Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

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**eMethods. Biochemical Measurement of Creatinine and Urea and Covariates**

**Biochemical measurement of creatinine and urea**
The umbilical blood and venous blood samples were analyzed for biochemical markers, including creatinine and urea, on standard hospital clinical biochemistry equipment. The blood samples were collected in serum vacutainers, and serum creatinine (µmol/L) and urea (mmol/L) concentrations were measured by the Cobas 6000, c501 module, using the CREAJ Gen.2, Cobas c, Integra and the UREAL, Cobas c, Integra reagents for creatinine and urea (Roche, Basel, Switzerland). Creatinine in µmol/L and urea in mmol/L were converted to conventional units, mg/dL.

**Covariates**
Demographics and data on newborns and mothers were extracted from the local obstetric and Astraia fetal medicine databases. Gestational age (GA) was determined from obstetric ultrasonography and given in weeks. Maternal age was registered at delivery. Maternal body mass index (BMI) was self-reported and calculated as weight before pregnancy in kilograms divided by height in meters squared. Birth weight and length were measured at birth. Neonatal Appearance, Pulse, Grimace, Activity and Respiration (APGAR) score was assessed one and five minutes after birth using a score from 1-10, 7 to 10 considered reassuring. Neonates small for gestational age (SGA) were identified by the formula presented by Marsal et al. SGA was defined as a birth weight below the 2.3rd percentile equivalent to a birth weight less than -22% of the average birth weight for a given gestational age. Placental weight was in grams (g). Placental-fetal weight ratio was determined as placental weight divided by birth weight and given in g/1g. Maternal and newborn diagnoses were registered using the International Classification of Diseases, Tenth Revision (ICD-10) codes. The following relevant morbidities are detailed in eTable 1: Maternal kidney disease, preeclampsia, maternal hypertension, maternal diabetes, placental insufficiency, and congenital malformation of the urinary system. Information on smoking is self-reported during pre-pregnancy interview with midwife in the first trimester. Umbilical cord blood refers to samples drawn from the umbilical vein after birth. Newborn venous blood and maternal venous blood refers to venous blood samples taken approximately 2 hours after birth. Child venous blood refers to blood samples taken at follow-up at 2 and 14-16 months, specified when used.
Serum creatinine and urea concentrations are frequently used to estimate GFR in neonates. Creatinine and urea pass the placenta passively from mother to fetus by simple diffusion reaching an equilibrium between fetal and maternal concentrations\(^4\)-\(^7\). This is supported by the presently observed high correlations between creatinine and urea concentrations in umbilical cord and maternal blood. Newborn concentrations have been suggested to reflect maternal concentrations for up to 72 hours\(^8,9\), with a gradual increase during the first days of life\(^10\)-\(^12\). In the present study, we do, however, observe the increase to occur within the first two hours after birth, suggesting newborn accumulation of creatinine after severing the umbilical cord. The exact mechanism underlying this accumulation is not certain, however, tubular reabsorption of creatinine across immature leaky tubules as well as dehydration may play a role\(^13,14\). Creatinine concentrations have been reported to start declining after the first days and the following year after birth\(^15,16\), which is also found in in this study, thus this result is confirmatory. Urea is a poor single parameter for renal function. The presently observed decrease at two months and later increase at 14-16 months is likely reflecting the dietary protein intake being low on breast milk and increased on toddlers' diet\(^7,10,17\).
| Diagnoses | ICD-10 codes | Description |
|-----------|--------------|-------------|
| Maternal kidney disease | N18, N189 | Chronic kidney disease |
| | N039 | Chronic glomerulonephritis |
| | N03 | Chronic nephritic syndrome |
| | N131, N133 | Hydronephrosis |
| | N139 | Obstructive and reflux uropathy |
| | N289 | Disorder of kidney and ureter incl. nephropathy |
| | Q600 | unilateral renal agenesis |
| | Q613 | polycystic kidney |
| | Q619 | cystic kidney disease |
| | Q638, Q649 | congenital malformations of the kidney or urinary system |
| Preeclampsia | O100 | Pre-existing essential hypertension complicating pregnancy, childbirth and puerperium |
| | O120 | Gestational edema and proteinuria without hypertension |
| | O121 | Gestational proteinuria |
| | O139 | Gestational hypertension |
| | O140 | Mild to moderate preeclampsia |
| | O141 | Severe preeclampsia |
| | O142 | HELLP (H=hemolysis; EL=Elevated Liver enzymes; LP=Low platelets) syndrome |
| | O159 | Eclampsia |
| Maternal hypertension | O100 | Pre-existing essential hypertension complicating pregnancy, childbirth, and puerperium |
| | O139 | Gestational hypertension |
| Maternal diabetes | O240 | preexisting type 1 diabetes mellitus |
| | O241 | preexisting type 2 diabetes mellitus |
| | O244D | gestational diabetes |
| | O244E | gestational diabetes treated with insulin |
newly discovered manifest diabetes during pregnancy

