Long-term mortality after childhood growth hormone treatment: the SAGhE cohort study

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Summary

Background Recombinant human growth hormone has been used for more than 30 years and its indications have increased worldwide. There is concern that this treatment might increase mortality, but published data are scarce. We present data from the entire dataset of all eight countries of the Safety and Appropriateness of Growth hormone treatments in Europe (SAGhE) consortium, with the aim of studying long-term overall and cause-specific mortality in young adult patients treated with recombinant human growth hormone during childhood and relating this to the underlying diagnosis.

Methods This cohort study was done in eight European countries (Belgium, France, Germany, Italy, The Netherlands, Sweden, Switzerland, and the UK). Patients were classified a priori based on pre-treatment perceived mortality risk from their underlying disease and followed up for cause-specific mortality. Person-years at risk of mortality and expected rates from general population data were used to calculate standardised mortality ratios (SMRs).

Findings The cohort comprised 24 232 patients treated with recombinant human growth hormone during childhood, with more than 400 000 patient-years of follow-up. In low-risk patients with isolated growth hormone deficiency or idiopathic short stature, all-cause mortality was not significantly increased (SMR 1·1, 95% CI 0·9–1·3). In children born small for gestational age, all-cause mortality was significantly increased when analysed for all countries (SMR 1·5, CI 1·1–1·9), but this result was driven by the French subcohort. In patients at moderate or high risk, mortality was increased (SMR 3·8, 3·3–4·4; and 17·1, 15·6–18·7, respectively). Mortality was not associated with mean daily or cumulative doses of recombinant human growth hormone for any of the risk groups. Cause-specific mortality from diseases of the circulatory and haematological systems was increased in all risk groups.

Interpretation In this cohort, the largest, to our knowledge, with long-term follow-up of patients treated with recombinant human growth hormone during childhood, all-cause mortality was associated with underlying diagnosis. In patients with isolated growth hormone deficiency or idiopathic short stature, recombinant human growth hormone treatment was not associated with increased all-cause mortality. However, mortality from certain causes was increased, emphasising the need for further long-term surveillance.

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Introduction

Recombinant human growth hormone has been used for more than three decades and its indications have expanded worldwide, including growth hormone deficiency and many other causes of short stature. The overall results from many thousands of patient-years of treatment suggest that recombinant human growth hormone is safe.[1] Nevertheless, a systematic review and meta-analysis of articles published up to September, 2013, showed a slight but significant increase in all-cause mortality in patients treated with recombinant human growth hormone in childhood and adolescence.[2]

Unfortunately, most knowledge regarding recombinant human growth hormone safety is based on cohort studies with short follow-up of adverse events within databases kept by pharmaceutical companies. To overcome these limitations and study the long-term safety of recombinant human growth hormone therapy, we set up a European consortium (Safety and Appropriateness of Growth hormone treatments in Europe [SAGhE]) that involved eight countries (Belgium, France, Germany, Italy, The Netherlands, Sweden, Switzerland, and the UK) and merged datasets on around 24 000 young adults treated with recombinant human growth hormone during childhood and adolescence.[3]

Two preliminary reports, based on a subset of local datasets within SAGhE, presented mortality data in young adult patients treated with recombinant human growth hormone during childhood for isolated idiopathic growth hormone deficiency, small for gestational age, or idiopathic short stature.[4,5] A French study[4] reported a significant increase in all-cause mortality and

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Research in context

Evidence before this study

In 2012, a preliminary report on mortality risk in patients previously treated with recombinant human growth hormone from the French SAGhE cohort raised substantial concerns about the long-term safety of this treatment. Previous reports from multiple post-marketing surveillance studies presented reassuring short-term on-treatment safety data in patients treated with recombinant human growth hormone. However, few previous studies have investigated long-term mortality in patients treated with recombinant human growth hormone during childhood.

We searched PubMed for articles published up to April 30, 2020, with no language restrictions, using the search terms "long-term mortality", "growth hormone", and "childhood". We did not identify any studies before 2012, when the preliminary reports from the SAGhE cohort were published, and thereafter found only one relevant study from Israel published in 2016. Patients in this study were risk classified with similar criteria as the SAGhE cohort, compared with the general Israeli population and the results showed no increased standardised mortality ratio (SMR) for all-cause mortality in low-risk patients (SMR 0·81, 95% CI 0·22–2·08) and increased SMR for intermediate-risk patients (4·05, 95% CI 1·62–8·34). However, the study had several limitations, including no information about treatment duration or dosage used, mean follow-up time of less than 10 years for the low-risk patients, and restricted statistical power shown by the wide CIs.

Added value of this study

To our knowledge, this is the first large population-based cohort study of patients treated with recombinant human growth hormone in childhood to report overall and cause-specific mortality data from all eight participating SAGhE countries, with more than 400 000 patient-years and up to 25 years of follow-up. All-cause mortality was associated with the underlying diagnosis and not significantly associated with increased mean or cumulative recombinant human growth hormone dose. In patients with isolated growth hormone deficiency or idiopathic short stature, recombinant human growth hormone treatment was not associated with significantly increased all-cause mortality. However, mortality from certain causes was increased.

