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Adult Growth Hormone Deficiency, Replacement Therapy, and Outcomes in Long-Term Childhood Cancer Survivors

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Abstract

Context: The consequences of untreated adult growth hormone deficiency (aGHD) among childhood cancer survivors are not well defined. The lack of evidence and socioeconomic factors may contribute to underutilization of growth hormone therapy (GHT) among survivors with aGHD.

Objectives: This work aimed to examine the association of GHT use with socioeconomic factors and to assess the effect of untreated aGHD in survivors using insulin-like growth factor-1 (IGF1) as a marker of GH action.

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Author Contributions

T.Y., Y.Y., and A.D. conceptualized and designed the study. K.K.N., M.M.H., and Y.Y. acquired funding. C.Y., C.L.W., D.A.M., S.B.D., I.-C.H., T.M.B., K.R.K., K.K.N, M.M.H., and A.D. supervised data collection; T.Y., J.L.B., H.W., Y.C., Y.Y., and A.D. curated data, performed formal analysis, and interpreted data: T.Y. drafted the manuscript. All authors provided scientific input on data interpretation, reviewed and edited the draft, and gave final approval of the manuscript. All authors contributed and agreed to be accountable for all aspects of the work.

Disclosure Statement

The authors declare no competing interests.

Methods: A total of 3902 five-year survivors of childhood cancer aged 18 years and older were included. The associations between GHT use and socioeconomic factors (health insurance coverage, income, area deprivation index), and associations between IGF1 levels and prevalences of adverse physical, neurocognitive, and psychosocial outcomes were assessed cross-sectionally by multivariable logistic regression adjusting for potential confounders.

Results: Among 354 survivors with severe aGHD, 9.0% were on GHT. Socioeconomic disadvantages were independently associated with less use of GHT (eg, odds ratio [OR] of GHT use 0.27; 95% CI, 0.08–0.84 for annual household income <$40 000 vs ≥$80 000). The low IGF1 group (z score ≤ −2) experienced significantly higher prevalences of various adverse outcomes compared to the normal IGF1 group (z score >0), including various neurocognitive impairment (eg, verbal reasoning [OR 2.79; 95% CI, 1.95–3.98]), diminished health-related quality of life (eg, physical functioning [1.97; 1.35–2.86]), abnormal glucose metabolism (1.82; 1.21–2.71), and abnormal fat percentage (3.16; 1.98–5.26).

Conclusion: Untreated aGHD potentially contributes to multidimensional adverse outcomes, and GHT may provide health benefits among survivors, though socioeconomic disadvantage may limit their access to GHT.

Keywords

childhood cancer survivors; growth hormone deficiency; health disparities; health insurance; IGF-1; recombinant human growth hormone

Introduction

Adult growth hormone deficiency (aGHD) includes adulthood-onset GHD and childhood-onset GHD that persists into adulthood (1, 2). While GHD is most commonly associated with growth impairment in childhood, GH also plays an important role in maintaining systemic health in adulthood (1–4). The negative health effects of aGHD that can be reversed by GH therapy (GHT) include abnormal body composition, metabolic and cardiovascular risks, and impaired quality of life (QOL) (1–4).

Childhood cancer survivors (survivors) are a growing population attributable to advancement in cancer therapy and supportive care (5). However, cancer treatments place survivors at risk for various late effects (5, 6). Survivors are at risk for early, potentially severe comorbidities of chronic health conditions as they age, including decreased bone mineral density (BMD), obesity, diabetes mellitus, and cardiometabolic diseases (5, 6). In addition, they are at higher risk for psychosocial and neurocognitive impairment compared to nonsurvivor populations (5). Survivors are also known to be more likely to have socioeconomic disadvantages compared to their peers, such as inadequate insurance coverage and lower income, resulting in financial hardship (7–10).

aGHD is one of the most common endocrine late effects among survivors, especially those with suprasellar tumors and those treated with radiation exposure to the hypothalamic-pituitary (HP) region (11, 12). It is possible that survivors may be affected more by untreated aGHD compared to other populations due to their preexisting or coexisting cancer treatment-related chronic health conditions, some of which may be worsened by

co-occurrence of aGHD. In addition, aGHD among survivors is often childhood-onset, increasing the likelihood of adverse effects compared to adulthood-onset aGHD due to the longer duration of GH deficiency, if untreated, including developmental years (4). Clinical guidelines recommend GHT for adult survivors with confirmed aGHD based on its safety (1, 2, 11, 13), though the majority of survivors with aGHD receive GHT during childhood only for linear growth and stop taking it after completion of growth (14). Comprehensive clinical data on outcomes of untreated aGHD specifically in the survivor population are scarce, which may contribute to undertreatment of aGHD among survivors. Additionally, lower socioeconomic status, including lack of health insurance coverage, is suggested to be a potential hindrance to accessing GHT in the general population (15–18). This may also be true among survivors, who are at high risk for having financial hardship and inadequate health insurance coverage (7–10). However, this potential health disparity has never been assessed in the survivor population. Because aGHD is a condition that can be modified by GHT, it is a potential target for interventions to improve QOL of adult survivors. Therefore, assessing the outcomes of, as well as potential barriers to, GHT administration in survivors is warranted.

In this study, we aimed to assess undertreatment of aGHD, using a large clinical cohort of childhood cancer survivors in the United States. First, we estimated the proportion of survivors with severe aGHD who were on GHT. Then, we examined the associations of GHT use with socioeconomic factors. Last, we assessed the clinical effect of untreated aGHD and potential benefits of GHT on physical, psychosocial, and neurocognitive outcomes through associations between these outcomes and levels of insulin-like growth factor-1 (IGF1), a marker of GH action that is commonly lower in severe aGHD and higher with replacement therapy or in milder/absence of aGHD (2, 11, 19, 20).

Materials and Methods

Study design and population

This is a cross-sectional analysis of participants in the St. Jude Lifetime Cohort Study (SJLIFE), a retrospective cohort with prospective longitudinal clinical follow-up of 5-year childhood cancer survivors treated at St. Jude Children’s Research Hospital (SJCRH, Memphis, Tennessee, USA) between 1962 and 2012 (21, 22). SJLIFE participants are invited to campus periodically (approximately every 5 years) and undergo routine comprehensive clinical assessments including laboratory (eg, IGF1 measurements, described later) and diagnostic evaluations of organ function, physical performance testing, neurocognitive assessment examined by certified psychological examiners, and questionnaires of patient-reported outcomes such as demographic/socioeconomic factors, health behaviors, and QOL. Participants who were age 18 years or older at the time of campus visit were included, and the information from the survivors’ latest campus visit was used to maximize follow-up time between cancer diagnosis/treatment and assessment of health conditions. Survivors with genetic or neurodevelopmental syndromes unrelated to cancer diagnosis or survivors on GHT for renal failure were excluded. The SJLIFE study protocol was approved by the institutional review board at SJCRH, and all participants provided written informed consent.

Growth hormone deficiency-related information

In SJLIFE, GH dynamic testing was not part of the routine assessments. However, if a survivor was diagnosed as having GHD through dynamic testing in either the retrospective or prospective parts of the SJLIFE study, the information was recorded in the data set as a clinical history of GHD diagnosis. The details of dynamic testing such as the peak serum GH value in response to stimulation and occasionally the exact date of the testing were unavailable from our data set. IGF1 and self-reported data regarding GHT use were routinely assessed as part of the comprehensive assessment at every campus visit, together with assessment of other health conditions. Thus, in this study, we used IGF1 as a surrogate marker of GH status at the time of the latest campus visit, in the absence of dynamic testing. IGF1 was measured using a fasting blood sample collected at 8 Am by electrochemiluminescent immunometric assays (Immulite 2000, Siemens Medical Solutions before 2014 and Liaison, DiaSorin after 2014). Although the assay changed in 2014, and reference ranges vary by age and sex across the lifespan, we used *z* scores in this study that were calculated using the normative ranges for each assay in the general population based on age and sex, so it was unlikely that the change affected the results across the time frame of this study. The self-reported questionnaires asked about previous and/or current use of GHT, and affirmative answers were confirmed by reviewing SJCRH medical records. Details of GHT such as dosing or duration of GHT were not recorded in the dataset and were therefore unavailable.

