.0 (Denmark). Descriptive data were presented as mean (standard deviation [SD]) for normally distributed data, median (interquartile range (IQR)) for continuous non-normally distributed data, and. count (proportion) was used ~~to describe~~for categorical variables. Since serum cystatin C was not normally distributed, it was log-transformed, before regression analyses. Estimates from these models were back-transformed and presented as a percentage change. The normality of the residuals was checked visually by histogram, pnorm, and qnorm plots. ~~Furthermore, r~~Residuals were plotted against the fitted values to check the homogeneity of variance of the residuals.

Linear growth velocity 0 to 6 years

The non-linear relationship of length/height as a function of age were modeled using a series of linear splines (37). Linear-spline multilevel (piecewise linear multilevel) models are increasingly used to model childhood growth since they address many of the challenges associated with analyzing longitudinal data (38,39) Knot points were placed at 3, 6, 24 and 48 months while taking into consideration data density, previous knowledge and model fit statistics. Linear growth velocity between 0 to 3 months is the difference between predicted length at 3 months and length at birth divided by 3 to get cm/month, and similarly for the other growth periods. These individual specific monthly linear length velocities over discrete time intervals from 0 to 6 years of age were generated using R version 4.2.0 (R Foundation for Statistical Computing).

Association of linear growth velocity with kidney function and size

Linear regression models were used to test associations of cystatin C and kidney size with estimates of each child's birth length, and length growth velocity from 0-3, 3-6, 6-24, 24-48, and 48-76 months. To obtain comparable estimates across the different growth periods, sex-based standardization of growth velocities was done by subtracting the mean from the individual's score and dividing by the standard deviation. These sex-based standardized growth velocities were used for subsequent multiple linear regression analyses as exposure variables. Thus, the estimates indicate the change in cystatin C or kidney size per study population SD increase in length/height velocity.

Three models were fitted separately for birth length and each of the length/height velocity exposures. Model 1 was adjusted for sex and current age. Model 2 additionally adjusted for birth weight, gestational age, birth order and current fat mass. The adjustment for current fat mass was done to remove any effect of fat mass on cystatin C measurements (40). Model 3 was additionally adjusted for maternal education and height at birth. Stata version 14 (StataCorp LLC College Station, Texas, USA) was used to fit the multiple linear regression models.

Sensitivity analyses

We investigated whether there was a difference identified in serum cystatin C level between low birth weight (LBW) and normal birth weight children who attended the 10^{th} follow-up. Cross-sectional analyses of associations of height at the latest follow-up with kidney parameters were carried to sense-check the results. Instead of total kidney volume, a separate regression model computed for kidney dimensions of each kidney. To investigate whether associations of growth with kidney size were driven by body surface area (BSA), sensitivity analyses investigated associations between linear growth velocities from 0 to 6 years with kidney volume divided by BSA (derived using the Boyd formula, BSA [m2] = Weight [kg]0.4838 × Height [cm]0.3 × 0.017827)).

Ethical considerations

Ethical permission was obtained from Jimma University Ethical Review Board (Letter No. IHRPHD/333/18), and London School of Hygiene and Tropical Medicine ethics committee. Parents/guardian signed consent forms before entry into iABC and the current 10 year follow-up. Any abnormal findings detected during clinical and laboratory evaluations were communicated to families of children and they were linked to Jimma University Medical Center for further evaluation.

Results

Characteristics of study participants and mothers

A total of 644 mother-infant pairs attended the birth visit. We excluded 10 preterm and 63 children not living in Jimma. The mean maternal age (±SD) at the infant's birth was 22.1 ± 4.5 years, and at the time, 61% of the mothers had attended primary school.

Of the remaining 571, 355 (62%) were recruited at age 7-12 for the 10-year follow-up visit for assessment of kidney function and size. ~~However, 2~~Two participants were excluded because they ~~only~~ had ~~1~~ only one height measurement from birth to 6 years, leaving 353 for the 10-year analysis (Figure 1). Of these 353 children ~~attended the 10th year follow-up~~, 51.8% were male, the mean (±SD) age was 9.8 ± 1.0 years, and 48.7% were first born (Table 1).

Children who were lost to follow-up were similar with respect to most variables, but had lower birth weight and birth length, and were less likely to be second- or third-born children compared to those who attended the current visit (Supplementary~~Supplemental~~ Table 1). Reasons for loss to follow-up were migration out of Jimma, death, and refusal to participate in further follow-up assessments. In addition, we could not obtain serum cystatin and kidney size measurements for 6 and 3 children respectively, because participants came from far away which meant that a reappointment was not possible.

Linear growth velocity between 0-6 years

The velocity of linear growth was fastest in the first 3 months of life (4.1cm/month), and then decreased with age. Males had faster linear growth velocity between 0-3 months while it was faster in females between 6 to 24 months of age (Table 2).

Kidney function and volume

The median (IQR) serum cystatin C and estimated glomerular filtration rate were 0.93 (0.83; 1.01) mg/dl and 82.7 (75.1; 94.4) ml/min per $1.73m^2$, respectively. The median (IQR) combined kidney volume was 117.2 (103.0; 132.4) cm^3 (Table 3). We found no evidence of a difference in serum cystatin C level between children with LBW and normal birth weight who attended the 10th follow-up (Supplementary table 2).

Association of linear growth velocity with kidney function

Associations of estimated standardized linear growth velocity between 0-3, 3-6, 6-24, 24-48 and 48-76 months with serum cystatin C are presented in Figure 2. In the fully adjusted models, there was no evidence that linear growth velocities at 0-3, 3-6, and 6-24 months were associated with log-serum cystatin C. However, between 24-48 and 48-76 months, a one SD higher linear growth velocity was associated with 2.3 % (95% CI 0.6, 4.2) and 2.1 % (95% CI 0.3, 4.0) higher serum cystatin C, respectively. Additionally, a positive and significant association ~~is~~ was observed between serum cystatin C and observed height at the 10th year follow-up (Supplementary Table 3).

Association of linear growth velocity and kidney size (volume)

Across all models, linear growth velocities between different knots from 0 to 6 years were positively associated with kidney volume at 10 years. ~~However, t~~The strongest association was seen for linear growth velocity from 48-76 months (Figure 3). In sensitivity analyses, linear growth at all intervals from 0-6 years was positively associated with both right and left kidney length (~~supplementary~~ Supplementary ~~figures1~~Figures 1 & 2). Conversely, only linear growth velocity after two years of age was associated with kidney anterior-posterior diameter (depth) (~~supplementary~~ Supplementary ~~figures~~ Figures 3 & 4). ~~Likewise, t~~There ~~is~~ was a positive association found between observed height at the 10th year follow-up and kidney size (Supplementary Table 3). As depicted in ~~supplementary~~ Supplementary Figure 7, once kidney volume was divided by BSA, there was no evidence for an association with linear growth velocities.

Discussion

In this study, linear growth velocities at 24-48 and 48-76 months, but not at other age intervals, were positively associated with serum cystatin C level, indicating that greater growth in these periods is associated with ~~worse kidney function.~~ comparatively lower kidney function when compared to peers. On the other hand, the observed positive association between faster linear growth velocity and cystatin C might partly explained by non-renal factors. Linear growth velocities between 0-6 years were consistently and positively associated with kidney volume at 7-12 years.

To the best of our knowledge, this study is the first to report the longitudinal relationship between early life linear growth velocities and cystatin C and kidney size in an African context. Although we cannot infer causality, our results suggest that faster linear growth beyond 2 years may be related to later life kidney function deficits. This finding is consistent with multiple studies ~~using other~~of cardiometabolic markers, including blood pressure, which ~~is positively associated~~ show a positive association with faster linear growth after 2 years of age (41–44).

The underlying mechanisms for the associations of linear growth between 2 to 6 years, and kidney function are not well understood. ~~However, o~~One potential explanation of the findings is that~~,~~ faster growth in children and adolescents imposes a greater functional burden on kidneys, and that demands on renal capacity made by rapid childhood growth after 24 months of age may not be entirely met by renal development, resulting in compensatory increase in blood pressure (45). ~~Likewise, a~~Although being taller as an adult appears healthier with lower non-communicable disease risk (46), the current study indicated that, having faster linear growth velocity in childhood after 2 years is not beneficial for kidney function. ~~In turn, t~~That would suggest that the more favorable pathways in terms of kidney function~~s~~ are for a child to realize its genetic growth potential before the age of 2 years.

In this study, faster growth velocities between 0-6 years were positively associated with kidney volume at 10 years. Our results are similar to other studies that performed radiological measurements of renal size (47,48). Kidney size, though an imperfect proxy for nephron number, is positively associated with kidney function (49). It is well known that in the context of reduced nephron number, the remaining nephrons increase in size (50). We speculate that the persisting positive association of linear growth with kidney size, as observed in this study, may be related to this compensatory mechanism to meet the child's metabolic requirements to reach the required BSA, but at the expense of kidney function. This is in line with associations of linear growth velocities and kidney volume appearing to be mediated by BSA at the latest follow-up.

Regression models for each kidney dimension separately (data shown in ~~supplementary~~ Supplementary Figures 1-6) confirm that associations are robust for both kidneys. On the other hand, only linear growth velocity after two years of age was associated with kidney anterior-posterior diameter (depth). Combined with the higher serum cystatin C levels with greater linear growth after two years, the results are consistent with a previous study of 8-year-old children in Nepal, in that "thicker" kidneys appear to be less favorable for cardio-metabolic health when compared to longer kidneys (51).

