Accepted author's manuscript. Published in final edited form as: The Lancet Diabetes & Endocrinology 2020; 8(8): 683-692. Publisher DOI: 10.1016/S2213-8587(20)30163-7

Mortality after childhood Growth Hormone treatment – the SAGhE study

Lars Sävendahl* M.D., Ph.D., Rosie Cooke, Anders Tidblad M.D., Ph.D., Dominique Beckers* M.D., Gary Butler* M.D., F.R.C.P.C.H., Stefano Cianfarani* M.D., Peter Clayton* M.D., Joël Coste* M.D., Ph.D., Anita C.S. Hokken-Koelega* M.D., Ph.D., Wieland Kiess* M.D., Claudia E. Kuehni* M.D., Kerstin Albertsson-Wikland M.D., Ph.D., Annalisa Deodati, Emmanuel Ecosse, Ruth Gausche, Claudio Giacomozzi M.D., Daniel Konrad M.D., Ph.D., Fabienne Landier, Roland Pfaeffle M.D., Grit Sommer Ph.D., Muriel Thomas M.D., Sally Tollerfield, Gladys R.J. Zandwijken M.D., Jean-Claude Carel*# M.D., Anthony J. Swerdlow*# Ph.D., D.M., D.Sc.

From Karolinska Institutet, Stockholm, Sweden (L.S., S.C., A.T.); Institute of Cancer Research, London, UK (R.C.; A.J.S.); University Paris Diderot, France (J-C.C., F.L.); University of Gothenburg, Sweden (K.A-W.); UCL Institute of Child Health, London, UK (G.B., A.D., S.T.); University of Rome Tor Vergata – "Bambino Gesù" Children's Hospital, Italy (S.C., A.D.); Centre for Pediatric Endocrinology, Pediatric Unit, Carlo Poma Hospital, Mantua, Italy (C.G.); University of Manchester, UK (P.C.); University Paris Descartes, France (J.C., E.E.); University of Leipzig, Germany (R.G., W.K, R.P.); Erasmus University Medical Center and Dutch Growth Research Foundation, Rotterdam, The Netherlands (A.C.S.H-K, G.R.J.Z.); Institute of Social and Preventive Medicine, University of Bern, Switzerland (C.E.K., G.S.), Pediatric Endocrinology, Diabetology and Metabolism, Department of Pediatrics, Inselspital, Bern University Hospital, Switzerland (C.E.K., G.S.); Division of Pediatric Endocrinology and Diabetology and Children's Research Centre, University Children's Hospital, Zurich, Switzerland (D.K.); Université Catholique de Louvain, Yvoir, Belgium (D.B); Belgian Society for Pediatric Endocrinology and Diabetology (BESPEED), Brussels, Belgium (D.B., M.T).

*Principal investigators of the SAGhE project in each country

#Equal contribution

Corresponding author: Prof Lars Sävendahl, Department of Women's and Children's Health, Karolinska Institutet and Pediatric Endocrinology Unit, Karolinska University Hospital J9:30,

Visionsgatan 4, SE-17164 Solna, Sweden. Telephone: +4670 5635120; email: lars.savendahl@ki.se

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.

Funding

The funding sources of the study had no role in the study design, data collection, data analyses, data interpretation, or writing of the report. All funding sources are listed under Declaration of 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.

Introduction

Recombinant human growth hormone (r-hGH) has been used for more than 3 decades and the indications have expanded worldwide, now including not only GH deficiency but also many other causes of short stature. The overall experience from many thousands of patient years of treatment suggests on balance that r-hGH is safe.[1] Nevertheless, a systematic review with meta-analysis of articles published until September 2013 showed a slight but significant increase in all-cause mortality in patients treated with r-hGH in childhood and adolescence.[2]

Unfortunately, most of our knowledge regarding r-hGH 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 r-hGH therapy, we set up a European consortium (SAGhE: Safety and Appropriateness of Growth hormone treatments in Europe) involving eight countries (Belgium, France, Germany, Italy, The Netherlands, Sweden, Switzerland, and United Kingdom) and merged datasets on ~24,000 young adults treated with r-hGH during childhood and adolescence.[3]

Two preliminary reports, based on a subset of local datasets within SAGhE, have presented mortality data in young adult patients who were treated with r-hGH during childhood for isolated idiopathic GH deficiency, small for gestational age or idiopathic short stature: a study[4] from France reported a significant increase in all-cause mortality and cause-specific mortality for bone tumours and cerebral haemorrhage in 6500 patients, while in an analysis[5] from Sweden, The Netherlands, and Belgium, no deaths from cancer or cerebrovascular disease were identified 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 who were treated with r-hGH during childhood and relate this to the underlying diagnosis. Secondary objectives included analyses of dose-response, mean and

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

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

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. 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.

