Missed diagnoses and health problems in adults with Prader-Willi syndrome
– recommendations for screening and treatment

Karlijn Pellikaan¹, BSc, Anna G. W. Rosenberg¹, BSc, Anja A. Kattentidt-Mouravieva², MD, Rogier Kersseboom², MD, PhD, Anja G. Bos-Roubos³, MSc, José M. C. Veen-Roelofs⁴, BSc, Nina van Aalst-van Wieringen⁵, BSc, Franciska M. E. Hoekstra¹,⁶, MD, PhD, Sjoerd A. A. van den Berg⁷, PhD, Aart Jan van der Lely¹, MD, PhD, Laura C. G. de Graaff¹,⁹,¹⁰, MD, PhD

¹ Internal Medicine, division of Endocrinology, Erasmus MC, University Medical Center Rotterdam, The Netherlands
² Stichting Zuidwester, Middelharnis, The Netherlands
³ Vincent van Gogh, Center of Excellence for Neuropsychiatry, Venray, the Netherlands
⁴ ‘s Heeren Loo, Care Providing Agency, Ede/Wekerom, The Netherlands
⁵ Department of Physical Therapy, Erasmus MC, University Medical Center Rotterdam, The Netherlands
⁶ Department of Internal Medicine, Reinier de Graaf hospital, Delft, the Netherlands
⁷ Department of Clinical Chemistry, Erasmus MC, University Medical Center Rotterdam, The Netherlands
⁹ Academic Center for Growth Disorders, Erasmus MC, University Medical Center Rotterdam, The Netherlands
¹⁰ Dutch Center of Reference for Prader-Willi syndrome

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Address correspondence and reprint requests to
Laura de Graaff, MD, PhD
Dept. of Internal Medicine
Erasmus MC, University Medical Center
Dr. Molewaterplein 40, 3015 GD Rotterdam, the Netherlands
Telephone: +31-618843010
E-mail l.degraaff@erasusmc.nl

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**Abbreviations**

ALAT = alanine transaminase  
ALP = alkaline phosphatase  
ASAT = aspartate transaminase  
BMI = body mass index  
BMR = basal metabolic rate  
CSA = central sleep apnea  
CV = cardiovascular  
DEXA = dual energy X-ray absorptiometry  
DM2 = type 2 diabetes mellitus  
eGFR = estimated glomerular filtration rate  
FSH = follicle-stimulating hormone  
FT4 = free thyroxin  
GH = growth hormone  
GGT = gamma glutamyl transpeptidase  
HbA1c = hemoglobin A1c  
ICD = imprinting center defect  
IQR = interquartile range  
LDH = lactate dehydrogenase  
LDL = low-density lipoprotein  
LH = luteinizing hormone  
LLN = lower limit of normal  
MCV = mean corpuscular volume  
mUPD = maternal uniparental disomy  
OHS = obesity hypoventilation syndrome  
OSA = obstructive sleep apnea
PG = polygraphy
PSG = polysomnography
PWS = Prader-Willi syndrome
SHBG = sex hormone binding globulin
TSH = thyroid stimulating hormone
ULN = upper limit of normal
Abstract

Context Prader-Willi syndrome (PWS) is a complex hypothalamic disorder, combining hyperphagia, hypotonia, intellectual disability and pituitary hormone deficiencies. Annual mortality of patients with PWS is high (3%). In half of the patients, the cause of death is obesity related and/or of cardiopulmonary origin. Health problems leading to this increased mortality often remain undetected due to the complexity and rareness of the syndrome.

Objective To assess the prevalence of health problems in adults with PWS retrospectively.

Patients, Design and Setting We systematically screened 115 PWS adults for undiagnosed health problems. All patients visited the multidisciplinary outpatient clinic for rare endocrine syndromes at the Erasmus University Medical Center, Rotterdam, the Netherlands. We collected results of medical questionnaires, interviews, physical examinations, biochemical measurements, poly(somno-)graphy and radiology.

Main outcome measures Presence or absence of endocrine and non-endocrine comorbidities in relation to living situation, body mass index, genotype and demographic factors.

Results Seventy patients (61%) had undiagnosed health problems, while one in every four patients had multiple undiagnosed health problems simultaneously. All males and 93% of females had hypogonadism, 74% scoliosis, 18% hypertension, 19% hypercholesterolemia, 17% type 2 diabetes mellitus and 17% hypothyroidism. Unfavourable lifestyle was common: 22% exercised too little (according to PWS criteria) and 37% did not see a dietitian.
**Conclusions** Systematic screening revealed many undiagnosed health problems in PWS-adults. Based on patient characteristics, we provide an algorithm for diagnostics and treatment, with the aim to prevent early complications and reduce mortality in this vulnerable patient group.

**Key words:** ‘Prader-Willi syndrome’ [MeSH], ‘cardiovascular system’ [MeSH], ‘missed diagnosis’ [MeSH], ‘comorbidity’ [MeSH], ‘Failure to Rescue, Health Care’ [MeSH].
Introduction

Prader-Willi syndrome (PWS) is a rare genetic, neuroendocrine condition caused by the absence of a normal paternal contribution to the 15q11-13 region. It is most commonly caused by a paternal deletion (65-75%) or a maternal uniparental disomy 15 (mUPD, 20-30%). In the minority of cases, PWS is caused by an imprinting center defect (ICD, 1-3%) or a paternal chromosomal translocation (0.1%) (1,2). The syndrome is characterized by hypotonia, behavioural challenges, typical dysmorphic features and hypothalamic dysfunction resulting in hyperphagia, pituitary hormone deficiencies, abnormal temperature regulation and inadequate pain registration (3-6).

Annual mortality in adults with PWS is high (3%) (7,8), compared to 1.3% annual mortality in non-PWS adults with an intellectual disability (9). More than half of these deaths are caused by cardiopulmonary pathology (8,10) and another 7% of deaths are directly related to obesity (8). Seventy-eight percent of deaths in patients with PWS are unexpected (11).

Multiple factors contribute to the increased risk of cardiopulmonary pathology in patients with PWS. Based on our clinical experience with more than a hundred PWS adults, we hypothesize that there is a complex interaction between obesity and behavioural, endocrine and cardiovascular (CV) risk factors that contribute to the high prevalence of cardiopulmonary disease in patients with PWS, as is shown in Figure 1.

Obesity in patients with PWS is caused by hyperphagia (leading to a high energy intake) combined with a low energy expenditure (12,13). This low energy expenditure is caused by low muscle mass, which is part of the syndrome. Untreated pituitary hormone deficiencies like hypogonadism, hypothyroidism and growth hormone deficiency can affect muscle mass and function, causing a further decrease in basal metabolic rate (BMR) (12,14-21).

The total energy expenditure in adults with PWS is 20% lower than in age-matched obese adults (22). This difference in energy expenditure should be compensated by
either a strict diet or by exercising for at least one hour a day (23). However exercise tolerance may be low, due to hypotonia, pituitary hormone deficiencies and (severe) vitamin D deficiency (14,24-29). Moreover, the typical behavioural phenotype and musculoskeletal problems like scoliosis, hypotonia and leg edema impair physical activity in adults with PWS. This results in a vicious circle of muscle weakness, exercise intolerance and a further decrease in physical activity. The subsequent sedentary lifestyle can induce CV risk factors like hypertension, hypercholesterolemia and type 2 diabetes mellitus (DM2) (30). Other CV risk factors often present in PWS are obesity hypoventilation syndrome (OHS) and sleep apnea, which can be central (CSA), obstructive (OSA) or both. CSA, OSA and OHS can lead to pulmonary hypertension (31,32), DM2 (33) and a further increase in obesity (34) and CV risk (35-38). Lastly, the cognitive phenotype of PWS (often higher verbal comprehension skills compared to performal/reasoning skills, which can easily lead to over-estimation) and autism-related behavioural challenges could induce stress. Stress can induce hypertension, another important CV risk factor (39). Moreover, psychosis is prevalent in patients with PWS, often requiring psychiatric drugs. As many psychiatric drugs have cardiovascular side effects, this can lead to a further increase in cardiovascular risk (40).

