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REVIEW ARTICLE

Efficacy and safety of growth hormone treatment in adults with growth hormone deficiency: a systematic review of studies on morbidity

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Summary

Due to the positive effects demonstrated in randomized clinical trials on cardiovascular surrogate markers and bone metabolism, a positive effect of growth hormone (GH) treatment on clinically relevant end-points seems feasible. In this review, we discuss the long-term efficacy and safety of GH treatment in adult patients with growth hormone deficiency (GHD) with emphasis on morbidity: fatal and nonfatal cardiovascular disease (CVD) and stroke, fractures, fatal and nonfatal malignancies and recurrences, and diabetes mellitus. A positive effect of GH treatment on CVD and fracture risk could be concluded, but study design limitations have to be considered. Stroke and secondary brain tumours remained more prevalent. However, other contributing factors have to be taken into account. Regrowth and recurrences of (peri)pituitary tumours were not increased in patients with GH treatment compared to similar patients without GH treatment. All fatal and nonfatal malignancies were not more prevalent in GH-treated adults compared to the general population. However, follow-up time is still relatively short. The studies on diabetes are difficult to interpret, and more evidence is awaited. In clinical practice, a more individualized assessment seems appropriate, taking into consideration the underlying diagnosis of GHD, other treatment regimens, metabolic profile and the additional beneficial effects of GH set against the possible risks. Large and thoroughly conducted observational studies are needed and seem the only feasible way to inform the ongoing debate on health care costs, drug safety and clinical outcomes.

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Introduction

Since the early sixties, growth hormone (GH) has been administered to children with impaired growth. Initially, GH was recovered from donor pituitaries and was therefore scarce. In 1985, GH treatment was banned because of the discovery of Creutzfeldt–Jakob disease in more than one recipient of human GH.[1] Almost at the same time, however, recombinant human GH was manufactured, and thereby, the shortage came to an end. Broadening of the indications for GH treatment was enabled.

Growth hormone deficiency (GHD) in adults has been recognized as a metabolic syndrome, characterized by an adverse body composition and lipid profile.[2] This negative metabolic profile has been hypothesized to be responsible for the increased cardiovascular mortality encountered in patients with hypopituitarism with all, but GH, substitution therapies.[3] In addition, there is decreased bone mineral density, muscle strength, exercise capacity, cognitive function and quality of life (QoL) in patients with severe GHD.[2] Since the late eighties, more and more studies, mostly short term, have demonstrated positive effects of GH treatment on the above-mentioned outcome measures.[4–9] Subsequently, it has been demonstrated that the effects of GHD in adults result in increased direct and indirect health care costs, including more inpatient care, use of disability pension and sick leave, compared with the general population.[10,11] Based on the above-mentioned studies, GH treatment was approved for adults with severe GHD in Europe in 1995 and in the United States (US) in 1996.

As GH treatment has been administered for more than 20 years to numerous adults with severe GHD, more data on long-term efficacy and safety should be arising. Most long-term data come from observational studies, mainly postmarketing surveillance databases (Pfizer International Metabolic Database (KIMS) and Hypopituitary Control and Complications Study (HypoCCS) from Eli Lilly & Company) and some national registries. These long-term studies, as recently described in a systematic review by Appelman-Dijkstra *et al.*,[12] demonstrated a sustained positive effect on QoL. The long-term results for

cardiovascular risk factors are variable. Whether long-term GH treatment has implications for the incidence of cardiovascular morbidity and fractures remains to be established. In a recent review, four studies investigating the effect of GH treatment on all-cause mortality are described, and no increased mortality was found in men compared to the general population. Women and patients from high-risk groups (previous craniopharyngioma, Cushing's disease, malignant causes of hypopituitarism or aggressive tumours) still have a slightly increased risk, but probably lower than in untreated GHD seen in earlier studies.[13] Next to efficacy, more data are awaited on safety measures. Active acromegaly, with pathologically high insulin-like growth factor-1 (IGF-1) levels, has been suggested to be associated with an increased risk for colonic neoplasia.[14] Epidemiological studies have reported associations of even high-normal IGF-1 levels with an increased risk of developing prostate and breast cancer,[15] while other studies have not.[16] IGF-1 is a key regulator of cell proliferation and an inhibitor of apoptosis and necrosis, but also acts as insulin antagonist. It has been demonstrated that adults with GHD have an impaired insulin sensitivity,[17] which deteriorates during the first months of treatment with GH.[18] Whether this subsequently leads to sustained impairment during long-term treatment, and to a higher incidence of diabetes mellitus, is unclear. The heterogeneity of adults with GHD, the mostly inevitable observational nature of studies, and the dependence on data from postmarketing studies make research in this field challenging.

In this review, we discuss the literature on the long-term efficacy and safety of GH treatment in adult patients with GHD, with particular emphasis on morbidity: fatal and nonfatal CVD and stroke, fractures, fatal and nonfatal malignancies and recurrences, and diabetes mellitus.

Search strategy and selection criteria

A review protocol was developed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.[19] Databases were searched from inception and PubMed up to 5 February 2014 and Embase.com and Wiley/Cochrane Library up to 11 February 2014. The following terms were used (including synonyms and closely related words) as index terms or free-text words: 'adult' or 'aged' and 'growth hormone deficiency' or 'hypopituitarism' and 'growth hormone' or 'somatotropin' and 'cardiovascular disorder' or 'cerebrovascular disorder' or 'mortality' or 'morbidity' or 'neoplasm' or 'diabetes mellitus' or 'bone fracture' and 'systematic review' or 'cohort study'. The full search strategy in Embase.com can be found in the Supplementary Information. Duplicate articles were excluded. All languages were accepted. Two reviewers assessed the title and abstract of studies identified by the search strategy, obtained the full text of relevant papers and screened them against the selection criteria: GH treatment in adults with GHD, clinical end-points of interest as outcome measure compared to a control group and only original articles. Relevant references cited in retrieved articles were reviewed. Figure 1 shows the results of the study selection. Data from included studies were extracted by one reviewer and checked by a second. The quality of the studies was assessed based on the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[20]

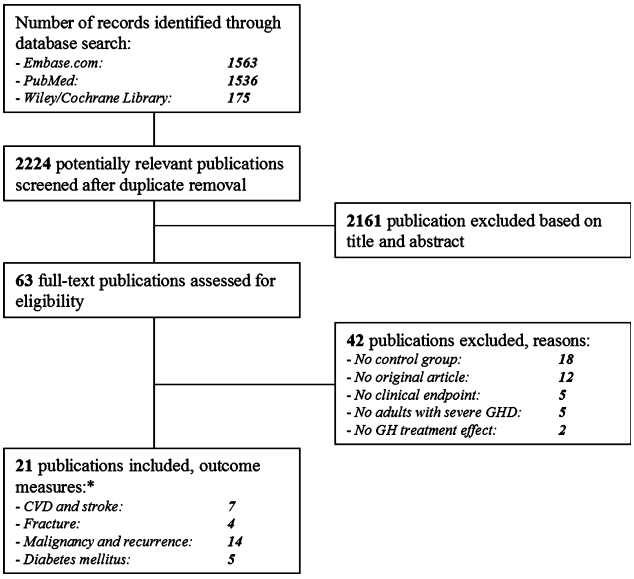

Fig. 1 Flow diagram of study selection. *One publication can cover multiple clinical end-points. GHD, growth hormone deficiency; GH, growth hormone; CVD, cardiovascular disease.

Results

Results of the systematic review on efficacy (CVD and stroke, and fractures) will be described per outcome measure, preceded by an introduction on the effects of untreated GHD and the outcome measure of interest, and some facts about the effects of GH treatment on the corresponding surrogate markers. Results of the systematic review on safety outcome measures (malignancies and recurrences, and diabetes mellitus) will be introduced by knowledge of untreated GHD and the outcome measure of interest and some data from studies in children with GH treatment.

