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Caffeine and kidney function at two years in former extremely low gestational age neonates

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AUTHOR CONTRIBUTIONS

M.W.H. made significant contributions to the design and conception, data analysis and interpretation, drafting the manuscript, critical revision of the manuscript and final approval. R.Griffin made significant contributions to the statistical analysis and interpretation, drafting the manuscript, and final approval. D.A. made significant contributions to the design, data interpretation, critical revision of the manuscript and final approval. M.F. made contributions to the design of the study, revision of the manuscript and final approval. R.Guillet made significant contributions to the design and conception, data interpretation, critical revision of the manuscript and final approval. M.F. made contributions to the design of the study, revision of the manuscript and final approval. M.S. made contributions to the design of the study, revision of the manuscript and final approval. C.S. made significant contributions to the design of the study, revision of the manuscript and final approval. R.W. made significant contributions to the design, data interpretation, critical revision of the manuscript and final approval. J.R.C. made significant contributions to the design and conception, data analysis and interpretation, critical revision of the manuscript and final approval.

COMPETING INTERESTS

All authors declare no real or perceived conflicts of interest that could affect the study design, collection, analysis, and interpretation of data, writing of the report, or the decision to submit for publication. For full disclosure, we provide here an additional list of other author's commitments and funding sources that are not directly related to this study: M.W.H. receives research funding unrelated to this project from the NIH, Wisconsin Partnership Program, and Meriter Foundation. D.J.A. is a consultant for Baxter, Nuwellis, Medtronic Bioporto, and Seastar. His institution receives grant funding for education and research that is not related to this project from NIH, Baxter, Nuwellis, Medtronic, Bioporto, and Seastar. He has patents pending on inventions to improve the kidney care of neonates. He is the Founder and Chief Scientific Officer for Zorro-Flow. J.R.C. is a consultant for Medtronics and investor in Zorro-Flow. She receives funding for research not related to this project from the NIH. She is Vice-President of the Neonatal Kidney Collaborative. R.Guillet is a consultant for NEMA Research. She receives funding for research not related to this project from NIH. C.S. is a consultant for AM Pharma which is unrelated to the content in this manuscript. Meredith Schuh receives research funding unrelated to this project from NIH and Otsuka

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Consent was required for parent study but not for this secondary analysis.

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Abstract

BACKGROUND: Extremely low gestational age neonates (ELGANs) are at risk for chronic kidney disease. The long-term kidney effects of neonatal caffeine are unknown. We hypothesize that prolonged caffeine exposure will improve kidney function at 22–26 months.

METHODS: Secondary analysis of the Preterm Erythropoietin Neuroprotection Trial of neonates <28 weeks' gestation. Participants included if any kidney outcomes were collected at 22–26 months corrected age. Exposure was post-menstrual age of caffeine discontinuation. Primary outcomes: 'reduced eGFR' <90 ml/min/1.73 m^2, 'albuminuria' (>30 mg albumin/g creatinine), or 'elevated blood pressure' (BP) >95th %tile. A general estimating equation logistic regression model stratified by bronchopulmonary dysplasia (BPD) status was used.

RESULTS: 598 participants had at least one kidney metric at follow up. Within the whole cohort, postmenstrual age of caffeine discontinuation was not associated with any abnormal measures of kidney function at 2 years. In the stratified analysis, for each additional week of caffeine, the no BPD group had a 21% decreased adjusted odds of eGFR <90 ml/min/1.73m^2 (aOR 0.78; CI 0.62–0.99) and the BPD group had a 15% increased adjusted odds of elevated BP (aOR 1.15; CI: 1.05–1.25).

CONCLUSIONS: Longer caffeine exposure during the neonatal period is associated with differential kidney outcomes at 22–26 months dependent on BPD status.

INTRODUCTION

Extremely low gestational age neonates (ELGANs; gestational age at birth <28 weeks) are born with decreased nephron endowment compared to term neonates.[1] In addition, life-saving interventions, hemodynamic instability, and nephrotoxic medication exposure that occur during the neonatal intensive care unit (NICU) hospitalization contribute to the prevalence of acute kidney injury (AKI) in this population.[2,3] Adult and pediatric studies have identified AKI as a risk factor for progression to CKD in as little as one to three years after AKI.[4,5] In addition, recent evidence suggests that ELGANs have a three times increased risk of developing chronic kidney disease (CKD) during adulthood compared to term babies.[6] Small single center studies suggest that AKI may accelerate the progression to CKD in former premature neonates,[7,8] while a larger multicenter study did not show AKI to be a risk factor for CKD during the early childhood years.[9] This larger study did however highlight that ELGANs are at significant risk for elevated blood pressure (BP), albuminuria, and decreased estimated glomerular filtration rate (eGFR<90 mL/min/1.73 m^2).[9] Although an eGFR >90 mL/min/1.73 m^2 is considered to be normal in this population, higher eGFR's can reflect hyperfiltration, a sign of an insufficient number of glomeruli. This is particularly relevant to the follow up of previous preterm neonates where hyperfiltration may precede a drop in eGFR and be identified at early follow-up visits from the NICU before CKD occurs.[10]

Despite the frequent occurrence of AKI in ELGANs, and the risk of progression to CKD in adulthood, little is known about how common NICU therapies affect the risk for AKI in the neonatal period and CKD during child or adulthood. Caffeine citrate is a methylxanthine that is typically started in preterm neonates in the first week after birth

to treat apnea of prematurity and prevent bronchopulmonary dysplasia (BPD). Caffeine is typically administered daily and continued until 33–35 weeks post menstrual age (PMA) or until off positive pressure support.[11] Recently, caffeine has been found to be associated with a reduced risk of AKI in preterm neonates.[12] Other methylxanthines such as theophylline reduce the rates of AKI in full term neonates with hypoxic ischemic encephalopathy.[13,14] However, little information exists about how early neonatal treatments, such as caffeine, may affect progression to CKD in early childhood. While neonatal caffeine exposure has beneficial effects on motor and cognitive development into mid-childhood, its effect on kidney outcomes has not been examined.[15,16]

In this secondary analysis of the Preterm Epo Neuroprotection Trial (PENUT Trial), we sought to evaluate if caffeine exposure in the first weeks after birth affects kidney function of ELGANs at 22–26 months corrected gestational age. We hypothesized that prolonged caffeine use would reduce rates of kidney dysfunction defined as any of the following: eGFR <90 mL/min/1.73 m^2, albumin creatinine ratio (ACR) >30 mg albumin/g creatinine, and high BP (>95th percentile for age and sex).

