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Review Article

Impact of short stature on quality of life: A systematic literature review

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ABSTRACT

Objective: We sought to obtain a better understanding of the burden of short stature using a systematic literature review.
Methods: Studies of the burden of short stature, of any cause in adults and children, were searched using Embase, MEDLINE and Cochrane databases in April 2020, capturing publications from 2008 onwards. Case series and populations with adult-onset growth hormone deficiency (GHD) were excluded.
Results: Of 1684 publications identified, 41 studies (33 in children, 8 in adults) were included. All studies assessed human burden. Most study populations in children included short stature due to GHD, idiopathic short stature (ISS) and short stature after being born small for gestational age (SGA). In these populations, four studies showed that quality of life (QoL) in children with short stature was significantly worse than in children with normal stature. A significant association between QoL and short stature was observed in children with chronic kidney disease (CKD) (3 studies), achondroplasia (1 study) and transfusion-dependent β-thalassaemia (1 study), and in samples with mixed causes of short stature (3 studies). Three studies (one in GHD/ISS/SGA and two in CKD) found no significant association between short stature and QoL, and several studies did not report statistical significance. Approximately half of adult studies showed that QoL was reduced with short stature, and the other half showed no association. Two studies, one in adults with Prader–Willi syndrome and one in children with GHD, suggested a potential association between short stature and poorer cognitive outcomes. Three studies demonstrated an increased caregiver burden in parents of children with short stature.
Conclusions: Evidence suggests that, compared with those with normal stature, children and adults with short stature of any cause may experience poorer QoL. Further research could extend our understanding of the human burden in this field.

1. Introduction

Short stature is defined as a height more than two standard deviations (SDs) below the mean height of a reference population matched for age, sex and pubertal stage [1,2]. By this definition approximately 2.5% of the general population are considered to be of short stature, because 95% of the general population fall within two SDs of the mean of a normal distribution. Short stature may be idiopathic, secondary to organ system disease (e.g. chronic kidney disease [CKD]) or arise from an endocrine disorder. Endocrine causes include childhood-onset growth hormone deficiency (GHD) and primary insulin-like growth factor I (IGF-—I) deficiency, as well as other defects of the growth hormone (GH)/IGF-I axis [3].

In children, treatment is available for short stature; e.g. recombinant human GH therapy for a range of causes of short stature [4] and recombinant human IGF-1 for severe primary IGF-I deficiency [5]. The primary goal of treatment is to increase growth to achieve an adult height within the target height range for the individual [5].

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Owing to the physical challenges of having short stature, it may be considered a disability in some countries; e.g. 'dwarfism', of any type, is a recognized condition under the Americans with Disabilities Act [6]. These challenges can make activities of daily living harder. As a result, it is possible that people with short stature, whatever the cause, may experience poorer quality of life (QoL) than people with normal stature. It is unclear whether short stature may also impose an economic burden on affected individuals and their families or caregivers. This social and economic burden of short stature may begin in childhood and remain present in adult life.

There is a lack of consolidated evidence on the level and type of burden of children and adults with short stature. Such evidence would provide a clearer understanding of the degree of burden, which could support treatment decisions in early childhood. We conducted a systematic literature review (SLR) to identify evidence of the burden of short stature of any cause.

2. Materials and methods

2.1. Search strategy

An SLR was carried out to identify studies reporting evidence on the burden of short stature. The databases searched on 29 April 2020 were: Ovid MEDLINE® In-Process & Other Non-Indexed Citations and Ovid MEDLINE®, 1946–present; Embase® 1974–present; and the Cochrane Library (Supplementary Table 1).

2.2. Eligibility criteria

We searched the literature for observational studies, clinical studies and economic evaluations that included adults and children with short stature, and assessed outcomes related to human or economic burden. Any cause of short stature was included; adult-onset GHD was excluded because onset of GHD during adulthood is not characterized by short stature. We applied publication date cut-offs to manage the number of search results (1364 abstracts were screened overall), allowing for a thorough systematic review of a recent period of time. For human burden studies, we chose the last 12 years (2008 onwards). The more recent publications make use of QoL assessments specific to short stature that have been introduced within the last 10 years (e.g. the Quality of Life of Short Stature Youth [QoLISSY] questionnaire). The development of the QoLISSY reflects the increased understanding of and interest in QoL over the past few years. We believe that older publications would be less valuable as they would not adequately reflect current understanding of QoL and its importance in assessment of children with short stature. For economic studies, where the value of cost data can change more rapidly over time, we chose the last 7 years (2013 onwards). Full eligibility criteria are presented in Table 1.

2.3. Supplementary searches

In addition to the electronic searches, supplementary searches were carried out to capture recent conference material (2017–2020) from: the International Society of Pharmacoeconomics and Outcomes Research (EU and US meetings); the European Society for Paediatric Endocrinology; the Pediatric Endocrine Society; and the International Congress of Endocrinology.

2.4. Screening and data extraction

Abstracts were screened against eligibility criteria to identify relevant studies. Full texts were reviewed to assess eligibility further. Screening and full text review were carried out by one reviewer, with uncertainties resolved by a second independent reviewer. When a final list of relevant studies was agreed, data were extracted from each study by one reviewer and validated by a second reviewer. Data were extracted for a range of variables, including study design, study population (including details of controls), sample size, age, height, outcome measure and key findings.

Table 1
Eligibility criteria of the systematic literature review.

Category	Inclusion criteria	Exclusion criteria
Population	General short stature (including ISS and SGA), growth failure (including GHD), severe primary IGF-I deficiency, severe insulin resistance, Laron syndrome, Turner syndrome, leprechaunism (Donohue syndrome), Rabson–Mendenhall syndrome	Adult-onset GHD
Intervention	Not restricted by intervention	
Comparator	Not restricted by comparator	
Outcomes	Human burden (humanistic, caregiver, employment, family and societal burden; patient-reported outcomes; QoL; patient preference) Economic burden (resource allocation; healthcare costs/utilization)	Outcomes other than those listed
Study design	Clinical and observational studies (prospective, retrospective, cross-sectional, randomized, non-randomized, open-label, cohort) Economic studies	Reviews, editorials, commentaries Systematic reviews Case studies/case series Animal studies
Date restrictions	2008 to present (human burden studies) 2013 to present (economic burden studies)	Published before 2008 (human burden studies) Published before 2013 (economic burden studies)
Language restrictions	English language	Non-English language
Country	Not restricted by country	

GHD, growth deficiency hormone; IGF-—I, insulin-like growth factor I; ISS, idiopathic short stature; QoL, quality of life; SGA, small for gestational age.

2.5. Quality assessment

The quality of each included observational study or randomized controlled trial was assessed using National Institute for Health and Care Excellence (NICE) methodology checklists [7]. During this assessment, studies were given a rating according to their level of potential bias in terms of internal validity and external validity.