Data collection

Demographic/socioeconomic information, cancer information (diagnosis, age at diagnosis, and radiotherapy [site and dose]), GHD-related information, and other endocrine conditions (hypogonadism, hypothyroidism, adrenal insufficiency) were abstracted from the SJLIFE dataset. Tumor in the HP region was defined when the tumor involved the thalamus, hypothalamus, optic chiasm, third ventricle, and sellar or parasellar region. Socioeconomic information such as annual household income and health insurance coverage was abstracted from a self-reported questionnaire. Each survivor's self-reported home address was geocoded and linked to the area deprivation index (ADI), which measures the neighborhood socioeconomic status (23). ADI comprises 17 socioeconomic status indicators at the census-track level including employment status from the American Community Survey, with scores ranging from the first percentile (indicating the least deprived neighborhood) to the 100th percentile (indicating the most deprived neighborhood).

Analysis Procedures

Demographic/socioeconomic analysis: Survivors were categorized into 4 groups based on their aGHD/GHT status (Fig. 1A). aGHD was considered present if the survivor met at least one of the following criteria: (i) clinical history of GHD based on dynamic testing; (ii) age- and sex-adjusted IGF1 *z* score ≤ -2 at the time of the latest SJLIFE visit; and/or (iii) self-reported history of GHT use. Severity of aGHD was estimated by age- and sex-adjusted IGF1 *z* scores, which are known to be typically low in patients with severe GHD (*z* score ≤ -2), while they are higher (typically *z* score <0 and > -2) with milder partial forms of GHD (19, 20). Based on this information, survivors with aGHD

were divided into 3 groups: aGHD on GHT group, untreated severe aGHD group (aGHD with IGF1 *z* score ≤ −2 without GHT), and untreated mild aGHD group (aGHD with IGF1 *z* score > −2 without GHT; Fig. 1A). Survivors in the aGHD on GHT group and untreated severe aGHD group were regarded as having severe aGHD, based on the general understanding that GHT is prescribed to patients with severe aGHD. Survivors with missing IGF1 values and/or with unreliable IGF1 values due to liver fibrosis/cirrhosis (conditions known to reduce IGF1 synthesis) were excluded from this analysis unless they were on GHT, whose grouping does not require IGF1 information.

We described demographic/cancer-related/socioeconomic/clinical information across the 4 groups. Then, focusing on survivors with severe aGHD (see Fig. 1A), the association between GHT use and socioeconomic factors (annual household income, health insurance coverage, ADI) among survivors with severe aGHD was assessed by multivariable logistic regression analysis, adjusting for sex, age at cancer diagnosis, and age at campus visit. We also examined the dose-response relationship of ordinal categories of socioeconomic factors and GHT use by trend test.

Insulin-like growth factor-1 analysis: Excluding survivors with missing/unreliable IGF1 (Fig 1B), we assessed the association between outcomes and IGF1 levels to determine the effect of untreated aGHD, using IGF1 as a surrogate for GH activity. Based on the known systemic effects of GH (1–4), multidimensional outcomes were assessed. Details of definitions and measurements are shown in Table 1. We assessed body composition/physical outcomes: obesity (body mass index [BMI] ≥ 30 kg/m^2) (24), abdominal obesity (waist-to-height ratio >0.5) (25), abnormal fat percentage (fat percentage ≥25% [males] or ≥35% [females] measured by dual-energy x-ray absorptiometry [DXA]) (26), low BMD (age- and sex-adjusted *z* scores <−2 for lumbar vertebrae L1 and L2 by DXA) (27), low lean muscle mass (age- and sex-adjusted *z* scores ≤ −1.5 by DXA) (30), weak hand grip strength (28), slow walking speed (29), and presence of frailty from physical performance testing (28–31, 41). As metabolic/cardiometabolic outcomes, presence of hypertension, hypercholesterolemia, hypertriglyceridemia, abnormal glucose metabolism, coronary artery disease, left ventricular systolic dysfunction, and cerebrovascular accident were assessed based on clinically validated grading using a modified version of the Common Terminology Criteria for Adverse Events, which is routinely used across survivor cohorts (32). Neurocognitive outcomes included global intelligence (verbal reasoning, nonverbal reasoning) (34) and 5 domains focusing on specific cognitive processes: academics (reading, mathematics) (35), attention (sustained attention, attention variability, focused attention, attention span) (36–38), processing speed (visual processing speed, visual-motor processing speed, motor processing speed) (36–38), memory (new learning, short-term/long-term verbal memory, visual memory) (39, 40), and executive function (working memory, cognitive flexibility, verbal fluency, perseveration, self-monitoring) (34, 36, 37). Impairment on each test was defined as age- and sex-adjusted *z* scores less than −1.3 (33). Health-related QOL was measured by the Medical Outcomes Study 36-Item Short Form Health Survey, including 8 domains of health status or functioning within the past 4 weeks (physical functioning, role limitation due to physical problems, general health perception, bodily pain, vitality, role limitation due to emotional problems, social functioning, mental health),

and 2 summary scores (physical component summary and mental component summary); age- and sex-adjusted *T* scores of 40 or less were defined as impairment (41, 42). We also assessed self-reported levels of psychological distress within the previous week (depression, somatization, anxiety) using the Brief Symptom Inventory-18, and a symptom was considered present when age- and sex-adjusted *T* scores were 63 or greater (43, 44).

IGF1 *z* scores were categorized into low (*z* score ≤ −2), low-normal (*z* score −2< to ≤0), and normal (*z* score >0) groups, based on reports in the general population that IGF1 *z* scores greater than 0 indicate a high probability of normal results on GH dynamic testing, and IGF1 *z* scores less than −2 are highly associated with a diagnosis of GHD (19, 45). Associations between the IGF1 groups and the prevalence of the outcomes were assessed by multivariable logistic regression adjusting for potential confounders (sex, race/ethnicity, age at cancer diagnosis, years since cancer diagnosis, tumor in the HP region, HP radiation dose, childhood GHT, history of hypogonadism/hypothyroidism/adrenal insufficiency, and socioeconomic variables [educational attainment, annual household income, health insurance coverage, ADI]). Socioeconomic variables were not adjusted for neurocognitive outcomes since these variables are downstream of neurocognitive impairment (46). Dose-response relationships between the ordinal IGF1 *z* score categories and the prevalence of outcomes were examined by trend test. While there were a multitude of outcomes, no adjustment for multiple testing was performed because each distinct outcome was hypothesized and tested separately.

Considering the possibility that low IGF1 was due to high BMI in some participants, as suggested in some literature (47, 48), we conducted a supplementary analysis excluding survivors with obesity (BMI ≥ 30 kg/m^2) using the same methods as in the main IGF1 analysis, without testing BMI-related outcomes: obesity, abdominal obesity, and abnormal fat percentage.

All tests were 2-sided, with *P* less than .05 considered statistically significant. Data were analyzed using R version 4.3.1 (R Core Team, 2023).

