Markers of Kidney Function in Early Childhood and Association With Maternal Comorbidity

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Abstract

Importance Kidney functional capacity is low at birth but doubles during the first 2 weeks of life and reaches near-adult levels at age 1 to 2 years. Existing reference intervals for markers of kidney function in newborns are mostly based on preterm newborns, newborns with illness, or small cohorts of term newborns, and the consequences of maternal comorbidities for newborn kidney function are sparsely described.

Objective To establish robust reference intervals for creatinine and urea in healthy children in early childhood and to assess whether maternal comorbidity is associated with newborn creatinine and urea concentrations.

Design, Setting, and Participants This multicenter, prospective, population-based cohort study assessed data and umbilical cord blood samples from participants in the Copenhagen Baby Heart Study (CBHS) who were born between April 1, 2016, and October 31, 2018, and venous blood samples from a subsample of CBHS participants who were enrolled in the COMPARE study between May 3, 2017, and November 4, 2018. Cord blood samples of 13,354 newborns from the CBHS and corresponding venous blood samples of 444 of those newborns from the COMPARE study were included. Blood samples were collected at birth, age 2 months, and age 14 to 16 months, with follow-up completed on February 12, 2020. Healthy nonadmitted term newborns from maternity wards at 3 hospitals in the Capital Region of Denmark were included.

Exposures Maternal comorbidity.

Main Outcomes and Measures Creatinine and urea concentrations.

Results Among 13,354 newborns in the CBHS cohort, characteristics of 12,938 children were stratified by sex and gestational age (GA). Of those, 6,567 children (50.8%) were male; 5,259 children (40.6%) were born at 37 to 39 weeks' GA, and 7,679 children (59.4%) were born at 40 to 42 weeks' GA. Compared with children born at 40 to 42 weeks' GA, those born at 37 to 39 weeks' GA had lower birth weight, Apgar scores at 5 minutes, placental weight, and placental-fetal weight ratio. Children born at 37 to 39 weeks' GA vs those born at 40 to 42 weeks' GA were more frequently small for GA at birth and more likely to have placental insufficiency and exposure to maternal preeclampsia, maternal diabetes, maternal kidney disease, and maternal hypertension. Among children born at 37 to 39 weeks' GA, reference intervals were 0.54 to 1.08 mg/dL for creatinine and 5.32 to 14.67 mg/dL for urea; among children born at 40 to 42 weeks' GA, reference intervals were 0.57 to 1.19 mg/dL for creatinine and 5.60 to 14.85 mg/dL for urea. At birth, multifactorially adjusted odds ratios among children exposed to preeclampsia were 9.40 (95% CI, 1.68-52.54) for a venous creatinine concentration higher than the upper reference limit, 4.29 (95% CI, 1.32-13.93) for a venous creatinine concentration higher than the upper reference limit, and 4.29 (95% CI, 1.32-13.93) for a venous creatinine concentration higher than the upper reference limit.
Abstract (continued)

concentration higher than the 90th percentile, and 3.10 (95% CI, 1.14-8.46) for a venous creatinine concentration higher than the 80th percentile.

CONCLUSIONS AND RELEVANCE In this study, improved reference intervals for creatinine and urea concentrations were generated. Preeclampsia was associated with an increased risk of high newborn creatinine concentrations, suggesting that newborns of mothers with preeclampsia need closer observation of their kidney function.


Introduction

Kidney functional capacity is low at birth but doubles during the first 2 weeks of life and reaches near-adult values at age 1 to 2 years. Existing reference intervals for markers of kidney function, such as creatinine and urea, in newborns are mostly based on findings in preterm newborns or newborns with illness (ranging from 38-580 newborns) or in small cohorts of term newborns (ranging from 5-74 newborns), hence, use of existing reference intervals may present challenges for clinical decision-making. In addition, the burden of maternal comorbidities, such as preeclampsia, diabetes, hypertension, and overweight, has increased during the last several decades, and knowledge of the implications of these factors for neonatal kidney function is sparse.

Assessment of kidney function is important for the detection of kidney disease and acute kidney injury (AKI) and for the ability to offer safe pharmacological treatment to neonates given that approximately 60% of all drugs are eliminated by the kidneys. Kidney functional capacity is low during fetal life, and homeostasis is sustained by the placenta. During the first weeks of life, kidney function increases rapidly and reaches 90% of adult levels at age 1 year. Serum creatinine is used as a crude measure of kidney function, refined by different formulas for estimated glomerular filtration rates (including creatinine, blood urea nitrogen, cystatin C, or height). During fetal life, creatinine and urea are transferred across the placental barrier, and fetal and newborn concentrations have been reported to correlate significantly with maternal concentrations. During the first few days of life, newborn creatinine concentration increases, leaving the reliability of creatinine as a marker of kidney function disputed in this early phase of life. An optimal marker is, however, still lacking. Cystatin C and β-trace protein have been suggested as alternative markers, but testing is costly and of limited availability, and the superiority of cystatin C has been questioned. The development of creatinine and urea concentrations over time during early life is not well described in healthy unselected nonhospitalized children. Furthermore, the consequences of maternal comorbidities during pregnancy for newborn kidney function are currently unknown.

