Long-Term Mortality after Recombinant Growth Hormone Treatment for Isolated Growth Hormone Deficiency or Childhood Short Stature: Preliminary Report of the French SAGhE Study

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Context: Little is known about the long-term health of subjects treated with GH in childhood, and Safety and Appropriateness of Growth hormone treatments in Europe (SAGhE) is a study addressing this question.

Objective: The objective of the study was to evaluate the long-term mortality of patients treated with recombinant GH in childhood in France.

Design: This was a population-based cohort study.

Setting: The setting of the study was a French population-based register.

Participants: A total of 6928 children with idiopathic isolated GH deficiency (n = 5162), neurosecretory dysfunction (n = 534), idiopathic short stature (n = 871), or born short for gestational age (n = 335) who started treatment between 1985 and 1996 participated in the study. Follow-up data on vital status were available in September 2009 for 94.7% of the patients.

Main outcome measures: All-cause and cause-specific mortality was measured in the study.

Results: All-cause mortality was increased in treated subjects [standardized mortality ratio (SMR) 1.33, 95% confidence interval (CI) 1.08–1.64]. In a multivariate analysis adjusted for height, the use of GH doses greater than 50 μg/kg · d was associated with mortality rates using external and internal references (SMR 2.94, 95% CI 1.22–7.07, hazard ratio 2.79, 95% CI 1.14–6.82). All type cancer-related mortality was not increased. Bone tumor-related mortality was increased (SMR 5.00, 95% CI 1.01–14.63). An increase in mortality due to diseases of the circulatory system (SMR 3.07, 95% CI 1.40–5.83) or subarachnoid or intracerebral hemorrhage (SMR 6.66, 95% CI 1.79–17.05) was observed.

Conclusions: Mortality rates were increased in this population of adults treated as children with recombinant GH, particularly in those who had received the highest doses. Specific effects were detected in terms of death due to bone tumors or cerebral hemorrhage but not for all cancers. These results highlight the need for additional studies of long-term mortality and morbidity after GH treatment in childhood. **(*J Clin Endocrinol Metab* 97: 416–425, 2012)**

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Abbreviations: CI, Confidence interval; HR, hazard ratio; SAGhE, Safety and Appropriateness of Growth hormone treatments in Europe; SDS, SD score; SMR, standardized mortality ratio.

Recombinant GH has been used since 1985 and has replaced GH extracted from human pituitaries in the treatment of short stature in children. The indications for GH have gradually extended from replacement therapy in severe GH deficiency to an increasing number of conditions in which short stature is not due to deficiency of GH secretion (1). This extension of GH indications has been accompanied by increases in mean treatment duration and dose (2).

In this context of increasing use of pharmacological doses of GH in short but otherwise normal children, the assessment of long-term safety is essential, but very little information is available concerning long-term outcome, particularly for individuals who have completed childhood GH treatment (3). The available information concerning the safety of GH was obtained from large samples of patients followed in postmarketing databases during and shortly after treatment (4–6). In 2002 a cohort study of patients treated with pituitary-derived GH in the United Kingdom reported a higher mortality risk from cancer overall and colorectal cancer and Hodgkin disease in particular (7). All-cause mortality was found to be higher in the United States cohort of pituitary-derived GH recipients (8), and the long-term risk of secondary tumors was found to be higher in a population of cancer survivors treated with GH, which was mostly recombinant (9).

In addition, variations of GH-IGF-I axis activity have been linked to health status in a number of situations, raising the possibility that the pharmacological administration of GH may increase the risk of morbidity. The production of excess endogenous GH in untreated acromegaly results in higher mortality rates and, possibly, an increase in cancer risk (10, 11). GH receptor deficiency with severe IGF-I deficiency is associated with a major decrease in pro-aging signaling, cancer, and diabetes in humans (12). The activity of the GH-IGF-I axis has also been linked to cancer risk in the general population (13).

We set up Safety and Appropriateness of Growth hormone treatments in Europe (SAGhE) (14), a large study aiming to evaluate the long-term health of about 30,000 patients treated with recombinant GH during childhood in the 1980s and 1990s in eight European countries, as a means of assessing the long-term safety of childhood GH treatment. Prespecified hypotheses of the study concerned all-cause and cancer related mortality. An earlier start of the study in France allows us to report here the results of the mortality analysis for the population-based cohort of patients treated in France for isolated short stature in childhood, with diagnoses of idiopathic GH deficiency, idiopathic short stature, or being born small for gestational age. Results on the other diagnostic groups will be reported as part of the European study as a whole.

