Supplementary data

Title: Missed Diagnoses and Health Problems in Adults With Prader-Willi Syndrome: Recommendations for Screening and Treatment

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Table S1a. Baseline characteristics by living situation

	PWS home[a] *N = 23*	**Non-PWS home**[b] *N = 61*	**Family**[c] *N=28*
Age in years, median [IQR]	26 [21 – 32]	36 [28 – 50]	19 [19 – 22]
BMI in kg/m^2, median [IQR]	27 [22 – 30]	30 [27 – 40]	28 [26 – 36]
Male gender, n (%)	9 (39%)	30 (49%)	15 (54%)
Genetic subtype			
Deletion, n (%)	16 (70%)	27 (44%)	18 (64%)
mUPD, n (%)[d]	6 (26%)	28 (46%)	7 (25%)
ICD, n (%)	0 (0%)	1 (2%)	2 (7%)
Unknown, n (%)	1 (4%)	5 (8%)	1 (4%)
Growth hormone treatment			
Only during childhood, n (%)	0 (0%)	6 (10%)	3 (11%)
Only during adulthood, n (%)	3 (13%)	0 (0%)	0 (0%)
Both, n (%)	12 (52%)	9 (15%)	19 (68%)
Never, n (%)	8 (35%)	46 (75%)	6 (22%)
Current growth hormone treatment, n (%)	14 (61%)	8 (13%)	19 (68%)
Use of hydrocortisone			
Daily, n (%)	0 (0%)	2 (3%)	2 (7%)
During physical or psychological stress, n (%)	16 (70%)	13 (21%)	17 (61%)
Scholar level			
Secondary vocational education, n (%)	0 (0%)	0 (0%)	4 (14%)
Pre-vocational secondary education, n (%)	1 (4%)	0 (0%)	2 (7%)
Special education, n (%)	16 (70%)	46 (75%)	19 (68%)
No education, n (%)	1 (4%)	3 (5%)	0 (0%)
Unknown, n (%)	5 (22%)	12 (20%)	3 (11%)
Mutism, n (%)	0 (0%)	3 (5%)	0 (0%)
Relationship status			
In a relationship with sexual intercourse, n (%)	0 (0%)	5 (8%)	2 (7%)
In a relationship without sexual intercourse, n (%)	5 (22%)	7 (12%)	5 (18%)
Not in a relationship, n (%)	14 (61%)	40 (66%)	21 (75%)
Unknown, n (%)	4 (17%)	9 (15%)	0 (0%)

Abbreviations: body mass index (BMI), interquartile range (IQR).

[a] Patients living in a specialized Prader-Willi syndrome home. [b] Patients living in a non-specialized group home.

[c] Patients living with family. [d] In 11 patients with an mUPD, the parents were not available for genetic testing.

Therefore, an ICD could not be ruled out with total certainty in these patients.

Table S1b. Baseline characteristics by genotype

	Deletion *N = 64*	**mUPD**[a] *N = 41*	**Other** *N = 10*
Age in years, median [IQR]	28 [21 – 36]	32 [21 – 49]	26 [22 – 48]
BMI in kg/m^2, median [IQR]	31 [26 – 38]	29 [25 – 34]	27 [24 – 28]
Male gender, n (%)	28 (44%)	20 (49%)	8 (80%)
Growth hormone treatment			
Only during childhood, n (%)	7 (11%)	1 (2%)	2 (20%)
Only during adulthood, n (%)	3 (5%)	0 (0%)	0 (0%)
Both, n (%)	20 (31%)	16 (39%)	4 (40%)
Never, n (%)	34 (53%)	24 (59%)	4 (40%)
Current growth hormone treatment, n (%)	22 (34%)	15 (37%)	4 (40%)
Use of hydrocortisone			
Daily, n (%)	3 (5%)	1 (2%)	0 (0%)
During physical or psychological stress, n (%)	24 (38%)	18 (44%)	5 (50%)
Living situation			
With family, n (%)	18 (28%)	7 (17%)	3 (30%)
In a specialized Prader-Willi group home, n (%)	16 (25%)	6 (15%)	1 (10%)
In a non-specialized group home, n (%)	27 (42%)	28 (68%)	6 (60%)
Assisted living, n (%)	3 (5%)	0 (0%)	0 (0%)
Scholar level			
Secondary vocational education, n (%)	6 (9%)	0 (0%)	0 (0%)
Pre-vocational secondary education, n (%)	1 (2%)	1 (2%)	1 (10%)
Special education, n (%)	46 (72%)	31 (76%)	5 (50%)
No education, n (%)	0 (0%)	4 (10%)	0 (0%)
Unknown, n (%)	11 (17%)	5 (12%)	4 (40%)
Mutism, n (%)	0 (0%)	2 (5%)	1 (10%)
Relationship status			
In a relationship with sexual intercourse, n (%)	6 (9%)	2 (5%)	0 (0%)
In a relationship without sexual intercourse, n (%)	15 (23%)	2 (5%)	1 (10%)
Not in a relationship, n (%)	41 (64%)	30 (73%)	5 (50%)
Unknown, n (%)	1 (2%)	7 (17%)	4 (40%)

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

[a] In 11 patients with an mUPD, the parents were not available for genetic testing. Therefore, an ICD could not be ruled out with total certainty in these patients.