The complex interplay between somatic and psychological factors requires a syndrome-specific approach of health problems. However, as PWS is a rare disorder (5), most physicians are unfamiliar with the syndrome and its associated comorbidities. Furthermore, the PWS-specific behavioural phenotype (high pain threshold and inability to express their complaints) often leads to underdiagnosis and undertreatment. Combined doctors’ and patients’ delay can lead to medical complications and hospital admission. Timely recognition of co-morbidities can reduce medical complications and the associated personal and financial burden (41).

Previous authors have reported health problems in adults with PWS (11,42-60). However, most of them did not perform a systematic screening, but only reported health problems that had already been diagnosed. As underdiagnosis is a serious problem in
this patient population, the prevalences reported in these studies are most likely underestimated. Data from systematic health screenings in adults with PWS are scarce (44,45,47,48,58) and little is known about the relation between patient characteristics (living situation, presence or absence of obesity, genotype and demographic factors) and health problems. As a consequence, there is no consensus about periodical screening.

In our reference center, we routinely perform a systematic health screening in all adults with PWS in order to detect comorbidities at an early stage. In the current article, we report the prevalence of the physical health problems detected by our screening. Based on their associations with the aforementioned patient characteristics, we provide practical advice for medical screening.

**Methods**

This study was approved by the Medical Ethics Committee of the Erasmus University Medical Center. In this retrospective study, we reviewed the medical files of all adults who visited the multidisciplinary outpatient clinic of the PWS reference center in the Erasmus University Medical Center, Rotterdam, the Netherlands, between January 2015 and April 2020 and who underwent routine systematic health screening. All patients that visited our outpatient clinic were already diagnosed with PWS, often years before visiting our outpatient clinic and / or during childhood. Before the launch of our multidisciplinary outpatient clinic in 2015, many Dutch adults with PWS were treated by their general practitioner or physician for people with intellectual disabilities (‘ID physician’).

Our systematic screening consists of a structured interview, a complete physical examination, a medical questionnaire, a review of the medical records, biochemical measurements and, if indicated and feasible, additional tests like dual energy X-ray absorptiometry (DEXA) and poly(somno)graphy. We report the ‘hidden’ health problems that were present but undetected and / or untreated until the moment of screening. Conditions that developed during later follow-up visits were not taken into account. Forty-two patients in the cohort that we describe, were also mentioned in a previous
study by Sinnema et al. (43), who gave an overview of 102 adults with PWS and the health problems that had already been diagnosed (without systematic screening).

**Genetic diagnosis** We performed genetic testing or collected previous genetic test results from other Dutch academic hospitals, to confirm the diagnosis PWS and to determine the genetic subtype.

**Medical questionnaire** As part of regular patient care, primary caregivers filled out a medical questionnaire before visiting the outpatient clinic. This questionnaire included questions on the patient’s medical history, medication, family history, symptoms of disease, physical complaints, behavioural challenges and social aspects like work, school, relationship and living situation. Symptoms of disease, physical complaints and behavioural challenges are rated on a 5-point Likert scale (1 = rarely or never, 2 = not often and/or not severe, 3 = quite often and/or quite severe, 4 = often and/or severe, 5 = very often and/or very severe). A score of 3 or higher was considered clinically relevant and was further explored during the visit. Mutism is defined as absence of speech.

**Biochemical analysis** During the visit, blood samples were taken for general medical screening, including evaluation of fat metabolism (low density lipoprotein (LDL)-cholesterol), glucose metabolism (non-fasting glucose, hemoglobin A1c), thyroid function (free T4), gonadal function (random LH, FSH, estradiol or testosterone, SHBG), liver enzymes (aspartate transaminase, alanine transaminase, alkaline phosphatase, gamma glutamyl transpeptidase, total bilirubin, lactate dehydrogenase), kidney function (urea, creatinine, estimated glomerular filtration rate (eGFR)), the hematopoietic system (hemoglobin, hematocrit, mean corpuscular volume, leukocytes, thrombocytes and, in case of microcytic anemia, ferritin) and vitamin D status (25-hydroxyvitamin D). The eGFR is estimated by the CKD-EPI formula.

**Cut-off levels** The diagnosis hypercholesterolemia was confirmed if the patient had a non-fasting LDL-cholesterol above 4.0 mmol/L. Type 2 diabetes mellitus was defined as
a repeated fasting glucose above 6.7 mmol/L (or non-fasting above 11.0 nmol/L). HbA1c was used to assess long-term glycemic control. As hypothyroidism in PWS can be both primary and central (61), hypothyroidism was defined as a free T4 below 11 pmol/L, regardless of TSH. Hypogonadism in males was defined as a morning testosterone level below 10.0 nmol/L or a random testosterone level below 10.0 nmol/L combined with clear clinical features or hypogonadism (sparse body hair, micropenis and absence or spontaneous morning erections). Hypogonadism in females was defined as absent, scarce or irregular menses. Diagnosis of hypogonadism was based on both laboratory values and clinical parameters because of the effect of adipose tissue aromatase activity on estradiol and testosterone levels (62) and the fact that hypogonadism in PWS can be both primary and central (63). Due to intellectual disability in most patients, gynaecological evaluation was not routinely performed. When females used oral contraceptives or estrogen replacement therapy before screening, we asked for the menstrual cycle before the start of estrogen replacement therapy.

Severe vitamin D deficiency was defined as a 25-hydroxyvitamin D level below 20 nmol/L, mild vitamin D deficiency as a 25-hydroxyvitamin D level below 50 nmol/L. When patients used cholesterol-lowering medication, oral anti-diabetics, insulin, levothyroxine or testosterone replacement therapy before the start of the screening, we requested pre-treatment laboratory values to verify the diagnosis.

**Additional tests** We screened for hypertension by measuring blood pressure. If the patient’s blood pressure was above 140/90 mmHg, the measurement was repeated and if it was still elevated, a 30-minute blood pressure measurement was performed. If the patient already used antihypertensive drugs, we requested pre-treatment blood pressure values.

If risk factors for osteoporosis were present (untreated hypogonadism, family history of osteoporosis, previous fractures, untreated vitamin D deficiency and / or corticosteroid treatment), we performed a DEXA scan to screen for osteoporosis or osteopenia.
Osteoporosis was defined as a T-score (comparison of a person's bone density with that of a healthy 30-year-old of the same sex) below -2.5, osteopenia as a T-score between -1.0 and -2.5.

If there was a clinical suspicion of scoliosis (based on a gibbus deformity during physical examination), we performed an X-ray of the spine if 1) the patient was not previously diagnosed with scoliosis, 2) the patient suffered from back pain or 3) the caregivers reported new or progressive postural abnormalities. Radiologically confirmed scoliosis was defined as a Cobb angle of 10 degrees or more as measured on a spinal X-ray.

