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

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Abstract: 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 $1 \cdot 1$, 95% CI $0 \cdot 9$-$1 \cdot 3$). In children born small for gestational age, all-cause mortality was significantly increased when analysed for all countries (SMR $1 \cdot 5$, CI $1 \cdot 1$-$1 \cdot 9$), but this result was driven by the French subcohort. In patients at moderate or high risk, mortality was increased (SMR $3 \cdot 8$, $3 \cdot 3$-$4 \cdot 4$; and $17 \cdot 1$, $15 \cdot 6$-$18 \cdot 7$, 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.

Mortality after childhood Growth Hormone treatment – the SAGhE study

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Summary

Background

Recombinant human growth hormone (r-hGH) has been used for more than 30 years and indications for r-hGH have multiplied worldwide. There has been concern that this treatment might raise mortality, but published data are limited.

Methods

The cohort comprised of 24,232 childhood r-hGH treated patients in eight European countries with >400,000 patient-years of follow-up. Patients were classified a priori based on pre-treatment perceived mortality risk from their underlying disease and followed for cause-specific mortality. Person-years at risk of mortality and expected rates from general population data were used to calculate standardized mortality ratios (SMRs).

Findings

In low-risk patients with isolated GH deficiency or idiopathic short stature all-cause mortality was not significantly increased [SMR 1·1 (95% confidence interval 0·9-1·3)] while in children born small for gestational age it was increased [SMR 1·5 (1·1-1·9)], driven by the French sub-cohort. In patients at moderate or high risk, mortality was clearly increased [SMR 3·8 (3·3-4·4) and 17·1 (15·6-18·7), respectively]. Mortality was not significantly associated with mean daily or cumulative doses of r-hGH 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 with long-term follow-up for r-hGH treated children, all-cause mortality was strongly related to underlying diagnosis. In patients with isolated GH deficiency or idiopathic short stature, r-hGH treatment was not associated with significantly increased all-cause mortality. However, mortality from certain causes was increased, emphasizing the need for further long-term surveillance.

1 **Funding**

2 The funding sources of the study had no role in the study design, data collection, data analyses,

3 data interpretation, or writing of the report. All funding sources are listed under Declaration of

4 interests.

Research in context

Evidence before this study

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

Added value of this study

This is the first large multi-national population-based cohort study of childhood r-hGH treated patients reporting overall- and cause-specific mortality data from all eight participating SAGhE countries with >400,000 patient-years and up to 25 years of follow-up. All-cause mortality was found to be strongly related to the underlying diagnosis and not significantly associated with increased mean or cumulative r-hGH dose. In patients with isolated GH deficiency or idiopathic short stature, r-hGH 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 enhances earlier published data from post-marketing surveillance studies suggesting no significant effect of childhood r-hGH treatment on overall mortality in patients with isolated GH deficiency or idiopathic short stature. For those patients with an inherent increased mortality risk, our study noted increased mortality rates most likely related to the underlying diagnosis. Although our present data are in general reassuring, we recommend continued long-term surveillance of childhood r-hGH treated patients to allow detection of any increased mortality risks later in life.

1 **Introduction**

2 Recombinant human growth hormone (r-hGH) has been used for more than 3 decades and the

3 indications have expanded worldwide, now including not only GH deficiency but also many

4 other causes of short stature. The overall experience from many thousands of patient years of

5 treatment suggests on balance that r-hGH is safe.[1] Nevertheless, a systematic review with meta-

6 analysis of articles published until September 2013 showed a slight but significant increase in

7 all-cause mortality in patients treated with r-hGH in childhood and adolescence.[2]

8 Unfortunately, most of our knowledge regarding r-hGH safety is based on cohort studies with

9 short follow-up of adverse events within databases kept by pharmaceutical companies. To

10 overcome these limitations and study the long-term safety of r-hGH therapy, we set up a

11 European consortium (SAGhE: Safety and Appropriateness of Growth hormone treatments in

12 Europe) involving eight countries (Belgium, France, Germany, Italy, The Netherlands, Sweden,

13 Switzerland, and United Kingdom) and merged datasets on ~24,000 young adults treated with

14 r-hGH during childhood and adolescence.[3]

15 Two preliminary reports, based on a subset of local datasets within SAGhE, have presented

16 mortality data in young adult patients who were treated with r-hGH during childhood for

17 isolated idiopathic GH deficiency, small for gestational age or idiopathic short stature: a study[4]

18 from France reported a significant increase in all-cause mortality and cause-specific mortality

19 for bone tumours and cerebral haemorrhage in 6500 patients, while in an analysis[5] from

20 Sweden, The Netherlands, and Belgium, no deaths from cancer or cerebrovascular disease were

21 identified among 2500 patients.

22 The current study presents data from the entire dataset of all eight countries of the SAGhE

23 consortium. Our main objective was to study long-term overall and cause-specific mortality in

24 young adult patients who were treated with r-hGH during childhood and relate this to the

25 underlying diagnosis. Secondary objectives included analyses of dose-response, mean and

1   cumulative r-hGH dose, impact of time since end of r-hGH treatment, and duration of r-hGH

2   treatment.

3

Methods

Study population and study design

The cohort study was conducted in eight European countries as described in detail earlier.[3] In brief, we attempted to identify, in each country, all resident patients who were born before 1991-5 (depending on the country), who had been treated with r-hGH during childhood from the time such treatment was first introduced (1984-6), irrespective of treatment duration, at any time up to a date during 2007-9 (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. Data on demographic and GH-related variables were extracted from existing databases and case-notes. We followed the participants for mortality via national population-based registries in Belgium, The Netherlands, Sweden, and UK and by a range of methods in the other four countries.[3] Mortality was followed from the earliest r-hGH treatment date (except Italy: January 1, 1999 or earliest r-hGH treatment date if later) until a censoring date which varied between countries (September 21, 2009-December 31, 2013). The 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) or from individual death certificates in Italy, Switzerland, and the UK, or from medical records and questionnaires in Germany and in The Netherlands from medical records. Information was missing regarding the specific causes of death for a few cases, as reflected by a slightly lower number of patient-years in those analyses (Table S2).