Implications of all the available evidence

Our large long-term study builds upon earlier published data from post-marketing surveillance studies that suggested no significant effect of childhood recombinant human growth hormone treatment on overall mortality in patients with isolated growth hormone deficiency or idiopathic short stature. For patients with an inherent increased mortality risk, our study noted increased mortality rates probably related to the underlying diagnosis. Although our data are reassuring, we recommend continued long-term surveillance of patients treated with recombinant human growth hormone in childhood to allow detection of any increased risks in later life.

cause-specific mortality for bone tumours and cerebral haemorrhage in 6500 patients, whereas an analysis[5] from Sweden, The Netherlands, and Belgium identified no deaths from cancer or cerebrovascular disease among 2500 patients.

The current study presents data from the entire dataset of all eight countries of the SAGhE consortium. Our main objective was to study long-term overall and cause-specific mortality in young adult patients treated with recombinant human growth hormone during childhood and relate this to the underlying diagnosis. Secondary objectives included analyses of dose–response, mean and cumulative recombinant human growth hormone dose, effect of time since end of recombinant human growth hormone treatment, and duration of recombinant human growth hormone treatment.

Methods

Study design and participants

This cohort study was done in eight European countries (Belgium, France, Germany, Italy, The Netherlands, Sweden, Switzerland, and the UK), as described previously.[3] Briefly, in each country, we attempted to identify all resident patients who were born before 1991–95 (depending on the country), who had been treated with recombinant human growth hormone during childhood from the time such treatment was first introduced (1984–86), irrespective of treatment duration, at any time up to a date during 2007–09 (or in France and Sweden up to 1997), and who had never been treated with human pituitary growth hormone.

In each country, appropriate ethics committee agreement was obtained. For all patients, either written informed consent was obtained, or an ethics committee agreed that consent was not required. The study complies with the ethical principles laid out in the Declaration of Helsinki.

Data on demographic and growth hormone-related variables were extracted from existing databases and case notes. We followed up participants for mortality via national population-based registries in Belgium, The Netherlands, Sweden, and the UK, and by a range of methods in the other four countries.[3] Mortality was followed up from the earliest recombinant human growth hormone treatment date (except Italy, Jan 1, 1999, or earliest recombinant human growth hormone treatment date if later) until a censoring date that varied between countries (between Sept 21, 2009, and Dec 31, 2013). Cause of death was retrieved from national sources in France (Certification électronique des causes de décès), Belgium (Federal and Regional death

registries), and Sweden (Swedish Death Causality Registry), from individual death certificates in Italy, Switzerland, and the UK, or from medical records and questionnaires in Germany and medical records in The Netherlands. Information was missing regarding the specific cause of death for a few cases, as reflected by a slightly lower number of patient-years in those analyses (appendix pp 3, 5, 11, 13, 15, 17).

As reported previously,[3] follow-up for mortality was 96·7% complete, excluding Italy, where information on completeness was not available. Cause-specific mortality data and population counts for the general population were obtained to derive expected mortality from national mortality statistics. Cancer mortality has previously been reported for this cohort.[6]

Risk group classification

Certain diagnoses leading to growth hormone treatment are known to be associated with increased mortality, which complicates analyses in a mixed cohort with underlying diagnoses that ranges from healthy individuals with idiopathic short stature to patients with a brain tumour or chronic renal failure diagnosed before treatment start. To overcome this problem, we categorised all patients a priori into three risk groups based on their diagnosis leading to growth hormone treatment. If a patient had several diagnoses, categorisation was based on the diagnoses belonging to the highest risk group.

The details of the risk classification have been described previously,[3] and we recorded the distribution of patients by country (panel; table 1). Risk group 1 was further subdivided into patients treated for isolated growth hormone deficiency or idiopathic short stature (group 1a) and short stature in children born small for gestational age (group 1b; birthweight or length less than two SDs below the mean according to the different national references).[7] Risk group 2 included treated patients with multiple pituitary hormone deficiencies (growth hormone and at least one additional pituitary hormone deficiency), clinically defined syndromes (such as Turner syndrome, Noonan syndrome, neurofibromatosis type 1, and Prader-Willi syndrome) known to be associated with an increased risk of mortality, benign pituitary tumours, severe craniofacial or other malformations, and severe paediatric chronic diseases. Risk group 3 included patients who had been treated for cancer, craniopharyngioma, and chronic renal failure.

Statistical analysis

We calculated person-years at risk of death for each patient by sex, 5-year age-group, single calendar year, and country, starting from the date of first treatment with recombinant human growth hormone and ending at death, loss to follow-up, or a fixed end date for each country as previously detailed, whichever occurred earliest.[3] Analyses were further stratified by different timescales and growth hormone dosing categories (table 2; appendix pp 2–17). The mean daily dose of recombinant human growth hormone was calculated from data retrieved at each clinic visit. Time-dependent variables (time since treatment and cumulative dose) were analysed in a time-dependent manner—person-years and events for each participant were split and allocated to the level of the variable the participant belonged to at each point in follow-up, so that they contributed to different levels of the variable as they

***Panel:* Classification of patients**

Risk group 1a*
- Isolated growth hormone deficiency
- Idiopathic short stature
- Mild skeletal dysplasia (hypochondroplasia or dyschondrosteosis)

Risk group 1b†
- Short stature in children born small for gestational age

Risk group 2
- Multiple pituitary hormone deficiency
- Severe cerebral malformation
- Short stature and severe extracerebral malformations
- Clinically defined syndromes, eg, Turner Syndrome, Noonan syndrome, neurofibromatosis type 1, and Prader-Willi syndrome
- Severe chronic paediatric diseases
- Long-term steroid use in chronic inflammatory diseases
- Benign pituitary tumours
- Cushing's syndrome

Risk group 3‡
- All malignancies
- Langerhans cell histiocytosis
- Chronic renal failure
- After bone marrow or solid transplantation
- Syndromes with known increased risk for malignancies, eg, Bloom syndrome, Fanconi syndrome, Down syndrome, and chromosomal breakage syndrome

For a more detailed description of the risk classifications, see Swerdlow et al.[3] *Also when associated with minor childhood diseases such as asthma. †Excludes defined syndromes such as Silver-Russell syndrome. ‡Patients are assigned to this risk group irrespective of their endocrine deficiency (severe *vs* non severe growth hormone deficiency, isolated *vs* multiple).