Patients and Methods

Patients

We used the mandatory register of all patients treated with GH in France until 1996 [Association France-Hypophyse (15, 16)] and selected those who had been treated exclusively with recombinant GH, as opposed to pituitary derived, and were born before January 1, 1990. Patients were assigned to three risk categories for long-term mortality, based on the clinical condition resulting in the initiation of GH treatment (Fig. 1). Patients were placed in the high-risk group if they had been treated for cancer, craniopharyngioma, or chronic renal failure. Intermediate risk was defined as treatment with GH in the context of multiple pituitary hormone deficiency (GH and at least one other pituitary hormone deficiency) or treatment in the context of defined pediatric syndromes (such as the Turner, Noonan, neurofibromatosis type 1, Prader-Willi, and Fanconi syndromes) known to be associated with an increased risk of mortality or in the context of benign pituitary tumors, severe craniofacial or other malformations, or severe pediatric chronic diseases. Low risk was defined as treatment for idiopathic isolated GH deficiency, idiopathic short stature, short stature in children born short for gestational age, or isolated GH deficiency associated with a minor craniofacial malformation, such as cleft lip. Patients in the low risk group were selected for this study.

Data collected

Data concerning the characteristics of the patients, treatment, and progression were routinely collected at baseline and at regular follow-up visits and were obtained from pediatric endocrinologists until 1996 when the national compulsory France-Hypophyse register was disbanded (16). Additional follow-up data on GH treatment were collected from clinical centers in 2008–2010. Birth weight, birth length, height, and weight were expressed in SD scores, as previously described (16). Information on vital status was collected from the Répertoire National d'Identification des Personnes Physiques (http://www.insee.fr/fr/methodes/default.asp?pagedefinitions/rnipp.htm) and the Répertoire National Inter-régimes de l'Assurance Maladie (http://www.insee.fr/fr/methodes/default.asp?pagedefinitions/rniam.htm). The cause of death, as indicated in death certificates, was obtained from the French Centre of Epidemiology on Medical Causes of Death (Institut National de la Santé et de la Recherche Médicale) and coded according to the revision of the *International Classification of Diseases* effective at the time of death and further bridge coded to the ninth revision. We set a census date of September 21, 2009.

Statistical analysis

External comparison with the general population

The risk of death was assessed by calculating the standardized mortality ratio (SMR), with adjustment for year, age and sex, using the French general population as the reference group. The number of person-years at risk was calculated for GH-treated subjects, for 5-yr age classes and 1-calendar-year time periods, separately for men and women, from the date of first administration of GH to the date of death, loss to follow-up, or September 21, 2009. National mortality data were obtained for each calendar year between 1985 and 2006 from the Centre of Epidemiology on Medical Causes of Death, and 5-yr class age- and sex-specific mortality rates were calculated for all causes and for each cause of death of interest (19).