| Diagnoses | ICD-10 codes | Description |
|-----------|---------------|-------------|
| Placental insufficiency | O365 | Maternal care for known or suspected poor fetal growth and placental insufficiency |
| | O438E | Placental dysfunction/infarction, subchorionic hematoma |
| | O431, O431E | Malformation of placenta (abnormal placenta nitric oxide synthase (NOS), circumvallate placenta) including vasa previa |
| Congenital malformation of the urinary system | Q600 | Unilateral renal agenesis |
| | Q613 | Polycystic kidney, unspecified |
| | Q619 | Cystic kidney disease, unspecified |
| | Q620A/B | Congenital unilateral or bilateral hydronephrosis |
| | Q639 | Congenital malformation of the kidney, unspecified |
| | Q649 | Congenital malformation of the urinary system, unspecified |

Registered ICD-10 (International Classification of Diseases, Tenth Revision) codes for maternal and newborn diagnoses used in the study.
### eTable 2. Assessment of Baseline Characteristics of Participants With and Without Missing Variables

| The Copenhagen Baby Heart Study (N=13,354) | Females n=6,557 (49%) | P-values | Males n=6,797 (51%) | P-values |
|-------------------------------------------|-----------------------|----------|---------------------|----------|
| n=871 (13.3%)                             | n=5,688 (86.7%)       |          | n=840 (12.4%)       |          |
| Gestational age, median (IQR), days       | 282 (275 – 287)       | 0.61     | 282 (274 – 288)     | 0.32     |
| Maternal Age, median (IQR), years         | 31 (29 – 35)          | 0.80     | 32 (29 – 35)        | 0.88     |
| Birth Weight, median (IQR), g             | 3456 (3138 – 3769)    | 0.18     | 3574 (3275 – 3875)  | 0.13     |
| Birth Length, median (IQR), cm            | 51 (50 – 53)          | 0.32     | 52 (51 – 53)        | 0.59     |
| Apgar Score, median (IQR), 5 min          | 10 (10 – 10)          | 0.14     | 10 (10 – 10)        | <0.001   |
| Small for Gestational Age, No. (%)        | 38 (4.4)              | 0.03     | 28 (3.3)            | 0.51     |
| Placental weight, median (IQR), g         | 615 (530 – 713)       | 0.10     | 630 (540 – 740)     | 0.05     |
| Placental-fetal weight ratio, median (IQR) | 0.18 (0.16 – 0.20)   | 0.28     | 0.18 (0.16 – 0.20)  | 0.14     |
| Placental insufficiency, No. (%)          | 46 (5.3)              | 0.54     | 45 (5.4)            | 0.26     |
| Congenital malformation of the urinary system, No. (%) | 0 (0.0) | 0.34 | 4 (0.5) | 0.11 |
| Maternal BMI, median (IQR), kg/m²          | 22 (21 – 25)          | 0.80     | 22 (20 – 25)        | 0.11     |
| Preeclampsia, No. (%)                     | 47 (5.4)              | 0.88     | 40 (4.8)            | 0.37     |
| Maternal diabetes, No. (%)                | 21 (2.4)              | 0.64     | 23 (2.7)            | 0.45     |
| Maternal Kidney Disease, No. (%)          | 3 (0.3)               | 0.02     | 0                  | 0.32     |
| Maternal Hypertension, No. (%)            | 22 (2.5)              | 0.66     | 25 (3.0)            | 0.62     |
| Maternal Smoking, No. (%)                 | 21 (2.8)              | 0.58     | 24 (3.4)            | 0.65     |

| Females n=217 (49%) | Males n=227 (51%) |
|---------------------|-------------------|
| n=30 (13.8%) | n=187 (86.2%) |
| Gestational age, median (IQR), days | 276 (272 – 288) | 0.44 | 280 (271 – 288) | 0.96 |
| Maternal Age, median (IQR), years | 32 (29-37) | 0.93 | 32 (28-35) | 0.80 |
| Birth Weight, median (IQR), g | 3415 (3049 – 3557) | 0.44 | 3549 (3362 – 3891) | 0.96 |
| Birth Length, median (IQR), cm | 51 (50 – 52) | 0.74 | 52 (50 – 54) | 0.59 |
| Apgar Score, median (IQR), 5 min | 10 (10 – 10) | 0.74 | 10 (10 – 10) | 0.20 |
| Small for Gestational Age, No. (%) | 2 (6.7) | 0.25 | 2 (5.1) | 0.17 |
| Placental weight, median (IQR), g | 650 (577 – 760) | 0.36 | 625 (578 – 785) | 0.66 |