Statistical analyses

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 r-hGH and ending at whichever occurred earliest of: death, loss to follow-up, or a fixed end-date for each country as previously detailed.[3] The analyses were further stratified by different time scales and GH-dosing categories as detailed in the tables. The mean daily dose of r-hGH 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 i.e. 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 progressed through these. 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 standardized mortality ratios (SMRs) and trends tested by the Poisson trend statistic. Absolute excess rates (AERs) 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. Conclusion about treatment effect was based on the confidence intervals reported. Sub-analyses included effects of mean and cumulative doses of r-hGH, impact of time since end of treatment, and duration of treatment. Sub-analyses were also performed stratifying data into France, and all other countries, to explore any country bias linked to the high proportion of patients from France. Another sub-analysis was conducted where the risk was recalculated once patients had ceased r-hGH for a period greater than two years, because an adverse event, irrespective of causality, often leads to treatment termination.[9] All p-values are 2-sided and a value of less than 0·05 was considered statistically significant.

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

Characteristics of the study cohort

The cohort consisted of 24,232 patients and of these 13,145 (54·2%) were classified as low risk (groups 1a and 1b), 7,188 (29·7%) moderate risk (group 2), 3,587 (14·8%) high risk (group 3), and 312 (1·3%) not classifiable. Patient characteristics by risk group are detailed in Table 3. There was a male predominance except in risk group 2, which included the patients with Turner syndrome. Between risk groups, there were small differences in age at treatment start (9·9-11·1 years) and treatment duration (4·5-6·0 years). The mean dose of r-hGH was lower in risk groups 1a and 3 (26·3 and 25·6 µg/kg/day, respectively) than in risk groups 1b and 2 (33·3 and 35·0 µg/kg/day, respectively). In total, 10,316 patients (42·6%) came from France and 13,916 (57·4%) from the other seven countries (Table 2).

Overall mortality by risk group

For patients in the low risk group 1a, overall mortality was not significantly increased [SMR 1·1 (95% confidence interval (CI) 0·9-1·3)] (Table 4). When analysed separately, this was true for both France [SMR 1·1 (0·9-1·4); Table S3] and the other seven countries [SMR 1·0 (0·7-1·4); Table S4]. Mean daily dose of r-hGH as well as the cumulative dose of r-hGH did not affect mortality in risk group 1a (Table 4). Time since start of r-hGH treatment was borderline significantly associated with mortality in risk group 1a (p trend = 0·05; Table 4). The highest SMR was seen for those with a treatment duration <2 years [SMR 1·6 (1·1-2·3)] and those with the shortest time since end of treatment [<1 year; SMR 3·3 (1·8-5·7); Table 4]. However, in the analysis with a 2-year lag period after end of r-hGH treatment, the SMR was no longer significant with treatment duration <2 years [SMR 1·2 (0·8-2·0); Table S5].

For patients belonging to risk group 1b, overall mortality was significantly increased when analysed for all countries [SMR 1·5 (1·1-1·9); Table 4]. When analysed separately, risk was significantly increased in France [SMR 1·7 (1·2-2·4); Table S3], but not significantly in the

other seven countries combined [SMR 1·2 (0·8-1·9) Table S4]. For cumulative dose of r-hGH and mean daily dose, there was no association with increased mortality, but for the highest mean daily dose category [> 50 μg/kg/d] a SMR of 2·7 (1·4-5·4) was noted (Table 4). Time since start of r-hGH treatment was not associated with mortality in risk group 1b, but an increased risk in the early years after end of treatment was found (Table 4).