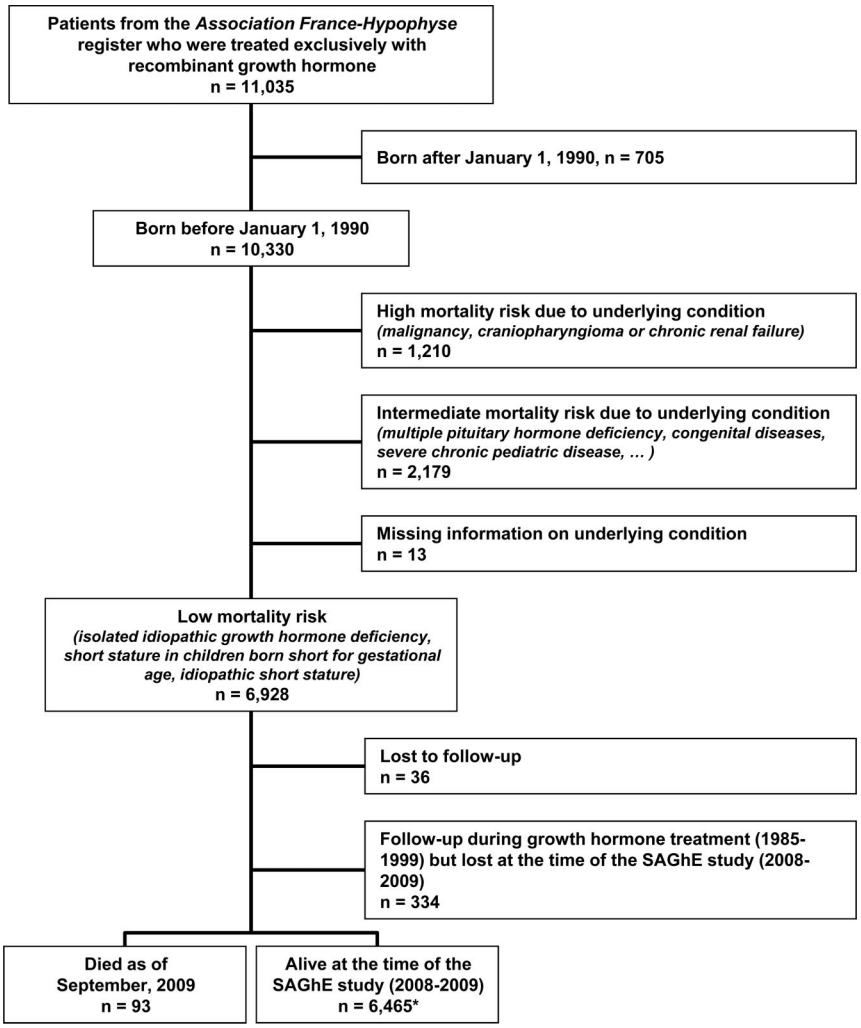

FIG. 1. Flow chart of the SAGhE study in France. *, For 6357 of 6465, vital status was obtained on September 21, 2009.

The expected number of deaths was then calculated for GH-treated subjects by multiplying the French age- and sex-specific mortality rates by the number of person-years at risk, for the period 1985–2009. SMR were estimated by dividing the number of observed deaths by the number of expected deaths.

Significance tests and 95% confidence intervals (CI) for the SMR were calculated with Byar's approximation to the exact Poisson test and the exact Poisson limits (20). We performed stratified analyses to detect the effect of treatment (dose, duration, and exposure defined as the product of dose by duration), the effect of potential confounders (sex, birth weight, birth length, age, and height at initiation of treatment, maximum stimulated GH), and, finally, to evaluate the influence of the duration of follow-up. Dose-effect relationships were analyzed through trend tests (20). A multivariate model was constructed from the variables significantly associated with mortality at the previous step, by Poisson regression analysis, with the logarithm of the expected number of deaths serving as the offset variable for calculating the adjusted SMR of one exposure group with respect to another (20, 21). We accounted for missing data for treatment duration by carrying out sensitivity analyses with both the last observation carried forward and multiple-imputation methods (22).

Internal comparison within the cohort

Treatment effects on all-cause mortality within the cohort were analyzed according to the rationale described above, by survival analysis and Cox proportional hazards models. Hazard ratios (HR) with 95% CI were calculated from the estimated regression coefficients. Exposure was considered as both a discrete and a continuous variable. Sensitivity analyses were conducted to evaluate the robustness of the results with respect to population composition and exposure level.

This study was approved by the Comité Consultatif sur le Traitement de l'Information en Matière de Recherche dans le Domaine de la Santé and the Commission Nationale de l'Informatique et des Libertés (the national data protection agency). The use of the Registre National Inter-Régimes de l'Assurance Maladie was approved by a specific statute (http://www.legifrance.gouv.fr/affichTexte.do?cidTexte=JORFTEXT000018332715&dateTexte=).

Results

Subjects had been selected for GH treatment, mostly in the prepubertal period, on the basis of GH stimulation tests (peak below 10 ng/ml) and nocturnal GH profiles, as described (15, 16); they had relatively short parents (Table 1). Subjects who had a peak GH greater than 10 μg/liter and who were not labeled as having neurosecretory dysfunction were classified as idiopathic short stature, although this is not an approved indication in France. GH doses were lower than those currently used, with only a small number (n = 281) of patients receiving mean doses higher than 50 μg/kg · d, within clinical trials conducted in partnership between the Association France-Hypophyse and pharmaceutical companies or at the request of the physician (n = 14). These trials concerned children born short for gestational age (n = 226) or with GH deficiency (n = 41). Patients receiving mean doses greater than 50 μg/kg · d, this threshold being the highest approved GH dose in the European Union, were treated for 3.5 ± 1.9 yr with a mean dose of 70.1 ± 17.2 μg/kg · d.

Ninety-three of the 6928 patients died during follow-up a mean of 7.8 ± 5.2 yr after the end of treatment (Fig. 1). Four patients died on treatment or a few days after stopping it. For seven patients the exact date of end of treatment could not be determined and two of those likely died on treatment. There were no baseline differences be-