Strengths and limitations

A major strength of the study is that it used prospectively measured growth data. To date, most such research has been conducted in high-income countries and studies that associated linear growth with the later development of non-communicable diseases generally and kidney diseases, particularly, are scarce. The observed effect estimates in the present study are not in the range where one would consider these to explain overt kidney disease in children, i.e. are associations within the norm. These associations may be important from an etiological and developmental perspective because the subclinical variation of kidney function in childhood may well impact later life kidney function, similar to the tracking of pediatric blood pressure measurements with later cardiovascular risk.(52)(53)(54). Future follow-ups of this cohort will investigate this as the children reach adulthood.

This study also has some limitations that could affect the interpretation of the results. The observed association between linear growth velocity with cystatin C and size could be confounded by other potential prenatal factors such as maternal morbidity status and diet. At this age, we cannot ascertain whether the observed associations represent early subclinical kidney function deficits or normal growth-related phenomena. We cannot exclude the possibility of reverse causality in the absence of kidney phenotyping prior to the current assessment. We used cystatin C instead of estimating the glomerular filtration rate as the existing formulas are not validated for our study setting. We were unable to obtain pubertal status, which in high income settings, has been associated with cystatin C in healthy children (55) . Additionally, the loss to follow-up of substantial number of children with LBW may introduce bias. However, we found no association between serum cystatin C level and LBW- status amongst children who attended the 10th follow-up, though this analyses may have been underpowered.

In conclusion, based on our findings, greater growth between 0 and 6 years favors kidney size to meet requirements of a given BSA, however greater growth after 2 years of age is associated with serum cystatin C level. Thus, existing programs that target the first 1000 days of life are still important and should be strengthened, but interventions to address linear growth in children over the age of two should also be in place. Additionally, we recommend other researchers ~~to~~ carry out similar studies with a sizable sample size in contexts of LMICs.

Acknowledgments

We are grateful to children and their families for participating in this study. Our gratitude goes to all individuals involved in the data collection and supervision.

Authors' contribution

The authors' contributions were as follows HF, JCKW, TG, GSA, RW, DN, SF, DY, and BZ designed the study. BZ, RA, and BSM supervised the data collection; HF, JCKW, TG, GSA, RW, MFO, DY, SF, DN, EA, MA, AA, MB, TB and BA participated in methodology. Data analysis done by BZ, RW and GSA. BZ wrote the first draft of the manuscript and had responsibility for the whole work. BZ, DY, DN, and HF had primary responsibility for the final content. All authors contributed to the manuscript revisions and read the final manuscript and approved it for submission.

References

1. Awazu K. Early life origins of human health and disease. Ir Med J [Internet]. 2010;103(8):2009–10. Available from: https://www.researchgate.net/publication/260744098_Early_Life_Origins_of_Human_Health_and_Disease

2. Tain YL, Hsu CN. Developmental origins of chronic kidney disease: Should we focus on early life? Int J Mol Sci [Internet]. 2017;18(2):1. Available from: https://pubmed.ncbi.nlm.nih.gov/28208659

3. Hsu CN, Tain YL. Developmental origins of kidney disease: Why oxidative stress matters? Antioxidants [Internet]. 2021;10(1):1–18. Available from: https://www.mdpi.com/2076-3921/10/1/33

4. Hoy WE, Hughson MD, Bertram JF, Douglas-Denton R, Amann K. Nephron number, hypertension, renal disease, and renal failure. J Am Soc Nephrol [Internet]. 2005;16(9):2559. Available from: https://jasn.asnjournals.org/content/jnephrol/16/9/2557.full.pdf

5. Luyckx VA, Brenner BM. The clinical importance of nephron mass. J Am Soc Nephrol [Internet]. 2010;21(6):1–3. Available from: https://www.researchgate.net/publication/41424947

6. Viviani S. Nephron Number in Patients with Primary Hypertension. N Engl J Med [Internet]. 2011;348(2):105. Available from: https://www.nejm.org/doi/full/10.1056/NEJMoa020549

7. Bertram JF, Douglas-Denton RN, Diouf B, Hughson MD, Hoy WE. Human nephron number: Implications for health and disease. Pediatr Nephrol [Internet]. 2011;26(9):1531–3. Available

from: https://pubmed.ncbi.nlm.nih.gov/21604189/

8. Luyckx VA, Bertram JF, Brenner BM, Fall C, Hoy WE, Ozanne SE, et al. Effect of fetal and child health on kidney development and long-term risk of hypertension and kidney disease. Lancet [Internet]. 2013;382(9888):275. Available from: http://dx.doi.org/10.1016/S0140-6736(13)60311-6

9. Puelles VG, Hoy WE, Hughson MD, Diouf B, Douglas-Denton RN, Bertram JF. Glomerular number and size variability and risk for kidney disease. Curr Opin Nephrol Hypertens [Internet]. 2011;20(1):7–8. Available from: https://pubmed.ncbi.nlm.nih.gov/21099687/

10. Hoy WE, Hughson MD, Bertram JF, Douglas-denton R, Amann K. Nephron Number, Hypertension, Renal Disease, and Renal Failure. J Am Soc Nephrol [Internet]. 2005;16:2557–8. Available from: https://europepmc.org/article/MED/16049069

11. Batty GD, Shipley MJ, Gunnell D, Huxley R, Kivimaki M, Woodward M, et al. Height, wealth, and health: An overview with new data from three longitudinal studies. Econ Hum Biol [Internet]. 2009;7(2):138. Available from: https://pubmed.ncbi.nlm.nih.gov/19628438/

12. Neal Halfon, Christopher B. Forrest, Richard M. Lerner EMF. Handbook of Life Course Health Development [Internet]. Springer; 2018. 1–2 p. Available from: https://www.ncbi.nlm.nih.gov/books/NBK543707/

13. Bogin B, Varela-Silva MI. Leg length, body proportion, and health: A review with a note on beauty. Int J Environ Res Public Health [Internet]. 2010;7(3):1047–75. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2872302/

14. Millward DJ. Nutrition, infection and stunting: The roles of deficiencies of individual nutrients and foods, and of inflammation, as determinants of reduced linear growth of children. Nutr Res Rev [Internet]. 2017;30(1):50–72. Available from: https://www.cambridge.org/core/journals/nutrition-research-reviews/article/nutrition-infection-and-stunting-the-roles-of-deficiencies-of-individual-nutrients-and-foods-and-of-inflammation-as-determinants-of-reduced-linear-growth-of-children/195A1401085226

15. Hoy WE, Hughson MD, Singh GR, Douglas-Denton R, Bertram JF. Reduced nephron number and glomerulomegaly in Australian Aborigines: A group at high risk for renal disease and hypertension. Kidney Int [Internet]. 2006;70(1):104–10. Available from: https://www.sciencedirect.com/science/article/pii/S0085253815517419

16. Atukunda P, Ngari M, Chen X, Westerberg AC, Iversen PO, Muhoozi G. Longitudinal assessments of child growth: A six-year follow-up of a cluster-randomized maternal education trial. Clin Nutr [Internet]. 2021;40(9):5106–13. Available from: https://doi.org/10.1016/j.clnu.2021.08.007

17. Takele BA, Gezie LD, Alamneh TS. Pooled prevalence of stunting and associated factors among children aged 6-59 months in Sub-Saharan Africa countries: A Bayesian multilevel approach. PLoS One [Internet]. 2022;17(10 October):1–19. Available from: http://dx.doi.org/10.1371/journal.pone.0275889

18. Brophy PD, Charlton JR, Carmody JB, Reidy KJ, Harshman L, Segar J, et al. Chronic Kidney Disease : A Life Course Health Development Perspective. 2018; Available from: https://www.ncbi.nlm.nih.gov/books/NBK543705/

19. Kayange NM, Smart LR, Tallman JE, Chu EY, Fitzgerald DW, Pain KJ, et al. Kidney disease among children in sub-Saharan Africa: Systematic review. Pediatr Res [Internet]. 2015;77(2):272–81. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4426498/

20. Jha V, Parameswaran S. Community-acquired acute kidney injury in tropical countries. Nat Rev Nephrol [Internet]. 2013;9(5):278–90. Available from: http://dx.doi.org/10.1038/nrneph.2013.36

21. Stanifer JW, Muiru A, Jafar TH, Patel UD. Chronic kidney disease in low- and middle-income countries. Nephrol Dial Transplant [Internet]. 2016;31(6):868–74. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4876969/

22. Schmidt IM, Mølgaard C, Main KM, Michaelsen KF. Effect of gender and lean body mass on kidney size in healthy 10-year-old children. Pediatr Nephrol [Internet]. 2001;16(4):366–70. Available from: https://link.springer.com/content/pdf/10.1007/s004670100568.pdf

23. Bakker H, Gaillard R, Franco OH, Hofman A, Der AJ Van, Steegers EAP, et al. Fetal and Infant Growth Patterns and Kidney Function at School Age. J Am Soc Nephrol [Internet]. 2014;25:2607–15. Available from: https://jasn.asnjournals.org/content/jnephrol/25/11/2607.full.pdf

24. Barker DJP, Osmond C, Forsén TJ, Kajantie E, Eriksson JG. Trajectories of Growth among Children Who Have Coronary Events as Adults. N Engl J Med [Internet]. 2005;353(17):1802–9. Available from: https://www.nejm.org/doi/10.1056/NEJMoa044160?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub 0www.ncbi.nlm.nih.gov

25. Bakker H, Gaillard R, Franco OH, Hofman A, Van Der Heijden AJ, Steegers EAP, et al. Fetal

and infant growth patterns and kidney function at school age. J Am Soc Nephrol. 2014;25(11):2607–15.

26. Andersen GS, Girma T, Wells JCK, Kæstel P, Leventi M, Hother AL, et al. Body composition from birth to 6 mo of age in Ethiopian infants: Reference data obtained by air-displacement plethysmography. Am J Clin Nutr. 2013;98(4):885–94.

