Urea Cycle Disorders Consortium Newsletter

2026

Dear Study Participants and Families,

This year marks a significant milestone—the Longitudinal Study of Urea Cycle Disorders is celebrating its 20th anniversary! Since enrolling our very first participant in February 2006 the UCDC has grown from five academic centers to 17 sites across the United States, Canada, Germany, and Switzerland, and has enrolled nearly 1,000 participants (988 participants have enrolled as of January 13, 2026). Thanks to your participation in this study, we have learned a lot and have published 49 manuscripts using data collected through the Longitudinal Study.

Thanks to the steadfast support of the National Institutes of Health (NIH) and our generous philanthropic partners, the consortium has thrived over the past two decades. While our NIH grant is concluding after 20 years of funding, our commitment to advancing research remains unwavering. With continued philanthropic support, we will continue to push forward with important research to better understand UCD and reduce its impact on individuals and families. We extend our heartfelt gratitude to all study participants—past, present, and future—for your invaluable contributions.

As we step into the new year, your partnership continues to be the cornerstone of our success.

Advancing together,

The UCDC Team

News and Events

- The **6th International Symposium on Urea Cycle Disorders** titled Advancements in Understanding: Global Perspectives and Innovations in Urea Cycle Disorders took place in Kyoto, Japan, September 1-2, 2025. The Urea Cycle Disorders Consortium (UCDC) hosted the event along with the National Urea Cycle Disorders Foundation (NUDCF), the Citrin Foundation, the European registry and network for Intoxication type Metabolic Diseases (EIMD) and the Japanese Society for Inherited Metabolic Diseases (JSIMD).

  Visit the past events page on the UCDC website to read more about the event and our speakers.

- **Two new UCDC sites:** Ann & Robert H. Lurie Children's Hospital of Chicago was added as a new site for the Longitudinal Study of Urea Cycle Disorders with Joshua Baker, DO, FAAP, FACMG as the site principal investigator. St. Jude Children's Research Hospital was added as a new site for the Longitudinal Study of Urea Cycle Disorders and the Incidence and Prevalence of Seizures in UCD Study with Andrea Gropman, MD as the site principal investigator.
- **How are we doing?** Leave your feedback about the UCDC newsletter by taking this quick survey.
- **If you are interested** in learning more about the UCDC and our research, please visit our website.

What's in this issue?

Comparing Two Ways to Track Diet in People with UCD

The study looked at eight people aged 16 to 63 who have urea cycle disorders (UCD). Researchers wanted to see if taking pictures of meals with a phone app was easier and more accurate than writing down foods on paper for three days. Both methods were compared to a scientific test called doubly labeled water, which measures how many calories a person uses. Participants were weight-stable and included people with OTC deficiency, ASS1 deficiency, and ASL deficiency. The goal was to find a better way to measure diet since nutrition is a key part of UCD care.

Key Takeaways

Both Methods Underreported Calories: On average, people reported eating 16% fewer calories with paper records and 22% fewer calories with the photo app compared to their actual energy use. This means neither method was fully accurate.

Protein Intake Was Similar Across Methods: Protein made up about 13% of calories with paper records and 15% with the app, which is close to normal diets. Most participants met or exceeded daily protein recommendations, even though they were told to limit protein.

No Big Difference in Macronutrients: Carbohydrate and fat intake were similar between the two methods. Both methods showed diets that looked like typical U.S. eating patterns: about 50% carbs and 37–38% fat.

Participants Preferred the App Slightly: About 67% of participants liked the photo app better for recording meals, but overall ease-of-use scores were similar for both methods.

Day-to-Day Eating Was Consistent: People tended to eat similar amounts of calories and protein each day, showing that UCD diets may be more repetitive than typical diets.

Why This Matters

Tracking diet is important for managing UCD, but this study shows that current methods still miss details. Understanding these limits helps researchers and clinicians improve tools for monitoring nutrition in people with UCD.

Sim E, Gregor A, MacLeod E, Moore R, Ravelli MN, Schoeller DA, Harding CO, Jacobs P, Gillingham MB. Measuring dietary intake among participants with a urea cycle disorder using standard diet records or a novel food photography app. Mol Genet Metab. 2025 Nov 12;146(4):109291. doi: 10.1016/j.ymgme.2025.109291. Epub ahead of print. PMID: 41242089.

Pregnancy in Women with OTC Deficiency: What the Research Shows

Researchers studied 49 women with OTCD who had a total of 109 pregnancies. The goal was to understand how pregnancy affects women with this condition, especially comparing those who have symptoms to those who do not. The study included women from a large U.S. and international research network and collected data both before and after enrollment in a long-term study. The team looked at things like episodes of high ammonia (hyperammonemia), ICU admissions, and pregnancy outcomes. This is the largest study so far to look at pregnancy safety in OTCD carriers.

Key Takeaways

Less Risk for Asymptomatic Women: Women without symptoms had no episodes of high ammonia during pregnancy or postpartum. They also had more living children on average (2.04) compared to symptomatic women (1.29).

Higher Risk for Symptomatic Women: Among women with symptoms, 5 out of 21 pregnancies (24%) had metabolic problems, all involving high ammonia. One woman needed ICU care, but there were no deaths.