METHODS

Study population

This is a retrospective secondary analysis of the prospective randomized clinical trial, PENUT.[17] Institutional review board approval was obtained from each individual site and informed consent was obtained prior to participation. In this placebo-controlled, double-blind clinical trial of recombinant human Erythropoietin (rhEpo), ELGANs admitted to 19 NICUs across the USA from January 2013 to September 2016 who were between the gestational ages of 24 0/7 and 27 6/7 weeks and less than 24 h of age were included. Exclusion criteria were major life-threatening anomalies, hematologic crises, hematocrit >65%, hydrops fetalis, and known congenital infection. Study participants were randomized to receive either 400 units/kg/dose of rhEpo intravenously followed by subcutaneous injections 3 times per week until 32 6/7 weeks PMA or placebo. Participants were followed until 22–26 months corrected gestational age (cGA) at which time they had a follow-up study visit. Study personnel and families remained blinded to randomization groups at the follow-up visit. At the time of the study visit follow-up, urine, blood, and blood pressure measurements were not a mandatory part of the original PENUT protocol. The collection of this data was encouraged by site personnel for inclusion in the Recombinant Erythropoietin for Protection of Infant Renal Disease (REPAIReD) study, an NIH R01 sponsored ancillary study. Further details on design, definitions of demographic factors and comorbidities, primary efficacy, and safety outcomes have been published.[17,18] Previous analyses have shown that while there were differences in the rates of those lost to follow-up between treatment arms, there were no statistically significant differences in the rates of blood, urine, and blood pressure measurement by treatment arm in study participants who survived to 2 year follow up and consented to biospecimen collection.[19] In addition, a sensitivity analysis was previously published to assess potential bias resulting from unequal representation and lost to follow-up status showing that baseline characteristics were similar between groups.[9]

Caffeine exposure

The exposure of interest was the duration of caffeine citrate (caffeine) administration. To define duration, we used the PMA that caffeine was discontinued to correct for the difference between gestational ages at birth, recognizing that ELGANs born earlier had the opportunity to be exposed to caffeine starting at an earlier gestational age and thus an increase in the total number of weeks of exposure. Neither caffeine dosage, nor caffeine levels were collected in the original PENUT study. Caffeine therapy was initiated and discontinued by the treating clinicians per local guidelines and not by any study protocols.

Variable definitions

Demographic data collected included gestational age (GA), sex, maternal race, ethnicity, and pregnancy conditions (multiple gestation, diabetes, hypertension, and pre-eclampsia). Neonatal factors included birth size (small for GA <10th percentile at birth), weight, length, occipitofrontal circumference, 1- and 5-min Apgar scores, and prenatal steroid doses. Delivery room information on resuscitation including intubation, surfactant administration, chest compressions and resuscitation drugs received were recorded. The following neonatal morbidities were recorded: bronchopulmonary dysplasia (BPD) defined as use of supplemental oxygen at 36 weeks of PMA, necrotizing enterocolitis (NEC) stage 2b or 3, patent ductus arteriosus (PDA) defined as requiring treatment, hypotension classified as requiring BP support with either vasopressors or hydrocortisone, culture proven sepsis, severe grade III or IV intraventricular hemorrhage (IVH), and nephrotoxic medication exposure including indomethacin, gentamicin, or vancomycin.

Kidney metrics at 22–26 months corrected GA(cGA)

We evaluated three primary outcomes as previously reported for this cohort.[9] Briefly, these include: low eGFR (<90 mL/min/1.73 m^2), albuminuria (albumin creatinine ratio (ACR) >30 mg albumin/g creatinine), and high BP (>95th percentile for age and sex based on 2017 AAP guidelines).[20] Serum creatinine samples from follow-up visits were analyzed in a central core lab using an enzymatic assay. Estimated GFR was calculated using age, sex, height, and serum creatinine (SCr) according to the CKiDU25 equation.[21] We also included hyperfiltration as a secondary outcome defined as an eGFR >120 mL/min/1.73 m^2[10] Urine was collected from a bag specimen or a cotton ball in the diaper. We defined the albuminuria threshold based on previous data showing this level as a surrogate outcome of chronic kidney disease (CKD) progression in children.[22] Blood pressure measurement was standardized across all sites and personnel. BP readings were obtained using a Briggs Mabic Healthcare Manual Sphygmomanometer with blood pressure cuff appropriate for patient size, (the inflatable bladder width at least 40% of the child's mid-upper arm circumference and the length between 80–100% of the mid-upper arm circumference). BP was measured twice with 5 min between readings. The lowest systolic blood pressure (sBP) and diastolic blood pressure (dBP) were recorded. We have reported BP > 90th percentile as an additional secondary outcome as in previous publications using this cohort.[9]

Statistical analysis

Histograms and boxplots of the distribution of PMA of caffeine discontinuation were produced by follow-up status and by gestational age. Univariate statistics were computed for categorical (*n*, %) and continuous variables (mean, standard deviation) for the neonatal, maternal and delivery characteristics of interest. A general linear model (GLM) was used to examine bivariate associations between the selected characteristics and post-menstrual age of caffeine discontinuation. A Fisher's exact test was used to assess bivariate associations of compare 22–26 month cGA kidney outcomes (i.e., eGFR <90 and >120 mL/min/1.73 m^2, ACR > 30 mg albumin/g creatinine, and hypertension (defined as >90th percentile and >95th percentile) and both PMA of caffeine discontinuation and gestational age.