For patients belonging to risk groups 2 and 3, overall mortality was markedly increased [SMRs 3·8 (3·3-4·4) and 17·1 (15·6-18·7), respectively; Table 4] and when analysed separately, the risk was similar in France [Table S3] and the other seven countries combined [Table S4]. Risks in these groups did not relate to daily dose or cumulative dose of GH and decreased with longer duration of treatment. As detailed in Table S1, all-cause mortality was increased for patients with several individual underlying diagnoses belonging to risk groups 2 and 3. The highest mortality was found in patients with tumour diagnoses prior to treatment start, greatest for patients with a pre-existing central nervous system tumour [SMR 23·6 (21·0-26·6); Table S1]. In risk group 3, a higher SMR was noted in females [33·2 (28·8-38·3)] compared with males [12·7 (11·2-14·3)], but the difference decreased notably when comparing AER [83·7 (71·9-96·9) and 73·4 (64·1-83·6) for females and males, respectively], Table S2.

Cause-specific mortality by risk group

Cause-specific mortality is detailed in Table 5. Although the category accidents and violence was by far the most common individual cause of death for risk groups 1a and 1b, the mortality rate from this cause was not significantly increased when compared with that in the general population. Mortality from neoplasms was also not increased for risk groups 1a and 1b [SMR 0·9 (0·4-1·8) and 0·6 (0·1-2·4), respectively]. In contrast, mortality from diseases in blood and blood forming organs was significantly increased for risk group 1a [SMR 8·2 (2·6- 25·4)]. Mortality from diseases of the circulatory system was significantly increased for both groups 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

driven by the French sub-cohort. Within the circulatory system, mortality due to cerebrovascular disease was significantly increased for risk group 1a [SMRs 4·7 (1·8-12·5)] while the risk of circulatory diseases other than ischemic heart disease and cerebrovascular disease was raised in group 1b [SMRs 5·0 (2·1-11·9)].

Table 6 details the cause of death for each of the 19 patients who died from a circulatory disease or a disease in blood and blood-forming organs in risk groups 1a (n=12) and 1b (n=7). A cardiac cause was reported in eight patients and a cerebrovascular disease was the second most common cause of death (n=5). 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 r-hGH dose (61·9 μg/kg/day). Of the four deaths from blood and blood-forming organs, two 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 most likely due to the underlying diagnosis within these risk 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

with increasing age. Another study on r-hGH treated low-risk patients also showed the importance of birth size in relation to mortality risk, where an increased SMR by conventional calculations normalized using a continuous hazard model also including birth characteristics.[15] Although mortality was increased for the highest dose category (>50 μg/kg/d), no overall association was found between daily or cumulative dose and mortality arguing against a relationship between r-hGH 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 adult- and childhood onset isolated GH deficiency patients.[12] Within circulatory diseases in our risk group 1a, mortality was increased in the sub-category cerebrovascular diseases in line with an earlier report[16] and a previous publication regarding cerebrovascular morbidity in the French SAGhE cohort.[17] Several possible mechanisms could be considered for this association. As recently reviewed by di Somma *et al,* both states of excess as well as insufficiency of GH are associated with increased cardiovascular risks.[18] Thus, it is likely that GH levels and cardiovascular health are related and that both excess and insufficiency of GH should be avoided.

In risk group 1b, the increased risk of circulatory mortality is in accordance with the known raised risks of cardiovascular diseases in patients born small for gestational age, as first reported by Barker *et al*[19] and later confirmed in large epidemiological studies.[20-22] Furthermore, subjects born small for gestational age are known to have higher blood pressure and increased risk for cardiovascular events at a relatively young age, which might contribute or even explain their higher vascular mortality.[23]

Cause-specific mortality from diseases of blood and blood forming organs seemed to be increased for both risk group 1a and 1b, but only significantly for group 1a. However, it is

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

Increased overall mortality was found in risk groups 2 and 3, but it is not possible to conclude that this is due to r-hGH treatment per se, since these groups have underlying diagnoses that are associated with increased mortality, as described in multiple reports in such untreated patients.[24,25] Furthermore, groups 2 and 3 did not show any relation of risk to daily or cumulative GH dose, which argues against an effect of GH 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 not surprising and likely related to the underlying diagnoses.[26,27] Furthermore, the overall SMR in risk group 3 was clearly higher in females compared with males, likely explained mainly by a lower mortality risk in the female general population, as indicated by the lesser difference in AERs. A higher mortality risk in females has also been reported in a large follow-up study of childhood cancer survivors.[27]