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| Baseline Characteristics in The Copenhagen Baby Heart Study and COMPARE study stratified by sex and complete cases and cases with more than 1 variable missing. Categorical variables are presented as numbers (percentages) and continuous variables as median (interquartile ranges). The variables are from the day of birth (2016-2018). Numbers may vary from flowchart due to missing variables. Gestational age (GA) was determined from obstetric ultrasonography and given in weeks. Maternal age was registered at delivery and given in years. Birth weight in grams and length in centimeters were measured at birth. Neonatal Appearance, Pulse, Grimace, Activity and Respiration (APGAR) score was assessed one and five minutes after birth using a score from 1-10, 7 to 10 considered reassuring. Small for gestational age was defined as a birth weight below the 2.3 percentile equivalent to a birth weight less than -22% of the average birth weight for a given gestational age 3. Placental weight was measured in grams. Placental-fetal weight ratio was determined as placental weight divided by birth weight and given in g/1g. Maternal body mass index (BMI) was calculated as self-reported weight before pregnancy in kilograms divided by height in meters squared. Placental insufficiency, congenital malformation of the urinary system, preeclampsia, maternal diabetes, maternal kidney disease and maternal hypertension are detailed in eTable 1 in the Supplementary. Information on smoking is self-reported during pre-pregnancy interview with midwife in the first trimester. P-values by Mann-Whitney U test or Pearson’s χ²-test. |
eTable 3. Creatinine Concentrations (mg/dL) Stratified by Gestational Age (GA) in Umbilical Cord Blood; Newborn Venous Blood at Birth, Age 2 Months, and Age 14-16 Months; and Maternal Venous Blood at Birth

| COMPARE - Creatinine concentration (mg/dL) | GA 37 – 39 | GA 40 - 42 | P-value |
|-------------------------------------------|------------|------------|---------|
| Umbilical cord blood                      | 0.64 (0.55 – 0.74) | 0.70 (0.63 – 0.80) | <0.001  |
|                                          | (n=153)     | (n=167)     |         |
| Newborn venous blood (Birth)              | 0.77 (0.70 – 0.88) | 0.84 (0.75 – 0.95) | <0.001  |
|                                          | (n=171)     | (n=182)     |         |
| Infant venous blood (Two months)          | 0.21 (0.19 – 0.25) | 0.21 (0.18 – 0.24) | 0.20    |
|                                          | (n=144)     | (n=169)     |         |
| Child venous blood (14-16 months)         | 0.27 (0.24 – 0.29) | 0.26 (0.21 – 0.29) | 0.18    |
|                                          | (n=63)      | (n=76)      |         |
| Maternal venous blood (Birth)             | 0.63 (0.54 – 0.72) | 0.66 (0.59 – 0.76) | 0.01    |
|                                          | (n=210)     | (n=231)     |         |

Copenhagen Baby Heart - Creatinine concentration (mg/dL)

|                               | GA 37 – 39 | GA 40 - 42 | P-value |
|-------------------------------|------------|------------|---------|
| Umbilical cord blood          | 0.67 (0.59 – 0.77) | 0.71 (0.63 – 0.81) | <0.001  |
|                               | (n=4,814)  | (n=6,980)  |         |

Creatinine concentrations are stratified by gestational age and presented as median (interquartile range) and n: number of individuals. P-values by Mann-Whitney U test. To convert mg/dL to µmol/L multiply by 88.4.
**eTable 4.** Urea Concentrations (mg/dL) Stratified by Gestational Age (GA) in Umbilical Cord Blood; Newborn Venous Blood at Birth, Age 2 Months, and Age 14-16 Months; and Maternal Venous Blood at Birth

|                      | GA 37 – 39                      | GA 40 - 42                      | P-value |
|----------------------|---------------------------------|---------------------------------|---------|
| **COMPARE - Urea concentration (mg/dL)** |                                 |                                 |         |
| Umbilical cord blood | 8.40 (7.28 – 10.36) (n=154)     | 9.80 (7.84 – 11.20) (n=171)     | 0.003   |
| Newborn venous blood (Birth) | 9.10 (7.28 – 10.92) (n=172) | 10.08 (8.40 – 11.76) (n=185) | <0.001 |
| Infant venous blood (Two months) | 6.16 (4.76 – 7.56) (n=152) | 6.16 (5.04 – 7.56) (n=176) | 0.85    |
| Child venous blood (14-16 months) | 14.01 (11.48 – 16.24) (n=63) | 12.89 (10.64 – 14.85) (n=78) | 0.02    |
| Maternal venous blood (Birth) | 7.70 (6.16 – 9.52) (n=210) | 8.40 (6.72 – 10.08) (n=230) | 0.02    |
| **Copenhagen Baby Heart - Urea concentration (mg/dL)** |                                 |                                 |         |
| Umbilical cord blood | 8.96 (7.28 – 10.92) (n=5,017) | 9.52 (7.84 – 11.20) (n=7,282) | <0.001 |

