Hormone Research in Paediatrics

Horm Res Paediatr , DOI: 10.1159/000539464
Received: April 19, 2024
Accepted: May 17, 2024
Published online: June 17, 2024

The birth prevalence of congenital hyperinsulinism: a narrative review of the epidemiology of a rare disease

Lapidus D, De León DD, Thornton PS, Hood D, Breit J, Raskin J, Pasquini TLS

ISSN: 1663-2818 (Print), eISSN: 1663-2826 (Online)
https://www.karger.com/HRP
Hormone Research in Paediatrics

Review Article
The birth prevalence of congenital hyperinsulinism: a narrative review of the epidemiology of a rare disease

David Lapidus[a], Diva D. De León[b], Paul S. Thornton[c], Davelyn Hood[d], Jeffrey Breit[d], Julie Raskin[e], Tai L.S. Pasquini[e]

[a] LapidusData Inc., Oklahoma City, OK, USA
[b] Congenital Hyperinsulinism Center and Division of Endocrinology and Diabetes, Department of Pediatrics, The Children's Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA
[c] Congenital Hyperinsulinism Center, Cook Children's Medical Center, Fort Worth, TX, USA
[d] Rezolute, Inc., Redwood City, CA, USA
[e] Congenital Hyperinsulinism International, Glen Ridge, NJ, USA

Short Title: Epidemiology of Congenital Hyperinsulinism

Corresponding Author: Tai L.S. Pasquini
E-mail address: tpasquini@congenitalhi.org

Keywords: Congenital hyperinsulinism, incidence, prevalence, epidemiology,

Target journal: *Hormone Research in Paediatrics*
Word count: 2998/3000
Number of figures: 1 (maximum 5)
Number of references: 34 (maximum 60)

Abstract (200/200)

Background
Congenital hyperinsulinism (HI) is a rare pediatric disease and the most common cause of severe, persistent hypoglycemia in childhood. It is characterized by the dysregulation of insulin secretion from the pancreas and can lead to irreversible brain damage with lifelong neurodisability.
Summary
The global birth prevalence of HI is currently unknown. An evidence-based estimate of HI birth prevalence is essential to improve diagnosis and patient management, to drive clinical research and the development of new treatments, and to inform public policy. In order to estimate the birth prevalence of persistent HI, a targeted literature review of studies that report HI epidemiological data was undertaken, and the strengths and limitations of each study were analyzed. Overall, eight global studies were identified that reported independently determined HI epidemiological data.
Key messages
The best estimate for the birth prevalence of persistent HI in European-ancestry populations is 3.5 per 100,000 births. Local consanguinity patterns appear to have a considerable impact on the birth prevalence of persistent HI in each country, precluding the application of this figure to all global populations. More epidemiological studies with robust methodology are needed to enable a reliable approximation of the incidence and prevalence of HI in global populations.

Introduction

Congenital hyperinsulinism (HI) is a rare and heterogenous pediatric disease, characterized by recurrent episodes of hypoglycemia with concurrent hypoketonemia, caused by the dysregulated secretion of insulin from pancreatic β-cells [1-5]. HI is the most common cause of severe, persistent hypoglycemia in infancy and childhood [2, 3, 6]. Early diagnosis and effective treatment are crucial to minimize the risk of death and irreversible brain damage with lifelong neurodisability [2, 3, 7].

The global incidence and prevalence of HI are currently unknown and reliable estimates are scarce. Determining the prevalence of HI is important because it raises awareness of the condition and allows for the estimation of the number of affected individuals in a given population [8, 9]. These data can then be used to determine shortfalls in the diagnosis pathway, by enabling a comparison between those affected and those who receive a diagnosis, and to assess the specific needs of patients with HI in the healthcare system [8, 9]. This in turn would enable better health resource and social services allocation, and inform focused service delivery that would be targeted at the specific needs of the patient population, thereby improving patient management [9]. One of the major barriers to obtaining a fast and accurate diagnosis is the lack of knowledge about HI among clinicians. As such, education and training could be provided to ensure that clinicians are able to recognize HI so that they can provide a quick and accurate diagnosis in infants [2, 4, 10]. This could then provide the basis for an increase of HI epidemiological data. Furthermore, accurate HI prevalence data would be essential for orphan drug legislation objectives, to improve research funding, to incentivize the development of novel therapies, and to facilitate the conduct of clinical trials [9, 11].