27. Wibaek R, Vistisen D, Girma T, Admassu B, Abera M, Abdissa A, et al. Body mass index trajectories in early childhood in relation to cardiometabolic risk profile and body composition at 5 years of age. Am J Clin Nutr. 2019;110(5):1175–85.

28. Payne RB. Tests of Kidney Function [Internet]. Second Edi. Scientific Foundations of Biochemistry in Clinical Practice. D. L. Williams and V. Marks; 1994. 325–337 p. Available from: http://dx.doi.org/10.1016/B978-0-7506-0167-2.50024-8

29. Wibaek R, Vistisen D, Girma T, Admassu B, Abera M, Abdissa A, et al. Associations of fat mass and fat-free mass accretion in infancy with body composition and cardiometabolic risk markers at 5 years : The Ethiopian iABC birth cohort study. PLoS Med [Internet]. 2019;16(8):1–22. Available from: https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1002888

30. Ellis KJ, Yao M, Shypailo RJ, Urlando A, Wong WW, Heird WC. Body-composition assessment in infancy: Air-displacement plethysmography compared with a reference 4-compartment model. Am J Clin Nutr [Internet]. 2007;85(1):90–5. Available from: https://pubmed.ncbi.nlm.nih.gov/17209182/

31. Ma G, Yao M, Lin Y, Lin A, Zou H, Urlando A, et al. Validation of a new pediatric air-displacement plethysmograph for assessing body composition in infants. Am J Clin Nutr [Internet]. 2004;79(4):653–60. Available from: https://academic.oup.com/ajcn/article/79/4/653/4690163

32. Mohamed M, Behery E, Ibrahiem MA, Siam S, Seksaka MA. Fetal Renal Volume and Fetal Doppler in Normal and Growth Restricted Fetuses : Is there a Correlation ? Gynecology & Obstetrics. 2012;2(2):2–6. Available from: https://www.longdom.org/open-access/fetal-renal-volume-and-fetal-doppler-in-normal-and-growth-restricted-fetuses-is-there-a-correlation-37756.html

33. Sampaio FJB. Theoretical kidney volume versus real kidney volume: comparative evaluation in fetuses. J Clin Anat [Internet]. 1995;71–5. Available from: https://link.springer.com/content/pdf/10.1007/BF01629504.pdf

34. Ferguson TW, Komenda P, Tangri N. Cystatin C as a biomarker for estimating glomerular filtration rate. Curr Opin Nephrol Hypertens. 2015;24(3):295–300.

35. Dönmez O, Korkmaz HA, Yldz N, Ediz B. Comparison of serum cystatin C and creatinine levels in determining glomerular filtration rate in children with stage i to III chronic renal disease. Ren Fail. 2015;37(5):784–90.

36. Zappitelli M, Parvex P, Joseph L, Paradis G, Grey V, Lau S, et al. Derivation and Validation of Cystatin C – Based Prediction Equations for GFR in Children. Am J Kidney Dis [Internet]. 2006;48(2):221–30. Available from: https://www.sciencedirect.com/science/article/pii/S0272638606008286?via%3Dihub

37. Pan H, Goldstein H. Multi-level repeated measures growth modelling using extended spline functions. Stat Med. 1998;17(23):2755–70.

38. Anderson EL, Tilling K, Fraser A, Macdonald-Wallis C, Emmett P, Cribb V, et al. Estimating trajectories of energy intake through childhood and adolescence using linear-spline multilevel models. Epidemiology [Internet]. 2013;24(4):507–15. Available from: https://journals.lww.com/epidem/Fulltext/2013/07000/Estimating_Trajectories_of_Energy_Intake_Through.5.aspx

39. Howe LD, Tilling K, Matijasevich A, Petherick ES, Santos AC, Fairley L, et al. Linear spline multilevel models for summarising childhood growth trajectories: A guide to their application using examples from five birth cohorts. Stat Methods Med Res [Internet]. 2016;25(5):1854–74. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4074455/pdf/10.1177_0962280213503925.pdf

40. Wang Y, Levey AS, Inker LA, Jessani S, Bux R, Samad Z, et al. Performance and Determinants of Serum Creatinine and Cystatin C–Based GFR Estimating Equations in South Asians. Kidney Int Reports [Internet]. 2021;6(4):962–75. Available from: https://doi.org/10.1016/j.ekir.2021.01.005

41. Zhang X, Martin RM, Oken E, Aris IM, Yang S, Kramer MS. Growth during Infancy and Early Childhood and Its Association with Metabolic Risk Biomarkers at 11.5 Years of Age. Am J Epidemiol [Internet]. 2020;189(4):286–93. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7305788/pdf/kwz234.pdf

42. Jones A, Charakida M, Falaschetti E, Hingorani AD, Finer N, Masi S, et al. Adipose and height

growth through childhood and blood pressure status in a large prospective cohort study. Hypertension [Internet]. 2012;59(5):919–25. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3428923/pdf/ukmss-47724.pdf

43. Regnault N, Kleinman KP, Rifas-Shiman SL, Langenberg C, Lipshultz SE, Gillman MW. Components of height and blood pressure in childhood. Int J Epidemiol [Internet]. 2014;43(1):149–59. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3937979/pdf/dyt248.pdf

44. Adair LS, Fall CHD, Osmond C, Stein AD, Martorell R, Ramirez-Zea M, et al. Associations of linear growth and relative weight gain during early life with adult health and human capital in countries of low and middle income: Findings from five birth cohort studies. Lancet [Internet]. 2013;382(9891):525–34. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3744751/

45. Weder AB, Schork NJ. Hypothesis Adaptation, Allometry, and Hypertension. Hypertensio. 1994;24:145–56.

46. Nüesch E, Dale C, Palmer TM, White J, Keating BJ, van Iperen EPA, et al. Adult height, coronary heart disease and stroke: A multi-locus Mendelian randomization meta-analysis. Int J Epidemiol. 2016;45(6):1927–37.

47. Dinkel E, Ertel M, Dittrich M, Peters H, Berres M, Wissermann HS. Pediatric Radiology Sonographical growth charts for kidney length and volume. Pediatr Radiol [Internet]. 1985;2:38–43. Available from: https://link.springer.com/content/pdf/10.1007/BF02387851.pdf

48. Whitehall J. Anthropometry and renal size of children suffering under sustained conflict in Sri Lanka. J Paediatr Child Health. 2008;44(11):656–60.

49. Bakker H, Kooijman MN, van der Heijden AJ, Hofman A, Franco OH, Taal HR, et al. Kidney size and function in a multi-ethnic population-based cohort of school-age children. Pediatr Nephrol [Internet]. 2014;29(9):1589–98. Available from: https://link.springer.com/content/pdf/10.1007/s00467-014-2793-8.pdf

50. Fong D, Denton KM, Moritz KM, Evans R, Singh RR. Compensatory responses to nephron deficiency: Adaptive or maladaptive? Nephrology. 2014;19(3):119–28.

51. Wells JCK, Devakumar D, Grijalva-eternod CS, Manandhar DS. Blood Pressure and the Capacity-Load Model in 8-Year-Old Children from Nepal : Testing the Contributions of Kidney Size and Intergenerational Effects. Am J ofHuman Biol. 2016;565:555–65.

52. Yang L, Magnussen CG, Yang L, Bovet P, Xi B. Elevated blood pressure in childhood or adolescence and cardiovascular outcomes in adulthood: A systematic review. Hypertension. 2020;948–55.

53. Juhola J, Magnussen CG, Viikari JSA, Kähönen M, Hutri-Kähönen N, Jula A, et al. Tracking of serum lipid levels, blood pressure, and body mass index from childhood to adulthood: The cardiovascular risk in young Finns study. J Pediatr. 2011;159(4):584–90.

54. Luyckx VA, Bertram JF, Brenner BM, Fall C, Hoy WE, Ozanne SE, et al. Effect of fetal and child health on kidney development and long-term risk of hypertension and kidney disease. Lancet [Internet]. 2013;382(9888):273–83. Available from: http://dx.doi.org/10.1016/S0140-

6736(13)60311-6

55. Nitsch D, Sandling JK, Byberg L, Larsson A, Tuvemo T, Syvnen AC, et al. Fetal, developmental, and parental influences on cystatin C in childhood: The uppsala family study. Am J Kidney Dis [Internet]. 2011;57(6):863–72. Available from: http://dx.doi.org/10.1053/j.ajkd.2010.12.025

Table1: Description of child and maternal characteristics.

Characteristics	N	Mean (±SD) or n (%)
Maternal characteristics at birth		
Age at delivery (years)	343	22.1 ± 4.5
Height (cm)	342	157.6 ± 5.9
Education	353	
No school		21 (6.0)
Primary school		214 (60.6)
Secondary school		67 (19.0)
Higher education		51 (14.4)
Child characteristics at birth		
Gestational age (weeks)	353	39.0 ± 1.0
Fat mass (kg)	349	0.22 ± 0.2
Fat free mass (kg)	349	2.84 ± 0.3
Birth weight (kg)	351	
<=2.5		30 (8.5)
>2.5 <=3.0		116 (33.1)
>3.0 <=3.5		152 (43.3)
>3.5		53 (15.1)
Birth order	351	
First born		171(48.7)
Second born		94 (26.8)

>= Third born		86 (24.5)
Current child characteristics		
Sex (male)	353	183 (51.8)
Age (years)	353	9.79 ± 1.0
Weight (kg)	353	27.3 ± 6.0
Height (cm)	353	132.2 ± 7.7
BMI (kg/m^2)	353	15.5 ± 2.2
Fat mass (kg)	351	5.6 ± 3.5
Fat free mass (kg)	351	21.7 ± 3.4

[1] Abbreviations: BMI, body mass index. [2] Data are mean (±SD) for continuous and count (%) for categorical variables

Table 2. Length at birth and ~~Non~~non-standardized linear growth at birth and growth velocity 0-6 years.