Our study has several limitations. First, this study, similarly to other r-hGH safety studies, lacked an untreated control group and we may therefore either have under- or overestimated any difference in mortality risk by comparing instead with the general population. In risk group 1a, underlying risk factors such as being born small for gestational age or having other severe diagnoses have been excluded, making them less likely to have certain underlying mortality risks compared with the general population, in contrast to the other risk groups, where the underlying diagnosis was expected to increase their mortality. Secondly, we have not been able to adjust for possible confounders, such as socio-economic factors or birth characteristics and we do not have any information on adult r-hGH treatment or adherence to the r-GH treatment which could influence mortality risks. Thirdly, although our cohort of treated patients is large, mortality in this age group is quite rare leading to wide confidence intervals and some uncertainty for certain point estimates of SMR. Fourthly, comparisons of SMRs rely for strict

validity on whether there was interaction, and will be less valid if there was appreciable interaction. Lastly, combining patients from eight different countries, with potential differences in diagnostic and clinical practice, may have created heterogeneity in the data.

In conclusion, this European multi-national collaborative study shows no significant increase in overall mortality in low-risk patients with isolated GH deficiency or idiopathic short stature, although the possibility of certain cause-specific cardiovascular and haematological mortality risks remains. For those patients with an inherent increased mortality risk, we confirmed increased mortality rates most likely related to the underlying diagnosis. Although our present data are in general reassuring, we acknowledge several limitations of our study and recommend continued long-term surveillance of childhood r-hGH treated patients to allow detection of any 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.

Declaration of interests

This work was supported by funding in all countries from the European Union (HEALTH-F2-2009-223497). In addition, there was funding, in Belgium, from the Belgian Study Group for Paediatric Endocrinology; in France, the Agence Française de Sécurité Sanitaire des Produits de Santé (the French drug safety agency; to J.-C.C.), Direction Générale de la Santé (French Ministry of Health; to J.-C.C.), and the Institut National du Cancer (to J.-C.C.); in Sweden, from the Swedish Research Council (K2014-55X-22516 and 2015-02406; to L.S.), Regional University Hospital Grants (20090376, 20120597, 20140566, 20150528 and 20170064; to L.S.), the Swedish Cancer Society (CAN 2011/704; to L.S.), the Swedish Childhood Cancer Foundation (PROJ11/100 and PR2014-0167; to L.S.), and from Government grants under the ALF agreement ALFGBG-812951 (to K.A.-W.); in Switzerland, from the Swiss Cancer League (KLS-02586-02-2010 and KLS-2948-02-2012); and in the United Kingdom, University College London and the UK Child Growth Foundation (to G.B.), and NHS funding to the NIHR Biomedical Research Centre (A.S.). The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

LS reports personal fees and non-financial support from Ascendis, Hexal, Merck, Novo Nordisk, Pfizer, and Sandoz, outside the submitted work. AT reports personal fees from Pfizer, outside the submitted work. DB reports personal fees from the Belgian Society for Paediatric Endocrinology and Diabetology, personal fees and non-financial support from Novo Nordisk, Merck, and Ferring, during the conduct of the study; personal fees and non-financial support from Novo Nordisk, Merck, and Ferring, outside the submitted work. GB reports other support from Novo Nordisk, Pfizer, Sandoz, and Ferring, outside the submitted work. SC reports personal fees from Merck, Pfizer, Sandoz, Novo Nordisk, and Merck, outside the submitted work. PC reports other support from Merck and Lumos, outside the submitted work. AHK reports personal fees from Pfizer and Novo Nordisk as member of Pfizer International Growth Database (KIGS) Steering Committee and Novo Nordisk Advisory Board on GH treatment, and personal fees from Novo Nordisk, Merck-Serono and Pfizer, outside the submitted work.