Therefore, we evaluated creatinine and urea concentrations in the first 16 months of life in umbilical cord blood and venous blood samples from healthy, nonadmitted newborns to define robust reference intervals at birth stratified by gestational age (GA). Furthermore, we examined the association of maternal comorbidities with creatinine and urea concentrations in newborns. The study included 13 354 newborns with umbilical cord blood samples from the prospective population-based Copenhagen Baby Heart Study (CBHS). Among those, 444 newborns included in the COMPARE study had corresponding venous blood samples collected at birth, 363 infants had venous samples collected at age 2 months, and 156 children had venous samples collected at age 14 to 16 months.
Methods

The CBHS and the COMPARE study adhered to the Declaration of Helsinki and were approved by the Regional Ethics Committee of the Capital Region of Denmark and the Danish Data Protection Agency. For all participants, written informed consent from legal guardians was obtained. Both studies followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies.

Copenhagen Baby Heart Study

The CBHS was a prospective multicenter population-based cohort study focusing on cardiac structure and function in 27,595 newborns and has been previously described in detail; follow-up of some participants is ongoing. Children born between April 1, 2016, and October 31, 2018, at Copenhagen University Hospital–Rigshospitalet (Rigshospitalet), Herlev Hospital, or Hvidovre Hospital were prenatally included in the study. Umbilical cord blood samples were collected immediately after birth in accordance with the CBHS study protocol. The CBHS had a high participation rate, with 55% of infants born in participating hospitals enrolled. Data on participant race and ethnicity were not included in the current study because analyses were primarily stratified by sex and GA; however, Vøgge et al reported that 78.9% of children in the CBHS had at least 1 parent with Danish citizenship, and 21.2% of mothers were of origins other than Denmark.

COMPARE Study

Mothers enrolled in the CBHS who delivered at Rigshospitalet were also offered enrollment in the COMPARE study between May 3, 2017, and November 4, 2018. Exclusion criteria for the COMPARE study were birth at less than 37 weeks’ GA or birth at 42 weeks’ GA or greater and birth weight lower than 2500 g. In this subcohort of the CBHS, the sampling of umbilical cord blood was followed by parallel sampling of venous blood from the newborn, mother, and father from the antecubital vein approximately 2 hours after birth. The collection of venous blood samples was repeated at 2 months after birth in infants and their parents and again at age 14 to 16 months in children and their mothers. Follow-up was completed on February 12, 2020.

Biochemical Measurements and Covariates

Umbilical blood and venous blood samples were analyzed for biochemical markers, including creatinine and urea, using standard hospital clinical biochemistry equipment. Creatinine and urea concentrations are reported in milligrams per deciliter (to convert creatinine from milligrams per deciliter to micromoles per liter, multiply by 88.4; to convert urea from milligrams per deciliter to millimoles per liter, multiply by 0.357). Additional information about biochemical measurements is provided in the eMethods in the Supplement.

Demographic and clinical characteristics of mothers and newborns were extracted from the local obstetric and fetal medicine databases. Maternal age was recorded at delivery. Maternal body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) was self-reported and calculated using weight before pregnancy. Gestational age was determined from obstetric ultrasonography. Neonatal Apgar (appearance, pulse, grimace, activity, and respiration) scores were assessed at 1 minute and 5 minutes after birth using a scale of 1 to 10, with scores of 7 to 10 considered good to excellent health. Birth weight and length were measured at birth; neonates who were small for GA (SGA) at birth were identified using the formula of Marsál et al, with SGA defined as birth weight lower than the 2.3 percentile and equivalent to a birth weight less than 22% of the mean birth weight for a given GA. The placental-fetal weight ratio was calculated as placental weight divided by birth weight and reported as grams of placental weight per 1 gram of fetal weight.

Maternal and newborn diagnoses were identified using International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) diagnostic codes. Relevant comorbidities included placental insufficiency, congenital malformation of the urinary system, and
maternal preeclampsia, diabetes, hypertension, and kidney disease. Information on smoking was self-reported during a prepregnancy interview with a midwife during the first trimester. (ICD-10 diagnosis codes are provided in eTable 1 in the Supplement.)

Statistical Analysis
Statistical analyses were conducted using Stata software, version 17.0 (StataCorp LLC), and R Studio software, version 3.6 (R Foundation for Statistical Computing). Categorical variables are reported as numbers and percentages, and continuous variables are reported as medians and IQRs. Two-sided \( P < .05 \) was considered statistically significant. The Mann-Whitney \( U \) test was applied for 2-group comparisons of unmatched continuous variables, and the Pearson \( \chi^2 \) test was applied for unmatched categorical variables. Unpaired \( t \) tests were used to compare maternal venous blood with umbilical cord blood and newborn venous blood, and paired \( t \) tests were used to compare umbilical cord blood with newborn venous blood. Pearson correlation coefficients and linear regression analyses were performed to describe the association between newborn venous blood and umbilical cord blood.

Reference intervals for concentrations in children's venous blood at birth, 2 months after birth, and 14 to 16 months after birth were established using the nonparametric method recommended in the Tietz Textbook of Clinical Chemistry and Molecular Diagnostics for laboratories of clinical biochemistry. Thus, outliers (defined as values outside of the first quartile minus 1.5 multiplied by IQR and values outside of the third quartile plus 1.5 multiplied by IQR) were removed. The 2.5 and 97.5 percentiles were defined using 4 different models: (1) no exclusions, (2) outliers removed according to the Tietz method, (3) individuals with exclusion criteria removed, and (4) both outliers and individuals with exclusion criteria removed. The exclusion criteria used in models 3 and 4 were defined as any record of preeclampsia, maternal diabetes, maternal kidney disease, congenital kidney deformity (diagnosis codes are available in eTable 1 in the Supplement), maternal BMI greater than 35, and SGA at birth. Newborn reference intervals were stratified by GA.