The indication for sleep studies was based on the presence of clinical signs of sleep apnea: severe snoring, witnessed apneas, daytime sleepiness, morning headaches, hypertension or waking up with shortness of breath, headaches or panic. If indicated and feasible, we performed polygraphy (PG, continuous recording of nasal airflow, thoracic and abdominal movements, heart rate and oxygen saturation during one night) or polysomnography (PSG, PG measurements and electroencephalography, electro-oculography and electromyography). Also, before the start of growth hormone (GH) treatment, we performed polysomnography to exclude sleep apnea, as untreated sleep apnea is an absolute contra-indication for GH treatment.

**Data analysis** Statistical analysis was performed using R version 3.6.3. Descriptive statistics for continuous variables are reported as median and interquartile range (IQR). For dichotomous variables we display the number of people and the percentage of total people, n (%). We used a chisquared test to compare the prevalence of health problems between different groups based on patient characteristics: genotype, living situation and gender. To investigate the relationship between BMI, age, patient characteristics and the prevalence of health problems, we used the Wilcoxon rank sum test. For the relationship between BMI, age and living situation, we used the Kruskal-Wallis test. A chi-squared test for trend was used to compare the number of undiagnosed health problems between subgroups. To investigate the relation between age and BMI, the Kendall rank correlation
test was used. To investigate the effect of BMI and age on health problems and number of undiagnosed health problems corrected for age and BMI respectively, logistic and ordinal regression models were used and a likelihood ratio test was performed.

**Literature review** We reviewed the literature for studies that report physical health problems in patients with PWS. Inclusion criteria were: original research articles, observational studies that reported the prevalence of physical health problems in a cohort of patients with PWS of 15 years or older. Exclusion criteria were: clinical trials, basic or translational research, case reports, case series that included less than 10 adults with PWS, articles that were not available online, articles that were not available in English, and mixed pediatric-adult articles that did not report separate prevalences for patients with PWS of 15 years or older. The full search strategy used is available upon request.

**Results**

We included 115 (56 male / 59 female) patients. Median age was 29 years (IQR 21 – 40) and median BMI 29 kg/m$^2$ (IQR 26 – 35). Baseline characteristics are shown in Table 1. The exact age at diagnosis was known for 72 patients, of which 59 patients were diagnosed during childhood. Of 115 patients, 42 underwent transition after years of medical supervision at the pediatric multidisciplinary outpatient clinic. All patients referred by the pediatrician had a personal care plan. Of the remaining 73 patients, 17 patients had been followed by an endocrinologist elsewhere during the year before the screening. Forty-six patient had been followed by an ID physician and 14 had never visited an adult endocrinologist or ID physician before.

We refer to the repository (64) for the following supplementary data: baseline characteristics and health problems by living situation and genotype; health problems by BMI, age and gender; information about lifestyle, behaviour and physical complaints; details of biochemical analysis (liver panel, kidney function, hematopoiesis and
electrolyte values); and data about sleep apnea, bone mineral density and vitamin D deficiency.

**Health problems detected by screening**

The results of our systematic health screening are shown in Table 2 and Figure 2. We found undetected health problems in 61% of adults with PWS. One fourth had more than one undetected simultaneous health problem. The most common undetected health problem was hypogonadism, which had gone unnoticed in 52% of males and 33% of females. Other undiagnosed health problems were scoliosis (20%), hypercholesterolemia (6%), DM2 (5%), hypertension (3%) and hypothyroidism (2%). Forty-five patients underwent DEXA scans as part of medical screening. This revealed three new cases of osteoporosis and eight cases of osteopenia, on top of the nine patients already known with osteoporosis and the 22 patients with osteopenia. Two males and one female (all older than 30 year during the screening) had osteoporosis despite previous treatment for hypogonadism. Both males had received testosterone replacement therapy for more than 15 years before screening. For the female, the exact duration of estrogen replacement therapy was unknown. Nine patients were known with sleep apnea before the screening. Nineteen patients underwent PG or PSG, of which eleven patients were diagnosed with sleep apnea.

**Comparison of health problems between groups**

*Living situation* Twenty-three patients lived in a specialized PWS group home (‘PWS home’), 61 in a non-specialized group home (‘non-PWS home’), 28 with family, and 3 in an assisted living facility. Patients living in non-PWS homes were significantly older (median age 36 years, IQR 28 – 50) than those living in PWS homes (median age 26 years, IQR 21 – 32) or with family (median age 19 years, IQR 19 – 22). BMI and prevalence of hypertension were significantly higher in patients living in non-PWS homes, see Table 3.
Patients in PWS homes exercised more than those living with family or in non-PWS homes. Patients in PWS homes all exercised at least 30 minutes a day, versus 75% and 70% of those living with family or in non-PWS homes. A dietitian was involved in 87% of patients living in PWS homes, 74% of those living in a non-PWS home and in 29% of those living with family.

**Genotype** When comparing health problems between the two largest genotypic subgroups (64 patients with a deletion and 41 with mUPD), scoliosis was more frequent in patients with a deletion than in patients with an mUPD (81% vs 59%, P=0.02). Other variables were not remarkably different between the genotypes, see **Table 3**.

**BMI** BMI increased with age (P=0.02). Patients with a higher BMI had a higher total number of undiagnosed health problems (P<0.001) and more hypercholesterolemia (P=0.01), see **Table 4**. This remained significant after correction for age.

**Age** Older patients had a higher prevalence of DM2 (P<0.001), hypertension (P<0.001), and hypercholesterolemia (P<0.002) and a higher total number of undiagnosed health problems (P=0.001), see **Table 4**. This remained significant after correction for BMI.

**Gender** BMI was significantly higher in females than in males (P=0.02). Hypothyroidism was more prevalent in females than in males (24% vs 9%, P=0.03), see **Table 4**.

**Gender and BMI** Thirteen patients had BMI < 25 kg/m2 and age < 25 years. None of these patients had diabetes mellitus, one patient had hypertension and two had hypercholesterolemia (of which one case was undiagnosed before screening).

**Fatigue and daytime sleepiness**

Fatigue and daytime sleepiness were common. One third of the patients (40 of 115) had clinically relevant daytime sleepiness (score of 3 or higher on a 5-point Likert scale). All of these 40 patients had either untreated vitamin D deficiency, untreated male hypogonadism (**Table 5**) or another treatable cause like sleep apnea, narcolepsia, nycturia or use of drugs that can cause sleepiness (anti-epileptic drugs, antipsychotics, benzodiazepines, tricyclic antidepressants or antihistamines). Daytime sleepiness was present in 62% of the patients with untreated vitamin D deficiency, versus 36% of the...
patients with normal vitamin D levels (P=0.02). It was also related to the severity of the deficiency: daytime sleepiness was present in 80% of the patients with untreated severe vitamin D deficiency, 57% of the patients with untreated mild vitamin D deficiency and 36% of the patients with normal vitamin D levels.

**Biochemical analysis**

Liver panel was normal in most patients. However, 19 patients had alkaline phosphatase levels above the upper limit of normal (ULN). The vast majority of them had potential underlying causes like vitamin D deficiency (63%) and / or obesity (58%). Normocytic anemia was common in males, but not in females. There were no cases of micro- or macrocytic anemia. Of the 17 males with anemia, 13 (76%) had untreated hypogonadism. Creatinine levels were generally low: 35 males (63%) and 28 females (47%) had creatinine levels below the lower limit of normal (LLN) and this was independent of BMI and of age. Of all males, 95% had creatinine levels between 46 – 93 µmol/L and eGFR levels between 93 – 149 ml/min/1.73 m². Of all females, 95% had creatinine levels between 37 – 76 µmol/L and eGFR levels between 98 – 140 ml/min/1.73 m².