TABLE 1. Principal characteristics of patients and GH treatment

Characteristics	Values
Number of patients (males)	6892 (4522)
Birth length (SDS for gestational age), n = 5433[a]	−1.2 ± 1.2
Birth weight (SDS for gestational age), n = 5671	−0.6 ± 1.1
Chronological age at start of treatment (yr), n = 6892	11.0 ± 3.4
Height at start of treatment (SDS), n = 6216	−2.7 ± 0.8
Height-midparental height at start of treatment (SDS), n = 5705	−1.6 ± 1.4
Weight at start of treatment (SDS), n = 5761	−1.6 ± 0.9
Indication for GH treatment	
Isolated GH deficiency	5162 (75%)
Maximum peak GH <3 μg/liter	301 (4%)
Maximum peak GH ≥3 μg/liter and <7 μg/liter	1563 (23%)
Maximum peak GH ≥7 μg/liter and <10 μg/liter	2737 (40%)
Missing value for maximum peak GH	561 (8%)
Maximum peak GH ≥10 μg/liter	1730 (25%)
Neurosecretory dysfunction	524 (8%)
Idiopathic short stature	871 (13%)
Small for gestational age	335 (5%)
Year of treatment start, number (%)	
1985–1987	510 (7%)
1988–1990	2481 (36%)
1991–1993	2381 (35%)
1994–1996	1520 (22%)
Chronological age at the end of treatment (yr), n = 6402	15.1 ± 2.7
Mean dose (μg/kg · d), n = 6333	24.6 ± 12.2
Treatment duration (yr), n = 6402	3.9 ± 2.6
Treatment exposure (mg/kg), n = 5875	37.2 ± 31.4
Person-years of observation (n)	116 403
Chronological age at the time of census or death (yr)	28.3 ± 5.3
Duration or follow-up from start of GH to time of census or death (yr)	17.3 ± 4.1

Mean ± SD or n (percentage) are shown; data from the 36 patients who were lost to follow-up and did not contribute person-years are not included.

[a] Number of patients without missing data among the 6892 included.

tween patients for whom vital status was available and those who were lost to follow-up. The mean follow-up time from treatment initiation to death or loss to follow-up or census was 17.3 ± 4.1 yr. All-cause mortality was significantly higher in patients treated with GH than would be expected on the basis of year, age, and sex (SMR 1.33, 95% CI 1.08–1.64, Table 2). Those who received higher mean doses of GH or were shorter at the start of treatment had significantly higher mortality rates (P for trend <0.04 and $P < 0.05$, respectively). Although strata with higher overall exposure levels or shorter treatment durations had significantly higher mortality rates, there was no significant trend along overall exposure or treatment duration. Excess mortality did not vary with sex, birth length, birth weight, GH peak during provocative testing, and age at start of treatment strata (Table 2). Mortality risk tended to increase with time after the end of treatment, although this was not significant. However, increased mortality would not have been detected if duration of follow-up had been limited to 5 or 10 yr after the end of treatment (Table 2). Poisson regression analysis showed that the highest treatment dose category was still significantly associated with mortality after adjustment for height SD score (SDS) at the start of treatment (Table 3). Sensitivity analyses used to account for missing data for dose or treatment duration gave results similar to those for the primary analysis (Supplemental Table 1, published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org).

Cox survival analysis showed that sex and dose were independent predictors of death (hazard ratio for mean GH doses >50 μg/kg · d, with the lowest dose category as a reference, adjusted for sex and height SDS: 2.79, 95% CI 1.14–6.82, Table 4). When missing values for doses were excluded, the risk of death appeared to be linearly related to dose, with no inflection point. The effect of sex reflects the higher mortality rate of men in this age group. Treatment duration, calendar year at treatment initiation, birth length, birth weight, age at start of treatment, peak GH levels, weight SDS, and height SDS were not associated with survival, although the relationship to height SDS was close to statistical significance in multivariate analysis (Table 4). Excluding subjects born small for gestational age from the analysis and/or considering a level of 40 μg/kg · d for the higher-dose regimen had no effect on the principal results (Supplemental Table 2).

The SMR for each *International Classification of Diseases*, ninth revision, category of the underlying cause of death showed a significant increase in mortality due to diseases of the circulatory system or due to ill-defined conditions, whereas other causes of mortality, including neoplasms in particular, were no more frequent than expected (Table 5). However, there was a significant, 5-fold increase in the number of deaths due to bone tumors (n = 3 *vs.* 0.6 expected). The number of deaths related to other types of cancer was not significantly reduced (SMR 0.41, 95% CI 0.05–1.46). For diseases of the circulatory system, we observed a 6.7-fold increase in deaths related to cerebral or subarachnoid hemorrhage (four observed *vs.* 0.6 expected), and a nonsignificant 7.1-fold increase in deaths related to cardiomyopathy and cardiomegaly (two observed *vs.* 0.28 expected).

Discussion

The SAGhE study aims to evaluate the long-term health of subjects treated with GH in childhood in eight European

TABLE 2. SMR of GH-treated patients and univariate analysis against selected factors