See Online for appendix

	1a	1b	2	3	Not classified	Total
Belgium	336	168	607	271	0	1382
Switzerland	293	76	257	120	5	751
France	5043	1823	2180	1245	25	10 316
Germany	789	168	644	178	5	1784
Italy	980	143	167	54	20	1364
Netherlands	434	210	782	320	22	1768
Sweden	953	623	852	338	199	2965
UK	462	644	1699	1061	36	3902
Total	9290	3855	7188	3587	312	24 232

***Table 1:* Number of patients by country and risk group**

progressed. The cumulative dose was calculated by multiplying the mean daily dose by the total number of treatment days. National population rates were used to calculate standardised mortality ratios (SMRs) and trends tested by the Poisson trend statistic.[8] Absolute excess rates were calculated by subtracting expected from observed numbers of cases, dividing by person-years at risk, and multiplying by 10 000.

Main outcome analyses included long-term overall and cause-specific mortality related to the underlying diagnosis. Conclusions about treatment effect were based on the CIs reported. Subanalyses included effects of mean and cumulative doses of recombinant human growth hormone, the effect of time since end of treatment, and duration of treatment. Subanalyses were also done to stratify data into France, and all other countries, to explore any country bias linked to the high proportion of patients from France. Another subanalysis was done in which the risk was recalculated once patients had ceased recombinant human growth hormone treatment for a period longer than 2 years because an adverse event, irrespective of causality, can often lead to treatment termination.[9] All p values are 2-sided and a value of less than 0·05 was considered statistically significant.

We used Stata/IC version 14.2 for statistical analyses.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The cohort comprised 24 232 patients. 13 145 (54·2%) were classified as low risk (groups 1a and 1b), 7188 (29·7%) as moderate risk (group 2), 3587 (14·8%) as high risk (group 3), and 312 (1·3%) were not classifiable. Patient characteristics by risk group are reported in table 3. There was a male predominance except in risk group 2, which included patients with Turner syndrome. Between risk groups there were small differences in age at treatment start and treatment duration. The mean dose of recombinant human growth hormone was lower in risk groups 1a and 3, than in risk groups 1b and 2. 10 316 patients (42·6%) came from France and 13 916 (57·4%) from the other seven countries (table 1).

For patients in the low risk group 1a, overall mortality was not significantly increased (SMR 1·1, 95% CI 0·9–1·3; table 2). When analysed separately, this result held for both France (1·1, 0·9–1·4; appendix p 6) and the other seven countries (1·0, 0·7–1·4; appendix p 10). The mean daily dose of recombinant human growth hormone and the cumulative dose of recombinant human growth hormone did not affect mortality in risk group 1a (table 2). The highest SMR was observed with a treatment duration less than 2 years (1·6, 1·1–2·3) and those with the shortest time since end of treatment (<1 year; 3·3, 1·8–5·7; table 2). However, in the analysis with a 2-year lag period after the end of recombinant human growth hormone treatment, the SMR was no longer significant with treatment duration less than 2 years (1·2, 0·8–2·0; appendix p 14).

For patients belonging to risk group 1b, overall mortality was significantly increased when analysed for all countries (SMR 1·5, 95% CI 1·1–1·9; table 2). When analysed separately, risk was significantly increased in France (1·7, 1·2–2·4; appendix p 6), but not significantly in the other seven countries combined (1·2, 0·8–1·9; appendix p 10). For cumulative dose of recombinant human growth hormone and mean daily dose, we found no association with increased mortality in risk group 1b, but for the highest mean daily dose category a SMR of 2·7 (95% CI 1·4–5·4) was noted (table 2). Time since start of recombinant human growth hormone treatment was not associated with mortality in risk group 1b, but we observed an increased risk in the early years after end of treatment (table 2).

For patients in risk groups 2 and 3, overall mortality was markedly increased (SMR 3·8, 95% CI 3·3–4·4 and 17·1, 15·6–18·7, respectively; table 2) and when analysed separately, the risk was similar in France (appendix p 8) and the other seven countries combined (appendix p 12). SMR in these groups did not relate to daily dose or cumulative dose of growth hormone and decreased with longer duration of treatment. All-cause mortality was increased for patients with several individual underlying diagnoses in risk groups 2 and 3 (appendix p 1). We observed the highest mortality in patients with tumour diagnoses before treatment start, and mortality was greatest for patients with a pre-existing CNS tumour (SMR 23·6, 95% CI 21·0–26·6; appendix p 1). In risk group 3, we observed a higher SMR in women (33·2, 28·8–38·3) than in men (12·7, 11·2–14·3; table 2), but this difference decreased notably when comparing absolute excess rates (83·7, 95% CI 71·9–96·9 and 73·4, 64·1–83·6 for women and men, respectively; appendix p 4).