Results

Among 5229 participants with a campus visit, 4364 survivors were eligible for this study. Of this population, 3902 survivors were included in the demographic/socioeconomic analysis, excluding survivors with missing/unreliable IGF1 (n = 462; see Fig. 1A). Characteristics of the 4 groups are shown in Table 2. Among 354 survivors with severe aGHD, 9.0% (32 in the aGHD on GHT group) were on GHT. There were 286 survivors in the untreated mild aGHD group and 3262 survivors in the non-aGHD group. Demographic and cancer-related factors such as sex, age at campus visit, and age at primary cancer diagnosis were comparable across the 4 groups. However, the aGHD on GHT group included more survivors with a central nervous system (CNS) tumor (23/32, 71.9%) specifically in the HP region (11/32, 34.4%), compared to other groups. Relatedly, among survivors with severe aGHD, CNS tumor survivors were more likely to be on GHT (23/158, 15.2%) compared to other types of primary cancer (7/152, 4.6% in any hematological malignancy; 2/51, 3.9% in any solid tumor). The majority of survivors with severe aGHD had HP radiation greater than or

equal to 18 Gy (24/32, 75.0% in the aGHD on GHT group; 234/322, 72.7% in untreated severe aGHD group). The median IGF1 *z* score in the GHD on GHT group was −0.1 (25th-75th percentile, −1.1 to 1.0), whereas that in the untreated severe aGHD group was −2.6 (25th-75th percentile, −3.2 to −2.2). The onset of GHD was mostly during childhood among survivors with aGHD in all GHD groups whose historical information was available. Compared to the other 3 groups, the aGHD on GHT group was characterized by higher socioeconomic status. They had the highest proportion of annual household income of $80 000 or greater (11/32, 34.4%), no one reported the absence of health insurance, and lived in less deprived neighborhoods (a median ADI score at the 43rd percentile). The proportion of never smoking was highest in this group (29/32, 90.6%). In contrast, the most disadvantaged socioeconomic status among the 4 groups was seen in the untreated severe aGHD group. This group included the lowest prevalence of survivors with an annual household income of $80 000 or greater (35/322, 10.9%), the highest proportion of uninsured status (42/322, 13.0%), and living in more deprived neighborhoods (a median ADI score at the 63rd percentile).

In the socioeconomic analysis of 354 survivors with severe aGHD (Table 3), lower annual household income was independently associated with less use of GHT compared to higher annual household income of $80 000 or greater with a dose-response relationship (odds ratio [OR] of GHT use 0.32; 95% CI, 0.10–0.99 in $40 000-$79 999; OR 0.28; 95% CI, 0.08–0.84 in <$40 000; *P*-trend .025). Lack of health insurance was also associated with less use of GHT (OR of GHT use 0.00; 95% CI, 0.00–0.59 vs insured; $P = .013$). Higher (more deprived) ADI had a significant trend with less use of GHT (OR of GHT use 0.31; 95% CI, 0.07–1.06 in the highest quartile; OR 0.63; 95% CI, 0.22–1.64 in the second highest quartile vs ADI below median value; *P*-trend .045).

Next, we performed the IGF1 analysis including 3899 survivors with available IGF1 information (see Fig. 1B). Statistically significant dose-response associations between higher prevalence of outcomes and IGF1 level categories (*P*-trend <.05) are shown in Fig. 2 (results of all outcomes are shown in Supplementary Table S1 (49)). Lower IGF1 was associated with higher prevalence of abnormal body composition (obesity, abdominal obesity, abnormal fat percentage, and low BMD) and weak handgrip strength with dose-response relationships. Among these outcomes, abnormal fat percentage had the highest OR of 3.16 (95% CI, 1.98–5.26) in the low IGF1 group vs normal IGF1 group. Similar dose-response relationships were observed between lower IGF1 and higher prevalence of metabolic/cardiovascular outcomes (hypertension, hypertriglyceridemia, and abnormal glucose metabolism). All tested neurocognitive outcomes were associated with lower IGF1 with a significant dose-response relationship. Of these, impairment in verbal reasoning, a measure of general cognitive function, showed the highest OR of 2.79 (95% CI, 1.95–3.98) in the low IGF1 group vs normal IGF1 group (*P*-trend <.0001). Statistically significant associations between lower IGF1 and impaired health-related QOL were mainly identified in physical-related domains, such as impairment in physical functioning (OR 1.97; 95% CI, 1.35–2.86 in the low IGF1 group vs normal IGF1 group; *P*-trend = .0014). Lower IGF1 was also associated with higher prevalence of depression (OR 1.58; 95% CI, 1.06–2.33 in the low IGF1 group vs normal IGF1 group; *P*-trend = .0041).

In the supplementary analysis limited to survivors without obesity, the sample size decreased from 3899 to 2367. Still, the statistically significant dose-response associations between higher prevalence of impairment and lower IGF1 levels were observed in most of the outcomes that showed significance in the main analysis (low BMD, weak handgrip strength, neurocognitive and health-related QOL outcomes; Supplementary Table S2 (50)), with additional significant associations between lower IGF1 and low lean muscle mass and frailty. There were no outcomes showing statistically significant dose-response relationships with IGF1 in metabolic/cardiovascular outcomes or psychological distress in this supplementary analysis.

Discussion

Childhood cancer survivors are a unique population characterized by substantial underlying medical vulnerability and whose overall health and QOL can be severely affected by untreated aGHD. Using SJLIFE, a large cohort of childhood cancer survivors, this is the first large study to comprehensively assess outcomes of untreated aGHD and potential socioeconomic barriers to GHT focusing on this population. The results of this study highlight the deleterious effects of untreated aGHD on a wide range of outcomes that may be potentially mitigated by GHT. However, our data also revealed that only 9% of survivors with severe aGHD in our cohort were on GHT, and that not being on treatment was associated with lower socioeconomic status measures in this United States–based cohort.

To our knowledge, this is the first study to find associations between IGF1 and neurocognitive outcomes in childhood cancer survivors. Neurocognitive impairment is known to be highly prevalent among survivors compared to the general population and adversely affects their daily productivity and overall well-being (46, 51, 52). The relationship between aGHD and neurocognitive impairment in the general population has been unclear (46, 53). However, our results identified a dose-response relationship between lower IGF1 and higher prevalence of neurocognitive impairments not only in general intelligence (verbal reasoning), but also in all other outcomes in various specific domains in survivors. Because neurocognitive impairment affects the QOL of survivors and can affect their education level or even employment status, it is important to examine this more closely, as GHT may be an intervention to improve survivors' QOL through potentially improving neurocognitive functioning.

We also observed associations between lower IGF1 and higher prevalence of depression and various health-related QOL outcomes. Associations among health-related QOL were mainly observed in physical outcomes, such as physical functioning. Relatedly, lower IGF1 was associated with a higher prevalence of weak handgrip strength, a reliable objective marker of physical functioning and longevity (54). In addition, in alignment with the general understanding of the benefits of GHT to achieve optimal body composition and bone health (1–4), we observed a clear dose-response relationship between IGF1 and abnormal body composition (obesity, abdominal obesity, abdominal fat percentage) and lower BMD in survivors.

Because of the existing evidence that high BMI can cause low serum IGF1 levels (47, 48), which is one of the limitations of using IGF-1 as a surrogate for GH status, we conducted a supplementary analysis limited to nonobese participants and outcomes not directly assessing BMI or fat mass. Despite the dramatic decrease in sample size from 3899 to 2367, we still observed dose-response relationships in most outcomes across domains, suggesting that in those outcomes, associations with IGF1 are not modified by high BMI and the observed associations are due to GHD, rather than obesity causing low IGF1. A minority of neurocognitive outcomes, mental health outcome in health-related QOL, and depression were not statistically significant in this supplementary analysis. Yet, the trend of decreased functioning with lower IGF1 remained consistent with the possibility that with the reduced sample size, there was insufficient power to detect a statistically significant trend. Furthermore, by limiting to nonobese participants, there were additional outcomes significantly associated with IGF1, such as low lean muscle mass and frailty. This suggests that these physical outcomes may be associated with IGF1 in the context of GHD, but not among survivors with low IGF1 caused by obesity. The association between lower IGF1 and these measures may also play a role in the effect of untreated aGHD on reduced physical performance, which can contribute to decreased physical function–related QOL among survivors. The main exception to the consistent findings between the main and supplementary analyses were metabolic/cardiovascular outcomes. Although there were significant dose-response relationships between lower IGF1 and hypertension, hypertriglyceridemia, and abnormal glucose metabolism in the main analysis, once obese participants were excluded, there was no significant association. Based on the well-known effect of obesity both on IGF-1 and metabolic/cardiovascular outcomes (47, 48, 55, 56), we speculate that the association between low IGF1 and these factors in the main analysis was likely driven by obesity. However, with the cross-sectional design of this study, we cannot comment on whether GHD (low IGF1) contributed to obesity leading to abnormalities in these metabolic/cardiovascular outcomes, or obesity caused both these abnormalities and lower IGF1. Future prospective research is needed to assess if GHT, which increases serum IGF1, can improve these metabolic/cardiovascular outcomes that can contribute to severe consequences such as coronary heart disease (56) among survivors regardless of BMI.

