Published in final edited form as:
*J Pediatr*. 2014 July ; 165(1): 154–162.e1. doi:10.1016/j.jpeds.2014.02.051.

# The effect of abnormal birth history on ambulatory blood pressure and disease progression in children with chronic kidney disease

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## Abstract

**Objective—**To examine the associations between abnormal birth history (birth weight [BW] <2500 grams, gestational age <36 weeks, or small for gestational age), BP, and renal function among 332 participants (97 with abnormal and 235 with normal birth history) in the Chronic Kidney Disease in Children (CKiD) Study, a cohort of children with chronic kidney disease (CKD).

**Study design—**Casual and 24-hour ambulatory BP were obtained. Glomerular filtration rate (GFR) was determined by iohexol disappearance. Confounders (birth and maternal characteristics, socioeconomic status) were used to generate predicted probabilities of abnormal birth history for



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[*]List of members of the CKiD Study is available at www.jpeds.com (Appendix).

The authors declare no conflicts of interest.

propensity score matching. Weighted linear and logistic regression models with adjustment for quintiles of propensity scores and CKD diagnosis were used to assess the impact of birth history on BP and GFR.

**Results—**Age at enrollment, percent with glomerular disease, and baseline GFR were similar between the groups. Those with abnormal birth history were more likely to be female, of Black race or Hispanic ethnicity, to have low household income, or part of a multiple birth. Unadjusted BP measurements, baseline GFR and change in GFR did not differ significantly between the groups; no differences were seen after adjusting for confounders by propensity score matching.

**Conclusions—**Abnormal birth history does not appear to have exerted a significant influence on BP or GFR in this cohort of children with CKD. The absence of an observed association is likely secondary to the dominant effects of underlying CKD and its treatment.

There is growing evidence that adverse events early in life, particularly *in utero*, increase the risk of chronic diseases. Children with chronic kidney disease (CKD) are more likely to have been premature, low-birth weight, or small for gestational age compared with children without chronic kidney disease [1,2]. Abnormal birth history (defined as premature, low-birth weight, or small for gestational age) may be an indicator of impaired nephrogenesis [3-6], which in turn may increase the risk for hypertension and chronic kidney disease [3,7].

In the general population, abnormal birth history is known to be associated with a higher incidence of adult cardiovascular disease [8,9]. The effect on adult blood pressure (BP) is reasonably well established [10-13]. Recent studies have found inverse associations between birth weight and several BP measaures, even in the pediatric age range [10, 14-21].

Among children with CKD, the effect of abnormal birth history on BP and renal function has not yet been studied. If abnormal birth history is associated with increased BPs or worsening renal function in the presence of CKD, such children may require more intensive monitoring and therapy early in life. The purpose of the present analysis is to investigate the effect of abnormal birth history on casual and ambulatory BP (ABP) and renal function among children with CKD.

## Methods

The Chronic Kidney Disease in Children (CKiD) Study is a prospective observational cohort study initiated in 2005 to investigate the natural history of chronic kidney disease (CKD) at 51 pediatric nephrology centers in North America [22]. A list of participating investigators and centers is included as Appendix 1 in the online supplement. The study protocol was approved by the Institutional Review Boards of each participating center and informed consent and assent were obtained from all participants according to local requirements.

Children were eligible for enrollment in CKiD based on age (1 to 16 years) and estimated Schwartz formula glomerular filtration rate (GFR) (30 to 90 mL/minute/1.73m$^2$ [23]). Clinical and demographic data were collected at baseline, including CKD diagnosis. The primary diagnosis of CKD was self-reported at baseline for each participant and categorized as either non-glomerular or glomerular. Full descriptions of the CKD diagnoses and their associated categories used in the CKiD study have been previously reported [2,22].

### Abnormal birth history

Low birth weight (LBW), premature birth and small for gestational age (SGA) were parent-reported at study entry with the following definitions: LBW was birth weight <2500g, prematurity was gestational age <36 weeks, and SGA was birth weight <10$^{th}$ percentile for gestational age as previously reported [2]. Abnormal birth history for purposes of this analysis was defined as the presence of any one of these abnormalities (LBW, premature or SGA).

### Outcomes

The primary outcomes of interest were BP levels and variability (casual and ambulatory), ambulatory heart rate (HR) variability, and change in GFR. Casual BP measurements were obtained at each CKiD study visit using an aneroid sphygmomanometer. At each study visit, three BP measurements at 30-second intervals were obtained by auscultation of the brachial artery using the first Korotkoff sound for SBP and the fifth Korotkoff sound for DBP. The average of the three BP measurements was recorded as the participant's casual BP for that visit. The CKiD Clinical Coordinating Centers provided all participating sites the same aneroid sphygmomanometer (Mabis MedicKit 5; Mabis Healthcare, Waukegan, IL). CKiD clinical staff were trained and certified yearly in the auscultatory BP measurement technique, and annual calibration of each center's aneroid device was performed. Details of the standardized casual BP measurement technique have been previously published [24].

Ambulatory BP monitoring (ABPM) was performed one year after study entry, and every other year thereafter using a SpaceLabs 90217 oscillometric device (SpaceLabs Healthcare, Issaquah, WA). Monitors are programmed centrally at the ABPM Center (University of Texas at Houston), shipped to the clinical sites, and placed on the subject's non-dominant arm. BP readings were obtained every 20 minutes throughout the monitoring period. All participating clinical sites received annual training in monitor placement from the ABPM Center. Details of the ABPM procedure have been previously described [25]. Because we were interested in the putative effect of abnormal birth history on ABP, the analysis was restricted to participants with available ABPM data.

