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Comorbidity and mortality burden among patients with hypochondroplasia in England between 1998–2019

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Introduction

- Hypochondroplasia (HCH) is a genetic growth-related condition resulting in disproportionate short stature
- The natural history of this rare skeletal dysplasia is poorly described, and the few available studies are small and predominantly limited to paediatric patients
- This study aims to describe the natural history of HCH compared with the general population, using data from a large cohort of children and adults in England

Methods

Study design
- Retrospective matched cohort study

Data source
- General practice-based, electronic medical record (EMR) database (CPRD Aurum) linked to hospitalisation (HES APC) and vital statistics data in England from 1998 to 2019

HCH cohort
- Defined by specific HCH SNOMED code or ICD-10 code Q77.4*
- Excluded any patient with codes for specified GSS conditions, including ACH

Control cohort
- Defined as those not in HCH cohort and without other growth-related conditions, including GSS

Patient matching
- Matched 1:4 to controls by sex, nearest birth year, and GP region
- Index date was first HCH record

*If first ICD-10 code was after ≥2 years of age and height not within 5–95th percentile of ACH growth curve[1]
ACH, achondroplasia; APC, Admitted Patient Care; CPRD, Clinical Practice Research Datalink; GSS, genetic short stature; HES, Hospital Episode Statistics; ICD-10, International Classification of Diseases, Tenth Revision; SNOMED, Systemized Nomenclature of Medicine

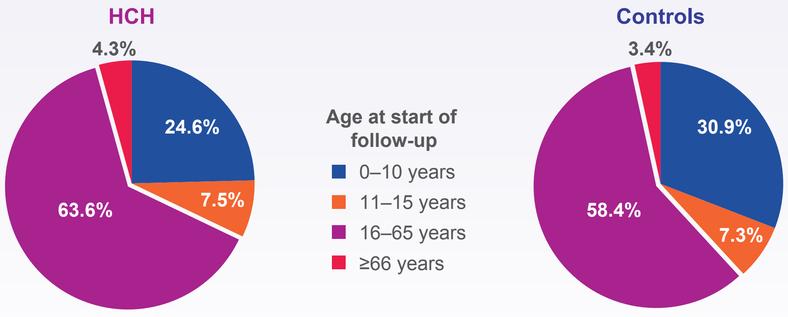
- Event rates (ERs) (number of events/100 person-years) with 95% confidence intervals (CIs) were calculated for all outcomes for patients with HCH and controls
- Matched rate ratios (RRs) with 95% CIs were calculated for selected comorbidities, healthcare use, and mortality to compare ER_{HCH} vs $ER_{Controls}$

Results

Demographics of HCH and matched controls cohorts

HCH (N=610)
- **7.4 (7.1) years***
  Mean (SD) follow-up time
- **50.0%** Female
- **85.3%** White

Controls (N=2440)
- **12.0 (7.3) years***
  Mean (SD) follow-up time
- **50.0%** Female
- **76.2%** White



*Total person-years=4520.9 (HCH) and 29,309.8 (controls)

- **335/610 (54.9%)** patients had a specific SNOMED code for HCH
- Approximately 60% of the overall study population were aged ≥16 years at index; mean age at first HCH code was 28 years among patients with HCH
- The overall population was broadly distributed throughout England

Strengths and limitations

- This study represents the largest HCH cohort to date and includes both paediatric and adult patients
- The use of robust and nationally representative EMR data and the matched cohort design allowed findings to be compared with those without the condition in England
- Height data for patients with HCH in this study were comparable to European HCH growth data[3], confirming that the cohort falls within the expected HCH height range (data not shown)
- Although healthcare professionals reviewed the selected medical codes, patients with HCH were identified based on medical codes with no additional clinical verification or genetic data available for confirmation of diagnosis
- The cross-sectional design within a 20-year study period did not account for secular changes in patient management
- Although this was a matched study, we were unable to completely control for differences in the age structure between groups, which may have contributed to some of the observed differences in burden between patients with HCH and controls

References

1. Hoover-Fong JE et al. *Orphanet J Rare Dis*. 2021;16(1):522. 2. Pimenta JM et al. *Orphanet J Rare Dis*. 2023;18(1):211.
3. Cheung MS et al. *Am J Med Genet A*. 2024;194(2):243-252.

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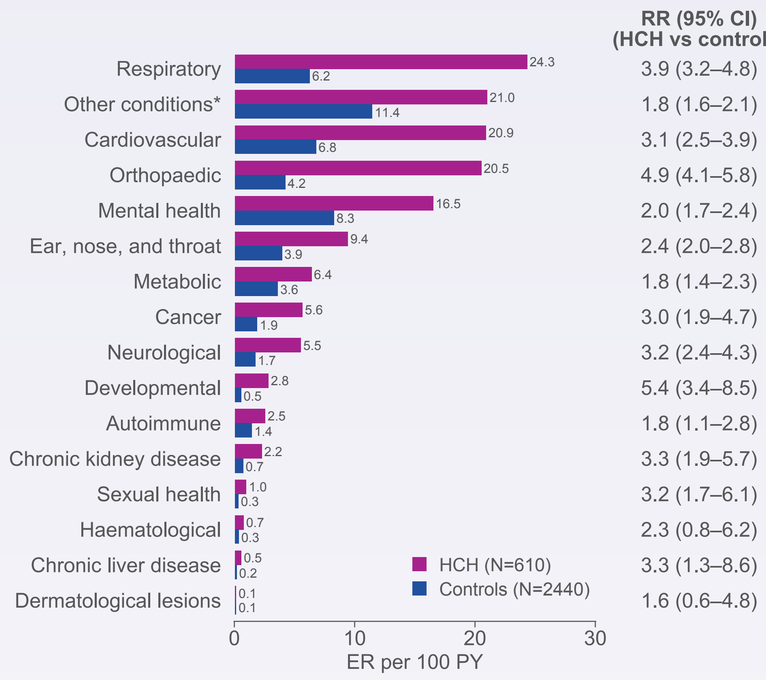
Comorbidity event rate by body system