Overall, we observed substantial associations between untreated aGHD not only in clinical outcomes but also in neurocognitive functioning and self-reported outcomes. Our findings support the need for future studies evaluating the effect of increasing IGF1 through treatment of aGHD among survivors, who often have multiple comorbid conditions contributing to impaired QOL.

Despite these findings suggesting the potential benefits of GHT, we also demonstrated low treatment rates in real-world practice in the United States. Although the limitations are noteworthy, in the United States, socioeconomic factors appear to be important barriers for GHT access, which is quite costly. In our study, untreated aGHD was associated with lack of health insurance coverage. All GHT users were insured, suggesting health insurance coverage was used to access GHT. However, even with health insurance coverage, survivors may experience financial difficulty in accessing GHT due to high copayment requirements (2, 17, 18), as shown in the association between annual household income and GHT use. The observed association between untreated aGHD and higher ADI also suggests that

socioeconomic factors within disadvantaged neighborhoods such as education and access to medical providers may affect GHT use. Identifying survivors living in disadvantaged neighborhoods who need socioeconomic support and health policy interventions to assist these at-risk individuals may also be important, together with proper education regarding risks and benefits when considering GHT in adult survivors. An important caveat to this aspect of our study is that our cohort resides only within the United States. The contribution of socioeconomic factors may differ by countries with different health policies and financial resources. Still, our results highlight the importance of the socioeconomic framework to support survivors to properly receive GHT when needed, and further research is needed in each country/region to assess more specific socioeconomic barriers to accessing GHT.

In addition to the findings regarding socioeconomic status, the proportion of survivors with severe aGHD receiving GHT was lower in those with hematological malignancies (4.6%) and solid tumors (3.9%), compared to those with CNS tumors (15.2%). In this study, the definition of severe aGHD was made not only by clinical history of GHD based on diagnostic dynamic testing but also by low IGF1 *z* score at the last campus visit in those without evidence of dynamic testing, and data were unavailable regarding whether survivors with severe aGHD were aware of their risk for aGHD and/or underwent diagnostic testing. There might have been higher GHD screening rates among CNS tumor survivors due to known GHD risks related to tumor location, that is, a subset of survivors of hematological malignancies and solid tumors in the untreated severe aGHD groups were never formally screened with diagnostic dynamic testing and thus may have been underdiagnosed for GHD in this group. If this is true, these populations await further attention to be appropriately screened for GHD, particularly among those with low IGF1 screening test results.

This study has several limitations that should be noted, in addition to the geographical considerations. There was limited available information on GHD-related diagnostic information. Thus, acknowledging that IGF1 is not a definitive diagnostic test for GHD, we used IGF1 values, which are systematically and prospectively measured in SJLIFE, to define the most recent GHD status of survivors as a surrogate for gold-standard dynamic testing for aGHD. There might be survivors who were misclassified by using IGF1, especially those with obesity or who received cranial radiation, which are factors that may affect serum IGF1 levels (19, 47, 48, 57). However, we did account for low IGF1 due to obesity in the supplementary analysis, and analyses were adjusted for cranial radiation dose. Relatedly, it was uncertain if survivors categorized in the untreated severe aGHD group were aware of their possible diagnosis of severe aGHD, which could affect the proportion of survivors offered GHT. We did not assess the degree of knowledge and practical experience with screening for aGHD among health care professionals or the frequency of referrals to endocrinologists, and these factors may also affect the portion of survivors who were on GHT in this study (16–18). There are additional potential barriers to accessing GHT that were not assessed in this study, such as requirement of daily injections or fear of side effects. Further research is required to examine how these factors influence access to GHT among survivors with aGHD. In the IGF1 analysis, historical information about the actual timing of onset of GHD, duration/dose of GHT, or interval between onset of GHD to start of GHT was unavailable in this cohort, and we could not account for this information in the analysis. Also, because of the cross-sectional nature of this study, we could assess associations only

between the current IGF1 level and the presence of health outcomes, and not the effect of IGF1 on future incidence of chronic health conditions, including mortality.

In summary, our data highlight the wide range of adverse outcomes of untreated aGHD among adult survivors of childhood cancer. The potential deleterious effects of untreated aGHD in this population included abnormalities in body composition, metabolic, cardiovascular, neurocognitive, and health-related QOL outcomes. It is important that medical providers screen for aGHD in at-risk survivors and discuss aGHD-associated benefits, risks, and harms with survivors to implement personalized treatment plans. A collaborative approach between oncologists, pediatric and adult endocrinologists, and primary care providers is needed in this regard, with resources provided to assist with access to this costly medication when needed. Since personal socioeconomic status may also affect survivors' access to GHT in the United States, this and other potential barriers should be considered in future interventions to improve long-term health outcomes in survivors with aGHD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability

Some or all data sets generated during and/or analyzed during the present study are not publicly available but are available from the corresponding authors on reasonable request.

Abbreviations

ADI	area deprivation index
aGHD	adult growth hormone deficiency
BMD	bone mineral density
BMI	body mass index
CNS	central nervous system
DXA	dual-energy x-ray absorptiometry
GH	growth hormone
GHT	growth hormone therapy
HP	hypothalamic-pituitary
IGF1	insulin-like growth factor-1

OR	odds ratio
QOL	quality of life
SJCRH	St. Jude Children's Research Hospital
SJLIFE	St. Jude Lifetime Cohort Study