Efficacy

Fatal and nonfatal cardiovascular disease and stroke. In untreated GHD, it has been demonstrated that there is an adverse metabolic profile reflected in many cardiovascular risk factors. Schneider *et al.*[21] demonstrated an increased 10-year risk for cardiovascular events in adult patients with GHD, calculated with the Prospective Cardiovascular Münster Heart Study score (PROCAM), compared to healthy controls (4·6 *vs* 3·7%). It has been suspected that there must be more cardiovascular morbidity in these patients, but only few studies were able to look at this clinical end-point. Bülow *et al.*[22] demonstrated in 2000 a threefold increased incidence rate of CVD in 33 female patients with hypopituitarism without GH treatment compared with a well-matched control group. In 2004, Svensson *et al.*[23]

investigated the risk for cardiovascular morbidity in 1411 hypopituitary patients without GH replacement (5593 patient-years). The total risks for myocardial infarction (men: risk ratio (RR), 1·20 (95% CI 0·88–1·60); women: RR, 1·87 (95% CI 1·27–2·65)) and cerebrovascular events (men: RR, 2·27 (95% CI 1·71–3·02); women: RR, 3·46 (95% CI 2·53–4·61)) were increased compared with the general population. In 2008, Stochholm *et al.*[24] published data on all and cause-specific morbidity in 1794 GHD patients compared to 8014 controls from Danish registries. Data were stratified for childhood- or adult-onset GHD and gender. In all groups, the cardiovascular morbidity was increased, although more in women than in men. Data on GH treatment were not included in this study so it is unclear whether this increased morbidity is primarily a result of the pituitary status despite treatment or lack of treatment. Overall, the aetiology of GHD, for instance craniopharyngioma, or (overtreatment of) other pituitary hormone deficiencies could be contributing factors.[25]

The effect of GH treatment on surrogate markers for CVD has been studied frequently. Salomon *et al.*[8] were among the first to demonstrate a positive effect on body composition in a blinded placebo-controlled clinical trial. Next to body composition, in short-term studies the lipid profile seems positively affected by GH treatment.[5] The evidence for a positive effect on other cardiovascular parameters is less clear, although several short-term studies have demonstrated increased left ventricular mass and stroke volume, and a decreased intima-media thickness after GH treatment.[26,27] Overall, taking different surrogate markers together, Schneider *et al.*[21] demonstrated in 344 adult patients with GHD treated with GH for 2 years a decrease in 10-year risk of cardiovascular events based on the PROCAM score (2·4 *vs* 4·6%).

The systematic literature search on the effect of GH treatment on the risk for CVD or cardiovascular mortality revealed seven studies (Table 1):[23,28–33] three only on cardiovascular mortality[28,30,31] and four on all cardiovascular events.[23,29,32,33] Five of the seven studies described nonfatal stroke or stroke mortality separately.[23,28,30–32] The duration of follow-up varied between 0·8 and 9·6 years. Only two studies used patients with GHD without GH treatment as a control group.[29,33] They described similar risks for CVD in both groups, but these studies had the shortest duration of follow-up (0·8 and 2·3 years). The other studies used the general population as reference and calculated standardized mortality ratio (SMR) or incidence ratio, occasionally stratified by gender. Svensson *et al.*[23] demonstrated in a Swedish single-centre cohort of 289 patients treated for 5 years a decreased risk for myocardial infarctions. The risk for cerebrovascular events was not increased. Holmer *et al.*[32] demonstrated in a national cohort of 750 GHD patients treated for 6 years a decreased incidence of CVD, but only in men. The incidence of nonfatal stroke was not increased in men and women. Three other studies looked at all-cause and cause-specific mortality.[28,30,31] The SMR for CVD mortality varied from 0·83 to 1·35, but was never significantly increased, except for women in one study.[31] Cerebrovascular mortality was analysed separately, and in two studies this was increased, with SMRs of 1·88 (95% CI, 1·44–2·41)[30] and 2·54 (95% CI, 1·41–4·59).[31]

In conclusion, seven studies investigated the morbidities CVD and stroke. Four studies were based on data from two postmarketing databases (probable overlap of patients), two studies from national registries and one single-centre study. The risk of CVD was not decreased after GH treatment compared to a group of patients with untreated GHD, which is unexpected. However, the follow-up duration was only 2·3 years, and stroke was included in the analyses. When the development of CVD or cardiovascular mortality was analysed in large national or international cohorts, the risk or mortality ratios seem comparable to the background population. One could conclude that GH treatment protects against the development of CVD, but in these observational studies, it is difficult to relate the effect fully to GH treatment due to missing information on other possible contributing factors such as concomitant medication and improvement of other treatment regimens over time. In the study by Holmer *et al.*,[32] concomitant medication was presented, and the authors conclude that the incidence of nonfatal cardiac events or stroke was no longer increased due to GH treatment, possibly together with cardioprotective medication. The effect is more obvious in men than in women in one study. However, in untreated GHD the risk ratio for CVD was already higher in women than in men. The mortality rate due to stroke remained increased in two of three studies. Of course, the effects of the underlying diagnosis of GHD, for instance large pituitary tumour masses with hypothalamic involvement, and cranial radiotherapy, have to be taken into account. Most studies demonstrated worse SMRs in high-risk patients, which underlines this argument.

Fractures. In both childhood- and adult-onset GHD, bone mineral content is reduced. Younger age and greater severity of GHD appear to be associated with low bone mineral density (BMD).[34] A number of studies have used BMD in adult patients with GHD as a surrogate marker for fracture risk. The risk of (non)vertebral fractures appears to be increased in GHD patients. Rosén *et al.*[35] demonstrated in a population of 107 hypopituitary patients without GH treatment an increased odds ratio (OR) compared with the background population during 13·4 year of follow-up. The OR for men was 3·97 (95% CI, 1·81–8·40) and 2·64 (95% CI, 0·89–7·81) in women. In KIMS, a subgroup of 264 patients aged more than 50 years were compared to healthy controls of the same age, and a 2·7-times higher fracture rate was found.[36] Other pituitary hormone deficiencies or their treatment regimens could also be related to an increased fracture risk. However, there was no significant difference in the prevalence of fractures between patients with isolated GHD and those with multiple pituitary hormone deficiencies.[37] Next to decreased BMD, it has to be considered that, especially in older patients with GHD, increased risk of fractures could also be because of more falls, which could be either due to visual deficits caused by pituitary tumours or their treatment or to decreased muscle strength.

Growth hormone treatment in adult patients with GHD increases bone turnover, which, in the first months of treatment,

Table 1. Summary of studies on the effect of GH treatment on cardiovascular disease and stroke

First author (postmarketing database)	Year of publication	Outcome measure	Aetiology GHD	Study population F: n, M: n CO/AO% Mean age (years) (SD/range)	Control group F: n, M: n CO/AO% Mean age (years) (SD/range) (if available)	Duration of GH treatment or follow-up (years)	Conclusions Estimate (95% CI)
Burman[29] (KIMS)	2013	Fatal CVD Fatal stroke	Mixed	F: 612, M: 674 29/71% 44·8 (16·3) (99·7% GH treatment)	General population	9·6	SMR CVD All: 1·21 (0·81–1·74) SMR Stroke All: 1·82 (0·91–3·26)
Hartman[30] (HypoCCS)	2013	Nonfatal CVD + stroke	Mixed	F: 875, M: 1113 16/84% 46 (15)	Untreated GHD F: 168, M: 274 55 (16)	2·3	CVD All: NS
Gaillard[31] (KIMS)	2012	Fatal CVD Fatal stroke	Mixed	F: 6809, M: 7174 23/77% 43·8 (15·4)	General population	4·9	SMR CVD All: 0·83 (0·63–1·08) SMR Stroke All: 1·88 (1·44–2·41)
van Bunderen[32]	2011	Fatal CVD Fatal stroke	Mixed	F: 1069, M: 1160 23/77% 42·6 (16·3)	General population	5·7	SMR CVD All: 1·35 (0·95–1·94), F: 2·52 (1·57–4·06), M: 0·84 (0·49–1·45) SMR Stroke All: 2·54 (1·41–4·59) F: 3·37 (1·51–7·50), M: 1·97 (0·82–4·73)
Holmer[33]	2007	Nonfatal CVD (cardiac event) Nonfatal stroke	Mixed	F: 351, M: 399 100% AO 59 (5th to 95th percentile 31–78) at end of study (93% GH treatment)	General population	6	IR CVD: F: 0·83 (0·28–2·52), M: 0·47 (0·23–0·94) IR Stroke: F: 0·97 (0·32–2·99), M: 1·58 (0·81–3·08)
Svensson[23]	2004	Fatal + nonfatal CVD (myocardial infarction) Fatal + nonfatal stroke	Mixed	F: 103, M 186 22/78% 47·6 (14·8)	General population	5	RR CVD All: 0·27 (0·03–0·99), F: 0 (0–3·15), M: 0·33 (0·04–1·18) RR Stroke All: 1·95 (0·78–4·02), F: 1·22 (0·02–6·80), M: 2·17 (0·79–4·71)
Abs[34] (KIMS)	1999	Nonfatal CVD	Mixed	F: 481, M: 553 27/73% 40·4 (NR)	Untreated GHD 39·7 (12·4)	0·8	CVD All: 0·03/year *vs* 0·01/year = NS