3. Results

3.1. Overview of studies

Of 1684 articles identified from the electronic databases and additional studies identified from congress searches, 41 studies were considered relevant for the burden of short stature and were included in the review (Fig. 1). All identified studies report findings on the human burden of short stature. No studies were identified for the economic burden of short stature. Thirty-three studies reported data on children with short stature, most of which included populations of children with GHD or idiopathic short stature (ISS), and those with short stature after being born small for gestational age (SGA) (Fig. 2). Eight studies reported evidence for adults with short stature, mostly caused by GHD (Fig. 2).

Of 41 studies, 39 were observational in design and two were randomized trials (one placebo-controlled and one with open-label comparators). Over half of the studies were assessed as having good internal validity; most studies did not have good external validity, mainly owing to highly selected sample populations (Table 2).

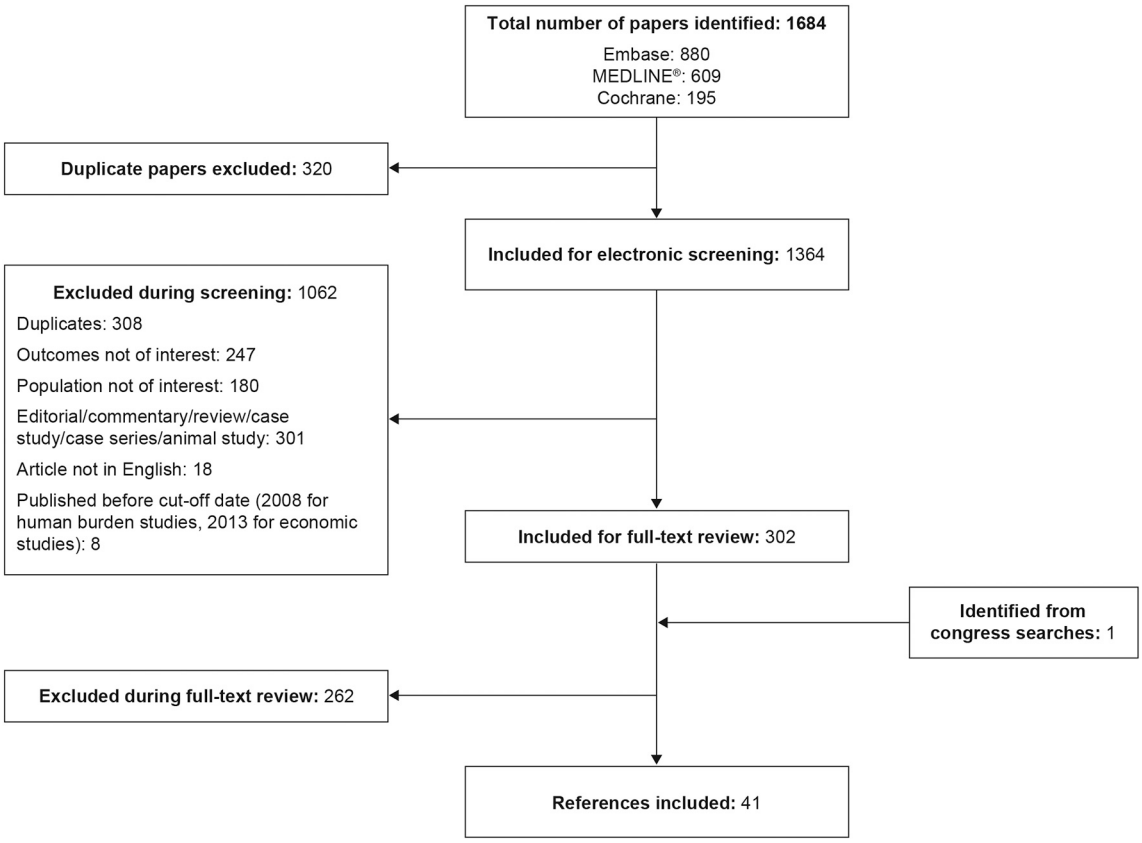

Fig. 1. PRISMA diagram to illustrate included studies.
Electronic searches were conducted on 29 April 2020.
PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

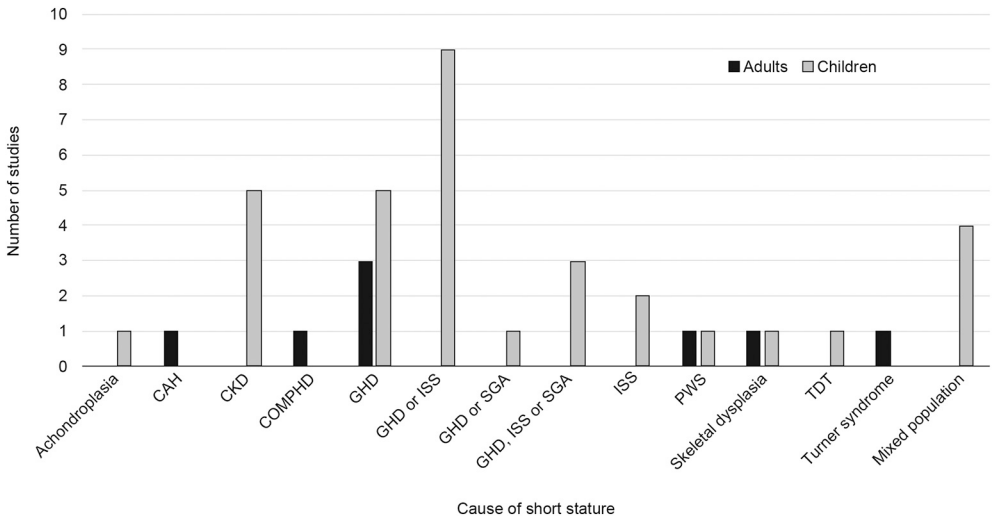

Fig. 2. Distribution of causes of short stature in the identified studies.
Note, mixed population describes studies in which the study sample includes more than one cause of short stature, beyond GHS, ISS and SGA, and does not report data separately by cause of short stature.
CAH, congenital adrenal hyperplasia; CKD, chronic kidney disease; COMPHD, childhood-onset multiple pituitary hormone deficiency; GHD, growth hormone deficiency; ISS, idiopathic short stature; PWS, Prader–Willi syndrome; SGA, small for gestational age; TDT, transfusion-dependent β-thalassaemia.

3.2. *Children with short stature*

3.2.1. *GHD, SGA, ISS*

Among the identified studies in children, the most represented study populations were children with short stature due to GHD, children with ISS, and children with short stature after being born SGA. Twenty studies reporting findings for these populations are summarized in Table 3 [8–27], three of which were derived from the same study sample [9,17,18].

Five studies compared QoL between children with short stature and children with normal stature [14,20,24–26], nine studies compared QoL between short stature subgroups [9,10,13,17,19,21,23,25,27], and eight studies measured the change in QoL over time in children with short stature receiving treatment [9,11,12,16–19,27] (Table 3).

3.2.1.1. Comparison with normal stature. Five studies compared QoL between children with short stature and control groups of children with normal stature. Four of these studies reported evidence of lower scores

Table 2
Study characteristics of all included studies ($N = 41$).