As detailed earlier, follow-up for mortality was 96.7% complete, excluding Italy, where information on completeness was not available.[3] Cause-specific mortality data and population

1   counts for the general population were obtained to derive expected mortality from national

2   mortality statistics. Cancer mortality has earlier been reported from this cohort.[6]

3   **Risk group classification**

4   Certain diagnoses leading to GH treatment are known to be themselves associated with

5   increased mortality, which complicates analyses in a mixed cohort with underlying diagnoses

6   stretching from healthy individuals with idiopathic short stature to those patients with a brain

7   tumour or chronic renal failure diagnosed prior to treatment start. In an attempt to overcome

8   this problem, we decided to categorize all patients a priori into three "risk groups" based on

9   their diagnosis leading to GH treatment. If a patient had several diagnoses, categorization was

10   based on the diagnoses belonging to the highest risk group.

11   The details of the risk classification have been described earlier[3] and the distribution by country

12   are presented in Tables 1 and 2, respectively. Risk group 1 was further sub-divided into patients

13   treated for isolated GH deficiency or idiopathic short stature (group 1a) and short children born

14   small for gestational age (group 1b; birth weight and/or length <-2SDS according to the

15   different national references).[7] Risk group 2 included treated patients with: multiple pituitary

16   hormone deficiency (GH and at least one additional pituitary hormone deficiency), defined

17   paediatric syndromes (such as Turner, Noonan, neurofibromatosis type 1, Prader-Willi and

18   Fanconi syndromes) known to be associated with an increased risk of mortality, benign pituitary

19   tumours, severe craniofacial or other malformations, and severe paediatric chronic diseases.

20   Risk group 3 included patients who had been treated for cancer, craniopharyngioma and chronic

21   renal failure.

22

1 **Statistical analyses**

2 We calculated person-years at risk of death for each patient by sex, 5 year age-group, single

3 calendar year, and country, starting from the date of first treatment with r-hGH and ending at

4 whichever occurred earliest of: death, loss to follow-up, or a fixed end-date for each country as

5 previously detailed.[3] The analyses were further stratified by different time scales and GH-

6 dosing categories as detailed in the tables. The mean daily dose of r-hGH was calculated from

7 data retrieved at each clinic visit. Time-dependent variables (time since treatment and

8 cumulative dose) were analysed in a time-dependent manner i.e. person-years and events for

9 each participant were split and allocated to the level of the variable the participant belonged to

10 at each point in follow-up, so that they contributed to different levels of the variable as they

11 progressed through these. The cumulative dose was calculated by multiplying the mean daily

12 dose by the total number of treatment days. National population rates were used to calculate

13 standardized mortality ratios (SMRs) and trends tested by the Poisson trend statistic. Absolute

14 excess rates (AERs) were calculated by subtracting expected from observed numbers of cases,

15 dividing by person-years at risk and multiplying by 10,000.

16 Main outcome analyses included long-term overall and cause-specific mortality related to the

17 underlying diagnosis. Conclusion about treatment effect was based on the confidence intervals

18 reported. Sub-analyses included effects of mean and cumulative doses of r-hGH, impact of

19 time since end of treatment, and duration of treatment. Sub-analyses were also performed

20 stratifying data into France, and all other countries, to explore any country bias linked to the

21 high proportion of patients from France. Another sub-analysis was conducted where the risk

22 was recalculated once patients had ceased r-hGH for a period greater than two years, because

23 an adverse event, irrespective of causality, often leads to treatment termination.[9] All p-values

24 are 2-sided and a value of less than 0·05 was considered statistically significant.

25

1 **Role of the funding source**

2 The funders of the study had no role in study design, data collection, data analysis, data

3 interpretation, or writing of the report. The corresponding author had full access to all the data

4 in the study and had final responsibility for the decision to submit for publication.

1   Results

2   Characteristics of the study cohort

3   The cohort consisted of 24,232 patients and of these 13,145 (54·2%) were classified as low risk

4   (groups 1a and 1b), 7,188 (29·7%) moderate risk (group 2), 3,587 (14·8%) high risk (group 3),

5   and 312 (1·3%) not classifiable. Patient characteristics by risk group are detailed in Table 3.

6   There was a male predominance except in risk group 2, which included the patients with Turner

7   syndrome. Between risk groups, there were small differences in age at treatment start (9·9-11·1

8   years) and treatment duration (4·5-6·0 years). The mean dose of r-hGH was lower in risk groups

9   1a and 3 (26·3 and 25·6 μg/kg/day, respectively) than in risk groups 1b and 2 (33·3 and 35·0

10   μg/kg/day, respectively). In total, 10,316 patients (42·6%) came from France and 13,916

11   (57·4%) from the other seven countries (Table 2).

12   Overall mortality by risk group

13   For patients in the low risk group 1a, overall mortality was not significantly increased [SMR

14   1·1 (95% confidence interval (CI) 0·9-1·3)] (Table 4). When analysed separately, this was true

15   for both France [SMR 1·1 (0·9-1·4); Table S3] and the other seven countries [SMR 1·0 (0·7-

16   1·4); Table S4]. Mean daily dose of r-hGH as well as the cumulative dose of r-hGH did not

17   affect mortality in risk group 1a (Table 4). Time since start of r-hGH treatment was borderline

18   significantly associated with mortality in risk group 1a (p trend = 0·05; Table 4). The highest

19   SMR was seen for those with a treatment duration <2 years [SMR 1·6 (1·1-2·3)] and those with

20   the shortest time since end of treatment [<1 year; SMR 3·3 (1·8-5·7); Table 4]. However, in the

21   analysis with a 2-year lag period after end of r-hGH treatment, the SMR was no longer

22   significant with treatment duration <2 years [SMR 1·2 (0·8-2·0); Table S5].

23   For patients belonging to risk group 1b, overall mortality was significantly increased when

24   analysed for all countries [SMR 1·5 (1·1-1·9); Table 4]. When analysed separately, risk was

25   significantly increased in France [SMR 1·7 (1·2-2·4); Table S3], but not significantly in the

1 other seven countries combined [SMR 1·2 (0·8-1·9) Table S4]. For cumulative dose of r-hGH

2 and mean daily dose, there was no association with increased mortality, but for the highest mean

3 daily dose category [> 50 µg/kg/d] a SMR of 2·7 (1·4-5·4) was noted (Table 4). Time since

4 start of r-hGH treatment was not associated with mortality in risk group 1b, but an increased

5 risk in the early years after end of treatment was found (Table 4).