Estimates are reported unadjusted, unless stated otherwise.
GHD, growth hormone deficiency; F, female; M, male; CO, childhood onset; AO, adult onset; GH, growth hormone; CI, confidence interval; CVD, cardiovascular disease; SMR, standardized mortality ratio; NS, not significant; IR, incidence rate; RR, risk ratio; NR, not reported.

is demonstrated by increased levels of markers for bone resorption.[38] The increase in BMD is larger in patients with childhood- than adult-onset GHD,[34] and more in men than in women.[39,40] Most studies on the long-term effects of GH treatment on bone metabolism describe an increase in BMD within the first 5 years and reaching a plateau phase,[12] even up to 15 years of follow-up, especially in men.[41] Possibly, the positive effect of GH treatment on muscle strength could contribute to the positive effect of GH on bone.

The systematic literature search revealed four studies on fracture risk in adult patients with GHD on GH treatment (Table 2). Two studies investigated the incidence of all fractures from information gained through questionnaires,[42] and when possible verified by radiological documentation in one.[36] Mazziotti *et al.*[43,44] reported twice on vertebral fractures judged by one trained observer based on morphometric analysis of X-ray examinations. Wüster *et al.*[36] studied the prevalence of all fractures in GH-naive and non-naive patients entered in the KIMS database. The non-naive patients were treated with GH for a mean duration of 1·8 years before entry. The prevalence of fractures was similar except for patients older than 50 years and in men <30 years of age where the prevalence was lower in the non-naive *vs* naive patients. Holmer *et al.*[42] demonstrated in a national study on 832 patients compared to matched population controls an increased incidence of all fractures only in GH-treated women with childhood-onset GHD. Mazziotti *et al.*[44] investigated the prevalence of radiological spinal deformities in 107 adult patients with GHD and demonstrated that GH treatment in 65 of them decreased the fracture rate significantly. In the GH-treated men, the OR was 1·3 (95% CI, 0·5–3·1) and in women, the risk remained elevated (OR, 4·0 (95% CI, 1·6–10·1)) compared to control patients with X-rays available (excluding patients with known diseases that affect bone status). Four years later, the same group reported the OR for fracture risk for untreated GHD men after adjustment for glucocorticoid dose and urinary cortisol levels. The risk was increased compared with the GH-treated male patients.[43]

In conclusion, GH treatment seems to decrease the risk of fractures to rates similar to the general population, especially in adult-onset GHD and men. GH treatment could protect against fractures, but the mechanism is not resolved. Still, the effect of GH on, for instance, muscle strength could be contributing. Next to that, the incidence of fractures measured by questionnaire is susceptible to underreporting. Also, vertebral fractures, not always noticed by subjects, are missed. Nevertheless, the control groups used were investigated similarly. Mazziotti *et al.*[44] demonstrated in a relatively small study population that the vertebral fracture risk is higher in untreated compared with GH-treated patients with GHD based on X-ray analysis. When compared to healthy controls, only the OR in GH-treated women remained increased.

Safety

Fatal and nonfatal malignancies and regrowth or recurrences. In early studies on patients with hypopituitarism, the data regarding the incidence of malignancies were conflicting.[45,46] A factor to take into account is the heterogeneity of patients with hypopituitarism and subsequent GHD. For instance, patients with pituitary adenomas already have a twice the standardized mortality rate from all-cause mortality, and excess mortality from tumours has also been observed.[47] Other studies have not found this increased mortality risk.[48,49] Popovic *et al.*[50] compared patients with acromegaly, prolactinoma and nonfunctioning pituitary adenomas to the general population and a control group of patients with Graves' disease followed in the same clinic up to 1998. They demonstrated the overall incidence of malignancies in patients with acromegaly and nonfunctioning pituitary adenomas to be higher than expected. The authors suggested that patients with pituitary adenomas could have an inherent increased risk for malignancies. However, a few years later, a study in 328 patients treated for a pituitary tumour did not confirm this increased risk.[51]

The effect of cranial radiotherapy on secondary intracranial malignancies should also be considered. In a study by Erfurth *et al.*,[52] an increased risk for secondary brain tumours was demonstrated by meta-analysis of three studies on irradiation for pituitary tumours. Later, Sattler *et al.*[53] compared 236 patients who received radiotherapy after pituitary surgery compared to 226 patients with surgery alone who were followed for a median of 14 years. The risk of intra- and extracranial tumours, as well as mortality, was not increased. In 1411 patients with hypopituitarism without GH treatment, the risk ratio for all fatal and nonfatal malignancies compared to the general Swedish population was 1·83 (95% CI, 1·53–2·17).[23] In the Danish nationwide study of patients suffering from GHD, the hazard ratio of cancer morbidity was increased in men and women, and in both childhood- and adult-onset GHD.[24] As publications on IGF-1 levels within the normal range being positively associated with the risk of developing malignancies, one study has investigated this relationship in adult GHD patients using GH treatment. They did not find an association with IGF-1 concentration, but did with IGFBP2 and BP3.[54] However, these associations are often looked at cross-sectionally, and a longitudinal approach could diminish the effect an active malignancy might have on circulating IGF-1 and IGFBP levels.

In children with GH treatment, more long-term and safety data are available. Of course, there are limitations, but most studies reveal an overall favourable safety profile. An increased risk of leukaemia, which was often feared, was no longer encountered.[55,56] There was some concern about second neoplasia in childhood cancer survivors, but the risk diminished with increased length of follow-up.[57] However, in a recent study combining two surveillance databases, an increased incidence of second neoplasia was demonstrated in childhood cancer survivors treated with GH. Nevertheless, follow-up was relatively short.[58] In GH-treated children without a history of prior cancer, or supposed predisposition, no evidence was found for an increased risk of cancer compared to the normal population.[59] In a recent French study in low-risk children, an increased risk for mortality due to bone tumours, next to cardiovascular disease, was demonstrated.[60] Studies from Savendahl *et al.*[61] and

Table 2. Summary of studies on the effect of GH treatment on fractures

First author (postmarketing database)	Year of publication	Outcome measure	Aetiology GHD	Study population F: n, M: n CO/AO% Mean age (years) (SD/range)	Control group F: n, M: n CO/AO% Mean age (years) (SD/range) (if available)	Duration of GH treatment or follow-up (years)	Conclusions Estimate (95% CI)
Mazziotti[44]	2010	Fractures (vertebral)	Mixed	F: 0, M: 21 100% AO 55 (23–81)	Untreated GHD F; 0, M: 30	3	OR (untreated GHD) M: 8·00 (2·23–28·60) adjusted for glucocorticoid use 4·71 (1·20–19·01)
Holmer[43]	2007	Fractures	Mixed	F: 399, M: 433 12/88% CO: 28 (5th to 95th percentile 23–53), AO: 58 (5th to 95th percentile 31–78) (CO: 99%, AO: 93% GH treatment)	General population F: 1273, M: 1308 Age matched	CO: 14 AO: 6	IR F: 1·28 (0·95–1·71), F CO: 2·29 (1·23–4·28), F AO: 1·08 (0·77–1·51) IR M: 0·56 (0·38–0·83), M CO: 0·61 (0·28–1·32), M AO: 0·54 (0·34–0·86)
Mazziotti[45]	2006	Fractures (vertebral)	Mixed	F: 28, M: 37 15/85% 47·5 (18–77)	General population Untreated GHD F: 12, M: 30 10/90% 48·5 (18–81)	4	Fracture prevalence All: 53·8 *vs* 78·6% $P = 0·009$ OR (untreated GHD) All: 6·1 (2·7–17·7), F: 4·8 (1·2–18·9), M: 7·1 (2·3–21·6) OR (GH treatment) All: 1·9 (1·0–3·5), F 4·0 (1·6–10·1), M 1·3 (0·5–3·1)
Wüster[37] (KIMS)	2001	Fractures	Mixed	F: 593, M: 678 25/75% (for both groups together) 50 (11)	Untreated GHD F: 379, M: 434	1·8	Fracture prevalence All NS, >50 years old: 27 *vs* 34% $P < 0·05$, M < 30 years old: 17 *vs* 32% $P < 0·05$