A general estimating equation (GEE) logistic regression clustered by study site was used to estimate odds ratios (ORs) and associated 95% confidence intervals for the association between 22–26 month cGA kidney outcomes and PMA of caffeine discontinuation. To create adjusted logistic models and ensure the consistency of the adjusted variables across the models, the GLM methodology described above was used to assess variables that were associated with PMA of caffeine discontinuation. Variables that had a $p < 0.1$ from the bivariate GLM analyses were included in a single model with PMA of caffeine discontinuation as the dependent variable, and a backward selection was used to identify variables with an association with PMA of caffeine discontinuation that had a $p < 0.05$. The variables included in the model at the end of the backward selection process (i.e., gestational age, maternal race, multiple gestation, size for gestational age, highest stage AKI, BPD, severe IVH, and vancomycin use) in addition to factors that were deemed clinically relevant (i.e., highest AKI stage and treatment group [erythropoietin or placebo] of parent trial) were used in each of the five logistic models created for the 22–26 month cGA outcomes. While not planned for a priori, since the timing of caffeine discontinuation is driven by a clinical need for positive pressure respiratory support, we stratified our analyses by BPD status by including an interaction of PMA of caffeine discontinuation and BPD status in adjusted logistic models. All analyses were performed using SAS version 9.4, and statistical significance was set at a 5% alpha level.

RESULTS

Demographics

Of the 941 study participants enrolled in the original study, the following were excluded from the current secondary data analysis: participants were not randomized ($n = 5$), died prior to NICU discharge ($n = 94$), and died prior to 22–26-month cGA ($n = 12$). Those who did not receive caffeine ($n = 9$) or who also received theophylline or aminophylline ($n = 40$) were excluded. Of the 780 study participants available at the time of a 22–26-month cGA follow-up visit, 182 did not have a kidney metric obtained. The final sample size included 598 study participants who had at least one kidney metric measured (eGFR, urine albumin, or blood pressure). Figure 1 shows that of the 598 study participants, 469 (78%) had blood pressure measured, 407 (68%) had urine obtained, and 316 (53%) had serum creatinine to calculate eGFR.

Of the study participants included in our analyses, 24% were born at 24-, 25-, and 26-weeks GA while 27% were born at 27 weeks GA (Table 1). The mean birth weight was 812 grams and 92% of their mothers received at least one dose of steroids prior to delivery. There was equal distribution of sex and 14% were born small for gestational age. For neonatal outcomes, 65% developed BPD, 42% had a PDA requiring treatment, and 11% had severe IVH. Nephrotoxic medication exposure was common with 96, 61, and 48% receiving at least one dose of gentamicin, vancomycin, and indomethacin, respectively. Demographic factors by BPD status are in Supplemental Table 1.

22–26 cGA Kidney Outcomes (Table 2)

Figure 2 is a graphical representation of the three primary outcomes: eGFR <90, albuminuria, and elevated BP >95th%. In those with eGFR measured, 18.0% (n = 58/323) were <90 mL/min/1.72 m^2 and 19.8% (n = 64/323) were >120 mL/min/1.72m^2. For ACR, 35.6% (n = 145/407) were >30 mg albumin/g creatinine with no significant differences by GA category. For those with BP measured, 21.4% (n = 79/369) had a systolic BP >95th %tile and 38.7% (n = 143/369) had a diastolic BP >95th %tile.

Caffeine discontinuation by PMA

The overall mean PMA of caffeine discontinuation for the entire cohort was 34.9 ± 2.7 weeks (Fig. 3). The distribution of PMA at caffeine discontinuation varied by GA at birth (24 wks = 35.3 ± 2.7 wks PMA, 25 wk = 35.6 ± 2.8 wks PMA, 26 wks = 34.2 ± 2.7 wks PMA, and 27 wks = 34.4 ± 2.3 wks PMA; $p < 0.01$, Kruskal–Wallis). Site specific differences in timing of caffeine discontinuation were evident ($p < 0.01$, Kruskal–Wallis, Supplementary Fig. 1).

Figure 4 shows the PMA of last caffeine administration stratified by the occurrence of a follow-up visit and BPD status. For both the no BPD and BPD groups, there were no differences at PMA of caffeine discontinuation in those that had follow-up compared to those who did not have follow up (p = 0.67 and 0.36, respectively). However, in the BPD compared to the no BPD groups, regardless of follow-up status, caffeine was discontinued at a later PMA in the BPD group (p <0.01).

Caffeine and 22–26 month cGA kidney outcomes

Table 3 includes the primary kidney outcomes of each of the GA strata at birth (24–27 wks GA) further stratified by PMA at caffeine discontinuation (<33, 33–35, >35 wks PMA). In each of the GA cohorts, there are no significant differences based on PMA of caffeine discontinuation.

Table 4 shows the crude and adjusted ORs for each additional week of PMA at caffeine discontinuation and each of three primary outcomes adjusted for GA, maternal race, multiple gestation, size for gestational age, highest stage AKI, BPD, severe IVH, vancomycin use, and treatment group (Epo or placebo) of parent trial. Overall, in the adjusted analysis there were no significant outcomes with any of the three primary kidney outcomes. There was an eight percent increased odds of albuminuria at 22–26 mo cGA for every 1-week increase in PMA at discontinuation of caffeine, but this did not reach

statistically significance (aOR 1.08, CI 1.0–1.16). When stratified by BPD status, the BPD group had 15% increased odds of BP >95th percentile for every one week increase in PMA at discontinuation of caffeine (aOR 1.15, CI: 1.05–1.25). Similarly, the BPD group had 15% increased odds of BP >90th percentile for every one week increase in PMA at discontinuation of caffeine (aOR 1.15, CI: 1.04–1.26). However, in the no BPD group, for each additional week caffeine was received, there was 22% decreased odds of eGFR <90 mL/min/1.73 m^2 (aOR 0.78, CI: 0.62–0.99) but no significant changes in blood pressure. With regards to hyperfiltration defined as eGFR >120 mL/min/1.73 m^2, there were no significant differences in the whole cohort analysis or the stratified analysis.