6 For patients belonging to risk groups 2 and 3, overall mortality was markedly increased [SMRs

7 3·8 (3·3-4·4) and 17·1 (15·6-18·7), respectively; Table 4] and when analysed separately, the

8 risk was similar in France [Table S3] and the other seven countries combined [Table S4]. Risks

9 in these groups did not relate to daily dose or cumulative dose of GH and decreased with longer

10 duration of treatment. As detailed in Table S1, all-cause mortality was increased for patients

11 with several individual underlying diagnoses belonging to risk groups 2 and 3. The highest

12 mortality was found in patients with tumour diagnoses prior to treatment start, greatest for

13 patients with a pre-existing central nervous system tumour [SMR 23·6 (21·0-26·6); Table S1].

14 In risk group 3, a higher SMR was noted in females [33·2 (28·8-38·3)] compared with males

15 [12·7 (11·2-14·3)], but the difference decreased notably when comparing AER [83·7 (71·9-

16 96·9) and 73·4 (64·1-83·6) for females and males, respectively], Table S2.

17 **Cause-specific mortality by risk group**

18 Cause-specific mortality is detailed in Table 5. Although the category accidents and violence

19 was by far the most common individual cause of death for risk groups 1a and 1b, the mortality

20 rate from this cause was not significantly increased when compared with that in the general

21 population. Mortality from neoplasms was also not increased for risk groups 1a and 1b [SMR

22 0·9 (0·4-1·8) and 0·6 (0·1-2·4), respectively]. In contrast, mortality from diseases in blood and

23 blood forming organs was significantly increased for risk group 1a [SMR 8·2 (2·6- 25·4)].

24 Mortality from diseases of the circulatory system was significantly increased for both groups

25 1a and 1b [SMR 2·4 (1·2-4·6) and 3·7 (1·7-8·3), respectively], where the risk for 1b was mostly

1   driven by the French sub-cohort. Within the circulatory system, mortality due to

2   cerebrovascular disease was significantly increased for risk group 1a [SMRs 4·7 (1·8-12·5)]

3   while the risk of circulatory diseases other than ischemic heart disease and cerebrovascular

4   disease was raised in group 1b [SMRs 5·0 (2·1-11·9)].

5   Table 6 details the cause of death for each of the 19 patients who died from a circulatory disease

6   or a disease in blood and blood-forming organs in risk groups 1a (n=12) and 1b (n=7). A cardiac

7   cause was reported in eight patients and a cerebrovascular disease was the second most common

8   cause of death (n=5). All patients in risk groups 1a and 1b who died from a circulatory cause

9   were treated within the approved dose ranges except for one patient who died from cardiac

10   arrest and was treated with a higher r-hGH dose (61·9 µg/kg/day). Of the four deaths from

11   blood and blood-forming organs, two were caused by immunodeficiency and one each by

12   aplastic anaemia and coagulation defect.

13   For the moderate and high-risk groups (groups 2 and 3), cause-specific mortality was increased

14   for several specific categories most likely due to the underlying diagnosis within these risk

15   groups (Table 5).

Discussion

Through a collaboration of eight European countries, creating a joint cohort of childhood r-hGH treated patients, we have been able to carry out the largest long-term mortality follow-up study of the included patient groups to date. Due to the heterogeneity of patients treated with r-hGH, a risk classification was carried out to investigate the overall and cause-specific mortality in the different risk groups. In patients with an a priori low mortality risk, no increased overall mortality was seen. 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, comprising isolated GH deficiency and idiopathic short stature, no increased overall mortality was found. This finding improves upon previous studies, as none of them are directly comparable to ours, since we have analysed a large patient group without an apparent underlying inherent increased mortality risk.[10-13] Furthermore, most earlier studies are smaller, include a mix of adult- and childhood-onset patients, differing in the indication of starting treatment, and with shorter follow-up time, which altogether limits possible conclusions of long-term mortality risks. There was a relation to short duration of treatment, but analyses with a 2-year lag period showed this likely to be an artefact of cessation of treatment in severely ill children. Moreover, no association was found between daily or cumulative dose and overall mortality, arguing against a relationship between r-hGH dose and overall mortality in this risk group.

In patients born small for gestational age, risk group 1b, we found an increased overall mortality, where a sensitivity analysis showed that this was driven by the French sub-cohort. It is uncertain if this increased risk could be attributed to the r-hGH treatment per se as it has been shown in a large population-based study that children born small for gestational age have an increased mortality risk at younger ages compared with normal birth weight children.[14] In contrast to our cohort, those risks were however reduced compared with the general population

1 with increasing age. Another study on r-hGH treated low-risk patients also showed the

2 importance of birth size in relation to mortality risk, where an increased SMR by conventional

3 calculations normalized using a continuous hazard model also including birth characteristics.[15]

4 Although mortality was increased for the highest dose category (>50 µg/kg/d), no overall

5 association was found between daily or cumulative dose and mortality arguing against a

6 relationship between r-hGH dose and mortality in risk group 1b. When analysing cause-specific

7 mortality for risk groups 1a and 1b, we found a significantly increased mortality risk due to

8 diseases of the circulatory system. In line with our findings, increased mortality risk due to

9 circulatory diseases has previously been reported in a mixed cohort of adult- and childhood

10 onset isolated GH deficiency patients.[12] Within circulatory diseases in our risk group 1a,

11 mortality was increased in the sub-category cerebrovascular diseases in line with an earlier

12 report[16] and a previous publication regarding cerebrovascular morbidity in the French SAGhE

13 cohort.[17] Several possible mechanisms could be considered for this association. As recently

14 reviewed by di Somma *et al,* both states of excess as well as insufficiency of GH are associated

15 with increased cardiovascular risks.[18] Thus, it is likely that GH levels and cardiovascular health

16 are related and that both excess and insufficiency of GH should be avoided.