Casual BP levels were summarized by age-, sex-, and height-adjusted z-scores [26] and were interpreted as standard deviation units from the mean of the normal population (z-score = 0). Summarized ABP levels are reported BP index, calculated as the mean ambulatory BP, by wake or sleep state, divided by the corresponding 95$^{th}$ percentile for age, sex, and height for the normal population as previously reported [25]. Ambulatory BP load represents the proportion of readings greater than the 95$^{th}$ percentile, by wake and sleep states. Mean systolic BP (SBP) or diastolic BP (DBP) levels above the 95$^{th}$ percentile or SBP or DBP loads greater than 25%, for each wake and sleep states were classified as having abnormal ABP [25].

GFR was determined at each annual CKiD study visit. Directly measured GFR (iGFR) by iohexol plasma clearance occurred at study entry, one year later and then biennially. When iohexol GFR was not measured, estimated GFR (eGFR) was used in its place [23], a validated approach used previously with CKiD data [27,28]. This combination of iGFR and

eGFR is hereafter referred to as ieGFR [27]. Individual regressions of ieGFR in the log scale (dependent variable) on time in years (independent variable) provided subject-specific intercepts and slopes [27], which are interpreted as GFR at study entry and the average change in GFR over time, respectively. The 332 subjects included in the analysis contributed 1736 ieGFR measurements and 50% of these subjects contributed 5 observations (approximately 4 years of follow-up). Urine protein:creatinine ratio (mg/mg of creatinine) was measured at each annual CKiD study visit [22].

## Propensity scores

In order to determine the effect of abnormal birth history on BP and GFR measurements, independent of confounders such as maternal factors and SES, propensity score matching and weighting methods [29,30] were used to create comparable groups of exposed subjects (children with abnormal birth history) and unexposed subjects (children without abnormal birth history) who were similar with respect to baseline characteristics. Matching of propensity scores, which reflect each child's predicted probability of having an abnormal birth history, was used to achieve balance in confounding variables between the exposed (abnormal birth history) and unexposed (normal birth history) children. The propensity scores were derived from a logistic regression model with the odds of abnormal birth history as a function of observed baseline demographic, clinical and maternal characteristics. Demographic variables included sex, race (black vs. non-black), ethnicity (Hispanic vs. non-Hispanic) and age of the child at time of study entry. Clinical variables included primary CKD diagnosis (glomerular vs. non-glomerular), percent of life with CKD (> 90%, 50 to 90%, <50%) and history of twin/multiple birth. Maternal variables were age at birth (< or ≥24 years), highest level of education attained, height, weight and BMI at time of study entry; and household socioeconomic status: household income (<$36 000/year), birth parents living separately, a family size of less than three, adult smoker in the household and no employer health insurance at the time of study entry.

Variables that were in the causal pathway from abnormal birth history and disease severity were excluded from matching because these would mediate the putative detrimental effects of abnormal birth history (for example, hospital intensive care after birth is a marker of abnormal birth history and not a predictor of the exposure).

For a small percentage of subjects, maternal height (7%) and weight (9%), and subsequently BMI (11%), were missing. We imputed the sample mean in these missing observations and created indicator (binary) variables for missingness. Previous work has suggested this approach is appropriate for propensity score matching [31]. Among variables where there was less than 5% missing, the sample mean was imputed to complete missing data.

## Matching method

Full constrained matching was used to create weighted pseudopopulations of exposed and unexposed subjects. The purpose of this matching method is to create matched sets of subjects with similar propensity scores that include either one exposed subject and multiple unexposed subjects, or one unexposed subject and multiple exposed subjects. Subject-specific weights were derived from these matched sets and used in regression models

described below. We imposed constraints adapted for this particular dataset, as recommended by Stuart & Green [32] that allowed poorly matched subjects to be discarded, at least one unexposed subject per exposed subject and no more than 10 unexposed subjects per exposed subjects. Other matching methods (1:1 nearest neighbor matching and unconstrained full matching) were explored in a sensitivity analysis by comparing standardized biases of the confounding variables, and the inferences remained unchanged.

### Statistical analyses

Clinical and demographic characteristics and outcome variables were compared based on birth history status and summarized by descriptive statistics. Outcome variables were converted to the log scale due to skewed distributions, and geometric means are presented, with the exception of BP z-scores, which were normally distributed. Two-sample t-tests in the log scale and Fisher exact tests were used to compare univariate differences by birth history status. To determine the effect of exposure, we used weighted linear and logistic regression models with a main effect of abnormal birth history and adjustment for quintiles of propensity scores (based on the distribution abnormal birth history subjects). Weights were derived from the matched sets defined from the full constrained matching algorithm. Specifically, weights were calculated as the relative number of exposed to unexposed subjects within each matched set and scaled to the ratio of exposed to unexposed subjects in the study sample in order to estimate the average treatment effect on the treated [30]. Interactions with quintiles of propensity scores were assessed and excluded if the interaction was not significant. The threshold for significance was $P< 0.05$. For continuous variables, adjusted mean values with 95% confidence intervals were reported for the reference group: subjects in the 3$^{rd}$ quintile of propensity score with and without abnormal birth history. For dichotomous variables, the adjusted proportion calculated from a logistic regression model for the same reference group with and without abnormal birth history was reported. We additionally adjusted for CKD diagnosis (glomerular versus non-glomerular) as a covariate in the weighted analysis. As sensitivity analyses, we repeated the weighted analyses and included proteinuria as a covariate in the model, and also conducted the same models excluding CKD diagnosis as a covariate. All statistical analyses were conducted in R, version 2.14.0, using the MATCHIT package [33,34]. This package allows for the generation of propensity scores, formation of matched sets and calculation of weights in a unified setting.