DISCUSSION

In this secondary evaluation of a prospective randomized control trial of ELGANs, we found that after adjusting for potential confounders, timing of caffeine discontinuation did not affect kidney outcomes at 22–26 months cGA in the whole cohort. In a secondary stratified analysis, among children without BPD, older age at caffeine discontinuation was associated with a decreased odds of reduced eGFR at 22–26 months cGA. However, among children with BPD, older age at caffeine discontinuation was associated with a greater odds of elevated BP. As previously reported from this cohort, abnormal kidney function (reduced eGFR, proteinuria, and elevated BP) is common in ELGANs at 22–26 months cGA. While there are clear positive short-term and long-term pulmonary and neurological effects of caffeine on preterm neonates, our findings on longer use of caffeine and 22–26 month kidney outcomes are mixed. This secondary study demonstrates that there is more to be learned about the relationship between caffeine and long-term kidney health. To understand this relationship more fully, future prospective studies must be designed to include more granular data about caffeine exposure and comprehensive prolonged follow-up of kidney outcomes.

Previous studies on the long-term effects of caffeine therapy in ELGANs focused on neurodevelopmental outcomes, but have not explored kidney function.[16,23] While randomization to caffeine vs placebo would not be ethical, it may be reasonable to examine the timing of caffeine initiation and discontinuation as there is disagreement in these areas. In a subgroup analysis of the caffeine for apnea of prematurity (CAP) trial, the respiratory benefits of caffeine were more significant when initiated earlier.[24] In the CAP trial, caffeine initiation was deemed ‘early’ if started by ten days of age. Subsequent studies analyzed the effects of caffeine starting within the first two postnatal days compared with between three and ten days of age. Dobson et al. found an increased risk of mortality with very early initiation, but Lodha et al. did not.[25,26] One previous retrospective study on neonates born <1250 grams categorized caffeine discontinuation into three groups: early cessation <14 days, intermediate cessation <30 days, and late cessation >30 days and found no differences in neurodevelopmental outcomes at 3 years of age.[27] In a more recent large cohort study of over 81,000 infants born less than 35 weeks GA, Ji et al. found that the mean PMA of caffeine discontinuation ranged from 32 to 37 weeks, but there was substantial variability among sites as well as respiratory support at the time of caffeine discontinuation.[11] Our study confirms this variability in PMA at caffeine discontinuation, with mean discontinuation between 34 to 35 weeks PMA, but with a standard deviation

of over two weeks. We did not have the data to evaluate the underlying cause of this variability. Given the variability in timing of caffeine discontinuation, a prospective clinical trial could be designed to evaluate the effect of PMA at caffeine discontinuation on a variety of outcomes, including kidney function, during childhood.

There are many possible speculations to explain the two significant results of this secondary study. First, high blood pressure was more common in the BPD subgroup with longer caffeine use. This may be secondary to the already enhanced risk of hypertension in neonates with BPD which could be exacerbated by longer use of caffeine.[28] In the whole cohort, there was a nearly significant increased risk for high blood pressure. This points to the possibility of other mechanisms through which caffeine may increase the risk of high blood pressure. These factors are being being evaluated in adults currently.[29] In subsequent studies, elevated blood pressure should be evaluated over time to determine if these are transient or persistent findings.

Our second significant finding was that caffeine might have a beneficial effect on eGFR in those without BPD. This is consistent with large systematic reviews and meta-analyses, coffee drinking in adults appears to reduce the risk of CKD, but the exact mechanism for this protection remains under investigation.[30] The caffeine in coffee is one potential mediator of reduced CKD. Caffeine affects kidney function through a variety of direct adenosine receptors but may also indirectly affect kidney function through inflammatory and endothelial mechanisms.[31] Caffeine's beneficial effect in decreasing intermittent hypoxia (IH) may be the mechanism through which caffeine may lead to improved kidney function during childhood. IH is common in preterm neonates, typically peaks 2–4 weeks after birth, and has been associated with numerous neurodevelopmental and respiratory morbidities in preterm neonates.[32,33] The effect of IH on kidney development and function has been evaluated in both animal models and adults. In a neonatal rat model of IH, the authors reported that neonatal IH causes severe damage as evidenced by increased apoptosis and necrosis in the developing kidney with associated elevations in vasoconstrictors.[34] In a recent study in adults, those with moderate to severe obstructive sleep apnea and significant IH had a 3 times higher risk of CKD progression.[35] In a prospective randomized clinical trial including 95 preterm infants, the authors found that extended caffeine treatment through 37 weeks' PMA effectively decreases IH.[36] Kidney-focused follow-up of the subjects in this study may help determine if the beneficial effects of caffeine are mediated through the decreased incidence and severity of IH. We hypothesize that for infants not on caffeine, IH may lead to worse kidney outcomes and that this potentially explains the lack of significant differences in kidney outcomes of neonates with BPD whom receive the longest duration of caffeine. We speculate that infants without BPD are more likely to be on room air and thus have their caffeine discontinued earlier, resulting in a lack of kidney protection from IH events at a critical PMA. This contrasts with infants with BPD who are more likely to receive a prolonged course of caffeine and be exposed to caffeine during this critical PMA of IH. Ultimately, this may contribute to the pathophysiology predisposing to CKD.