Urea concentrations are stratified by gestational age and presented as median (interquartile range) and n: number of individuals. P-values by Mann-Whitney U test. To convert mg/dL to mmol/L multiply by 0.357.
**eTable 5.** Creatinine Concentrations (mg/dL) Stratified by Sex in Umbilical Cord Blood; Newborn Venous Blood at Birth, Age 2 Months, and Age 14-16 Months; and Maternal Venous Blood at Birth

|                         | Females | Males | P-value |
|-------------------------|---------|-------|---------|
| **COMPARE - Creatinine concentration (mg/dL)** |         |       |         |
| Umbilical cord blood    | 0.68 (0.60 – 0.75) (n=158) | 0.68 (0.58 – 0.79) (n=162) | 0.70 |
| Newborn venous blood (Birth) | 0.79 (0.71 – 0.92) (n=172) | 0.83 (0.72 – 0.98) (n=181) | 0.06 |
| Infant venous blood (Two months) | 0.21 (0.18 – 0.24) (n=142) | 0.21 (0.18 – 0.25) (n=171) | 0.76 |
| Child venous blood (14-16 months) | 0.26 (0.24 – 0.29) (n=67) | 0.26 (0.23 – 0.29) (n=72) | 0.75 |
| Maternal venous blood (Birth) | 0.64 (0.58 – 0.72) (n=215) | 0.64 (0.57 – 0.75) (n=226) | 0.89 |
| **Copenhagen Baby Heart - Creatinine concentration (mg/dL)** |         |       |         |
| Umbilical cord blood    | 0.69 (0.60 – 0.78) (n=5,954) | 0.71 (0.61 – 0.80) (n=6,215) | <0.001 |

Creatinine concentrations are stratified by sex and presented as median (interquartile range) and n: number of individuals. P-values by Mann-Whitney U test. To convert mg/dL to µmol/L multiply by 88.4.
**eTable 6.** Urea Concentrations (mg/dL) Stratified by Sex in Umbilical Cord Blood; Newborn Venous Blood at Birth, Age 2 Months, and Age 14-16 Months; and Maternal Venous Blood at Birth

| COMPARE - Urea concentration (mg/dL) | Females | Males | P-value |
|--------------------------------------|---------|-------|---------|
| Umbilical cord blood                 | 9.10 (7.56 – 10.64) (n=162) | 8.96 (7.56 – 11.48) (n=163) | 0.33 |
| Newborn venous blood (Birth)         | 9.52 (7.28 – 10.92) (n=175) | 9.80 (7.84 – 11.76) (n=182) | 0.07 |
| Infant venous blood (Two months)     | 6.72 (5.04 – 8.12) (n=146) | 5.88 (4.76 – 7.28) (n=182) | 0.003 |
| Child venous blood (14-16 months)    | 13.17 (10.64 – 15.69) (n=68) | 12.9 (10.64 – 15.13) (n=73) | 0.97 |
| Maternal venous blood (Birth)        | 7.84 (6.16 – 9.52) (n=215) | 8.40 (6.72 – 10.08) (n=225) | 0.03 |

| Copenhagen Baby Heart - Urea concentration (mg/dL) | Females | Males | P-value |
|-----------------------------------------------------|---------|-------|---------|
| Umbilical cord blood                                | 9.24 (7.56 – 11.20) (n=6,207) | 9.24 (7.84 – 11.20) (n=6,482) | <0.001 |

Urea concentrations are stratified by sex and presented as median (interquartile range) and n: number of individuals. P-values by Mann-Whitney U test. To convert mg/dL to mmol/L multiply by 0.357.
### eTable 7. Reference Intervals for Creatinine Concentrations in Children’s Venous Blood

| Creatinine concentration (mg/dL) | Newborn (GA 37-39) | Newborn (GA 40-42) | Infant (2 months) | Child (14-16 months) |
|----------------------------------|--------------------|--------------------|-------------------|---------------------|
| Model 1 (n)                      | 0.49 – 1.13 (171)  | 0.52 – 1.32 (182)  | 0.10 – 0.32 (313) | 0.18 – 0.40 (139)  |
| Model 2 (n)                      | 0.51 – 1.10 (167)  | 0.55 – 1.19 (176)  | 0.12 – 0.31 (305) | 0.18 – 0.34 (131)  |
| Model 3 (n)                      | 0.49 – 1.08 (145)  | 0.54 – 1.32 (167)  | 0.11 – 0.33 (276) | 0.17 – 0.40 (122)  |
| Model 4 (n)                      | 0.54 – 1.08 (144)  | 0.57 – 1.19 (162)  | 0.13 – 0.31 (268) | 0.18 – 0.34 (115)  |
| Existing local reference intervals (Rigshospitalet, Copenhagen, Denmark) | 0.42 – 0.92 (0 – 1 days) | 0.19 – 0.46 (14 days – 2 months) | 0.17 – 0.35 (1 – 3 years) |