## Results

Baseline demographic and clinical characteristics of subjects, stratified by birth history status, are presented in Table I. Subjects with abnormal birth history were more likely to be female, Black, part of a multiple birth and have characteristics related to lower SES (household income < $36 000, birth parents not living together, younger maternal age at birth, household less likely to have employer-based insurance). There was no difference in antihypertensive medication use (any, ACEi, ARB or diuretics) between subjects with normal and abnormal birth history. Variables listed in Table I, except for glomerular diagnosis and use of antihypertensive medications, were included as predictors in the logistic model to generate propensity scores.

The Figure presents the distribution of the propensity scores before and after full constrained matching by birth history status, displaying individual subjects as well as overall distributions by boxplots. The unmatched distributions demonstrate that the subjects with abnormal birth history had a higher propensity for abnormal birth and the normal subjects did not, providing support for the validity of our model. Importantly, there was substantial overlap, or common support, between the two distributions, which is an important condition for matching methods. Three subjects with abnormal birth history with high propensity for the exposure were discarded because there were no appropriate matches among the normal subjects. Similarly, 23 normal subjects with birth history were discarded, and these subjects had low propensity for being abnormal. The discontinuous boxplots represent the weighted distributions after matching and describe the 94 abnormal and 212 normal subjects with birth history used in the final (weighted/adjusted) analysis. These distributions were similar by birth history status; however, the upper 25$^{th}$ percentile tended to have lower propensity scores among normal subjects birth history.

Casual BP, ambulatory BP variables (mean and summarized levels), ambulatory BP and HR variability and renal outcomes (GFR level at study entry and % change per year) among the unmatched study sample (n=332) are presented in Table II. The casual median SBP and DBP z-scores in the study subjects were higher than a normal population. Although SBP tended to be higher among children with abnormal birth history (z-score= 0.39 vs. 0.18, p= 0.255), DBP was similar in the two groups (z-score= 0.24 vs. 0.28, p= 0.918). Ambulatory BP was also elevated in both groups of CKD patients, and approached the clinical definition of hypertension as indicated by BP Indices (mean BP level divided by the 95$^{th}$ percentile limit) ranging from 0.83-0.92. The proportion of subjects with abnormal ambulatory BP (as defined by either elevated mean levels or load) was also similar regardless of birth history status. GFR at entry was similar in CKD patients with and without an abnormal birth history (geometric means were 46.7 vs. 45.6 ml/min/1.73m$^2$, p= 0.573) as was proteinuria (geometric means 0.45 mg/mg creatinine vs 0.45, p= 0.948). Both groups demonstrated substantial declines in renal function over time (about 4% and 5% per year, on average).

Table III presents the estimated means and proportions of the same outcomes, with appropriate weighting by the propensity score matching process as well as adjustment for CKD diagnosis. Even though diagnosis was not associated with the exposure (Table I), previous reports from the CKiD Study have described different disease severity and progression of glomerular vs. non-glomerular diagnoses [35].These results present the estimated mean (or probability of having this outcome) of a subject in the 3$^{rd}$ quintile of propensity score (the reference group). The results were consistent with the unadjusted values, with subjects presenting with elevated BP values, a high prevalence of abnormal ABP and low ieGFR at study entry. For casual BP measurements, the differences by birth history status were attenuated compared with the univariate (unweighted and unmatched) results. A similar result was observed for ambulatory BP and HR measurements: there were no significant differences by birth history status for major BP values, BP variation and HR. There were a higher proportion of subjects with abnormal birth history with elevated DBP load (ie, DBP load > 25%) compared with normal subjects (18% vs. 11%) and this effect was borderline significant (p= 0.072). The effect sizes were relatively small, indicating that the lack of significance was not related to sample size. The models also suggested subjects

with a glomerular diagnosis were not at higher risk for BP abnormalities than those with a non-glomerular diagnosis, although they were at higher risk for accelerated GFR decline, as previously reported [35].

We conducted two sensitivity analyses. First, we included proteinuria as a covariate in the weighted regression models. Second, we excluded CKD diagnosis as a covariate from the models. In both sensitivity analyses, the effect of abnormal birth history remained unchanged.

## Discussion

Although the concept of perinatal programming as an important influence on the development of adult cardiovascular disease has become widely accepted in the literature, we did not see a significant effect of abnormal birth history on either BP or decline in renal function in the among children with CKD. There are a number of possible explanations for the lack of effect of birth history on BP in the CKiD cohort, including the young age of the subjects, the impact of treatment of hypertension, and, perhaps most importantly, the dominant effect of the underlying CKD on these outcomes.