The association of maternal comorbidities with creatinine and urea concentrations in children were examined using logistic regression analysis, with maternal comorbidities as exposures and high creatinine and urea at different cutoffs as end points. The models were adjusted for maternal age at birth, child's sex, GA, birth weight, birth length, multiple births, and placental-fetal weight ratio higher or lower than the median. Sensitivity analyses additionally adjusted for maternal creatinine and urea concentrations in the COMPRESE study were also performed.

Results

Study Participants
A flowchart of the enrollment process, number of participants, and blood samples collected in the CBHS and COMPRESE studies is shown in eFigure 1 in the Supplement. The current study included umbilical cord blood samples from 13 354 newborns, with 444 parallel newborn venous blood samples collected at birth, 363 venous samples collected at age 2 months, and 156 venous samples collected at age 14 to 16 months.

Characteristics of the Study Population
Characteristics of 12 938 children in the CBHS and 444 children in the COMPRESE study, stratified by sex and GA, are shown in Table 1. Among 12 938 children in the CBHS cohort, 6371 children (49.2%) were female, 6567 children (50.8%) were male; 5259 children (40.6%) were born at 37 to 39 weeks’ GA, and 7679 children (59.4%) were born at 40 to 42 weeks’ GA. The median maternal age in the CBHS cohort was 31 years (IQR, 29-35 years), and the median maternal BMI was 22 (IQR, 21-25). Additional characteristics, such as maternal socioeconomic status, educational level, and ethnicity, have previously been described in detail. Most children (78.9%) in the CBHS had at least 1 parent with Danish citizenship. Values for some variables were missing among 1711 of 13 354 participants in the CBHS cohort. An assessment of missing values is shown in eTable 2 in the Supplement.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Female participants, No./total No. (%)</th>
<th>Male participants, No./total No. (%)</th>
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<tr>
<td></td>
<td>GA, wk</td>
<td>P value</td>
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</tr>
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<td>Participants</td>
<td>2521/12 938 (19.5)</td>
<td>3850/12 938 (29.8)</td>
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<td>Maternal age, median (IQR), y&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>31 (29-34)</td>
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<td>3601 (3324-3896)</td>
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<td>Birth length, median (IQR), cm&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>10 (10-10)</td>
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<td>SGA&lt;sup&gt;a&lt;/sup&gt;</td>
<td>89/2521 (3.5)</td>
<td>98/3850 (2.5)</td>
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<td>Placental weight, median (IQR), g</td>
<td>615 (530-710)</td>
<td>640 (553-724)</td>
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<tr>
<td>Placental-fetal weight ratio, median (IQR), g/1 g of fetal weight</td>
<td>0.19 (0.17-0.21)</td>
<td>0.18 (0.16-0.20)</td>
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<td>Placental insufficiency&lt;sup&gt;j&lt;/sup&gt;</td>
<td>203/2518 (8.1)</td>
<td>142/3850 (3.7)</td>
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<td>Congenital malformation of the urinary system&lt;sup&gt;j&lt;/sup&gt;</td>
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<td>3/3848 (0.1)</td>
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<td>22 (21-25)</td>
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<td>Smoking&lt;sup;l&lt;/sup&gt;</td>
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<td>98/3850 (2.5)</td>
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<td>COMPARE study&lt;sup&gt;d&lt;/sup&gt;</td>
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<td></td>
</tr>
<tr>
<td>Participants</td>
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<td>111/444 (25.0)</td>
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<td>Maternal age, median (IQR), y&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>32 (29-35)</td>
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<td>3521 (3335-3779)</td>
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<td>Birth length, median (IQR), cm&lt;sup&gt;a&lt;/sup&gt;</td>
<td>51 (50-52)</td>
<td>52 (51-53)</td>
</tr>
<tr>
<td>Apgar score at 5 min, median (IQR)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>10 (10-10)</td>
<td>10 (10-10)</td>
</tr>
<tr>
<td>SGA&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>6/111 (5.4)</td>
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<td>Placental weight, median (IQR), g</td>
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<td>618 (540-700)</td>
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<tr>
<td>Placental-fetal weight ratio, median (IQR), g/1 g of fetal weight</td>
<td>0.19 (0.18-0.22)</td>
<td>0.17 (0.15-0.19)</td>
</tr>
<tr>
<td>Placental insufficiency&lt;sup&gt;j&lt;/sup&gt;</td>
<td>7/106 (6.6)</td>
<td>4/111 (3.6)</td>
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<tr>
<td>Congenital malformation of the urinary system&lt;sup&gt;j&lt;/sup&gt;</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Maternal BMI, median (IQR)&lt;sup&gt;k&lt;/sup&gt;</td>
<td>7/106 (6.6)</td>
<td>5/111 (4.5)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3/106 (2.8)</td>
<td>0</td>
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<tr>
<td>Kidney disease</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5/106 (4.7)</td>
<td>3/111 (2.7)</td>
</tr>
<tr>
<td>Smoking&lt;sup;l&lt;/sup&gt;</td>
<td>2/103 (2.0)</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); GA, gestational age; NA, not applicable; SGA, small for gestational age.