Estimates are reported unadjusted, unless stated otherwise.
GHD, growth hormone deficiency; F, female; M, male; CO, childhood onset; AO, adult onset; GH, growth hormone; CI, confidence interval; OR, odds ratio; IR, incidence rate; NS, not significant.

Mo *et al.*[62] could not confirm these findings in similar populations from other countries. The aetiology of childhood-onset GHD was found to be of great influence on mortality outcome in a Danish national study.[63]

The systematic literature search on malignancies and regrowth or recurrence in adult patients with GHD on GH treatment revealed 14 studies. Nine of these studies looked at regrowth or recurrence of (peri)pituitary tumours, mostly based on brain imaging (Table 3A),[29,33,64–70] and six investigated all malignancies or malignancy as cause of death in mixed aetiologies of GHD (Table 3B).[23,28–31,71] One study looked at both outcomes.[29] Three studies only investigated mortality rates due to malignancies compared to mortality rates in the general population. Gaillard *et al.*[30] investigated 13,983 GHD patients in KIMS, treated for a mean duration of 4·9 years, where Burman *et al.*[28] further described causes of death in the Swedish patients in KIMS. Together with a Dutch national study of 2229 patients with GH treatment,[31] all three did not find increased mortality rates due to all malignancies (SMRs ranging from 0·86 to 0·92). However, Burman *et al.*[28] did find an increased SMR for secondary brain tumours (SMR, 9·40 (95% CI, 4·50–17·29)). Six of the eight patients with a *de novo* brain malignancy had received cranial radiotherapy. The study by Svensson *et al.*[23] calculated the risk ratio for all observed malignancies in 289 patients on GH treatment in one centre compared to the expected rate from the Swedish population and found an RR of 0·88 (95% CI, 0·35–1·80). HypoCCS studied the incidence of all malignancies in 6840 GH-treated patients with at least one follow-up visit and 940 patients with untreated GHD.[71] Rates for both groups were comparable to data from the general populations of Europe and the Unites States. In 2013, HypoCCS compared 1988 GH-treated patients from the Unites States with 442 untreated patients and found no significant difference in serious adverse events related to malignancies (new or recurrent) (1·61 *vs* 2·71%, $P = 0·57$ adjusted for baseline differences).[29] The follow-up time for the studies on all fatal or nonfatal malignancies varied between 2·3 and 9·6 year. The studies focusing on regrowth and recurrence of (peri)pituitary tumours included three studies with 10 or

Table 3. Summary of studies on the effect of GH treatment on regrowth or recurrences (A) and on all malignancies (B)

First author (postmarketing database)	Year of publication	Outcome measure	Aetiology GHD	Study population F: n, M: n CO/AO% Mean age (years) (SD/range)	Control group F: n, M: n CO/AO% Mean age (years) (SD/range) (if available)	Duration of GH treatment or follow-up (years)	Conclusions Estimate (95% CI)
A							
Hartman[30] (HypoCCS)	2013	Regrowth or recurrence	Mixed	F: 875, M: 1113 16/84% 46 (15)	Untreated GHD F: 168, M: 274 55 (16)	2·3	Prevalence NFPA All: 2·5 *vs* 4·4% $P = 0·21$ Prevalence craniopharyngioma All: 3·8 *vs* 5·6% $P = 0·82$, both adjusted for baseline differences
Olsson[65]	2012	Regrowth or recurrence	Craniopharyngioma	F: 24, M: 32 NR 46·6 (16·1)	Untreated GHD in craniopharyngioma F: 36, M: 34 45·7 (16·2)	13·5	10-years progression-free survival All: 85% *vs* 65% = NS adjusted for CNS irradiation, residual tumour, gender HR All 0·57 (0·26–1·3)
Mackenzie[66]	2011	Regrowth or recurrence	CNS irradiation	F: 50, M: 60 37/63% 33 (14–45)	Untreated (not GHD) after CNS irradiation F: 57, M: 53 29 (13–47)	14·5	Recurrence All: 6 *vs* 8 = NS
Olsson[68]	2009	Regrowth or recurrence	NFPA	F: 41, M: 80 100% AO 66·7 (11·2)	Untreated GHD in NFPA F: 30, M: 84 100% AO 66·7 (11)	10	10-years progression-free survival All: 74% *vs* 70% = NS
Arnold[67]	2009	Regrowth or recurrence	NFPA	F: 7, M: 16 100% AO 53·7 (14·6)	Untreated GHD in NFPA F: 46, M: 61 100% AO 56·2 (14)	4·6	Tumour progression All: 35 *vs* 36% HR All: 0·51 (0·24–1·12) adjusted for age, sex, cavernous sinus invasion, total/partial removal
Buchfelder[69]	2007	Regrowth or recurrence	NFPA	F: 31, M: 24 100% AO 50·6 (9·7)	Untreated GHD in NFPA F: 23, M: 32 100% AO 55·5 (13)	5	Tumour progression All: 29·1 *vs* 21·8% $P = 0·248$
Karavitaki[70]	2006	Regrowth or recurrence	Craniopharyngioma	F: 10, M: 22 66/34% 17·6 (14·3)	Untreated GHD in craniopharyngioma F: 23, M: 30 38·8 (16·8)	6·3	HR All: 0·309 (0·092–1·040) adjusted for sex, age, tumour therapy
Hatrick[71]	2002	Regrowth or recurrence	Mixed pituitary tumours	F: 25, M: 22 100% AO 49 (20–69)	Untreated GHD in pituitary tumours F: 10, M: 18 100% AO 52 (31–73)	3·6	Tumour progression All: 4·3 *vs* 7·1% RR 0·596 (0·09–3·99) OR All: 1·02 (0·31–3·32) adjusted for tumour size
Abs[34] (KIMS)	1999	Regrowth or recurrence	Mixed	F: 481, M: 553 27/73% 40·4 (NR)	Untreated GHD 39·7 (12·4)	0·8	Recurrences All: 6 *vs* 4 = NS

Table 3. (Continued)

First author (postmarketing database)	Year of publication	Outcome measure	Aetiology GHD	Study population F: n, M: n CO/AO% Mean age (years) (SD/range)	Control group F: n, M: n CO/AO% Mean age (years) (SD/range) (if available)	Duration of GH treatment or follow-up (years)	Conclusions Estimate (95% CI)
B							
Burman[29] (KIMS)	2013	Fatal malignancy	Mixed	F: 612, M: 674 29/71% 44·8 (16·3) (99·7% GH treatment)	General population	9·6	SMR All: 0·92 (0·61–1·34)
Hartman[30] (HypoCCS)	2013	Nonfatal malignancy	Mixed	F: 875, M: 1113 16/84% 46 (15)	Untreated GHD F: 168, M: 274 55 (16)	2·3	Prevalence All: 1·61 *vs* 2·71%, $P = 0·57$ adjusted for baseline differences
Gaillard[31] (KIMS)	2012	Fatal malignancy	Mixed	F: 6809, M: 7174 23/77% 43·8 (15·4)	General population	4·9	SMR All: 0·88 (0·74–1·03)
van Bunderen[32]	2011	Fatal malignancy	Mixed	F: 1069, M: 1160 23/77% 42·6 (16·3)	General population	5·7	SMR All: 0·86 (0·60–1·25), F: 1·12 (0·66–1·88), M: 0·70 (0·42–1·19)
Child[72] (HypoCCS)	2011	Nonfatal malignancy	Mixed	F: 3269, M: 3571 19/81% 46·4 (Q1–Q3 34·1–56·3)	General population Untreated GHD F: 391, M: 549 14/86% 54·5 (Q1–Q3 42·2–65·6)	3·7	SIR Overall All: 0·88 (0·74–1·04) SIR US (GH treatment) All: 0·94 (0·73–1·18) SIR US (untreated GHD) All: 1·16 (0·76–1·69)
Svensson[23]	2004	Fatal + nonfatal malignancies	Mixed	F: 103, M: 186 22/78% 47·6 (14·8)	General population	5	RR All: 0·88 (0·35–1·80), F: 0·34 (0·01–1·92), M: 1·17 (0·43–2·56)