REFERENCES

1. Molitch ME, Clemmons DR, Malozowski S, Merriam GR, Vance ML. Evaluation and treatment of adult growth hormone deficiency: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2011;96(6):1587–1609. [PubMed: 21602453]
2. Yuen KCJ, Biller BMK, Radovick S, et al. American association of clinical endocrinologists and American college of endocrinology guidelines for management of growth hormone deficiency in adults and patients transitioning from pediatric to adult care. Endocr Pract. 2019;25(11):1191–1232. [PubMed: 31760824]
3. Olarescu NC, Gunawardane K, Hansen TK, et al. Normal physiology of growth hormone in adults. In: Feingold KR, Anawalt B, Boyce A, eds. Endotext. MDText.com, Inc.; 2000–2022. 2015.
4. Feldt-Rasmussen U, Klose M. Adult growth hormone deficiency- clinical management. In: Feingold KR, Anawalt B, Blackman MR, eds. Endotext. MDText.com, Inc.; 2000-. 2017.
5. Robison LL, Hudson MM. Survivors of childhood and adolescent cancer: life-long risks and responsibilities. Nat Rev Cancer. 2014;14(1):61–70. [PubMed: 24304873]
6. Bhakta N, Liu Q, Ness KK, et al. The cumulative burden of surviving childhood cancer: an initial report from the St Jude Lifetime Cohort Study (SJLIFE). Lancet. 2017;390(10112):2569–2582. [PubMed: 28890157]
7. Park ER, Li FP, Liu Y, et al. Health insurance coverage in survivors of childhood cancer: the childhood cancer survivor study. J Clin Oncol. 2005;23(36):9187–9197. [PubMed: 16361621]
8. Kirchhoff AC, Krull KR, Ness KK, et al. Occupational outcomes of adult childhood cancer survivors: a report from the childhood cancer survivor study. Cancer. 2011;117(13):3033–3044. [PubMed: 21246530]
9. Zheng Z, Yabroff KR. The Long Shadow of Childhood Cancer: Lasting Risk of Medical Financial Hardship. Vol 111. Oxford University Press; 2019; pp. 105–106.
10. Nathan PC, Huang I-C, Chen Y, et al. Financial hardship in adult survivors of childhood cancer in the era after implementation of the affordable care act: a report from the childhood cancer survivor study. J Clin Oncol. 2023;41(5):1000–1010. [PubMed: 36179267]
11. Sklar CA, Antal Z, Chemaitilly W, et al. Hypothalamic-pituitary and growth disorders in survivors of childhood cancer: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2018;103(8):2761–2784. [PubMed: 29982476]
12. van Iersel L, Li Z, Srivastava DK, et al. Hypothalamic-pituitary disorders in childhood cancer survivors: prevalence, risk factors and long- term health outcomes. J Clin Endocrinol Metab. 2019;104(12): 6101–6115. [PubMed: 31373627]
13. Boguszewski MCS, Boguszewski CL, Chemaitilly W, et al. Safety of growth hormone replacement in survivors of cancer and intracranial and pituitary tumours: a consensus statement. Eur J Endocrinol. 2022;186(6):P35–p52. [PubMed: 35319491]
14. Alter C, Boguszewski M, Clemmons D, et al. Insights from an advisory board: facilitating transition of care into adulthood in brain cancer survivors with acquired pediatric growth hormone deficiency. Growth Horm IGF Res. 2024;74:101573. [PubMed: 38368660]
15. Shimon I, Badiu C, Bossowski A, et al. Adult growth hormone def iciency in CEE region: heterogeneity of the patient pathway. Growth Horm IGF Res. 2019;46–47:44–49.
16. Martel-Duguech LM, Jorgensen JOL, Korbonits M, et al. ESE audit on management of adult growth hormone deficiency in clinical practice. Eur J Endocrinol. 2021;184(2):321–332.

17. Yuen KCJ. Adult growth hormone deficiency guidelines: more diff icult than it seems to incorporate into clinical practice universally. Eur J Endocrinol. 2021;184(4):C5–c7. [PubMed: 33524002]
18. Yuen KCJ, Alter CA, Miller BS, et al. Adult growth hormone deficiency: optimizing transition of care from pediatric to adult services. Growth Horm IGF Res. 2021;56:101375. [PubMed: 33341524]
19. Juul A, Kastrup KW, Pedersen SA, Skakkebaek NE. Growth hormone (GH) provocative retesting of 108 young adults with childhood-onset GH deficiency and the diagnostic value of insulin- like growth factor I (IGF-I) and IGF-binding protein-3. J Clin Endocrinol Metab. 1997;82(4):1195–1201. [PubMed: 9100596]
20. Kwan AY, Hartman ML. IGF-I measurements in the diagnosis of adult growth hormone deficiency. Pituitary. 2007;10(2):151–157. [PubMed: 17429593]
21. Hudson MM, Ness KK, Nolan VG, et al. Prospective medical assessment of adults surviving childhood cancer: study design, cohort characteristics, and feasibility of the St. Jude Lifetime Cohort study. Pediatr Blood Cancer. 2011;56(5):825–836. [PubMed: 21370418]
22. Howell CR, Bjornard KL, Ness KK, et al. Cohort profile: the St. Jude Lifetime Cohort Study (SJLIFE) for paediatric cancer survivors. Int J Epidemiol. 2021;50(1):39–49. [PubMed: 33374007]
23. Kind AJH, Buckingham WR. Making neighborhood-disadvantage metrics accessible—the neighborhood atlas. N Engl J Med. 2018;378(26):2456–2458. [PubMed: 29949490]
24. World Health Organisation. Obesity: Preventing and Managing the Global Epidemic: Report of a WHO Consultation. WHO; 2000.
25. Ashwell M, Gunn P, Gibson S. Waist-to-height ratio is a better screening tool than waist circumference and BMI for adult cardiometabolic risk factors: systematic review and meta-analysis. Obes Rev. 2012;13(3):275–286. [PubMed: 22106927]
26. Romero-Corral A, Somers VK, Sierra-Johnson J, et al. Accuracy of body mass index in diagnosing obesity in the adult general population. Int J Obes (Lond). 2008;32(6):959–966. [PubMed: 18283284]
27. Shuhart CR, Yeap SS, Anderson PA, et al. Executive summary of the 2019 ISCD position development conference on monitoring treatment, DXA cross-calibration and least significant change, spinal cord injury, peri-prosthetic and orthopedic bone health, transgender medicine, and pediatrics. J Clin Densitom. 2019;22(4): 453–471. [PubMed: 31400968]
28. Mathiowetz V, Kashman N, Volland G, Weber K, Dowe M, Rogers S. Grip and pinch strength: normative data for adults. Arch Phys Med Rehabil. 1985;66(2):69–74. [PubMed: 3970660]
29. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56(3): M146–M156. [PubMed: 11253156]
30. Kelly TL, Wilson KE, Heymsfield SB. Dual energy X-ray absorptiometry body composition reference values from NHANES. PLoS One. 2009;4(9):e7038. [PubMed: 19753111]
31. Ness KK, Krull KR, Jones KE, et al. Physiologic frailty as a sign of accelerated aging among adult survivors of childhood cancer: a report from the St Jude Lifetime cohort study. J Clin Oncol. 2013;31(36):4496–4503. [PubMed: 24248696]
32. Hudson MM, Ehrhardt MJ, Bhakta N, et al. Approach for classification and severity grading of long-term and late-onset health events among childhood cancer survivors in the St. Jude Lifetime Cohort. Cancer Epidemiol Biomarkers Prev. 2017;26(5):666–674. [PubMed: 28035022]
33. Guilmette TJ, Sweet JJ, Hebben N, et al. American academy of clinical neuropsychology consensus conference statement on uniform labeling of performance test scores. Clin Neuropsychol. 2020;34(3):437–453. [PubMed: 32037942]
34. Wechsler D Wechsler Abbreviated Scale of Intelligence. Psychological Corporation; 1999.
35. Woodcock RW, McGrew KS, Mather N. Woodcock-Johnson III Tests of Achievement. Riverside Publishing; 2001.
36. Conners CK, Connelly V, Campbell S, MacLean M, Barnes J. Conners' Continuous Performance Test (ed 2). Multi-Health Systems; 2003.
37. Strauss E, Sherman E, Spreen O. A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary. Third ed. Oxford University Press; 2006.
38. Wechsler D Wechsler Adult Intelligence Scale (ed 4). Pyschological Corporation; 2008.