**Literature review**

We found 21 publications reporting one or more of the following health problems in PWS: hypogonadism, hypothyroidism, DM2, hypertension, hypercholesterolemia, scoliosis, vitamin D deficiency, sleep apnea or osteoporosis / osteopenia. Outcomes of these studies are summarized in **Table 6 and 7**. None of the papers reported the prevalence of vitamin D deficiency in PWS.
Algorithm for diagnostics and treatment

Based on our analysis of patients data and the literature review, we defined diagnostic and therapeutic recommendations, presented in the algorithm in Figure 3.

Discussion

We found a large number of undetected health problems among adults with PWS during our systematic health screening. To our knowledge, we are the first to translate this into an evidence-based algorithm for screening and treatment of adults with PWS. We hypothesize that the high prevalence of undiagnosed health problems is the result of unfamiliarity of most physicians with the syndrome, in combination with the complex PWS-specific behavioral phenotype.

Previous studies have reported prevalences of health problems in adults with PWS. However, most studies (11,42,43,46,49-53) did not perform a systematic screening. Of the four studies that performed a systematic health screening (44,45,47,48,58), only two (Laurier et al.(44) and Coupaye et al.(45)) included a substantial number of (over twenty) patients. Six studies (54-57,59,60) performed a systematic screening, but focussed on only one health problem of interest. Compared to the systematic screening described by Laurier et al.(44) and Coupaye et al.(45), we found a lower prevalence of DM2, scoliosis and hypothyroidism. The difference in the prevalence of DM2 could be partly explained by the large difference in BMI, which was much lower in our cohort than in the French cohorts (Table 7). Moreover, the patients in our cohort had more often been treated with GH during childhood. Although GH treatment may have a short-term negative effect on glucose homeostasis due to increased insulin resistance, GH treatment also improves body composition and exercise tolerance, which has positive effects on glucose metabolism in the long term (69-71).
**PWS homes and non-PWS homes** Patients in specialized PWS homes had a lower BMI and a lower frequency of hypertension than patients living in non-PWS homes. This could probably be largely explained by the age difference between the groups. Another contributing factor could be that patients in a specialized PWS home are subject to strict supervision from trained personnel. In PWS homes, food is kept out of sight and food storages are locked. According to caregivers, this greatly reduces stress and conflicts caused by food-seeking behaviour. We hypothesize it might even prevent stress-related hypertension. The fact that all patients living in PWS homes receive portion controlled meals (as determined by a dietitian) and often exercise under supervision probably explained part of the difference in BMI between patients living in PWS homes and those living in non-PWS homes.

**Fatigue and daytime sleepiness** were very common problems among adults with PWS. According to caregivers, these complaints often prevented them from taking part in day trips and physical activities. Daytime sleepiness is usually attributed to lack of hypothalamic arousal, and regarded as a problem that is inherent to the syndrome. However, when we looked more in detail, all patients with clinically relevant fatigue or daytime sleepiness had treatable underlying problems like sleep apnea, narcolepsia, nycturia, vitamin D deficiency, untreated male hypogonadism or use of drugs that can cause sleepiness. Although we could not perform a randomized controlled trial to assess whether treating these underlying problems resolved the complaints, our clinical experience is that the majority of the patients reported less fatigue after treatment of the underlying cause. Also, caregivers reported that these patients were more actively participating in daily activities. This indicates that daytime sleepiness is not necessarily just ‘part of the syndrome’, but could be the symptom of an underlying, treatable problem. Treating the underlying cause is important to reduce daytime sleepiness and increase physical activity.
Vitamin D deficiency and hypogonadism are frequently present in adults with PWS. Low levels of vitamin D and testosterone are often attributed to obesity, as vitamin D is fat-soluble and testosterone production can be diminished by increased estradiol levels due to adipose tissue aromatase activity. However, also lean male patients had hypogonadism and vitamin D deficiency. Although there is no consensus on the clinical effects of vitamin D (25,72-74), we found a clear relation between (the severity of) vitamin D deficiency and daytime sleepiness. Although the cause of daytime sleepiness in this complex patient population is likely to be multifactorial, we believe that prescribing vitamin D may be beneficial for all PWS adults with vitamin D deficiency. The high prevalence of osteoporosis and osteopenia in adults with PWS combined with the fact that vitamin D knows little side effects (75) are additional arguments for treatment. Therefore, we recommend prescribing vitamin D supplementation in all adults with PWS with a vitamin D level below 50 ng/mL.

Creatinine levels were low in the majority of patients, regardless of sex and BMI. This indicates that normal creatinine in patients with PWS are lower than in healthy controls, which is explained by their low muscle mass (13). Therefore, in PWS patients, presence of high-normal creatinine levels might actually indicate impaired renal function. We recommend to adjust reference values with 24% for males and 18% for females. In our hospital, the PWS-specific reference range for creatinine is 46 – 93 µmol/L (compared to 65 - 115 µmol/L for non-PWS adult males) and 37 – 76 µmol/L for females (compared to 55-90 µmol/L for non-PWS adult females). For the same reasons, we propose to use PWS-specific reference values for eGFR of >98 ml/min/1.73 m² for PWS adult males and >93 ml/min/1.73 m² for PWS adult females.
Adrenal insufficiency is rare in adults with PWS (68). However, in case of clinical signs of hypocortisolism, we recommend to assess the hypothalamic-pituitary-adrenal axis using the metyrapone test or, in the absence of contra-indications, the insulin tolerance test (ITT), see Figure 3.

Strengths and limitations Like every study, our study has strengths and limitations. Strengths of our study are the large sample size, considering the fact that PWS is a rare syndrome. Also the focus on adults and the fact that we investigated health problems in relation to living situation, body mass index, genotype and demographic factors makes our study a powerful source of new information. Limitations may include selection bias (due to selective referral to our specialized facility) and survival bias. Moreover, we have many missing values for osteoporosis and sleep apnea. These additional tests were not always performed because they were not indicated, or impossible due to behavioural issues. Therefore these results should be interpreted with caution.

In conclusion, we found undetected health problems in 61% of adults with PWS. On top of this, one third of the patients had clinically relevant fatigue or daytime sleepiness which, according to caregivers, prevented them from taking part in physical activities. Although daytime sleepiness is usually considered just ‘part of the syndrome’, all of these patients turned out to have treatable causes like sleep apnea, narcolepsy, nycturia, vitamin D deficiency, untreated male hypogonadism or use of drugs that can cause sleepiness. Therefore, fatigue and daytime sleepiness should be considered not just ‘part of the syndrome’, but the symptom of an underlying health problem. We recommend to explore and treat these underlying causes, in order to optimize physical activity and prevent obesity-related cardiopulmonary problems. We provide an algorithm for diagnostics and treatment, taking into account PWS-specific pitfalls like falsely-low creatinine levels and false-normal cardiac markers. Use of the algorithm will optimize mental and physical health of adults with PWS. This will improve exercise tolerance and reduce the personal and financial burden of cardiopulmonary complications in this vulnerable patient group.
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DATA AVAILABILITY

The datasets generated during and / or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.
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Legends for tables and figures

Table 1. Baseline characteristics of 115 adults with Prader-Willi syndrome
Abbreviations: body mass index (BMI), imprinting center defect (ICD), interquartile range (IQR), maternal uniparental disomy (mUPD), Prader-Willi syndrome (PWS). a In 11 patients with an mUPD, the parents were not available for genetic testing. Therefore, mUPD is the most likely genotype, but an ICD could not be ruled out in these patients.