RP reports personal fees from Novo Nordisk, Pfizer, Merck Serono, Ipsen, and Sandoz, outside the submitted work. GS reports non-financial support from Novo Nordisk, outside the submitted work. ST reports personal fees from Merck, Novo Nordisk, Ferring, and Sandoz, outside the submitted work. JCC reports other support from Lilly and Pfizer, outside the submitted work. All the other authors report no competing interests.

Data sharing

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

Acknowledgements

We gratefully acknowledge the assistance in all countries of the GH patients and their families. We also thank: in Belgium, Colienne de la Barre, Christine Derycke, Siska Verlinde for collecting and verifying data, the members of the Belgian Society for Pediatric Endocrinology and Diabetology (BESPEED, previously BSGPE), Liesbet van Eycken and the persons of the Belgian Cancer Registry, the persons of the National Population Registry, the Federal and Regional Death Registries for their essential contribution sharing their data with us, and Professor Marc Maes; in France, Caroline Arnaud-Sarthou, Vean-Eng Ly, and Florentia Kaguelidou for their invaluable contributions. Members of the French SAGhE study steering committee, Jean-Louis Chaussain (Académie de Médecine), Natalie Hoog-Labouret (INCa). We thank all the physicians involved in the follow-up of patients and in the review process at Association France Hypophyse and, in particular, those who contributed to the collection of data for the study; in Germany, the physicians and nurses caring for the GH patients and their families, and Mandy Vogel, Leipzig; in Italy, Flavia Pricci, Rome; Pietro Panei, Rome; Giuseppe Scirè, Rome; Gian Luigi Spadoni, Rome; Franco Cavallo, Torino; Patrizia Matarazzo, Torino; Gianluca Aimaretti, Torino; Laura Perrone, Napoli; in The Netherlands, we thank the research assistants of the Dutch Growth Research Foundation for verifying data. We thank the members of the Dutch Growth Hormone Advisory Board of the Dutch Society for Paediatrics, involved in GH treatment of children, and the registration teams of the Comprehensive Cancer Centre Netherlands and Comprehensive Cancer Centre South for the collection of data for The Netherlands Cancer Registry and the scientific staff of the Comprehensive Cancer Centre Netherlands; in Sweden, Birgit Borgström, member of the Swedish SAGhE team, the Board of the National Growth Hormone Registry and also *Principle investigator for national r-hGH trials 1985-1997; *Kerstin Albertsson-Wikland, Stefan Aronson, Peter Bang, Jovanna Dahlgren, Maria Elfving, Jan Gustafsson, Claude Marcus, Svante Norgren, Martin Ritzén,

Johan Svensson, Ulf Westgren, Otto Westphal, and all pediatric endocrinologists and pediatricians involved in the GH treatment of children for their assistance in collecting and verifying data; in Switzerland, Rahel Kuonen, Bern for collecting the data; Urs Eiholzer, Zurich; Jürg Girard, Basel; Sylvia Gschwendt, Zug; Michael Hauschild, Lausanne; Marco Janner, Bern; Beatrice Kuhlmann, Aarau; Dagmar L'Allemand, St. Gallen; Udo Meinhardt, Zurich; Christa Flück, Bern; Franziska Phan-Hug, Lausanne; Eugen Schoenle, Zurich; Michael Steigert; Chur; Urs Zumsteg, Basel for sharing the data; in the UK, the members of the British Society for Paediatric Endocrinology and Diabetes in the 21 historic UK Growth centres for tracking down and contacting former and current patients, in particular; Justin Davies, Southampton; Jo Blair, Liverpool; Fiona Ryan, Oxford; Liz Crowne, Bristol; Savitha Shenoy, Leicester; Jeremy Kirk, Birmingham; Tim Cheetham, Newcastle; Leo Dunkel, London Barts; Tabitha Randell, Nottingham; Sabah Alvi, Leeds; Neil Wright, Sheffield; Justin Warner, Cardiff; Amalia Mayo, Aberdeen; Guftar Shaikh, Glasgow; Louise Bath, Edinburgh; the National Institute for Health Research Medicines for Children Research Network and the Scottish Medicines for Children Network who supported the network of research nurses; the former Pfizer UK KIGS team for assistance in making electronic database records of treated patients available to the local investigators at each of the UK Growth Centres, and Michael Jones and Sharon Squires, London.