According to the Barker hypothesis, low birth weight is strongly associated with the development of future cardiovascular disease. Several population-based studies have shown that for each kilogram increase in birth weight, adult systolic BP is 1-2 mmHg lower [20,36]. Other large studies have shown that low birth weight is associated with greater rates of coronary heart disease and the metabolic syndrome in adults [37,38]. The rate of early weight gain has also been shown to be an important predictor of later cardiovascular risk, with those individuals experiencing a more rapid weight gain in early childhood at increased risk [36,39,40]. The duration of time required to see these abnormalities is unclear. Most of the studies supporting the Barker hypothesis have been conducted in adults, and studies that have examined the effect of abnormal birth history on BP levels in pediatric patients have had conflicting results [16], with at least one recent study suggesting that postnatal factors may be more important than prenatal factors [41].

On the other hand, several recent studies have demonstrated that effects of birth weight on BP can be detectable during childhood using ambulatory BP monitoring. Lurbe and co-workers studied 630 healthy children, all of whom had been delivered at full term, by ABPM at a mean age of 9.9 years [42]. Although the strongest predictor of current 24-hr systolic BP was current weight, birth weight had a significant inverse relationship on both 24-hour systolic BP and BP variability – in other words, children with lower birth weight had higher 24-hr systolic BP and higher 24-hr systolic BP variability. Bayrakci et al performed ABPM in 41 children born preterm, 30 of whom were small-for-gestational age, and compared the results with those in a group of children born at term who were also appropriate-for-gestational age [43]. The preterm group had higher nocturnal systolic BP, elevated nocturnal systolic & diastolic BP loads, and blunted nocturnal dipping. The trend toward higher nocturnal systolic BP was most pronounced in the group who were most light-for-date. Additionally, using linear regression, they demonstrated that SGA status was a major predictor of nocturnal & daytime systolic BP SDS.

Despite the availability of complete ABPM data for a relatively large number of well-characterized participants with CKD, we were unable to detect significant effects of abnormal birth history on any BP measure, including variables for which ABPM is uniquely suited such as nocturnal dipping and BP variability. The young age of our cohort could be one potential explanation for the lack of significant differences between the birth history groups, although the fact that Lurbe and Bayrakci [42,43] showed significant BP abnormalities in children of similar age would argue against this. A more likely explanation is that our participants' underlying CKD is playing a more significant role than birth history. We have previously demonstrated, for example, that as in adults with CKD, children with CKD have abnormal BP variability, [44] which is likely related to abnormalities of sympathetic nervous system function that are common in patients with CKD [45]. Additionally, as demonstrated in this analysis, a large number of CKiD subjects (69%) are receiving active treatment for hypertension; despite the fact that not all CKiD subjects achieve control of hypertension [24]. It is likely that treatment of hypertension masks any contribution of abnormal birth history to BP outcomes.

With respect to the effects of birth history on renal function, the Brenner hypothesis argues that low birth weight is associated with a reduction in nephron number, which increases the risk for hypertension and chronic kidney disease [3,7,46]. Low nephron number causes focal segmental glomerulosclerosis (FSGS) in experimental animals and is theorized to cause FSGS in humans [47]. Furthermore, low birth weight is known to be a risk factor for a less favorable prognosis in a variety of chronic kidney diseases [5,6,48-50].

Given this background, we examined whether the high prevalence of abnormal birth history in the CKiD cohort would be associated with effects on renal function. However, no such effect was demonstrated in our analysis for GFR, GFR decline or initial proteinuria levels. We believe that the predominance of non-glomerular forms of CKD in the CKiD cohort is the most plausible explanation for the lack of significant differences in renal function – many of the non-glomerular forms of CKiD are diagnosed at birth or shortly thereafter, making it difficult to discern any separate effect of abnormal birth history. In addition, the CKiD cohort only includes patients with a baseline GFR within a specific range. Hence, it would not enable detection of any effect of birth history prior to enrollment in the cohort, unlike previous studies that compare GFR among patients with the same diagnosis [5,6,48]. Nonetheless, even though the GFR range for study entry was relatively wide (30 to 90 ml/min|1.73m$^2$), children abnormal birth history did not present with substantially lower GFR levels compared with those with normal birth history.

In contrast to abnormal birth history, postnatal factors are likely more important and clinically meaningful mediators of hypertension and renal function in patients with chronic kidney disease. This is particularly important because these potentially modifiable factors allow opportunities for intervention. For example, the CKiD study has demonstrated that proteinuria is associated with increased likelihood of abnormal ambulatory BP [25]: higher levels of proteinuria and increasing proteinuria over time both increased the odds of having an abnormal ambulatory BP study. Additionally, proteinuria is associated with accelerated disease progression in the CKiD cohort [51]. Both of these findings are notable given that effective pharmacological intervention to reduce proteinuria is available. Other modifiable

postnatal factors with important effects on GFR include anemia, calcium & phosphorus metabolism, and albumin [35]. Exposure to second-hand smoke in this population is associated with increased proteinuria [52], and lower family income level is a marker for individuals at higher risk of poor BP control and deficits in growth [54]. Effective therapy of modifiable factors and intensive clinical care of higher risk groups could very well have influenced the rate of decline of GFR and severity of hypertension in the CKiD cohort. Thus, the results of the present analysis, which demonstrate that non-modifiable perinatal effects do not significantly influence BP in children with CKD, are consistent with prior studies examining factors that influence CKD progression in children.