	Observed	Expected	SMR	(95% CI)
Overall	93	69.67	1.33	(1.08–1.64)
GH exposure				
Mean GH dose (μg/kg · d)				
0–20 (n = 2277)	32	29.77	1.07	(0.74–1.52)
20–30 (n = 3195)	35	29.07	1.20	(0.84–1.67)
30–50 (n = 580)	5	3.54	1.41	(0.46–3.30)
>50 (n = 281)	6	1.76	3.41	(1.25–7.42)
			P_{trend} 0.04	
Treatment duration (yr)				
0–2 (n = 1467)	29	15.87	1.83	(1.22–2.62)
2–4 (n = 2650)	36	29.72	1.21	(0.85–1.68)
>4 (n = 2285)	26	21.12	1.23	(0.80–1.80)
			P_{trend} 0.17	
Overall exposure (mg/kg)				
<16.0 mg/kg (n = 1381)	22	17.03	1.29	(0.81–1.96)
16.0–27.0 mg/kg (n = 1524)	17	17.97	0.95	(0.55–1.51)
27.0–47.0 mg/kg (n = 1543)	17	15.52	1.10	(0.64–1.75)
≥47.0 mg/kg (n = 1427)	20	10.86	1.84	(1.13–2.84)
			P_{trend} 0.32	
Characteristics of the patients				
Sex				
Female (n = 2370)	13	10.70	1.21	(0.65–2.08)
Male (n = 4522)	80	58.96	1.36	(1.08–1.69)
Birth length (SDS for gestational age)				
≤−2 (n = 1334)	15	11.19	1.34	(0.75–2.21)
>−2 (n = 4099)	44	43.00	1.02	(0.74–1.37)
Birth weight (SDS for gestational age)				
≤−2 (n = 510)	3	4.60	0.65	(0.13–1.91)
>−2 (n = 5161)	67	53.25	1.26	(0.98–1.60)
Age at initiation of treatment (yr)				
<6 (n = 703)	7	3.96	1.77	(0.71–3.64)
6–10 (n = 1635)	14	11.65	1.20	(0.66–2.02)
10–13 (n = 2424)	35	22.27	1.57	(1.09–2.19)
>13 (n = 2130)	37	31.79	1.16	(0.82–1.60)
			P_{trend} 0.43	
Height at initiation of treatment (SDS)				
≥−2 (n = 950)	8	9.73	0.82	(0.35–1.62)
−2 to −3 (n = 3378)	37	34.83	1.06	(0.75–1.46)
≤−3 (n = 1888)	30	19.07	1.57	(1.06–2.25)
			P_{trend} 0.05	
Maximum stimulated GH peak (mg/liter)				
<3 (n = 301)	3	3.01	1.00	(0.21–2.91)
3–7 (n = 1563)	15	16.09	0.93	(0.52–1.54)
7–10 (n = 2902)	38	29.32	1.30	(0.92–1.78)
>10 (n = 1565)	22	15.42	1.43	(0.89–2.16)
			P_{trend} 0.18	
Duration of follow-up				
Duration of follow-up after the end of treatment (yr)				
≤5 (n = 6402)	31	25.93	1.20	(0.81–1.70)
≤10 (n = 6402)	57	46.32	1.23	(0.93–1.59)
≤15 (n = 6402)	83	61.38	1.35	(1.08–1.68)
Time after the end of treatment (yr)				
≤5 (n = 6402)	31	25.93	1.20	(0.81–1.70)
>5 and ≤10 (n = 6035)	26	20.39	1.28	(0.83–1.87)
>10 and ≤15 (n = 5316)	26	15.06	1.73	(1.13–2.53)
			P_{trend} 0.17	

In some of the analyses, the sum of expected and observed numbers of deaths is not equal to the total number of death due to missing values.

countries. In France, where the study was initiated 3 yr before its start date in the rest of Europe, we were able to evaluate the mortality in a large group of patients, based on a national exhaustive register with a high follow-up rate and a mean follow-up of 17.3 yr. These patients displayed a 33% increase in all-cause mortality, and careful multivariate analysis with external and internal references showed that GH treatment with doses exceeding 50 μg/

TABLE 3. Adjusted SMR of GH-treated patients: final Poisson regression model

	SMR	(95% CI)
Mean GH dose: 0–20 μg/kg · d	1.00	
Mean GH dose: 20–30 μg/kg · d	0.95	(0.58–1.57)
Mean GH dose: 30–50 μg/kg · d	1.34	(0.52–3.43)
Mean GH dose: >50 μg/kg · d	2.94	(1.22–7.07)
Height at initiation of treatment ≥−2 SDS	1.00	
Height at initiation of treatment: −2 to −3 SDS	1.62	(0.69–3.84)
Height at initiation of treatment: <−3 SDS	2.31	(0.96–5.59)

Adjusted SMR are expressed with reference to the categories of children who received the lowest dose of treatment (0–20 μg/kg · d) or who were the tallest before treatment (≥−2 SDS). Variables not independently associated with higher mortality and not kept in the final model included treatment duration, overall exposure, and age at initiation of treatment.

kg · d was associated with a risk of mortality 2.7–2.9 times higher than for the low-dose regimen. Cause-specific mortality analyses were based on a limited number of events and found no increase in the overall risk of cancer-related deaths. However, we identified warning signals, suggesting a higher frequency of deaths due to bone tumors and cardiovascular diseases, including cerebrovascular hemorrhagic events in particular.

