Received: 19 August 2020 | Revised: 16 September 2020 | Accepted: 16 November 2020

DOI: 10.1111/cen.14372

ORIGINAL ARTICLE

WILEY

The use of growth hormone therapy in adults with Prader-Willi syndrome: A systematic review

Mikaela Frixou | Diane Vlek | Angela K. Lucas-Herald | Lindsay Keir | Andreas Kyriakou | M. Guftar Shaikh

Developmental Endocrinology Research Group, Royal Hospital for Children, University of Glasgow, Glasgow, UK

Correspondence
M. Guftar Shaikh, Developmental Endocrinology Research Group, Royal Hospital for Children, 1345 Govan Road, Glasgow G51 4TF, UK.
Email: Guftar.shaikh@ggc.scot.nhs.uk

Funding information
University of Glasgow

Abstract

Objective: Despite clear benefits in the management of children with Prader–Willi syndrome (PWS), the role of growth hormone (GH) in adults is unclear. The aim of this study was to conduct a systematic review to evaluate the effects of GH on body composition, bone health and cardiovascular health in adults with PWS.

Design: A systematic computerized literature search of the PubMed database was conducted by two independent reviewers. Inclusion criteria were individuals over the age of 16 years with a genetic diagnosis of PWS who had received GH therapy, together with assessment of body composition, bone health or cardiovascular health.

Results: Twenty full-text papers met the inclusion criteria, encompassing 364 unique patients. No differences in body mass index (BMI) were noted, although 2 studies reported increased BMI after GH cessation. Data demonstrated statistically significant increases in lean body mass and reductions in percentage fat mass. Studies reported inconsistent effects of GH on cholesterol and echocardiography parameters. No studies reported differences in bone mineral density, although one reported improved bone geometry. Minor adverse events including pretibial oedema, headache and transient impaired glucose tolerance were reported in 7 studies.

Conclusions: These data suggest that GH is safe and well tolerated in adults with PWS, with evidence of improvement in body composition. Further longitudinal studies are still required to investigate the effects of GH on bone and cardiovascular health. Where GH is used in adults with PWS, this should be managed by a specialist multidisciplinary team with regular monitoring initiated.

KEYWORDS
body mass, bone, cardiovascular, GH, growth, PWS

1 | INTRODUCTION

Prader-Willi syndrome (PWS) is a condition with a prevalence of between 1 in 10,000 and 1 in 30,000,[1,2] which can arise from deletion of the paternal chromosome 15 (del15q11-q13), maternal uniparental disomy of chromosome 15 (UPD15) or genetic imprinting errors.[3] Children with PWS have altered body composition, with generally lower lean body mass (LBM) and higher fat mass (FM) percentages than healthy individuals.[4-6] Patients with PWS have hyperphagia, reduced muscle mass and exercise capacity, which can lead to obesity, further exacerbating the abnormal body composition and resulting in a high rate of comorbidities including metabolic

Mikaela Frixou and Diane Vlek joint first authors.

syndrome and hepatic steatosis.[3] A high incidence of osteoporosis at younger ages is also observed in PWS patients, and it is estimated that between 60% and 90% of these individuals become osteoporotic in their lifetime with high rates of associated scoliosis requiring intervention.[7]

The high incidence of obesity in PWS contributes to the development of many cardiovascular risk factors, including the development of type 2 diabetes mellitus (T2DM), abnormal lipid profiles and high blood pressure (BP).[3] Adults with PWS are also known to have higher rates of electrical and structural cardiac abnormalities than healthy adults, with evidence of microvascular dysfunction.[8]

Growth hormone levels are low in 60%-100% of children with PWS, and GH replacement therapy has been licensed for use in children since 2000.[9] Although PWS children tend to have short stature, the indication for GH therapy is not to primarily increase height, but rather to help to improve body composition and increase LBM, which may subsequently reduce hypotonia and therefore increase muscle and motor function.[9] More recently, studies have even demonstrated higher vocabulary IQ scores in paediatric PWS patients treated with GH compared with non-GH groups.[10] In previously treated young adults with PWS, approximately 1 in 7 demonstrated GH insufficiency on GHRH-arginine testing, but none fulfilled the consensus criteria for adult GHD.[11]

A meta-analysis published in 2012 demonstrated that GH may improve body composition in adults with PWS.[12] In addition, a previous review by our group suggested that continuous GH use is beneficial in adolescents.[13] However, currently GH use in adulthood is not licensed unless there is confirmed GHD. Consequently, when transitioning to adult endocrine services, GH therapy is likely to be discontinued.

The aim of this systematic review was to update the current literature by summarizing the findings of all studies exploring GH use in adults with PWS, and its effects on body composition, bone and cardiovascular health. As a secondary objective, the safety of using GH in adults and data regarding the reported side effects for patients on treatment were also collated.

2 | METHODS

2.1 | Types of studies

A systematic search of the literature was conducted for all studies examining GH treatment in adults with PWS, including those with or without a control group and with or without placebo.

2.2 | Types of participants

For inclusion in the review, studies had to include participants with a genetically verified diagnosis of PWS and who were aged 16 years or older.

2.3 | Types of interventions

Studies were included where any dose of growth hormone was given for any period.

2.4 | Types of outcome measures

Primary outcomes included changes in bone health, cardiovascular health and body composition from baseline and during GH treatment, as well as after cessation of GH treatment. For body composition, we looked at change in LBM (kg), body mass index (BMI) and FM (%). Bone health parameters included bone mineral density and bone geometry. Cardiovascular health parameters included BP, cholesterol and triglyceride levels and echocardiography data.

2.5 | Search methods for identification of studies

The PubMed database was searched for all studies (from 1960 to March 2020), using an advanced search for the terms 'Growth hormone' OR 'GH' AND 'Prader-Willi syndrome' OR 'Prader Willi' OR 'PWS'. We did not impose language restrictions. We also reviewed the references lists of all studies included.

2.6 | Data collection and analysis

Two authors independently reviewed the titles, abstracts and bodies of all studies identified by the search, to identify which met the above inclusion criteria. After independent evaluation, the authors convened and discussed articles included. Disagreements were evaluated by a third author. Figure 1 demonstrates the numbers of papers considered at each stage.