The aim of this study was to determine the best estimate of HI birth prevalence based on available studies, and to assess whether or not persistent HI has a similar birth prevalence in all ancestry groups. A targeted literature review of epidemiological data on HI was performed and an analysis of the strengths and limitations of the identified studies was undertaken. To utilize the correct terminology, we chose to consistently use the term 'birth prevalence' throughout this article in place of the term 'incidence' frequently used in the referenced studies.

HI disease background

Determining who to count as 'a person with HI' is challenging owing to the heterogeneous nature of the subtypes and classifications of the disease. HI that occurs in the neonatal period may be either acquired or genetic [4]. Acquired forms of HI can be caused by birth asphyxia or intrauterine growth restriction, or by maternal factors such as hypertension/preeclampsia [3, 4]. These forms of HI are called perinatal stress HI, are often transient, and usually resolve within days or weeks [3, 4]. Other forms of transient acquired HI include those of infants of mothers with diabetes, and those of infants exposed to certain drugs through the placenta or high glucose infusions during delivery [4]. Genetic forms of HI can cause isolated dysfunction of the pancreas, or they can be associated with syndromes that affect multiple organs [2, 4]. Genetic HI is usually caused by single gene variants in the insulin secretory pathway. The most frequent causes – approximately 60% of all identifiable variants – are inactivating variants in *ABCC8* or *KCNJ11*, the genes that encode the β-cell ATP-dependent potassium channel (K_{ATP}) [1, 12, 13]. Pathogenic variants in over 30 genes have been identified to date as underlying causes for genetic HI [12]. However, for approximately 40–50% of children with persistent forms of HI, there is no known genetic cause [13], suggesting that a potentially large number of causative pathogenic variants remain to be identified. To add further complexity, some transient forms of newborn HI have genetic causes that may have implications for later life, such as those caused by *HNF1A* and *HNF4A* variants that indicate a predisposition for maturity-onset diabetes of the young [4]. Histologically, the most common form of HI (K_{ATP} HI) can be classified as focal or diffuse [3, 13]. In diffuse HI, all β-cells of the pancreas are affected. This form of HI occurs when the infant has inherited recessive mutations from both parents or a dominant variant from one of the parents [3, 6]. Focal HI is limited to certain areas of the pancreas and typically occurs when the infant

carries a paternal recessive mutation and the maternal allele is lost, resulting in paternal uniparental isodisomy [3, 14].

Challenges with determining HI birth prevalence

Determining the global birth prevalence of HI is challenging for several reasons. Primarily, because of the scarcity and diversity of the available evidence, much of which is not standardized and thus hard to combine [9]. Most available studies are case reports, single-center studies, or studies undertaken in specific cohorts or in populations with incomplete ascertainment. The challenges arising from low case numbers are further aggravated by the clinical heterogeneity of the patient population, the overlap with congenital disorders of glycosylation or conditions such as Turner syndrome, Kabuki syndrome or Beckwith–Wiedemann syndrome, and the frequent delay in diagnosis or even lack of diagnosis [3, 8, 9]. Furthermore, the birth prevalence of HI may differ widely between populations of high and low consanguinity [3], or across different geographic areas, owing to genetic diversity, environmental, or societal pressures [9]. There is also some evidence suggesting that a small but significant percentage of unexplained neonatal deaths might be due to undiagnosed cases of HI, especially in regions with higher rates of consanguinity [7]. Therefore, some babies may die before being diagnosed with HI and, as such, may not be included in studies evaluating HI birth prevalence. Currently, HI is not included in any mandatory or voluntary rare disease surveillance studies, which would allow for more complete case ascertainment within a specific geographic region. Finally, each of the previous studies that determined HI birth prevalence defined the patient populations differently, which makes the comparison of these studies challenging.