A potential limitation of this study is the use of parental recall for birth history information, which might have led to some misclassification of birth history exposures. However, parental recall has been shown to be reasonably accurate for birth weight and other early life events [54.55] and is therefore usually an accepted practice in epidemiological studies. Additionally, we used a broad definition of abnormal birth history which differs from that used in many studies of the effects of birth history on cardiovascular and renal outcomes. This was necessary because of the relatively small number of children in the CKiD cohort for whom complete ambulatory BP data were available. We actually had a larger sample than Bayrakci et al, who were able to demonstrate abnormal circadian BP variation in a small number of children born preterm using ABPM [40]. Thus, we should have been able to detect a difference had it been present. Lastly, although abnormal birth history does not appear to exacerbate the effect of CKD on BP and GFR, it should be noted that abnormal birth history is more common in CKiD than the general population [2]. Even though we are unable to determine the extent to which abnormal birth history places an individual at increased risk for pediatric CKD, our study sought to determine the impact of abnormal birth history on indicators of health in the presence of pediatric CKD.

We previously demonstrated that abnormal birth history is a novel risk factor for short stature and lower weight percentiles in children with mild to moderate CKD [2]. In contrast, this analysis indicates that abnormal birth history does not appear to exert a significant influence on BP and GFR at the time of entry to CKiD, or accelerated GFR decline, compared with subjects with normal birth history. Hence, in the presence of CKD, an abnormal birth history, although associated with a variety of morbidities including short stature, does not appear to have significant impact on BP or GFR decline in children.

## Acknowledgments

Funded by the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute of Child Health and Human Development, and the National Heart, Lung, and Blood Institute (U01-DK-66143, U01-DK-66174, U01DK-082194, U01-DK-66116).

## Appendix. CKiD Study Investigators

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## Abbreviations

| | |
|---|---|
| **ABP** | ambulatory blood pressure |
| **ABPM** | ambulatory blood pressure monitoring |
| **BP** | blood pressure |
| **BW** | birth weight |
| **CKD** | chronic kidney disease |
| **CKiD** | Chronic Kidney Disease in Children |
| **DBP** | diastolic blood pressure |
| **GFR** | glomerular filtration rate |
| **SBP** | systolic blood pressure |

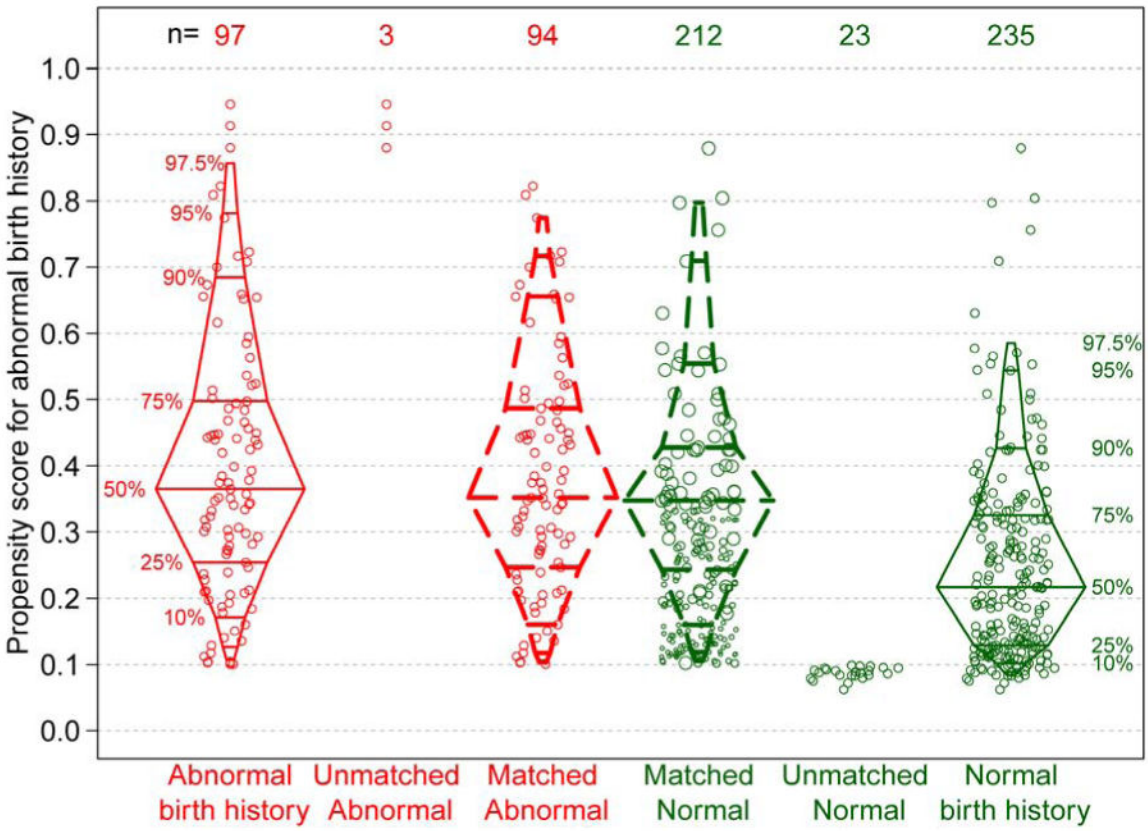


**Figure 1.**

Distribution of propensity scores, by BH status and matched data with weighting, based on full constrained matching. The box plots represent the distribution of propensity scores (predicted probabilities) by BH (abnormal and normal) based on the logistic regression model described in the Methods. The unmatched data points are not included in the final analysis. The matched data points are included in the final analysis. All matched subjects with an abnormal BH have a weight equal to 1, matched subjects with a normal BH are represented by a dot size proportional to the weight based on the matching algorithm. The discontinuous boxplots represent the weighted distributions of propensity scores.