The strength of this study was the large number of neonatal participants followed prospectively from multiple centers across the United States. The original PENUT cohort was well characterized and had excellent rates of follow-up. However, we recognize that

the REPAIReD cohort, recruited into the ancillary portion of this study, may only have one or two of the outcomes, instead of all three, measured, limiting the interpretation of their CKD status. This study had a few additional limitations: lack of follow-up kidney metrics on 182 subjects, lack of specific caffeine data (dosage, frequency, levels, caffeine use after discharge), 'long-term' follow-up was limited to two years, potential bias in the loss to follow-up group, only a single randomly collected urine sample, and two BP measurements on a single day. Although a 2 year follow up is relatively short in terms of defining kidney disease, adult GFR is established by 1.5–2 years.[37] Although we found no association between caffeine exposure and hyperfiltration as defined by an eGFR>120 ml/min/1.73m^2, a validated definition for hyperfiltration has not been established in this population. Furthermore, it is important to acknowledge that those neonates with a "normal GFR" may have a lower nephron number and be experiencing hyperfiltration. Further studies are necessary to determine if eGFR<90 ml/min/1.73m^2 in this patient population will be harbinger of progressive kidney disease. Finally, we report only an association and not causality, ultimately supporting the need for hypothesis-driven studies to further explore these relationships.

In conclusion, the 22–26-month cGA kidney outcomes of children born at 24–27 weeks GA are very concerning for the high incidence of early findings of kidney dysfunction. Prolonged caffeine duration may result in a differential effect on blood pressure and eGFR for individuals with and without BPD. Longer follow-up of this cohort is crucial to our understanding of the relationship between caffeine and kidney health in ELGANs. In the interim, current clinical trials on caffeine involving ELGANs should include kidney-related data and outcomes in follow-up assessments.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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DATA AVAILABILITY

The datasets analyzed during the current study can be requested from the NINDS at the following website: https://www.ninds.nih.gov/current-research/research-funded-ninds/clinical-research/archived-clinical-research-datasets.

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IMPACT:

- In participants born <28 weeks' gestation, discontinuation of caffeine at a later post menstrual age was not associated with abnormal kidney outcomes at 22–26 months corrected age.
- When assessed at 2 years of age, later discontinuation of caffeine in children born <28 weeks' gestation was associated with a greater risk of reduced eGFR in those without a history of BPD and an increased odds of hypertension in those with a history of BPD.
- More work is necessary to understand the long-term impact of caffeine on the developing kidney.

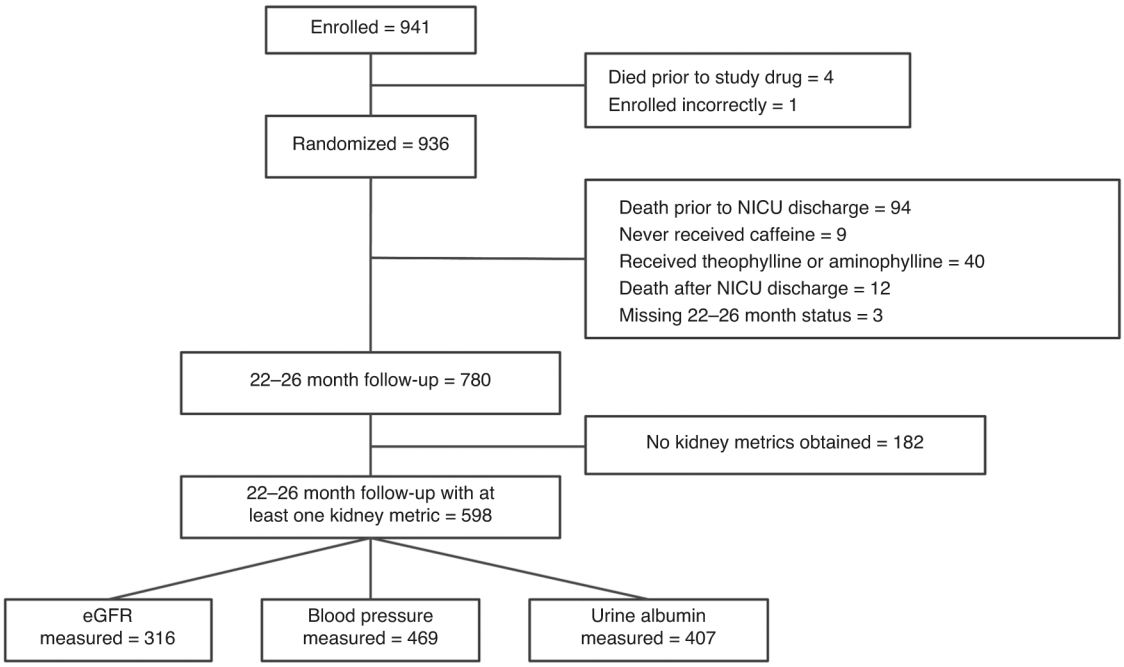

Fig. 1. Consort diagram.

Of 941 participants enrolled in the original trial, 598 subjects had a 22–26-month corrected age follow-up visit with at least one kidney metric obtained. The figure details participants who did not meet the inclusion criteria and the number who had specific kidney metrics obtained. eGFR estimated Glomerular Filtration Rate). Created with BioRender.com.

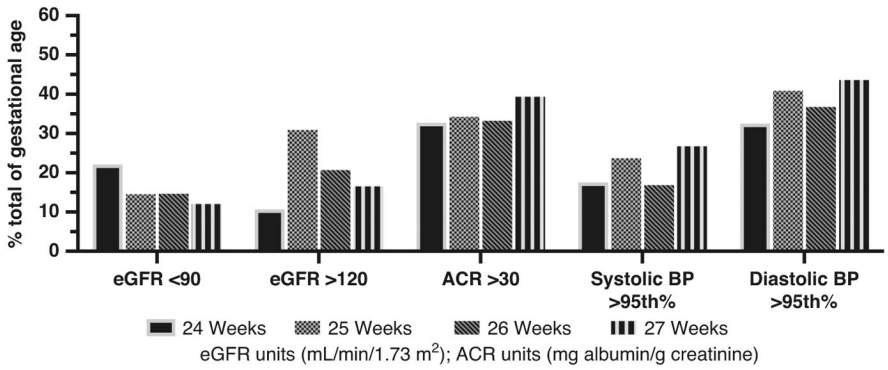

Fig. 2. 22–26 month corrected gestational age kidney outcomes.