In total, 20 studies were deemed to be eligible for inclusion from 546 titles identified from the initial search, as demonstrated in Figure 2.

2.7 | Data extracted

Two authors independently extracted the data from the studies that met the inclusion criteria and quality standards. Data extracted included the following: authors, year and location of studies, type of study, use of controls, number of participants (sex, age), dose and duration of GH treatment (including length of follow-up), adverse events and the relevant parameters addressed in each study.

2.8 | Quality review

Assessment of bias was undertaken using the Cochrane Risk of Bias Assessment tools for non-randomized and randomized studies of

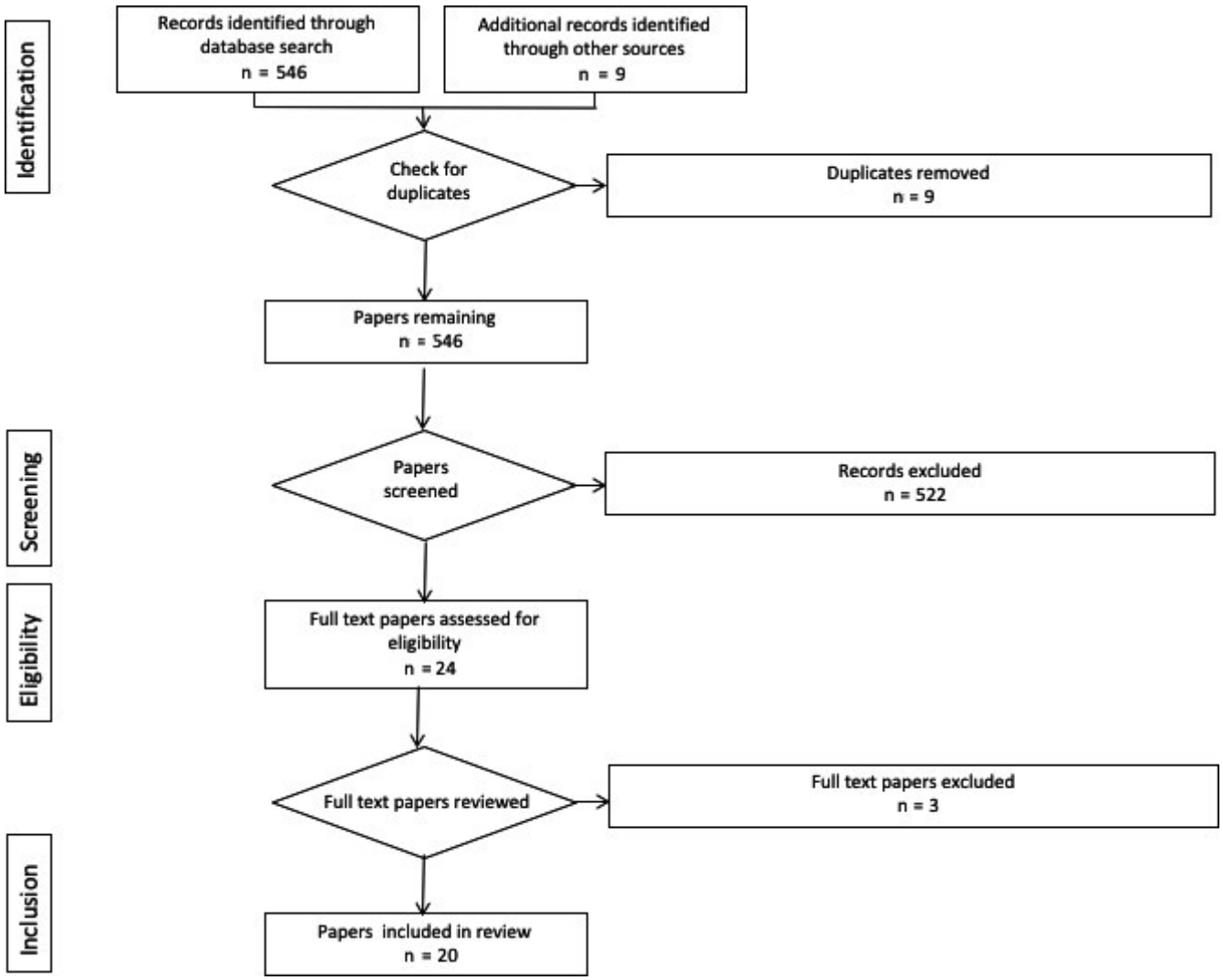

FIGURE 1 Flow diagram demonstrating selection of papers

interventions.[14,15] This was performed independently by two reviewers. Disagreements were resolved by a third reviewer. The quality assessment is demonstrated in Table S1.

3 | RESULTS

The characteristics of the studies included in our analysis are summarized in Table 1. A total of 20 papers were selected as relevant. Of the 20 papers excluded for having irrelevant outcomes in the body of the text, nine were primarily paediatric cohorts and it was impossible to extract data specific to adults. Two addressed determination of GH deficiency in adulthood but not the effects of GH.[16,17] One study demonstrated an increase in BMI in adulthood after cessation of GH in childhood but not the effects during treatment,[18] and one showed that in childhood, GH treatment reduced BMI differences between UPD and deletion genotypes.[19] Two papers demonstrated increased mental and cognitive function with GH treatment,[20,21] and one showed that PWS patients rated their quality of life and mental health higher after initiation of GH treatment in adulthood compared with before.[22] One study showed that GH treatment did not affect levels of interleukin-6 and C-reactive protein.[23] One study investigated oxytocin and ghrelin levels in PWS patients on GH treatment. [24] One study validated the use of DXA scanning to accurately determine visceral adiposity in PWS patients but not bone health.[25] One study demonstrated increased fasting and 2-hour glucose levels during OGTT at different BMI groups, but these were not the effects of GH specifically.[26]

In total, the included studies investigated 424 participants with PWS, of whom 51% were male. Of note, 60 (14%) of these individuals were recruited to more than one published study,[27-33] leaving 364 unique patients included. The median (range) age of participants across the studies was 26.2 (17, 42) years. GH doses varied and in some studies were prescribed according to weight or body surface area, but the median (range) dose of GH used in the studies was approximately 0.8 mg/day (0.5, 1.0) and the median (range) duration of GH treatment was 1 (0.5, 5) years. The median (range) length of follow-up in the studies was 2 (1, 6) years.