<sup>a</sup> Baseline characteristics on the day of birth (2016-2018) stratified by sex and GA.

<sup>b</sup> Gestational age was determined from obstetric ultrasonography.

<sup>c</sup> P values were derived from a Mann-Whitney U test or a Pearson χ² test.

<sup>d</sup> Numbers (including total number of participants in the Copenhagen Baby Heart Study) may vary from the flowchart (eFigure 1 in the Supplement) due to missing variables.

<sup>e</sup> Maternal age was recorded at delivery.

<sup>f</sup> Birth weight and birth length were measured at birth.

<sup>g</sup> Apgar scores were assessed at 1 minute and 5 minutes after birth using a scale ranging from 1 to 10, with scores of 7 to 10 considered good to excellent health.

<sup>h</sup> Small for gestational age: birth weight below the 2.3 percentile and equivalent to a birth weight less than 22% of the mean birth weight for gestational age.

<sup>i</sup> Placental-fetal weight ratio was calculated as placental weight divided by birth weight and reported as grams of placental weight per 1 gram of fetal weight.

<sup>j</sup> Additional details about placental insufficiency, congenital malformation of the urinary system, and maternal comorbidities (preeclampsia, diabetes, kidney disease, and hypertension) are available in Table 1 in the Supplement.

<sup>k</sup> Maternal BMI was self-reported and calculated using weight before pregnancy.

<sup>l</sup> Information about smoking was self-reported during a prepregnancy interview with a midwife in the first trimester.
Among 444 children in the COMPARE subcohort, 217 (48.9%) were female, and 227 (51.1%) were male; 211 children (47.5%) were born at 37 to 39 weeks’ GA, and 233 (52.5%) were born at 40 to 42 weeks’ GA. The median maternal age in the COMPARE subcohort was 32 years (IQR, 29-36 years), and the median maternal BMI was 23 (IQR, 21-25). In both cohorts, the incidence of maternal comorbidities was low (eg, preeclampsia: 671 women [5.2%] in the CBHS cohort vs 27 women [6.1%] in the COMPARE subcohort; diabetes: 347 women [2.7%] in the CBHS cohort vs 14 women [3.2%] in the COMPARE subcohort).

In the CBHS cohort, compared with children born at 40 to 42 weeks’ GA, those born at 37 to 39 weeks’ GA had lower birth weight (median [IQR], 3360 [3075-3644] g vs 3680 [3400-3980] g; \( P < .001 \)), birth length (median [IQR], 51 [50-52] cm vs 52 [51-54] cm; \( P < .001 \)), Apgar scores at 5 minutes (median [IQR], 10 [10-10] vs 10 [10-10]; \( P = .01 \)), placental weight (median [IQR], 623 [534-720] g vs 648 [560-735] g; \( P < .001 \)), and placental-fetal weight ratio (median [IQR], 0.19 [0.16-0.21] g/g of fetal weight vs 0.18 [0.16-0.20] g/g of fetal weight; \( P < .001 \)). Children born at 37 to 39 weeks’ GA (n = 5259) vs those born at 40 to 42 weeks’ GA (n = 7679) were more frequently SGA at birth (180 children [3.4%] vs 190 children [2.5%]; \( P = .001 \)) and more likely to have placental insufficiency (397 children [7.5%] vs 224 children [2.9%]; \( P < .001 \)) and exposure to maternal preeclampsia (412 children [7.8%] vs 259 children [3.4%]; \( P < .001 \)), maternal diabetes (263 children [5.0%] vs 84 children [1.1%]; \( P < .001 \)), maternal kidney disease (9 children [0.2%] vs 2 children [0.03%; \( P = .005 \)), and maternal hypertension (218 children [4.1%] vs 124 children [1.6%]; \( P < .001 \)).

Comparison of Umbilical Cord Blood, Maternal Venous Blood, and Newborn Venous Blood at Birth
The distributions of creatinine and urea concentrations in umbilical cord blood, maternal venous blood, and newborn venous blood at birth are shown in Figure 1. Median umbilical cord concentrations did not differ from maternal venous concentrations for creatinine (0.68 mg/dL vs 0.64 mg/dL; mean difference, 0.022; 95% CI, −0.002 to 0.045; \( P = .10 \)) but were higher for urea (8.96 mg/dL vs 8.12 mg/dL; mean difference, 1.03; 95% CI, 0.63-1.42; \( P < .001 \)). Median newborn venous concentrations at 2 hours were higher than maternal venous concentrations (creatinine: 0.80 mg/dL vs 0.64 mg/dL; mean difference, 0.17 [95% CI, 0.15-0.20; \( P < .001 \)]; urea: 9.52 mg/dL vs

The area under the density curve represents probability and therefore sums to 1. The scale of the y-axis in each density plot was determined by the range of the x-axis and ranges from 1 to infinity. \( P \) values were derived from unpaired t tests comparing maternal venous blood with newborn venous blood and umbilical cord blood. Paired t tests were used to compare newborn venous blood with umbilical cord blood. Equations used in the linear regression modeling of newborn venous blood as a function of umbilical cord blood, stratified by gestational age, are provided in the Results section under Comparison of Umbilical Cord Blood, Maternal Venous Blood, and Newborn Venous Blood at Birth.