This histogram depicts frequencies of specific kidney outcomes by gestational age category. The x-axis displays the categories of kidney outcomes while the y axis is percent total of gestational age categories represented by the different bars with key beneath.

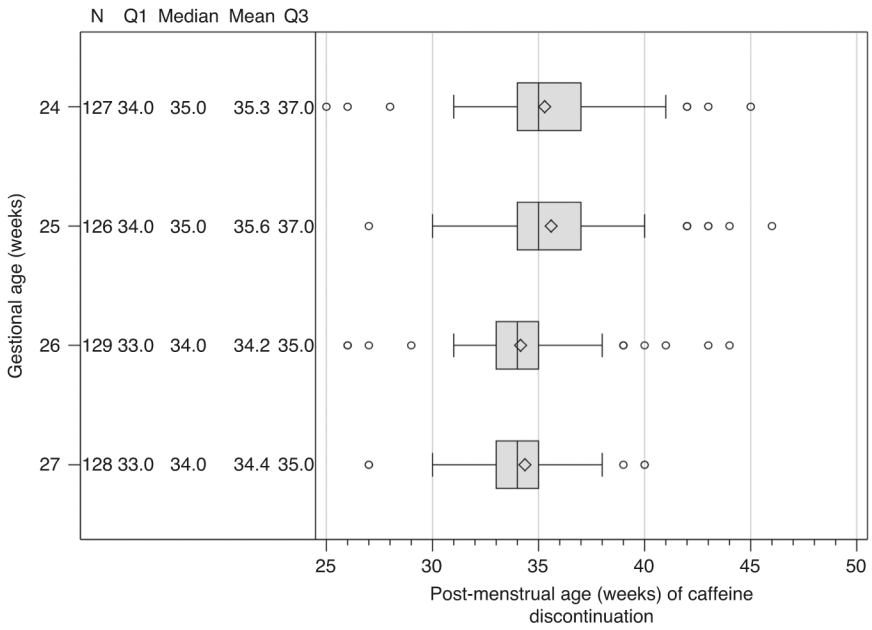

Fig. 3. Last caffeine administration by post menstrual age.

This boxplot depicts the timing of caffeine discontinuation. The *x*-axis is the postmenstrual age of caffeine discontinuation, and the *y* axis is gestational age at birth.

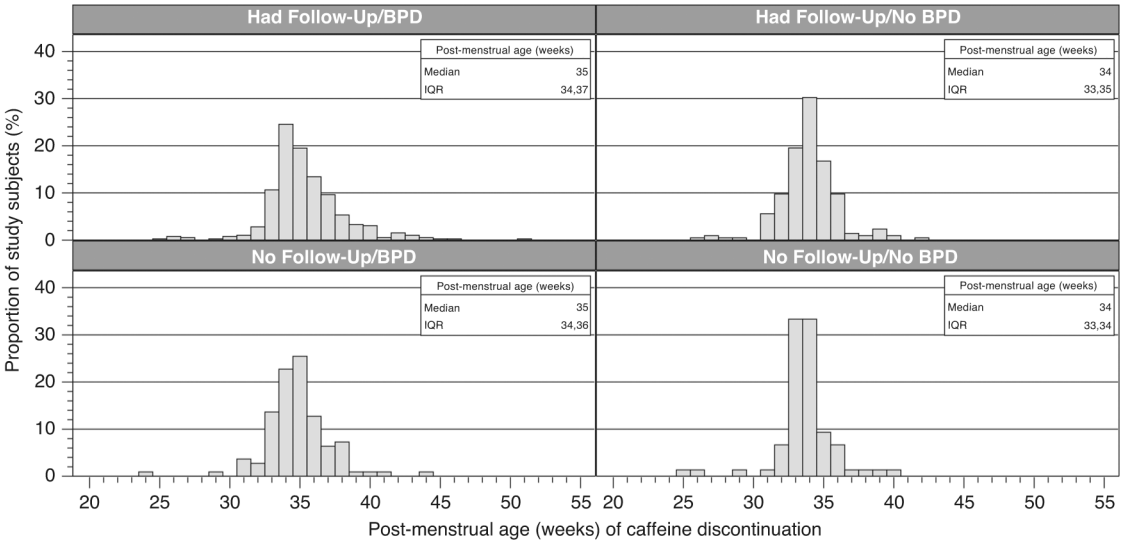

Fig. 4. Post menstrual age at caffeine discontinuation stratified by bronchopulmonary dysplasia status and follow-up at 22–26 months corrected gestational age.

This histogram depicts frequencies of the timing of caffeine discontinuation based on follow-up status and bronchopulmonary dysplasia (BPD) status. Each of the 4 panes represents a combination of those two possibilities: Follow-up with BPD, follow-up without BPD, no follow-up with BPD, and no follow-up without BPD. The x-axis is the postmenstrual age, and the y axis is number of study subjects.

Table 1.

Neonatal, maternal and delivery characteristics and associations with post-menstrual weeks of caffeine discontinuation.