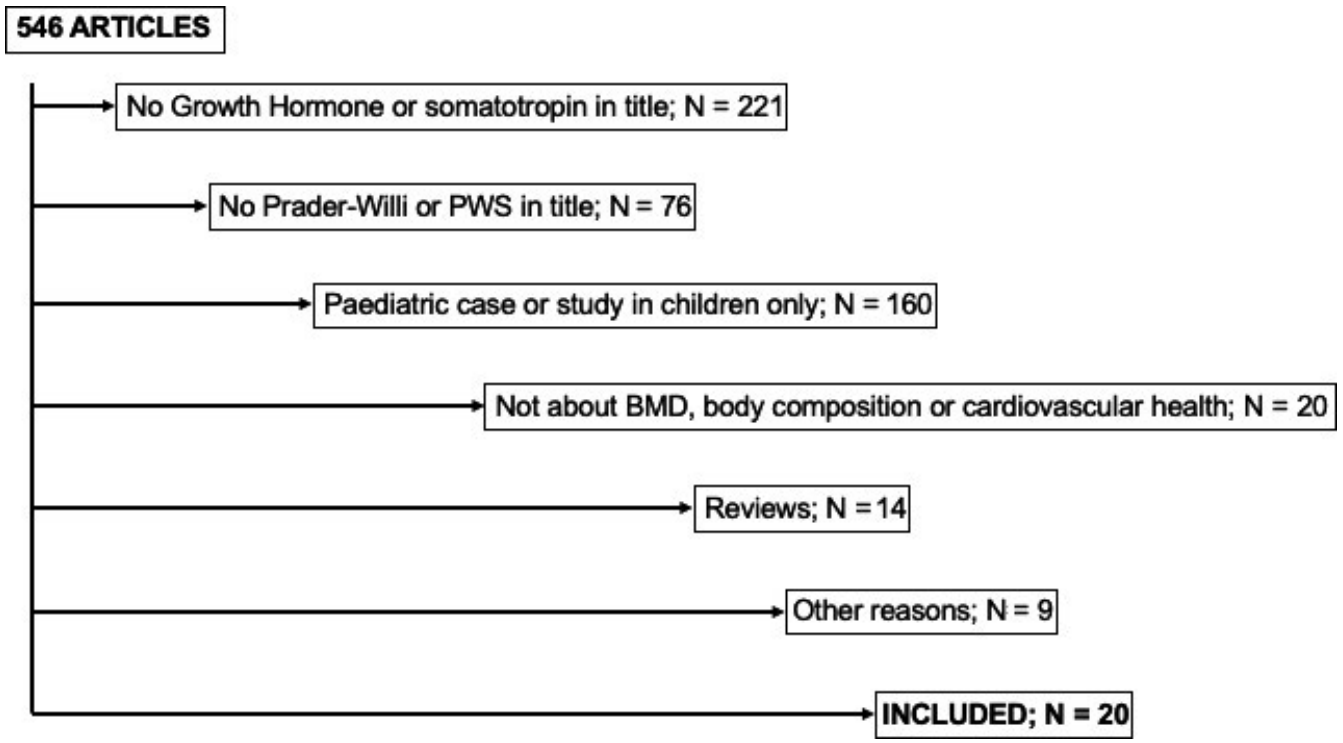

FIGURE 2 Reasons for exclusion of papers

Investigation of GH sufficiency was reported in 17 studies (85%), encompassing 326 participants. Of these, 157 (48%) had evidence of GH insufficiency using dynamic function testing, most commonly using a GHRH and arginine test (n = 9 studies),[26,28-30,34-38] insulin tolerance test (n = 1 study)[30] or L-dopa stimulation test (n = 1 study)[39] with the type of test unreported in the rest. Growth hormone cut-offs ranged from 4.1 μg/L to 10 μg/L depending on the test and local assay. Two studies used a low IGF-1 as a marker for GH insufficiency, encompassing 22 patients (7%).

Sex steroid replacement was reported in 13 (65%) studies, with 106 (25%) of the included participants in this study receiving concomitant sex steroid therapy.

3.1 | Primary outcomes

18 of the 20 (90%) papers included measurements of body composition, 8 (40%) included measurements of cardiovascular health, and 5 (25%) studied bone health. We evaluated each of these parameters separately. The statistically significant results are summarized in Table 2.

3.2 | Body composition

Body composition was evaluated as: BMI (kg/m2), LBM (kg) and FM (%). BMI was included in 16 of the 18 papers discussing body composition. In 2 papers, there was a statistically significant increase in BMI after discontinuation of GH treatment.[33,40] Koizumi et al (2018) looked at the effects of discontinuation of GH treatment on body composition of PWS patients, and determined that BMI increased and LBM decreased as a result of the change.[40] Similar effects were obtained by Kuppens et. al (2016) in their crossover study of PWS participants; they found that when the GH treatment group switched to placebo group, their fat mass increased by 21.5% (p = .001).[33] They also showed a positive effect of resuming GH therapy, with the overall LBM being higher and FM lower in the GH-treated group compared with placebo; this was a result reproduced by most of the studies looking into body composition, as shown in Table 2.

One study showed a lower BMI in the GH-treated group (not significant),[27] and 13 studies showed no statistically significant change in BMI. LBM is evaluated in 15 studies, with all showing LBM increased with GH treatment (12 statistically significant). FM was evaluated in 16 studies and decreased in all (12 statistically significant).