Review of HI epidemiological data

For the present review of HI birth prevalence data, a targeted literature review of the available epidemiological data on HI was performed. On 25 May 2022, a PubMed search was conducted using the search strings “epidemiology OR incident OR incidence OR prevalent OR prevalence” AND “congenital hyperinsulinism”, which identified 125 articles. This search was supplemented with additional searches using the search strings a) “congenital hyperinsulinism" AND “focal” AND “diffuse”, and b) "congenital hyperinsulinism" AND “diazoxide” AND “response OR responsive OR responsiveness”. A gray literature search with the same search strings yielded no additional results. The abstracts of the articles that were identified, or the titles if no abstract was available, were reviewed and relevant articles selected for full text review. This yielded 23 articles, of which only eight studies were found to have independently determined HI incidence or prevalence rather than citing estimates from other studies. The characteristics and results of these eight studies are summarized in Table 1 and Fig. 1.

Two additional studies were excluded from this analysis. The study conducted by Otonkoski and colleagues [15] in Finland before the year 2000 was excluded because it was considered obsolete to the more recent study by Männistö et al. [16]. The study by Glaser and colleagues in a cohort of Ashkenazi Jewish individuals in Israel [17] was excluded because it used carrier frequency of two *ABCC8* variants to calculate the risk of focal HI, rather than reporting focal HI disease frequency.

Table 1. Studies reporting HI incidence or prevalence data.

Fig.1. HI birth prevalence reported in available studies.

Overall, the available studies do not adequately address the question of whether or not persistent HI has a similar birth prevalence in all ancestry groups. The majority of the studies used either a ‘sample of convenience’ or were conducted in subpopulations so that no overall birth prevalence can be derived for the country where the study took place.

Studies with incomplete ascertainment

The studies by Yamada et al. [19] and Bruining et al. [24] are subject to incomplete ascertainment. Yamada et al. [19] fielded a survey to Japanese clinics that treated patients with HI in 2017/2018 and approximately half of the clinics responded. It is unclear whether the clinics that did not respond had patients with HI that they are not reporting, or if they had no patients with HI. Of those that responded positively, stating that they had patients with endogenous hyperinsulinemic hypoglycemia, approximately half returned responses to a secondary survey requesting condition-specific details. For that reason, the reported birth prevalence for persistent HI, 3.2 cases per 100,000 births, is likely an underestimate. The same limitation applies to the reported birth prevalence of transient HI of approximately 7.4 per 100,000 births and the combined birth prevalence of 10.5 per 100,000 births for HI overall.

The Dutch study by Bruining et al. [24] is not a true epidemiological study but a review article in which the author states that his team saw a case of HI once every 2 years at a constant rate for the previous 10 years. This would be equivalent to a birth prevalence of approximately 2.0 cases in 100,000 births. However, the author only refers to his own clinic in Rotterdam, and it is unclear if any efforts were made to capture cases outside of the author's clinic. Therefore, this figure must also be considered a potential underestimate.

Studies in subpopulations

In addition to the studies with uncertain ascertainment, three further studies – by Nóvoa-Medina et al. [18], Snider et al. [22], and Mathew et al. [23] – were conducted in subpopulations within Spain, the USA, and Saudi Arabia, respectively, and do not represent the country overall.

The birth prevalence of persistent HI reported by Nóvoa-Medina and colleagues for Spain's Canary Islands of Gran Canaria and Lanzarote was 6.4 in 100,000 births [18], while Mathew et al. found a birth prevalence of 37.4 per 100,000 births for Saudi Arabia's Eastern Province [23]. The latter is the highest birth prevalence reported in any of the studies included in this review, reflecting the increased level of consanguinity in Saudi Arabia compared with European-ancestry populations.

Snider and colleagues [22], in contrast, conducted a study at a specialized center for HI in Philadelphia, USA, between 1997 and 2010. Although this center is a large referral hospital caring for patients with HI across the USA, the study did not include patients who might be cared for by other US providers. In addition, the prevalence figure identified in this study is limited to a subpopulation of patients with K_{ATP} variants of HI. For these reasons, the final birth prevalence calculated, 1.3 –1.6 per 100,000 births, is likely an underestimate.