One key unanswered question concerns the relationship of the increased mortality to GH treatment *per se* or to residual confounding. We addressed this question by carrying out several stratified analyses and constructing multivariate models with both internal and external references, to determine whether exposure to treatment or the intrinsic characteristics of treated patients were associated with mortality. One striking finding was the positive trend for mortality with increasing doses of GH, both in internal and external comparisons and the 170–190% increase in the risk of death observed for doses of more than 50 μg/kg · d. Patients who received higher doses were mostly short children born short for gestational age with normal GH levels, who were included in clinical trials after thorough clinical examination and exclusion of severe diseases by pediatric endocrinologists. Given the small number of patients treated with doses of more than 50 μg/kg · d (or even 40 μg/kg · d) and the small number of events, the dose-effect relationship that we identified needs to be further investigated. Mortality is increased in untreated acromegaly, a model of chronic GH excess (10, 11). However, the duration of GH excess is much longer and the age of occurrence is much older in acromegaly than in GH-treated subjects.

Children with extremely short stature, with a height SDS below −3 SD, also had a higher risk of mortality in univariate but not in multivariate analysis, suggesting a possible role for intrinsic factors influencing mortality. It remains possible that an underlying disease associated with an increased risk of death may have been missed in some cases of very short stature, despite careful examination by pediatric endocrinologists. The increased mortality observed in shorter children also raises the question of the validity of the French general population reference for calculating the number of expected cases in our cohort of GH-treated children. Several studies have found increased all-cause mortality in middle-aged shorter individuals, therefore suggesting that the increased mortality observed could be intrinsic to short individuals and unrelated to treatment (24–26). However, this relationship has not been evaluated in younger individuals, representative of the age range of the patients of our study. Conversely, the use of general population data as an external reference may have resulted in an overestimation of the number of expected cases in our highly selected group of short patients in which many standard established diseases were ruled out through careful examination by pediatric endocrinologists (27). The use of the general population as an external reference may also lead to overestimation of the number of expected cases for some conditions, notably cancers, for which short stature has been shown to be protective (28).

The influence of specific conditions, such as isolated GH deficiency or smallness at birth, also merits consideration. It is unlikely that GH deficiency affected mortality in our patients, for several reasons. First, few of the patients in our low-risk cohort had severe endocrine deficiency and internal and external analyses revealed that mortality was not increased in those with the lowest levels of GH. Second, most patients, although considered GH deficient, had normal GH levels, according to conservative standards. Furthermore, GH peak during provocative tests is normal after puberty in the vast majority of such patients, making it unlikely that untreated adult GH deficiency contributed to the excess mortality observed (29). Smallness at birth, which was noted for 34% of the patients in our cohort, is associated with an increased risk of developing coronary heart disease and could have influenced mortality (30). We found no significant influence of birth characteristics on mortality and the association of a high-dose regimen with mortality persisted when individuals born small for gestational age were excluded: doses above 40 μg/kg · d, a commonly used dose in the United States, were associated with an adjusted mortality HR of 5.05 (95% CI 1.16–22.09). In addition, increased risk of coronary disease is associated with catch-up growth in infancy and individuals who remain short and are candidates for GH treatment are not at a higher risk of cardiovascular diseases (31). It is therefore unlikely that smallness at birth played a role in the excess mortality observed here. Altogether, careful multivariate

TABLE 4. Survival analysis (Cox proportional hazards models) to determine the association between individual variables and mortality in GH-treated patients