Table S2a. Health problems before and after our systematic screening by living situation

	PWS home[a] *N = 23*			Non-PWS home[b] *N = 61*			Family[c] *N=28*			P-value
	Before	**After**	**Missing**	**Before**	**After**	**Missing**	**Before**	**After**	**Missing**	
Hypogonadism										
Male (n=54)	5 (56%)	9 (100%)	0	10 (36%)	28 (100%)	2	10 (67%)	15 (100%)	0	NA
Female (n=58)[d]	10 (100%)	10 (100%)	4	10 (43%)	20 (87%)	8	6 (60%)	10 (100%)	3	0.2
Hypothyroidism	3 (13%)	4 (17%)	0	11 (18%)	12 (20%)	0	3 (11%)	3 (11%)	0	0.6
Type 2 diabetes mellitus	2 (9%)	2 (9%)	0	9 (15%)	13 (22%)	2	1 (4%)	3 (11%)	0	0.2
Hypertension	0 (0%)	0 (0%)	1	11 (19%)	17 (29%)	2	1 (4%)	2 (7%)	0	0.002
Hypercholesterolemia	2 (9%)	4 (17%)	0	9 (15%)	15 (25%)	2	2 (7%)	2 (7%)	0	0.1
Scoliosis	15 (65%)	18 (78%)	0	31 (53%)	44 (76%)	3	14 (50%)	19 (68%)	0	0.6
Vitamin D deficiency	11 (69%)	14 (88%)	7	7 (27%)	22 (85%)	35	8 (32%)	16 (64%)	3	

Data are presented as n (%).

All P-values show the difference in both groups after screening.

[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] (Caregivers of) 15 female patients did not recall whether they had had a normal menstrual cycle before the start of oral contraceptives or before reaching menopausal age.

Table S2b. Health problems after our systematic screening by genotype

	Deletion *N = 64*	**Missing**	**mUPD** *N = 41*	**Missing**	P-value
Hypogonadism					
Male (n=48)	27 (100%)	1	19 (100%)	1	NA
Female (n=57)[a]	25 (93%)	9	14 (93%)	6	0.9
Hypothyroidism	11 (17%)	0	7 (17%)	0	0.99
Type 2 diabetes mellitus	8 (13%)	0	10 (24%)	2	0.1
Hypertension	9 (15%)	0	8 (20%)	2	0.5
Hypercholesterolemia	11 (17%)	1	8 (20%)	1	0.7
Scoliosis	51 (81%)	2	23 (59%)	1	0.02
Vitamin D deficiency	33 (80%)	16	19 (76%)	23	

Data are presented as n (%).

Abbreviations: maternal uniparental disomy (mUPD).

[a] (Caregivers of) 15 female patients did not recall whether they had had a normal menstrual cycle before the start of oral contraceptives or before reaching menopausal age.

Table S2c. Health problems after our systematic screening by BMI

	BMI <25 kg/m² *N = 24*	**Missing**	**BMI 25-30 kg/m²** *N = 43*	**Missing**	**BMI >30 kg/m²** *N = 48*	**Missing**	P-value
Hypogonadism							
Male (n=56)	11 (100%)	1	27 (100%)	1	16 (100%)	0	NA
Female (n=59)[a]	6 (100%)	6	12 (92%)	2	22 (92%)	8	0.9
Hypothyroidism	5 (21%)	0	7 (16%)	0	7 (15%)	0	0.5
Type 2 diabetes mellitus	2 (8%)	0	7 (17%)	1	10 (21%)	1	0.2
Hypertension	3 (13%)	0	6 (15%)	2	11 (23%)	1	0.4
Hypercholesterolemia	4 (17%)	0	4 (10%)	1	14 (30%)	1	0.01
Scoliosis	12 (79%)	0	30 (71%)	1	34 (74%)	2	0.3
Vitamin D deficiency	12 (75%)	8	20 (77%)	17	22 (81%)	21	

Data are presented as n (%).

Abbreviations: body mass index (BMI).

[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.