## Table 1

Baseline demographic and clinical characteristics of 332 subjects with complete ABPM data by abnormal BH status (low birth weight, premature or small for gestational age).

| Table | Normal BH n= 235 | Abnormal BH n= 97 | P value |
|---|---|---|---|
| Age at study entry (yrs) | 12.1 [8.44, 14.76] | 11.28 [7.98, 14.39] | 0.202 |
| Female | 35% (83) | 58% (56) | **<0.001** |
| Black race | 13% (30) | 26% (25) | **0.006** |
| Hispanic ethnicity | 13% (29) | 21% (20) | 0.060 |
| Glomerular disease | 20% (47) | 18% (17) | 0.649 |
| Percent of life with CKD | 91% [36%, 100%] | 86% [35%, 100%] | 0.521 |
| Percent of life with CKD | | | |
| > 90% | 50% (118) | 46% (45) | 0.548 |
| 50% to ≤90% | 20% (46) | 23% (22) | 0.551 |
| <50 % | 30% (71) | 31% (30) | 0.896 |
| Multiple birth | 5% (12) | 15% (15) | **0.003** |
| Maternal height (in) at study entry | 64 [63, 66] | 64 [62, 66] | 0.269 |
| Maternal weight (lb) at study entry | 155.5 [136, 188] | 157.5 [130, 186] | 0.738 |
| Maternal BMI ($kg/m^2$) at study entry | 27.28 [23.49, 32.1] | 28.49 [22.91, 32.49] | 0.694 |
| Household Income < $36000 | 34% (80) | 47% (46) | **0.025** |
| Maternal education ≤ high school | 39% (91) | 44% (42) | 0.457 |
| Birth parents not living together | 31% (72) | 44% (43) | **0.022** |
| Maternal age at birth <24 years | 25% (58) | 37% (36) | **0.032** |
| Adult smoker in household | 30% (71) | 35% (34) | 0.365 |
| Family has employer insurance | 66% (150) | 53% (48) | **0.039** |
| Family has state-based insurance | 18% (41) | 26% (23) | 0.160 |
| Family size ≤ 3 people | 22% (52) | 21% (20) | 0.884 |
| Any antihypertensive medication[a] | 69% (161) | 69% (67) | 0.999 |

[a] Self-reported medication use.

## Table 2

Descriptive statistics of ABPM outcomes, by normal and abnormal birth history.

| Outcome | Normal birth history n= 235 | Abnormal birth history n= 97 | P-value |
|---|---|---|---|
| *Casual BP* | | | |
| Casual SBP z-score[a] | 0.24 (-0.87, 1.35) | 0.41 (-0.75, 1.55) | 0.214 |
| Casual DBP z-score[a] | 0.36 (-0.67, 1.39) | 0.40 (-0.60, 1.39) | 0.761 |
| *Ambulatory BP* | | | |
| Wake SBP Mean | 115 (105, 128) | 115 (104,127) | 0.674 |
| Sleep SBP Mean | 102 (92, 114) | 103 (92,114) | 0.950 |
| Wake DBP Mean | 71 (63, 80) | 71 (63,81) | 0.923 |
| Sleep DBP Mean | 59 (51, 68) | 59 (51,68) | 0.882 |
| Wake MAP Mean | 87 (79, 95) | 86 (78, 95) | 0.833 |
| Sleep MAP Mean | 75 (68, 84) | 75 (67, 84) | 0.865 |
| *Summarized ambulatory BP* | | | |
| Wake SBP Index[b] | 0.90 (0.82, 0.99) | 0.91 (0.83, 1.00) | 0.413 |
| Sleep SBP Index[b] | 0.91 (0.81, 1.02) | 0.92 (0.83,1.03) | 0.303 |
| Wake DBP Index[b] | 0.84 (0.75, 0.94) | 0.85 (0.75, 0.96) | 0.648 |
| Sleep DBP Index[b] | 0.89 (0.77, 1.02) | 0.89 (0.77, 1.03) | 0.853 |
| Wake SBP > 95$^{th}$ Limit | 11.1% (26) | 12.4% (12) | 0.709 |
| Sleep SBP > 95$^{th}$ Limit | 16.2% (38) | 20.6% (20) | 0.343 |
| Wake DBP > 95$^{th}$ Limit | 5.5% (13) | 10.3% (10) | 0.152 |
| Sleep DBP > 95$^{th}$ Limit | 19.1% (45) | 15.5% (15) | 0.531 |
| Wake SBP load > 25% | 24.7% (58) | 30.9% (30) | 0.274 |
| Sleep SBP load > 25% | 29.4% (69) | 36.1% (35) | 0.243 |
| Wake DBP load > 25% | 18.3% (43) | 25.8% (25) | 0.136 |
| Sleep DBP load > 25% | 37.0% (87) | 37.1% (36) | 1.000 |
| Abnormal ABP[c] | 49.8% (117) | 49.5% (48) | 1.000 |
| *Ambulatory BP variability* | | | |
| Wake SBP SD | 9.9 (8.1, 12.3) | 9.8 (7.7, 12.5) | 0.731 |
| Sleep SBP SD | 8.1 (5.9, 11.1) | 7.9 (5.9, 10.5) | 0.514 |
| Wake DBP SD | 9.3 (7.6, 11.4) | 9.3 (7.4, 11.6) | 0.903 |
| Sleep DBP SD | 7.6 (5.7, 10.0) | 7.8 (6.1, 9.8) | 0.435 |
| Wake SBP CV | 0.09 (0.07,0.11) | 0.08 (0.07, 0.11) | 0.856 |
| Sleep SBP CV | 0.08 (0.06, 0.11) | 0.08 (0.06,0.11) | 0.581 |
| Wake DBP CV | 0.13 (0.10, 0.17) | 0.13 (0.10, 0.17) | 0.915 |
| Sleep DBP CV | 0.13 (0.10, 0.17) | 0.13 (0.10, 0.17) | 0.363 |
| Wake MAP SD | 8.7 (7.1, 10.6) | 8.8 (7.2, 10.9) | 0.399 |
| Sleep MAP SD | 7.0 (5.2, 9.3) | 6.9 (5.3, 9.0) | 0.769 |
| Wake MAP CV | 0.10 (0.08, 0.13) | 0.10 (0.08, 0.13) | 0.323 |
| Sleep MAP CV | 0.09 (0.07, 0.12) | 0.09 (0.07,0.12) | 0.691 |

