Association Of Early Life Hypoglycemia With Later Neurological Outcomes In Congenital Hyperinsulinism: A US Claims Based Study

SAT-221

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Background

- Congenital hyperinsulinism (cHI) is marked by dysfunctional secretion of insulin from the pancreas, leading to hypoglycemia and glucose deficiency in the brain.
- cHI is a leading cause of persistent hypoglycemia in infants and children, with an estimated incidence of approximately 1 per 28,000[1,2].
- Although neurologic consequences are estimated to occur in approximately half of individuals with cHI, the correlation between hypoglycemia exposure and subsequent neurologic sequelae remains unclear. [2]

Objective

To explore the longitudinal association between early hypoglycemia events and subsequent neurological outcomes, to inform a disease model.

Methods

- cHI individuals were identified in claims data between 2017 and 2025 using a set of diagnostic rules based on hypoglycemia, pancreatectomy, and cHI-related medication use.
- Sequence analysis was conducted based on data from 1,557 individuals, with their first claim before one year of age due to hypoglycemia.
- Each year, individuals were categorized into one of four mutually exclusive health states:
  1. **Hypoglycemia (Hypo):** having any claims for hypoglycemia;
  2. **Hypo + neuro:** having any claims for both hypoglycemia and neurological sequelae;
  3. **Neuro:** having any claims for neurological sequelae;
  4. **Unknown:** no registered claims for hypoglycemia or neurological sequelae.
- Health states were defined using the ICD-10 codes for hypoglycemia (E16.1, E16.2, P70.4) and for neurological conditions including developmental delay and intellectual disability, attention-deficit/hyperactivity disorder (ADHD), autism, cerebral palsy, epilepsy, motor impairment, hearing impairment, visual impairment and behavioral disorders.
- Neurological sequelae were assumed to be irreversible. Consequently, once a patient had a claim for neurological sequelae, all subsequent years without health claims were imputed as “neuro,” and those with only hypoglycemia claims as “Hypo + neuro.”
- We estimated the longitudinal distribution of health states and the probabilities of transition between them.

Results

Figure 2. Percentage range of cHI patients affected by different neurological sequelae across 72 studies

1. Population characteristics

- Among 1,557 individuals, there were 277,118 claims between 2017-2025. All patients were born in 2017 or later, meaning that the age at the claims ranged from 0 to 8.
- Most of the sample (73.2%) had at least one claim due to neurological sequelae (**Table 1**)
- Most frequent neurological sequelae (**Table 2**):
  - Developmental delay/ intellectual disability
  - Speech impairment
  - Motor impairment

Table 1. Population characteristics (N=1,577) n

	n	Proportion
Hypoglycemia	1,557	100%
Neurological sequelae	1,140	73.2%
Diazoxide use	1,153	74.1%
Octreotide use	63	4.0%
Glucagon use	875	56.2%
G-tube use	281	18.0%
Pancreatectomy	40	2.6%
Diabetes post-pancreatectomy	21	1.3%

Table 2. Neurological sequelae (N=1,557)

	n	Proportion
Developmental delay	864	55.5%
Speech impairment	543	34.9%
Motor impairment	376	24.1%
Hearing impairment	253	16.2%
Autism	166	10.7%
Epilepsy	156	10.0%
Behavioral	147	9.4%
ADHD	95	6.1%
Cerebral	59	3.8%
Visual	24	1.5%

2. Longitudinal distribution of health states

- The number of available observations per year of age decreases as only patients born in 2017 or later were included in the analysis **(Table 3)**.
- The proportion of children with hypoglycemia was high at ages 0 and 1 (Table 3), declining by a factor of 0.78 per year between age 0 and 8 years (Figure 2).
- The proportion of any neurological sequelae between age 0 and 8 years, increased from 37.2% to 81.8% **(Figure 3)**.

Figure 2. Sequence Distribution of Health States

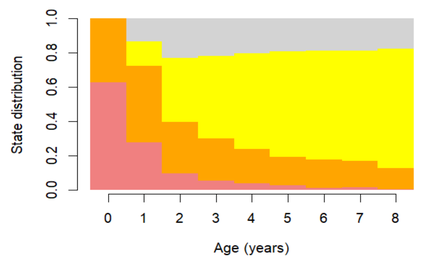
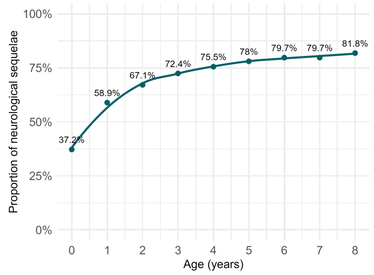


Figure 3. Probability of Neurological Sequelae in Children with Initial Hypoglycemia



3. Transition probabilities

- Between age <1 and 8 years, the yearly probability of transitioning from hypoglycemia to hypoglycemia with neurological sequelae was 21.6%, and to neurological sequelae alone was 7.3%, resulting in a combined 28.9% yearly probability of developing any neurological sequelae following hypoglycemia **(Table 4)**.
- Misclassification may occur as cHI is coded under a non-specific ICD-10 code.
- Data reflect individuals with healthcare access; transition probabilities may be different than in underserved populations.
- Unknown state may mask whether patients were cured, died, or had other outcomes.

Table 3. Health state distribution

Age	n	Hypo	Hypo + neuro	Neuro	Unknown
0	1557	62.8%	37.2%	0.0%	0.0%
1	1532	27.8%	44.7%	14.2%	13.3%
2	1398	9.7%	30.0%	37.1%	23.2%
3	1232	5.7%	24.4%	48.1%	21.9%
4	1037	4.1%	20.1%	55.4%	20.4%
5	841	2.7%	16.5%	61.5%	19.3%
6	605	1.5%	16.2%	63.5%	18.8%
7	375	1.6%	15.5%	64.3%	18.7%
8	181	0.6%	12.2%	69.6%	17.7%

Table 4. Yearly Transition Probabilities Between 0-8 years

	Hypo	Hypo + Neuro	Neuro	Unknown
Hypo >	41.9%	21.6%	7.3%	29.2%
Hypo + neuro>	0.0%	63.4%	36.6%	0.0%
Neuro >	0.0%	6.5%	93.5%	0.0%
Unknown >	4.3%	0.9%	8.6%	86.2%

Key Takeaways

- Findings suggest a possible association between early hypoglycemia and later neurological sequelae.
- The persistence of hypoglycemia highlights the need for early diagnosis and more effective management.
- Future research should account for confounders and use robust designs to better assess causal relationships

Abbreviations: cHI: congenital hyperinsulinism, n: sample size, neuro: neurological sequelae

References: 1. Lapidus D, et al. Horm Res Paediatr. 2024. 2. Banerjee I, et al. Orphanet J Rare Dis. 2022.

PRESENTED AT THE ENDOCRINE SOCIETY ANNUAL MEETING (ENDO); JUNE 13-16, 2026; CHICAGO, ILLINOIS, USA