	Crude HR	95% CI crude HR	Adjusted HR	95% CI-adjusted HR
GH exposure				
Mean GH dose (μg/kg · d)				
0–20	1		1	
20–30	1.12	0.68–1.83	1.10	0.67–1.81
30–50	1.27	0.49–3.30	1.24	0.47–3.25
>50	2.73	1.13–6.62	2.79	1.14–6.83
Missing	2.43	1.31–4.51	1.24	0.38–4.01
Mean GH dose (μg/kg · d; quantitative variable)	1.01	1.00–1.03		
Treatment duration (yr)				
0–2	1			
2–4	0.72	0.44–1.18		
>4	0.80	0.46–1.36		
Missing	1	NC		
Treatment duration (yr; quantitative variable)	0.97	0.88–1.08		
Characteristics of the patients				
Sex				
Female	1		1	
Male	3.17	1.76–5.70	3.32	1.84–5.99
Birth length (SDS for gestational age)				
>−2	1			
≤−2	1.37	0.82–2.29		
Missing	1.97	1.21–3.21		
Birth length (SDS for gestational age; quantitative variable)	1.13	0.92–1.40		
Birth weight (SDS for gestational age)				
>−2	1			
≤−2	1.11	0.57–2.16		
Missing	1.21	0.69–2.12		
Birth weight or length ≤−2 SDS for gestational age				
No	1			
Yes	1.54	0.98–2.43		
Missing	1.50	0.83–2.71		
Birth weight (SDS for gestational age; quantitative variable)	1.07	0.88–1.29		
Age at initiation of treatment (yr)				
<6	1			
6–10	0.68	0.28–1.69		
10–13	0.87	0.38–1.96		
>13	0.98	0.44–2.22		
Age at initiation of treatment (yr; quantitative variable)	1.03	0.97–1.11		
Height at initiation of treatment (SDS)				
≥−2	1		1	1
−2 to −3	1.26	0.58–2.71	1.23	0.57–2.65
≤−3	1.96	0.90–4.27	1.99	0.90–4.36
Missing	3.22	1.34–7.40	2.81	0.82–9.64
Height at initiation of treatment (SDS; quantitative variable)	0.67	0.53–0.86		
Maximum stimulated GH peak (ng/ml)				
<3	0.84	0.25–2.78		
3–7	0.66	0.35–1.28		
7–10	0.89	0.53–1.50		
>10	1			
Missing	1.79	0.94–3.39		
Maximum stimulated GH peak (ng/ml; quantitative variable)	0.99	0.96–1.03		

NC, Not calculable.

analysis using the best available external reference indicated a role for GH dose with no obvious confounding, and internal comparisons gave similar results, confirming the validity of the external reference.

The small number of events (93) makes it difficult to determine the precise relationship between GH treatment and specific causes of death. There was no overall increase in the number of cancer-related deaths and we found no evidence of the increased risk of colon cancer or Hodgkin disease-related deaths reported in patients treated before 1985 (7). Given the low mortality rate from these cancers during the study period, this result was somewhat expected and should

TABLE 5. SMR by *International Classification of Diseases*, Ninth Revision (ICD-9) category and selected causes of death

	Observed	Expected	SMR	(95% CI)
ICD-9 categories				
Infectious and parasitic diseases (001–139)	3	1.05	2.86	(0.57–8.35)
Neoplasms (140–239)	7	6.89	1.02	(0.41–2.09)
Endocrine, nutritional, and metabolic diseases and immunity disorders (240–279)	2	0.31	6.50	(0.73–23.46)
Diseases of the blood and blood-forming organs (280–289)	1	0.88	1.13	(0.01–6.30)
Mental disorders (290–319)	1	1.32	0.75	(0.01–4.20)
Diseases of the nervous system and sense organs (320–389)	3	2.71	1.11	(0.22–3.24)
Diseases of the circulatory system (390–459)	9	2.93	3.07	(1.40–5.83)
Diseases of the respiratory system (460–519)	2	1.08	1.85	(0.21–6.66)
Diseases of the digestive system (520–579)	0	0.48		
Diseases of the genitourinary system (580–629)	0	0.02		
Complications of pregnancy, childbirth, and the puerperium (630–676)	0	0.14		
Diseases of the skin and sc tissue (680–709)	0	0.12		
Diseases of the musculoskeletal system and connective tissue (710–739)	0	0.09		
Congenital abnormalities (740–759)	0	0.01		
Certain conditions originating in the perinatal period (760–779)	1	1.14	0.88	(0.01–4.90)
Symptoms, signs, and ill-defined conditions (780–799)	21[a]	6.28	3.35	(2.07–5.11)
Injury and poisoning (800–999)	43	44.22	0.97	(0.70–1.31)
Neoplasms (140–239)	7	6.89	1.02	(0.41–2.09)
Malignant neoplasm of lymphatic and hematopoietic tissue (200–208)	2	1.36	1.47	(0.17–5.31)
Malignant neoplasm of bone and articular cartilage (170)	3	0.60	5.00	(1.01–14.61)
All other neoplasms[b]	2	4.93	0.41	(0.05–1.46)
Diseases of the circulatory system (390–459)	9	2.93	3.07	(1.40–5.83)
Other disorders of circulatory system (390–409. 415–419. 424. 439–459)	1	0.66	1.53	(0.02–8.49)
Other heart diseases (420–423. 425–429)	4	1.19	3.37	(0.91–8.64)
including cardiomyopathy and cardiomegaly (425. 429.3)	2	0.28	7.11	(0.80–25.67)
Cerebrovascular disease (430–438)	4	0.76	5.29	(1.42–13.55)
including subarachnoid hemorrhage, intracerebral hemorrhage and other non-traumatic intracranial hemorrhages (430–432)	4	0.60	6.66	(1.79–17.05

[a] Includes five deaths that occurred abroad, for which the cause of death is not available.