Figure 1. Creatinine and Urea Concentrations in Maternal Venous, Umbilical Cord, and Newborn Venous Blood at Birth

The area under the density curve represents probability and therefore sums to 1. The scale of the y-axis in each density plot was determined by the range of the x-axis and ranges from 1 to infinity. \( P \) values were derived from unpaired t tests comparing maternal venous blood with newborn venous blood and umbilical cord blood. Paired t tests were used to compare newborn venous blood with umbilical cord blood. Equations used in the linear regression modeling of newborn venous blood as a function of umbilical cord blood, stratified by gestational age, are provided in the Results section under Comparison of Umbilical Cord Blood, Maternal Venous Blood, and Newborn Venous Blood at Birth.
8.12 mg/dL; mean difference, 1.43 [95% CI, 1.07-1.80; P < .001]) and umbilical concentrations 
(creatinine: 0.80 mg/dL vs 0.68 mg/dL; mean difference, 0.14 [95% CI, 0.13-0.16; P < .001]; urea: 
9.52 mg/dL vs 8.96 mg/dL; mean difference, 0.32 [95% CI, 0.24-0.40; P < .001]).

Pearson correlation coefficients between newborn venous blood and umbilical cord blood 
concentrations were 0.72 (95% CI, 0.66-0.77) for creatinine and 0.97 (95% CI, 0.96-0.97) for urea. 
Therefore, we created models describing the association between concentrations of creatinine and 
urea in newborn venous and umbilical cord blood.

For creatinine, the equations were as follows:

Newborn Cr = (0.73 × Umbilical Creatinine) + 0.33;
Newborn Cr at 37 to 39 Weeks' GA = (0.61 × Umbilical Creatinine) + 0.40;
Newborn Cr at 40 to 42 Weeks' GA = (0.82 × Umbilical Creatinine) + 0.27;

where Cr indicates creatinine and all values are given in mg/dL.

For urea, the equations were as follows:

Newborn Urea = (0.97 × Umbilical Urea) + 0.60;
Newborn Urea at 37 to 39 Weeks' GA = (0.97 × Umbilical Urea) + 0.58;
Newborn Urea at 40 to 42 Weeks' GA = (0.97 × Umbilical Urea) + 0.66,

where all values are given in mg/dL.

**Creatinine and Urea Concentrations at Birth, Age 2 Months, and Age 14 to 16 Months**
Changes in creatinine and urea concentrations from birth to age 2 months and birth to age 14 to 16 months are shown in Figure 2. In children's venous blood, the medians for creatinine concentrations were 0.80 mg/dL (IQR, 0.71-0.93 mg/dL) at birth, 0.21 mg/dL (IQR, 0.18-0.25 mg/dL) at age 2 months, and 0.26 mg/dL (IQR, 0.24-0.29 mg/dL) at age 14 to 16 months. The medians for urea concentrations were 9.52 mg/dL (IQR, 7.84-11.20 mg/dL) at birth, 6.16 mg/dL (IQR, 4.90-7.56 mg/dL) at age 2 months, and 13.17 mg/dL (IQR, 10.64-15.13 mg/dL) at age 14 to 16 months.

**Reference Intervals for Creatinine and Urea in Children at Birth, Age 2 Months, and Age 14 to 16 Months**
At the time of birth, GA was found to be associated with newborn venous blood concentrations of both creatinine (median [IQR], 0.77 [0.70-0.88] mg/dL for 37-39 weeks' GA vs 0.84 [0.75-0.95] mg/dL for 40-42 weeks' GA; P < .001) and urea (median [IQR], 9.10 [7.28-10.92] mg/dL for 37-39 weeks' GA vs 10.08 [8.40-11.76] mg/dL for 40-42 weeks' GA; P < .001). However, sex was not associated with concentrations of creatinine (median [IQR], 0.79 [0.71-0.92] mg/dL for female newborns vs 0.83 [0.72-0.98] mg/dL for male newborns; P = .06) or urea (median [IQR], 9.52 [7.28-10.92] mg/dL for female newborns vs 9.80 [7.84-11.76] mg/dL for male newborns; P = .07) (eTables 3-6 in the Supplement). Thus, reference intervals for newborns at the time of birth were stratified by GA (37-39 weeks and 40-42 weeks).

Reference intervals for creatinine and urea concentrations accounting for maternal comorbidty 
and outliers (model 4) are shown in Table 2 (with existing local reference intervals from 
Rigshospitalet provided for comparison). Reference intervals for creatinine concentrations were 0.54 
to 1.08 mg/dL for newborns born at 37 to 39 weeks' GA, 0.57 to 1.19 mg/dL for newborns born at 40 
to 42 weeks' GA, 0.13 to 0.31 mg/dL for infants aged 2 months, and 0.18 to 0.34 mg/dL for children 
aged 14 to 16 months. Reference intervals for urea concentrations were 5.32 to 14.67 mg/dL for for 
newborns born at 37 to 39 weeks' GA, 5.60 to 14.85 mg/dL for at newborns born at 40 to 42 weeks' 
GA, 3.08-10.08 mg/dL for infants aged 2 months, and 8.12-17.95 mg/dL for children aged 14 to 
16 months.
Figure 2. Development of Creatinine and Urea Concentrations in Venous Blood in Early Childhood

A) At birth

B) Age 2 mo

C) Age 14-16 mo

D) At birth

E) Age 2 mo

F) Age 14-16 mo

The area under the density curve represents probability and therefore sums to 1. The scale of the y-axis in each density plot was determined by the range of the x-axis and ranges from 1 to infinity. P-values were derived from unpaired t tests.
Reference intervals for creatinine and urea concentrations for all 4 models are provided in eTable 7 and eTable 8 in the Supplement. Across the 4 models, the reference intervals for levels of creatinine and urea only varied slightly in both venous blood at birth, 2 months after birth, and 14 to 16 months after birth. The number of children with concentrations categorized as low or high using the presently generated and existing reference intervals are shown in eTable 9 in the Supplement.