Overall Outcomes Were Good: Across all pregnancies, 83% resulted in live births, with miscarriage (10%) and termination (6%) rates similar between groups. No cases of coma, dialysis, or maternal death were reported.

Routine Risk Factors Did Not Explain Differences: Conditions like preeclampsia, gestational diabetes, or advanced maternal age were not more common in symptomatic women, so the extra risk seems linked to OTCD itself.

Close Monitoring Is Key: All women in this study were followed by metabolic specialists, which may have helped prevent serious complications. Past reports show much higher risks when OTCD is undiagnosed or unmanaged.

Why This Matters

This research helps clarify that pregnancy can be safe for women with OTCD, especially if they have no symptoms and receive specialized care. For those with symptoms, extra monitoring and planning are important to reduce risks.

Breilyn MS, Simpson K, Elsbecker SA, Barber JR, Bryan K, Berry SA. Maternal Health Outcomes in Ornithine Transcarbamylase Deficiency: A Comparative Analysis of Pregnancies in Symptomatic and Asymptomatic Heterozygotes. Mol Genet Metab. Mol Genet Metab. 2025 April;144(4):109083. doi: 10.1016/j.ymgme.2025.109083

Does Early Dialysis Help Babies with UCD? New Study Explores the Impact

This study looked at 108 babies with severe forms of UCD, including male OTC deficiency (mOTC-D), citrullinemia type 1 (CTLN1), and argininosuccinic aciduria (ASA). All had very high ammonia levels during their first metabolic crisis, and some received dialysis while others did not. The goal was to see if early dialysis improves survival or short-term brain health compared to standard treatment alone. Researchers used a severity-adjusted approach to make fair comparisons between groups. Data came from the Urea Cycle Disorders Consortium and covered cases from 2000 to 2018.

Key Takeaways

Survival Depends on Ammonia Level, Not Dialysis in mOTC-D: For babies with male OTC deficiency, survival was linked to how high the first ammonia level was. Each extra 100 µmol/L above 564 µmol/L increased death risk by 5%. Dialysis did not improve survival in this group.

Dialysis May Help in CTLN1 and ASA: Babies with citrullinemia type 1 had better survival with dialysis (100%) compared to those without it. ASA showed a similar trend, but the numbers were small, so more research is needed.

No Difference in Brain Outcomes: Among survivors, dialysis did not reduce motor problems or improve thinking scores. Both groups had similar results, suggesting that once ammonia is very high, brain injury may already occur.

Future Crises Still Happen: Dialysis during the first crisis did not lower the number of later ammonia episodes. This means ongoing treatment and monitoring remain essential.

Early Action Is Key: The study suggests that starting treatment before ammonia gets extremely high may matter more than dialysis alone.

Why This Matters

For families and doctors, this research shows that dialysis is not a guaranteed solution for all UCD types. It may help some babies, but early diagnosis and quick action to lower ammonia are critical for survival and brain health.

Zielonka M, Kölker S, Garbade SF, Gleich F, Nagamani SCS, Gropman AL, Druck AC, Ramdhouni N, Göde L, Hoffmann GF, Posset R. Severity-adjusted evaluation of initial dialysis on short-term health outcomes in urea cycle disorders.. Molecular Genetics and Metabolism. Zielonka M, Kölker S, Garbade SF, Gleich F, Nagamani SCS, Gropman AL, Druck AC, Ramdhouni N, Göde L, Hoffmann GF, Posset R; Urea Cycle Disorders Consortium (UCDC). Severity-adjusted evaluation of initial dialysis on short-term health outcomes in urea cycle disorders. Mol Genet Metab. 2024 Sep-Oct;143(1-2):108566. doi: 10.1016/j.ymgme.2024.108566. Epub 2024 Aug 19. PMID: 39299137.

Two OTC Gene Variants Linked to Late-Onset UCD Symptoms

Researchers studied two common genetic changes in the OTC gene often found during carrier screening or genetic testing. They discovered these variants can be associated with cause late-onset hyperammonemia (after the neonatal period) in males.

Key Takeaways

Late-Onset Risk in Males: Neither variant has been reported to cause neonatal-onset hyperammonemia in males. However, 6 of 8 males with p.(Arg40Cys) and 2 of 9 males with p.(Phe354Cys) had hyperammonemia later in life at ages ranging from 9 to 68 years.

Females Rarely Affected: None of the females with these variants had documented hyperammonemia. Most were identified through carrier screening or family testing.

Functional Testing Shows Reduced Activity: Lab tests using yeast showed both variants reduce OTC enzyme function to a “hypomorphic” level (about 28–36% of normal growth), which matches late-onset disease risk.

Triggers and Outcomes: Common triggers included fasting, illness, and high-protein diets. Some crises were fatal—3 deaths in the p.(Arg40Cys) group and 1 in the p.(Phe354Cys) group—often due to delayed diagnosis.

Counseling Is Essential: People with these variants should know warning signs and avoid triggers like fasting, certain medications (e.g., valproic acid), and high-protein diets. Emergency letters and medical ID bracelets are recommended.