[b] The two cases of fatal neoplasms observed were a malignant neoplasm of the lip, oral cavity, and pharynx (140–149) and a malignant melanoma of the skin (172).

be completed by morbidity data (32). We found 5 times more bone tumor-related deaths than expected (two cases of osteosarcoma and one case of Ewing tumor). Despite the small number of cases, such an effect is biologically plausible because these tumors mostly occur during phases of rapid bone growth, seem to be related to height (33), and are related to the IGF-I system (13, 34, 35). The use of GH was associated with an increased the risk of osteosarcoma by a factor of 56 (95% CI 9.4–331.4) in leukemia/lymphoma survivors (36) and osteosarcomas have been reported as frequent secondary malignancies in GH-treated patients: three of 20 in one study (9), seven of 49 in another (5), and five of 30 in a third study (8).

Another striking finding was the almost 7 times increase in mortality due to cerebrovascular diseases, including subarachnoid or intracerebral hemorrhage in particular. IGF-I is a potent stimulator of vascular smooth muscle cell proliferation and migration (35). The risk of death due to cerebrovascular diseases is significantly increased by acromegaly and is linked to disease activity (11, 37). Conversely, an inverse relationship between cerebrovascular diseases and height has been reported in some (25, 38, 39) but not all (40) studies, raising the possibility that the increased risk observed may be related to short stature, although the effect size observed in these studies is lower than the increase we observed.

The difference with results of large postmarketing surveillance programs that did not identify findings such as those observed here is likely due to the duration of follow-up, which is in average less than 3.5 yr in postmarketing surveys but was almost 17 yr in our study (5, 6). Indeed, similar findings to ours were made in the U.S. cohort of pituitary-derived GH recipients with extended follow-up (8) and increased mortality was detected in our cohort

only if the follow-up period was extended beyond 10 yr after the end of treatment.

The mean dose of GH used was 25 μg/kg · d, whereas the dose currently approved for the treatment of childhood GH deficiency is 25–35 μg/kg · d in Europe and up to 100 μg/kg · d for pubertal patients in the United States (41). In children born small for gestational age, the recommended dose is 35 μg/kg · d in Europe and 69 μg/kg · d in the United States (42), whereas for idiopathic short stature, an indication approved only in the United States, a dose of up to 67 μg/kg · d is recommended (42). Thus, our cohort of patients from the 1990s was exposed to lower levels of GH than are currently used. Furthermore, the range of treatment duration was relatively narrow, with only a few cases exceeding 5 yr. The paucity of lengthy treatment, particularly at high doses, which were given for only short periods, may account for the absence of an effect of duration of exposure on mortality in this study. Our conclusions may also be called into question due to the large amount of missing data. Clinical data were recorded prospectively until 1997, when Association France-Hypophyse was disbanded, whereas approximately 20% of the patients in our cohort were still being treated. As part of this study, we collected additional data from the medical records of patients treated throughout the country, but we were confronted with problems of access to old data and refusals from some pediatric endocrinologists. We used several imputation methods based on both multiple imputations and maximal bias approaches to evaluate the potential biases and obtained results similar to those for the primary analysis. Another concern is the large number of deaths (n = 21) classified as resulting from ill-defined conditions, resulting in a marked increase in SMR (3.35, 95% CI 2.07–5.11) in this category. Unfortunately, we were unable to obtain additional information on the cause of death of these patients (five of whom died abroad) that might have made it possible to determine the precise risk of death due to specific causes. We can only hypothesize that ill-defined conditions may conceal important diseases, such as cardiovascular diseases or suicide (17, 18). Lastly, it is well known that the diagnosis of GH deficiency as well as the reagents used to define it have varied with time and country (23). Most subjects of our cohort would not have been diagnosed with GH deficiency if more stringent criteria had been used.

In conclusion, despite the low statistical power of our study due to the low frequency of events, we detected an increase in mortality in a population of short children treated with recombinant GH. High GH dose, above 50 μg/kg · d, was consistently associated with increased mortality in analyses with both internal and external references. No increase in cancer-related deaths overall was detected. Specific effects on death associated with bone tumors and cerebrovascular diseases were detected, with plausible biological explanations in both cases. Overall, our results do not allow the conclusion of the causal role of GH treatment in the findings but highlight the need for additional studies on long-term morbidity and mortality after GH treatment in childhood, in particular when high doses have been used.

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Disclosure Summary: J.-C.C. has the following conflicts of interest to declare, all outside the scope of the submitted work: investigator in clinical trials using GH sponsored by Pfizer and by Lilly and in postmarketing studies using several brands of GH, member of the French advisory board of the KIGS (Kabi International Growth Study) postmarketing study (Pfizer), and support for travel to international meetings from several GH manufacturers. F.L. has received support for travel to an international meeting from a GH manufacturer. E.E., D.M.-H., F.K., G.R., and J.C. have nothing to declare.

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