Studies without major methodological concerns

The studies by Männistö et al. [16], Yau et al. [20], and Rozenkova et al. [21] were conducted in European-ancestry populations. They have no major cause for concern about methodology and can thus be considered the highest quality data available. The retrospective study by Männistö and colleagues collected epidemiological data from patients across all of Finland, and is the most extensive analysis of all of the studies. The authors reported a national birth prevalence of 3.9 per 100,000 births for persistent HI and 8.8 per 100,000 births for HI overall (transient and persistent HI) between 1972 and 2015. However, when cases were limited to a more recent period (2000–2015), the birth prevalence increased to 7.4 per 100,000 births for persistent HI and 13.5 per 100,000 births for transient HI, and an overall birth prevalence of 21.0 per 100,000 births. The authors attributed the increase to more accurate documentation of HI diagnosis and improved protocols for blood glucose screening in at-risk newborns. They also noted that HI may be more common in Finland than in other European nations owing to its genetic isolation and known HI founder effects [16].

In contrast, Yau and colleagues conducted an assessment of patients with clinically and biochemically confirmed HI who were referred to a single national laboratory for genetic testing, as well as annual birth rates from census data. From these data, they calculated the birth prevalence of persistent HI in the United Kingdom between 2007 and 2016 to be 3.5 per 100,000 births [20]. This should be

considered a minimum value because only patients who were referred for genetic testing were included. Patients who received a diagnosis of HI without genetic testing would be missed; however, because all patients with HI in the UK receive clinical care through just two specialized national centers, the rate of referral for genetic testing is high.
Finally, Rozenkova et al. collected clinical information from all centers caring for patients with HI in the Czech Republic between 1997 to 2014, identifying an overall (transient and persistent) HI birth prevalence of 2.2 per 100,000 births. This figure is remarkably low when compared with the birth prevalence identified by Männistö et al. in Finland and by Yamada et al. in Japan. However, the authors state that the birth prevalence appears to increase in the later years of the analysis period. Of note, patients from the Czech Republic had a lower proportion of homozygous *ABCC8/KCNJ11* gene variants and higher proportion of *HNF1A* variants than cohorts in other studies. In addition, this cohort appears to have a low level of consanguinity, reported for only 1 of 40 patients (2.5%), whereas consanguinity was reported for 24 of 278 patients (8.6%) in the UK cohort [20, 21].

Conclusion

Based on the assessment of all studies that independently reported HI epidemiological data, the birth prevalence figure identified by Yau et al. in the UK, 3.5 per 100,000 births [20], can be considered the most suitable approximation for the birth prevalence of persistent HI in populations with European ancestry. For the reason outlined earlier, this should be considered a minimum figure. Among the other two previously mentioned studies that had no major methodological concerns, the study by Rozenkova et al. [21] only provided a recent (2009–2013) birth prevalence figure for transient and persistent HI combined, while the study by Männistö et al. [16] showed that the Finnish population is subject to HI founder effects, which makes the birth prevalence stated in this study unsuitable to serve as a generalizable value for populations with European ancestry.
Owing to the lack of data from Southern European populations, it is unknown whether the HI birth prevalence identified for the UK applies across all of Europe. Many genetic diseases display a north–south gradient [25]; thus, application of this figure to Southern European populations – or indeed non-European populations – may be problematic. As HI birth prevalence appears to vary considerably depending on local consanguinity patterns, the UK figure may only be applicable to European-ancestry populations with a similar level of consanguinity and without significant founder effects. Unfortunately, the only studies that reported separate figures for the birth prevalence of transient HI (Männistö et al. [16] and Yamada et al. [19]) have limitations that preclude the application of their results as a general estimate to other populations. Interestingly, these studies showed that the birth prevalence of transient HI was approximately or slightly more than double the birth prevalence of persistent HI. Thus, although acquired HI is heavily influenced by perinatal factors, it appears to be significantly more frequent than genetic HI.
More studies with robust methodology are needed to enable a reliable approximation of the birth prevalence of all types of HI in global populations. The collection of HI epidemiological data is complicated by several other factors. This includes the absence of specific International Classification of Diseases (ICD) codes for HI, and many other rare diseases [26]. The absence of dedicated ICD, Healthcare Common Procedure Coding System, and Current Procedural Terminology codes also impedes an assessment of HI epidemiology via HI-related insurance claims. The same applies for the use of other HI-associated codes, such as those for treatment, surgery, or nutritional support. Therefore, it is crucial that HI-specific codes are established that differ from the 'other hypoglycemia' or 'hypoglycemia, unspecified' codes that are currently used for HI. In addition, there is an urgent need to develop a universal nomenclature for all types of HI, including a better definition of transient and persistent HI. At present, the definitions used in the literature are inconsistent, which means that the patient cohorts selected for epidemiological studies can vary considerably based on a clinical team's definition of HI subtypes. Furthermore, agreement needs to be reached within the HI clinical community about what constitutes a 'person with HI'. This involves clarity around the question of