17 In risk group 1b, the increased risk of circulatory mortality is in accordance with the known

18 raised risks of cardiovascular diseases in patients born small for gestational age, as first reported

19 by Barker *et al*[19] and later confirmed in large epidemiological studies.[20-22] Furthermore, subjects

20 born small for gestational age are known to have higher blood pressure and increased risk for

21 cardiovascular events at a relatively young age, which might contribute or even explain their

22 higher vascular mortality.[23]

23 Cause-specific mortality from diseases of blood and blood forming organs seemed to be

24 increased for both risk group 1a and 1b, but only significantly for group 1a. However, it is

1 important to note that the total number of deaths was low; in risk group 1a three cases and in

2 group 1b only one case.

3 Increased overall mortality was found in risk groups 2 and 3, but it is not possible to conclude

4 that this is due to r-hGH treatment per se, since these groups have underlying diagnoses that are

5 associated with increased mortality, as described in multiple reports in such untreated

6 patients.[24,25] Furthermore, groups 2 and 3 did not show any relation of risk to daily or

7 cumulative GH dose, which argues against an effect of GH treatment on mortality. Patients in

8 risk group 2, and particularly those in risk group 3, were found to have increased cause-specific

9 mortality for neoplasms which is not surprising and likely related to the underlying

10 diagnoses.[26,27] Furthermore, the overall SMR in risk group 3 was clearly higher in females

11 compared with males, likely explained mainly by a lower mortality risk in the female general

12 population, as indicated by the lesser difference in AERs. A higher mortality risk in females

13 has also been reported in a large follow-up study of childhood cancer survivors.[27]

14 Our study has several limitations. First, this study, similarly to other r-hGH safety studies,

15 lacked an untreated control group and we may therefore either have under- or overestimated

16 any difference in mortality risk by comparing instead with the general population. In risk group

17 1a, underlying risk factors such as being born small for gestational age or having other severe

18 diagnoses have been excluded, making them less likely to have certain underlying mortality

19 risks compared with the general population, in contrast to the other risk groups, where the

20 underlying diagnosis was expected to increase their mortality. Secondly, we have not been able

21 to adjust for possible confounders, such as socio-economic factors or birth characteristics and

22 we do not have any information on adult r-hGH treatment or adherence to the r-GH treatment

23 which could influence mortality risks. Thirdly, although our cohort of treated patients is large,

24 mortality in this age group is quite rare leading to wide confidence intervals and some

25 uncertainty for certain point estimates of SMR. Fourthly, comparisons of SMRs rely for strict

1   validity on whether there was interaction, and will be less valid if there was appreciable

2   interaction. Lastly, combining patients from eight different countries, with potential differences

3   in diagnostic and clinical practice, may have created heterogeneity in the data.

4   In conclusion, this European multi-national collaborative study shows no significant increase

5   in overall mortality in low-risk patients with isolated GH deficiency or idiopathic short stature,

6   although the possibility of certain cause-specific cardiovascular and haematological mortality

7   risks remains. For those patients with an inherent increased mortality risk, we confirmed

8   increased mortality rates most likely related to the underlying diagnosis. Although our present

9   data are in general reassuring, we acknowledge several limitations of our study and recommend

10   continued long-term surveillance of childhood r-hGH treated patients to allow detection of any

11   increased mortality risks later in life.

12

1   **Contributors**

2   LS, GB, SC, PC, JC, AHK, WK, RP, JCC and AJS conceived the study and formulated the

3   analysis plan. RC and AJS did the statistical analyses. LS and AT wrote the manuscript. All

4   authors contributed to the interpretation of the data, critical revision of the manuscript and

5   approval of the final manuscript.

6

Data sharing

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

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Mortality after childhood Growth Hormone treatment – the SAGhE study

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Summary

Background

Recombinant human growth hormone (r-hGH) has been used for more than 30 years and indications for r-hGH have multiplied worldwide. There has been concern that this treatment might raise mortality, but published data are limited.

Methods

The cohort comprised of 24,232 childhood r-hGH treated patients in eight European countries with >400,000 patient-years of follow-up. Patients were classified a priori based on pre-treatment perceived mortality risk from their underlying disease and followed for cause-specific mortality. Person-years at risk of mortality and expected rates from general population data were used to calculate standardized mortality ratios (SMRs).

Findings

In low-risk patients with isolated GH deficiency or idiopathic short stature all-cause mortality was not significantly increased [SMR 1·1 (95% confidence interval 0·9-1·3)] while in children born small for gestational age it was increased [SMR 1·5 (1·1-1·9)], driven by the French sub-cohort. In patients at moderate or high risk, mortality was clearly increased [SMR 3·8 (3·3-4·4) and 17·1 (15·6-18·7), respectively]. Mortality was not significantly associated with mean daily or cumulative doses of r-hGH 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 with long-term follow-up for r-hGH treated children, all-cause mortality was strongly related to underlying diagnosis. In patients with isolated GH deficiency or idiopathic short stature, r-hGH treatment was not associated with significantly increased all-cause mortality. However, mortality from certain causes was increased, emphasizing the need for further long-term surveillance.

1 **Funding**

2 The funding sources of the study had no role in the study design, data collection, data analyses,

3 data interpretation, or writing of the report. All funding sources are listed under Declaration of

4 interests.

Research in context

Evidence before this study

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

Added value of this study

This is the first large multi-national population-based cohort study of childhood r-hGH treated patients reporting overall- and cause-specific mortality data from all eight participating SAGhE countries with >400,000 patient-years and up to 25 years of follow-up. All-cause mortality was found to be strongly related to the underlying diagnosis and not significantly associated with increased mean or cumulative r-hGH dose. In patients with isolated GH deficiency or idiopathic short stature, r-hGH 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 enhances earlier published data from post-marketing surveillance studies suggesting no significant effect of childhood r-hGH treatment on overall mortality in patients with isolated GH deficiency or idiopathic short stature. For those patients with an inherent increased mortality risk, our study noted increased mortality rates most likely related to the underlying diagnosis. Although our present data are in general reassuring, we recommend continued long-term surveillance of childhood r-hGH treated patients to allow detection of any increased mortality risks later in life.