39. Delis D, Kramer J, Kaplan E, Ober BA. California Verbal Learning Test. 2nd ed. Psychological Corporation; 2000.
40. Reynolds CR, Voress JK. Test of Memory and Learning, Manual (ed 2). Pro-Ed, Inc; 2007.
41. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992;30(6):473–483. [PubMed: 1593914]
42. Fernandez-Pineda I, Hudson M, Pappo A, et al. Long-term functional outcomes and quality of life in adult survivors of childhood extremity sarcomas: a report from the St. Jude Lifetime Cohort Study. J Cancer Surviv. 2017;11(1):1–12. [PubMed: 27262580]
43. Derogatis LR. Brief Symptom Inventory - 18 (BSI - 18) - administration, scoring and procedures manual. NCS Pearson; 2000.
44. Huang I-C, Brinkman TM, Kenzik K, et al. Association between the prevalence of symptoms and health-related quality of life in adult survivors of childhood cancer: a report from the St Jude Lifetime Cohort study. J Clin Oncol. 2013;31(33):4242–4251. [PubMed: 24127449]
45. Grimberg A, DiVall SA, Polychronakos C, et al. Guidelines for growth hormone and insulin-like growth factor-I treatment in children and adolescents: growth hormone deficiency, idiopathic short stature, and primary insulin-like growth factor-I deficiency. Horm Res Paediatr. 2016;86(6):361–397. [PubMed: 27884013]
46. Krull KR, Hardy KK, Kahalley LS, Schuitema I, Kesler SR. Neurocognitive outcomes and interventions in long-term survivors of childhood cancer. J Clin Oncol. 2018;36(21):2181–2189. [PubMed: 29874137]
47. Schneider HJ, Saller B, Klotsche J, et al. Opposite associations of age-dependent insulin-like growth factor-I standard deviation scores with nutritional state in normal weight and obese subjects. Eur J Endocrinol. 2006;154(5):699–706. [PubMed: 16645017]
48. Sherlala RA, Kammerer CM, Kuipers AL, et al. Relationship between Serum IGF-1 and BMI differs by age. J Gerontol A Biol Sci Med Sci. 2021;76(7):1303–1308. [PubMed: 33180942]
49. Yoshida T, Baedke JL, Wang H, et al. 2025. Supplementary Table 1 for Adult Growth Hormone Deficiency, Replacement Therapy, and Outcomes in Long-Term Childhood Cancer Survivors. Figshare. Doi:10.6084/m9.figshare.28147145.v1
50. Yoshida T, Baedke JL, Wang H, et al. 2025. Supplementary Table 2 for Adult Growth Hormone Deficiency, Replacement Therapy, and Outcomes in Long-Term Childhood Cancer Survivors. Figshare. Doi:10.6084/m9.figshare.28147175.v1
51. Ellenberg L, Liu Q, Gioia G, et al. Neurocognitive status in long-term survivors of childhood CNS malignancies: a report from the childhood cancer survivor study. Neuropsychology. 2009;23(6):705–717. [PubMed: 19899829]
52. Prasad PK, Hardy KK, Zhang N, et al. Psychosocial and neurocognitive outcomes in adult survivors of adolescent and early young adult cancer: a report from the childhood cancer survivor study. J Clin Oncol. 2015;33(23):2545–2552. [PubMed: 26150441]
53. Nyberg F, Hallberg M. Growth hormone and cognitive function. Nat Rev Endocrinol. 2013;9(6):357–365. [PubMed: 23629538]
54. Cheung AT, Li WHC, Ho LLK, et al. Associations of physical activity and handgrip strength with different domains of quality of life in pediatric cancer survivors. Cancers (Basel). 2022;14(10):2554. [PubMed: 35626159]
55. Subramanian S, Chait A. Hypertriglyceridemia secondary to obesity and diabetes. Biochimica et Biophysica Acta (BBA)-Molecular and Cell Biology of Lipids. 2012;1821(5):819–825. [PubMed: 22005032]
56. Grundy SM. Metabolic syndrome update. Trends Cardiovasc Med. 2016;26(4):364–373. [PubMed: 26654259]
57. Pollock NI, Cohen LE. Growth hormone deficiency and treatment in childhood cancer survivors. Front Endocrinol (Lausanne). 2021;12:745932. [PubMed: 34745010]

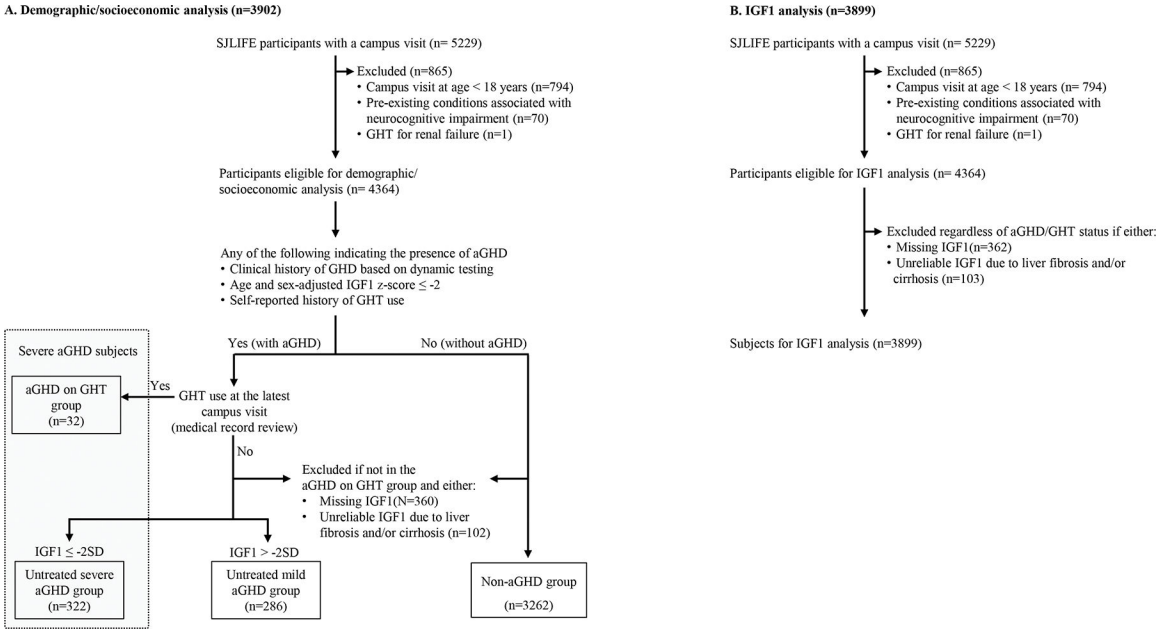

Figure 1. Study participants

A, Demographic/socioeconomic analysis; B, IGF1 analysis. The shaded square in A shows individuals with severe aGHD, who were included in the socioeconomic analysis.

Abbreviations: aGHD, adult growth hormone deficiency; GHT, growth hormone therapy; IGF1, insulin-like growth factor-1; SJLIFE, St. Jude Lifetime Cohort Study.