Cause-specific mortality is reported in table 4. Although accidents and violence were the most common individual cause of death for risk groups 1a and 1b, the mortality rate from this cause was not significantly increased compared with that in the general population. Mortality from neoplasms was also not increased for risk groups 1a and 1b (SMR 0·9, 95% CI 0·4–1·8 and 0·6, 0·1–2·4, respectively). By contrast, mortality from diseases in blood and blood-forming organs was significantly increased for risk group 1a (8·2, 2·6–25·4). Mortality from diseases of the circulatory system was significantly increased for both groups 1a and 1b (2·4, 1·2–4·6 and 3·7, 1·7–8·3, respectively), and the risk for 1b was mostly driven by the French subcohort. Within the circulatory system, mortality due to cerebrovascular disease was significantly increased for risk group 1a (4·7, 1·8–12·5), and the risk of circulatory diseases other than ischaemic heart disease and

	Risk group 1a				Risk group 1b				Risk group 2				Risk group 3			
	Obs	Exp	SMR (95% CI)	p_{trend}	Obs	Exp	SMR (95% CI)	p_{trend}	Obs	Exp	SMR (95% CI)	p_{trend}	Obs	Exp	SMR (95% CI)	p_{trend}
Overall	90	84·2	1·1 (0·9–1·3)	..	49	33·5	1·5 (1·1–1·9)	..	192	50·0	3·8 (3·3–4·4)	..	456	26·7	17·1 (15·6–18·7)	..
Sex																
Male	76	70·8	1·1 (0·9–1·3)	..	40	26·6	1·5 (1·1–2·0)	..	88	26·0	3·4 (2·7–4·2)	..	266	21·0	12·7 (11·2–14·3)	..
Female	14	13·4	1·0 (0·6–1·8)	..	9	6·9	1·3 (0·7–2·5)	..	104	24·0	4·3 (3·6–5·3)	..	190	5·7	33·2 (28·8–38·3)	..
Time since start of treatment (years)	..	..	..	0·051	..	..	..	0·38	..	..	..	0·042	..	..	..	<0·0001
0–4	15	19·3	0·8 (0·5–1·3)	..	10	8·3	1·2 (0·6–2·2)	..	47	16·3	2·9 (2·2–3·8)	..	149	6·4	23·2 (19·8–27·2)	..
5–9	21	23·2	0·9 (0·6–1·4)	..	14	8·3	1·7 (1·0–2·9)	..	45	10·9	4·1 (3·1–5·5)	..	137	7·4	18·4 (15·6–21·8)	..
10–14	30	23·3	1·3 (0·9–1·8)	..	9	9·2	1·0 (0·5–1·9)	..	51	11·6	4·4 (3·4–5·8)	..	91	7·2	12·6 (10·3–15·5)	..
15–19	19	15·2	1·3 (0·8–2·0)	..	13	6·1	2·1 (1·2–3·7)	..	36	8·2	4·4 (3·2–6·1)	..	60	4·3	14·1 (11·0–18·2)	..
20–24	5	3·0	1·7 (0·7–4·0)	..	3	1·6	1·9 (0·6–5·8)	..	12	2·8	4·3 (2·4–7·5)	..	19	1·3	14·7 (9·4–23·1)	..
25–29	0	0·1	0	..	0	0·1	0	..	1	0·2	4·6 (0·6–32·7)	..	0	0·1	0	..
Duration of treatment (years)	..	..	..	0·13	..	..	..	0·016	..	..	..	<0·0001	..	..	..	<0·0001
<2	26	16·3	1·6 (1·1–2·3)	..	14	5·6	2·5 (1·5–4·2)	..	48	5·1	9·5 (7·2–12·6)	..	126	3·9	32·6 (27·4–38·8)	..
2	12	15·0	0·8 (0·5–1·4)	..	9	5·6	1·6 (0·8–3·1)	..	21	4·2	4·9 (3·2–7·6)	..	71	3·6	19·9 (15·7–25·0)	..
3	15	13·9	1·1 (0·7–1·8)	..	8	5·0	1·6 (0·8–3·2)	..	24	5·1	4·7 (3·2–7·0)	..	56	3·9	14·4 (11·1–18·7)	..
4–5	14	15·4	0·9 (0·5–1·5)	..	8	6·4	1·3 (0·6–2·5)	..	31	8·8	3·5 (2·5–5·0)	..	81	5·7	14·2 (11·4–17·7)	..
6–9	12	11·0	1·1 (0·6–1·9)	..	5	5·8	0·9 (0·4–2·1)	..	40	10·6	3·8 (2·8–5·1)	..	71	5·4	13·3 (10·5–16·7)	..
≥10	4	5·7	0·7 (0·3–1·9)	..	3	3·4	0·9 (0·3–2·8)	..	9	10·8	0·8 (0·4–1·6)	..	12	2·0	5·9 (3·4–10·5)	..
Unknown	7	6·8	1·0 (0·5–2·1)	..	2	1·8	1·1 (0·3–4·5)	..	19	5·3	3·6 (2·3–5·6)	..	39	2·3	16·8 (12·3–23·0)	..
Time since end of treatment (years)	..	..	..	0·11	..	..	..	0·044	..	..	..	<0·0001	..	..	..	0·45
During	2	13·7	0·1 (0·0–0·6)	..	1	6·8	0·1 (0·0–1·1)	..	12	14·8	0·8 (0·5–1·4)	..	12	5·1	2·4 (1·3–4·2)	..
<1	12	3·7	3·3 (1·8–5·7)	..	3	1·5	2·1 (0·7–6·4)	..	25	2·1	11·7 (7·9–17·4)	..	93	1·3	70·0 (57·1–85·7)	..
1–2	8	3·9	2·0 (1·0–4·1)	..	7	1·5	4·7 (2·2–9·9)	..	12	2·2	5·5 (3·1–9·6)	..	59	1·4	43·0 (33·3–55·5)	..
2–4	13	13·5	1·0 (0·6–1·7)	..	10	5·2	1·9 (1·0–3·6)	..	35	6·9	5·1 (3·7–7·1)	..	94	4·4	21·2 (17·3–25·9)	..
5–9	19	21·7	0·9 (0·6–1·4)	..	13	8·6	1·5 (0·9–2·6)	..	46	9·9	4·6 (3·5–6·2)	..	95	6·7	14·2 (11·6–17·3)	..
10–14	23	15·0	1·5 (1·0–2·3)	..	10	5·9	1·7 (0·9–3·2)	..	33	6·2	5·4 (3·8–7·5)	..	47	4·0	11·8 (8·9–15·8)	..
15–19	5	5·4	0·9 (0·4–2·2)	..	4	2·3	1·7 (0·7–4·7)	..	13	2·4	5·4 (3·2–9·4)	..	19	1·4	13·3 (8·5–20·9)	..
20–25	1	0·4	2·9 (0·4–20·5)	..	1	0·3	3·2 (0·5–22·8)	..	0	0·4	0	..	3	0·2	12·4 (4·0–38·3)	..
Unknown	7	6·9	1·0 (0·5–2·1)	..	0	1·6	0	..	16	5·2	3·1 (1·9–5·0)	..	34	2·2	15·7 (11·2–21·9)	..

