Achondroplasia and Hypochondroplasia in France: a nationwide epidemiological analysis

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Introduction

- Achondroplasia (ACH) and hypohondroplasia (HCH) are among the most common forms of skeletal dysplasia, both caused by gain-of-function pathogenic variants in the fibroblast growth factor receptor 3 gene *(FGFR3)*, leading to inhibited endochondral bone development with disproportionate short stature[1]. While the birth prevalence of ACH has been previously described in Europe (3.72 per 100,000)[2] and worldwide (4.6 per 100,000)[3], it is not known whether these figures are applicable to France, given the significant rate of medical terminations of pregnancy due to achondroplasia in France and increased paternal age.[4]
  HCH birth prevalence remains poorly defined.

Objective

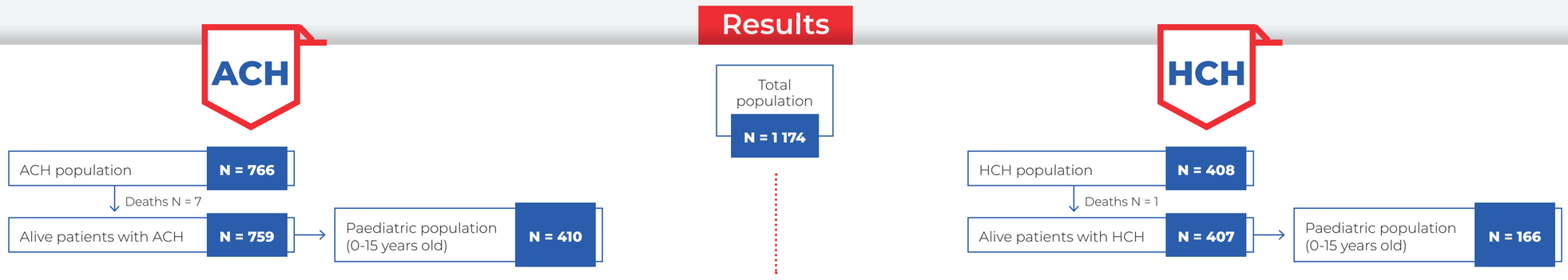
- To provide the first nationwide estimates of live birth prevalence for ACH and HCH in France.

Methods

This is a retrospective nationwide study

- **Data Source**
  The French National Registry of Rare Diseases (Banque Nationale de Données Maladies Rares, BNDMR) collects and centralizes medical data from all patients monitored within the rare disease expert network in France. Deidentification is ensured through the national rare disease identifier (Identifiant Maladie Rare, IdMR), a permanent 20-digit code that maintains patient privacy while enabling tracking across multiple centers. Generated from an exact match of surname, first name, date of birth, and sex.[5] Data cut-off date for the present study: Jan 1st, 2024.
- **Included Patients**
  All patients with ACH and HCH diagnosis (ORPHA codes: 15 & 429 respectively) included in BNDMR, and who consented to reuse their data. It should be noted that all prenatal diagnoses ending in termination of pregnancy (ToP) are not recorded in BNDMR; therefore, fetal cases were excluded.
- **Statistical Analysis**
  Due to an incomplete coverage of the BNDMR database observed before 2008, the live birth prevalence was estimated by determining the mean number of live births with ACH or HCH, divided by the total number of live births in France during the 2008–2023 period. The yearly number of live births in France was provided by INSEE.[6]

Results



DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

Table 1. Patients with ACH of all ages in France

	ACH patients (N = 766)
Alive, n	759
Deceased, n	7
Age, years	n = 756
Mean ±SD age	19.1 ± 14.5
Median age (IQR) (range)	15 (8–28) (0–85)
Sex, n (%)	N = 756
Male	334 (44.2)
Female	422 (55.8)
Timing of diagnosis, n (%)	N = 743
Prenatal	244 (32.8)
At birth	243 (32.7)
Postnatal	111 (14.9)
Indeterminate	145 (19.5)
Follow-up period, years	N = 759
Mean ±SD duration	9.0 ± 5.4
Median (IQR) duration (range)	9 (5–14) (0–28)

Disease inheritance pattern
Sporadic: 85.5%
Familial: 14.5%

It is to note that the percentage of ACH prenatal diagnosis here refers only to alive patients, since pregnancy interruptions are not systematically registered in BNDMR.

71.3% of ACH patients are under the care of constitutional bone diseases (MOC, maladies osseuses constitutionnelles) centers.

Disease inheritance pattern
Sporadic: 57.2%
Familial: 42.8%

HCH postnatal diagnosis occured more frequently than ACH, as it is well known that the body height growth curve in HCH starts to shift away from the expected height of the general population after the first year of life.

63.4% of HCH patients are under the care of constitutional bone diseases (MOC, maladies osseuses constitutionnelles) centers.

Table 2. Patients with HCH of all ages in France

	HCH patients (N = 408)
Alive, n	407
Deceased, n	1
Age, years	n = 407
Mean ±SD age	21.5 ± 14.9
Median age (IQR) (range)	18 (11–27) (0–80)
Sex, n (%)	N = 407
Male	194 (47.7)
Female	213 (52.3)
Timing of diagnosis, n (%)	N = 321
Prenatal	43 (13.4)
At birth	31 (9.7)
Postnatal	142 (44.2)
Indeterminate	105 (32.7)
Follow-up period, years	N = 406
Mean ±SD duration	9.7 ± 5.6
Median (IQR) duration (range)	9 (5–14) (0–31)

BIRTH PREVALENCE IN FRANCE

- ✓ Mean annual number of live births **with ACH** in France is **25.6** (median, 27; range, 14–33)
- ✓ Mean birth prevalence of ACH is **3.27 per 100,000 live births** (range, 1.90–4.03)