First author (year), country	Study design	Study population (control group, if applicable)	Sample size	Age, years, at baseline	Height, cm/height SDS in short stature study population	Internal validity rating[a]	External validity rating[a]
Al-Uzri (2013) [28], USA	Prospective, longitudinal, observational study	Children with CKD, with and without short stature	483 (inc. 71 with short stature)	Mean (SD) 10.37 (4.47) in children with short stature, 11.28 (4.31) in children with normal stature	NR	++	–
Aparicio-Lopez (2013) [29], Spain	Cross-sectional study	Children with CKD, with and without short stature	71 (inc. 38 with short stature)	Mean (SD) 12.8 (6.48)	NR	–	–
Barbosa (2009) [45], Brazil	Questionnaire	Adults with isolated GHD (controls: matched adults residing in the same community)	40 (inc. 20 controls)	Mean (SD) 45.50 (14.34) in adults with short stature, 46.50 (13.97) in controls	NR, but described as severe short stature	–	–
Bettini (2019) [8], Italy	Longitudinal prospective study	Children with GHD	80	Mean (SD) 12.07 (3.51)	NR	–	–
Bloemeke (2019) [9], Germany	Prospective observational study	Children with GHD, ISS or short stature after being born SGA	154	Mean (SD) 8.09 (3.34) in children with idiopathic GHD, 6.55 (2.64) in children born SGA, 9.45 (3.49) in children with ISS	Mean (SD) height, cm: 117.11 (17.44) in children with idiopathic GHD, 108.01 (13.45) in children born SGA, 126.24 (18.86) in children with ISS	–	–
Bullinger (2013) [10], France, Germany, Spain, Sweden and UK	Questionnaire	Children with GHD or ISS	268	Range 8–18	Height SDS, 0 to –1.499 (n = 77); height SDS, –1.50 to –2.499 (n = 115); height SDS, ≤ –2.50 (n = 53)[b]	–	++
Bullinger (2018) [11], USA and Chile	Randomized, open-label, comparator trial	Children (boys only) with ISS	76	Mean (SE) 14.0 (0.8)	Mean (SE) height SDS –2.3 (0.0)	+[c]	–[c]
Butler (2019) [12], UK	National, prospective, controlled study	Children with isolated GHD, acquired GHD or TS (controls: children with untreated short stature [ISS or constitutional growth delay])	189 (inc. 49 controls)	Range 6–16	NR	–	–
Dhiman (2017) [41], USA	Online survey	Adults with short stature skeletal dysplasia	189	Range 19–80	NR	++	+
Drosatou (2019) [13], Greece	Observational study	Children with GHD or ISS	198	Range 4–18	Height SDS > –2.0 (n = 105); height SDS ≤ −2.0 (n = 82)[b]	–	–
Francis (2018) [30], Australia and New Zealand	Cross-sectional study	Children with CKD, with and without short stature	375 (inc. 87 with short stature)	Median 12.6	NR	++	+
Geisler (2012) [14], Germany	Prospective, cross-sectional study	Children with GHD (controls: age- and gender-matched children without GHD, with either normal stature or similar height to the children with GHD)	570 (inc. 190 controls)	Mean (SD) 12.7 (2.4) in children with GHD, 12.6 (2.5) in children without GHD and with reduced height, 12.6 (2.5) in children without GHD and with normal stature	Mean (SD) height, cm: 145.0 (12.8) in children with GHD, 144.3 (12.5) in children without GHD and with reduced height	++	–
Gerson (2010) [31], USA	Cross-sectional study	Children with CKD, with and without short stature	402 (inc. 86 with short stature)	Mean (SD) 11 (4)	< 5th percentile	++	–
Gonzalez Briceno (2019) [33], France	Prospective, observational study	Children with GHD, ISS, bone dysplasia or short stature after being born SGA	80	Median (range) 10.9 (4.1–16.6)	Range height SDS: –2.5 (–5.0 to –2.0)	+	–
Han (2014) [42], UK	Cross-sectional study	Adults with CAH	196 (inc. 62 men with classic CAH, 103 women with classic CAH, 31 women with non-classic CAH)	Mean (SD) 32.3 (10.2) in men with classic CAH, 33.5 (10.4) in women with classic CAH, 42.5 (12.9) in women with non-classic CAH	NR	++	+

First author (year), country	Study design	Study population (control group, if applicable)	Sample size	Age, years, at baseline	Height, cm/height SDS in short stature study population	Internal validity rating[a]	External validity rating[a]
Harmer (2019) [32], UK	Single-centre, cross-sectional, observational study	Children with CKD, with and without short stature	46 (inc. 12 with short stature)	Mean (SD) 10.50 (4.19)	Mean (IQR) height SDS: –0.65 (2.03)	++	–
Jez (2018) [46], Poland	Prospective, observational study	Women with TS	176	Mean (SD) 25 (7.6)	Mean (SD) height, cm: 144.7 (7.2)	+	–
Kao (2015) [44], Australia	Prospective, case control, cross-sectional study	Adults with COMPHD (controls: age- and gender-matched adults without COMPHD)	184 (inc. 92 controls)	Mean (SD) 29.7 (8.16)	Mean (SD) height, m: 1.64 (0.12)	+	+
Lorne (2020) [37], Switzerland	Observational study	Children with short stature skeletal dysplasia	8	Mean (SD) 11.1 (3.33)	Mean (SD) height SDS: –4.71 (1.34)	–	–
Mao (2019) [39], China	NR	Children with PWS	32	NR	NR	–	–
Mettananda (2019) [38], Sri Lanka	Case control study	Children with TDT (controls: children without TDT)	525 (inc. 254 controls)	Mean (SD) 10.9 (3.6) in children with TDT, 10.4 (3.5) in children without TDT	NR	++	–
Oliveira (2017) [48], Brazil	Cross-sectional study	Adults with isolated GHD (controls: age- and sex-matched adults with normal height who are homozygous for the wild-type GHRHR allele)	42 (inc. 21 controls)	Mean (SD) 43.5 (13.6)	Mean (SD) height, m: 1.25 (0.08)	+	–
Otero (2013) [40], UK	Comparative study	Children with GHD or TS	144	Range 10–16	NR	–	–
Quitmann (2016a) [15], France, Germany, Spain, Sweden, UK	Questionnaire based study	Children with GHD or ISS	137	Mean (SD) 13.3 (2.74)	Height SDS > –2.0 (n = 24); height SDS ≤ –2.0 (n = 71)[b]	+	–
Quitmann (2016b) [16], Belgium Sweden, Germany, France, Netherlands UK, Spain	Cross-sectional study	Children with GHD or ISS	345	Mean 10.39	Height SDS > –2.0 (n = 191); height SDS ≤ –2.0 (n = 220)[b]	++	–
Quitmann (2019a) [17], Germany	Prospective observational study	Children with GHD, ISS or short stature after being born SGA	111	Mean (SD) 8.40 (3.32) in children with GHD, 6.90 (2.78) in children born SGA, 9.33 (3.34) in children with ISS	Mean (SD) height, cm/SDS: 119.02 (17.22)/–2.53 (0.57) in children with GHD, 110.18 (13.68)/–2.63 (0.65) in children born SGA, 124.97 (17.81)/–2.21 (0.53) in children with ISS	–	–
Quitmann (2019b) [18], Germany	Prospective observational study	Children with GHD, ISS or short stature after being born SGA	154	Mean (SD) 8.09 (3.34) in children with idiopathic GHD, 6.55 (2.64) in children born SGA, 9.45 (3.49) in children with ISS	Mean (SD) height, cm/SDS: 117.11 (17.44)/–2.61 (0.61) in children with idiopathic GHD, 108.01 (13.45)/–2.65 (0.63) in children born SGA, 126.24 (18.86)/–2.11 (0.51) in children with ISS	–	–
Shemesh-Iron (2019) [19], Israel	Prospective double-blind placebo-controlled study	Children (boys only) with ISS	60	Mean (SD) 10.0 (1.4)	Mean (SD) height SDS: −2.38 (0.30)	++[c]	+[c]
Shimatsu (2011) [43], Japan	Observational study	Adults with childhood-onset GHD	69	Mean (SD) 28.0 (8.6)	NR	+	+
Silva (2013) [20], France, Germany, Spain, Sweden and UK	Cross-sectional, multicentre study	Children with GHD or ISS	110	Mean 12.34	Height SDS ≤ –2	++	–
Silva (2018) [21], France,	Cross-sectional, multicentre study	Children with GHD or ISS	238	NR	Height SDS > –2.0 (n = 115); height SDS ≤ –2.0 (n =	++	–