Reference intervals are presented as 2.5 and 97.5 percentiles (number of individuals) and are from newborn venous blood at the time of birth (2016-2018), infant venous blood at 2 months and child venous blood at 14-16 months after birth (2016-2020). Newborn reference intervals from the time of birth are stratified by gestational age. In model 1 the 2.5 and 97.5 percentiles unadjusted are shown. Model 2 is the 2.5 and 97.5 percentiles adjusted for outliers as recommended by Tietz. Model 3 is the 2.5 and 97.5 percentiles adjusted for the following exclusion criteria: preeclampsia, maternal diabetes, maternal kidney disease, congenital kidney deformity, maternal BMI >35 and neonates born small for gestational age. In model 4 the 2.5 and 97.5 percentiles adjusted for outliers and exclusion criteria are shown. The existing local reference intervals are from the Clinical Biochemical Department on Rigshospitalet, Copenhagen, Denmark, and are determined from Boer et al. (0 – 1 days and 14 days – 2 months) and Ceriotti et al. (1 – 3 years). To convert mg/dL to µmol/L multiply by 88.4. GA: Gestational age.
**eTable 8. Reference Intervals for Urea Concentrations in Children’s Venous Blood**

| Urea concentration (mg/dL)   | Newborn (GA 37-39) | Newborn (GA 40-42) | Infant (2 months) | Child (14-16 months) |
|------------------------------|--------------------|--------------------|-------------------|----------------------|
| Model 1 (n)                  | 5.32 – 16.06 (172) | 5.60 – 15.88 (185) | 3.14 – 10.64 (328) | 6.60 – 19.17 (141)   |
| Model 2 (n)                  | 5.32 – 14.79 (167) | 5.60 – 14.85 (179) | 3.14 – 10.64 (328) | 8.12 – 17.84 (131)   |
| Model 3 (n)                  | 5.32 – 15.13 (146) | 5.60 – 16.08 (171) | 3.08 – 10.08 (288) | 6.48 – 19.26 (124)   |
| Model 4 (n)                  | 5.32 – 14.67 (144) | 5.60 – 14.85 (165) | 3.08 – 10.08 (288) | 8.12 – 17.95 (116)   |
| Existing local reference intervals (Rigshospitalet, Copenhagen, Denmark) | 3.92 – 15.1 (0 – 2 months) | 5.04 – 15.1 (2 months – 2 years) |

Reference intervals are presented as 2.5 and 97.5 percentiles (number of individuals) and are from newborn venous blood at the time of birth (2016-2018), infant venous blood at 2 months and child venous blood at 14-16 months after birth (2016-2020). Newborn reference intervals from the time of birth are stratified by gestational age. In model 1 the 2.5 and 97.5 percentiles unadjusted are shown. Model 2 is the 2.5 and 97.5 percentiles adjusted for outliers as recommended by Tietz. Model 3 is the 2.5 and 97.5 percentiles adjusted for the following exclusion criteria: preeclampsia, maternal diabetes, maternal kidney disease, congenital kidney deformity, maternal BMI >35 and neonates born small for gestational age. In model 4 the 2.5 and 97.5 percentiles adjusted for outliers and exclusion criteria are shown. The existing local reference intervals are from the Clinical Biochemical Department on Rigshospitalet, Copenhagen, Denmark. To convert mg/dL to µmol/L multiply by 0.357. GA: Gestational age.
### eTable 9. New and Existing Reference Intervals for Creatinine and Urea Concentrations and Number of Children From the COMPARE Study With Concentrations Higher and Lower Than the Reference Limits

