

# 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) <sup>1</sup> n, %	Controls (N=2,052) <sup>1</sup> n, %
<b>Gender</b>		
Female	264 (49)	1001 (49)
Male	277 (51)	1051 (51)
<b>Country</b>		
England	366 (68)	1,394 (68)
N. Ireland	13 (2)	50 (2)
Scotland	87 (16)	332 (16)
Wales	75 (14)	276 (14)
<b>Age<sup>2</sup></b>		
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)

<sup>1</sup> Mean (SD) follow-up time in primary care was 9.0 years (6.9) in cases and 11.7 years (7.0) in controls  
<sup>2</sup> 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 <sup>1</sup>
<b>Any Non-skeletal</b>	<b>1.80 (1.58-2.04)</b>			
<b>Developmental</b>	8.84 (4.18-18.72)	Developmental delay Speech delay	8.80 (3.02-25.68) 7.61 (3.03-19.13)	-- Motor delay
<b>Neurological</b>	7.56 (4.24-13.50)	Seizures Hydrocephalus/ventriculomegaly	4.01 (1.52-10.58) Cases only	Dementia Craniocervical stenosis Failure to thrive Subdural haematoma
<b>Respiratory</b>	4.15 (2.51-6.88)	Apnoea/sleep disordered breathing	25.81 (10.0-66.60)	Sleep disorder --
<b>ENT</b>	2.98 (2.43-3.65)	Enlarged tonsils Hearing loss/deafness Otitis media	3.34 (1.26-8.86) 3.50 (2.50-4.89) 3.11 (2.45-3.94)	Sinusitis Voice abnormality Middle ear dysfunction Tracheomalacia Bronchomalacia
<b>Metabolic</b>	1.65 (1.24-2.18)	Obesity	2.59 (2.26-2.97)	Diabetes Hyperlipidaemia --
<b>Mental Health</b>	1.62 (1.21-2.17)	ADD/ADHD/adjustment disorder Depression/anxiety Self-harm/suicidal ideation	3.44 (1.13-10.51) 1.51 (1.09-2.08) 3.71 (1.17-11.77)	Substance abuse 'Other' mental health
<b>Cardiovascular</b>	1.17 (0.92-1.49)	--	--	Chest pain/angina Coronary disease Hypertension Myocardial infarction Stroke --
<b>Other</b>	1.76 (1.52-2.03)	Gastrointestinal issues Pain-musculoskeletal	1.66 (1.31-2.09) 1.84 (1.58-2.15)	Headache Sexual health / gynaecological issues --

<sup>1</sup> 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.**