First author (year), country	Study design	Study population (control group, if applicable)	Sample size	Age, years, at baseline	Height, cm/height SDS in short stature study population	Internal validity rating[a]	External validity rating[a]
Germany, Spain, Sweden and UK					119)[b]		
Sommer (2017) [22], France, UK, Sweden, Spain and Germany	Qualitative study	Children with GHD or ISS	84	Range 4–18	NR	–	–
Sommer (2018) [23], Germany	Prospective longitudinal study	Children with short stature after being born SGA	65	Range 4–18	Height SDS > –2.0 (n = 7); height SDS ≤ –2.0 (n = 56)[b]	–	–
Stephen (2011) [24], USA	Cross-sectional study	Children with GHD or ISS (controls: children without short stature)	1348 (inc. 1259 controls)	Mean (SD) age in months, 136.25 (34.24) in children with untreated short stature, 156.56 (26.13) in children initiated on treatment with HGH	Mean height, cm/SDS, 129.16/–2.56 in children with untreated short stature, 123.15/–4.55 in children initiated on treatment with HGH	++	–
Stheneur (2011) [25], France	Postal survey	Adolescents and young adults with GHD treated with GH during childhood	34	Mean (SD) 20.5 (4.9)	Mean (SD) adult height, cm: 171.1 (4.8) in males, 156.1 (6.1) in females	–	–
Tanaka (2009) [26], Japan	Observational study	Children with GHD or ISS (controls: children without short stature)	243 (inc. 5159 controls])	Mean (SD) 9.12 (3.09) in children with GHD, 8.45 (2.64) in children with ISS	Mean (SD) height, cm/SDS: 117.44 (17.55)/–2.91 (1.15) in children with GHD, 116.61 (13.89)/–2.39 (0.41) in children with ISS	–	+
Tanaka (2014) [27], Japan	Prospective observational study	Children with GHD or ISS	281	Mean (SD) 9.1 (3.0) in children with GHD, 8.3 (2.8) in children with ISS	Mean (SD) height, cm/SDS: 117 (16)/–2.87 (0.51) in children with GHD, 116 (14)/–2.44 (0.35) in children with ISS	–	+
Van Nieuwpoort (2011) [47], Netherlands	Comparative study	Adults with PWS (controls: siblings without PWS)	29 (inc. 14 controls)	Median (range) 22.0 (19.2–42.9)	Median (range) height, m: 1.58 (1.44–1.67)	–	–
Varni (2012) [34], USA	Exploratory study (non-interventional)	Children with short stature – cause not specified, but most commonly GHD and constitutional growth delay (controls: children with cancer without short stature and healthy children without short stature)	1751 (29 with short stature)	Mean (SD) 11.51 (3.41) in children with short stature, 10.10 (4.48) and 13.68 (2.17) in children without short stature who completed PedsQL 4.0 Generic Core Scales and Multidimensional Fatigue Scale, respectively, 8.22 (4.82) in children with cancer	NR	+	–
Witt (2019) [36], Germany	Cross-sectional study	Children with achondroplasia	73	Mean (SD) 9.75 (3.02)	Mean (SD) height SDS: –5.25 (1.26)	++	–
Wu (2013) [35], China	Observational study	Children with GHD, ISS, TS or short stature after being born SGA	201	Range 8–18	Height SDS ≤ –2	–	–

[a] Quality assessment of internal and external validity of the study. Internal validity addresses whether there is a risk of bias in the study findings, including selection bias, performance bias, attrition bias and detection bias. External validity addresses whether the findings for the study participants apply to the whole source population and if similar findings are likely to be replicated in a different setting with a similar population. For both types of validity, the ratings are defined as follows: ++ (shaded green above), all or most of the checklist criteria have been fulfilled, where they have not been fulfilled the conclusions are very unlikely to alter; + (shaded orange above), some of the checklist criteria have been fulfilled, where they have not been fulfilled, or not adequately described, the conclusions are unlikely to alter; – (shaded red above), few or no checklist criteria have been fulfilled and the conclusions are likely or very likely to alter. Source: NICE checklists for cohort studies or case control studies (The social care guidance manual. Appendices D and E. Available at: https://www.nice.org.uk/process/pmg10/chapter/introduction [accessed 3 August 2020]).

[b] Height deviation data were missing in some patients.

[c] Quality assessment for these studies used the NICE checklists for randomized controlled studies (The social care guidance manual. Appendix C. Available at: https://www.nice.org.uk/process/pmg10/chapter/introduction [accessed 3 August 2020]).

CAH, congenital adrenal hyperplasia; CKD, chronic kidney disease; COMPHD, childhood-onset multiple pituitary hormone deficiency; GH, growth hormone; GHD, growth hormone deficiency; GHRHR, growth hormone-releasing hormone receptor; HGH, human growth hormone; inc., including; IQR, interquartile range; ISS, idiopathic short stature; NR, not reported; PedsQL, Pediatric Quality of Life Inventory; PWS, Prader–Willi syndrome; SD, standard deviation; SDS, standard deviation score; SE, standard error; SGA, small for gestational age; TDT, transfusion-dependent β-thalassaemia; TS, Turner syndrome.