Figure 1

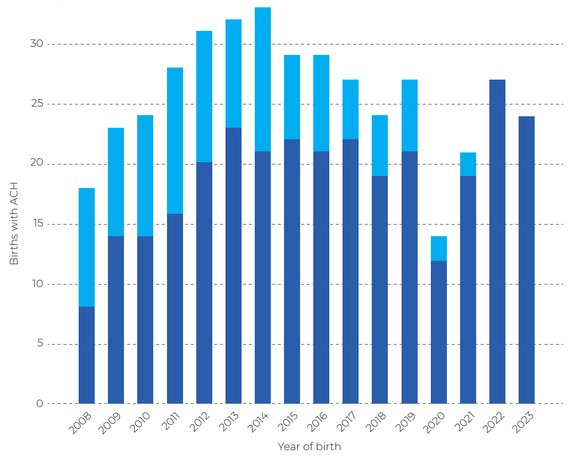


Table 4. Live births and live births with ACH in 2008-2023

Year	Number of live births in France*	Number of live births with ACH#	Prevalence of ACH per 100,000 live births
2008	898,404	18	2.00
2009	824,641	23	2.79
2010	832,799	24	2.88
2011	823,394	28	3.40
2012	821,047	31	3.78
2013	811,510	32	3.94
2014	818,565	33	4.03
2015	798,948	29	3.63
2016	783,640	29	3.70
2017	769,553	27	3.51
2018	758,590	24	3.16
2019	753,383	27	3.58
2020	735,196	14	1.90
2021	742,052	21	2.83
2022	725,997	27	3.72
2023	678,000	24	3.54

Fig 1. Number of paediatric patients (0–15 years) with ACH recorded in the BNDMR by year of birth
■ : Paediatric patients with at least one follow-up visit with the ACH expert recorded within the last two years
■ : Paediatric patients who have not had a follow-up visit recorded by the centre's leader within the last two years, but who are potentially being monitored by a ACH specialist at this centre without being registered with the BNDMR

Table 4. *As determined by INSEE. #Registered in the BNDMR

- ✓ Mean annual number of live births **with HCH** in France is **10.4** (median, 11; range, 4–16)
- ✓ Mean birth prevalence of HCH is **1.31 per 100,000 live births** (range, 0.59–2.08)

Figure 2

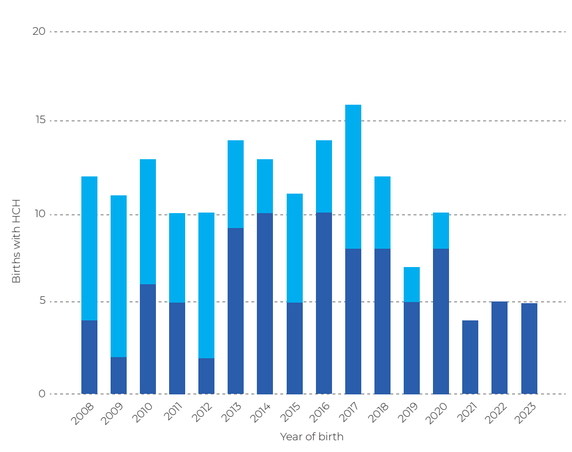


Table 5. Live births and live births with HCH in 2008-2023

Year	Number of live births in France*	Number of live births with HCH#	Prevalence of HCH per 100,000 live births
2008	898,404	12	1.34
2009	824,641	11	1.33
2010	832,799	13	1.56
2011	823,394	10	1.21
2012	821,047	10	1.22
2013	811,510	14	1.73
2014	818,565	13	1.59
2015	798,948	11	1.38
2016	783,640	14	1.79
2017	769,553	16	2.08
2018	758,590	12	1.58
2019	753,383	< 10	0.93
2020	735,196	10	1.36
2021	742,052	< 10	0.54
2022	725,997	< 10	0.60
2023	678,000	< 10	0.59

Fig 2. Number of paediatric patients (0–15 years) with HCH recorded in the BNDMR by year of birth
■ : Paediatric patients with at least one follow-up visit with the HCH expert recorded within the last two years
■ : Paediatric patients who have not had a follow-up visit recorded by the centre's leader within the last two years, but who are potentially being monitored by a HCH specialist at this centre without being registered with the BNDMR

Table 5. *As determined by INSEE. #Registered in the BNDMR

These numbers refer to patients seeking care for their condition in an expert center

Conclusions

- Leveraging data from the national rare diseases database BNDMR, this study provides the first birth prevalence estimates for ACH (3.27 per 100,000) and HCH (1.31 per 100,000) in France, addressing an important gap in the literature. The birth prevalence of ACH observed in our study aligns with that of previous European (3.72 per 100,000)[2] and worldwide (4.6 per 100,000)[3] populations.
- Diagnosis of ACH is often supported by prenatal monitoring and early referral to expert centers. In contrast, HCH is more frequently diagnosed postnatally and may remain underdiagnosed in milder cases. Future efforts should focus on improving early recognition of HCH through increased awareness among healthcare providers and broader access to genetic testing.
- Moreover, given the availability of targeted therapy for ACH and the anticipated development of treatments for HCH, it is increasingly important to strengthen regular care pathways within expert specialized centers, ensuring timely and equitable access to accurate information and appropriate interventions.

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Disclosures

GB declares competing interests for advisory consultancy and expert report production for BioMarin, QED, Ascendis and Tyra; participation in scientific work for Incyte, Ipsen, QED, Ascendis, BioMarin, Alexion, Clementia, and Therachon Pfizer; and writing articles and interventions for Elsevier, BioMarin, Ipsen, and Alexion. MAH is a BioMarin employee and has stock options. ASJ and PK have no conflicts of interest to declare. VCD declares competing interests related to advisory consultancy or interventions for BioMarin and QED.

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