Estimates are reported unadjusted, unless stated otherwise.
GHD, growth hormone deficiency; F, female; M, male; CO, childhood onset; AO, adult onset; GH, growth hormone; CI, confidence interval; SMR, standardized mortality ratio; NS, not significant; CNS, central nervous system; HR, hazard ratio; SIR, standardized incidence ratio; US, United States; NFPA, nonfunctioning pituitary adenoma; RR, risk ratio; NR, not reported.

more years of observation time.[64,65,67] Most of the studies compared data with patients with the same aetiology of GHD but without GH treatment. However, population sizes were limited. Progression-free survival was never significantly lower in GH-treated patients. Hazard or odds ratios, even after adjustment for patient and tumour characteristics, were never increased.

In conclusion, six relatively large studies investigated the incidence of all fatal or nonfatal malignancies in GH-treated adult patients with mixed aetiologies of GHD. None encountered an increased rate compared to the background population. All SMRs or RRs were <1·00, which on the one hand is reassuring, but on the other hand raises some questions. As mentioned before, the heterogeneous group of patients with hypopituitarism might already have an increased risk for malignancies without the interference of GHD and GH treatment. The higher number of patients who have received cranial radiotherapy or GH treatment in childhood, compared to the background population, might lead to an increased risk of secondary (brain) neoplasia. Nevertheless, GH treatment in adults does not seem to induce the development of all malignancies. However, for this important clinical outcome, the follow-up duration is still rather short. The increased risk for secondary brain tumours seemed to be related to cranial radiotherapy rather than GH treatment but merits caution. Despite limitations of study size, recurrence or regrowth of (peri)pituitary tumours did not seem to be affected by GH treatment. Follow-up duration was up to 14·5 years, and outcomes were compared to 'natural' recurrence rates in the absence of GH treatment. The imaging methods may have differed over time, but still this outcome was consistent.

Diabetes mellitus. In adults with untreated GHD, it has been demonstrated that there is reduced insulin sensitivity compared to healthy controls.[17] In 1999, Abs *et al.*[33] evaluated a number of cardiovascular risk factors in 1034 patients enrolled in the KIMS database. Diabetes mellitus seemed more prevalent, especially in female patients, compared to epidemiological studies of the general population. Recently, the same group described the prevalence of diabetes in 6050 enrolled patients. Compared to the general population, the standardized prevalence proportion ratio in patients with GHD was 1·13 (95% CI, 1·04–1·23).[72] HypoCCS described the prevalence of diabetes mellitus at enrolment to be comparable to population reference data.[73]

Data on the effect on glucose metabolism of GH treatment in adults with GHD are controversial. It has been suggested that GH treatment may increase the risk of developing diabetes mellitus because, on the one hand, GH causes insulin resistance. On the other hand, GH treatment reduces abdominal fat mass and is therefore proposed to have a beneficial effect on insulin resistance and could improve glucose homeostasis. In children who have received GH treatment in childhood, the incidence of mainly type 2 diabetes was sixfold higher than in children not treated with GH. The incidence of type 1 diabetes was not increased. The authors suggest an acceleration of the disorder in predisposed individuals and advise careful monitoring of glucose metabolism before and during GH treatment.[74] These findings cannot be extrapolated to adult patients as it has to be realized that children are administered considerably higher doses of GH than adults.

The systematic search for studies investigating the risk for diabetes mellitus during GH treatment in adult patients revealed five studies (Table 4). In a national study in GHD adults by Holmer *et al.*,[32] the prevalence of diabetes was increased in women but not in men after 6 years of GH treatment compared to population controls. After excluding patients with previous acromegaly or Cushing's disease, adjusting for body mass index (BMI) and physical activity diminished this increased prevalence. Due to the lack of information on incidence of diabetes before initiation of GH treatment, it cannot be concluded whether the prevalence increased or decreased during GH treatment. The two postmarketing surveillance databases have reported on diabetes during GH treatment. KIMS demonstrated an increased risk for diabetes in 5143 patients followed for almost 4 years compared to a reference population.[75] HypoCCS, on the other hand, concluded there was no significant increased incidence of diabetes in 2922 US and 3709 European patients followed for 4·1 year compared to several reference populations.[73] They demonstrated in a proportional hazard model that increased incidence of diabetes is positively associated with age and BMI. Associations with IGF-1 level or GH dose could not be found in either observational study.

In conclusion, only the two postmarketing databases and one national study reported on the risk for diabetes mellitus during GH treatment. The postmarketing databases describe contradictory results, depending on which reference population was used. In KIMS, the risk seems to be increased, but not in HypoCCS. Of course, in these observational studies, there are some limitations to take into account, for example reporting and definition bias. In addition, because of the international aspect and the potential changes over time, it is difficult to find an accurate reference population. Furthermore, in the observational studies, the incidence of diabetes mellitus seemed to decrease over time, perhaps due to the positive effect of GH on abdominal fat mass. If the development of diabetes mellitus was solely related to GH treatment, an association with IGF-1 level or GH dose would be found. However, a relationship with BMI was demonstrated in all studies. Other factors such as physical activity should also be taken into account to fully investigate the effect of GH itself on the development of diabetes, and firm conclusions cannot be drawn at this time.

Methodological comments and future perspectives

The quality of the studies was assessed based on the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[20] The retrieved cohort and case–control studies were of fairly good quality. Mostly, information was lacking on the description of effects of potential sources of bias, methods of handling missing data and reports of number of individuals at each stage and reasons for nonparticipating. The lack of these items makes observational studies susceptible to bias. Loss to follow-up or dropout information is appropriate,

Table 4. Summary of studies on the effect of GH treatment on diabetes mellitus

First author (postmarketing database)	Year of publication	Outcome measure	Aetiology GHD	Study population F: n, M: n CO/AO% Mean age (years) (SD/range)	Control group F: n, M: n CO/AO% Mean age (years) (SD/range) (if available)	Duration of GH treatment or follow-up (years)	Conclusions Estimate (95% CI)
Hartman[30] (HypoCCS)	2013	Diabetes mellitus	Mixed	F: 875, M: 1113 16/84% 46 (15)	Untreated GHD F: 168, M: 274 55 (16)	2·3	Prevalence All: <2% NS
Luger[76] (KIMS)	2011	Diabetes mellitus	Mixed	F: 2577, M: 2566 100% AO 49 (13)	General population	3·9	O/E (compared to Sweden) All: 6·0 (5·5–6·6) O/E (compared to EU/US) All: 2·11–5·22
Attanasio[74] (HypoCCS)	2011	Diabetes mellitus	Mixed	F: 2797, M: 3042 NR 44·7 (14·8)	General population	4·1	IR US All: 10·6 (8·1–13·0), compared to 7·1 (6·0–8·1) IR Germany All: 7·5 *vs* 7·3 IR Sweden All: 5·6 (2·6–8·7) compared to 2·6 (2·6–2·7)
Holmer[33]	2007	Diabetes mellitus	Mixed	F: 351, M: 399 100% AO 59 (5th to 95th percentile 31–78) at end of study (93% GH treatment)	General population	6	POR F: 2·53 (1·54–4·13), M: 1·07 (0·68–1·68)
Abs[34] (KIMS)	1999	Diabetes mellitus	Mixed	F: 481, M: 553 27/73% 40·4 (NR)	Untreated GHD 39·7 (12·4)	0·8	Diabetes All: 0·11/year *vs* 0·11/year = NS