Table S2d. Health problems after our systematic screening by age

	Age < 25 year *N = 43*	**Missing**	**Age 25-30 year** *N = 21*	**Missing**	**Age > 30 year** *N = 51*	**Missing**	P-value
Hypogonadism							
Male (n=59)	20 (100%)	0	7 (100%)	1	27 (100%)	1	NA
Female (n=56)[a]	18 (100%)	5	9 (90%)	3	13 (87%)	8	0.2
Hypothyroidism	10 (23%)	0	5 (24%)	0	4 (8%)	0	0.2
Type 2 diabetes mellitus	2 (5%)	0	2 (10%)	0	15 (31%)	2	<0.001
Hypertension	3 (7%)	1	1 (5%)	2	16 (31%)	0	<0.001
Hypercholesterolemia	3 (7%)	0	2 (10%)	0	17 (35%)	2	0.002
Scoliosis	30 (70%)	0	19 (90%)	0	34 (71%)	3	0.9
Vitamin D deficiency	27 (69%)	4	10 (91%)	10	17 (89%)	32	

Data are presented as n (%).

[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.

Table S2e. Health problems after our systematic screening by gender

	Male *N = 56*	**Missing**	**Female** *N = 59*	**Missing**	P-value
Hypothyroidism	5 (9%)	0	14 (24%)	0	0.03
Type 2 diabetes mellitus	13 (24%)	1	6 (10%)	1	0.06
Hypertension	9 (17%)	2	11 (19%)	1	0.8
Hypercholesterolemia	10 (18%)	1	12 (21%)	1	0.7
Scoliosis	42 (76%)	1	41 (72%)	2	0.6
Vitamin D deficiency	25 (83%)	26	29 (74%)	20	

Data are presented as n (%).

Table S3. Lifestyle and behaviour

	Missing	Total *N = 115*	PWS home[a] *N = 23*	Non-PWS home[b] *N = 61*	Family[c] *N = 28*
Physical exercise <30 minutes a day	0	25 (22%)	0 (0%)	18 (30%)	7 (25%)
No dietitian	0	42 (37%)	3 (13%)	16 (26%)	20 (71%)
Increasing weight	0	44 (38%)	5 (22%)	15 (25%)	15 (54%)
Problems regarding living, work, daytime activities or care takers	24	41 (45%)	5 (22%)	25 (52%)	11 (39%)
Difficulties dealing with behavioural problems	26	42 (47%)	4 (17%)	28 (46%)	9 (32%)

Data are presented as n (%).

[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.

Table S4. Total physical complaints

	Missing	Total *N = 115*
Skin picking	21	53 (56%)
Food seeking behaviour	23	42 (46%)
Daytime sleepiness	19	41 (43%)
Temper tantrums	20	40 (42%)
Leg edema	20	32 (34%)
Snoring	19	32 (33%)
Foot complaints	20	30 (32%)
Nycturia	21	28 (30%)
Fatigue	22	23 (25%)
Feeling cold	22	22 (24%)
Constipation	18	21 (22%)
Thirst	26	19 (21%)
Visual complaints	23	18 (20%)
Stomach ache	20	15 (16%)
Diarrhea	19	15 (16%)
Backache	22	15 (16%)
Pyrosis / ructus	22	13 (14%)
Pica (eating nonfood items)	23	10 (11%)
Sexual problems	22	9 (10%)
Difficulty sleeping	22	9 (10%)
Urinary incontinence	20	9 (9%)
Fecal incontinence	21	6 (6%)
Chestpain	24	4 (4%)
Bone fractures	19	3 (3%)
Orthopnea	25	3 (3%)
Vomiting	20	0 (0%)

Complaints are scored as present when the caregivers indicated a score of 3 or higher on a 5-point Likertscale.