|                     | Newborn (GA 37-39) | Newborn (GA 40-42) | Infant (2 months) | Child (14-16 months) |
|---------------------|---------------------|---------------------|-------------------|----------------------|
| **Creatinine, mg/dL** | 0.54 – 1.08 (144)   | 0.57 – 1.19 (162)   | 0.13 – 0.31 (268) | 0.18 – 0.34 (115)   |
| Children outside reference limits, No. (%) | 5 (2.9%) and 9 (5.3%) | 5 (2.8%) and 7 (3.9%) | 13 (4.2%) and 10 (3.2%) | 3 (2.2%) and 9 (6.5%) |
| **Existing local reference intervals** (Rigshospitalet, Copenhagen, Denmark) | 0.42 – 0.92 (5) (0 – 1 days) | 0.19 – 0.46 (95) (14 days – 2 months) | 0.17 – 0.35 (45) (1 – 3 years) |
| Children outside reference limits, No. (%) | 2 (0.6%) and 93 (26.4%) | 86 (27.5%) and 0 | 1 (0.7%) and 8 (5.8%) |
| **Urea, mmol/L** | 5.32 – 14.67 (144) | 5.60 – 14.85 (165) | 3.08 – 10.08 (288) | 8.12 – 17.95 (116) |
| Children outside reference limits, No. (%) | 3 (1.7%) and 9 (5.2%) | 3 (1.6%) and 9 (4.9%) | 4 (1.2%) and 10 (3.1%) | 6 (4.3%) and 8 (5.7%) |
| **Existing local reference intervals** (Rigshospitalet, Copenhagen, Denmark) | 3.92 – 15.1 (0 – 2 months) | 5.04 – 15.1 (2 months – 2 years) |
| Children outside reference limits, No. (%) | 2 (0.6%) and 11 (3.1%) | 82 (25.0%) and 0 | 2 (1.4%) and 32 (22.7%) |

Reference intervals are presented as 2.5 and 97.5 percentiles (number of individuals) adjusted for outliers and exclusion criteria and are from newborn venous blood at the time of birth (2016-2018), infant venous blood at 2 months and child venous blood at 14-16 months after birth (2016-2020). Newborn reference intervals from the time of birth are stratified by gestational age. Outliers were adjusted as recommended by Tietz. Exclusion criteria were preeclampsia, maternal diabetes, maternal kidney disease, congenital kidney deformity, maternal BMI >35 and neonates born small for gestational age. The existing local reference intervals are from the Clinical Biochemical Department on Rigshospitalet, Copenhagen, Denmark, and are determined from Boer et al. (0 – 1 days and 14 days – 2 months) and Ceriotti et al. (1 – 3 years) for creatinine. The number of children concentrations outside the reference intervals are given for each interval. GA: Gestational age. a To convert mg/dL to µmol/L multiply by 88.4. b To convert mg/dL to µg/dL multiply by 0.357.
### eTable 10. Reference Intervals for Creatinine Concentrations in Umbilical Cord Blood

| Creatinine concentration (µmol/L) | GA 37-39 | GA 40-42 | Combined |
|-----------------------------------|----------|----------|----------|
| **Model 1 (n)**                   | 0.38 – 1.06 (4,814) | 0.42 – 1.14 (6,980) | 0.41 – 1.11 (11,794) |
| **Model 2 (n)**                   | 0.43 – 0.96 (4,606) | 0.49 – 1.01 (6,630) | 0.45 – 0.98 (11,230) |
| **Model 3 (n)**                   | 0.37 – 1.04 (3,959) | 0.43 – 1.12 (6,362) | 0.40 – 1.09 (10,321) |
| **Model 4 (n)**                   | 0.43 – 0.95 (3,805) | 0.49 – 1.01 (6,062) | 0.45 – 0.98 (9,861) |
| **Existing local reference intervals** | No existing reference intervals |

Reference intervals are presented as 2.5 and 97.5 percentiles (number of individuals) and are from umbilical cord blood (2016-2018) and are presented stratified by gestational age 37-39 weeks and 40-42 weeks and combined. In model 1 the 2.5 and 97.5 percentiles unadjusted are shown. Model 2 is the 2.5 and 97.5 percentiles adjusted for outliers as recommended by Tietz. Model 3 is the 2.5 and 97.5 percentiles adjusted for the following exclusion criteria: preeclampsia, maternal diabetes, maternal kidney disease, congenital kidney deformity, maternal BMI >35 and neonates born small for gestational age. In model 4 the 2.5 and 97.5 percentiles adjusted for outliers and exclusion criteria are shown. To convert mg/dL to µmol/L multiply by 88.4. GA: Gestational age.
eTable 11. Reference Intervals for Urea Concentrations in Umbilical Cord Blood

| Urea concentration (mmol/L) | GA 37-39 | GA 40-42 | Combined |
|----------------------------|----------|----------|----------|
| Model 1 (n)                | 5.04 – 15.97 (5,017) | 5.32 – 16.25 (7,282) | 5.04 – 16.25 (12,299) |
| Model 2 (n)                | 5.04 – 14.29 (4,836)  | 5.32 – 14.29 (7,012)  | 5.32 – 14.29 (11,848) |
| Model 3 (n)                | 4.76 – 15.41 (4,143)  | 5.32 – 15.97 (6,635)  | 5.04 – 15.97 (10,778) |
| Model 4 (n)                | 5.04 – 14.01 (4,032)  | 5.32 – 14.29 (6,407)  | 5.32 – 14.29 (10,439) |