when a person's HI is considered ‘cured’ or ‘resolved’ if that person transitions to diabetes, and what it means if a person who is born with HI no longer experiences symptoms or no longer requires medications or extra-nutritional carbohydrates to main normal blood glucose levels.
In the authors’ opinion, a reliable method to obtain an accurate total population sample of HI would require the compulsory reporting of HI by healthcare professionals, which is mandatory for some other rare diseases. Currently, no healthcare system worldwide has mandatory reporting of HI cases. However, there are individual national approaches, such as the Italian National Registry of Rare Diseases [27] or the Canadian Chronic Disease Surveillance System [28], that may serve as models for a population-wide surveillance system that is able to gather epidemiological information for a subset of rare diseases across the entire population of a country. Besides compulsory reporting in healthcare systems, country-specific patient registries and patient advocacy groups play an important part in obtaining reliable epidemiological data [29, 30]. The patient-initiated HI Global Registry (HIGR) is available for worldwide participation of families affected by HI [31]. As its reach expands with the introduction of new languages, HIGR may become a crucial tool in providing more reliable figures for global HI prevalence in the future. Reliable epidemiological data on HI are urgently needed to pave the way for public health approaches, defining the impact of HI on populations, examining cost, and improving patient management. Reliable data would also facilitate drug development and implementation of clinical trials by defining a worldwide need for novel treatments of HI [11].

Statements

Acknowledgement

Medical writing and editorial assistance for this manuscript were provided by Claudia Brockmeyer PhD and Grant Womack BSc of Oxford PharmaGenesis, Oxford, United Kingdom.

Conflict of Interest Statement

DDDL has received consulting fees from Crinetics Pharmaceuticals, Eiger Pharma, Hanmi Pharmaceuticals, Rhythm Pharmaceuticals, Twist Biosciences, and Zealand Pharma A/S,; and has received research funding from Crinetics Pharmaceuticals, Eiger Pharma, Hanmi Pharmaceuticals, Rezolute, Twist Biosciences, Ultragenyx, and Zealand Pharma A/S for studies not discussed in this manuscript.

PST has received consulting fees from Crinetics Pharmaceuticals, Neurocrine, Spruce Biosciences and Zealand Pharma A/S; has received research funding from Rezolute and Zealand Pharma A/S for research related to this article; and has received research funding from Ascendis, Novo Nordisk, and Pfizer for research not related to this project.

DH and JB are employed by and stock shareholders in Rezolute, Inc.

JR and TLSP are employees of Congenital Hyperinsulinism International (CHI), which has received sponsorships for events from Amidebio, Betabionics, Crinetics Pharmaceuticals, Eiger, Hanmi, Rezolute, Rhythm Pharmaceuticals, Twist, Xeris, and Zealand Pharma A/S over the past 3 years. Crinetics Pharmaceuticals, Eiger, Hanmi Pharmaceuticals, Rezolute and Zealand Pharma have been sponsors of the HI Global Registry over the last 3 years. They do not receive any fees directly from these companies.

DL has no potential conflicts of interest to declare.

Funding Sources

Rezolute provided partial support to Congenital Hyperinsulinism International (CHI) for the study design and implementation, and for the writing of this report.