(Table 3 continues on next page)

	Risk group 1a				Risk group 1b				Risk group 2				Risk group 3			
	Obs	Exp	SMR (95% CI)	p_{trend}	Obs	Exp	SMR (95% CI)	p_{trend}	Obs	Exp	SMR (95% CI)	p_{trend}	Obs	Exp	SMR (95% CI)	p_{trend}
(Continued from previous page)																
Mean daily dose of recombinant human growth hormone (μg/kg/day)	..	..	..	0·85	..	..	..	0·60	..	..	..	0·78	..	..	..	0·68
<15	3	4·3	0·7 (0·2–2·1)	..	3	1·8	1·7 (0·5–5·2)	..	4	1·2	3·5 (1·3–9·2)	..	39	1·9	20·5 (15·0–28·0)	..
15–19	20	19·7	1·0 (0·7–1·6)	..	7	5·8	1·2 (0·6–2·5)	..	15	3·3	4·5 (2·7–7·4)	..	59	3·7	15·9 (12·3–20·6)	..
20–24	11	14·4	0·8 (0·4–1·4)	..	9	5·1	1·8 (0·9–3·4)	..	24	4·8	5·0 (3·4–7·5)	..	76	5·6	13·7 (10·9–17·1)	..
25–29	10	10·0	1·0 (0·5–1·9)	..	5	4·3	1·2 (0·5–2·8)	..	21	5·9	3·6 (2·3–5·5)	..	70	4·2	16·8 (13·3–21·3)	..
30–34	7	7·1	1·0 (0·5–2·1)	..	8	4·8	1·7 (0·8–3·3)	..	21	6·2	3·4 (2·2–5·2)	..	53	2·4	22·2 (17·0–29·0)	..
35–39	2	2·3	0·9 (0·2–3·5)	..	0	1·3	0	..	16	5·4	3·0 (1·8–4·8)	..	19	1·0	20·0 (12·7–31·3)	..
40–49	3	1·8	1·7 (0·5–5·2)	..	0	1·2	0	..	28	6·6	4·2 (2·9–6·1)	..	9	0·9	9·9 (5·2–19·1)	..
≥50	0	1·0	0	..	8	3·0	2·7 (1·4–5·4)	..	10	2·0	5·1 (2·7–9·5)	..	8	0·3	27·2 (13·6–54·3)	..
Unknown	34	23·6	1·4 (1·0–2·0)	..	9	6·3	1·4 (0·7–2·8)	..	53	14·6	3·6 (2·8–4·7)	..	123	6·9	17·9 (15·0–21·4)	..
Cumulative recombinant human growth factor dose (mg/kg)	..	..	..	0·77	..	..	..	0·40	..	..	..	0·48	..	..	..	0·0014
<25	31	35·2	0·9 (0·6–1·3)	..	20	13·7	1·5 (0·9–2·3)	..	50	13·6	3·7 (2·8–4·9)	..	171	8·7	19·7 (17·0–22·9)	..
25–49	17	18·5	0·9 (0·6–1·5)	..	15	7·7	1·9 (1·2–3·2)	..	40	11·3	3·6 (2·6–4·8)	..	120	7·7	15·7 (13·1–18·7)	..
50–99	10	9·6	1·0 (0·6–1·9)	..	4	6·0	0·7 (0·2–1·8)	..	45	11·5	3·9 (2·9–5·3)	..	59	4·5	13·2 (10·3–17·1)	..
≥100	2	2·4	0·8 (0·2–3·3)	..	3	2·2	1·4 (0·4–4·3)	..	24	5·5	4·4 (2·9–6·5)	..	11	0·9	12·8 (7·1–23·1)	..
Unknown	30	18·4	1·6 (1·1–2·3)	..	7	3·9	1·8 (0·9–3·8)	..	33	8·2	4·0 (2·9–5·6)	..	95	5·1	18·7 (15·3–22·8)	..