	N (%)	Beta[a]	p-value[a]
Gestational Age			
24 Weeks	142 (23.8)	0.87	0.0038
25 Weeks	146 (24.4)	1.17	<0.0001
26 Weeks	146 (24.4)	−0.21	0.4803
27 Weeks	164 (27.4)	Referent	
Sex			
Female	290 (48.5)	Referent	
Male	308 (51.5)	0.33	0.1332
Maternal Race			
Black/African American	140 (23.4)	−0.74	0.0042
Other	36 (6.0)	0.07	0.8717
Unknown	14 (2.3)	−0.54	0.4557
White	408 (68.2)	Referent	
Maternal Ethnicity			
Hispanic/Latino	133 (22.2)	Referent	
Not Hispanic/Latino	457 (76.4)	0.15	0.5774
Unknown	8 (1.3)	−0.12	0.9020
Maternal characteristics			
Multiple gestations	157 (26.3)	−0.58	0.0193
Diabetes	35 (5.9)	−0.06	0.8911
Hypertension	418 (8.0)	−0.20	0.6115
Pre-eclampsia	90 (15.1)	−0.04	0.8943
Size			
Normal or Large for Gestational Age	512 (85.9)	Referent	
Small for Gestational Age	84 (14.1)	0.85	0.0069
Birth weight, g, mean (SD)	812.0 (190.5)	−0.003	<0.0001
Birth length, cm, mean (SD)	33.0 (3.0)	−0.18	<0.0001
Occipitofrontal circumference, cm, mean (SD)	23.2 (1.9)	−0.21	0.0002

	N (%)	Beta[a]	p-value[a]
Apgar 1 min, median (IQR)	4 (2–6)	−0.06	0.1860
Apgar 5 min, median (IQR)	7 (5–8)	−0.10	0.0801
Prenatal steroids, *n* (%)			
None	45 (7.7)	−0.41	0.4573
1 dose	122 (20.8)	0.15	0.7405
2 doses	369 (63.0)	0.25	0.5352
3 doses	50 (8.5)	Referent	
Delivery Room Resuscitation			
Any	576 (96.5)	−0.49	0.4087
Intubation	482 (80.6)	−0.18	0.5058
Surfactant	309 (51.7)	−0.11	0.6022
Chest compressions	43 (7.2)	−0.26	0.5419
Resuscitation drugs	19 (3.2)	0.69	0.2634
Infant Outcomes			
BPD	386 (64.6)	1.40	<0.0001
Necrotizing enterocolitis (Bells stage 2a or higher)	51 (8.5)	0.95	0.0143
Patent ductus arteriosus	253 (42.4)	0.68	0.0019
Vasopressor Medications			
None	385 (64.4)	−0.80	0.0042
Vasopressors alone	94 (15.7)	−0.60	0.1005
Vasopressors + hydrocortisone	119 (19.9)	Referent	
Culture proven Sepsis	35 (5.9)	0.25	0.5964
Severe IVH	68 (11.4)	1.20	0.0004
Nephrotoxic Meds			
Indomethacin	284 (47.5)	0.14	0.5319
Gentamicin	576 (96.3)	0.04	0.9480
Vancomycin	365 (61.0)	0.81	0.0003

[a] Estimated from a general linear model.

Table 2.

22–26 month corrected gestational age kidney outcomes by gestational age week at birth.

	GA 24 weeks (*n* = 142)	GA 25 weeks (*n* = 146)	GA 26 weeks (*n* = 146)	GA 27 weeks (*n* = 164)	*p*-value[a]
Overall					
eGFR <90 (*n* = 323)	20/75 (26.6)	14/81 (17.3)	12/82 (14.6)	12/85 (14.1)	0.18
eGFR >120 (*n* = 323)	8/75 (10.7)	25/81 (30.9)	17/82 (20.7)	14/85 (16.5)	0.01
Albumin/Creatinine ratio >30 mg albumin/g cr (*n* = 407)	36/105 (34.3)	35/99 (35.4)	35/104 (33.7)	39/99 (39.4)	0.84
Hypertension (*n* = 369)					
≥90th percentile	39/80 (48.8)	53/93 (57.0)	51/95 (53.7)	61/101 (60.4)	0.45
>95th percentile	30/80 (37.5)	43/93 (46.2)	42/95 (44.2)	51/101 (50.5)	0.38
Systolic pressure-based (*n* = 369)					
<90th percentile	58/80 (72.5)	60/93 (64.5)	73/95 (76.8)	67/101 (66.3)	0.37
90–94th percentile	8/80 (10.0)	11/93 (11.8)	6/95 (6.3)	7/101 (6.9)	
>95th percentile	14/80 (17.5)	22/93 (23.7)	16/95 (16.8)	27/101 (26.7)	
Diastolic pressure-based					
<90th percentile	46/80 (57.5)	43/93 (46.2)	49/95 (51.6)	43/101 (42.6)	0.61
90–94th percentile	8/80 (10.0)	12/93 (12.9)	11/95 (11.6)	14/101 (13.9)	
>95th percentile	26/80 (32.5)	38/93 (40.9)	35/95 (36.8)	44/101 (43.6)	

GA Gestational age, *eGFR* estimated glomerular filtration rate.

[a]Estimated from a Fisher's exact test.

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Table 3.

22–26 month corrected gestational age kidney outcomes for entire cohort with at least one kidney measure at follow-up by post menstrual age week of caffeine discontinuation.