(i.e. an increased burden) in children with short stature compared with children with normal stature [20,24–26]. Two of these studies found significantly reduced QoL in some of the short stature subgroups, or in some subdomains of the QoL scale, but no significant difference between short stature and normal stature in the overall study population, or for total QoL score [25,26]. One study found that controls with normal stature had significantly better QoL and cognitive function than children with GHD or ISS [24]. One study found no difference in QoL between untreated children with short stature and the reference QoL scores of children with normal stature, but children with short stature who were treated had better QoL than the reference scores [20]. Only one study found no difference in QoL between children with short stature and children with normal stature. However, that same study found that height as a continuous variable was a significant predictor of QoL overall

Table 3
Key findings in studies of children with GHD or ISS or children with short stature who were born SGA ($N = 20$).

First author (year), country	Outcome measure (assessment tool)	Subgroup (sample size)	Total QoL score at baseline	Total QoL score at follow-up	Within-group change in QoL from baseline to follow-up, after treatment[a]	Between-group comparison: vs other short stature	Between-group comparison: vs normal stature
Bettini (2019) [8], Italy	Disease-specific HRQoL (QoLISSY)	GHD ($n = 80$)	"Satisfying" score for 85.7% of patients	NA	NA	NA	NA
Bloemeke (2019) [9], Germany	Disease-specific HRQoL (QoLISSY)	GHD or SGA ($n = 123$)	Mean (SD) score: Overall, 48.88 (24.17) Patients who achieved normal height after 12 months treatment, 55.16 (28.06) Patients who still had short stature after 12 months treatment, 55.42 (22.94)	Mean (SD) score (12 months): Overall, 61.60 (22.88) Patients who achieved normal height after 12 months treatment, 61.15 (21.17) Patients who still had short stature after 12 months treatment, 61.24 (26.34)	Improvement was statistically significant (p value NR)	In all subgroups, there was no significant difference between changes in total score between treated and untreated groups There was no significant difference between changes in total score between treated patients who achieved normal height and treated patients who still had short stature	NA
		ISS ($n = 31$)	Mean (SD), 69.01 (19.50)	Mean (SD) at 12 months, 60.88 (24.20)	NR		NA
Bullinger (2013) [10], France, Germany, Spain, Sweden and UK	Disease-specific HRQoL (QoLISSY)	GHD or ISS ($n = 268$)	Mean (SD) score: Overall, 73.10 (21.39) Height SDS 0 to −1.49, 85.59 (13.90) Height SDS 1.5 to −2.49, 69.33 (21.67) Height SDS ≤ −2.5, 59.47 (19.60)	NA	NA	$p < 0.001$ for difference between height subgroups	NA
Bullinger (2018) [11], USA and Chile	Disease-specific HRQoL (QoLISSY)	ISS ($n = 76$)	Mean score: Treated with AI, 66.1 Treated with GH, 57.8 Treated with AI and GH, 64.8	Mean score at 24 months: Treated with AI, 71.5 Treated with GH, 74.1 Treated with AI and GH, 81.3	p value: Treated with AI, 0.12 Treated with GH, 0.01 Treated with AI and GH, < 0.01	NA	NA
Butler (2019) [12], UK	Generic HRQoL (PedsQL); psychological problems (SDQ[a])	Isolated GHD ($n = 73$)	Mean SDQ total difficulties score, 14.89	SDQ total difficulties score at 12 months, 11.36	Increase in PedsQL score over 12 months, 8.5	NA	NA
		Non-GHD short stature, $n = 49$	Mean SDQ total difficulties score, 12.47	SDQ total difficulties score at 12 months, 6.21	Increase in PedsQL score over 12 months, 8.2	NA	NA
Drosatou (2019) [13], Greece	Disease-specific HRQoL (QoLISSY)	GHD ($n = 176$) and ISS ($n = 22$)	Mean (SD) score: Height SDS ≤ −2.0, 75.37 (13.45) Height SDS > −2.0, 79.81 (13.27)	NA	NA	$p = 0.003$ for difference between height subgroups There was no significant difference in scores between GHD and ISS subgroups	NA
Geisler (2012) [14], Germany	Generic HRQoL (KINDL)	GHD ($n = 95$)	Mean (SD), 74 (13)	NA	NA	NA	There was no difference in QoL between short and normal stature groups
		Reduced height and no GHD ($n = 190$)	Mean (SD), 72 (12)	NA	NA	NA	
		Healthy children with normal stature ($n = 285$)	Mean (SD), 75 (10)	NA	NA	NA	
Quitmann (2016a) [15], France, Germany,	Generic HRQoL (KIDSCREEN-10); disease-specific HRQoL (QoLISSY)	GHD or ISS ($n = 137$)	Mean (SD) scores: KIDSCREEN-10, 77.02 (14.02)	NA	NA	NA	NA

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Table 3 (*continued*)

First author (year), country	Outcome measure (assessment tool)	Subgroup (sample size)	Total QoL score at baseline	Total QoL score at follow-up	Within-group change in QoL from baseline to follow-up, after treatment[a]	Between-group comparison: vs other short stature	Between-group comparison: vs normal stature
Spain, Sweden, UK			QoLISSY, 75.34 (20.66)				
Quitmann (2016b) [16], Belgium Sweden, Germany, France, Netherlands UK, Spain	Generic HRQoL (KIDSCREEN-10); disease-specific HRQoL (QoLISSY); psychological problems (SDQ)[b]	GHD (n = 152) or ISS (n = 269)	Mean (SD) scores (achieved short stature / current short stature subgroups): KIDSCREEN, 79.43 (11.29)/78.56 (11.10) QoLISSY, 84.86 (12.16)/58.76 (25.29) Based on SDQ cut-off values, 7.6% of children reported clinically significant psychological problems	NA	NA	Generic HRQoL was similar between children with current short stature and those who achieved short stature, but disease-specific QoL was poorer Statistical significance was NR	NA
Quitmann (2019a) [17], Germany	Disease-specific HRQoL (QoLISSY)	GHD (n = 48)	Mean (SD), 48.01 (26.01)[c]	Mean (SD) at 12 months, 53.61 (24.39)[c]	In the GHD, SGA and ISS groups overall, time was not significantly associated with follow-up QoL (i.e. scores did not significantly improve from baseline to 12 months in the overall study sample)	Diagnosis (i.e. GHD, SGA or ISS) was not associated with QoL at 12 months	NA
		SGA (n = 42)	Mean (SD), 47.77 (18.97)[c]	Mean (SD) at 12 months, 60.24 (22.12)[c]			NA
		ISS (n = 21)	Mean (SD), 60.20 (22.71)[c]	Mean (SD) at 12 months, 59.57 (25.15)[c]			NA
Quitmann (2019b) [18], Germany	Disease-specific HRQoL (QoLISSY)	Idiopathic GHD (n = 65) or SGA (n = 58) (treated with GH)	Mean (SD), 48.88 (24.17)	Mean (SD) at 12 months, 61.60 (22.88)	NR	There was a significant difference ($p < 0.01$) in change in QoL over 12 months between children with idiopathic GHD or short children born SGA who were treated and children with ISS who were untreated	NA
		ISS (n = 31) (untreated)	Mean (SD), 69.01 (19.50)	Mean (SD) at 12 months, 60.88 (24.20)	NR		
Shemesh-Iron (2019) [19], Israel	Generic HRQoL (PedsQL); child behavioral and emotional problems (CBCL)	ISS receiving GH (n = 40)	Mean (SD) PedsQL score, 76.7 (13.0) CBCL values NR	Mean (SD) PedsQL score at 12 months, 76.9 (11.6) CBCL values NR	NA	No significant difference in PedsQL or CBCL scores between treatment and placebo groups at baseline or 12 months	NA
		ISS receiving placebo (n = 20)	Mean (SD) PedsQL score, 78.9 (10.2) CBCL values NR	Mean (SD) PedsQL score at 12 months, 81.4 (10.7) CBCL values NR	NA		NA
Silva (2013) [20], France, Germany, Spain, Sweden and UK	Generic HRQoL (KIDSCREEN-10)	GHD or ISS (n = 59) (treated)	Mean (SD) score: Height SDS ≤ -2.0, 80.63 (12.56) Height SDS > -2.0, 79.17 (12.88)	NA	NA	NA	Treated children with short stature had significantly better QoL than European KIDSCREEN norms (mean [SD], 74.07 [14.94]), in both height deviation subgroups ($p = 0.03$ and $p = 0.02$, respectively)
		GHD or ISS (n = 16) (untreated)	Mean (SD) score: Height SDS ≤ -2.0, 73.41 (16.71) Height SDS > -2.0, 79.50 (12.17)	NA	NA	NA	There was no significant difference between QoL of untreated children with short stature and European KIDSCREEN norms (mean [SD], 74.07 [14.94]), in either height deviation