For creatinine, 26.4% of newborns assessed using the existing reference intervals would have been categorized as having high venous concentrations compared with 4.5% of newborns assessed using the reference intervals generated in this study. Reference intervals for umbilical blood are presented for creatinine in eTable 10 in the Supplement and for urea in eTable 11 in the Supplement.

Maternal Comorbidity and Risk of High Concentrations of Creatinine and Urea in Umbilical Cord Blood

To examine the association of maternal comorbidity with creatinine and urea concentrations in umbilical cord blood, odds ratios (ORs) were calculated using a logistic regression analysis with cutoffs corresponding to the upper reference interval limit (0.98 mg/dL for creatinine and 14.29 mg/dL for urea) (eTable 10 and eTable 11 in the Supplement). The models included umbilical cord blood samples from newborns of all GAs; however, a sensitivity analysis including only those born at 37 to 42 weeks’ GA yielded similar results. Multifactorially adjusted ORs for umbilical cord concentrations higher than the upper reference interval limit in newborns exposed to maternal preeclampsia were 3.56 (95% CI, 2.77-4.57) for creatinine and 3.91 (95% CI, 3.21-4.91) for urea. Corresponding adjusted ORs were 1.58 (95% CI, 1.02-2.44) for creatinine and 2.76 (95% CI, 1.97-3.86) for urea among newborns exposed to maternal diabetes, 1.79 (95% CI, 1.19-2.70) for creatinine and 2.21 (95% CI, 1.57-3.13) for urea among newborns exposed to maternal hypertension.

### Table 2. Reference Intervals for Creatinine and Urea Concentrations in Children’s Venous Blood

<table>
<thead>
<tr>
<th>Venous blood concentration</th>
<th>Reference interval (No. of participants)</th>
<th>Infant (age 2 mo)</th>
<th>Child (age 14-16 mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Creatinine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New reference interval from current study, 2.5-97.5 percentile, mg/dL&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.54-1.08 (144)</td>
<td>0.57-1.19 (162)</td>
<td>0.13-0.31 (268)</td>
</tr>
<tr>
<td>Existing local reference interval, mg/dL&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.42-0.92 (5)</td>
<td>0.19-0.46 (95)</td>
<td>0.17-0.35 (45)</td>
</tr>
<tr>
<td><strong>Urea</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New reference interval from current study, 2.5-97.5 percentile, mg/dL&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5.32-14.67 (144)</td>
<td>5.60-14.85 (165)</td>
<td>3.08-10.08 (288)</td>
</tr>
<tr>
<td>Existing local reference interval, mg/dL&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3.92-15.10 (NR)</td>
<td>5.04-15.10 (NR)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: GA, gestational age; NR, not reported.

SI conversion factors: To convert creatinine from milligrams per deciliter to micromoles per liter, multiply by 88.4; to convert urea from milligrams per deciliter to millimoles per liter, multiply by 0.357.

<sup>a</sup> Reference intervals were adjusted for outliers and exclusion criteria and were derived from newborn venous blood at the time of birth (2016-2018), infant venous blood at age 2 months, and children’s venous blood at age 14 to 16 months (2016-2020). Outliers were adjusted as recommended by the *Tietz Textbook of Clinical Chemistry and Molecular Diagnostics*.<sup>36</sup> Exclusion criteria were preeclampsia, maternal diabetes, maternal kidney disease, congenital kidney deformity, maternal body mass index (calculated as weight in kilograms divided by height in meters squared) greater than 35, and small for GA at birth. Newborn reference intervals from the time of birth were stratified by GA.

<sup>b</sup> The existing local reference intervals were from the Clinical Biochemical Department of Copenhagen University Hospital—Rigshospitalet in Copenhagen, Denmark.

<sup>c</sup> At age 0 to 1 day (determined from Boer et al<sup>a</sup>).

<sup>d</sup> At age 14 days to 2 months (determined from Boer et al<sup>a</sup>).

<sup>e</sup> At age 1 to 3 years (determined from Ceriotti et al<sup>10</sup>).

<sup>f</sup> At age 0 to 2 months.

<sup>g</sup> At age 2 months to 2 years.
1.46 (95% CI, 1.23-1.74) for creatinine and 1.19 (95% CI, 1.00-1.41) for urea among newborns exposed to maternal overweight (defined as BMI ≥25), and 1.03 (95% CI, 0.65-1.64) for creatinine and 0.72 (95% CI, 0.43-1.19) for urea among newborns exposed to maternal smoking (Figure 3; eFigure 2 in the Supplement). The adjusted ORs for newborns exposed to maternal kidney disease were 5.04 (95% CI, 1.06-24.00) for creatinine and 3.55 (95% CI, 0.77-16.32) for urea.