	Male (N=183)	Female (N=170)	P-value
Length at birth (cm)	49.61 ± 1.6	49.0 ± 1.5	<0.001
Growth velocity 0-3 months (cm/month)	4.09 ± 0.3	3.93 ± 0.22	<0.001
Growth velocity 3-6 months (cm/month)	1.72 ± 0.2	1.74 ± 0.19	0.63~~33~~
Growth velocity 6-24 months (cm/month)	0.91 ± 0.1	0.94 ± 0.11	0.03~~264~~
Growth velocity 24-48 months (cm/month)	0.60 ± 0.2	0.60 ± 0.06	0.46~~11~~
Growth velocity 48-76 months (cm/month)	0.56 ± 0.02	0.56 ± 0.02	0.~~8487~~85

[1] Data presented by mean (±SD). [2] Independent samples t-test.

Table 3: Markers of kidney function and kidney volume at the age of 7-12 years

Kidney outcomes	**Median (IQR)**	
	Male	Female
Serum cystatin C (mg/dl)	0.93 (0.83; 1.00)	0.94 (0.83; 1.01)
Estimated $GFR_{cystatin\ C}$ (ml/min per 1.73m²)	~~82.67~~83 (~~75.50~~76; 94~~.43~~)	~~81.64~~82 (75~~.06~~; 94~~.44~~)
Right kidney volume (cm³)	~~53.50~~54 (~~46.72~~47; 63~~.24~~)	53~~.43~~ (45~~.36~~; ~~60.73~~61)
Left kidney volume (cm³)	~~63.62~~ 64 (~~55.91~~56; ~~73.73~~74)	~~62.82~~63 (~~56.62~~57; 72~~.24~~)
Combined kidney volume (cm³)	~~116.63~~117 (~~103.62~~104; ~~135.58~~136)	117~~.36~~ (~~102.79~~103; ~~131.74~~132)

[1]Abbreviations: GFR, Glomerular Filtration Rate. [2] Data are presented on median (Interquartile range)

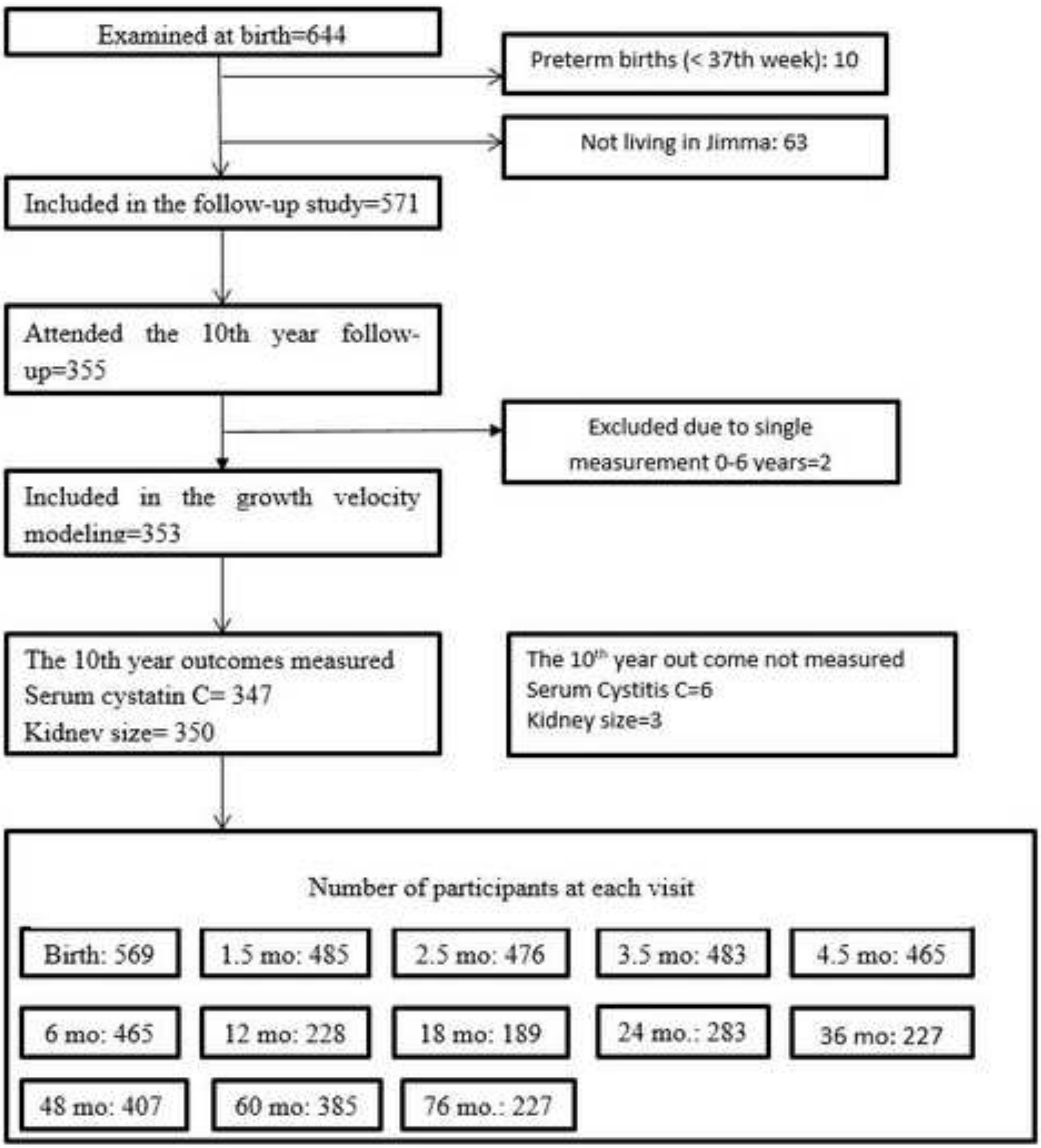
Figure legends

Fig 1: Flow diagram showing number of participants followed up at different time points. Out of 355 recruited at 10-year follow-up, 2 were excluded analysis they only had 1 height measurement from birth to 6 years, which makes the final sample for the 10-year analysis 353.

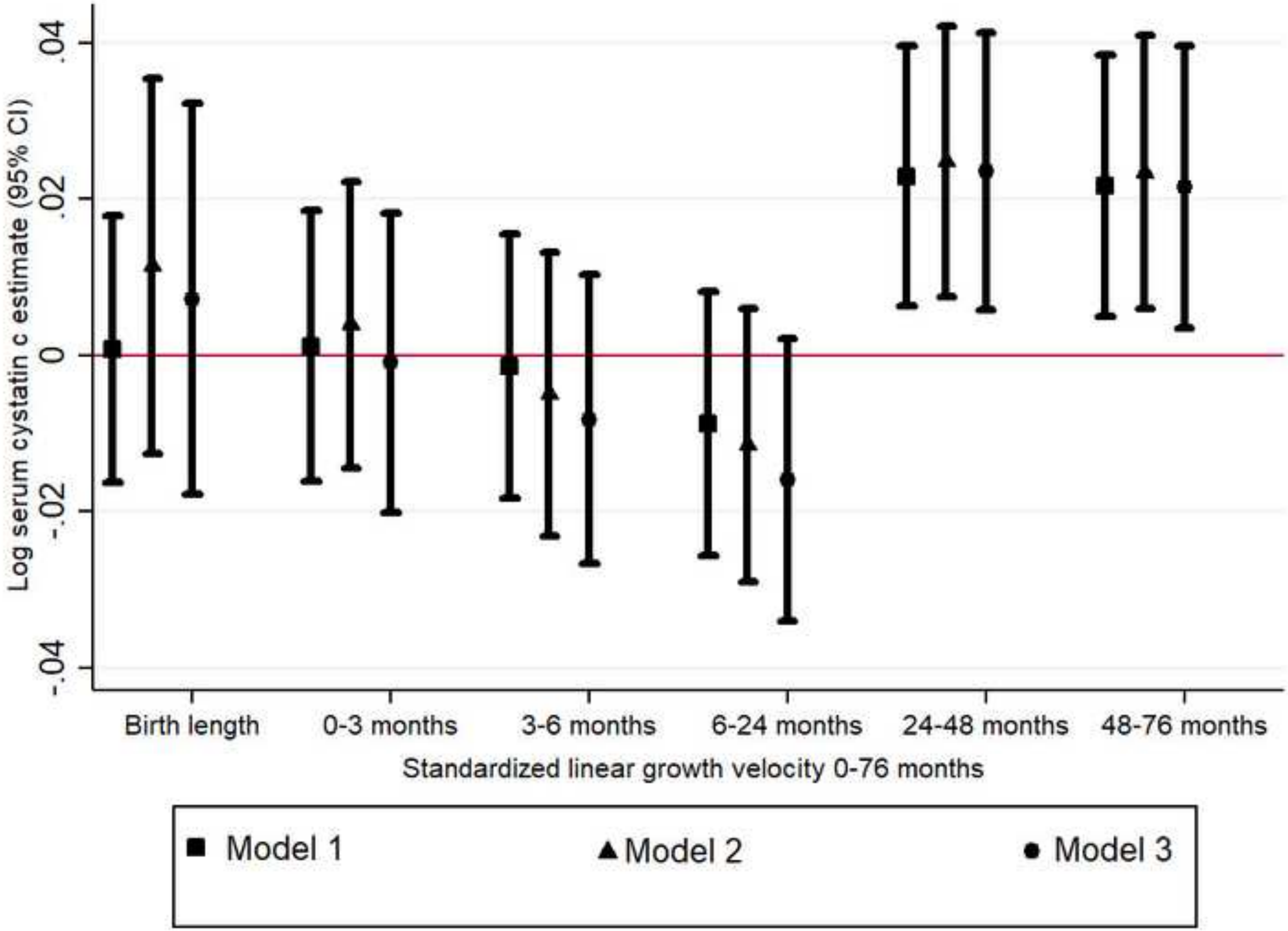
Fig 2: Association of standardized linear growth velocities 0-76 months with Log serum cystatin C at age of 10 years. The Y-axis represents the estimate with 95% CI. Model 1: Adjusted for sex and Current age. Model 2: as model 1, further adjusted for birth weight, gestational age, birth order and fat mass at 10^{th} follow-up. Model 3**:** as model 2, further adjusted for maternal education and maternal post-partum height.