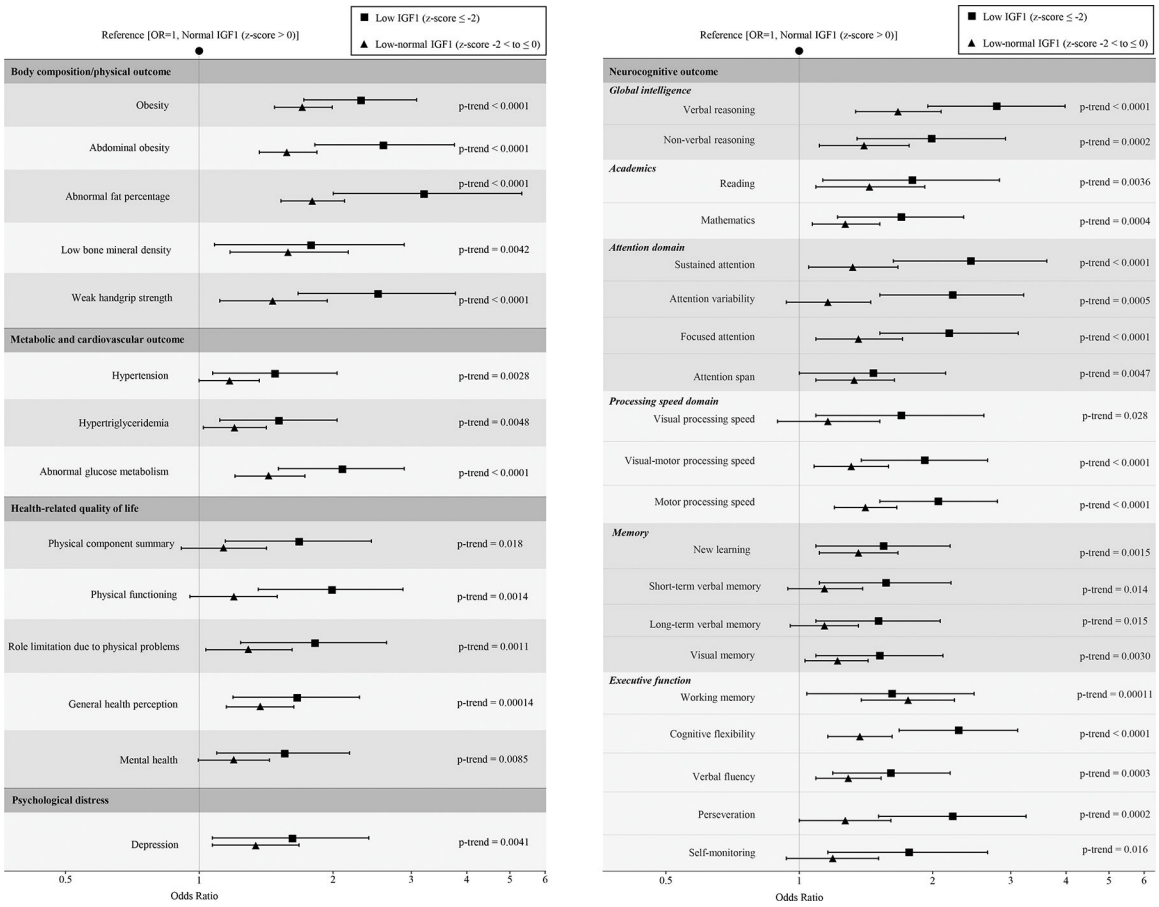

Figure 2. Insulin-like growth factor-1 (IGF1) levels and prevalence of adverse outcomes.

Associations between IGF1 levels and prevalence of outcomes were assessed in 3899 survivors. The dots and error bars show adjusted odds ratios (ORs) and 95% CIs for the risk of having each outcome. The black square and triangle indicate IGF1 *z* score category of low (≤−2) and low-normal (>−2 to ≤0), respectively. The black circle and broken line represent the null reference association (OR = 1, normal IGF1, *z* score >0). *P*-trend indicates the *P* value from the trend test, treating 3 IGF1 *z* score categories as an ordinal variable to examine the dose-dependent relationship. All analyses were adjusted for potential confounders (sex, race/ethnicity, age at cancer diagnosis, years since cancer diagnosis, tumor in the hypothalamic-pituitary [HP] region, HP radiation dose, use of growth hormone therapy in childhood, hypogonadism, hypothyroidism, adrenal insufficiency). Analyses exclusive of neurocognitive outcomes were also adjusted for educational attainment, annual household income, health insurance coverage, and area deprivation index.

Table 1.

Definitions and measurements of outcomes in IGF1 analysis

Outcome	Measurement/Data source	Definition
Body composition/physical outcome [a]		
Obesity	Height and weight measurement	BMI ≥ 30kg/m (24)
Abdominal obesity	Height and waist circumference measurement	Waist-to-height ratio of more than 0.5 (25)
Abnormal fat percentage	Dual x-ray absorptiometry	Fat percentage of ≥25% (males) or ≥35% (females) (26)
Low BMD	Dual x-ray absorptiometry	Average BMD of lumbar vertebrae L1 and L2 being Z-score < -2 (27)[b]
Weak hand grip strength	Hand grip strength	Sitting hand grip strength in less than BMI-specific cut-point (29)
Slowness in walking speed	Walking speed test	Seven or more seconds to walk 15 feet (women < 159 cm tall and men < 173cm tall), or six or more seconds to complete the distance (women ≥ 159cm tall and men ≥ 173cm tall) (30)
Low lean muscle mass	Dual x-ray absorptiometry	Lean muscle mass being Z-score ≤-1.5 compared to data from national samples (28)[b]
Frailty	Hand grip strength Walking speed test Dual x-ray absorptiometry SF-36 NHNES Physical Activity Questionnaire	Three or more among the following criteria (30,31): (i) Weak hand grip test, (ii) Slowness in walking speed, (iii) Low lean muscle mass, (iv) Decreased vitality (scores < -1.3SD on the vitality subscale of SF-36), (v) Poor physical activity [expending < 383 kcal/week (men) and < 270 kcal/week (women) in NHANES questionnaire]
Metabolic/cardiovascular outcome [a]		
Hypertension	Modified version of CTCAE (33)[c]	Resting blood pressure >140 mmHg (systolic) or >90 mmHg (diastolic); recurrent or persistent for 24+ hours; medical intervention indicated or initiated (Grade ≥2)
Hypercholesterolemia		Fasting total cholesterol level >200 mg/dL and/or on medication (Grade ≥1)[d]
Hypertriglyceridemia		Fasting triglyceride level of >150 mg/dL and/or on medication (Grade ≥1)[d]
Abnormal glucose metabolism		Fasting blood glucose ≥100 mg/dL in isolation and/or hemoglobin A1c ≥5.7% and/or meets criteria for diagnosis of diabetes mellitus and medication indicated or initiated (Grade ≥2)[d]
Coronary artery disease		Mild symptoms of cardiac ischemia and cardiac enzymes minimally abnormal and no evidence of ischemic electrocardiogram changes[e] (Grade ≥2)
Left ventricular systolic dysfunction		Resting ejection fraction <50% and >10% absolute drop from baseline and/or medication (Grade ≥2)
Cerebrovascular accident		Moderate neurologic deficite (Grade ≥2)
Neurocognitive outcome [a]		
Domain: Global intelligence		

Outcome	Measurement/Data source	Definition
Verbal reasoning	Wechsler Abbreviated Scale of Intelligence (vocabulary) (34)	
Non-verbal reasoning	Wechsler Abbreviated Scale of Intelligence (matrix reasoning) (34)	
Domain: Academics		
Reading	Woodcock-Johnson III NU Tests of Achievement (letter-Word Identification) (35)	
Mathematics	Woodcock-Johnson III NU Tests of Achievement (calculation) (35)	
Domain: Attention		
Sustained attention	Conners Continuous Performance Test (omissions) (36)	
Attention variability	Conners Continuous Performance Test (variability) (36)	Z-scores < -1.3 in each assessment was defined as impairment (41)[b]
Focused attention	Trail Making Test Part A (37)	
Attention span	Wechsler Adult Intelligence Scale (digit span forward) (38)	
Domain: Processing speed		
Visual processing speed	Conners Continuous Performance Test (hit reaction time) (36)	
Visual-motor processing speed	Wechsler Adult Intelligence Scale (coding) (38)	
Motor processing speed	Grooved pegboard (dominant hand) (37)	
Domain: Memory		
New learning	California Verbal Learning Test (total learning 1–5) (39)	
Short-term verbal recall	California Verbal Learning Test (short delay free recall) (39)	
Long-term verbal recall	California Verbal Learning Test (long delay free recall) (39)	
Visual memory	Test of Memory and Learning (visual selective reminding) (40)	
Domain: Executive function		
Working memory	Wechsler Abbreviated Scale of Intelligence (digit span backwards) (34)	
Cognitive flexibility	Trail Making Test Part B (37)	
Verbal fluency	Controlled Oral Word Association Test (37)	
Perseveration	Conners Continuous Performance Test (Perseverations) (36)	
Self-monitoring	Conners Continuous Performance Test (commissions) (36)	
Health-related quality of lifef		
Physical component summary	SF-36 (32)[g]	T-scores ≤40 in each subscale was defined as impairment (42)[b]

Outcome	Measurement/Data source	Definition
Physical functioning		
Role limitation due to physical problems		
General health perception		
Bodily pain		
Mental component summary		
Mental health		
Role limitation due to emotional problems		
Social functioning		
Vitality		
Psychological distress [f]		
Depression	Brief Symptom Inventory-18 (43)[h]	T-scores ≥63 in each subscale was defined as having symptom (44)[b]
Somatization		
Anxiety		

[a] Assessed on campus.

[b] Z-scores and T-scores were calculated adjusting for age and sex.

[c] Utilized for all metabolic/cardiovascular outcomes.