1 Introduction

2   Recombinant human growth hormone (r-hGH) has been used for more than 3 decades and the

3   indications have expanded worldwide, now including not only GH deficiency but also many

4   other causes of short stature. The overall experience from many thousands of patient years of

5   treatment suggests on balance that r-hGH is safe.[1] Nevertheless, a systematic review with meta-

6   analysis of articles published until September 2013 showed a slight but significant increase in

7   all-cause mortality in patients treated with r-hGH in childhood and adolescence.[2]

8   Unfortunately, most of our knowledge regarding r-hGH safety is based on cohort studies with

9   short follow-up of adverse events within databases kept by pharmaceutical companies. To

10 overcome these limitations and study the long-term safety of r-hGH therapy, we set up a

11 European consortium (SAGhE: Safety and Appropriateness of Growth hormone treatments in

12 Europe) involving eight countries (Belgium, France, Germany, Italy, The Netherlands, Sweden,

13 Switzerland, and United Kingdom) and merged datasets on ~24,000 young adults treated with

14 r-hGH during childhood and adolescence.[3]

15 Two preliminary reports, based on a subset of local datasets within SAGhE, have presented

16 mortality data in young adult patients who were treated with r-hGH during childhood for

17 isolated idiopathic GH deficiency, small for gestational age or idiopathic short stature: a study[4]

18 from France reported a significant increase in all-cause mortality and cause-specific mortality

19 for bone tumours and cerebral haemorrhage in 6500 patients, while in an analysis[5] from

20 Sweden, The Netherlands, and Belgium, no deaths from cancer or cerebrovascular disease were

21 identified among 2500 patients.

22 The current study presents data from the entire dataset of all eight countries of the SAGhE

23 consortium. Our main objective was to study long-term overall and cause-specific mortality in

24 young adult patients who were treated with r-hGH during childhood and relate this to the

25 underlying diagnosis. Secondary objectives included analyses of dose-response, mean and

1   cumulative r-hGH dose, impact of time since end of r-hGH treatment, and duration of r-hGH

2   treatment.

3

Methods

Study population and study design

The cohort study was conducted in eight European countries as described in detail earlier.[3] In brief, we attempted to identify, in each country, all resident patients who were born before 1991-5 (depending on the country), who had been treated with r-hGH during childhood from the time such treatment was first introduced (1984-6), irrespective of treatment duration, at any time up to a date during 2007-9 (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. Data on demographic and GH-related variables were extracted from existing databases and case-notes. We followed the participants for mortality via national population-based registries in Belgium, The Netherlands, Sweden, and UK and by a range of methods in the other four countries (Supplementary Appendix)..[3] Mortality was followed from the earliest r-hGH treatment date (except Italy: January 1, 1999 or earliest r-hGH treatment date if later) until a censoring date which varied between countries (September 21, 2009-December 31, 2013). The 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) or from individual death certificates in Italy, Switzerland, and the UK, or from medical records and questionnaires in Germany and in The Netherlands from medical records. Information was missing regarding the specific causes of death for a few cases, as reflected by a slightly lower number of patient-years in those analyses (Table S2).

As detailed earlier, follow-up for mortality was 96.7% complete, excluding Italy, where information on completeness was not available.[3] Cause-specific mortality data and population

counts for the general population were obtained to derive expected mortality from national mortality statistics. Cancer mortality has earlier been reported from this cohort.[6]

Risk group classification

Certain diagnoses leading to GH treatment are known to be themselves associated with increased mortality, which complicates analyses in a mixed cohort with underlying diagnoses stretching from healthy individuals with idiopathic short stature to those patients with a brain tumour or chronic renal failure diagnosed prior to treatment start. In an attempt to overcome this problem, we decided to categorize all patients a priori into three "risk groups" based on their diagnosis leading to GH treatment, as previously[3] described (Supplementary Appendix and Table S1).. If a patient had several diagnoses, categorization was based on the diagnoses belonging to the highest risk group.

The details of the risk classification have been described earlier[3] and the distribution by country are presented in Tables 1 and 2, respectively. Risk group 1 was further sub-divided into patients treated for isolated GH deficiency or idiopathic short stature (group 1a) and short children born small for gestational age (group 1b; birth weight and/or length <-2SDS according to the different national references).[7] Risk group 2 included treated patients with: multiple pituitary hormone deficiency (GH and at least one additional pituitary hormone deficiency), defined paediatric syndromes (such as Turner, Noonan, neurofibromatosis type 1, Prader-Willi and Fanconi syndromes) 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.

1   **Statistical analyses**

2   We calculated person-years at risk of death for each patient by sex, 5 year age-group, single

3   calendar year, and country, starting from the date of first treatment with r-hGH and ending at

4   whichever occurred earliest of: death, loss to follow-up, or a fixed end-date for each country as

5   previously detailed.[3] The analyses were further stratified by different time scales and GH-

6   dosing categories as detailed in the tables. The mean daily dose of r-hGH was calculated from

7   data retrieved at each clinic visit. Time-dependent variables (time since treatment and

8   cumulative dose) were analysed in a time-dependent manner i.e. person-years and events for

9   each participant were split and allocated to the level of the variable the participant belonged to

10 at each point in follow-up, so that they contributed to different levels of the variable as they

11 progressed through these. The cumulative dose was calculated by multiplying the mean daily

12 dose by the total number of treatment days. National population rates were used to calculate

13 standardized mortality ratios (SMRs) and trends tested by the Poisson trend statistic.[7] Absolute

14 excess rates (AERs) were calculated by subtracting expected from observed numbers of cases,

15 dividing by person-years at risk and multiplying by 10,000.

16 Main outcome analyses included long-term overall and cause-specific mortality related to the

17 underlying diagnosis. Conclusion about treatment effect was based on the confidence intervals

18 reported. Sub-analyses included effects of mean and cumulative doses of r-hGH, impact of

19 time since end of treatment, and duration of treatment. Sub-analyses were also performed

20 stratifying data into France, and all other countries, to explore any country bias linked to the

21 high proportion of patients from France. Another sub-analysis was conducted where the risk

22 was recalculated once patients had ceased r-hGH for a period greater than two years, because

23 an adverse event, irrespective of causality, often leads to treatment termination.[89] All p-values

24 are 2-sided and a value of less than 0·05 was considered statistically significant.