In addition to increased LBM, there seemed to be a functional increase in muscle strength in GH-treated PWS adults, as shown by Lafortuna et al (2014), where grip muscle strength increased by 13% (p < .001) and exercise endurance by 17% (p < .05) in PWS patients after 24 months of GH treatment.[37] Sode-Carlsen et al (2011) also showed a rise in peak expiratory flow by 12% (p < .001) that they attributed to increased skeletal muscle function.[29]

3.3 | Cardiovascular health

Eight studies assessed the effect of GH treatment on cardiovascular health. Of these, two investigated the effects of GH on echocardiography, demonstrating statistically significant increases in left

TABLE 1 Summary of papers included in this review

Author, year	Country of origin	Type of study	Controls	Number of participants (M:F)	Mean age (years) of participants (Mean ± SD or mean [range])	Parameters assessed	Duration of GH treatment (years)	Dose of GH	Length of follow-up (years)
Koizumi et al, 2018	Japan	Retrospective	Cessation of GH- no control	7 (3:4)	18.9 ± 1.8	Body composition Cardiovascular	N/A	0.05–0.15 mg/kg/week	N/A
Donze et al, 2018	Netherlands	Double-blind crossover	Crossover using placebo	27 (8:19)	17.2 ± 1.8	Bone health	1	0.17 mg/kg/week	2
Kuppens et al, 2017	Netherlands	Double-blind crossover	Crossover using placebo	27 (8:19)	17.2 ± 1.8	Cardiovascular	1	0.67 mg/m^2/day	2
Kuppens et al, 2016	Netherlands	Double-blind crossover	Crossover using placebo	27 (8:19)	17.2 ± 1.8	Body composition	1	0.67 mg/m^2/day	2
Marzullo et al, 2015	Italy	Prospective	Non-PWS controls matched for age, sex, BMI	9 (6:3)	26.4 ± 3.7	Cardiovascular Body composition	4	0.97 mg/day	4
Longhi et al, 2015	Italy	Cross-sectional	Healthy controls	41 (17:24)	29.4 ± 8.6	Body composition Bone health	N/A	N/A	N/A
Höybye, 2015	Sweden	Cross-sectional	No control	5 (5:0)	44 ± 4	Body composition	5	0.2–0.6 mg	N/A
Lafortuna et al, 2014	Italy	Crossover	Crossover using placebo	15 (9:6)	26.1 ± 5.4 (19–35)	Cardiovascular Body composition	2	0.034 mg/kg/week	2
Jørgensen et al, 2013	Norway, Denmark	Double-blind RCT	PWS controls using placebo	42 (21:21)	28.5 ± 6.7	Bone health	2	0.6 mg	3
Butler et al, 2013	USA	Prospective	No controls	11 (5:6)	32.3 ± 11.1	Cardiovascular Body composition Bone health	1	0.13 mg/kg/week	2
Sode-Carlsen R et al, 2011	Denmark, Norway, Sweden	Cross-sectional	PWS controls using placebo	39 (originally 43) (19:24)	29.5 (17–42)	Body composition	2	0.6 mg/day	3
Sode-Carlsen et al, 2010	Denmark, Norway, Sweden	Double-blind RCT	PWS controls using placebo	46 (21:25)	28 (16–50)	Body composition	2	0.6–0.8 mg/day	1
Gondoni et al, 2008	Italy	Prospective	None	12 (7:5)	26.4 ± 4.4	Body composition	1	0.9 mg/day	1
Mogul et al, 2008	USA	Prospective	None	30 (N/A)	30.5 ± 1.5	Body composition	0.5–1	1.0 mg/day	1
Höybye et al, 2007	Sweden	Retrospective	None	14 (7:7)	22–44	Body composition	1	0.2–0.5 mg/day	6
Marzullo et al, 2007	Italy	Prospective	None	13 (7:6)	26.9 ± 1.2	Cardiovascular Body composition	1	1.0 mg/day	1
Höybye et al, 2005	Sweden	Prospective	None	6 (4:2)	19–37	Body composition	1	0.5–0.8 mg/day	1
Höybye et al, 2004	Sweden	Prospective	Healthy controls	17 (9:8)	25 (17–37)	Body composition	1	0.5 mg/day	1
Höybye 2004	Sweden	Prospective RCT	PWS controls using placebo	19 (9:8)	25 (17–37)	Body composition	1	0.5 mg/day	1
Höybye et al, 2003	Sweden	Prospective RCT	PWS controls using placebo	17 (9:8)	25 (17–37)	Body composition	1	0.5 mg/day	1

Abbreviations: CI, confidence interval; GH, growth hormone; N/A, not available; PWS, Prader-Willi syndrome; RCT, randomised controlled trial; SD, standard deviation.

TABLE 2 Statistically significant effects of GH on body composition, bone health and cardiovascular health

			Growth hormone effect on				
			Body composition				
Author, year	Evidence of GH insufficiency/ deficiency	Proportion of patients on sex steroid replacement	BMI (kg/ m^2)	lean body mass (kg)	Fat mass (%)	Bone health	Cardiovascular
Koizumi et al, 2018	N/A	1/7	↓	⟷	↑	⟷	↓ LDL cholesterol
Donze et al, 2018	N/A	12/27				⟷	
Kuppens et al, 2017	N/A	N/A					↔
Kuppens et al, 2016	N/A	12/27	↓	↑	↓		
Marzullo et al, 2015	4/9 GHD	1/9	↔	↔	↓		↑ left ventricular mass ↔ cardiac function
Longhi et al, 2015	14/23 GHD	14/23	↔	↑	↓	↑ geometry	
Höybye et al, 2015	5/5 GHD	2/5	↓	↑	↓		↔
Lafortuna et al, 2014	6/15 GHD	N/A	↔	↑	↓	↔	↑ exercise capacity
Jørgensen et al, 2013	6/42 GHD	15/42	↔			↔	
Butler et al, 2013	11/11 low IGF1	N/A	↔	↑	↓		↑ HDL cholesterol ↓ LDL cholesterol
Sode-Carlsen et al, 2011	6/39 GHD	15/39	↔	↑	↓		
Sode-Carlsen et al, 2010	6/46 GHD	16/46	↔	↑	↓		
Gondoni et al, 2008	4/12 GHD 11/12 low IGF1	2/12	↔	↑	↓		↑ exercise capacity
Mogul et al, 2008	38/38 GHD	13/38	↔	↑	↓		
Höybye, 2007	NA	N/A	↔	↑	↔		
Marzullo et al, 2007	11/13 GHD	2/13	↔	↑	↓		↑ left ventricular mass ↓ LVEF
Höybye et al., 2005	6/6 GHD	N/A	↔		↓		
Höybye et al, 2004	17/17 GHD	N/A	↔	↑	↓		
Höybye., 2004	15/19 GHD	1/19	↔	↔	↓		
Höybye et al, 2003	19/19 GHD	N/A	↔	↑	↓		

Abbreviations: BMD, bone mineral density; BMI, body mass index; GH, growth hormone; GHD, growth hormone deficiency; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LV, left ventricle; LVEF, left ventricular ejection fraction; N/A, not available; NS, not significant.