Fig 3: Association of standardized linear growth velocities 0-6 years with kidney volume at 10 years at age of 10 years. The Y-axis represents the estimate with 95% CI. Model 1: Adjusted for sex and current age. Model 2: as model 1, further adjusted for birth weight, gestational age, birth order, and fat mass at 10^{th} follow-up. Model 3: as model 2, further adjusted for maternal education and maternal post-partum height.

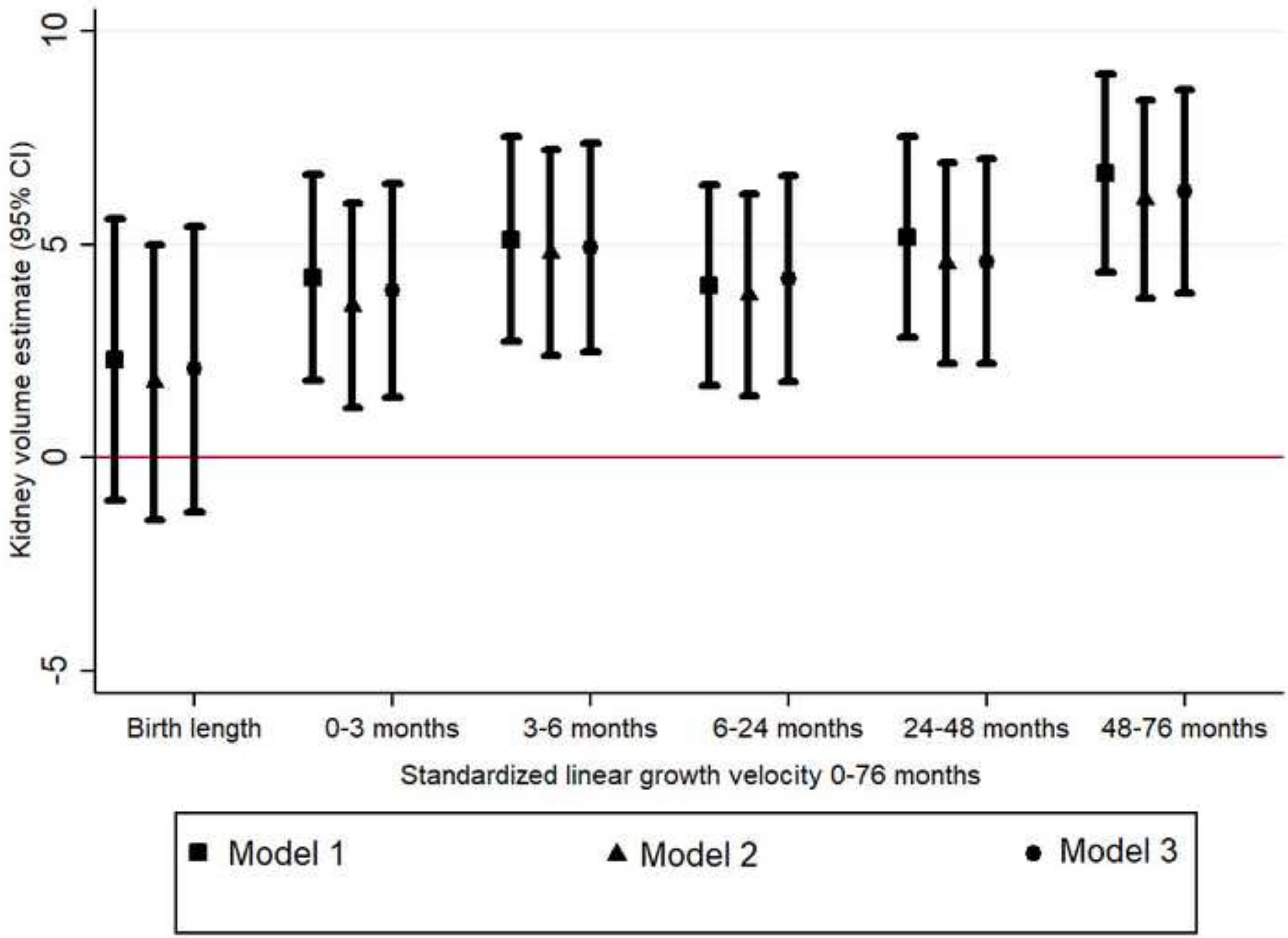
Flow diagram Click here to access/download;Figure;Figure 1.jpeg



Association of standardized linear growth velocities 0-76 months with Log serum cystatin C



Association of standardized linear growth velocities 0-6 years with kidney volume



Title: Association of linear growth velocities between 0 and 6 years with kidney function and size at 10 years: a birth cohort study in Ethiopia.

First author's name: Beakal Zinab

Supporting information's

Supplementary Table 1: Comparison of child and maternal characteristics between children who attended the 10th year visit and not.

	Attended 7-12 years follow-up(N=347)	**Missed 7-12 years follow-up (N=224)**	**P-value**
Birth characteristics			
Gender			0.33
Male	180 (51.9)	107 (47.8)	
Female	167 (48.1)	117 (52.2)	
Birth weight	3.06 ± 0.41	2.98 ± 0.41	0.03
Length at birth	49.2 ± 1.96	48.8 ± 1.99	0.01
Gestation	38.99 ± 0.92	39.05 ± 1.02	0.48
Birth order			0.01
First born	166 (48.1)	134 (61.5)	
Second born	94 (27.2)	45 (20.6)	
>= Third born	85 (24.6)	39 (17.9)	
Maternal characteristics			
Height at birth	157.6 ± 5.79	157.47 ± 5.91	0.75
School			0.38
No school	19 (5.5)	19 (8.5)	
Primary school	212 (61.1)	139 (62.1)	
Secondary school	66 (19.0)	37 (16.5)	
Higher education	50 (14.4)	29 (12.9)	

[1] Data are mean (±SD) for continuous and count (%) for categorical variables. [2] Chi-square test or independent samples t-test.

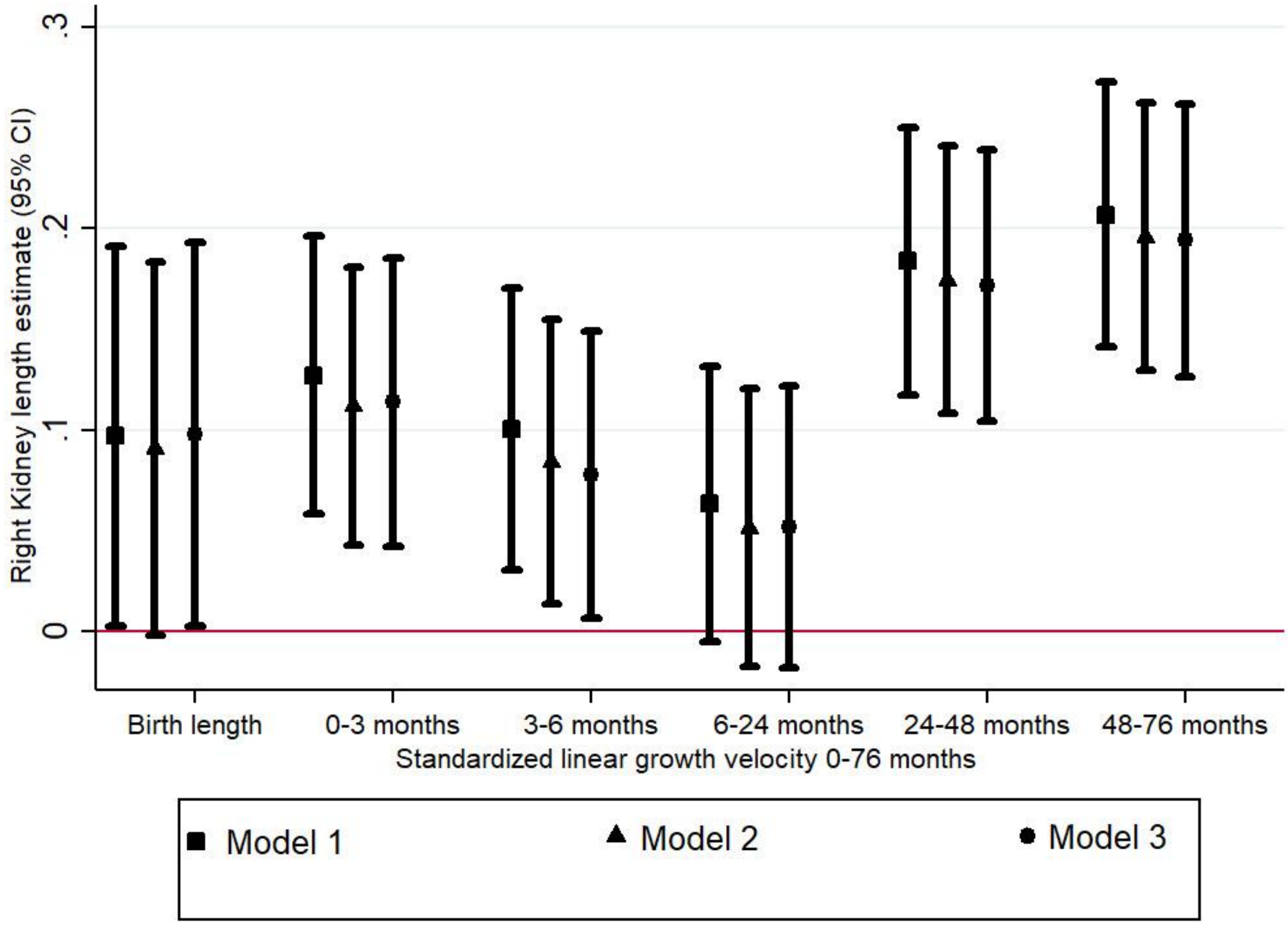
Supplementary Table 2: T-test Comparing low birth weight and normal birth weight children on serum cystatin C level.