25

1   **Role of the funding source**

2   The funders of the study had no role in study design, data collection, data analysis, data

3   interpretation, or writing of the report. The corresponding author had full access to all the data

4   in the study and had final responsibility for the decision to submit for publication.

1 # Results

2 **Characteristics of the study cohort**

3 The cohort consisted of 24,232 patients and of these 13,145 (54·2%) were classified as low risk

4 (groups 1a and 1b), 7,188 (29·7%) moderate risk (group 2), 3,587 (14·8%) high risk (group 3),

5 and 312 (1·3%) not classifiable. Patient characteristics by risk group are detailed in Table ~~1~~3.

6 There was a male predominance except in risk group 2, which included the patients with Turner

7 syndrome. Between risk groups, there were small differences in age at treatment start (9·9-11·1

8 years) and treatment duration (4·5-6·0 years). The mean dose of r-hGH was lower in risk groups

9 1a and 3 (26·3 and 25·6 µg/kg/day, respectively) than in risk groups 1b and 2 (33·3 and 35·0

10 µg/kg/day, respectively). In total, 10,316 patients (42·6%) came from France and 13,916

11 (57·4%) from the other seven countries (Table ~~S2~~2).

12 **Overall mortality by risk group**

13 For patients in the low risk group 1a, overall mortality was not significantly increased [SMR

14 1·1 (95% confidence interval (CI) 0·9-1·3)] (Table ~~2~~4). When analysed separately, this was

15 true for both France [SMR 1·1 (0·9-1·4); Table ~~S5~~S3] and the other seven countries [SMR 1·0

16 (0·7-1·4); Table ~~S6~~S4]. Mean daily dose of r-hGH as well as the cumulative dose of r-hGH did

17 not affect mortality in risk group 1a (Table ~~2~~4). Time since start of r-hGH treatment was

18 borderline significantly associated with mortality in risk group 1a (p trend = 0·05; Table ~~2~~4).

19 The highest SMR was seen for those with a treatment duration <2 years [SMR 1·6 (1·1-2·3)]

20 and those with the shortest time since end of treatment [<1 year; SMR 3·3 (1·8-5·7); Table ~~2~~4].

21 However, in the analysis with a 2-year lag period after end of r-hGH treatment, the SMR was

22 no longer significant with treatment duration <2 years [SMR 1·2 (0·8-2·0); Table ~~S7~~S5].

23 For patients belonging to risk group 1b, overall mortality was significantly increased when

24 analysed for all countries [SMR 1·5 (1·1-1·9); Table ~~2~~4]. When analysed separately, risk was

25 significantly increased in France [SMR 1·7 (1·2-2·4); Table ~~S5~~S3], but not significantly in the

1   other seven countries combined [SMR 1·2 (0·8-1·9) Table ~~S6~~S4]. For cumulative dose of r-

2   hGH and mean daily dose, there was no association with increased mortality, but for the highest

3   mean daily dose category [> 50 µg/kg/d] a SMR of 2·7 (1·4-5·4) was noted (Table ~~2~~4). Time

4   since start of r-hGH treatment was not associated with mortality in risk group 1b, but an

5   increased risk in the early years after end of treatment was found (Table ~~2~~4).

6   For patients belonging to risk groups 2 and 3, overall mortality was markedly increased [SMRs

7   3·8 (3·3-4·4) and 17·1 (15·6-18·7), respectively; Table ~~2~~4] and when analysed separately, the

8   risk was similar in France [Table ~~S5~~S3] and the other seven countries combined [Table ~~S6~~S4].

9   Risks in these groups did not relate to daily dose or cumulative dose of GH and decreased with

10   longer duration of treatment. As detailed in Table ~~S3~~S1, all-cause mortality was increased for

11   patients with several individual underlying diagnoses belonging to risk groups 2 and 3. The

12   highest mortality was found in patients with tumour diagnoses prior to treatment start, greatest

13   for patients with a pre-existing central nervous system tumour [SMR 23·6 (21·0-26·6); Table

14   ~~S3~~S1]. In risk group 3, a higher SMR was noted in females [33·2 (28·8-38·3)] compared with

15   males [12·7 (11·2-14·3)], but the difference decreased notably when comparing AER [83·7

16   (71·9-96·9) and 73·4 (64·1-83·6) for females and males, respectively], Table ~~S4~~S2.

17   **Cause-specific mortality by risk group**

18   Cause-specific mortality is detailed in Table ~~3~~5. Although the category accidents and violence

19   was by far the most common individual cause of death for risk groups 1a and 1b, the mortality

20   rate from this cause was not significantly increased when compared with that in the general

21   population. Mortality from neoplasms was also not increased for risk groups 1a and 1b [SMR

22   0·9 (0·4-1·8) and 0·6 (0·1-2·4), respectively]. In contrast, mortality from diseases in blood and

23   blood forming organs was significantly increased for risk group 1a [SMR 8·2 (2·6- 25·4)].

24   Mortality from diseases of the circulatory system was significantly increased for both groups

25   1a and 1b [SMR 2·4 (1·2-4·6) and 3·7 (1·7-8·3), respectively], where the risk for 1b was mostly

1 driven by the French sub-cohort. Within the circulatory system, mortality due to

2 cerebrovascular disease was significantly increased for risk group 1a [SMRs 4·7 (1·8-12·5)]

3 while the risk of circulatory diseases other than ischemic heart disease and cerebrovascular

4 disease was raised in group 1b [SMRs 5·0 (2·1-11·9)].

5 Table 46 details the cause of death for each of the 19 patients who died from a circulatory

6 disease or a disease in blood and blood-forming organs in risk groups 1a (n=12) and 1b (n=7).

7 A cardiac cause was reported in eight patients and a cerebrovascular disease was the second

8 most common cause of death (n=5). All patients in risk groups 1a and 1b who died from a

9 circulatory cause were treated within the approved dose ranges except for one patient who died

10 from cardiac arrest and was treated with a higher r-hGH dose (61·9 µg/kg/day). Of the four

11 deaths from blood and blood-forming organs, two were caused by immunodeficiency and one

12 each by aplastic anaemia and coagulation defect.