Table 2. Health problems in 115 adults with PWS before and after systematic screening
Data are presented as n (% of total). a (Caregivers of) 16 female patients did not recall whether they had had a normal menstrual cycle before the start of oral contraceptives or before reaching menopausal age. b Twenty-eight patients had clear scoliosis at physical examination, but X-ray was not performed due to practical / behavioural issues, 55 cases were radiologically confirmed. c Four patients received antihypertensive medication before screening, but the indication was unknown. d Blood pressure was high in 2 patients, but the measurement was not repeated due to practical / behavioural issues. e In 2 patients vitamin D was not measured and 44 patients used vitamin D supplementation before the screening, but it was unknown whether they had low vitamin D values before the start of vitamin D supplementation.

Table 3. Health problems according to living situation and genotype
Data are presented as n (% of total). Abbreviations: body mass index (BMI), interquartile range (IQR), maternal uniparental disomy (mUPD). a Patients living in a specialized Prader-Willi syndrome group home. b Patients living in a non-specialized group home. c Patients living with family. d Undiagnosed health problems are: hypogonadism, hypothyroidism, type 2 diabetes mellitus, hypertension, hypercholesterolemia, scoliosis and vitamin D deficiency. e Not applicable as hypogonadism is present in 100%, regardless of patient characteristics. f (Caregivers of) 16 female patients did not recall whether they had had a normal menstrual cycle before the start of oral contraceptives or before reaching menopausal age. g In 2 patients vitamin D was not measured and 44 patients used vitamin D supplementation before the screening, but it was unknown whether they had low vitamin D values before the start of vitamin D supplementation. h A P-value could not be calculated due to selective missings.

Table 4. Health problems according to BMI, age and gender
Abbreviations: body mass index (BMI), interquartile range (IQR). a P-value calculated with BMI and age as continuous variables. b P-value corrected for age using regression models. c P-value corrected for BMI using regression models. d A P-value could not be calculated due to selective missings.
Table 5. Fatigue and daytime sleepiness and potential underlying causes

Abbreviations: treated (T), untreated (UT), vitamin D (Vit D). Physical complaints were scored on a 5-point Likert scale. A score of 3 or higher was seen as clinically relevant (+), a score below 3 was seen as not clinically relevant (−). a Treated with testosterone replacement therapy. b Untreated hypogonadism.

Table 6. Patient characteristics of cohorts assessed by previous studies

Abbreviations: body mass index (BMI), females (F), growth hormone (GH), interviews (I), imprinting center defect (ICD), males (M), medical records (MR), maternal uniparental disomy (mUPD), paternal deletion (deletion), physical examination (PE), questionnaires (Q), systematic screening (SS). Systematic screening is defined as a systematic analysis of all outcomes in which all patients are subject to I, PE, Q, laboratory analysis and/or additional testing in order to detect or exclude each diagnosis. a When a subgroup analysis was performed, the N and age range for the adult group (15 years or older) is reported. b Approximation based on mean weight and height in the total population. c Percentages or values based on the whole cohort of children and adults as the values for the adult group alone are unknown. d BMI level at greatest weight. e Patients with current GH treatment were excluded.

Table 7. Health problems assessed by previous studies

Abbreviations: female s (F); laboratory measurements, diagnosis of hypogonadism was based on LH, FSH and/or estrogen (LM); males (M); menstrual cycle, diagnosis of hypogonadism was based on amenorrhea or oligomenorrhea (MC); replacement therapy, diagnosis of hypogonadism was based on use of estrogen (RT). a 58% hypogonadism in females was reported, however the method of evaluation was not described. b Percentages or values based on the whole cohort of children and adults as the values for the adult group alone are unknown. c Reported, but to our knowledge not based on systematic screening. d Total cholesterol was less than 5 mmol/liter in 16 of 19 patients and 7 patients had LDL cholesterol above 3 mmol/liter, but the highest level found was 4.2 mmol/liter. e Hyperlipidemia in 10% (hypercholesterolemia was not described). f Dyslipidemia in 54% (hypercholesterolemia was not described). g As polysomnography and DEXA scans are not always indicated or feasible, we had many missing values for sleep apnea and osteoporosis. As the missing values were not random, we were only able to provide ranges for the prevalence of sleep apnea and osteoporosis.
Figure 1. Factors contributing to cardiopulmonary disease in patients with PWS

Abbreviations: BMR (basal metabolic rate), diet (dietitian), endo (endocrinologist), ID (physician for people with intellectual disabilities), lean body mass (LBM), OAHS (obesity associated hypoventilation syndrome), physio (physiotherapist), psych (psychologist). Legend: Black arrows indicate a cause and effect relationship. The dotted lines indicate an intervention. The • stands for an intervention with medication. Black borders indicate that the factor is inherent to the syndrome. The dotted black border indicates that the factor is inherent to the syndrome, but can be aggravated by cardiopulmonary disease. (12-39)

Figure 2. Health problems detected by systematic health screening in 115 adults with PWS

Legend: In black the percentage of health problems already diagnosed before the screening. In gray the health problems that were revealed by the screening.

Figure 3. Algorithm for diagnostics and treatment in adults with PWS

Abbreviations: body mass index (BMI), dual energy X-ray absorptiometry (DEXA), follicle-stimulating hormone (FSH), free thyroxin (FT4), hemoglobin A1c (HbA1c), insulin tolerance test (ITT), low density lipoprotein (LDL), luteinizing hormone (LH), metyrapone test (MTP), sex hormone binding globulin (SHBG). a Recommendation based on expert opinion and literature review (65-67). b Based on data published previously (68).
Table 1. Baseline characteristics of 115 adults with Prader-Willi syndrome

| Characteristic                                      | Total | N = 115 |
|-----------------------------------------------------|-------|---------|
| **Age in years, median [IQR]**                      |       |         |
| BMI in kg/m², median [IQR]                          |       |         |
| Male gender, n (%)                                  |       |         |
| Genetic subtype                                     |       |         |
| Deletion, n (%)                                     | 64 (56%) |        |
| mUPD, n (%)                                         | 41 (36%) |        |
| ICD, n (%)                                          | 3 (3%) |         |
| Unknown, n (%)                                      | 7 (6%) |         |
| Growth hormone treatment                            |       |         |
| Only during childhood, n (%)                        | 10 (9%) |        |
| Only during adulthood, n (%)                        | 3 (3%) |         |
| Both, n (%)                                         | 40 (35%) |        |
| Never, n (%)                                        | 62 (54%) |        |
| Current growth hormone treatment, n (%)             | 41 (36%) |        |
| Use of hydrocortisone                               |       |         |
| Daily, n (%)                                        | 4 (4%) |         |
| During physical or psychological stress, n (%)      | 47 (41%) |        |
| Use of estrogen replacement therapy or oral contraceptives, n (%) | 34/59 females (58%) |        |
| Use of levothyroxine, n (%)                         | 17 (15%) |        |
| Living situation                                    |       |         |
| With family, n (%)                                  | 28 (24%) |        |
| In a specialized PWS group home, n (%)              | 23 (20%) |        |
| In a non-specialized group home, n (%)              | 61 (53%) |        |
| Assisted living, n (%)                              | 3 (3%) |         |
| Scholar level                                       |       |         |
| Secondary vocational education, n (%)               | 6 (5%) |         |
| Pre-vocational secondary education, n (%)           | 3 (3%) |         |
| Special education, n (%)                            | 82 (71%) |        |
| No education, n (%)                                 | 4 (4%) |         |
| Unknown, n (%)                                      | 20 (17%) |        |
| Mutism, n (%)                                       | 3 (3%) |         |
| Relationship status                                 |       |         |
| In a relationship with sexual intercourse, n (%)     | 8 (7%) |         |
| In a relationship without sexual intercourse, n (%)  | 18 (16%) |        |
| Not in a relationship, n (%)                        | 76 (66%) |        |
| Unknown, n (%)                                      | 13 (11%) |        |

Abbreviations: body mass index (BMI), imprinting center defect (ICD), interquartile range (IQR), maternal uniparental disomy (mUPD), Prader-Willi syndrome (PWS).