Group	Mean	SD	CI (95%) for mean difference	P-value
Normal Birth weight	0.912	0.145	-0.084, 0.024	0.28
Low Birth Weight	0.942	0.143		

Supplementary Table 3: Association of standardized height with Log serum cystatin C and kidney size at age of 10 years.

Exposure	**Outcome**			
Height at 10th year follow-up	**Log Cystatin C**		**Kidney volume**	
	β	**CI (95%)**	**β**	**CI (95%)**
Model 1	0.003	0.0004, 0.006	1.48	1.10, 1.87
Model 2	0.003	0.0004, 0.006	1.36	0.96, 1.76
Model 3	0.003	0.00003, 0.006	1.47	1.06, 1.90

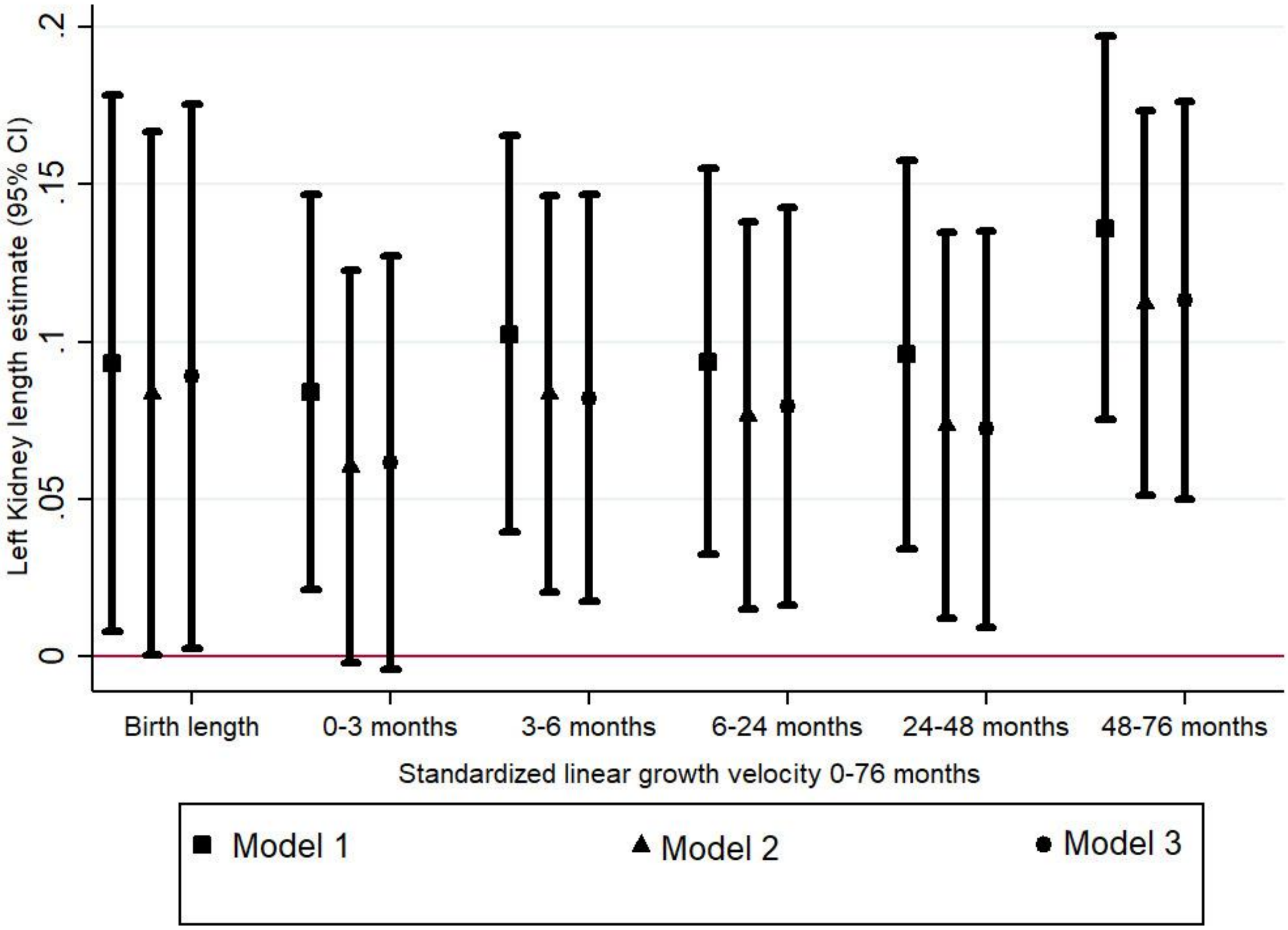
[1] Model 1 adjusts for age and gender. [2] Model 2 is Model 1 plus head circumference at birth, birth order and gestational age. [3] Model 3 is Model 2 plus maternal schooling at birth, wealth index at birth, and school type.



Supplementary figure 1: Association standardized linear growth velocities 0-6yrs with Right kidney length at 10 years.

The vertical bars from left to right represent models 1, 2, and 3, respectively.

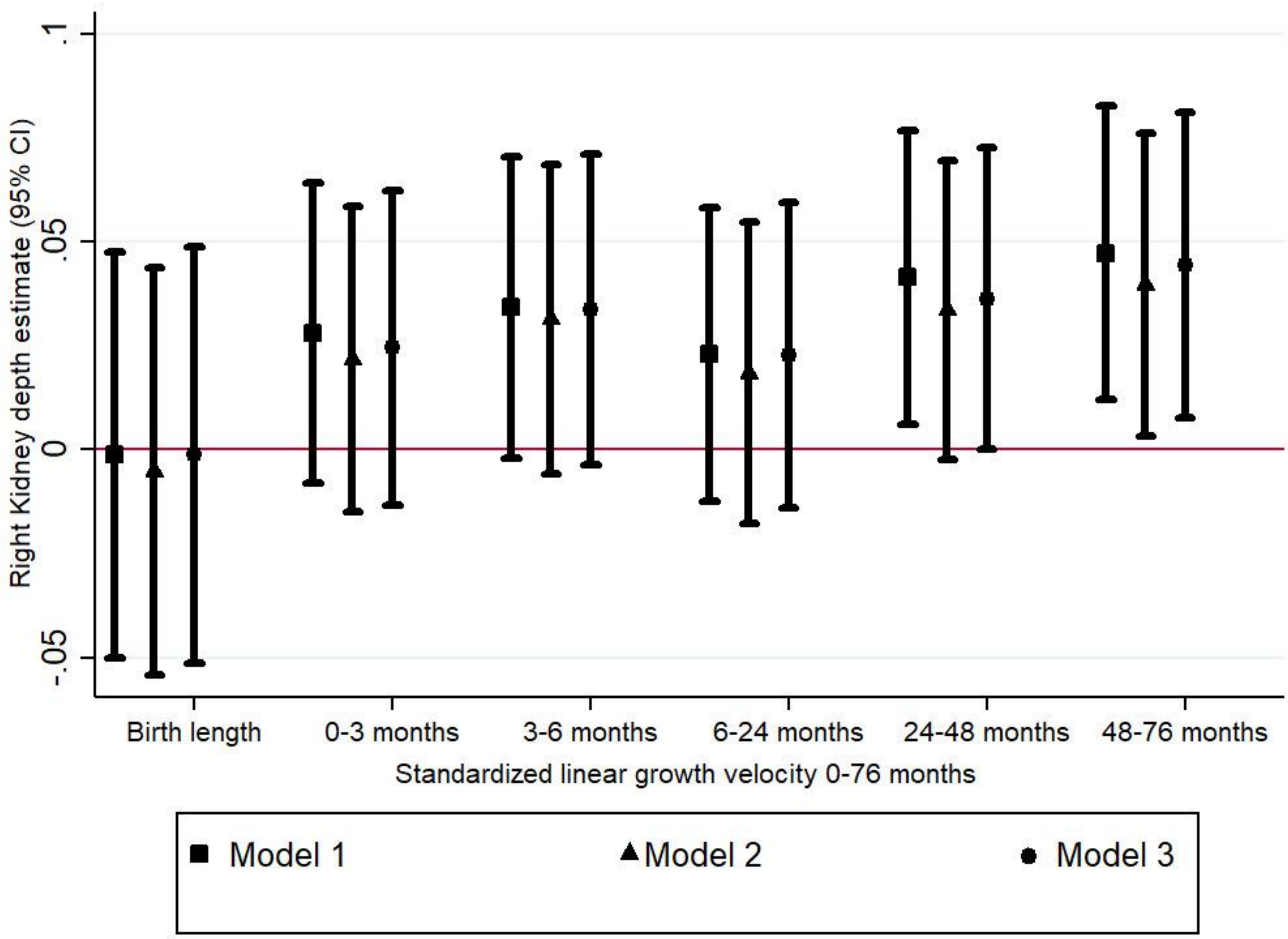
Model 1: Adjusted for sex and current age (years). Model 2: as model 1, further adjusted for birth weight (Kg), Gestational age (weeks), Birth order, and Fat mass (Kg) at 10[th] follow-up. Model 3: as model 2, further adjusted for maternal education and maternal post-partum height (meter).