| Outcome | Normal birth history n= 235 | Abnormal birth history n= 97 | P-value |
|---|---|---|---|
| SBP % dipping | 10.6 (5.8, 19.3) | 10.2 (5.5, 18.6) | 0.561 |
| DBP % dipping | 15.8 (8.8, 28.4) | 16.3 (10.5, 25.4) | 0.599 |
| SBP % dipping < 10% | 34.5% (81) | 39.2% (38) | 0.451 |
| DBP % dipping < 10% | 14.5% (34) | 14.4% (14) | 1.000 |
| *Ambulatory HR variability* | | | |
| Wake HR SD | 12.0 (8.8, 16.4) | 11.7 (8.8, 15.5) | 0.436 |
| Sleep HR SD | 8.4 (5.8, 12.1) | 8.3 (5.7, 12.3) | 0.960 |
| Wake HR CV | 0.14 (0.10, 0.19) | 0.13 (0.10, 0.18) | 0.334 |
| Sleep HR CV | 0.15 (0.08, 0.17) | 0.11 (0.08, 0.16) | 0.680 |
| *Renal outcomes* | | | |
| ieGFR at entry[d] | 46.7 (32.5, 67.3) | 45.6 (31.4, 66.9) | 0.573 |
| Annual ieGFR change[d] | -8.7% (-22.5%, +7.5%) | -8.2% (-19.9%, +5.2%) | 0.753 |
| Urine protein (mg/mg Creatinine) | 0.45 (0.13, 1.54) | 0.45 (0.13, 1.53) | 0.948 |

Geometric means (-1 SD, +1 SD), with the exception of z-scores (in which means are presented).

Univariate p-values are based on t-tests and Fisher exact test (ie, unweighted and unadjusted).

[a] Mean casual BP z-scores calculated by Fourth Report, adjusted for age, sex, and height;

[b] Index variables calculated as mean wake or sleep BP measurements divided by 95$^{th}$ percentile limit;

[c] Abnormal ABP defined as elevated SBP or DBP (ie, > 95$^{th}$ percentile) and abnormally high SBP or DBP loads (ie, > 25%) for either wake or sleep states [25];

[d] ieGFR refers to GFR data based primarily on iohexol measurements, but also estimated GFR when the iohexol measurement was not obtained, as previously described [27].

## Table 3

Adjusted means (95%CI) of BP and GFR outcomes, by abnormal birth history.