* In 11 patients with an mUPD, the parents were not available for genetic testing. Therefore, mUPD is the most likely genotype, but an ICD could not be ruled out in these patients.
Table 2. Health problems in 115 adults with PWS before and after systematic screening

|                  | Total | Missing |
|------------------|-------|---------|
|                  | N = 115 |         |
|                  | Before Screening | Detected by screening | After screening |
| Hypogonadism     |             |                     |                 |
| Male (n=56)      | 56 (48%) | +52%     | 54 (100%) | 2 |
| Female (n=59)    | 59 (60%) | +33%     | 40 (93%)  | 16a |
| Scoliosis        | 61 (54%) | +20%     | 83 (74%)b | 3 |
| Hypercholesterolemia | 14 (13%) | +6%      | 22 (19%)  | 2 |
| Type 2 diabetes mellitus | 13 (12%) | +5%     | 19 (17%)  | 2 |
| Hypertension     | 17 (15%)c | +3%     | 20 (18%)  | 3d |
| Hypothyroidism   | 17 (15%) | +2%      | 19 (17%)  | 0 |
| Vitamin D deficiency | 26 (38%) | +40%     | 54 (78%)  | 46a |
| Severe vitamin D deficiency |         |         | 8 (13%)  | 55 |
| Total undiagnosed health problems | 70 (61%) |         |         | |
| At least one     |         |         |         | |
| At least two     | 28 (24%) |         |         | |
| Three or more    | 10 (9%)  |         |         | |

Data are presented as n (% of total).a (Caregivers of) 16 female patients did not recall whether they had had a normal menstrual cycle before the start of oral contraceptives or before reaching menopausal age. b Twenty-eight patients had clear scoliosis at physical examination, but X-ray was not performed due to practical / behavioural issues, 55 cases were radiologically confirmed. c Four patients received antihypertensive medication before screening, but the indication was unknown. d Blood pressure was high in 2 patients, but the measurement was not repeated due to practical / behavioural issues.e In 2 patients vitamin D was not measured and 44 patients used vitamin D supplementation before the screening, but it was unknown whether they had low vitamin D values before the start of vitamin D supplementation.
Table 3. Health problems according to living situation and genotype

| Missing | PWS homea | Non-PWS homeb | Familyc | P-value | Deletion N = 64 | mUPD N = 41 | P-value |
|---------|-----------|---------------|---------|---------|----------------|-------------|---------|
|         | N = 23 | N = 61 | N = 28 |         |                |             |         |
| Age, median [IQR] | 0 | 26 [21 – 32] | 36 [28 – 50] | 19 [19 – 22] | <0.001 | 28 [21 – 36] | 32 [21 – 49] | 0.2 |
| BMI, median [IQR] | 0 | 27 [22 – 30] | 30 [27 – 40] | 28 [26 – 36] | 0.004 | 31 [26 – 38] | 29 [25 – 34] | 0.3 |
| Undiagnosed health problemsd |         |         |         |         |                |             |         |
| At least one | 9 (39%) | 44 (72%) | 15 (54%) | 0.16 | 37 (58%) | 25 (61%) |         |
| At least two | 2 (9%) | 19 (31%) | 5 (18%) | 0.2 | 14 (22%) | 12 (29%) | 0.7 |
| Three or more | 2 (9%) | 4 (7%) | 4 (14%) |         | 6 (9%) | 3 (7%) |         |
| Hypogonadism |         |         |         |         |                |             |         |
| Male (n=56) | 2 | 9 (100%) | 28 (100%) | 15 (100%) | NAe | 27 (100%) | 19 (100%) | NAe |
| Female (n=59) | 16f | 10 (100%) | 20 (87%) | 10 (100%) | 0.2 | 25 (93%) | 14 (93%) | 0.9 |
| Hypothyroidism |         |         |         |         |                |             |         |
| 0 | 4 (17%) | 12 (20%) | 3 (11%) | 0.6 | 11 (17%) | 7 (17%) | 0.99 |
| Type 2 diabetes mellitus |         |         |         |         |                |             |         |
| 2 | 2 (9%) | 13 (22%) | 3 (11%) | 0.2 | 8 (13%) | 10 (24%) | 0.1 |
| Hypertension |         |         |         |         |                |             |         |
| 3 | 0 (0%) | 17 (29%) | 2 (7%) | 0.002 | 9 (15%) | 8 (20%) | 0.5 |
| Hypercholesterolemia |         |         |         |         |                |             |         |
| 2 | 4 (17%) | 15 (25%) | 2 (7%) | 0.1 | 11 (17%) | 8 (20%) | 0.7 |
| Scoliosis |         |         |         |         |                |             |         |
| 3 | 18 (78%) | 44 (76%) | 19 (68%) | 0.6 | 51 (81%) | 23 (59%) | 0.02 |
| Vitamin D deficiency | 46g | 14 (88%) | 22 (85%) | 16 (64%) | NAh | 33 (80%) | 19 (76%) | NAh |

Data are presented as n (% of total). Abbreviations: body mass index (BMI), interquartile range (IQR), maternal uniparental disomy (mUPD). a Patients living in a specialized Prader-Willi syndrome group home. b Patients living in a non-specialized group home. c Patients living with family. d Undiagnosed health problems are: hypogonadism, hypothyroidism, type 2 diabetes mellitus, hypertension, hypercholesterolemia, scoliosis and vitamin D deficiency. e Not applicable as hypogonadism is present in 100%, regardless of patient characteristics. f (Caregivers of) 16 female patients did not recall whether they had had a normal menstrual cycle before the start of oral contraceptives or before reaching menopausal age. g In 2 patients vitamin D was not measured and 44 patients used vitamin D supplementation before the screening, but it was unknown whether they had low vitamin D values before the start of vitamin D supplementation. h A P-value could not be calculated due to selective missings.
Table 4. Health problems according to BMI, age and gender