[d] Measurement used morning fasting blood samples.

[e] Conditions more severe than the definition listed are treated as positive for the condition.

[f] Participants completed SF-36 and Brief Symptom Inventory-18 surveys in alignment with campus visits.

[g] Applied for all the health-related quality of life outcomes.

[h] Appliedfor all the psychological outcomes.

BMD, bone mineral density; BMI, body mass index; CTCAE, the modified National Cancer Institute Common Terminology Criteria for Adverse Events; NHANES, National Health and Nutrition Examination Study; SD, standard deviation; SF-36, the Medical Outcomes Survey Short Form 36.

Table 2.

Characteristics of study participants in demographic/socioeconomic analysis

	aGHD on GHT group N=32		Untreated severe aGHD group N=322		Untreated mild aGHD group N=286		Non-aGHD group N=3262	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Demographic factors								
Sex								
Female	13	40.6	166	51.6	92	32.2	1586	48.6
Male	19	59.4	156	48.4	194	67.8	1676	51.4
Race								
Non-Hispanic White	29	90.6	270	83.9	226	79.0	2559	78.4
Non-Hispanic Black	1	3.1	40	12.4	37	12.9	552	16.9
Hispanic	1	3.1	8	2.5	20	7.0	96	2.9
Other	1	3.1	4	1.2	3	1.0	55	1.7
Age at the campus visit, median years old (25th-75th percentile)	27.8 (21.4–32.4)		31.9 (26.0–40.3)		29.1 (23.6–34.4)		32.1 (25.3–40.6)	
Cancer information								
Age at primary cancer diagnosis (years old)								
0–4	11	34.4	128	39.8	136	47.6	1102	33.8
5–9	16	50.0	93	28.9	91	31.8	683	20.9
10–14	4	12.5	67	20.8	44	15.4	828	25.4
15–19	1	3.1	33	10.2	12	4.2	613	18.8
20–24	0	0.0	1	0.3	3	1.0	36	1.1
Age at primary cancer diagnosis, median years old (25th-75th percentile)	6.5 (4.1–8.7)		6.2 (3.5–11.3)		5.3 (2.8–9.0)		8.8 (3.6–14.1)	
Primary cancer diagnosis								
Any hematological malignancies	7	21.9	145	45.0	124	43.4	1814	55.6
Acute lymphoblastic leukemia	6	18.8	128	39.8	85	29.7	969	29.7
Acute myeloblastic leukemia	0	0.0	2	0.6	17	5.9	124	3.8
Lymphoma	1	3.1	15	4.7	11	3.8	655	20.1
Other hematological malignancies	0	0.0	0	0.0	11	3.8	66	2.0
Any CNS tumor	23	71.9	128	39.8	132	46.2	301	9.2
Astrocytoma	5	15.6	19	5.9	24	8.4	120	3.7
Craniopharyngioma	7	21.9	32	9.9	6	2.1	1	0.0
Ependymoma	2	6.3	9	2.8	12	4.2	39	1.2
Medulloblastoma	8	25.0	37	11.5	65	22.7	40	1.2
Other CNS tumor	1	3.1	31	9.6	25	8.7	101	3.1
Any solid tumor	2	6.3	49	15.2	29	10.1	1140	34.9
Ewing Sarcoma	0	0.0	6	1.9	0	0.0	97	3.0
Osteosarcoma	0	0.0	4	1.2	5	1.7	144	4.4
Neuroblastoma	0	0.0	2	0.6	3	1.0	156	4.8
Rhabdomyosarcoma	2	6.3	15	4.7	9	3.1	106	3.2

	aGHD on GHT group N=32		Untreated severe aGHD group N=322		Untreated mild aGHD group N=286		Non-aGHD group N=3262	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Wilms tumor	0	0.0	3	0.9	4	1.4	213	6.5
Other solid tumor	0	0.0	19	5.9	8	2.8	424	13.0
Others[a]	0	0.0	0	0.0	1	0.3	7	0.2
Tumor in the hypothalamic-pituitary region								
Yes	11	34.4	65	20.2	26	9.1	26	0.8
No	21	65.6	257	79.8	260	90.9	3236	99.2
Radiation dose to the hypothalamic-pituitary region								
≤2 Gy	5	15.6	74	23.0	73	25.5	2562	78.5
2< to <18 Gy	0	0.0	1	0.3	24	8.4	99	3.0
≥18 Gy	24	75.0	234	72.7	177	61.9	526	16.1
Missing	3	9.4	13	4.0	12	4.2	75	2.3
Clinical information								
IGF1 z-score, median (25th-75th percentile)	−0.1 (−1.1 – 1.0)		−2.6 (−3.2 – −2.2)		−0.5 (−1.3 – 0.3)		0.2 (−0.6 – 0.9)	
Onset of GHD								
Childhood-onset	30	93.7	130	40.3	240	83.9		
Adulthood-onset	2	6.3	16	5.0	19	6.6		
Unknown	0	0.0	176	54.7	27	9.4		
Socioeconomic status								
Annual household income								
<$40,000	6	18.8	124	38.5	92	32.2	964	29.6
$40,000-$79,999	6	18.8	79	24.5	60	21.0	814	25.0
≥$80,000	11	34.4	35	10.9	60	21.0	817	25.0
Missing	9	28.1	84	26.1	74	25.9	667	20.4
Health insurance								
Private	18	56.3	129	40.1	147	51.4	1844	56.5
Public	10	31.3	93	28.9	64	22.4	511	15.7
Private and public	2	6.3	16	5.0	12	4.2	78	2.4
Uninsured	0	0.0	42	13.0	25	8.7	394	12.1
Others	1	3.1	10	3.1	12	4.2	113	3.5
Missing	1	3.1	32	9.9	26	9.1	322	9.9
Area deprivation index, median (25th-75th percentile)	43 (36–67)		63 (41–82)		50 (33–72)		57 (36–78)	
Educational attainment								
Below high school	3	9.4	41	12.7	34	11.9	243	7.4
High school graduate/General Educational Development	5	15.6	75	23.3	60	21.0	487	14.9
Some college/training after high school	8	25.0	87	27.0	71	24.8	970	29.7

	aGHD on GHT group N=32		Untreated severe aGHD group N=322		Untreated mild aGHD group N=286		Non-aGHD group N=3262	
	N	%	N	%	N	%	N	%
College graduate and above	11	34.4	74	23.0	85	29.7	1159	35.5
Missing Smoking	5	15.6	45	14.0	36	12.6	403	12.4
Smoking								
Current	1	3.1	41	12.7	30	10.5	548	16.8
Past	1	3.1	14	4.3	19	6.6	375	11.5
Never	29	90.6	239	74.2	215	75.2	2021	62.0
Missing	1	3.1	28	8.7	22	7.7	318	9.7

[a]Included desmoid tumor, malignant hydatidiform mole, solid pseudopapillary tumor.

aGHD, adult growth hormone deficiency; GHT, growth hormone therapy; IGF1, insulin-like growth factor-1.

Table 3.

The association between the use of GHT and socioeconomic factors among survivors with severe aGHD[a]

Socioeconomic factor	Odds ratio	95% confidence interval	p-value
Household income in US dollars (Reference: ≥$80,000)			
$40,000-$79,999	0.32	0.10–0.99	0.025[b]
<$40,000	0.27	0.08–0.84	
Health insurance coverage (Reference: insured)			
Uninsured	0.00	0.00–0.59	0.013
Area deprivation index (Reference: 1–50)			
51–75	0.63	0.22–1.64	0.045[b]
76–100	0.31	0.07–1.06	

[a]This analysis was adjusted for sex, age at campus visit, and age at primary cancer diagnosis.

[b]P-value from a trend test, setting each category as ordinal variable.

Categories for missing/other values of the three socioeconomic factors were included to maximize the modelling population but are not shown.

aGHD, adult growth hormone deficiency; GHT, growth hormone therapy.