Author Contributions

DL conducted the literature search, analyzed the literature, wrote an initial report about the results, and implemented feedback from the other authors on the initial report. DDDL and PST provided expertise on the medical and clinical interpretation of the results, helped to define the parameters for the study, and provided feedback on the initial report. DH and JB proposed the initial study objectives, provided feedback on the initial report, and conducted complementary studies to test the results. JR and TLSP outlined and further defined the study objectives, engaged DDDL and PST, coordinated feedback from the other authors on the initial report, provided editorial and contextual feedback on the report, and provided data from complimentary studies to inform the interpretation of results. All authors interpreted the data, reviewed and provided feedback on the manuscript drafts, and approved the final version for publication.

References

1. Adzick N, De Leon D, States L, Lord K, Bhatti T, Becker S, et al. Surgical treatment of congenital hyperinsulinism: results from 500 pancreatectomies in neonates and children. J Pediatr Surg. 2019;54(1):27–32.
2. Banerjee I, Raskin J, Arnoux JB, De Leon DD, Weinzimer SA, Hammer M, et al. Congenital hyperinsulinism in infancy and childhood: challenges, unmet needs and the perspective of patients and families. Orphanet J Rare Dis. 2022;17(1):61.
3. Banerjee I, Salomon-Estebanez M, Shah P, Nicholson J, Cosgrove KE, Dunne MJ. Therapies and outcomes of congenital hyperinsulinism-induced hypoglycaemia. Diabet Med. 2019;36(1):9–21.
4. De Leon DD, Arnoux JB, Banerjee I, Bergada I, Bhatti T, Conwell LS, et al. International guidelines for the diagnosis and management of hyperinsulinism. Horm Res Paediatr. 2023. 10.1159/000531766.
5. Rosenfeld E, Ganguly A, De Leon DD. Congenital hyperinsulinism disorders: genetic and clinical characteristics. Am J Med Genet C Semin Med Genet. 2019;181(4):682–92.
6. Arnoux JB, Verkarre V, Saint-Martin C, Montravers F, Brassier A, Valayannopoulos V, et al. Congenital hyperinsulinism: current trends in diagnosis and therapy. Orphanet J Rare Dis. 2011;6:63.
7. Amaratunga SA, Hussein Tayeb T, Rozenkova K, Kucerova P, Pruhova S, Lebl J. Congenital Hyperinsulinism caused by novel homozygous KATP channel gene variants may be linked to unexplained neonatal deaths among Kurdish consanguineous families. Horm Res Paediatr. 2020;93(1):58–65.
8. Bainbridge MN. Determining the incidence of rare diseases. Hum Genet. 2020;139(5):569–74.
9. Nguengang Wakap S, Lambert DM, Olry A, Rodwell C, Gueydan C, Lanneau V, et al. Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. Eur J Hum Genet. 2020;28(2):165–73.
10. Chung CCY, Hong Kong Genome Project, Chu ATW, Chung BHY. Rare disease emerging as a global public health priority. Front Public Health. 2022;10:1028545.
11. Bruckner-Tuderman L. Epidemiology of rare diseases is important. J Eur Acad Dermatol Venereol. 2021;35(4):783–84.
12. Hewat TI, Johnson MB, Flanagan SE. Congenital hyperinsulinism: current laboratory-based approaches to the genetic diagnosis of a heterogeneous disease. Front Endocrinol (Lausanne). 2022;13:873254.
13. Vajravelu ME, De Leon DD. Genetic characteristics of patients with congenital hyperinsulinism. Curr Opin Pediatr. 2018;30(4):568–75.
14. Yorifuji T, Kawakita R, Nagai S, Sugimine A, Doi H, Nomura A, et al. Molecular and clinical analysis of Japanese patients with persistent congenital hyperinsulinism: predominance of paternally inherited monoallelic mutations in the KATP channel genes. J Clin Endocrinol Metab. 2011;96(1):E141–E45.
15. Otonkoski T, Ammala C, Huopio H, Cote GJ, Chapman J, Cosgrove K, et al. A point mutation inactivating the sulfonylurea receptor causes the severe form of persistent hyperinsulinemic hypoglycemia of infancy in Finland. Diabetes. 1999;48(2):408–15.
16. Mannisto JME, Jaaskelainen J, Otonkoski T, Huopio H. Long-term outcome and treatment in persistent and transient congenital hyperinsulinism: a Finnish population-based study. J Clin Endocrinol Metab. 2021;106(4):e1542–e51.
17. Glaser B, Blech I, Krakinovsky Y, Ekstein J, Gillis D, Mazor-Aronovitch K, et al. ABCC8 mutation allele frequency in the Ashkenazi Jewish population and risk of focal hyperinsulinemic hypoglycemia. Genet Med. 2011;13(10):891–94.
18. Nóvoa-Medina Y, Domínguez García A, Quinteiro González S, García Cruz LM, Santana Rodríguez A. Congenital hyperinsulinism in Gran Canaria, Canary Isles. An Pediatr (Engl Ed). 2021;95(2):93–100.
19. Yamada Y, Kitayama K, Oyachi M, Higuchi S, Kawakita R, Kanamori Y, et al. Nationwide survey of endogenous hyperinsulinemic hypoglycemia in Japan (2017-2018): congenital hyperinsulinism, insulinoma, non-insulinoma pancreatogenous hypoglycemia syndrome and insulin autoimmune syndrome (Hirata's disease). J Diabetes Investig. 2020;11(3):554–63.
20. Yau D, Laver TW, Dastamani A, Senniappan S, Houghton JAL, Shaikh G, et al. Using referral rates for genetic testing to determine the incidence of a rare disease: the minimal incidence of congenital hyperinsulinism in the UK is 1 in 28,389. PLoS One. 2020;15(2):e0228417.