Existing local reference intervals (Rigshospitalet, Copenhagen, Denmark) No existing reference intervals

Reference intervals are presented as 2.5 and 97.5 percentiles (number of individuals) and are from umbilical cord blood (2016-2018) and are presented stratified by gestational age 37-39 weeks and 40-42 weeks and combined. In model 1 the 2.5 and 97.5 percentiles unadjusted are shown. Model 2 is the 2.5 and 97.5 percentiles adjusted for outliers as recommended by Tietz. Model 3 is the 2.5 and 97.5 percentiles adjusted for the following exclusion criteria: preeclampsia, maternal diabetes, maternal kidney disease, congenital kidney deformity, maternal BMI >35 and neonates born small for gestational age. In model 4 the 2.5 and 97.5 percentiles adjusted for outliers and exclusion criteria are shown. To convert mg/dL to mmol/L multiply by 0.357. GA: Gestational age.
Flowchart illustrating the recruitment and exclusion of participants in the Copenhagen Baby Heart Study and the COMPARE study cohorts. Numbers (n) of individuals and blood samples analyzed for creatinine and urea in umbilical cord blood and child venous blood at birth, two months and 14-16 months after birth are shown.

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eFigure 2. Consequences of Maternal Comorbidities for the Risk of High Urea Concentrations in the Newborn

Forest plot showing odds ratios of the newborn having an umbilical cord blood urea concentration above the upper reference limit as a function of maternal comorbidities. Odds ratios, confidence intervals and p-values are from logistic regression. Individuals represent the number of newborns with or without the maternal comorbidity registered. Events represent the number of newborns with a urea concentration above the upper reference limit. In the multifactorially adjusted model odds ratios were adjusted for maternal age at birth, child’s sex, gestational age, birth weight, birth length, multiple births, and placental-fetal weight ratio above or below the median. To convert mg/dL to mmol/L multiply by 0.357.

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eFigure 3. Consequences of Maternal Preeclampsia for the Risk of High Creatinine Concentrations in Newborn Venous Blood at Birth

Forest plot showing odds ratios of the newborn having a venous blood creatinine concentration at birth above the upper reference limit (1.14 mg/dL), above the 90th percentile (1.06 mg/dL), above the 80th percentile (0.96 mg/dL) and above the 50th percentile (0.80 mg/dL) as a function of maternal preeclampsia. Odds ratios, confidence intervals and p-values are from logistic regression. Individuals represent the number of newborns with or without a mother with registered preeclampsia. Events represent the number of newborns with a creatinine concentration above the cut-off value. In the multifactorially adjusted model odds ratios were adjusted for maternal age at birth, child’s sex, gestational age, birth weight, birth length, multiple births, and placental-fetal weight ratio above or below the median. To convert mg/dL to µmol/L multiply by 88.4.
**eFigure 4.** Consequences of Maternal Preeclampsia for the Risk of High Creatinine Concentrations in Infant Venous Blood at 2 Months

| Creatinine concentration at two months | Unadjusted | Multifactorially adjusted |
|---------------------------------------|------------|--------------------------|
|                                       | Individuals | Events | Odds ratio (CI) | P-value | Individuals | Events | Odds ratio (CI) | P-value |
| > upper reference (0.31 mg/dL)        |             |         |                 |         |             |         |                 |         |
| No preeclampsia                      | 293        | 10      |                 |         | 290        | 10      |                 |         |
| Preeclampsia                         | 20         | 0       |                 |         | No events  | 19      | 0                |         |
| > 90th percentile (0.27 mg/dL)       |             |         |                 |         |             |         |                 |         |
| No preeclampsia                      | 293        | 27      | 1.00 (reference) |         | 290        | 27      | 1.00 (reference) |         |
| Preeclampsia                         | 20         | 3       | 1.74 (0.48, 6.31) | 0.40     | 19         | 3       | 1.75 (0.46, 6.63) | 0.41     |
| > 80th percentile (0.25 mg/dL)       |             |         |                 |         |             |         |                 |         |
| No preeclampsia                      | 293        | 56      | 1.00 (reference) |         | 290        | 56      | 1.00 (reference) |         |
| Preeclampsia                         | 20         | 6       | 1.81 (0.67, 4.93) | 0.24     | 19         | 6       | 1.76 (0.62, 4.98) | 0.28     |
| > 50th percentile (0.21 mg/dL)       |             |         |                 |         |             |         |                 |         |
| No preeclampsia                      | 293        | 126     | 1.00 (reference) |         | 290        | 126     | 1.00 (reference) |         |
| Preeclampsia                         | 20         | 9       | 1.08 (0.44, 2.70) | 0.86     | 19         | 9       | 1.17 (0.45, 3.05) | 0.74     |