References

1. Rosenfeld RG, Cohen P, Robison LL, et al. Long-term surveillance of growth hormone therapy. *The Journal of clinical endocrinology and metabolism* 2012; **97**(1): 68-72.
2. Deodati A, Ferroli BB, Cianfarani S. Association between growth hormone therapy and mortality, cancer and cardiovascular risk: systematic review and meta-analysis. *Growth hormone & IGF research : official journal of the Growth Hormone Research Society and the International IGF Research Society* 2014; **24**(4): 105-11.
3. Swerdlow AJ, Cooke R, Albertsson-Wikland K, 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**(3): 172-83.
4. Carel JC, Ecosse E, Landier F, et al. Long-term mortality after recombinant growth hormone treatment for isolated growth hormone deficiency or childhood short stature: preliminary report of the French SAGhE study. *The Journal of clinical endocrinology and metabolism* 2012; **97**(2): 416-25.
5. Savendahl L, Maes M, Albertsson-Wikland K, et al. Long-term mortality and causes of death in isolated GHD, ISS, and SGA patients treated with recombinant growth hormone during childhood in Belgium, The Netherlands, and Sweden: preliminary report of 3 countries participating in the EU SAGhE study. *The Journal of clinical endocrinology and metabolism* 2012; **97**(2): E213-7.
6. Swerdlow AJ, Cooke R, Beckers D, et al. Cancer risks in patients treated with growth hormone in childhood: the SAGhE European cohort study. *The Journal of clinical endocrinology and metabolism* 2017.
7. Clayton PE, Cianfarani S, Czernichow P, Johannsson G, Rapaport R, Rogol A. Management of the child born small for gestational age through to adulthood: a consensus statement of the International Societies of Pediatric Endocrinology and the Growth Hormone Research Society. *The Journal of clinical endocrinology and metabolism* 2007; **92**(3): 804-10.
8. Breslow NE, Day NE. Statistical methods in cancer research. Volume I - The analysis of case-control studies. *IARC Sci Publ* 1980; (32): 5-338.
9. Savendahl L, Pournara E, Pedersen BT, Blankenstein O. Is safety of childhood growth hormone therapy related to dose? Data from a large observational study. *Eur J Endocrinol* 2016; **174**(5): 681-91.
10. Mo D, Hardin DS, Erfurth EM, Melmed S. Adult mortality or morbidity is not increased in childhood-onset growth hormone deficient patients who received pediatric GH treatment: an analysis of the Hypopituitary Control and Complications Study (HypoCCS). *Pituitary* 2014; **17**(5): 477-85.
11. Child CJ, Zimmermann AG, Chrousos GP, et al. Safety Outcomes During Pediatric GH Therapy: Final Results From the Prospective GeNeSIS Observational Program. *The Journal of clinical endocrinology and metabolism* 2019; **104**(2): 379-89.
12. van Bunderen CC, van Nieuwpoort IC, Arwert LI, et al. Does growth hormone replacement therapy reduce mortality in adults with growth hormone deficiency? Data from the Dutch National Registry of Growth Hormone Treatment in adults. *The Journal of clinical endocrinology and metabolism* 2011; **96**(10): 3151-9.
13. Quigley CA, Child CJ, Zimmermann AG, Rosenfeld RG, Robison LL, Blum WF. Mortality in Children Receiving Growth Hormone Treatment of Growth Disorders: Data From the Genetics and Neuroendocrinology of Short Stature International Study. *The Journal of clinical endocrinology and metabolism* 2017; **102**(9): 3195-205.
14. Wennerstrom EC, Simonsen J, Melbye M. Long-Term Survival of Individuals Born Small and Large for Gestational Age. *PloS one* 2015; **10**(9): e0138594.