| BMI <25 kg/m² | BMI 25-30 kg/m² | BMI >30 kg/m² | P-value* | Age < 25 year | Age 25-30 year | Age > 30 year | P-value* | Male N = 56 | Female N = 59 | P-value |
|---------------|-----------------|---------------|----------|---------------|---------------|---------------|----------|-------------|--------------|---------|
| Age, median [IQR] | 24 [20–33] | 27 [20–40] | 32 [25–42] | 0.02 | NA | 20 [19–22] | 28 [26–29] | 41 [34–52] | NA | NA | 31 [20–43] | 28 [22–38] | 0.5 |
| BMI median [IQR] | 22 [21–23] | 27 [27–29] | 38 [34–46] | NA | NA | 27 [23–31] | 29 [26–35] | 31 [27–42] | 0.02 | NA | 27 [25–32] | 32 [27–40] | 0.02 |
| Undiagnosed health problems | | | | | | | | | | | | |
| At least one | 8 (33%) | 24 (56%) | 38 (79%) | <0.001 | <0.001 | 19 (44%) | 6 (14%) | 42 (82%) | 0.001 | 0.02 | 37 (66%) | 17 (30%) | 11 (19%) | 0.1 |
| At least two | 2 (8%) | 9 (21%) | 17 (35%) | 3 (7%) | 4 (19%) | 18 (35%) | | | | | | |
| Three or more | 0 (0%) | 4 (9%) | 6 (13%) | | | | | | | | | |
| Hypogonadism | | | | | | | | | | | | |
| Male (n=56) | 11 (100%) | 27 (100%) | 16 (100%) | NA | NA | 20 (100%) | 18 (100%) | 27 (100%) | NA | NA | 54 (100%) | 40 (93%) | NA |
| Female (n=59) | 6 (100%) | 12 (92%) | 22 (92%) | 0.9 | 0.3 | 7 (100%) | 9 (90%) | 13 (87%) | 0.2 | 0.1 | 40 (100%) | 40 (93%) | NA |
| Hypothyroidism | 5 (21%) | 7 (16%) | 7 (15%) | 0.5 | 0.8 | 10 (23%) | 5 (24%) | 4 (8%) | 0.2 | 0.4 | 5 (9%) | 14 (24%) | 0.03 |
| Type 2 diabetes mellitus | 2 (8%) | 7 (17%) | 10 (21%) | 0.2 | 0.6 | 2 (5%) | 2 (10%) | 15 (31%) | 0.2 | 0.4 | 5 (9%) | 14 (24%) | 0.06 |
| Hypertension | 3 (13%) | 6 (15%) | 11 (23%) | 0.4 | 0.7 | 3 (7%) | 1 (5%) | 16 (31%) | <0.001 | <0.001 | 9 (17%) | 11 (19%) | 0.8 |
| Hypercholesterolemia | 4 (17%) | 4 (10%) | 14 (30%) | 0.01 | 0.01 | 3 (7%) | 2 (10%) | 17 (35%) | 0.002 | 0.01 | 10 (18%) | 12 (21%) | 0.7 |
| Scoliosis | 12 (79%) | 30 (71%) | 34 (74%) | 0.3 | 0.2 | 30 (70%) | 19 (90%) | 34 (71%) | 0.9 | 0.5 | 42 (76%) | 41 (72%) | 0.6 |
| Vitamin D deficiency | 12 (75%) | 20 (77%) | 22 (81%) | NA* | NA* | 27 (69%) | 10 (91%) | 17 (89%) | NA* | NA* | 25 (83%) | 29 (74%) | NA* |

Abbreviations: body mass index (BMI), interquartile range (IQR). a P-value calculated with BMI and age as continuous variables. b P-value corrected for age using regression models. c P-value corrected for BMI using regression models. d A P-value could not be calculated due to selective missings.
Table 5. Fatigue and daytime sleepiness and potential underlying causes

|                     | Difficulty sleeping | P-value | Nycturia | P-value | Snoring | P-value | Male hypogonadism | P-value | Hypothyroidism | P-value | Untreated Vit D deficiency | P-value |
|---------------------|---------------------|---------|----------|---------|---------|---------|-------------------|---------|----------------|---------|--------------------------|---------|
| N                   | 84                  | 9       | 66       | 28      | 64      | 32      | 24                | 31      | 96             | 19      | 85                       | 28      |
| Fatigue             | 18 (22%) 4 (44%)    | 0.1     | 12 (18%) | 11 (41%)| 0.03    | 11 (18%)| 12 (41%)         | 0.02    | 4 (19%)        | 7 (28%) | 0.5                      | 18 (23%)| 5 (31%)                   | 0.5     | 15 (22%) 8 (32%)          | 0.3     |
| Daytime sleepiness  | 32 (38%) 8 (89%)    | 0.003   | 23 (35%) | 17 (61%)| 0.02    | 18 (29%)| 22 (71%)         | <0.001  | 7 (33%)        | 17 (65%)| 0.03                     | 35 (44%)| 6 (35%)                   | 0.5     | 25 (36%) 16 (62%)          | 0.02    |

Abbreviations: treated (T), untreated (UT), vitamin D (Vit D). Physical complaints were scored on a 5-point Likert scale. A score of 3 or higher was seen as clinically relevant (‘+’), a score below 3 was seen as not clinically relevant (‘−’). a Treated with testosterone replacement therapy. b Untreated hypogonadism.
| Article                                      | N | Country         | Data-collection | Age range (years)* | Genotype (deletion / mUPD / ICD / translocation) | Sex | Mean BMI (kg/m\(^2\)) | Previous GH treatment (%) |
|---------------------------------------------|---|-----------------|-----------------|-------------------|-------------------------------------------------|-----|------------------------|--------------------------|
| **Papers without systematic screening**     |   |                 |                 |                   |                                                  |     |                        |                          |
| Laurance et al. (1981) (51)                 | 24 | United Kingdom  | NA              | 15-41             | NA                                              | 7 M, 11 F | 13 M, 11 F | NA                      |
| Greenswag (1987) (52)                       | 232| United States of America | Q            | 16-64            | NA                                              | 115 M, 117 F | 34\(^b\) | NA                      |
| Partch et al. (2000) (46)                   | 19 | United Kingdom  | MR, I, PE       | 18-34             | NA                                              | 7 M, 12 F | 46 | NA                      |
| Marzullo et al. (2005) (50)                 | 13 | Italy           | MR              | 18-NA mean ± SD: 27 ± 1 | 85%/15%/-/-                                      | 7 M, 6 F | 46 | 38%                     |
| Butler et al. (2002) (53)                   | 58 | United Kingdom  | I and MR        | 18-46             | NA                                              | 32 M, 26 F | 35 | 13%                     |
| Thomson et al. (2006) (42)                  | 30 | Australia       | State health data sets | 15-48         | 44%/10%/-/-\(^c\) (54% NA)\(^d\)                | 23 M, 23 F | NA | NA                      |
| Sinnema et al. (2011) (43)                  | 102| The Netherlands | I and MR        | 18-66             | 54%/43%/3%/-                                       | 49 M, 53 F | 32 | 13%                     |
| Grugni et al. (2013) (49)                   | 108| Italy           | MR and PE       | 18-43             | 68%/25%/2%/2%\(^c\) (6% NA)                      | 47 M, 61 F | NA | NA                      |
| Proffitt et al. (2019) (11)                 | 202| United States of America | Q            | 0 - 84            | 42%/19%/2%/2%\(^c\) (37% NA)                     | 934 M, 1000\(^c\) | NA | NA                      |
| **Papers with systematic screening**        |   |                 |                 |                   |                                                  |     |                        |                          |
| Hertz et al. (1993) (54)                    | 15 | United States of America | MR after SS  | 18-47             | 47%/-/-/-\(^c\) (53% NA)                          | 7 M, 8 F | 38 | 8%\(^c\)                |
| Richards et al. (1994) (55)                 | 14 | United Kingdom  | SS              | 16-39             | NA                                              | 9 M, 5 F | 30 | NA                      |
| Höybye et al. (2002) (47)                   | 19 | Sweden          | SS              | 17-37             | NA                                              | 10 M, 9 F | 36 | 0%                      |
| Eldar-Geva et al. (2009) (56)               | 10 | Israel          | SS              | 15-32             | 50%/40%/10%/-                                      | 10 F | 36 | 0%                      |
| Nakamura et al. (2009) (57)                 | 34 | Japan           | MR after SS     | 16-51             | 79%/NA/NA/NA\(^c\)                               | NA | NA | NA                      |
| Van Nieuwpoort et al. (2011) (48) & Van Nieuwpoort et al. (2018) (58) | 15 | The Netherlands | SS              | 19-43             | 93%/7%//-/-                                        | 4 M, 11 F | Median: 28 | 27%\(^e\)                |
| Laurier et al. (2015) (44)                  | 154| France          | MR after SS     | 16-54             | 66%/16%/2%/2%\(^c\) (15% NA)                      | 68 M, 86 F | 42 | 24%                     |
| Coupaye et al. (2016) (45)                  | 73 | France          | MR after SS     | 16-58             | 64%/36%/-/-                                        | 35 M, 38 F | Deletion: 41/ | 36%                     |