	PMA < 33 weeks	PMA 33–35 6/7 weeks	PMA ≥ 36 weeks	*p*-value[a]
GA 24 weeks (*n* = 142)				
N	9	79	54	
eGFR <90 mL/min/1.73m^2	0/3 (0.0)	10/42 (23.8)	10/31 (32.3)	0.52
eGFR >120 mL/min/1.73m^2	1/3 (33.3)	5/42 (11.9)	2/30 (6.7)	0.30
ACR > 30 mg albumin/g cr	2/8(25.0)	22/58 (37.9)	12/39 (30.8)	0.69
BP				
>95th percentile	3/6 (50.0)	15/45 (33.3)	12/29 (41.4)	0.68
SBP >95th	2/6 (33.3)	7/45 (15.6)	5/29 (17.2)	0.59
DBP >95th	3/6 (50.0)	13/45 (28.9)	10/29 (34.4)	0.53
GA 25 weeks (*n* = 146)				
N	9	72	65	
eGFR <90 mL/min/1.73 m^2	1/5 (20.0)	8/42 (19.0)	5/35 (14.3)	0.90
eGFR >120 mL/min/1.73 m^2	2/5 (40.0)	10/42 (23.8)	13/34 (38.2)	0.35
ACR > 30 mg albumin/g cr	1/9 (11.1)	16/48 (33.3)	18/42 (42.9)	0.18
BP				
>95th percentile	4/8 (50.0)	17/44 (38.6)	22/41 (53.7)	0.37
SBP >95th	1/8 (12.5)	8/44 (18.2)	13/41 (31.7)	0.33
DBP >95th	4/8 (50.0)	15/44 (34.1)	19/41 (46.3)	0.44
GA 26 weeks (*n* = 146)				
N	25	87	34	
eGFR <90 mL/min/1.73 m^2	2/10 (20.0)	5/48 (10.6)	5/24 (20.8)	0.40
eGFR >120 mL/min/1.73 m^2	2/10 (20.0)	10/48 (20.8)	5/24 (20.8)	1.00
ACR > 30 mg albumin/g cr	8/19 (42.1)	17/65 (26.2)	10/20 (50.0)	0.10
HTN				
>95th percentile	5/18 (27.8)	27/56 (48.2)	10/21 (47.6)	0.33
SBP >95th	1/18 (5.6)	13/56 (23.2)	2/21 (9.5)	0.17
DBP >95th	4/18 (22.2)	23/56 (41.1)	8/21 (38.1)	0.36

	PMA < 33 weeks	PMA 33–35 6/7 weeks	PMA ≥ 36 weeks	*p*-value[a]
GA 27 weeks (*n* = 164)				
N	19	113	32	
eGFR <90 mL/min/1.73 m^2	1/5 (20.0)	8/61 (13.1)	3/15 (15.0)	0.76
eGFR >120 mL/min/1.73 m^2	2/5 (40.0)	10/61 (16.4)	2/19 (10.5)	0.24
ACR > 30 mg albumin/g cr	6/12 (50.0)	25/70 (35.7)	8/17 (47.1)	0.47
BP				
>95th percentile	7/11 (63.6)	36/71 (50.7)	8/19 (42.1)	0.54
SBP >95th	3/11 (27.3)	20/71 (28.2)	4/19 (21.1)	0.94
DBP >95th	6/11 (54.5)	30/71 (42.2)	8/19 (42.1)	0.77

PMA Post-Menstrual age, *GA* Gestational age, *eGFR* estimated glomerular filtration rate, *ACR* albumin creatinine ratio, *HTN* hypertension, *SBP* systolic blood pressure, *DBP* diastolic blood pressure.

[a]Estimated from a Fisher's exact test.

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Table 4.

Odds ratios and associated 95% confidence intervals for the association between post menstrual week at caffeine discontinuation and 22–26-month corrected gestational age outcomes stratified by bronchopulmonary dysplasia status at 36 weeks postmenstrual age.

24-month Outcome	*N* (%)	Crude OR[a] (95% CI)	Adjusted OR[a,b] (95% CI)
Overall			
eGFR<90 mL/min/1.73 m^2 (*n* = 326)	58 (17.8)	1.03 (0.93–1.13)	0.98 (0.87–1.11)
eGFR>120 mL/min/1.73 m^2 (*n* = 323)	64 (19.8)	0.97 (0.93–1.02)	0.96 (0.91–1.01)
ACR > 30 mg albumin/g creatinine (*n* = 407)	145 (35.6)	1.03 (0.98–1.09)	1.08 (1.00–1.16)
BP > 90th percentile (*n* = 469)	222 (58.9)	1.03 (0.95–1.12)	1.09 (0.99–1.20)
BP > 95th percentile (*n* = 469)	222 (47.3)	1.05 (0.97–1.13)	1.10 (0.99–1.22)
BPD			
eGFR<90 mL/min/1.73 m^2 (*n* = 220)	45 (20.5)	1.04 (0.93–1.17)	1.02 (0.89–1.18)
eGFR>120 mL/min/1.73 m^2 (*n* = 218)	39 (12.1)	0.99 (0.92–1.07)	0.96 (0.88–1.05)
ACR> 30 mg albumin/g creatinine (*n* = 265)	85 (32.1)	1.07 (0.98–1.16)	1.08 (0.98–1.19)
BP > 90th percentile (*n* = 300)	169 (56.3)	1.09 (1.00–1.18)	1.15 (1.04–1.26)
BP > 95th percentile (*n* = 300)	135 (45.0)	1.10 (1.02–1.20)	1.15 (1.05–1.25)
NO BPD			
eGFR<90 mL/min/1.73 m^2 (*n* = 106)	13 (12.3)	0.82 (0.66–1.00)	0.78 (0.62–0.99)
eGFR>120 mL/min/1.73 m^2 (*n* = 106)	25 (7.7)	0.98 (0.88–1.09)	0.95 (0.84–1.07)
ACR> 30 mg albumin/g creatinine (*n* = 142)	60 (42.3)	1.04 (0.93–1.16)	1.07 (0.98–1.18)
BP > 90th percentile (*n* = 169)	107 (63.3)	0.93 (0.80–1.08)	0.95 (0.78–1.15)
BP > 95th percentile (*n* = 169)	87 (51.5)	0.95 (0.80–1.14)	0.96 (0.75–1.24)

BPD bronchopulmonary dysplasia, *eGFR* estimated glomerular filtration rate, *ACR* albumin creatinine ratio, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *OR* odds ratio.

[a]Estimated from a general estimating equation logistic regression to account for clustering by study site.

[b]Adjusted for gestational age, maternal race, multiple gestation, size for gestational age, highest stage AKI, BPD, severe IVH, vancomycin use, and treatment group (Epo or placebo) of parent trial.