TABLE 3 Adverse events associated with GH treatment

Author, year	Number of participants (M:F)	Number of adverse events	Details of adverse events
Butler et al, 2013	11 (5:6)	5	Pretibial oedema (*n* = 1); impaired glucose tolerance (*n* = 4)
Sode-Carlsen et al, 2011	39 (19:24)	5	Headache (*n* = 2); pretibial oedema (*n* = 2); carpal tunnel syndrome (*n* = 1)
Sode-Carlsen et al, 2010	46 (21:25)	8	Headache (*n* = 1); nausea (*n* = 1); pretibial oedema (*n* = 7)
Gondoni et al, 2008	12 (7:5)	3	Pretibial oedema (*n* = 1)
Mogul et al, 2008	30 (N/A)	5	Pretibial oedema (*n* = 1)
Höybye et al, 2004	17 (9:8)	8	Pretibial oedema (*n* = 3); impaired glucose tolerance (*n* = 5)
Höybye et al, 2003	17 (9:8)	8	Pretibial oedema (*n* = 3); impaired glucose tolerance (*n* = 5)

Abbreviation: N/A, not applicable.

ventricle (LV) mass and reduced right ventricular ejection fraction (RVEF) and a trend towards reduced left ventricular ejection fraction (LVEF).[34,35]

Two studies[40,41] demonstrated improvements in cholesterol levels, with reduced LDL and increased HDL cholesterol, whilst two other studies did not.[32,42] Two studies reported increased cardiorespiratory exercise capacity.[37,38] BP was reported in 9 of 20 (45%) studies, with none demonstrating any statistically significant changes [29,30,33-35,37-39,42] during GH treatment or after cessation.[40]

3.4 | Bone health

Five studies evaluated bone health, with none reporting statistically significant alterations in bone mineral density.[31,36,37,40,43] One of the studies reported improved bone geometry, namely a statistically significant increase in bone size and strength.[36] This study compared the effects of sex steroids and GH on bone geometry in 13 females and 1 male on sex hormone replacement for a mean duration of 8 ± 5 years. This study also investigated the effects of concurrent sex steroids and found sex steroids impaired bone cross-sectional area, cortical area and the bending breaking resistance index, whereas GH had no effect on these parameters. The combination of GH and sex steroids does not seem to statistically affect bone density.[36]

3.5 | Adverse events

Of the 20 studies, 7 (35%) did not mention adverse events. Of the studies, where adverse events were addressed, 7 (54%) reported adverse events in 172 participants. Of this cohort, none reported any major adverse events; however, there were 43 minor adverse events reported. Eleven (26%) of these were oedema, mostly in lower leg in the first month of treatment[28-30,38,39,41]; one (2%) reported nausea,[28] and one (2%) developed carpal tunnel syndrome.[29] Three (7%) participants experienced headaches.[28,29] These data are summarized in Table 3.

3.6 | Diabetes and glucose tolerance

Due to the well-known links between glucose tolerance and GH, as a secondary outcome we evaluated the effects of GH therapy in the included studies by looking at oral glucose tolerance test (OGTT) results and HbA1c levels. Thirteen (65%) papers included glucose control and development of diabetes mellitus. Ten of these studies (77%) showed that no patients on GH therapy developed new diabetes mellitus or impaired glucose tolerance (IGT).[44,45] Some studies showed an increase in fasting glucose, which was not statistically significant and was well within the normal range.[27,30,32-35,37,41] Other studies also reported increases in HOMA-IR and fasting insulin, but these were transient.[38] Studies by Sode-Carlsen et al showed that among 12 patients with IGT after 1 year of GH treatment,[28] 3 reverted to normal glucose tolerance, whilst 3 progressed to overt diabetes at 2 years of GH treatment.[29]

4 | DISCUSSION

The twenty papers included in this study used different methods of measuring each of our primary outcomes, which made it difficult to compare the outcomes. The heterogeneity of these studies and their

methods used did not allow for a meta-analysis of the results, and thus, trends in each of the primary outcomes were stated instead.

Due to the rarity of PWS, there was a large disparity in the characteristics of the participants. In addition, each study individually had only a small number of patients, increasing potential risk of bias. This may be secondary to the relatively small number of PWS patients likely to be treated at each centre and the difficulties that may be encountered in terms of recruiting and consenting adult PWS patients to studies. In addition, it may be secondary to the high variability of PWS phenotypes and genotypes. However, this highlights the need for this review, as the papers combined provide a total number of 364 unique patients, allowing identification of reliable trends to guide evidence-based clinical practice and making this the largest review of GH in adults with PWS to date. Most of the studies had similar outcomes and were in agreement with each other, suggesting reliable and reproducible results. Additionally, the disparity of the phenotypes gives a more realistic picture of this cohort of patients and those seen in clinical practice.

Conclusions must be taken into consideration along with the fact that most of the patients included in the studies had some evidence of GH deficiency or insufficiency, as evidenced by low levels of IGF-1 or confirmed GHD on stimulation testing. These data may therefore not be representative of PWS patients who have normal hypothalamic-pituitary axis function. In addition, the median age of the participants in these studies was only 26.2 (17, 42) years and it was not possible to separate the patient populations in the studies to determine whether there were differences between younger or older patients. These issues highlight a need for further trials in older patients with PWS and also long-term data.

4.1 | Body composition

Results showed that in most studies, GH therapy has a positive effect on body composition, with statistically significant benefits in LBM and FM with LBM. LBM consists primarily of skeletal muscle. This is metabolically active and an important regulator of physical strength, mobility, stamina and balance resulting in healthy muscle ageing.[46]

The fact that there was no overall effect on BMI is important to note, as this may have an impact on how patients are followed up in clinic whilst on GH treatment. We propose that BMI measurements would therefore not be sufficient to determine the efficacy of the treatment.

4.2 | Cardiovascular health

Only 8 papers included cardiovascular health as outcomes in the investigation of the effects of GH in adults with PWS. Cardiopulmonary disorders remain a leading cause of death in individuals with PWS, particularly in those with the maternal disomy 15 subtype compared with the deletion subtype.[47] Echocardiography and non-invasive vascular ultrasounds have been undertaken and tolerated well by patients with PWS, and are simple investigations to perform in this higher risk patient group[8] so these should be considered in any studies investigating the effects of GH in PWS.