- Considering all pre-defined comorbidities, patients with HCH (all ages) experienced nearly triple the ER compared with controls (RR=2.7, 95% CI 2.6–2.9)
- Respiratory, cardiovascular, orthopaedic, and mental health-related events were most frequent among patients with HCH of all ages
- Among patients with HCH aged <16 years, ear, nose, and throat, respiratory, orthopaedic, and neurological events were most common (ER=14.9, 13.7, 5.5, 5.1; RR=2.3, 2.2, 1.9, 9.8; respectively, all statistically significant, data not displayed)



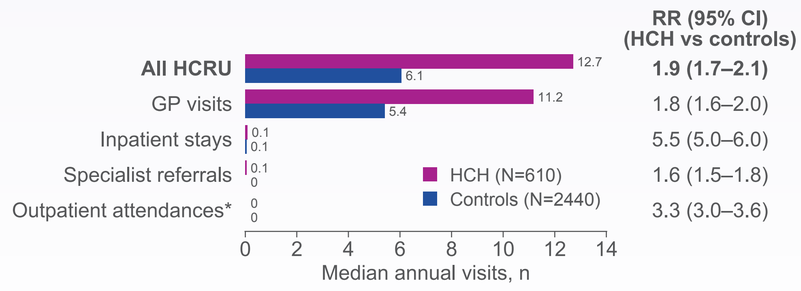
Notes: ER reported as the number of unique comorbidity episodes per 100 PY. Only the first occurring event within a 30-day period was counted to avoid over-counting events from the same episode
**"Other conditions" category includes congenital renal anomalies and hydronephrosis, gastroesophageal reflux disease, headache, hypothyroidism, lymphatic dysplasia, musculoskeletal pain, other thyroid conditions, and urinary tract infections
PY, person-years

Surgical burden

- Overall, patients with HCH reported higher rates of surgeries than controls (RR [95% CI]=5.3 [3.9–7.2]), which was largely driven by respiratory, orthopaedic, and ear, nose, and throat surgeries
- RRs (95% CI) were 9.7 (3.6–26.2) for limb surgery, 6.3 (3.2–12.7) for joint replacement, 4.2 (1.8–9.8) for hearing implants, 3.2 (0.8–13.5) for spinal surgery, and 2.4 (1.3–4.2) for tonsillectomy/adenoidectomy

Healthcare visits

- Patients with HCH had a higher number of annual GP visits compared with controls (median **11.2** vs **5.4**), with an RR (95% CI) of 1.8 (1.6–2.0)
- This increased rate extended to less common visit types, including inpatient hospitalisations (RR=5.5, 95% CI 5.0–6.0), with longer average duration of hospital stays (**5.6** vs **3.8** days) seen in patients with HCH



Note: Annual visits calculated for 1998–2019
*Outpatient attendances refer to attendances at a hospital outpatient department clinic
GP, general practice; HCRU, healthcare resource utilisation

Mortality by age

- Patients with HCH, mostly adults, showed higher mortality rates compared with controls, similar to rates seen in achondroplasia[2]
- Mortality rates were comparable by sex
- Cardiovascular and respiratory diseases were the most common causes of death among patients with HCH; cardiovascular and oncological diseases were the most common among controls

	Patients with HCH (N=610)	Controls (N=2440)
ER (95% CI) per 100 PY	0.8 (0.5–1.1)	0.2 (0.2–0.3)
RR (95% CI)	3.4 (1.9–6.3)	
Age group	**Number of deaths**	
0–15 years	<5*	0
16–65 years	16	19
≥66 years	15	45

*Small event numbers are reported as <5 due to CPRD reporting requirements
PY, person-years

Conclusions

- This retrospective study, composed of mainly adult patients, demonstrated that patients with HCH experienced higher rates of both skeletal and non-skeletal comorbidity events than controls across the age spectrum
- The use of general practice-based EMR data allowed for a holistic assessment of medical impact and was not limited to the specialist care setting
- New insights into mortality risk, predominantly in adults, were shown, and further understanding of the underlying mechanism is warranted
- These results underscore the need for coordinated and multidisciplinary management in HCH starting in early life

Disclosures

- JMP and SM are employees of BioMarin; SRR and JS were contracted by BioMarin to work on this study; HS and RW are employees of CPRD; MC has received consulting fees from Ascendis Pharma, BioMarin, and Tyra Biosciences; MI has received honoraria from BioMarin for speaking, for participating in advisory board meetings, and as a member of the vosoritide experts steering committee.
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