\(^a\) Data not collected. 
\(^b\) Previous GH treatment. 
\(^c\) Patients with systemic screening. 
\(^d\) Median in non-obese: 26. Median in obese: 45. 
\(^e\) Median: 28. 
\(^f\) Median: 45. 
\(^g\) Median: 28. 
\(^h\) Median: 45.
| Study               | Country | Gender   | Age Range | mUPD | Males | Females |_green| Chart|  
|--------------------|---------|----------|-----------|------|-------|---------|------|------|  
| Fintini et al. (2016) (59) | Italy   | MR after SS | 18-50 | 66%/32%/-/-<sup>c</sup> (2% NA) | 59 M, 86 F | 41 | 15% |  
| Ghergan et al. (2017) (60) | France  | SS       | 16-54    | 65%/28%/2%/- (5% NA) | 26 M, 34 F | 39 | 27% |  
| Pellikaan et al. (2020)    | The Netherlands | MR after SS | 18-72 | 56%/36%/3%/- (6% NA) | 56 M, 59 F | 32 | 46% |  

Abbreviations: body mass index (BMI), females (F), growth hormone (GH), interviews (I), imprinting center defect (ICD), males (M), medical records (MR), maternal uniparental disomy (mUPD), paternal deletion (deletion), physical examination (PE), questionnaires (Q), systematic screening (SS). Systematic screening is defined as a systematic analysis of all outcomes in which all patients are subject to I, PE, Q, laboratory analysis and/or additional testing in order to detect or exclude each diagnosis.<sup>a</sup>

When a subgroup analysis was performed, the N and age range for the adult group (15 years or older) is reported.<sup>b</sup> Approximation based on mean weight and height in the total population.<sup>c</sup> Percentages or values based on the whole cohort of children and adults as the values for the adult group alone are unknown.<sup>d</sup> BMI level at greatest weight.<sup>e</sup> Patients with current GH treatment were excluded.
Table 7. Health problems assessed by previous studies

| Article                        | Hypertension (%) | Type 2 diabetes mellitus (%) | Hypercholesterolemia (%) | Sleep apnea (%) | Scoliosis (%) | Osteoporosis (%) | Hypogonadism (%) | Hypothyroidism (%) |
|-------------------------------|------------------|-----------------------------|--------------------------|-----------------|--------------|------------------|------------------|--------------------|
| Laurance et al. (1981) (51)   | -                | 17%                         | -                        | -               | 58%          | -                | 92% F (MC)        | -                  |
| Greenswag (1987) (52)         | 17%              | 19%                         | -                        | -               | ± 50%        | -                | 94% F (MC)        | -                  |
| Partsch et al. (2000) (46)    | 16%              | 16%                         | 37%                      | 58%             | 37%          | -                | 100% M / 100% F (MC) | -                  |
| Marzullo et al. (2005) (50)   | 23%              | 8%                          | -                        | -               | -            | -                | 100% F (MC)       | -                  |
| Butler et al. (2002) (53)     | 13%              | 24%                         | -                        | -               | 34%          | 2%               | -                | -                  |
| Thomson et al. (2006) (42)    | -                | 13%                         | -                        | -               | 37%          | 3%               | 58% F, 100% F (MC) | -                  |
| Sinnema et al. (2011) (43)    | 9%               | 17%                         | -                        | -               | 10%          | 56%              | 16%              | 91% F (MC)         | 9%                 |
| Grugni et al. (2013) (49)     | 48%              | 21%                         | -                        | -               | -            | -                | -                | 5%                 |
| Proffitt et al. (2019) (11)   | -                | -                           | -                        | 45%b            | 33%b         | 9%b              | -                | 9%b                |
| Hertz et al. (1993) (54)      | -                | -                           | 7%                       | -               | -            | -                | -                | -                  |
| Richards et al. (1994) (55)   | -                | 29%c                        | 86%                      | -               | -            | -                | -                | -                  |
| Höybye et al. (2002) (47)     | 21%              | 5%                          | -                        | -               | -            | Osteoporosis: 21% | 63% (LM)         | 0%                 |
| Eldar-Geva et al. (2009) (56) | -                | 10%c                        | -                        | -               | -            | -                | 40% F (LM), 100% F (MC) | -                  |
| Nakamura et al. (2009) (57)   | -                | -                           | -                        | -               | 44%          | -                | -                | -                  |
| Van Nieuwpoort et al. (2011) (48) & Van Nieuwpoort et al. (2018) (58) | - | 7% | - | - | - | Osteoporosis: 13% | 100% M / 82% F (MC) | 13% |
| Laurier et al. (2015) (44)    | 25%              | 25%                         | -                        | -               | 35%          | 75%              | -                | 26%                |
| Coupaye et al. (2016) (45)    | 16%              | 19%                         | 10%                      | -               | 78%          | -                | 96% (LM + RT)      | 26%                |
| Fintini et al. (2016) (59)    | -                | 21%                         | -                        | -               | -            | -                | -                | -                  |
Abbreviations: female s (F); laboratory measurements, diagnosis of hypogonadism was based on LH, FSH and/or estrogen (LM); males (M); menstrual cycle, diagnosis of hypogonadism was based on amenorrhea or oligomenorrhea (MC); replacement therapy, diagnosis of hypogonadism was based on use of estrogen (RT).

a 58% hypogonadism in females was reported, however the method of evaluation was not described. b Percentages or values based on the whole cohort of children and adults as the values for the adult group alone are unknown. c Reported, but to our knowledge not based on systematic screening. d Total cholesterol was less than 5 mmol/liter in 16 of 19 patients and 7 patients had LDL cholesterol above 3 mmol/liter, but the highest level found was 4.2 mmol/liter. e Hyperlipidemia in 10% (hypercholesterolemia was not described). f Dyslipidemia in 54% (hypercholesterolemia was not described). g As poly(somno)graphy and DEXA scans are not always indicated or feasible, we had many missing values for sleep apnea and osteoporosis. As the missing values were not random, we were only able to provide ranges for the prevalence of sleep apnea and osteoporosis.
Figure 1. Factors contributing to cardiopulmonary disease in patients with PWS

Abbreviations: BMR (basal metabolic rate), diet (dietitian), endo (endocrinologist), ID (physician for people with intellectual disabilities), lean body mass (LBM), OAHS (obesity associated hypoventilation syndrome), physio (physiotherapist), psych (psychologist). Legend: Black arrows indicate a cause and effect relationship. The dotted lines indicate an intervention. The ☠ stands for an intervention with medication. Black borders indicate that the factor is inherent to the syndrome. The dotted black border indicates that the factor is inherent to the syndrome, but can be aggravated by cardiopulmonary disease. (12-39)
Figure 2. Health problems detected by systematic health screening in 115 adults with PWS

Legend: In black the percentage of health problems already diagnosed before the screening. In gray the health problems that were revealed by the screening.
Figure 3. Algorithm for diagnostics and treatment in adults with PWS

Abbreviations: body mass index (BMI), dual energy X-ray absorptiometry (DEXA), follicle-stimulating hormone (FSH), free thyroxin (FT4), hemoglobin A1c (HbA1c), insulin tolerance test (ITT), low density lipoprotein (LDL), luteinizing hormone (LH), metyrapone test (MTP), sex hormone binding globulin (SHBG). a Recommendation based on expert opinion and literature review (65-67). b Based on data published previously (68).