Supplementary files

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	2
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	2-3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	2-3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	3-4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3-4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	3-4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	3-4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4-5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	4-5

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	4-5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	4-5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5-6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	5-6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7-10
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	6-10
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	6-10
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	6-10
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	6-10
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10-11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10-11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10-11
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	11

Supplementary file 1- PRISMA Checklist

Excluded studies after full text analysis	Exclusion reason
Butler MG, Matthews NA, Patel N, Surampalli A, Gold JA, Khare M, Thompson T, Cassidy SB, Kimonis VE. Impact of genetic subtypes of Prader-Willi syndrome with growth hormone therapy on intelligence and body mass iindex. Am J Med Genet A. 2019 Sep;179(9):1826-1835.	Mixed of children and adult data. No information about dose and age that rhGH started. No SDS data.
Butler MG, Lee J, Cox DM, Manzardo AM, Gold JA, Miller JL, Roof E, Dykens E, Kimonis V, Driscoll DJ. Growth Charts for Prader-Willi Syndrome During Growth Hormone Treatment. Clin Pediatr (Phila). 2016 Sep;55(10):957-74.	No possibility of accurate data from graph
Coupaye M, Lorenzini F, Lloret-Linares C, Molinas C, Pinto G, Diene G, Mimoun E, Demeer G, Labrousse F, Jauregi J, Laurier V, Basdevant A, Polak M, Thuilleaux D, Tauber M, Poitou C. Growth hormone therapy for children and adolescents with Prader-Willi syndrome is associated with improved body composition and metabolic status in adulthood. Clin Endocrinol Metab. 2013 Feb;98(2):E328-35.	No possibility of data inclusion
Scheermeyer E, Hughes I, Harris M, Ambler G, Crock P, Verge CF, Craig ME, Bergman P, Werther G, van Driel M, Davies PS, Choong CS.Response to growth hormone treatment in Prader–Willi syndrome: Auxological criteria versus genetic diagnosis. J Paediatr Child Health. 2013 Dec;49(12):1045-51.	Same Australian cohort
Fillion M, Deal C, Van Vliet G. Retrospective study of the potential benefits and adverse events during growth hormone treatment in children with Prader-Willi syndrome. J Pediatr. 2009 Feb;154(2):230-3.	No SDS data
Kuo JY, Ditchekenian V, Manna TD, Kuperman H, Damiani D, Setian N.Prader-Willi syndrome: metabolic aspects related to growth hormone treatment. Arq Bras Endocrinol Metabol. 2007 Feb;51(1):92-8.	No SD data
Festen DA, van Toorenenbergen A, Duivenvoorden HJ, Hokken-Koelega AC. Adiponectin levels in prepubertal children with Prader-Willi syndrome before and during growth hormone therapy. J Clin Endocrinol Metab. 2007 Apr;92(4):1549-54.	Same data as Festen 2008
Craig ME, Cowell CT, Larsson P, Zipf WB, Reiter EO, Albertsson Wikland K, Ranke MB, Price DA; KIGS International Board. Growth hormone treatment and adverse events in Prader-Willi syndrome: data from KIGS (the Pfizer International Growth Database).Clin Endocrinol (Oxf). 2006 Aug;65(2):178-85.	Duplicated from Pfizer
Whitman B, Carrel A, Bekx T, Weber C, Allen D, Myers S. Growth hormone improves body composition and motor development in infants with Prader-Willi syndrome after six months.J Pediatr Endocrinol Metab. 2004 Apr;17(4):591-600.	Less than 6 months of rhGH
Haqq AM, Stadler DD, Jackson RH, Rosenfeld RG, Purnell JQ, LaFranchi SH. Effects of growth hormone on pulmonary function, sleep quality, behavior, cognition, growth velocity, body composition, and resting energy expenditure in Prader-Willi syndrome. J Clin Endocrinol Metab. 2003 May;88(5):2206-12	Less than 6 months of rhGH
Eiholzer U, l'Allemand D, van der Sluis I, Steinert H, Gasser T, Ellis K. Body composition abnormalities in children with Prader-Willi syndrome and long-term effects of growth hormone therapy. Horm Res. 2000;53(4):200-6.	No SDS data
Eiholzer U, l'Allemand D. Growth hormone normalises height, prediction of final height and hand length in children with Prader-Willi syndrome after 4 years of therapy. Horm Res. 2000;53(4):185-92.	No SDS data
Myers SE, Carrel AL, Whitman BY, Allen DB. Physical effects of growth hormone treatment in children with Prader-Willi syndrome. Acta Paediatr Suppl. 1999 Dec;88(433):112-4.	Similar data to Carrel 1999
Lindgren AC, Ritzén EM.Five years of growth hormone treatment in children with Prader-Willi Syndrome. Acta Paediatr Suppl. 1999 Dec;88(433):109-11.	No possibility of accurate data from graph
Davies PSW, Evans S, Broomhead S, Clough H, Day JME, LaidlawA, Barnes ND. Effect of growth hormone on height, weight, and body composition in Prader-Willi syndrome. Arch Dis Child 1998;78:474–476	Less than 6 months of rhGH
Eiholzer U, Bodmer P, Bühler M, Döhmann U, Meyer G, Reinhard P, Schimert G, Varga G, Wälli R, Largo R, Molinari L. Longitudinal monthly body measurements from 1 to 12 months of age: a study by practitioners for practitioners. Zurich Association of Practicing Paediatricians.Eur J Pediatr. 1998 Jul;157(7):547-52.	No SDS data
Lindgren AC, Hagenäs L, Müller J, Blichfeldt S, Rosenborg M, Brismar T, Ritzén EM. Effects of growth hormone treatment on growth and body composition in Prader-Willi syndrome: a preliminary report. The Swedish National Growth Hormone Advisory Group.Acta Paediatr Suppl. 1997 Nov;423:60-2.	Similar data to Lindgreen 1998
Hauffa BP. One-year results of growth hormone treatment of short stature in Prader-Willi syndrome. Acta Paediatr Suppl. 1997 Nov;423:63-5.	No SDS data