15. Albertsson-Wikland K, Martensson A, Savendahl L, et al. Mortality Is Not Increased in Recombinant Human Growth Hormone-treated Patients When Adjusting for Birth Characteristics. *The Journal of clinical endocrinology and metabolism* 2016; **101**(5): 2149-59.
16. Gaillard RC, Mattsson AF, Akerblad AC, et al. Overall and cause-specific mortality in GH-deficient adults on GH replacement. *European journal of endocrinology / European Federation of Endocrine Societies* 2012; **166**(6): 1069-77.
17. Poidvin A, Touze E, Ecosse E, et al. Growth hormone treatment for childhood short stature and risk of stroke in early adulthood. *Neurology* 2014; **83**(9): 780-6.
18. Di Somma C, Scarano E, Savastano S, Savanelli MC, Pivonello R, Colao A. Cardiovascular alterations in adult GH deficiency. *Best practice & research Clinical endocrinology & metabolism* 2017; **31**(1): 25-34.
19. Barker DJ. Fetal origins of coronary heart disease. *Bmj* 1995; **311**(6998): 171-4.
20. Kajantie E, Osmond C, Barker DJ, Forsen T, Phillips DI, Eriksson JG. Size at birth as a predictor of mortality in adulthood: a follow-up of 350 000 person-years. *International journal of epidemiology* 2005; **34**(3): 655-63.
21. Baker JL, Olsen LW, Sorensen TI. Weight at birth and all-cause mortality in adulthood. *Epidemiology (Cambridge, Mass)* 2008; **19**(2): 197-203.
22. Risnes KR, Vatten LJ, Baker JL, et al. Birthweight and mortality in adulthood: a systematic review and meta-analysis. *International journal of epidemiology* 2011; **40**(3): 647-61.
23. Arends NJ, Boonstra VH, Duivenvoorden HJ, Hofman PL, Cutfield WS, Hokken-Koelega AC. Reduced insulin sensitivity and the presence of cardiovascular risk factors in short prepubertal children born small for gestational age (SGA). *Clin Endocrinol (Oxf)* 2005; **62**(1): 44-50.
24. Stochholm K, Hjerrild B, Mortensen KH, Juul S, Frydenberg M, Gravholt CH. Socioeconomic parameters and mortality in Turner syndrome. *Eur J Endocrinol* 2012; **166**(6): 1013-9.
25. Reiss U, Wingen AM, Scharer K. Mortality trends in pediatric patients with chronic renal failure. *Pediatr Nephrol* 1996; **10**(1): 41-5.
26. Schoemaker MJ, Swerdlow AJ, Higgins CD, Wright AF, Jacobs PA, Group UKCC. Cancer incidence in women with Turner syndrome in Great Britain: a national cohort study. *Lancet Oncol* 2008; **9**(3): 239-46.
27. Fidler MM, Reulen RC, Winter DL, et al. Long term cause specific mortality among 34 489 five year survivors of childhood cancer in Great Britain: population based cohort study. *Bmj* 2016; **354**: i4351.

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

	Risk group					
Country	**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

		Risk group			
	All groups	**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

	Risk group 1a			Risk group 1b			Risk group 2			Risk group 3		
Cause (ICD code)	**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

Table 6: Patients in risk groups 1a and 1b who died from circulatory disease or disease from blood and blood-forming organs

Sex	Risk group	Age of death (years)	Cause of death-death; circulatory diseases
F	1a	28	Pulmonary embolism without mention of acute cor pulmonale
M	1a	24	Cardiac arrest
M	1a	29	Subarachnoid hemorrhage, unspecified
M	1a	19	Acute myocardial infarction, unspecified
F	1a	27	Cardiomegaly
M	1a	19	Other subarachnoid hemorrhage
M	1a	21	Intracerebral hemorrhage, unspecified
M	1a	18	Intracerebral hemorrhage, unspecified
M	1a	19	Sudden cardiac death
M	1b	29	Pulmonary embolism without mention of acute cor pulmonale
M	1b	19	Other primary cardiomyopathies
M	1b	13	Other primary cardiomyopathies
M	1b	32	Intracerebral hemorrhage, intraventricular
M	1b	25	Cardiac arrest, unspecified
M	1b	24	Cardiac arrest, unspecified
Sex	**Risk group**	**Age of death (years)**	**Cause of death-death; diseases of blood and blood-forming organs**
M	1a	12	Immunodeficiency, increased immunoglobulin M
M	1a	31	Coagulation defect, unspecified
M	1a	14	Aplastic anemia, unspecified
M	1b	22	Other combined immunodeficiencies

r-hGH =Recombinant human Growth Hormone