21. Rozenkova K, Malikova J, Nessa A, Dusatkova L, Bjorkhaug L, Obermannova B, et al. High incidence of heterozygous ABCC8 and HNF1A mutations in Czech patients with congenital hyperinsulinism. J Clin Endocrinol Metab. 2015;100(12):E1540–E49.
22. Snider KE, Becker S, Boyajian L, Shyng SL, MacMullen C, Hughes N, et al. Genotype and phenotype correlations in 417 children with congenital hyperinsulinism. J Clin Endocrinol Metab. 2013;98(2):E355–63.
23. Mathew PM, Young JM, Abu-Osba YK, Mulhern BD, Hammoudi S, Hamdan JA, et al. Persistent neonatal hyperinsulinism. Clin Pediatr (Phila). 1988;27(3):148–51.
24. Bruining GJ. Recent advances in hyperinsulinsim and the pathogenesis of diabetes mellitus. Curr Opin Pediatr. 1990;2:758–65.
25. Seldin MF, Shigeta R, Villoslada P, Selmi C, Tuomilehto J, Silva G, et al. European population substructure: clustering of northern and southern populations. PLoS Genet. 2006;2(9):e143.
26. Fung KW, Richesson R, Bodenreider O. Coverage of rare disease names in standard terminologies and implications for patients, providers, and research. AMIA Annu Symp Proc. 2014;2014:564–72.
27. Taruscio D, Vittozzi L, Rocchetti A, Torreri P, Ferrari L. The occurrence of 275 rare diseases and 47 rare disease groups in Italy. Results from the National Registry of Rare Diseases. Int J Environ Res Public Health. 2018;15(7):1470.
28. Government of Canada. Canadian Chronic Disease Surveillance System (CCDSS). 2024 [cited 2024 Mar 15]; Available from: https://health-infobase.canada.ca/ccdss/Index.
29. Groft SC, Posada de la Paz M. Rare diseases: joining mainstream research and treatment based on reliable epidemiological data. Adv Exp Med Biol. 2017;1031:3–21.
30. Pasquini TLS, Mesfin M, Schmitt J, Raskin J. Global registries in congenital hyperinsulinism. Front Endocrinol (Lausanne). 2022;13:876903.
31. Congenital Hyperinsulinism International. The HI Global Registry. 2024 [cited 2024 Mar 15]; Available from: https://congenitalhi.org/higlobalregistry/.

Figure Legends

Fig.1.: HI birth prevalence reported in available studies.