Obs=observed. Exp=expected. SMR=standardised mortality ratio.

Table 2: **Overall mortality by risk group, sex, and treatment**

cerebrovascular disease was raised in group 1b (5·0, 2·1–11·9).

Table 5 shows the cause of death for each of the 19 patients who died from a circulatory disease or disease of the blood or blood-forming organs in risk groups 1a (12 participants) and 1b (seven participants). A cardiac cause of death was reported in eight patients and a cerebrovascular disease was the second most common cause of death (five participants). All patients in risk groups 1a and 1b who died from a circulatory cause were treated within the approved dose ranges, except for one patient who died from cardiac arrest and was treated with a higher recombinant human growth hormone dose (61·9 μg/kg/day). Two of four deaths from diseases of the blood and blood-forming organs were caused by immunodeficiency, and one each by aplastic anaemia and coagulation defect.

For the moderate and high-risk groups (groups 2 and 3), cause-specific mortality was increased for several specific categories, probably due to the underlying diagnosis within these risk groups (table 4).

Discussion

Through a collaboration between eight European countries creating a joint cohort of patients treated with recombinant human growth hormone during childhood, we have been able to do, to our knowledge, the largest long-term mortality follow-up study to date. We did a risk classification to investigate overall and cause-specific mortality in the different risk groups because of the heterogeneity of patients treated with recombinant human growth hormone. In patients with an a priori low mortality risk, we observed no increase in overall mortality. However, an increased overall mortality was confirmed for patients whose underlying diagnosis was known a priori to be associated with increased mortality risk.

For risk group 1a, which comprised isolated growth hormone deficiency and idiopathic short stature, we observed no increase in overall mortality. This finding builds upon the results of previous studies;[10–13] however, no study is directly comparable with ours, since we analysed a large patient group with no apparent underlying inherent increased mortality risk. Furthermore, most previous studies were small, included a mix of adult-onset and childhood-onset patients, differed in the indication for starting treatment, and had shorter follow-up time, which limits possible conclusions of long-term mortality risk. Our study found an increased SMR for patients with the shortest treatment duration, but analyses with a 2-year lag showed this was probably an artefact of cessation of treatment in severely ill children. Moreover, we found no association between daily or cumulative dose and overall mortality.

In patients born small for gestational age—risk group 1b—we observed increased overall mortality, and a sensitivity analysis showed that this was driven by the French subcohort. Whether this increased risk could be attributed to recombinant human growth hormone

	Total (n=24 232)*	1a (n=9290)	1b (n=3855)	2 (n=7188)	3 (n=3587)
Mean follow-up, years	16·5 (5·0)	16·3 (4·8)	17·2 (4·6)	17·0 (5·0)	15·4 (5·6)
Person-years at risk of death	400 229*	151 004	66 229	122 319	55 392
Sex					
Male	13 425 (55·4%)	6331 (68·1%)	2409 (62·5%)	2329 (32·4%)	2168 (60·4%)
Female	10 807 (44·6%)	2959 (31·9%)	1446 (37·5%)	4859 (67·6%)	1419 (39·6%)
Birthweight SD score†	−0·79 (1·32)	−0·35 (1·02)	−1·65 (1·35)	−0·98 (1·34)	−0·23 (1·15)
Height SD score at treatment start	−2·69 (1·53)	−2·71 (0·92)	−2·95 (2·23)	−3·03 (1·49)	−1·67 (1·40)
Age at treatment start, years	10·5 (3·6)	10·9 (3·3)	10·0 (3·5)	9·9 (3·9)	11·1 (3·2)
Treatment duration, years	5·0 (3·3)	4·5 (3·0)	4·8 (3·1)	6·0 (3·6)	4·8 (3·1)
Duration between growth hormone start and death, years	9·2 (5·7)	10·8 (5·4)	11·4 (5·6)	9·6 (5·7)	8·3 (5·5)
Attained age at death, years	20·1 (6·5)	22·2 (6·1)	23·6 (5·7)	20·2 (7·5)	19·1 (6·0)
Dose of growth hormone (μg/kg/day)	30·1 (12·7)	26·3 (11·0)	33·3 (17·4)	35·0 (10·8)	25·6 (8·6)

Data are mean (SD) or n (%), unless otherwise indicated. *In total, 312 patients (188 men and 124 women) could not be classified and were not included in the analyses (5285 person-years at risk of death excluded). †Missing data for 6510 (26·9%) participants.