Indeed, the limited echocardiographic data associated with GH in PWS are contrasting. A meta-analysis into the cardiac effects of GH treatment in adults with GHD has previously shown that GH treatment resulted in positive effects on left ventricular mass, stroke volume, intraventricular septum thickness, left ventricular posterior wall diameter and left ventricular end-diastolic diameter.[48] It is therefore unusual that in individuals with PWS, increased left ventricular mass and a trend towards reduced left ventricular ejection fraction are demonstrated, although these improve with body composition.[34,35] Individuals with PWS differ from typical GHD populations, in that evidence of increased cardiac collagen deposition, perturbation of sympathetic nervous system, impaired autonomic regulation, impaired cardiorespiratory response to hypoxia and increased risk of sleep apnoea have all been described, all of which may contribute to vascular change.[35] These data therefore suggest that in PWS adults receiving GH, cardiovascular monitoring should be initiated as routine.

Fortunately, no major adverse cardiovascular events were reported in any patients included in these studies and there were no adverse effects on blood pressure. The data regarding improvements in cholesterol are contrasting, with no clear differences in the methodologies of papers to explain statistically significant changes in some over others.[32,42] Further studies are therefore required to investigate the effects of GH on cholesterol.

4.3 | Bone health

Studies showed that GH therapy did not have a significant effect on BMD, although one study showed improved bone geometry. These results may reflect the short duration of follow-up of the studies, as changes in BMD are more likely to occur over a longer time period. As such, studies of longer duration are required to convincingly demonstrate the effects of GH on BMD. LBM has consistently been reported to be positively associated with bone mass and bone mineral density, although this may reflect direct mechanical effects of muscle on bone, genetic factors or lifestyle factors.[49] Therefore, by improving LBM, this may have a positive effect on bone health in the longer term when combined with exercise. In future studies regarding bone health, it may be useful to explore the effects of LBM, exercise and diet in Prader-Willi syndrome and assess effects on BMD longer term.

4.4 | Adverse events and glucose tolerance

The reported prevalence of adverse events was low between the studies. This is of particular note given the doses of GH used in these studies were relatively high, averaging 0.8 mg/daily compared with

the recommended starting dose of 0.1–0.2 mg/day,[9] albeit acceptable side effect profiles were reported. Current consensus guidelines suggest that where GH is used on adults with GH, the dose should be titrated according to the an IGF-1 level of between 0 and +2 SDS for age-mated controls, to enable maximal benefit with minimal risk of side effects.[9] Children with PWS are more sensitive to GH therapy and tend to have higher IGF-1 levels, although bioactivity is similar; therefore, using normal reference ranges for IGF-1 for monitoring may not be ideal.[50]

That said, it is known that GH treatment can lead to impaired glucose tolerance. Cutfield et al found that children treated with GH were 6 times more likely to develop T2DM than their non–GH-treated counterparts.[51] In general, the majority of the included studies did not show impaired glucose tolerance with GH therapy; however, non-significant increases in fasting glucose were recorded, but these all remained in the normal range. One group showed the progression of 3 patients from IGT to overt DM during GH therapy; however, this may be due to lifestyle factors, rather than GH therapy alone,[28,29] and a recent study, published after this systematic search, confirmed that fasting glucose and insulin levels remained stable after 3 years of GH therapy.[52] Höybye (2004) suggested that GH treatment should be combined with lifestyle changes and exercise, in order to reduce the negative outcomes on glucose tolerance.[30] This further supports previous recommendations that transition to adult services should be supported by a multidisciplinary team, including a dietitian.[13]

4.5 | Recommendations

The data from the 20 studies included in this systematic review suggest that GH therapy in adults with PWS is likely to result in favourable outcomes, particularly with regard to body composition. Most of the studies focused mainly on body composition and indirect cardiovascular health factors, and few focused on direct cardiovascular health and bone health; therefore, more studies are required looking at these parameters. The duration of follow-up in the studies included was also relatively short, so longer-term longitudinal studies are recommended to confirm the effects of GH in this group of patients.

In the meantime, GH therapy appears to be well tolerated and should be considered in adults with PWS but only in specialist centres with access to a multidisciplinary team. Where GH therapy is used in adults, regular monitoring should be initiated, with particular emphasis on echocardiograms, oral glucose tolerance tests and IGF-1 and cholesterol measurements.

5 | CONCLUSION

The use of GH therapy in adults has shown favourable outcomes, particularly in body composition, without significant changes in bone and cardiovascular health in the short term. No major adverse events were seen, and therefore, overall the use of GH therapy in adults has been shown to be beneficial and safe. As a result of this, we would recommend the use of GH therapy in PWS adults, supported by a multidisciplinary team to monitor their progress and record any side effects. It is, however, essential that longitudinal studies on GH in PWS be conducted to confirm these findings in patients receiving long-term GH. As such, we would recommend that where GH is prescribed for adults with PWS, data should also be collected regarding efficacy and safety in a systematic way to ensure that such these important data are available.

CONFLICT OF INTEREST

The authors confirm there are no conflicts of interest.

FUNDING INFORMATION

ALH is funded by the Gardiner Clinical Lectureship at the University of Glasgow.

ACKNOWLEDGEMENT

No financial support was received for this study.

AUTHOR CONTRIBUTION

MF and DV performed the literature search, selected the titles and prepared the manuscript. ALH designed the study, discussed the inclusion of papers and revised the manuscript. LM independently reviewed the inclusion of papers. AK reviewed the data and advised on data selection and study design. GS conceptualized the study and revised the manuscript. All authors read and approved the final report.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon request.