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Table 3 (*continued*)

First author (year), country	Outcome measure (assessment tool)	Subgroup (sample size)	Total QoL score at baseline	Total QoL score at follow-up	Within-group change in QoL from baseline to follow-up, after treatment[a]	Between-group comparison: vs other short stature	Between-group comparison: vs normal stature
							subgroup ($p = 0.90$ and $p = 0.38$, respectively)
Silva (2018) [21], France, Germany, Spain, Sweden and UK	Disease-specific HRQoL (QoLISSY); psychological problems (SDQ); caregiver QoL (EUROHIS-QOL-8 index)	GHD ($n = 99$)	Mean (SD) scores: QoLISSY physical HRQoL, 80.91 (20.16) SDQ internalizing problems, 4.03 (3.32) SDQ externalizing problems, 5.77 (3.93)	NA	NA	Scores for QoL and psychological problems were not significantly different between GHD and ISS groups Untreated patients had significantly poorer physical HRQoL than treated patients (65.23 [23.56] vs 81.10 [19.82], $p \leq 0.05$)	NA
		ISS ($n = 139$)	Mean (SD) scores: QoLISSY physical HRQoL, 68.64 (23.59) SDQ internalizing problems, 4.72 (3.26) SDQ externalizing problems, 5.72 (3.32)	NA	NA		NA
Sommer (2017) [22], France, UK, Sweden, Spain and Germany	Focus group interviews related to QoLISSY subdomains	GHD or ISS ($n = 84$)	During interviews, the highest number of statements produced by the children and parents were related to social (29%) and emotional needs and concerns (28%)	NA	NA	NA	NA
Sommer (2018) [23], Germany	Disease-specific HRQoL (QoLISSY)	SGA (n = 65)	Mean (SD), 49.0 (23.96)	NA	NA	Total score was significantly higher ($p = 0.001$) for a reference population of children with ISS than the study population of children with short stature born SGA	NA
Stephen (2011) [24], USA	Generic HRQoL (PedsQL); cognitive function (PedsQL)	Untreated short stature (GHD or ISS) (n = 48)	Mean (SD) PedsQL score: Total, 79.28 (11.17) Cognitive[b], 78.59 (23.08)	NA	NA	NA	Controls with normal stature have significantly greater ($p < 0.05$) PedsQL total and cognitive scores than the short stature subgroups
		Treated short stature (GHD or ISS) ($n = 41$)	Mean (SD) PedsQL score: Total, 82.56 (12.16) Cognitive[b], 76.07 (20.20)	NA	NA	NA	
		Controls with normal stature ($n = 1259$)	Mean (SD) PedsQL score: Total, 86.19 (11.57) Cognitive[b], 86.62 (16.36)	NA	NA	NA	
Stheneur (2011) [25], France	Generic HRQoL (SF-36); life satisfaction (QLS-H)	GHD or SGA ($n = 34$)	Mean (SD) QLS-H score: Boys, 62.0 (33.5) Girls, 31.5 (44.2) GHD, 46.3 (11.0) SGA, 35.7 (12.5) SF-36 values NR	NA	NA	No significant difference in mean QLS-H score ($p = 0.56$) between GHD and SGA	No significant difference in mean QLS-H score (p value NR) between short stature and reference population with normal stature No difference in SF-36 scores between boys with short stature and reference population with normal stature In girls, physical pain SF-36 score was significantly greater in those with short stature than the reference population (+13.86, $p = 0.01$) and mental health SF-36 score was
		Reference population (normal stature) (sample size NR)	Mean (SD) QLS-H score: Boys, 52.4 (32) Girls, 36.4 (33.5) SF-36 values NR	NA	NA		

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Table 3 (*continued*)

First author (year), country	Outcome measure (assessment tool)	Subgroup (sample size)	Total QoL score at baseline	Total QoL score at follow-up	Within-group change in QoL from baseline to follow-up, after treatment[a]	Between-group comparison: vs other short stature	Between-group comparison: vs normal stature
							significantly lower in those with short stature than the reference population (−9.37, $p = 0.03$)
Tanaka (2009) [26], Japan	Child behavioral and emotional problems (CBCL)	GHD (n = 127), ISS (n = 116), healthy controls (n = 5159)	NR	NA	NA	NA	Total CBCL score was significantly greater ($p < 0.05$) in 4–11-year-old males with GHD or ISS than in 4–11-year-old controls with normal stature Total CBCl score was significantly greater ($p < 0.05$) in 4–11-year-old females with ISS and 12–15-year-old males with GHD than controls with normal stature of the same age and sex Total CBCL score was not significantly different between 4 and 11-year-old females with GHD and controls with normal stature, and between 12 and 15-year-old males with ISS and controls with normal stature
Tanaka (2014) [27], Japan	Child behavioral and emotional problems (CBCL)	GHD (n = 152)	NA	NA	Mean (SD) change over 12 months, −3.42 (11.21); $p < 0.001$	No significant difference in CBCL score between the GHD and ISS groups at 12 months	NA
		ISS (n = 129)	NA	NA	Mean (SD) change over 12 months, −4.82 (10.09); $p < 0.001$		NA

Note, all scores are child-reported except where indicated otherwise.
AI, aromatase inhibitors; CBCL, Child Behavior Checklist; EUROHIS-QOL-8 index; European Health Interview Survey-Quality of Life 8-item index; GH, growth hormone; GHD, growth hormone deficiency; HRQoL, health-related quality of life; ISS, idiopathic short stature; NA, not applicable; NR, not reported; PedsQL, Pediatric Quality of Life Inventory; QLS-H, Questions on Life Satisfaction-Hypopituitarism; QoL, quality of life; QoLISSY, Quality of Life of Short Stature Youth questionnaire; SD, standard deviation; SDQ, Strengths and Difficulties Questionnaire; SDS, standard deviation score; SF-36, 36-item Short-Form Health Survey; SGA, small for gestational age.
[a] p values, where reported, indicate the statistical significance of the difference in QoL between baseline and follow-up.
[b] Higher scores mean more problems.
[c] Parent-reported.