Table 3: **Patient characteristics by risk group**

	Risk group 1a			Risk group 1b			Risk group 2			Risk group 3		
	Obs	Exp	SMR (95% CI)	Obs	Exp	SMR (95% CI)	Obs	Exp	SMR (95% CI)	Obs	Exp	SMR (95% CI)
Infectious and parasitic disease (A00–B99)	3	1·1	2·7 (0·9–8·2)	0	0·5	0	0	0·9	0	5	0·4	11·9 (5·0–28·7)
Neoplasms (C00–D48)	7	8·1	0·9 (0·4–1·8)	2	3·4	0·6 (0·1–2·4)	14	5·8	2·4 (1·4–4·1)	334	2·9	117·3 (105·4–130·6)
Diseases of blood and blood-forming organs (D50–D89)	3	0·4	8·2 (2·6–25·4)	1	0·2	6·4 (0·9–45·2)	8	0·3	30·9 (15·5–61·9)	7	0·1	56·8 (27·1–119·1)
Endocrine, nutritional, and metabolic disease (E00–E90)	1	1·2	0·8 (0·1–5·9)	1	0·6	1·8 (0·2–12·5)	18	1·1	16·6 (10·5–26·4)	4	0·5	8·1 (3·0–21·5)
Mental and behavioural disorders (F00–F99)	1	1·8	0·6 (0·1–3·9)	0	0·7	0	3	1·2	2·5 (0·8–7·9)	1	0·7	1·4 (0·2–9·7)
Diseases of nervous system, eye, and ear (G00–H95)	2	3·2	0·6 (0·2–2·5)	2	1·5	1·4 (0·3–5·5)	9	2·3	3·9 (2·1–7·6)	12	1·2	9·7 (5·5–17·2)
Diseases of circulatory system (I00–I99)	9	3·8	2·4 (1·2–4·6)	6	1·6	3·7 (1·7–8·3)	33	2·6	12·8 (9·1–18·0)	19	1·4	13·9 (8·9–21·8)
Diseases of respiratory system (J00–J99)	2	1·4	1·4 (0·4–5·7)	1	0·7	1·5 (0·2–10·7)	11	1·2	8·8 (4·9–16·0)	13	0·6	23·3 (13·5–40·2)
Diseases of digestive system (K00–K93)	1	0·9	1·1 (0·2–8·0)	0	0·4	0	3	0·8	3·7 (1·2–11·6)	8	0·4	20·1 (10·1–40·2)
Diseases of skin and subcutaneous tissue (L00–L99)	0	0·0	0	0	0·0	0	0	0·0	0	0	0·0	0
Diseases of musculoskeletal system and connective tissue (M00–M99)	0	0·2	0	0	0·1	0	5	0·2	26·9 (11·2–64·7)	4	0·1	49·6 (18·6–132·2)
Diseases of genitourinary system (N00–N99)	0	0·2	0	0	0·1	0	2	0·1	15·2 (3·8–60·7)	12	0·1	194·1 (110·2–341·7)
Pregnancy, childbirth and the puerperium (O00–O99)	0	0·1	0	0	0·0	0	0	0·2	0	0	0·0	0
Conditions originating in perinatal period (P00–P96)	0	1·2	0	0	0·8	0	0	1·8	0	0	0·3	0
Congenital anomalies (Q00–Q99)	2	2·4	0·8 (0·2–3·3)	2	1·3	1·5 (0·4–6·1)	33	2·8	11·9 (8·5–16·7)	10	0·9	11·6 (6·3–21·6)
Symptoms, signs, and ill-defined conditions (R00–R99)	13	7·1	1·8 (1·1–3·1)	10	2·7	3·7 (2·0–6·9)	25	4·1	6·1 (4·1–9·0)	13	1·6	7·9 (4·6–13·7)
Accidents and violence (V00–Y98)	45	50·0	0·9 (0·7–1·2)	24	18·3	1·3 (0·9–2·0)	28	22·5	1·2 (0·9–1·8)	14	15·1	0·9 (0·5–1·6)
Ischaemic heart disease	1	0·5	2·2 (0·3–15·7)	0	0·2	0	2	0·3	7·1 (1·8–28·3)	1	0·2	5·6 (0·8–39·5)
Cerebrovascular disease	4	0·9	4·7 (1·8–12·5)	1	0·4	2·8 (0·4–20·2)	4	0·6	6·7 (2·5–17·8)	4	0·3	13·3 (5·0–35·5)
Other circulatory disease	3	2·3	1·3 (0·4–4·1)	5	1·0	5·0 (2·1–11·9)	23	1·5	14·9 (9·9–22·4)	13	0·8	15·4 (8·9–26·5)

Obs=observed. Exp=expected. SMR=standardised mortality ratio.

Table 4: **Cause-specific mortality by risk group**

	Sex	Age of death (years)	Cause of death
1a	Female	28	Pulmonary embolism without mention of acute cor pulmonale
1a	Male	24	Cardiac arrest
1a	Male	29	Subarachnoid haemorrhage, unspecified
1a	Male	19	Acute myocardial infarction, unspecified
1a	Female	27	Cardiomegaly
1a	Male	19	Other subarachnoid haemorrhage
1a	Male	21	Intracerebral haemorrhage, unspecified
1a	Male	18	Intracerebral haemorrhage, unspecified
1a	Male	19	Sudden cardiac death
1b	Male	29	Pulmonary embolism without mention of acute cor pulmonale
1b	Male	19	Other primary cardiomyopathies
1b	Male	13	Other primary cardiomyopathies
1b	Male	32	Intracerebral haemorrhage, intraventricular
1b	Male	25	Cardiac arrest, unspecified
1b	Male	24	Cardiac arrest, unspecified
1a	Male	12	Immunodeficiency, increased IgM
1a	Male	31	Coagulation defect, unspecified
1a	Male	14	Aplastic anaemia, unspecified
1b	Male	22	Other combined immunodeficiencies