ORCID

Angela K. Lucas-Herald https://orcid.org/0000-0003-2662-1684
Andreas Kyriakou https://orcid.org/0000-0002-5634-2574
M. Guftar Shaikh https://orcid.org/0000-0002-2316-3334

REFERENCES

1. McCandless SE, Suh M, Yin D, et al. SUN-604 US prevalence & mortality of Prader-Willi syndrome: a population-based study of medical claims. *J Endocrine Soc*. 2020;4(Supplement_1).A504–A505.
2. Vogels A, Van Den Ende J, Keymolen K, et al. Minimum prevalence, birth incidence and cause of death for Prader-Willi syndrome in Flanders. *Eur J Hum Genet*. 2004;12(3):238-240.
3. Grugni G, Sartorio A, Crinò A. Growth hormone therapy for Prader-Willi syndrome: challenges and solutions. *Ther Clin Risk Manag*. 2016;12:873.
4. Brambilla P, Bosio L, Manzoni P, Pietrobelli A, Beccaria L, Chiumello G. Peculiar body composition in patients with Prader-Labhart-Willi syndrome. *Am J Clin Nutr*. 1997;65(5):1369-1374.
5. Carrel AL, Myers SE, Whitman BY, Allen DB. Growth hormone improves body composition, fat utilization, physical strength and agility, and growth in Prader-Willi syndrome: a controlled study. *J Pediatr*. 1999;134(2):215-221.

6. Theodoro MF, Talebizadeh Z, Butler MG. Body composition and fatness patterns in Prader-Willi syndrome: comparison with simple obesity. *Obesity*. 2006;14(10):1685-1690.
7. Nakamura Y, Murakami N, Iida T, Asano S, Ozeki S, Nagai T. Growth hormone treatment for osteoporosis in patients with scoliosis of Prader-Willi syndrome. *J Orthop Sci*. 2014;19(6):877-882.
8. Patel S, Harmer JA, Loughnan G, Skilton MR, Steinbeck K, Celermajer DS. Characteristics of cardiac and vascular structure and function in Prader-Willi syndrome. *Clin Endocrinol*. 2007;66(6):771-777.
9. Deal CL, Tony M, Höybye C, Allen DB, Tauber M, Christiansen JS. Participants GHiP-WSCCGW: growth hormone research society workshop summary: consensus guidelines for recombinant human growth hormone therapy in Prader-Willi syndrome. *J Clin Endocrinol Metab*. 2013;98(6):E1072-E1087.
10. Butler MG, Matthews NA, Patel N, et al. Impact of genetic subtypes of Prader-Willi syndrome with growth hormone therapy on intelligence and body mass index. *Am J Med Genet A*. 2019;179(9):1826-1835.
11. Donze SH, Damen L, van Alfen-van der Velden J, et al. Prevalence of growth hormone (GH) deficiency in previously GH-treated young adults with Prader-Willi syndrome. *Clin Endocrinol (Oxf)*. 2019;91(1):118-123.
12. Sanchez-Ortiga R, Klibanski A, Tritos NA. Effects of recombinant human growth hormone therapy in adults with Prader-Willi syndrome: a meta-analysis. *Clin Endocrinol*. 2012;77(1):86-93.
13. Lucas-Herald AK, Perry CG, Shaikh MG. Review of growth hormone therapy in adolescents and young adults with Prader-Willi syndrome. *Exp Rev Endocrinol Metab*. 2015;10(2):259-267.
14. A Cochrane Risk Of Bias Assessment Tool: for Non-Randomized Studies of Interventions (ACROBAT-NRSI), Version 1.0.0, 24 September 2014.
15. Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.
16. Höybye C, Tauber M, Angulo MA, et al. Clinical, Organisation SABoTIPWS: Letter regarding" Prevalence of growth hormone deficiency in previously GH-treated young adults with Prader-Willi syndrome" by Donze et al. *Clin Endocrinol*. 2019;91(4):578-579.
17. Grugni G, Marzullo P, Ragusa L, et al. Impairment of GH responsiveness to combined GH-releasing hormone and arginine administration in adult patients with Prader-Willi syndrome. *Clin Endocrinol*. 2006;65(4):492-499.
18. Oto Y, Tanaka Y, Abe Y, et al. Exacerbation of BMI after cessation of growth hormone therapy in patients with Prader-Willi syndrome. *Am J Med Genet A*. 2014;164(3):671-675.
19. Coupaye M, Tauber M, Cuisset L, et al. Effect of genotype and previous GH treatment on adiposity in adults with Prader-Willi syndrome. *J Clin Endocrinol Metab*. 2016;101(12):4895-4903.
20. Höybye C, Thoren M, Böhm B. Cognitive, emotional, physical and social effects of growth hormone treatment in adults with Prader-Willi syndrome. *J Intellect Disabil Res*. 2005;49(4):245-252.
21. Kuppens R, Mahabier E, Bakker N, Siemensma E, Donze S, Hokken-Koelega A. Effect of cessation of GH treatment on cognition during transition phase in Prader-Willi syndrome: results of a 2-year crossover GH trial. *Orphanet J Rare Dis*. 2016;11(1):153.
22. Bertella L, Mori I, Grugni G, et al. Quality of life and psychological well-being in GH-treated, adult PWS patients: a longitudinal study. *J Intellect Disabil Res*. 2007;51(4):302-311.
23. Höybye C. Inflammatory markers in adults with Prader-Willi syndrome before and during 12 months growth hormone treatment. *Horm Res Paediatr*. 2006;66(1):27-32.
24. Höybye C, Barkeling B, Espelund U, Petersson M, Thorén M. Peptides associated with hyperphagia in adults with Prader-Willi syndrome before and during GH treatment. *Growth Hormon IGF Res*. 2003;13(6):322-327.
25. Olarescu NC, Jørgensen AP, Godang K, Jurik AG, Frøslie KF, Bollerslev J. Dual-energy X-ray absorptiometry is a valid method to estimatimate visceral adipose tissue in adult patients with prader-willi syndrome during treatment with growth hormone. *J Clin Endocrinol Metab*. 2014;99(9):E1727-E1731.
26. Jørgensen AP, Ueland T, Sode-Carlsen R, et al. Glucose homeostasis in adults with Prader-Willi syndrome during treatment with growth hormone: results from a 12-month prospective study. *Growth Hormon IGF Res*. 2014;24(1):16-21.
27. Höybye C, Hilding A, Jacobsson H, Thorén M. Growth hormone treatment improves body composition in adults with Prader-Willi syndrome. *Clin Endocrinol*. 2003;58(5):653-661.
28. Sode-Carlsen R, Farholt S, Rabben KF, et al. One year of growth hormone treatment in adults with Prader-Willi syndrome improves body composition: results from a randomized, placebo-controlled study. *J Clin Endocrinol Metab*. 2010;95(11):4943-4950.
29. Sode-Carlsen R, Farholt S, Rabben KF, et al. Growth hormone treatment for two years is safe and effective in adults with Prader-Willi syndrome. *Growth Hormon IGF Res*. 2011;21(4):185-190.
30. Höybye C. Endocrine and metabolic aspects of adult Prader-Willi syndrome with special emphasis on the effect of growth hormone treatment. *Growth Hormon IGF Res*. 2004;14(1):1-15.
31. Donze SH, Kuppens RJ, Bakker NE, van Alfen-van der Velden JA, Hokken-Koelega AC. Bone mineral density in young adults with Prader-Willi syndrome: a randomized, placebo-controlled, crossover GH trial. *Clin Endocrinol*. 2018;88(6):806-812.
32. Kuppens R, Bakker N, Siemensma E, Donze S, Stijnen T, Hokken-Koelega A. Metabolic health profile in young adults with Prader-Willi syndrome: results of a 2-year randomized, placebo-controlled, crossover GH trial. *Clin Endocrinol*. 2017;86(2):297-304.
33. Kuppens RJ, Bakker NE, Siemensma EP, et al. Beneficial effects of GH in young adults with Prader-Willi syndrome: a 2-year crossover trial. *J Clin Endocrinol Metab*. 2016;101(11):4110-4116.
34. Marzullo P, Marcassa C, Campini R, et al. Conditional cardiovascular response to growth hormone therapy in adult patients with Prader-Willi syndrome. *J Clin Endocrinol Metab*. 2007;92(4):1364-1371.
35. Marzullo P, Marcassa C, Minocci A, et al. Long-term echocardiographic and cardioscintigraphic effects of growth hormone treatment in adults with Prader-Willi syndrome. *J Clin Endocrinol Metab*. 2015;100(5):2106-2114.
36. Longhi S, Grugni G, Gatti D, et al. Adults with Prader-Willi syndrome have weaker bones: effect of treatment with GH and sex steroids. *Calcif Tissue Int*. 2015;96(2):160-166.
37. Lafortuna CL, Minocci A, Capodaglio P, et al. Skeletal muscle characteristics and motor performance after 2-year growth hormone treatment in adults with Prader-Willi syndrome. *J Clin Endocrinol Metab*. 2014;99(5):1816-1824.
38. Gondoni L, Vismara L, Marzullo P, Vettor R, Liuzzi A, Grugni G. Growth hormone therapy improves exercise capacity in adult patients with Prader-Willi syndrome. *J Endocrinol Invest*. 2008;31(9):765-772.
39. Mogul HR, Lee PD, Whitman BY, et al. Growth hormone treatment of adults with Prader-Willi syndrome and growth hormone deficiency improves lean body mass, fractional body fat, and serum triiodothyronine without glucose impairment: results from the United States multicenter trial. *J Clin Endocrinol Metab*. 2008;93(4):1238-1245.
40. Koizumi M, Ida S, Shoji Y, Nishimoto Y, Etani Y, Kawai M. Visceral adipose tissue increases shortly after the cessation of GH therapy in adults with Prader-Willi syndrome. *Endocr J*. 2018;65:1127-1137.
41. Butler MG, Smith BK, Lee J, et al. Effects of growth hormone treatment in adults with Prader-Willi syndrome. *Growth Hormon IGF Res*. 2013;23(3):81-87.
42. Höybye C. Growth hormone treatment of Prader-Willi syndrome has long-term, positive effects on body composition. *Acta Paediatr*. 2015;104(4):422-427.
43. Jørgensen A, Ueland T, Sode-Carlsen R, et al. Two years of growth hormone treatment in adults with Prader-Willi syndrome do not