**Maternal Comorbidities and Risk of High Concentrations of Creatinine and Urea in Children’s Venous Blood**

Because maternal preeclampsia was the most significant exposure for high creatinine (OR, 3.56; 95% CI, 2.77-4.57) and urea (OR, 3.91; 95% CI, 3.21-4.91) concentrations in umbilical cord blood at birth (Figure 3; eFigure 2 in the Supplement), we also tested newborn venous blood. At birth, multifactorially adjusted ORs among newborns exposed to maternal preeclampsia were 9.40 (95% CI, 1.68-52.54) for the risk of a venous creatinine concentration higher than the upper reference limit, 4.29 (95% CI, 1.32-13.93) for the risk of a venous creatinine concentration higher than the 90th percentile, 3.10 (95% CI, 1.14-8.46) for the risk of a venous creatinine concentration higher than the 80th percentile, and 1.65 (95% CI, 0.63-4.27) for the risk of a venous creatinine concentration higher than the 50th percentile (eFigure 3 in the Supplement). Results remained significant when additionally adjusting for maternal creatinine concentrations at birth (higher than the upper reference limit: OR, 112.31; 95% CI, 4.18-3016.38; \( P = .005 \)). Similar patterns were observed at age 2 months (>90th percentile: OR, 1.75; 95% CI, 0.46-6.63; \( P = .41 \)) (eFigure 4 in the Supplement) and age 14 to 16 months (>80th percentile: OR, 2.58; 95% CI, 0.40-16.50; \( P = .32 \)); however, the results were not statistically significant. Preeclampsia was found to be associated with a 3-fold increase in the risk of children’s urea concentrations higher than the 50th percentile at birth (OR, 3.44; 95% CI, 1.25-9.47; \( P = .02 \)) (eFigure 5 in the Supplement). When adjusting for maternal urea concentration at birth, the association between preeclampsia and high newborn urea concentration was attenuated (higher than the upper reference limit: OR, 0.03 (95% CI, 0-11.44; \( P = .26 \)). No associations between preeclampsia and urea concentrations were found at 2 months after birth (higher than the upper

Figure 3. Association of Maternal Comorbidities With Risk of High Neonatal Creatinine Concentrations

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Individuals</th>
<th>Events</th>
<th>OR (95% CI)</th>
<th>Unadjusted</th>
<th>Multifactorially adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preeclampsia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>11492</td>
<td>572</td>
<td>1.00 [Reference]</td>
<td>11294</td>
<td>556</td>
</tr>
<tr>
<td>Yes</td>
<td>671</td>
<td>90</td>
<td>2.96 (2.33-3.75)</td>
<td>&lt;.001</td>
<td>661</td>
</tr>
<tr>
<td>Maternal diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>11800</td>
<td>638</td>
<td>1.00 [Reference]</td>
<td>11595</td>
<td>620</td>
</tr>
<tr>
<td>Yes</td>
<td>363</td>
<td>24</td>
<td>1.24 (0.81-1.89)</td>
<td>.32</td>
<td>360</td>
</tr>
<tr>
<td>Maternal hypertension</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>11829</td>
<td>635</td>
<td>1.00 [Reference]</td>
<td>11623</td>
<td>617</td>
</tr>
<tr>
<td>Yes</td>
<td>334</td>
<td>27</td>
<td>1.55 (1.04-2.23)</td>
<td>.03</td>
<td>332</td>
</tr>
<tr>
<td>Maternal BMI ≥25</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>8989</td>
<td>441</td>
<td>1.00 [Reference]</td>
<td>8824</td>
<td>428</td>
</tr>
<tr>
<td>Yes</td>
<td>3160</td>
<td>221</td>
<td>1.46 (1.23-1.72)</td>
<td>&lt;.001</td>
<td>3111</td>
</tr>
<tr>
<td>Maternal smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>11512</td>
<td>625</td>
<td>1.00 [Reference]</td>
<td>11312</td>
<td>608</td>
</tr>
<tr>
<td>Yes</td>
<td>375</td>
<td>20</td>
<td>0.98 (0.62-1.55)</td>
<td>0.94</td>
<td>366</td>
</tr>
</tbody>
</table>

Odds ratios (ORs) of a newborn having an umbilical cord blood creatinine concentration higher than the upper reference limit (0.98 mg/dL) as a function of maternal comorbidities. The ORs, 95% CIs, and \( P \) values were derived from logistic regression analysis. Individuals represent the number of newborns with and without recorded maternal comorbidity. Events represent the number of newborns with a creatinine concentration higher than the upper reference limit. In the multifactorially adjusted model, ORs were adjusted for maternal age at birth, child’s sex, gestational age, birth weight, birth length, multiple births, and placental-fetal weight ratio higher or lower than the median. BMI indicates body mass index (calculated as weight in kilograms divided by height in meters squared).
Discussion

The principal contribution of the present large cohort study was the generation of more robust and GA-dependent reference intervals for creatinine and urea in newborns. Furthermore, maternal preeclampsia was found to be associated with an increased risk of high newborn creatinine and urea concentrations.