Supplementary file 2- Excluded RCT and NRCT studies after full text analysis and exclusion reasons

	Certainty assessment							№ of patients		Effect	Certainty
	№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	rhGH	no treatment	Absolute (95% CI)	
Z-Stature	9	randomized trials	serious	very serious [a]	not serious	not serious	very strong association	177	151	MD **1.44 higher** (1.05 higher to 1.82 higher)	⊕⊕⊕◯ MODERATE
Z-Stature >3.5years	5	randomized trials	serious	serious [b]	not serious	not serious	very strong association	116	93	MD **1.87 higher** (1.71 higher to 2.02 higher)	⊕⊕⊕⊕ HIGH
Z-Stature <3.5years	4	randomized trials	serious	not serious	not serious	not serious	very strong association	61	58	MD **1.08 higher** (0.81 higher to 1.35 higher)	⊕⊕⊕⊕ HIGH
Growth Velocity	3	randomized trials	serious	very serious [a]	not serious	not serious	strong association	65	47	MD **5.44 higher** (3.27 higher to 7.61 higher)	⊕⊕◯◯ LOW
Z-BMI	4	randomized trials	serious	not serious	not serious	not serious	very strong association	64	55	MD **0.67 lower** (0.87 lower to 0.47 lower)	⊕⊕⊕⊕ HIGH
%Fat mass	6	randomized trials	very serious	not serious	not serious	not serious	very strong association	113	91	MD **6.5 lower** (8.46 lower to 4.54 lower)	⊕⊕⊕⊕ HIGH
Lean Mass SDS	2	randomized trials	serious	very serious [a]	not serious	not serious	very strong association	37	75	MD **2.03 higher** (1.34 higher to 2.71 higher)	⊕⊕⊕◯ MODERATE
Lean Mass kg	2	randomized trials	serious	not serious	not serious	not serious	very strong association	50	31	MD **4.2 higher** (2.18 higher to 6.22 higher)	⊕⊕⊕⊕ HIGH
Head Circumf.	3	randomized trials	serious	serious [b]	not serious	not serious	strong association	59	55	MD **0.55 higher** (0.25 higher to 0.86 higher)	⊕⊕⊕◯ MODERATE

CI: Confidence interval; **MD:** Mean difference [a]. heterogenicity > 80%; [b]. heterogenicity > 50%

Supplementary file 3 – Quality of evidence analysis for rhGH use according to Z-stature, growth velocity, %fat mass, LBM-SDS and head circumference in RCTs (GRADE pro)[2]

	Certainty assessment							№ of patients		Effect	Certainty
	№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention]	[comparação]	Absolute (95% CI)	
Z-Stature	14	observational studies	not serious [a]	serious [b]	not serious	not serious	strong association	2909	2909	MD **1.52 lower** (2.18 lower to 0.86 lower)	⊕⊕◯◯ LOW
Z-BMI	3	observational studies	not serious	very serious [b]	not serious	not serious	strong association	90	90	MD **11.56 lower** (13.66 lower to 9.46 lower)	⊕◯◯◯ VERY LOW
%Fat Mass	11	observational studies	not serious	serious [b]	not serious	not serious	very strong association	0/2755 (0.0%)	217/2755 (7.9%)	**110 more per 1 000** (from 40 more to 170 more)	⊕⊕⊕◯ MODERATE

	Certainty assessment							№ of patients		Effect	Certainty
	№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention]	[comparação]	Absolute (95% CI)	
Adverse effects	13	observational studies	not serious	serious [b]	not serious	not serious	none	10828	10828	MD **20 more** per 1000	⨁⨁⨁◯ MODERATE

Supplementary file 4– Quality of evidence analysis for rhGH use according to Z-stature; Z-BMI, fat mass and adverse effects in NRCTs