Table 5: **Patients in risk groups 1a and 1b who died from circulatory disease or disease of blood and blood-forming organs, by risk group**

treatment itself is unclear, as in a large population-based study of children born small for gestational age had an increased mortality risk at younger ages compared with healthy birthweight children.[14] However, in contrast to our cohort, these risks were reduced compared with the general population with increasing age. Another study of low-risk patients treated with recombinant human growth hormone showed the importance of birth size in relation to mortality risk, as an increased SMR by conventional calculations normalised with a continuous hazard model that also included birth characteristics.[15] Although mortality was increased for the highest dose category in our study (≥50 µg/kg/day), we observed no overall association between daily or cumulative dose and mortality, indicating no association between recombinant human growth hormone dose and mortality in risk group 1b. When analysing cause-specific mortality for risk groups 1a and 1b, we found a significantly increased mortality risk due to diseases of the circulatory system. In line with our findings, increased mortality risk due to circulatory diseases has previously been reported in a mixed cohort of patients with adult-onset and childhood-onset isolated growth hormone deficiency.[12] Within circulatory diseases in our risk group 1a, mortality was increased in the subcategory of cerebrovascular diseases in line with a previous report[16] and publication regarding cerebrovascular morbidity in the French SAGhE cohort.[17] Several possible mechanisms could be considered for this association. States of excess and insufficiency of growth hormone are both associated with increased cardiovascular risks.[18] Thus, it is possible that growth hormone levels and cardiovascular health are associated and that both excess and insufficiency of growth hormone should be avoided.

In risk group 1b, the increased risk of circulatory mortality was in accordance with the known increased risk of cardiovascular diseases in patients born small for gestational age, first reported by Barker,[19] and confirmed in large epidemiological studies.[20–22] Furthermore, individuals born small for gestational age are known to have higher blood pressure and increased risk for cardiovascular events at a young age, which might contribute to or even explain their increased vascular mortality.[23] Cause-specific mortality from diseases of the blood and blood-forming organs was significantly increased for risk group 1a. However, the total number of deaths was low.

We observed increased overall mortality in risk groups 2 and 3, but we cannot conclude that this is due to recombinant human growth hormone treatment itself, since these groups have underlying diagnoses that are associated with increased mortality, as described in multiple reports in untreated patients.[24,25] Furthermore, groups 2 and 3 did not show any association between increased SMRs and daily or cumulative growth hormone dose, which indicated there may be no effect of growth hormone treatment on mortality. Patients in risk group 2, and particularly those in risk group 3, were found to have increased cause-specific mortality for neoplasms, which is unsurprising and probably related to their underlying diagnoses.[26,27] Furthermore, the overall SMR in risk group 3 was higher in women compared with men, possibly explained by a lower mortality risk in the female general population, as indicated by the smaller difference in absolute excess rates. A higher mortality risk in women has also been reported in a large follow-up study of childhood cancer survivors.[27]

Our study has several limitations. First, similar to other recombinant human growth hormone safety studies, our study lacked an untreated control group and we might therefore either have underestimated or overestimated any difference in mortality risk by comparing with the general population. In risk group 1a, underlying risk factors such as being born small for gestational age or having other severe diagnoses were excluded, making these participants less likely to have certain underlying mortality risks compared with the general population, in contrast to the other risk groups, in which the underlying diagnosis was expected to increase their mortality. Second, we could not adjust for potential confounders, such as socioeconomic factors or birth characteristics, and we do not have information on adult recombinant human growth hormone treatment or adherence to growth hormone treatment, which could influence mortality risks. Third, although our cohort of treated patients is large, mortality in this age group is rare, leading to wide CIs and

uncertainty for certain point estimates of SMR. Fourth, comparisons of SMRs rely on whether there was interaction for strict validity and will be less valid if there was an appreciable interaction. Finally, combining patients from eight different countries, with potential differences in diagnostic and clinical practice, might have created heterogeneity in the data.

In conclusion, this European collaborative study found no significant increase in overall mortality in low-risk patients with isolated growth hormone deficiency or idiopathic short stature, although the possibility of certain cause-specific cardiovascular and haematological mortality risks remains. For patients with an inherent increased mortality risk, we found that increased mortality rates are probably related to the underlying diagnosis. Although our present data are reassuring, we acknowledge several limitations of our study and recommend continued long-term surveillance of patients treated with recombinant human growth hormone during childhood to allow detection of any increased mortality risk later in life.

Contributors

LS, GB, SC, PC, JC, ACSH-K, WK, RP, J-CC, and AJS conceived the study and formulated the analysis plan. RC and AJS did the statistical analyses. LS and AT wrote the manuscript. All authors contributed to interpretation of the data, critical revision of the manuscript, and approval of the final manuscript.

Declaration of interests

LS reports personal fees and non-financial support from Ascendis, Hexal, Merck, Novo Nordisk, Pfizer, and Sandoz. AT reports personal fees from Pfizer. DB reports personal fees from the Belgian Society for Paediatric Endocrinology and Diabetology and personal fees and non-financial support from Novo Nordisk, Merck, and Ferring. GB reports lecture honoraria from Novo Nordisk, Pfizer, and Sandoz and professional consultation for Ferring. SC reports personal fees from Merck, Pfizer, Sandoz, Novo Nordisk, and Merck. PC reports consulting fees paid by Merck to University of Manchester for work on the PREDICT clinical trial. ACSH-K reports personal fees from Pfizer and Novo Nordisk, as a member of Pfizer International Growth Database Steering Committee and Novo Nordisk Advisory Board on growth hormone treatment, and personal fees from Novo Nordisk, Merck Serono, and Pfizer. RP reports personal fees from Novo Nordisk, Pfizer, Merck Serono, Ipsen, and Sandoz. GS reports non-financial support from Novo Nordisk. ST reports personal fees from Merck, Novo Nordisk, Ferring, and Sandoz. J-CC has been investigator in clinical trials run by Lilly and Pfizer and has received travel support to international meetings from Ipsen and Pfizer. All other authors declare no competing interests.

Data sharing

Data obtained for this study will not be made available to others.

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