Supplementary figure 2: Association standardized linear growth velocities 0-6yrs with Left kidney length at the age of 10 yrs.

The vertical bars from left to right represent models 1, 2, and 3, respectively.

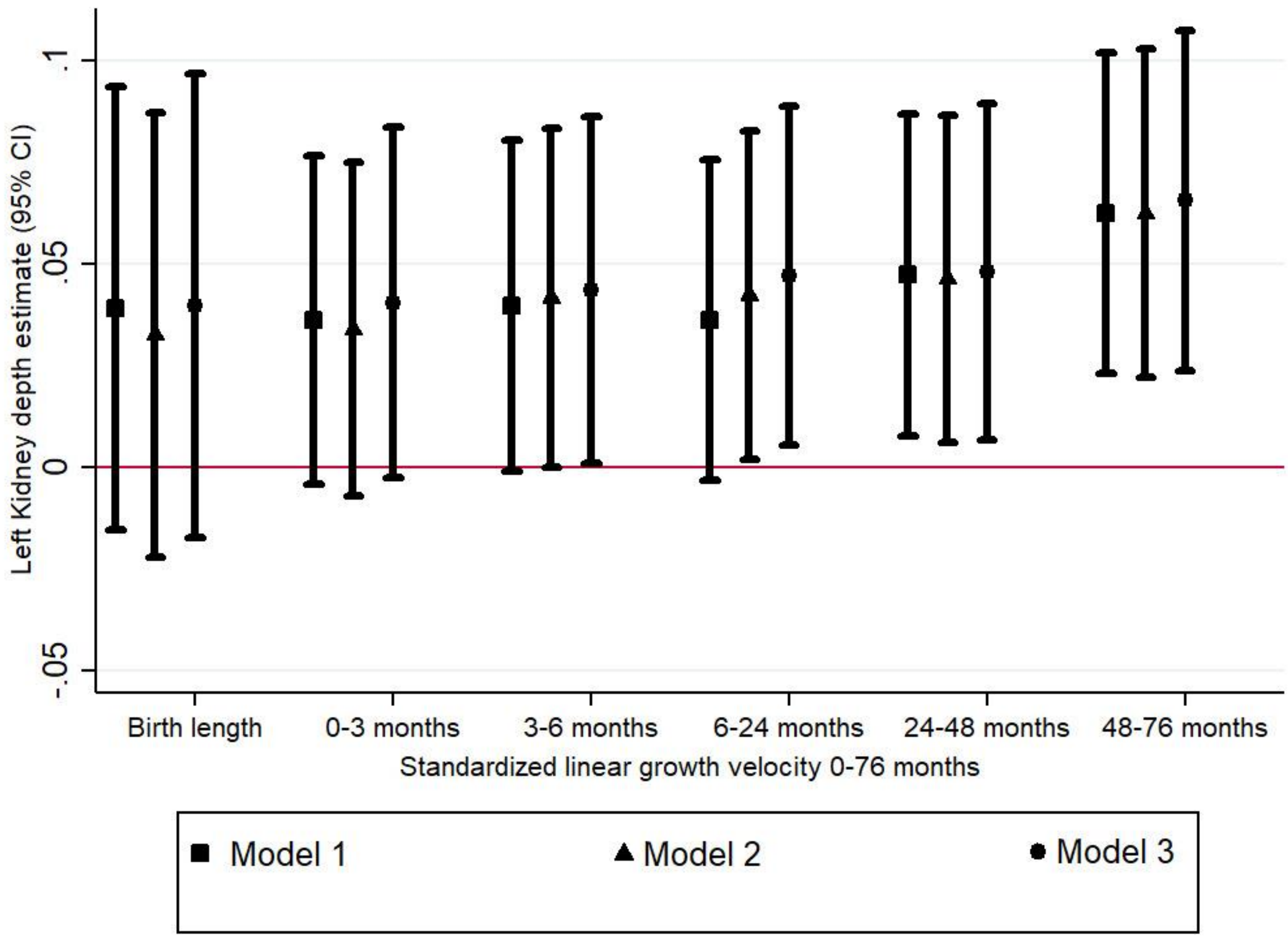
Model 1: Adjusted for sex and current age (years). Model 2: as model 1, further adjusted for birth weight (Kg), Gestational age (weeks), Birth order, and Fat mass (Kg) at 10th follow-up. Model 3: as model 2, further adjusted for maternal education and maternal post-partum height (meter).



Supplementary figure 3: Association of standardized linear growth velocities 0-6yrs with right kidney depth at 10 yrs.

The vertical bars from left to right represent models 1, 2, and 3, respectively.

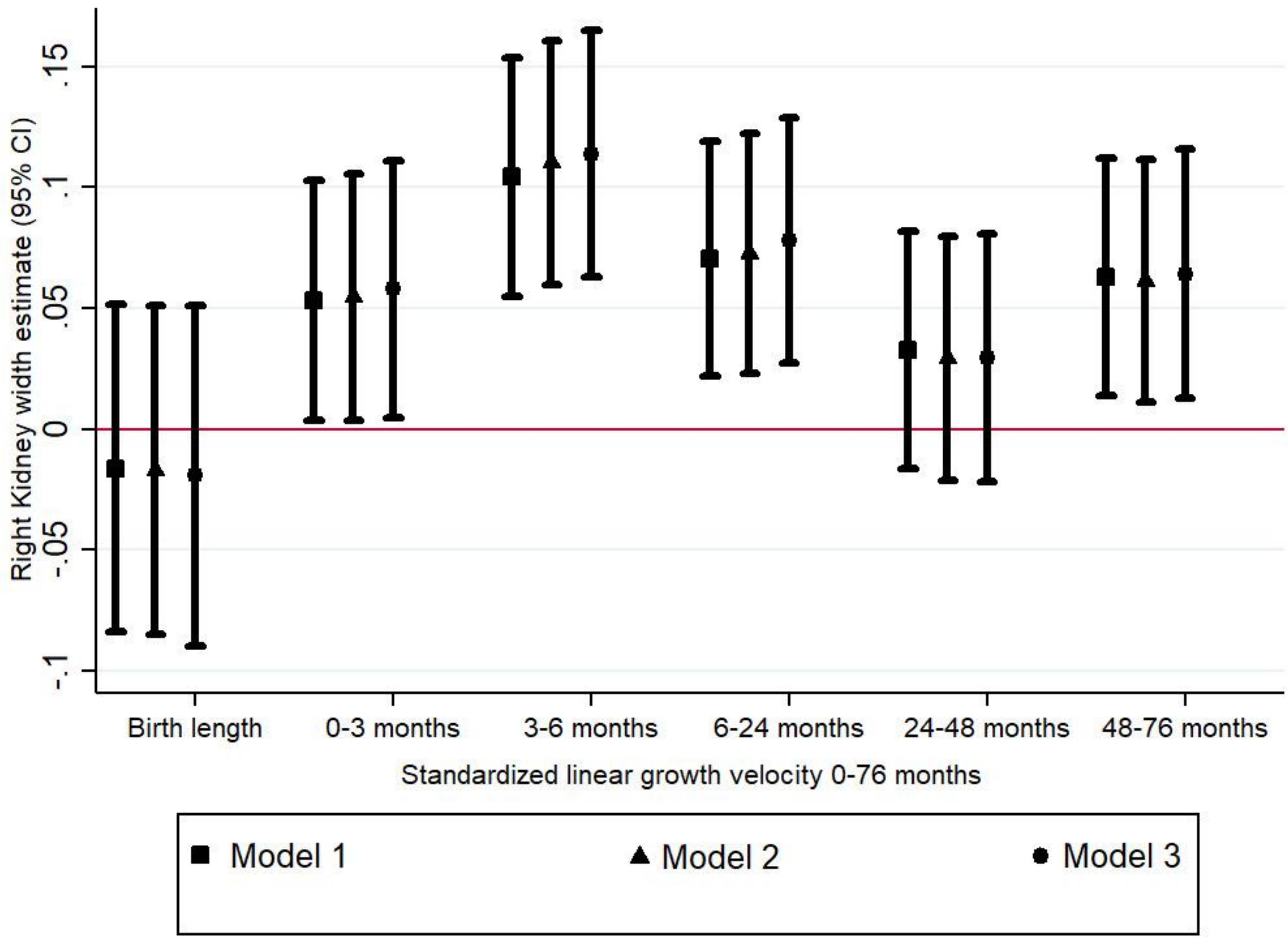
Model 1: Adjusted for sex and current age (years). Model 2: as model 1, further adjusted for birth weight (Kg), Gestational age (weeks), Birth order, and Fat mass (Kg) at 10th follow-up. Model 3: as model 2, further adjusted for maternal education and maternal post-partum height (meter).



Supplementary figure 4: Association of standardized linear growth velocities 0-6yrs with left kidney depth at the age of 10 yrs.

The vertical bars from left to right represent models 1, 2, and 3, respectively.