Estimates are reported unadjusted, unless stated otherwise.
GHD, growth hormone deficiency; F, female; M, male; CO, childhood onset; AO, adult onset; GH, growth hormone; CI, confidence interval; US, United States; NS, not significant; O/E, observed/expected; EU, Europe; IR, incidence rate; POR, prevalence odds ratio; NR, not reported.

especially when investigating morbidity or mortality, as this could be correlated. Another potential source of bias is the non-randomized aspect of untreated GHD as a control group. The reasons for not initiating GH treatment are not always explained, and again, this could be correlated with the risks for morbidity or mortality. The initiation (and also ceasing) of GH treatment, and thereby entry in a registry, is based on the judgement of the treating physician in agreement with the patient. Morbidity is an important reason for withholding GH treatment, which could result in underreporting of several morbidities and mortality. This selection bias, which is often described in the discussion section of most of the observational studies, is difficult to overcome due to the design of observational databases. In observational studies, the collection of (follow-up) data is not always conducted in a standardized manner. For instance, in the postmarketing databases, data are based on information entered by the attending physician and their willingness and efforts could be variable. In some national studies, data collection was performed in a more structured manner, but possible differences in definitions of specific morbidities with the reference populations might still occur. Arranging a proper control group is one of the biggest challenges in observational research. When comparing GH-treated patients with severe GHD to 'healthy' controls in relation to morbidity and mortality, the fact that the study population is possibly predisposed to higher incidences of CVD, malignancies and diabetes, might influence the (interpretation of the) results. Confounding variables such as body composition, physical activity and concomitant medication use are not always available and are likely to differ. So, both options, untreated GHD and the general population as a control group, have their pros and cons.

Eight of the 21 studies identified through our systematic literature search originated from two postmarketing databases sponsored by pharmaceutical companies that produce GH. Overlap of patients in the described studies by postmarketing databases is present, and therefore, the origin of the study is indicated in the tables. This should be taken into account when interpreting the data in the present review. Next, although disclosures and conflict of interest are properly stated in every publication, these cannot be brushed aside. However, as the largest and longest followed cohorts, they are rather important contributors on information on clinically relevant end-points and could remain so in the coming years. Ideally, a large randomized controlled trial is needed to explore the effect of GH treatment compared to untreated GHD adults. However, when looking at morbidity and mortality, large groups will be necessary in both arms as will be an especially long follow-up. This is both unpractical and unethical. The 'next-best-thing' is

observational epidemiology. Despite the lack of a good control group and the risks for incompleteness and disputable quality of follow-up data, large observational databases (preferably without disputable interests) are capable of gathering large number of patients and following them for considerable amount of time to generate enough power to draw firm conclusion for these important clinical end-points.

Concluding remarks

Due to the positive effects demonstrated in multiple randomized clinical trials on cardiovascular surrogate markers and bone metabolism, a positive effect of growth hormone treatment on cardiovascular morbidity and fracture risk seems feasible. Continuous long-term treatment has subsequently raised the question of safety, particularly with respect to malignancies and glucose metabolism. In this review, we discussed the long-term efficacy and safety of growth hormone treatment in adult patients with growth hormone deficiency, with emphasis on morbidity: fatal and nonfatal cardiovascular disease and stroke, fractures, fatal and nonfatal malignancies and recurrences, and diabetes mellitus. Our systematic review of the literature demonstrated no increased risk for cardiovascular disease and fractures compared to the general population. This was especially seen in men. The gender difference merits further investigation. A positive effect of growth hormone treatment could be concluded, but study design limitations have to be considered. The effect of growth hormone treatment on stroke was less evident, and of course, the underlying diagnosis of growth hormone deficiency and the amount of cranial radiotherapy differ significantly with the controls that might influence this result.

With respect to the safety of long-term growth hormone treatment in adult patients with growth hormone deficiency, the outcome of our systematic review of the literature demonstrated reassuring results for malignancy risk. Regrowth and recurrences of (peri)pituitary tumours were not increased in patients receiving growth hormone treatment compared to similar patients without growth hormone treatment. All fatal and nonfatal malignancies did not seem more prevalent in growth hormone-treated adult patients compared to the general population. However, the follow-up time for this outcome is still relatively short, and therefore, firm conclusions cannot be drawn. The studies on diabetes mellitus are difficult to interpret as there are differences in definition and in predisposing variables between the study and the reference populations used.

In clinical practice, for every adult patient on growth hormone or with the intention to start growth hormone treatment, an individualized assessment seems appropriate to consider the underlying diagnosis, other treatments, metabolic profile and the beneficial effects of growth hormone set against the possible risks. Unfortunately, not many studies on the long-term effects in specific aetiologies or in growth hormone deficiency patients with specific characteristics exist. Large and thoroughly conducted observational studies are needed and seem the only feasible way to inform the ongoing debate on health care costs, drug safety and clinical outcomes.

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References

1 Buchanan, C.R., Preece, M.A. & Milner, R.D. (1991) Mortality, neoplasia, and Creutzfeldt-Jakob disease in patients treated with human pituitary growth hormone in the United Kingdom. *BMJ*, **302**, 824–828.
2 de Boer, H., Blok, G.J. & Van der Veen, E.A. (1995) Clinical aspects of growth hormone deficiency in adults. *Endocrine Reviews*, **16**, 63–86.
3 Rosèn, T. & Bengtsson, B.A. (1990) Premature mortality due to cardiovascular disease in hypopituitarism. *Lancet*, **336**, 285–288.
4 Ahmad, A.M., Hopkins, M.T., Thomas, J. *et al.* (2001) Body composition and quality of life in adults with growth hormone deficiency; effects of low-dose growth hormone replacement. *Clinical Endocrinology (Oxford)*, **54**, 709–717.
5 Maison, P., Griffin, S., Nicoue-Beglah, M. *et al.* (2004) Impact of growth hormone (GH) treatment on cardiovascular risk factors in GH-deficient adults: a Metaanalysis of Blinded, Randomized, Placebo-Controlled Trials. *Journal of Clinical Endocrinology and Metabolism*, **89**, 2192–2199.
6 de Boer, H., Blok, G.J., Voerman, B. *et al.* (1995) The optimal growth hormone replacement dose in adults, derived from bioimpedance analysis. *Journal of Clinical Endocrinology and Metabolism*, **80**, 2069–2076.
7 Jorgensen, J.O., Pedersen, S.A., Thuesen, L. *et al.* (1989) Beneficial effects of growth hormone treatment in GH-deficient adults. *Lancet*, **1**, 1221–1225.
8 Salomon, F., Cuneo, R.C., Hesp, R. *et al.* (1989) The effects of treatment with recombinant human growth hormone on body composition and metabolism in adults with growth hormone deficiency. *New England Journal of Medicine*, **321**, 1797–1803.
9 Weaver, J.U., Monson, J.P., Noonan, K. *et al.* (1995) The effect of low dose recombinant human growth hormone replacement on regional fat distribution, insulin sensitivity, and cardiovascular risk factors in hypopituitary adults. *Journal of Clinical Endocrinology and Metabolism*, **80**, 153–159.
10 Ehrnborg, C., Hakkaart-Van Roijen, L., Jonsson, B. *et al.* (2000) Cost of illness in adult patients with hypopituitarism. *Pharmacoeconomics*, **17**, 621–628.
11 Hakkaart-Van Roijen, L., Beckers, A., Stevenaert, A. *et al.* (1998) The burden of illness of hypopituitary adults with growth hormone deficiency. *Pharmacoeconomics*, **14**, 395–403.
12 Appelman-Dijkstra, N.M., Claessen, K.M.J.A., Roelfsema, F. *et al.* (2013) Therapy of Endocrine disease: long-term effects of recombinant human GH replacement in adults with GH deficiency: a systematic review. *European Journal of Endocrinology*, **169**, R1–R14.
13 Erfurth, E.M. (2013) Update in mortality in GH-treated patients. *Journal of Clinical Endocrinology and Metabolism*, **98**, 4219–4226.
14 Schneider, H.J., Klotsche, J., Saller, B. *et al.* (2008) Associations of age-dependent IGF-I SDS with cardiovascular diseases and