Forest plot showing the odds ratio of the infant having a venous blood creatinine concentration at two months above the upper reference limit (0.31 mg/dL), above the 90th percentile (0.27 mg/dL), above the 80th percentile (0.25 mg/dL) and above the 50th percentile (0.21 mg/dL) as a function of maternal preeclampsia. Odds ratios, confidence intervals and p-values are from logistic regression. Individuals represent the number of infants with or without a mother with registered preeclampsia. Events represent the number of infants with a creatinine concentration above the cut-off value. In the multifactorially adjusted model odds ratios were adjusted for maternal age at birth, child’s sex, gestational age, birth weight, birth length, multiple births, and placental-fetal weight ratio above or below the median. To convert mg/dL to µmol/L multiply by 88.4.
eFigure 5. Consequences of Maternal Preeclampsia for Urea Concentrations in Newborn Venous Blood at Birth

Forest plot showing the impact of maternal preeclampsia on the odds ratio of the newborn having a venous blood urea concentration at birth above the upper reference limit (14.9 mg/dL), above the 90th percentile (13.7 mg/dL), above the 80th percentile (11.8 mg/dL) and above the 50th percentile (9.52 mg/dL) respectively. Odds ratios, confidence intervals and p-values are from logistic regression. Individuals represent the number of newborns with or without registration of preeclampsia. Events represent the number of newborns with a urea concentration above the cut-off value. In the multifactorially adjusted model odds ratios were adjusted for maternal age at birth, child’s sex, gestational age, birth weight, birth length, multiple births, and placental-fetal weight ratio above or below the median. To convert mg/dL to mmol/L multiply by 0.357.
**eFigure 6. Consequences of Maternal Preeclampsia for Urea Concentrations in Infant Venous Blood at 2 Months**

| Urea concentration at two months | Unadjusted | Multifactorially adjusted |
|---------------------------------|------------|--------------------------|
|                                 | Individuals | Events | Odds ratio (CI) | P-value | Individuals | Events | Odds ratio (CI) | P-value |
| > upper reference (10.1 mg/dL)  |            |        |                |         |            |        |                |         |
| No preeclampsia                 | 334        | 15     | 1.00 (reference) | 1.00 | 330 | 15 | 1.00 (reference) | 1.00 |
| Preeclampsia                    | 23         | 2      | 1.66 (0.20, 13.7) | 0.64 | 22 | 1 | 1.98 (0.20, 19.3) | 0.56 |
| > 90th percentile (8.68 mg/dL)  |            |        |                |         |            |        |                |         |
| No preeclampsia                 | 334        | 29     | 1.00 (reference) | 1.00 | 330 | 28 | 1.00 (reference) | 1.00 |
| Preeclampsia                    | 23         | 4      | 1.14 (0.25, 5.16) | 0.87 | 22 | 3 | 1.33 (0.26, 6.67) | 0.73 |
| > 80th percentile (8.12 mg/dL)  |            |        |                |         |            |        |                |         |
| No preeclampsia                 | 334        | 62     | 1.00 (reference) | 1.00 | 330 | 61 | 1.00 (reference) | 1.00 |
| Preeclampsia                    | 23         | 8      | 0.82 (0.23, 2.68) | 0.75 | 22 | 7 | 0.91 (0.24, 3.43) | 0.89 |
| > 50th percentile (6.16 mg/dL)  |            |        |                |         |            |        |                |         |
| No preeclampsia                 | 334        | 160    | 1.00 (reference) | 1.00 | 330 | 159 | 1.00 (reference) | 1.00 |
| Preeclampsia                    | 23         | 16     | 1.28 (0.53, 3.10) | 0.59 | 22 | 15 | 1.44 (0.56, 3.66) | 0.45 |

Forest plot showing the impact of maternal preeclampsia on the odds ratio of the infant having a venous blood urea concentration at two months above the upper reference limit (10.1 mg/dL), above the 90th percentile (8.68 mg/dL), above the 80th percentile (8.12 mg/dL) and above the 50th percentile (6.16 mg/dL). Odds ratios, confidence intervals and p-values are from logistic regression. Individuals represent the number of infants with or without registration of preeclampsia. Events represent the number of infants with a urea concentration above the cut-off value. In the multifactorially adjusted model odds ratios were adjusted for maternal age at birth, child’s sex, gestational age, birth weight, birth length, multiple births, and placental-fetal weight ratio above or below the median. To convert mg/dL to mmol/L multiply by 0.357.

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