improve the low BMD. *J Clin Endocrinol Metab*. 2013;98(4):E753-E760.
44. Hoybye C, Bruun JM, Richelsen B, Flyvbjerg A, Frystyk J. Serum adiponectin levels in adults with Prader-Willi syndrome are independent of anthropometrical parameters and do not change with GH treatment. *Eur J Endocrinol*. 2004;151(4):457-462.
45. Höybye C, Hilding A, Marcus C, Thorén M. Growth hormone induced lipolysis during short-and long-term administration in adult Prader-Willi patients. *Growth Hormon IGF Res*. 2005;15(6):411-415.
46. Zillikens MC, Demissie S, Hsu Y-H, et al. Large meta-analysis of genome-wide association studies identifies five loci for lean body mass. *Nat Commun*. 2017;8(1):80.
47. Butler MG, Manzardo AM, Heinemann J, Loker C, Loker J. Causes of death in Prader-Willi syndrome: Prader-Willi Syndrome Association (USA) 40-year mortality survey. *Genet Med*. 2017;19(6):635-642.
48. Maison P, Chanson P. Cardiac effects of growth hormone in adults with growth hormone deficiency: a meta-analysis. *Circulation*. 2003;108(21):2648-2652.
49. Zhu K, Briffa K, Smith A, et al. Gender differences in the relationships between lean body mass, fat mass and peak bone mass in young adults. *Osteoporos Int*. 2014;25(5):1563-1570.
50. Bakker NE, van Doorn J, Renes JS, Donker GH, Hokken-Koelega AC. IGF-1 levels, complex formation, and IGF bioactivity in growth hormone-treated children with Prader-Willi syndrome. *J Clin Endocrinol Metab*. 2015;100(8):3041-3049.
51. Cutfield WS, Wilton P, Bennmarker H, et al. Incidence of diabetes mellitus and impaired glucose tolerance in children and adolescents receiving growth-hormone treatment. *Lancet*. 2000;355(9204):610-613.
52. Damen L, Grootjen LN, Donze SH, et al. Three years of growth hormone treatment in young adults with Prader-Willi Syndrome previously treated with growth hormone in childhood: effects on glucose homeostasis and metabolic syndrome. *Clin Endocrinol*. 2020;93(4):439-448.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Frixou M, Vlek D, Lucas-Herald AK, Keir L, Kyriakou A, Shaikh MG. The use of growth hormone therapy in adults with Prader-Willi syndrome: A systematic review. *Clin Endocrinol*. 2020;00:1–11. https://doi.org/10.1111/cen.14372