risk conditions: cross-sectional study in 6773 primary care patients. *European Journal of Endocrinology*, **158**, 153–161.
15 Renehan, A.G., Zwahlen, M., Minder, C. *et al.* (2004) Insulin-like growth factor (IGF)-I, IGF binding protein-3, and cancer risk: systematic review and meta-regression analysis. *Lancet*, **363**, 1346–1353.
16 van Bunderen, C.C., van Nieuwpoort, I.C., van Schoor, N.M. *et al.* (2010) The association of serum insulin-like growth factor-I with mortality, cardiovascular disease, and cancer in the elderly: a population-based study. *Journal of Clinical Endocrinology and Metabolism*, **95**, 4616–4624.
17 Hew, F.L., Koschmann, M., Christopher, M. *et al.* (1996) Insulin resistance in growth hormone-deficient adults: defects in glucose utilization and glycogen synthase activity. *Journal of Clinical Endocrinology and Metabolism*, **81**, 555–564.
18 O'Neal, D.N., Kalfas, A., Dunning, P.L. *et al.* (1994) The effect of 3 months of recombinant human growth hormone (GH) therapy on insulin and glucose-mediated glucose disposal and insulin secretion in GH-deficient adults: a minimal model analysis. *Journal of Clinical Endocrinology and Metabolism*, **79**, 975–983.
19 Liberati, A., Altman, D.G., Tetzlaff, J. *et al.* (2009) The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Medicine*, **6**, e1000100.
20 von Elm, E., Altman, D.G., Egger, M. *et al.* (2007) The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet*, **370**, 1453–1457.
21 Schneider, H.J., Klotsche, J., Wittchen, H.U. *et al.* (2011) Effects of growth hormone replacement within the KIMS survey on estimated cardiovascular risk and predictors of risk reduction in patients with growth hormone deficiency. *Clinical Endocrinology (Oxford)*, **75**, 825–830.
22 Bulow, B., Hagmar, L., Eskilsson, J. *et al.* (2000) Hypopituitary females have a high incidence of cardiovascular morbidity and an increased prevalence of cardiovascular risk factors. *Journal of Clinical Endocrinology and Metabolism*, **85**, 574–584.
23 Svensson, J., Bengtsson, B.A., Rosen, T. *et al.* (2004) Malignant disease and cardiovascular morbidity in hypopituitary adults with or without growth hormone replacement therapy. *Journal of Clinical Endocrinology and Metabolism*, **89**, 3306–3312.
24 Stochholm, K., Laursen, T., Green, A. *et al.* (2008) Morbidity and GH deficiency: a nationwide study. *European Journal of Endocrinology*, **158**, 447–457.
25 Erfurth, E.M., Siesjo, P. & Bjork-Eriksson, T. (2013) Pituitary disease mortality: is it fiction? *Pituitary*, **16**, 402–412.
26 Colao, A., Di Somma, C., Cuocolo, A. *et al.* (2005) Does a gender-related effect of growth hormone (GH) replacement exist on cardiovascular risk factors, cardiac morphology, and performance and atherosclerosis? Results of a two-year open, prospective study in young adult men and women with severe GH deficiency. *Journal of Clinical Endocrinology and Metabolism*, **90**, 5146–5155.
27 Colao, A., Di Somma, C., Spiezia, S. *et al.* (2008) Growth hormone treatment on atherosclerosis: results of a 5-year open, prospective, controlled study in male patients with severe growth hormone deficiency. *Journal of Clinical Endocrinology and Metabolism*, **93**, 3416–3424.
28 Burman, P., Mattsson, A.F., Johannsson, G. *et al.* (2013) Deaths among adult patients with hypopituitarism: hypocortisolism during acute stress, and de novo malignant brain tumors contribute to an increased mortality. *Journal of Clinical Endocrinology and Metabolism*, **98**, 1466–1475.
29 Hartman, M.L., Xu, R., Crowe, B.J. *et al.* (2013) Prospective safety surveillance of GH-deficient adults: comparison of GH-treated vs untreated patients. *Journal of Clinical Endocrinology and Metabolism*, **98**, 980–988.
30 Gaillard, R.C., Mattsson, A.F., Akerblad, A.C. *et al.* (2012) Overall and cause-specific mortality in GH-deficient adults on GH replacement. *European Journal of Endocrinology*, **166**, 1069–1077.
31 van Bunderen, C.C., van Nieuwpoort, I.C., Arwert, L.I. *et al.* (2011) 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. *Journal of Clinical Endocrinology and Metabolism*, **96**, 3151–3159.
32 Holmer, H., Svensson, J., Rylander, L. *et al.* (2007) Nonfatal stroke, cardiac disease, and diabetes mellitus in hypopituitary patients on hormone replacement including growth hormone. *Journal of Clinical Endocrinology and Metabolism*, **92**, 3560–3567.
33 Abs, R., Bengtsson, B.A., Hernberg-Stahl, E. *et al.* (1999) GH replacement in 1034 growth hormone deficient hypopituitary adults: demographic and clinical characteristics, dosing and safety. *Clinical Endocrinology (Oxford)*, **50**, 703–713.
34 Koranyi, J., Svensson, J., Gotherstrom, G. *et al.* (2001) Baseline characteristics and the effects of five years of GH replacement therapy in adults with GH deficiency of childhood or adulthood onset: a comparative, prospective study. *Journal of Clinical Endocrinology and Metabolism*, **86**, 4693–4699.
35 Rosen, T., Wilhelmsen, L., Landin-Wilhelmsen, K. *et al.* (1997) Increased fracture frequency in adult patients with hypopituitarism and GH deficiency. *European Journal of Endocrinology*, **137**, 240–245.
36 Wuster, C., Abs, R., Bengtsson, B.A. *et al.* (2001) The influence of growth hormone deficiency, growth hormone replacement therapy, and other aspects of hypopituitarism on fracture rate and bone mineral density. *Journal of Bone and Mineral Research*, **16**, 398–405.
37 Abs, R., Mattsson, A.F., Bengtsson, B.A. *et al.* (2005) Isolated growth hormone (GH) deficiency in adult patients: baseline clinical characteristics and responses to GH replacement in comparison with hypopituitary patients. A sub-analysis of the KIMS database. *Growth Hormone and IGF Research*, **15**, 349–359.
38 Tritos, N.A. & Biller, B.M.K. (2009) Growth hormone and bone. *Current opinion in Endocrinology, Diabetes, and Obesity*, **16**, 415–422.
39 Gotherstrom, G., Svensson, J., Koranyi, J. *et al.* (2001) A prospective study of 5 years of GH replacement therapy in GH-deficient adults: sustained effects on body composition, bone mass, and metabolic indices. *Journal of Clinical Endocrinology and Metabolism*, **86**, 4657–4665.
40 Johansson, A.G., Engstrom, B.E., Ljunghall, S. *et al.* (1999) Gender differences in the effects of long term growth hormone (GH) treatment on bone in adults with GH deficiency. *Journal of Clinical Endocrinology and Metabolism*, **84**, 2002–2007.
41 Elbornsson, M., Gotherstrom, G., Bosaeus, I. *et al.* (2012) Fifteen years of GH replacement increases bone mineral density in hypopituitary patients with adult-onset GH deficiency. *European Journal of Endocrinology*, **166**, 787–795.
42 Holmer, H., Svensson, J., Rylander, L. *et al.* (2007) Fracture incidence in GH-deficient patients on complete hormone replacement

