

Higher rates of non-skeletal complications in achondroplasia compared to the general population: a UK matched cohort study using the CPRD database

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Background

- Achondroplasia (ACH) is a rare, genetic skeletal dysplasia, resulting in impaired endochondral bone growth.
- We estimated rates of non-skeletal complications in patients with ACH compared with general population controls.

Methods

- Matched retrospective cohort study using UK Clinical Practice Research Datalink (CPRD-GOLD).
- Study index date was first ACH record within study period of 01/01/1987 - 31/12/2018.
- Control patients defined as those without evidence of skeletal/growth disorders.
- ACH cases index date matched (1:4) by age, sex, general practitioner (practice-level) and linkage ability to Hospital Episode Statistics database.
- ACH cases, controls and complications defined using READ codes.
- Incidence rates per 100 person-year (PY) calculated overall and by age-group; rate ratios (RR) and 95% confidence intervals (CI), accounting for matching, used to compare between cohorts.
- Since ACH is a skeletal disorder, orthopaedic complications included as a 'positive control', as would expect higher rates in ACH cases compared to control, thereby validating study methods.

Results

- We identified 541 cases and 2,052 matched controls (Table 1).

Table 1: Demographics of ACH cases and controls

	ACH cases (N=541) ¹ n, %	Controls (N=2,052) ¹ n, %
Gender		
Female	264 (49)	1001 (49)
Male	277 (51)	1051 (51)
Country		
England	366 (68)	1,394 (68)
N. Ireland	13 (2)	50 (2)
Scotland	87 (16)	332 (16)
Wales	75 (14)	276 (14)
Age²		
0-10 years	148 (27)	558 (27)
11-17 years	32 (6)	120 (6)
18-59 years	305 (56)	1,159 (56)
60+ years	56 (10)	215 (10)
Median (Q1-Q3)	29 (9-43)	29 (9-44)

¹ Mean (SD) follow-up time in primary care was 9.0 years (6.9) in cases and 11.7 years (7.0) in controls
² Age at start of analysis period

- As expected, rate ratios of orthopaedic complications were significantly higher among ACH cases than controls (RR = 4.01 (3.17-5.07), ranging between 14.39 (5.45-37.99) for leg deformities including genu varum to 30.52 (16.28-57.19) for spinal stenosis / cord compression.
- Among all body systems, except cardiovascular, rate ratios of all non-skeletal complications were significantly higher among ACH cases compared to controls (Table 2).

Table 2: Rate ratios (95% CI) for non-skeletal complications

Body system	Rate Ratio, RR (95% CIs)	Specific complications		
		Statistically significantly higher RR in ACH compared to controls	No difference in RR between ACH cases and controls	Condition included in body system but <5 events ¹
Any Non-skeletal	1.80 (1.58-2.04)			
Developmental	8.84 (4.18-18.72)	Developmental delay 8.80 (3.02-25.68) Speech delay 7.61 (3.03-19.13)	--	Motor delay
Neurological	7.56 (4.24-13.50)	Seizures 4.01 (1.52-10.58) Hydrocephalus/ventriculomegaly Cases only	Dementia	Craniocervical stenosis Failure to thrive Subdural haematoma
Respiratory	4.15 (2.51-6.88)	Apnoea/sleep disordered breathing 25.81 (10.0-66.60)	Sleep disorder	--
ENT	2.98 (2.43-3.65)	Enlarged tonsils 3.34 (1.26-8.86) Hearing loss/deafness 3.50 (2.50-4.89) Otitis media 3.11 (2.45-3.94)	Sinusitis Voice abnormality	Middle ear dysfunction Tracheomalacia Bronchomalacia
Metabolic	1.65 (1.24-2.18)	Obesity 2.59 (2.26-2.97)	Diabetes Hyperlipidaemia	--
Mental Health	1.62 (1.21-2.17)	ADD/ADHD/adjustment disorder 3.44 (1.13-10.51) Depression/anxiety 1.51 (1.09-2.08) Self-harm/suicidal ideation 3.71 (1.17-11.77)	Substance abuse	'Other' mental health
Cardiovascular	1.17 (0.92-1.49)	--	Chest pain/angina Coronary disease Hypertension Myocardial infarction Stroke	--
Other	1.76 (1.52-2.03)	Gastrointestinal issues 1.66 (1.31-2.09) Pain-musculoskeletal 1.84 (1.58-2.15)	Headache Sexual health / gynaecological issues	--

¹ Due to database requirements, data for cases or controls which have less than 5 events are not permitted to be reported

- Complications differed by age when compared to controls:
 - Among <18 years, rate ratios for developmental delay, enlarged tonsils and headaches were higher in ACH patients. Among ≥ 18 years, rate ratios for depression/anxiety and seizures were higher in ACH patients. Regardless of age group, hearing loss, otitis media, obesity, gastrointestinal issues and musculoskeletal pain were higher in ACH patients.

Conclusions

- This study is the first to assess complications in ACH compared to an appropriate matched general population control group.
- We demonstrate that in addition to skeletal conditions, ACH patients have significantly more non-skeletal multisystemic complications compared to the general population which are present throughout the lifespan.