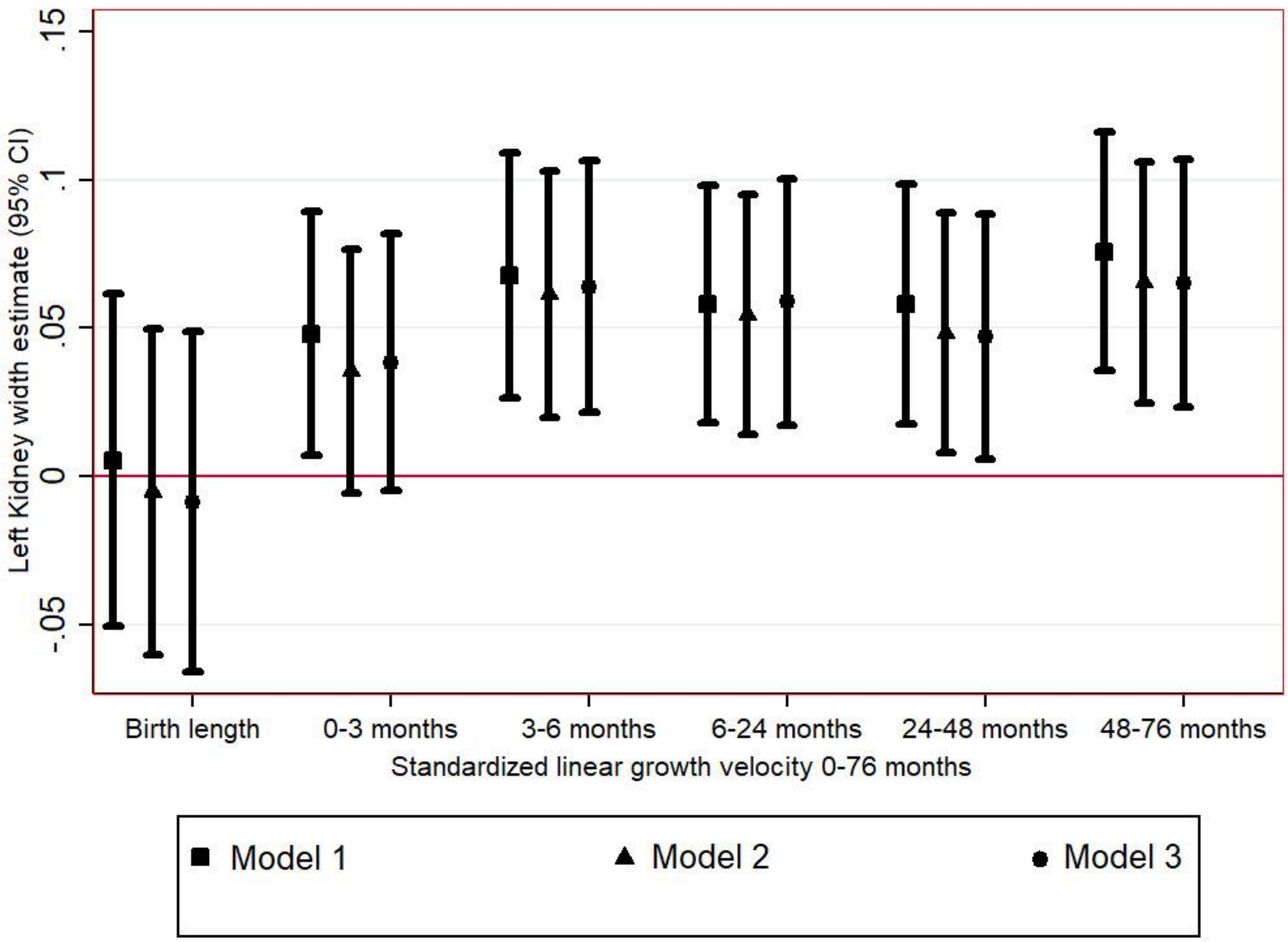
Model 1: Adjusted for sex and current age (years). Model 2: as model 1, further adjusted for birth weight (Kg), Gestational age (weeks), Birth order, and Fat mass (Kg) at 10^{th} follow-up. Model 3: as model 2, further adjusted for maternal education and maternal post-partum height (meter).



Supplementary figure 5: Association of standardized linear growth velocities 0-6yrs with right kidney width at the age of 10 yrs.

The vertical bars from left to right represent models 1, 2, and 3, respectively.

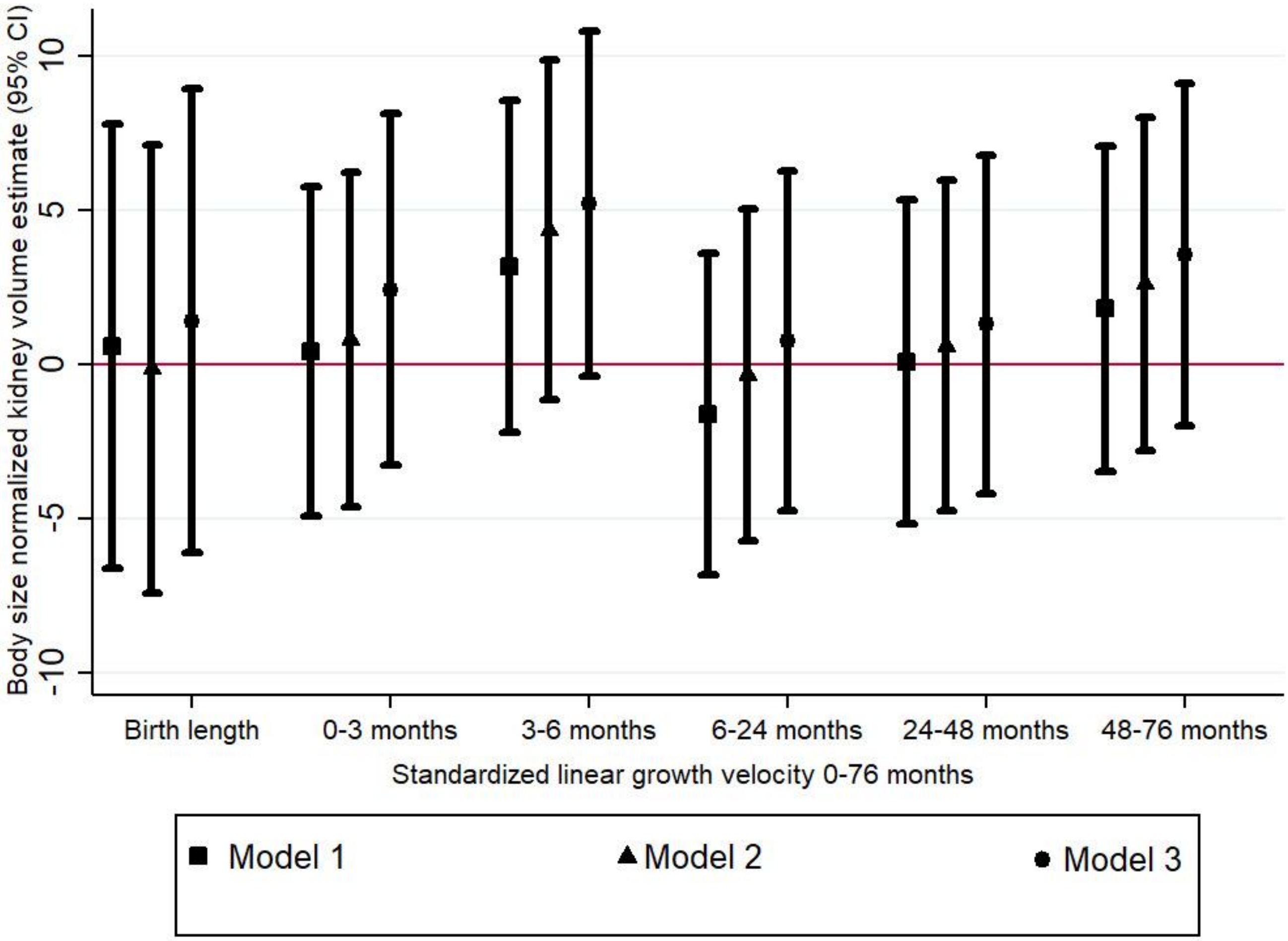
Model 1: Adjusted for sex and current age (years). Model 2: as model 1, further adjusted for birth weight (Kg), Gestational age (weeks), Birth order, and Fat mass (Kg) at 10th follow-up. Model 3: as model 2, further adjusted for maternal education and maternal post-partum height (meter).



Supplementary figure 6: Association of standardized linear growth velocities 0-6yrs with left kidney width at the age of 10 yrs.

The vertical bars from left to right represent models 1, 2, and 3, respectively.

Model 1: Adjusted for sex and current age (years). Model 2: as model 1, further adjusted for birth weight (Kg), Gestational age (weeks), Birth order, and Fat mass (Kg) at 10th follow-up. Model 3: as model 2, further adjusted for maternal education and maternal post-partum height (meter).



Supplementary figure 7: Association of standardized linear growth velocities 0-6yrs with body size normalized kidney volume at the age of 10 yrs.

Body Surface Area BSA [m^2] = Weight [kg] $^{0.4838}$ × Height [cm] $^{0.3}$ × 0.017827)

The vertical bars from left to right represent models 1, 2, and 3, respectively.

Model 1: Adjusted for sex and current age (years). Model 2: as model 1, further adjusted for birth weight (Kg), Gestational age (weeks), Birth order, and Fat mass (Kg) at 10^{th} follow-up. Model 3: as model 2, further adjusted for maternal education and maternal post-partum height (meter).