13 For the moderate and high-risk groups (groups 2 and 3), cause-specific mortality was increased

14 for several specific categories most likely due to the underlying diagnosis within these risk

15 groups (Table 35).

1 **Discussion**

2 Through a collaboration of eight European countries, creating a joint cohort of childhood r-

3 hGH treated patients, we have been able to carry out the largest long-term mortality follow-up

4 study of the included patient groups to date. Due to the heterogeneity of patients treated with r-

5 hGH, a risk classification was carried out to investigate the overall and cause-specific mortality

6 in the different risk groups. In patients with an a priori low mortality risk, no increased overall

7 mortality was seen. However, an increased overall mortality was confirmed for patients whose

8 underlying diagnosis was known a priori to be associated with increased mortality risk.

9 For risk group 1a, comprising isolated GH deficiency and idiopathic short stature, no increased

10 overall mortality was found. This finding improves upon previous studies, as none of them are

11 directly comparable to ours, since we have analysed a large patient group without an apparent

12 underlying inherent increased mortality risk.[9-12][10-13] Furthermore, most earlier studies are

13 smaller, include a mix of adult- and childhood-onset patients, differing in the indication of

14 starting treatment, and with shorter follow-up time, which altogether limits possible conclusions

15 of long-term mortality risks. There was a relation to short duration of treatment, but analyses

16 with a 2-year lag period showed this likely to be an artefact of cessation of treatment in severely

17 ill children. Moreover, no association was found between daily or cumulative dose and overall

18 mortality, arguing against a relationship between r-hGH dose and overall mortality in this risk

19 group.

20 In patients born small for gestational age, risk group 1b, we found an increased overall

21 mortality, where a sensitivity analysis showed that this was driven by the French sub-cohort. It

22 is uncertain if this increased risk could be attributed to the r-hGH treatment per se as it has been

23 shown in a large population-based study that children born small for gestational age have an

24 increased mortality risk at younger ages compared with normal birth weight children.[13][14] In

25 contrast to our cohort, those risks were however reduced compared with the general population

1   with increasing age. Another study on r-hGH treated low-risk patients also showed the

2   importance of birth size in relation to mortality risk, where an increased SMR by conventional

3   calculations normalized using a continuous hazard model also including birth

4   characteristics.[14][15] Although mortality was increased for the highest dose category (>50

5   µg/kg/d), no overall association was found between daily or cumulative dose and mortality

6   arguing against a relationship between r-hGH dose and mortality in risk group 1b. When

7   analysing cause-specific mortality for risk groups 1a and 1b, we found a significantly increased

8   mortality risk due to diseases of the circulatory system. In line with our findings, increased

9   mortality risk due to circulatory diseases has previously been reported in a mixed cohort of

10   adult- and childhood onset isolated GH deficiency patients.[11][12] Within circulatory diseases in

11   our risk group 1a, mortality was increased in the sub-category cerebrovascular diseases in line

12   with an earlier report[15][16] and a previous publication regarding cerebrovascular morbidity in the

13   French SAGhE cohort.[16][17] Several possible mechanisms could be considered for this

14   association. As recently reviewed by di Somma *et al,* both states of excess as well as

15   insufficiency of GH are associated with increased cardiovascular risks.[17][18] Thus, it is likely that

16   GH levels and cardiovascular health are related and that both excess and insufficiency of GH

17   should be avoided.

18   In risk group 1b, the increased risk of circulatory mortality is in accordance with the known

19   raised risks of cardiovascular diseases in patients born small for gestational age, as first reported

20   by Barker *et al*[18] ~~and later confirmed in large epidemiological studies.[19]~~ and later confirmed in

21   large epidemiological studies. [19-21][20-22] Furthermore, subjects born small for gestational age are

22   known to have higher blood pressure and increased risk for cardiovascular events at a relatively

23   young age, which might contribute or even explain their higher vascular mortality.[22][23]

24   Cause-specific mortality from diseases of blood and blood forming organs seemed to be

25   increased for both risk group 1a and 1b, but only significantly for group 1a. However, it is

1   important to note that the total number of deaths was low; in risk group 1a three cases and in

2   group 1b only one case.

3   Increased overall mortality was found in risk groups 2 and 3, but it is not possible to conclude

4   that this is due to r-hGH treatment per se, since these groups have underlying diagnoses that are

5   associated with increased mortality, as described in multiple reports in such untreated

6   patients.[23,24,25] Furthermore, groups 2 and 3 did not show any relation of risk to daily or

7   cumulative GH dose, which argues against an effect of GH treatment on mortality. Patients in

8   risk group 2, and particularly those in risk group 3, were found to have increased cause-specific

9   mortality for neoplasms which is not surprising and likely related to the underlying

10   diagnoses.[25,26,27] Furthermore, the overall SMR in risk group 3 was clearly higher in females

11   compared with males, likely explained mainly by a lower mortality risk in the female general

12   population, as indicated by the lesser difference in AERs. A higher mortality risk in females

13   has also been reported in a large follow-up study of childhood cancer survivors.[2627]

14   Our study has several limitations. First, this study, similarly to other r-hGH safety studies,

15   lacked an untreated control group and we may therefore either have under- or overestimated

16   any difference in mortality risk by comparing instead with the general population. In risk group

17   1a, underlying risk factors such as being born small for gestational age or having other severe

18   diagnoses have been excluded, making them less likely to have certain underlying mortality

19   risks compared with the general population, in contrast to the other risk groups, where the

20   underlying diagnosis was expected to increase their mortality. Secondly, we have not been able

21   to adjust for possible confounders, such as socio-economic factors or birth characteristics.

22   Thirdly, and we do not have any information on adult r-hGH treatment andor adherence to the

23   r-GH treatment which could influence mortality risks. Thirdly, although our cohort of treated

24   patients is large, mortality in this age group is quite rare leading to wide confidence intervals

25   and some uncertainty for certain point estimates of SMR. Fourthly, comparisons of SMRs rely

1   for strict validity on whether there was interaction, and will be less valid if there was appreciable

2   interaction. Lastly, combining patients from eight different countries, with potential differences

3   in diagnostic and clinical practice, may have created heterogeneity in the data.