| Variable | Normal birth history n= 212 | Abnormal birth history n= 94 | P-value |
|---|---|---|---|
| *Casual BP* | | | |
| Casual SBP z-score | 0.24 (-0.06, 0.54) | 0.33 (-0.02, 0.67) | 0.526 |
| Casual DBP z-score | 0.3 (0.03, 0.56) | 0.27 (-0.04, 0.57) | 0.819 |
| *Ambulatory BP* | | | |
| Wake SBP Mean | 116 (113, 119.36) | 116 (113, 120) | 0.917 |
| Sleep SBP Mean | 104 (101, 107) | 104 (101, 107) | 0.742 |
| Wake DBP Mean | 71 (69, 73) | 70 (68, 73) | 0.740 |
| Sleep DBP Mean | 59 (57, 61) | 59 (56, 61) | 0.551 |
| Wake MAP Mean | 86 (84, 88) | 86 (83, 88) | 0.854 |
| Sleep MAP Mean | 75 (73, 78) | 75 (73, 78) | 0.934 |
| *Summarized ambulatory BP* | | | |
| Wake SBP Index | 0.90 (0.88, 0.92) | 0.91 (0.88, 0.93) | 0.447 |
| Sleep SBP Index | 0.92 (0.90, 0.95) | 0.93 (0.9, 0.97) | 0.364 |
| Wake DBP Index | 0.83 (0.81, 0.86) | 0.83 (0.8, 0.86) | 0.908 |
| Sleep DBP Index | 0.9 (0.86, 0.93) | 0.89 (0.85, 0.93) | 0.796 |
| Wake SBP > 95$^{th}$ Limit | 6.1% (2.6%, 13.7%) | 8.4% (3.1%, 20.5%) | 0.402 |
| Sleep SBP > 95$^{th}$ Limit | 9.2% (4.6%, 17.5%) | 11.2% (5%, 23.2%) | 0.513 |
| Wake DBP > 95$^{th}$ Limit | 4.5% (1.7%, 11.5%) | 7% (2.3%, 19.3%) | 0.306 |
| Sleep DBP > 95$^{th}$ Limit | 15.7% (9.1%, 25.6%) | 10.6% (5%, 21.2%) | 0.179 |
| Wake SBP load > 25% | 17.3% (10.6%, 27%) | 21.7% (12.1%, 35.6%) | 0.320 |
| Sleep SBP load > 25% | 17% (10.3%, 26.7%) | 20% (11.1%, 33.3%) | 0.455 |
| Wake DBP load > 25% | 12.5% (7%, 21.3%) | 19.8% (10.4%, 34.3%) | 0.072 |
| Sleep DBP load > 25% | 26% (17.5%, 36.7%) | 23.6% (14%, 36.9%) | 0.630 |
| Abnormal ABP[c] | 41.1% (30.8%, 52.2%) | 37.6% (25.1%, 52%) | 0.569 |
| *Ambulatory BP variability* | | | |
| Wake SBP SD | 9.75 (9.2, 10.34) | 9.68 (9.06, 10.35) | 0.803 |
| Sleep SBP SD | 8.47 (7.81, 9.19) | 8.47 (7.72, 9.3) | 0.992 |
| Wake SBP CV | 0.08 (0.08, 0.09) | 0.08 (0.08, 0.09) | 0.662 |
| Sleep SBP CV | 0.08 (0.08, 0.09) | 0.08 (0.07, 0.09) | 0.986 |
| Wake DBP SD | 9.48 (8.99, 9.99) | 9.39 (8.84, 9.98) | 0.732 |
| Sleep DBP SD | 7.87 (7.34, 8.43) | 8.13 (7.51, 8.8) | 0.315 |
| Wake DBP CV | 0.13 (0.13, 0.14) | 0.13 (0.12, 0.14) | 0.912 |
| Sleep DBP CV | 0.13 (0.12, 0.14) | 0.14 (0.13, 0.15) | 0.181 |
| Wake MAP SD | 8.68 (8.22, 9.16) | 8.83 (8.3, 9.39) | 0.497 |
| Sleep MAP SD | 7.31 (6.79, 7.86) | 7.25 (6.67, 7.88) | 0.816 |
| Wake MAP CV | 0.1 (0.09, 0.11) | 0.1 (0.1, 0.11) | 0.387 |
| Sleep MAP CV | 0.1 (0.09, 0.1) | 0.1 (0.09, 0.1) | 0.804 |
| SBP % dipping | 9 (7.45, 10.86) | 9.04 (7.28, 11.22) | 0.958 |

| Variable | Normal birth history n= 212 | Abnormal birth history n= 94 | P-value |
|---|---|---|---|
| DBP % dipping | 14.61 (12.66, 16.87) | 15.33 (13.01, 18.07) | 0.479 |
| SBP % dipping < 10% | 23.2% (15.3%, 33.6%) | 26.5% (15.9%, 40.7%) | 0.503 |
| DBP % dipping < 10% | 11.3% (6%, 20.3%) | 10.4% (4.6%, 22%) | 0.812 |
| *Ambulatory HR variability* | | | |
| Wake HR SD | 12.11 (11.23, 13.06) | 11.62 (10.67, 12.67) | 0.248 |
| Sleep HR SD | 8.19 (7.46, 9) | 8.78 (7.88, 9.78) | 0.120 |
| Wake HR CV | 0.14 (0.13, 0.15) | 0.13 (0.12, 0.15) | 0.352 |
| Sleep HR CV | 0.11 (0.1, 0.12) | 0.12 (0.11, 0.14) | 0.083 |
| *Renal outcomes* | | | |
| ieGFR at entry[d] | 45.51 (41.16, 50.33) | 43.11 (38.43, 48.37) | 0.253 |
| Annual ieGFR change[d] | -8.6% (-12.6%, -4.4%) | -8.3% (-12.9%, -3.5%) | 0.877 |
| Urine protein (mg/mg Creatinine) | 0.35 (0.26, 0.48) | 0.38 (0.27, 0.54) | 0.545 |

Estimated adjusted means are from weighted linear regression in the log scale, based on full constrained matching, with adjustment for quintiles of propensity scores (defined by subjects with abnormal birth history) and CKD diagnosis. Proportions are calculated from logistic regressions with the same adjustment. The reference group is a subject with non-glomerular CKD and with a probability of being abnormal birth between 0.32 and 0.42 (the $40^{th}$-$60^{th}$ percentiles of propensity scores).

[a] Casual BP z-scores calculated by $4^{th}$ report, adjusted for age, sex, and height;

[b] Index variables calculated as mean wake or sleep BP measurements divided by the $95^{th}$ percentile limit for state-specific mean;

[c] Abnormal ABP defined as elevated SBP or DBP (ie, > $95^{th}$ percentile) and abnormally high SBP or DBP loads (ie, > 25%) for either wake or sleep states, as previously defined [25];

[d] ieGFR refers to a combination of iohexol and estimated GFR as previously described [27].