In this study of umbilical and venous creatinine and urea concentrations in a large cohort of healthy term newborns with follow-up and parallel maternal venous samples, findings were consistent with previous studies reporting correlations of creatinine and urea in maternal venous blood with either fetal, umbilical cord, or newborn venous blood. Overall, creatinine and urea concentrations in umbilical and maternal blood were similar, whereas concentrations in newborn venous blood collected approximately 2 hours after birth differed significantly from those in umbilical and maternal blood, suggesting an accumulation after umbilical cord clamping. The equations provided in this study, however, enabled estimation of newborn creatinine and urea concentrations from umbilical cord blood and may thus prevent some venipuncture procedures in newborns.

Robust reference intervals are important for clinical decision-making; however, current Danish reference intervals of creatinine concentrations through the first year of life have been determined based on small groups of children (ranging from 5-95 children). In the present study, we were able to generate reference intervals based on healthy term infants, and we included a sufficient number of individuals to justify stratification by GA given that creatinine and urea concentrations differed significantly by GA. Stratification by GA was also supported by a recent review. In addition, newborns were excluded if their mothers had diagnoses that may have had implications for kidney function markers, which avoided confounding of the reference intervals by extreme values. Compared with previous studies, the presently generated reference intervals for creatinine concentrations at birth were based on a larger number of individuals and a more homogeneous population. A previous study, which included a similar number of children aged approximately 14 to 16 months and was comparable in size with our study, supported the present findings. In addition, the presently generated reference intervals categorized substantially fewer children with low or high creatinine and urea concentrations compared with existing Danish intervals and may thus provide a better basis for clinical decision-making when assessing term neonates. Furthermore, the reference intervals may help to identify children at risk of AKI. The reference intervals for urea found in the present study were narrower and applied to more well-defined age groups compared with current Danish reference intervals.

Notably, we found maternal comorbidity to be associated with the risk of high creatinine and urea concentrations in the newborn. Preeclampsia, maternal diabetes, maternal hypertension, and maternal overweight were associated with an increased risk of high creatinine and urea concentrations in the newborn, supporting previous observations on the risk of kidney disease associated with these comorbidities. Preeclampsia was associated with an up to 4-fold increased risk of high newborn creatinine (OR, 3.56) or urea (OR, 3.91) concentration in umbilical cord blood. This increased risk was sustained in newborn venous blood samples at birth, and a pattern was present at age 2 months, suggesting that attention should be given to kidney function in these children. This finding was supported by previous studies reporting pregnancy-induced hypertension to be associated with high creatinine concentrations and AKI in premature or hospitalized neonates. Because preeclampsia has been reported to be associated with high maternal creatinine concentrations, it is uncertain whether the risk of high newborn creatinine and urea concentrations associated with preeclampsia reflected higher maternal concentrations. Notably, we were able to adjust for maternal creatinine serum levels. The association between preeclampsia and
high newborn creatinine concentrations persisted after this adjustment, suggesting that our findings could not solely be explained by maternal concentrations. More in-depth discussion is provided in the eDiscussion in the Supplement.

Strengths and Limitations
This study has several strengths, including the large prospective population-based cohort of healthy term newborns, with 13,354 umbilical cord blood samples and parallel venous blood samples collected from 444 individuals at birth and follow-up conducted among 363 children at age 2 months and 156 children at age 14 to 16 months. This large sample combined with follow-up allowed us to generate reference intervals of kidney function markers in 3 age groups during the first 16 months of life in healthy children. Other major strengths are the paired samples from both maternal venous blood and umbilical cord and newborn venous blood at birth; the extensive information on diagnoses; and the high participation rate in the CBHS, with enrollment of 55% of infants born in the participating hospitals.33

The study also has limitations, including the overrepresentation of participants with higher socioeconomic status and educational level and mothers with Danish ethnicity.33 These limitations are, however, well-known issues in voluntary epidemiological studies and are, to some extent, compensated for by the high participation rate of the study. The maternal population had low BMI and a low incidence of comorbidities; however, these characteristics are representative of the entire population giving birth during the same period in the same hospitals.33 The number of newborn venous samples (n = 444) is small compared with the number of umbilical cord samples (n = 13,354); the venous samples were, however, collected from healthy newborns who did not otherwise require blood sampling. The equations for estimating newborn concentrations from umbilical blood provided in this study warrant validation in other cohorts of healthy term children. Moreover, the study mainly includes healthy term newborns; thus, it is not certain whether the results are generalizable to preterm newborns or newborns with illness. As suggested by the Tietz method,36 at least 120 individuals are recommended for creating reference intervals. This sample size was only just violated in the age 14- to 16-month group after exclusion of outliers and exclusion criteria due to less willingness to continue study participation as the children grew older. However, considerably more individuals are included in the presently generated reference intervals compared with existing intervals.

Conclusions
This cohort study generated robust reference intervals for creatinine and urea concentrations stratified by GA at birth, age 2 months, and age 14 to 16 months and described the development of creatinine and urea concentrations in the first period of life. Furthermore, the study found an association between maternal comorbidities, especially preeclampsia, and an increased risk of high newborn creatinine and urea concentrations. This association suggests that more attention should be given to kidney function in children of mothers with preeclampsia. These novel findings may improve clinical decision-making and increase understanding of the consequences of maternal comorbidities for kidney function in newborns and infants.
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Supervision: Juul Rasmussen, Axelson Raja, Schmidt, Bundgaard, Frikke-Schmidt.

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REFERENCES


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