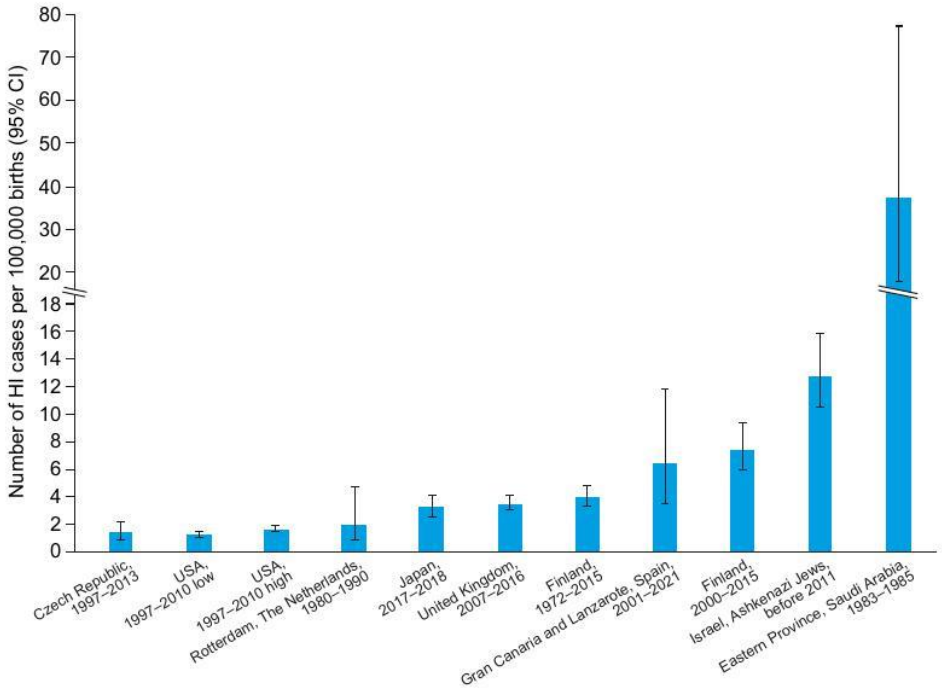

Table 1. Studies reporting HI incidence or prevalence data. The HI birth prevalence reported in this table was calculated based on the HI incidence or prevalence data and the total number of births reported in each article.

Article	Region, year	**HI birth prevalence** HI cases per 100,000 births (95% CI)	Note
Persistent HI (genetic or likely genetic) only			
Männistö et al., 2021 [16]	Finland, 1972–2015	3.9 (3.3–4.8)	–
	Finland, 2000–2015	7.4 (5.9–9.4)	–
Nóvoa-Medina et al., 2021 [18]	Gran Canaria and Lanzarote, Spain, 2001–2021	6.4 (3.5–11.8)	Special population or subpopulation
Yamada et al., 2020 [19]	Japan, 2017–2018	3.2 (2.5–4.1)	Incomplete ascertainment
Yau et al., 2020 [20]	United Kingdom, 2007–2016	3.5 (3.1–4.0)	–
Rozenkova et al., 2015 [21]	Czech Republic, 1997–2014	1.4 (0.9–2.1)	–
Snider et al., 2013* [22]	USA, 1997–2010	1.3 (1.0–1.5) to 1.6 (1.4–1.9)	Special population or subpopulation
Mathew et al., 1988 [23]	Eastern Province, Saudi Arabia, 1983–1985	37.4 (18.1–77.1)	Special population or subpopulation
Bruining et al., 1990 [24]	Rotterdam, The Netherlands, 1980–1990	2.0 (0.9–4.7)	Incomplete ascertainment
Transient (mostly acquired) and persistent (genetic or likely genetic) HI combined			
Männistö et al., 2021 [16]	Finland, 1972–2015	8.8 (7.8–10.0)	–
	Finland, 2000–2015	21.0 (18.3–24.2)	–
Yamada et al., 2020 [19]	Japan, 2017–2018	10.5 (9.1–12.1)	Incomplete ascertainment
Rozenkova et al., 2015 [21]	Czech Republic, 1997–2014	2.2 (1.6–3.1)	–
	Czech Republic, 2009–2014	4.1 (2.7–6.2)	–

CI, confidence interval; HI, congenital hyperinsulinism.

*Data from a specialized HI center in Philadelphia, USA. Opposed to other studies, this study reported a range for the prevalence.