[14] (Table 3).

3.2.1.2. Comparisons among short stature subgroups. Five of nine studies found no significant differences in QoL based on different causes of short stature or treatment status [9,17,19,25,27]. However, two studies, one in children who had been treated with aromatase inhibitors or GH [10] and one in a mixed sample of treated and untreated children [13], found that QoL was significantly better in children with less severe short stature than in children with more severe short stature [10,13]. In addition, one study found that children with ISS had better QoL than children with short stature after being born SGA [23], and one study found no difference between ISS and GHD but found that treated children had significantly better physical health-related quality of life (HRQoL) than untreated children [21] (Table 3).

3.2.1.3. Changes following treatment. Among the eight studies measuring the change in QoL over time in children with short stature receiving treatment, four studies showed that there was a significant association between treatment and better QoL [9,11,18,27], and two studies showed improvement in QoL with treatment or height gain, but did not report statistical significance [12,16]. Of the two remaining studies, one study found that there was no change in QoL after treatment [19], and one study found that QoL scores did not significantly improve after 12 months of treatment in a combined group of children with GHD, ISS and short stature after being born SGA [17].

3.2.2. Chronic kidney disease

Five studies evaluated QoL of children with CKD [28–32]. The proportion of children with short stature in the study samples was in the range 15–54%. In three studies, all of which used generic HRQoL assessments (Health Utilities Index or Pediatric Quality of Life Inventory [PedsQL]), short stature was significantly associated with poorer HRQoL after adjusting for CKD characteristics [30–32]. In one of these studies, significant findings were limited to the physical domain of HRQoL and

to parent-reported scores only [31]. Two studies found no difference in QoL between children with CKD with short stature and those without short stature [28,29]. However, in one of these studies, there were significant associations between increase in height over 2 years and improvements in HRQoL among the children with short stature treated with GH, after adjusting for confounders [28].

3.2.3. Mixed populations

Three studies evaluated mixed populations of children with short stature; these included children with different causes of short stature in the same study sample. Causes of short stature included GHD, ISS, Turner syndrome (TS), skeletal dysplasias and short stature after being born SGA. In all three studies, children with short stature had significantly poorer QoL scores (PedsQL) than children with normal stature [33–35]. Two of these studies demonstrated that more severe short stature was associated with poorer QoL than less severe short stature, in terms of total score and several subdomains [33,35]. One study showed that fatigue (according to the PedsQL Multidimensional Fatigue Scale) was significantly worse in children with short stature than those with normal stature [34].

3.2.4. Other causes of short stature

Other causes of short stature included achondroplasia [36], other skeletal dysplasias [37], transfusion-dependent β-thalassaemia [38] and TS [12], investigated in one study each. Children with achondroplasia and transfusion-dependent β-thalassaemia had significantly lower overall HRQoL (PedsQL) than healthy control children [36,38]. In the study of transfusion-dependent β-thalassaemia, this association was adjusted for age, sex and type of thalassaemia [38]. Children and adolescents with skeletal dysplasias associated with short stature reported lower HRQoL scores (QoLISSY questionnaire), especially in the physical and social domains, than reference values listed in the QoLISSY manual for children with ISS and GHD [37]. Finally, in the study of girls with TS, QoL (PedsQL) improved after 1 year of GH therapy (*p* value not reported) [12].

3.3. Caregivers of children with short stature

Seven studies explored the burden in parents or caregivers of children with short stature [13,17,21,23,33,36,39]. Three of these studies demonstrated an increased burden compared with parents of children with normal stature [21,36,39], four studies found that caregiver stress varied over different causes of short stature [17,21,23], and one study did not find any evidence that caregiver burden was affected by the height of children with GHD or ISS [13].

Among the studies that demonstrated increased caregiver burden, parents of children with achondroplasia had a significantly increased psychological burden; as determined by comparing their scores on the mental component domain of a Short-Form 8-item questionnaire with normal values from a German population [36]. In another study, primary caregivers of young children with Prader–Willi syndrome (PWS) had lower QoL than a healthy comparison group (details not provided in source). The responses showed that QoL was negatively influenced by caregivers' concern about the child [39]. One study of children with ISS or GHD receiving GH therapy found that parents whose child still had short stature reported greater caregiving stress (indicated by higher scores on the 'effects on parents' QoLISSY domain) than those whose child had achieved normal stature [21].

Among the studies that showed varying caregiver stress depending on short stature type, findings suggested greater stress in parents of children with ISS than in those with GHD [17,21], and different levels of stress for parents of treated children than untreated children; in one study there was more caregiver stress in parents of treated children [23] and in one study there was more stress in the parents of untreated children [21]. One study of a mixed population (GHD, SGA, bone dysplasia, ISS) found that 'effects on parents' score did not significantly change after 1 year of GH therapy [33].

3.3.1. Agreement between child-rated and parent-rated QoL

Six studies investigated the agreement between child-reported QoL and parent-reported QoL [15,20,24,28,34,40]. Four of these six studies demonstrated good agreement between child and parent scores [15,20,24,28]. Of these, three studies were in children with ISS or GHD, and found good agreement on the KIDSCREEN-10 [15,20], PedsQL [24] and QoLISSY assessments [15]. One study of children with CKD also demonstrated good agreement on the PedsQL assessment [28]. Two of the six studies (both with mixed etiologies) found poor agreement between child and parent scores on the PedsQL assessment [34,40].

3.4. Adults with short stature

Of eight studies in adults with short stature, four studies evaluated generic HRQoL (12-Item Short Form Health Survey [41], 36-Item Short Form Health Survey [42,43], World Health Organization Quality of Life [WHOQOL-BREF] [44]), two evaluated life satisfaction [45,46], one study evaluated both disease-specific HRQoL using the Quality of Life-Assessment of Growth Hormone Deficiency in Adults (QoL-AGHDA) and cognitive function [47], and one study evaluated sleep quality [48]. Cause of short stature varied among the studies; childhood-onset GHD was the only cause assessed in more than one study (Fig. 2).

Generic HRQoL was significantly poorer in adults with skeletal dysplasia [41], childhood-onset multiple pituitary hormone deficiency [44] and congenital adrenal hyperplasia (CAH) [42] than in healthy control groups. HRQoL was also poorer in adults with GHD, who were either treated or not treated with GH therapy, than in healthy adults, but this result was not statistically significant [43]. In the study of adults with CAH, adult height was not correlated with QoL [42].