4   In conclusion, this European multi-national collaborative study shows no significant increase

5   in overall mortality in low-risk patients with isolated GH deficiency or idiopathic short stature,

6   although the possibility of certain cause-specific cardiovascular and haematological mortality

7   risks remains. For those patients with an inherent increased mortality risk, we confirmed

8   increased mortality rates most likely related to the underlying diagnosis. Although our present

9   data are in general reassuring, we acknowledge several limitations of our study and recommend

10 continued long-term surveillance of childhood r-hGH treated patients to allow detection of any

11 increased mortality risks later in life.

Contributors

LS, GB, SC, PC, JC, AHK, WK, RP, JCC 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 the interpretation of the data, critical revision of the manuscript and approval of the final manuscript.

Data sharing

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

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38

Table 1: Classification of patients[*]

RISK GROUP 1a[†]	RISK GROUP 2	RISK GROUP 3[§]
Isolated growth hormone deficiency	Multiple pituitary hormone deficiency	All malignancies
Idiopathic short stature	Severe cerebral malformation	Langerhans cell histiocytosis
Mild skeletal dysplasia (hypochondroplasia, dyschondrosteosis)	Short stature and severe extra-cerebral malformations	Chronic renal failure
	Chromosomal anomalies incl Turner syndrome	After bone marrow- or solid transplantation
	Clinically defined syndromes	Syndromes with known increased risk for malignancies; e.g. Bloom, Fanconi, Down, and chromosomal breakage syndromes
RISK GROUP 1b[‡]	Severe chronic paediatric diseases	
Short stature in children born small for age	Long-term steroid use in chronic inflammatory diseases	
	Benign pituitary tumours	
	Cushing syndrome	

[*]For more detailed description of risk classification, please see Table A2 in Swerdlow et al. Description of the SAGhE Cohort: A Large European Study of Mortality and Cancer Incidence Risks after Childhood Treatment with Recombinant Growth Hormone. Hormone Research in Paediatrics 2015;84:172-83.
[†]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 irrespectively of their endocrine deficiency (severe vs non severe GH deficiency, isolated vs multiple).

Table 2: Number of patients by country and risk group

Country	Risk group 1a	1b	2	3	U/K	Total
Belgium	336	168	607	271	0	1,382
Switzerland	293	76	257	120	5	751
France	5,043	1,823	2,180	1,245	25	10,316
Germany	789	168	644	178	5	1,784
Italy	980	143	167	54	20	1,364
Netherlands	402	244	780	320	22	1,768
Sweden	974	602	852	338	199	2,965
UK	463	643	1,699	1,061	36	3,902
Total	**9,280**	**3,867**	**7,186**	**3,587**	**312**	**24,232**

U/K = Not classifiable

Table 3: Patient characteristics by risk group

	All groups	Risk group 1a	1b	2	3
Number of patients	24,232	9,290	3,855	7,188	3,587
Mean follow-up period, years	16·5	16·3	17·2	17·0	15·4
Person-years^	400,229	151,004	66,229	122,319	55,392
Number of male patients[†]	13,425 (55·4)	6,331 (68·1)	2,409 (62·5)	2,329 (32·4)	2,168 (60·4)
Birth weight SDS[*‡]	-0·79 (1·32)	-0·35 (1·02)	-1·65 (1·35)	-0·98 (1·34)	-0·23 (1·15)
Height SDS 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 GH 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)
Mean dose of GH (µg/kg/d)[*]	30·1 (12·7)	26·3 (11·0)	33·3 (17·4)	35·0 (10·8)	25·6 (8·6)

^Person-years at risk of death[3]
[*]Mean (SD)
[†]N (%)
[‡]Missing data for 26·9%
SDS = Standard Deviation Score
GH = Growth Hormone

Table 4: Overall mortality by risk group, sex and treatment

	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)
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)												
0-4	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	0·1	0·0 (·, ·)	1	0·2	4·6 (0·6, 32·7)	0	0·1	0·0 (·, ·)
p trend		0·05			0·38			0·04			<0·001	
Duration of treatment (years)												
<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)
p trend		0·13			0·02			<0·001			<0·001	
Time since end of treatment (years)												
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	0·0 (·, ·)	3	0·2	12·4 (4·0, 38·3)
Unknown	7	6·9	1·0 (0·5, 2·1)	0	1·6	0·0 (·, ·)	16	5·2	3·1 (1·9, 5·0)	34	2·2	15·7 (11·2, 21·9)
p trend		0·11			0·04			<0·001			0·45	
Mean daily dose of r-hGH (µg/kg/d)												
<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	0·0 (·, ·)	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	0·0 (·, ·)	28	6·6	4·2 (2·9, 6·1)	9	0·9	9·9 (5·2, 19·1)
≥50	0	1·0	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)
p trend		0·85			0·60			0·78			0·68	
Cumulative r-hGH dose (mg/kg)												
<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)
p trend		0·77			0·40			0·48			<0·001	

SMR = Standardized Mortality Ratio

r-hGH =Recombinant human Growth Hormone

Table 5: Cause-specific mortality by risk group

Cause (ICD code)	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	0·9	0·0 (·, ·)	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 & 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 & behavioral disorders (F00-F99)	1	1·8	0·6 (0·1, 3·9)	0	0·7	0·0 (·, ·)	3	1·2	2·5 (0·8, 7·9)	1	0·7	1·4 (0·2, 9·7)
Diseases of nervous system, eye & 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	0·0 (·, ·)	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	0·0	0·0 (·, ·)
Diseases of musculoskeletal system & connective tissue (M00-M99)	0	0·2	0·0 (·, ·)	0	0·1	0·0 (·, ·)	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	0·1	0·0 (·, ·)	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 (·, ·)	0	0·2	0·0 (·, ·)	0	0·0	0·0 (·, ·)
Conditions originating in perinatal period (P00-P96)	0	1·2	0·0 (·, ·)	0	0·8	0·0 (·, ·)	0	1·8	0·0 (·, ·)	0	0·3	0·0 (·, ·)
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 & 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)
By circulatory cause												
Ischemic heart disease	1	0·5	2·2 (0·3, 15·7)	0	0·2	0·0 (·, ·)	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)

SMR = Standardized Mortality Ratio