Why This Matters

As genetic testing becomes more common, more people with these OTC variants might be detected. This research helps explain what these findings mean and highlights the importance of education and emergency planning to prevent life-threatening crises.

Lang SH, Lo RS, Cromie GA, Dudley AM, Mew NA, Simpson K, Sutton VR, Darilek S, Ali S, Snyder MT, Lee B, Marom R, Nagamani SCS, Burrage LC. Two commonly reported incidental variants in OTC are associated with late-onset disease. HGG Adv. 2025 Oct 16;7(1):100531. doi: 10.1016/j.xhgg.2025.100531. Epub ahead of print. PMID: 41108081.

Liver Scarring Found in UCD patients, Especially ASLD

In this study, researchers looked at liver samples from 66 people with different types of UCD who had either a liver transplant or a biopsy. The goal was to find out how often liver scarring (fibrosis) and fat buildup (steatosis) happen in these patients. The group included children and adults, from newborns to age 41, and covered several UCD types like OTCD, ASLD, ASS1D, CPS1D, and ARG1D. Researchers also checked if routine blood tests or imaging could predict liver problems. This is the first large study to measure these issues in UCD patients in a systematic way.

Key Takeaways

Fibrosis is Common in ASLD: About 23% of all patients had significant liver scarring, but in ASLD, it was much higher—80% (12 out of 15 people). This included children as young as 8 months old, showing that scarring can start early.

Other UCD Types Show Lower Rates: Only 10% of males with OTCD and 20% of those with ARG1D had significant fibrosis. No cases of severe scarring were found in ASS1D or CPS1D patients.

Fat in the Liver (Steatosis): Fat buildup was seen in 18% of patients. It was most common in ASLD and ARG1D and often appeared alongside fibrosis. Severe fat buildup was rare.

Routine Tests Did Not Predict Scarring: Blood tests like AST and ALT and imaging like ultrasound did not reliably show who had serious liver scarring. Some patients with severe fibrosis had only mild lab changes.

No Tumors Found, but Glycogen Was High: No liver tumors were detected in any sample. Almost all samples showed extra glycogen in the liver cells, which is typical in UCD.

Why This Matters

This research shows that liver problems are more likely to develop in the ASLD population, and may start very early. Knowing this helps patients and doctors understand the importance of monitoring liver health as part of UCD care.

Ali S, Nisar A, Zhang A, Nagamani S, Aceves-Ewing NM, Rawls B, Quan T, Enns G, Goss J, Leung DH, Shneider BL, Jain S, Hazard FK, Schady D, Burrage LC. Prevalence of fibrosis in hepatic explants and biopsies from individuals with urea cycle disorders. Mol Genet Metab. 2025 Aug;145(4):109175. doi: 10.1016/j.ymgme.2025.109175. Epub 2025 Jun 13. PMID: 40540899; PMCID: PMC12573283.

Seizures and Ammonia Levels in UCD: What This Study Reveals

This study looked at 85 people enrolled in the UCDC longitudinal study. The goal was to understand how often seizures happen, what types occur, and whether ammonia and glutamine levels predict seizure risk during hyperammonemic crises. Researchers also examined the role of EEG in detecting seizures that are not obvious clinically. The group included both early-onset and late-onset UCD cases across several subtypes like OTCD, ASLD, ARG1D, CPS1D, and others. Data covered seizure history, EEG findings, and biochemical profiles during crises.

Key Takeaways

Seizures Are Common in UCD: About 34% of individuals had seizures at some point. Seizures occurred in 13% of hyperammonemic events, and most early-onset seizures happened during crises.

Epilepsy Risk Is Higher in Certain UCD Types: Overall, 12% developed epilepsy, mainly in distal UCD types like ASLD (22%) and ARG1D (50%). Late-onset seizures unrelated to crises were most likely to progress to epilepsy.

Ammonia and Glutamine Predict Seizure Risk: For every 100 μmol/L increase in ammonia, seizure odds rose 2.65 times; for glutamine, odds rose 1.14 times. Higher initial levels signal greater risk.

EEG Detects Hidden Seizures: EEG found subclinical seizures in 53% of crises with clinical seizures and 27% of crises with encephalopathy only. This shows why EEG monitoring is important during severe episodes.

Treatment During Crises: Seizures were managed with antiseizure medications (phenobarbital was most common) plus ammonia-lowering therapies like nitrogen scavengers and dialysis.

Why This Matters

Understanding seizure risk and epilepsy in UCD helps families and doctors plan care. Monitoring ammonia and using EEG during crises can prevent missed seizures and reduce brain injury.

Chanvanichtrakool M, Schreiber JM, Chen WL, Barber J, Zhang A, Ah Mew N, Schulze A, Wilkening G, Nagamani SCS, Gropman A; Urea Cycle Disease Consortium. Unraveling the Link: Seizure Characteristics and Ammonia Levels in Urea Cycle Disorder During Hyperammonemic Crises. Pediatr Neurol. 2024 Oct;159:48-55. doi: 10.1016/j.pediatrneurol.2024.06.013. Epub 2024 Jun 29. PMID: 39121557; PMCID: PMC11381174.