In two more studies of GHD, one showed that there were no significant differences between patients with isolated GHD and controls in scores on the Life Satisfaction Hypopituitarism Module [45], and one study demonstrated poorer sleep quality in adults with isolated GHD than in age- and sex-matched controls with normal stature [48].

In a study of women with TS, 73.3% reported that they were satisfied with life. There was a positive correlation between height and life satisfaction [46].

Adults with PWS were found to have significantly poorer scores than their healthy siblings on nine of eleven cognitive tests performed [47]. Further, the adults with PWS had significantly higher scores than their siblings on the QoL-AGHDA assessment: although this assessment has some disease-specific items, its overall score is correlated with general QoL [49,50].

4. Discussion

Findings from this SLR suggest that adults and children with short stature may experience poorer QoL than those with normal stature. Despite this, it should be noted that in some cases findings were inconsistent, even among studies of patients with the same cause of short stature, and quality of evidence varied. Evidence also suggests an increased burden in caregivers of children with short stature when compared with caregivers of children with normal stature.

The burden of short stature was observed across different causes of short stature. It is difficult to compare findings across different causes, owing to the heterogeneity of the patient populations. For example, while ISS is characterized by short stature only, CKD is associated with a range of symptoms. Any additional symptoms may impact HRQoL and so it is important that comparisons of children with short and normal stature account for potential confounders related to the cause of short stature in the children. Our findings showed that results in children with causes of short stature characterized by other comorbidities that influence HRQoL were robust after allowing for these potential confounders. For example, all four studies reporting generic QoL in CKD and a study in

transfusion-dependent β-thalassaemia adjusted their scores for potential confounders. All but one demonstrated a significant association between short stature and QoL, independent of other disease characteristics. Although the adjustment for important factors adds to the robustness of the findings, there could still be bias present owing to unmeasured confounders.

Most studies identified were in children with short stature. Over a quarter of these studies measured burden using the QoLISSY assessment, which measures QoL specific to children with short stature and has been externally validated in several populations and countries [10,13]. The QoLISSY is able to measure caregiver stress via its 'effects on parents' domain. The data identified in this SLR suggest that there may be an increased burden in caregivers of children with short stature. This may differ according to cause of short stature, with several studies suggesting that parents of children with ISS had greater burden than those of children with GHD or children with short stature after being born SGA. The increased burden in parents of children with ISS versus GHD is not surprising: parents and caregivers of children with ISS may feel anxiety in not knowing the underlying cause of their short stature and in the uncertainty about a good response to GH therapy.

Overall, few studies evaluated change in caregiver QoL following their child's treatment, and there was no clear trend of improved caregiver QoL among these studies. The supportive evidence for treatment, however, is clearer for the children themselves, with six studies in this review showing that children who received GH therapy experienced improvements in QoL or had better QoL than untreated children. This has been observed in children with GHD and ISS, and in children with short stature after being born SGA; however, findings suggest that there may be varying levels of benefit depending on the cause.

Although several studies demonstrate that greater height gain is associated with improved QoL, the current literature does not provide enough evidence to suggest a potential height gain threshold beyond which QoL benefit is no longer gained. However, a survey of adult height and HRQoL in a UK general population [51] demonstrated poorer HRQoL even with less extreme short stature; adults with a height SD score (SDS) of −0.5 to −1.0 had significantly poorer 5-dimension EuroQol questionnaire (EQ-5D) scores than adults with a height SDS of 0–0.5. The difference was close to being a minimum important difference according to the 5-level EQ-5D (EQ-5D-5L) [52]. There was no difference in HRQoL between groups with a height SDS of −0.5 to 0 and 0–0.5 [51]. Knowledge of the degree of height gain and QoL improvement in children with short stature receiving GH therapy would be valuable for treatment management.

Owing to the subjective nature of QoL assessment, differences in QoL may arise between treated and untreated children, in both directions, for reasons other than height gain. There may be a disparity at baseline (before treatment), because those who are about to start treatment were seeking treatment because they already experience greater burden from their condition than those who are not seeking treatment; and, therefore, they may have poorer QoL scores than untreated children. Once treatment has begun, those receiving it could experience reassurance from being treated and therefore feel an ease in their burden compared with untreated children, indicated by better QoL scores. Furthermore, there may be other benefits of therapy that improve QoL, such as potential improvement in motor skills. When looking at changes over time, baseline level of QoL may affect the likelihood of detecting a difference resulting from treatment. For example, if QoL was already high, perhaps owing to adequate coping strategies or support, additional QoL benefits may not be gained, even with effective treatment.

Interpretation of QoL findings is made even more complex due to the potential differences in QoL measures when reported by the child or by the parent, with some studies reporting poor agreement. This is an issue that affects child- and parent-reported questionnaire data in any field. A recent study suggested that such data could vary widely, and showed that agreement could be influenced by child or parent gender [53]. There is also the possibility that parental perception can influence the child's perception of their burden and lead to a biased child-reported QoL. Parental perception may also influence the decision to seek treatment. Another topic of interest is the impact of treatment burden. This type of burden was not studied in the current review, but there could be substantial treatment burden of GH therapy, both financially [54] and in terms of the child's QoL [55].

The evidence of benefit of treatment intervention during childhood is especially relevant because studies have shown that the increased burden of short stature can persist into adulthood. More evidence is needed, however, with only eight adult studies identified during the current review. None of these studies specified whether the adults had been treated during childhood. Evidence for other types of burden was also limited. For example, cognitive function outcomes were captured by only two studies. These studies suggested that cognitive function could be poorer in children and adults with short stature than in controls with normal stature. This has been found in other studies, although differences in cognitive performance have not been substantial [56]. The reason for such differences may be dependent on the underlying cause of short stature, rather than short stature itself [56], and these differences in neurocognition may also impact overall QoL.

The strength of this review is its comprehensiveness, capturing relevant literature from the past 12 years on short stature of any cause. The review was designed and conducted using robust methodology in accordance with the 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, and included a quality assessment of the literature. The review also has several limitations. As mentioned earlier in this section, the presence of comorbidities can make it difficult to assess independent associations between short stature and QoL. Almost half of the included studies were assessed as having poor internal validity, largely due to the absence of controlling for potential confounding. These findings should be interpreted with care. In general, it is difficult to isolate the effect of short stature or height gain on QoL alongside other factors that may influence QoL, such as other disease characteristics and benefits of GH therapy not related to height gain. However, for several complex conditions (e.g. CKD), studies took measures to reduce bias due to confounding. The findings of the review are also limited because studies used a range of QoL assessments, so results may not be comparable. There was an evidence gap in terms of human burden in rare growth disorders such as severe primary IGF-I deficiency, and the potential economic burden in people with short stature.

In conclusion, evidence from the literature suggests that there may be an increased human burden in adults and children with short stature, of any cause, and in caregivers of children with short stature. Potential improvements in QoL and other types of burden could be gained via intervention in children; however, more research is needed to extend understanding in this area.

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Declaration of interest

None.

Appendix A. Supplementary data

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