including GH. *Journal of Bone and Mineral Research*, **22**, 1842–1850.
43 Mazziotti, G., Porcelli, T., Bianchi, A. *et al.* (2010) Glucocorticoid replacement therapy and vertebral fractures in hypopituitary adult males with GH deficiency. *European Journal of Endocrinology*, **163**, 15–20.
44 Mazziotti, G., Bianchi, A., Bonadonna, S. *et al.* (2006) Increased prevalence of radiological spinal deformities in adult patients with GH deficiency: influence of GH replacement therapy. *Journal of Bone and Mineral Research*, **21**, 520–528.
45 Bates, A.S., Van't Hoff, W., Jones, P.J. *et al.* (1996) The effect of hypopituitarism on life expectancy. *Journal of Clinical Endocrinology and Metabolism*, **81**, 1169–1172.
46 Rosen, T., Eden, S., Larson, G. *et al.* (1993) Cardiovascular risk factors in adult patients with growth hormone deficiency. *Acta Endocrinologica*, **129**, 195–200.
47 Nilsson, B., Gustavasson-Kadaka, E., Bengtsson, B.A. *et al.* (2000) Pituitary adenomas in Sweden between 1958 and 1991: incidence, survival, and mortality. *Journal of Clinical Endocrinology and Metabolism*, **85**, 1420–1425.
48 Bulow, B., Hagmar, L., Mikoczy, Z. *et al.* (1997) Increased cerebrovascular mortality in patients with hypopituitarism. *Clinical Endocrinology (Oxford)*, **46**, 75–81.
49 Tomlinson, J.W., Holden, N., Hills, R.K. *et al.* (2001) Association between premature mortality and hypopituitarism. West Midlands Prospective Hypopituitary Study Group. *Lancet*, **357**, 425–431.
50 Popovic, V., Damjanovic, S., Micic, D. *et al.* (1998) Increased incidence of neoplasia in patients with pituitary adenomas. The Pituitary Study Group. *Clinical Endocrinology (Oxford)*, **49**, 441–445.
51 Erfurth, E.M., Bulow, B., Mikoczy, Z. *et al.* (2001) Incidence of a second tumor in hypopituitary patients operated for pituitary tumors. *Journal of Clinical Endocrinology and Metabolism*, **86**, 659–662.
52 Erfurth, E.M., Bulow, B., Mikoczy, Z. *et al.* (2001) Is there an increase in second brain tumours after surgery and irradiation for a pituitary tumour? *Clinical Endocrinology (Oxford)*, **55**, 613–616.
53 Sattler, M.G.A., van Beek, A.P., Wolffenbuttel, B.H.R. *et al.* (2012) The incidence of second tumours and mortality in pituitary adenoma patients treated with postoperative radiotherapy versus surgery alone. *Radiotherapy and Oncology*, **104**, 125–130.
54 Popovic, V., Mattsson, A.F., Gaillard, R.C. *et al.* (2010) Serum insulin-like growth factor I (IGF-I), IGF-binding proteins 2 and 3, and the risk for development of malignancies in adults with growth hormone (GH) deficiency treated with GH: data from KIMS (Pfizer International Metabolic Database). *Journal of Clinical Endocrinology and Metabolism*, **95**, 4449–4454.
55 Bell, J., Parker, K.L., Swinford, R.D. *et al.* (2010) Long-term safety of recombinant human growth hormone in children. *Journal of Clinical Endocrinology and Metabolism*, **95**, 167–177.
56 Swerdlow, A.J., Higgins, C.D., Adlard, P. *et al.* (2002) Risk of cancer in patients treated with human pituitary growth hormone in the UK, 1959-85: a cohort study. *Lancet*, **360**, 273–277.
57 Ergun-Longmire, B., Mertens, A.C., Mitby, P. *et al.* (2006) Growth hormone treatment and risk of second neoplasms in the childhood cancer survivor. *Journal of Clinical Endocrinology and Metabolism*, **91**, 3494–3498.
58 Woodmansee, W.W., Zimmermann, A.G., Child, C.J. *et al.* (2013) Incidence of second neoplasm in childhood cancer survivors treated with GH: an analysis of GeNeSIS and HypoCCS. *European Journal of Endocrinology*, **168**, 565–573.
59 Wilton, P., Mattsson, A.F. & Darendeliler, F. (2010) Growth hormone treatment in children is not associated with an increase in the incidence of cancer: experience from KIGS (Pfizer International Growth Database). *Journal of Pediatrics*, **157**, 265–270.
60 Carel, J.C., Ecosse, E., Landier, F. *et al.* (2012) Long-term mortality after recombinant growth hormone treatment for isolated growth hormone deficiency or childhood short stature: preliminary report of the French SAGhE study. *Journal of Clinical Endocrinology and Metabolism*, **97**, 416–425.
61 Savendahl, L., Maes, M., Albertsson-Wikland, K. *et al.* (2012) 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. *Journal of Clinical Endocrinology and Metabolism*, **97**, E213–E217.
62 Mo, D., Hardin, D., Erfurth, E. *et al.* (2013) 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* [Epub ahead of print] DOI 10.1007/s11102-013-0529-6.
63 Stochholm, K., Juul, S., Christiansen, J.S. *et al.* (2012) Mortality and socioeconomic status in adults with childhood onset GH deficiency (GHD) is highly dependent on the primary cause of GHD. *European Journal of Endocrinology*, **167**, 663–670.
64 Olsson, D.S., Buchfelder, M., Wiendieck, K. *et al.* (2012) Tumour recurrence and enlargement in patients with craniopharyngioma with and without GH replacement therapy during more than 10 years of follow-up. *European Journal of Endocrinology*, **166**, 1061–1068.
65 Mackenzie, S., Craven, T., Gattamaneni, H.R. *et al.* (2011) Long-term safety of growth hormone replacement after CNS irradiation. *Journal of Clinical Endocrinology and Metabolism*, **96**, 2756–2761.
66 Arnold, J.R., Arnold, D.F., Marland, A. *et al.* (2009) GH replacement in patients with non-functioning pituitary adenoma (NFA) treated solely by surgery is not associated with increased risk of tumour recurrence. *Clinical Endocrinology (Oxford)*, **70**, 435–438.
67 Olsson, D.S., Buchfelder, M., Schlaffer, S. *et al.* (2009) Comparing progression of non-functioning pituitary adenomas in hypopituitarism patients with and without long-term GH replacement therapy. *European Journal of Endocrinology*, **161**, 663–669.
68 Buchfelder, M., Kann, P.H., Wuster, C. *et al.* (2007) Influence of GH substitution therapy in deficient adults on the recurrence rate of hormonally inactive pituitary adenomas: a case control study. *European Journal of Endocrinology*, **157**, 149–156.
69 Karavitaki, N., Warner, J.T., Marland, A. *et al.* (2006) GH replacement does not increase the risk of recurrence in patients with craniopharyngioma. *Clinical Endocrinology (Oxford)*, **64**, 556–560.
70 Hatrick, A.G., Boghalo, P., Bingham, J.B. *et al.* (2002) Does GH replacement therapy in adult GH-deficient patients result in recurrence or increase in size of pituitary tumours? *European Journal of Endocrinology*, **146**, 807–811.
71 Child, C.J., Zimmermann, A.G., Woodmansee, W.W. *et al.* (2011) Assessment of primary cancers in GH-treated adult hypo-

pituitary patients: an analysis from the Hypopituitary Control and Complications Study. *European Journal of Endocrinology*, **165**, 217–223.

72 Abs, R., Mattsson, A.F., Thunander, M. *et al.* (2013) Prevalence of diabetes mellitus in 6050 hypopituitary patients with adult-onset GH deficiency before GH replacement: a KIMS analysis. *European Journal of Endocrinology*, **168**, 297–305.

73 Attanasio, A.F., Jung, H., Mo, D. *et al.* (2011) Prevalence and incidence of diabetes mellitus in adult patients on growth hormone replacement for growth hormone deficiency: a surveillance database analysis. *Journal of Clinical Endocrinology and Metabolism*, **96**, 2255–2261.

74 Cutfield, W.S., Wilton, P., Bennmarker, H. *et al.* (2000) Incidence of diabetes mellitus and impaired glucose tolerance in children and adolescents receiving growth-hormone treatment. *Lancet*, **355**, 610–613.

75 Luger, A., Mattsson, A.F., Koltowska-Haggstrom, M. *et al.* (2012) Incidence of diabetes mellitus and evolution of glucose parameters in growth hormone-deficient subjects during growth hormone replacement therapy: a long-term observational study. *Diabetes Care*, **35**, 57–62.

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