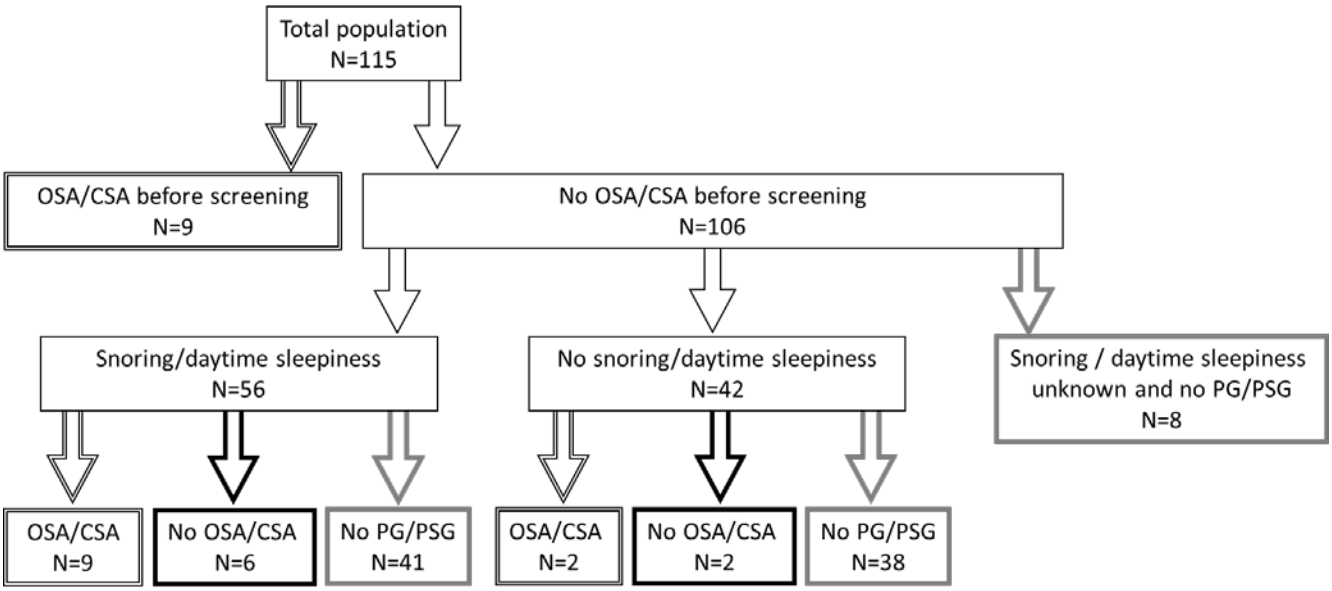
Data are presented as n (%).

Table S5. Liver panel, kidney function, hematopoiesis and electrolyte values of 115 adults with PWS

		N	Reference range	Median [IQR]	Min-max	Patients below LLN, n (%)	Patients above ULN, n (%)
ASAT (U/L)	Male	54	<35	21 [18 – 25]	11 – 82	NA[a]	2 (4%)
	Female	55	<31	20 [17 – 25]	11 – 52		4 (7%)
ALAT (U/L)	Male	54	<45	21 [16 – 28]	10 – 149	NA[a]	5 (9%)
	Female	56	<34	20 [15 – 23]	9 – 76		5 (9%)
ALP (U/L)	Male	52	<115	86 [65 – 107]	17 – 180	NA[a]	8 (15%)
	Female	52	<98	77 [60 – 96]	25 – 211		11 (21%)
GGT (U/L)	Male	54	<55	18 [15 – 27]	9 – 165	NA[a]	2 (4%)
	Female	53	<38	19 [13 – 31]	9 – 85		9 (17%)
Total bilirubin (µmol/L)	Male	48	<17	5.0 [4.0 – 8.0]	3.0 – 25	NA[a]	2 (4%)
	Female	49	<17	4.0 [3.5 – 6.0]	3.0 – 18		1 (2%)
LDH (U/L)	Male	50	<248	200 [170 – 223]	118 – 270	NA[a]	4 (8%)
	Female	50	<247	178 [166 – 213]	132 – 299		5 (10%)
Urea (mmol/L)		107	2.5 – 7.5	4.4 [3.7 – 5.0]	1.8 – 10.6	2 (2%)	3 (3%)
Creatinine (µmol/L)	Male	56	65 – 115	61 [51 – 72]	40 – 109	35 (63%)	0 (0%)
	Female	59	55 – 90	56 [49 – 65]	31 – 89	28 (47%)	0 (0%)
Hemoglobin (mmol/L)	Male	55	8.6 – 10.5	8.9 [8.4 – 9.4]	7.3 – 10.1	17 (31%)	0 (0%)
	Female	53	7.5 – 9.5	8.2 [8.0 – 9.0]	6.8 – 9.7	1 (2%)	1 (2%)
MCV (fL)		111	80 – 100	90 [87 – 92]	78 – 101	1 (1%)	1 (1%)
Sodium (mmol/L)		111	136 – 145	140 [138 – 142]	130 – 145	8 (7%)	0 (0%)
Potassium (mmol/L)		111	3.5 – 5.1	4.3 [4.1 – 4.5]	3.4 – 5.4	1 (1%)	2 (2%)
Calcium (mmol/L)		107	2.20 – 2.65	2.4 [2.3 – 2.5]	1.2 – 4.0	3 (3%)	2 (2%)
Albumin (g/L)		105	35 – 50	45 [42 – 48]	30 – 53	3 (3%)	5 (5%)

Abbreviations: upper limit of normal (ULN), lower limit opf normal (LLN), alanine transaminase (ALAT), alkaline phosphatase (ALP), aspartate transaminase (ASAT), gamma glutamyl transpeptidase (GGT), interquartile range (IQR), lactate dehydrogenase (LDH), mean corpuscular volume (MCV). a Unknown, because LLN not defined.

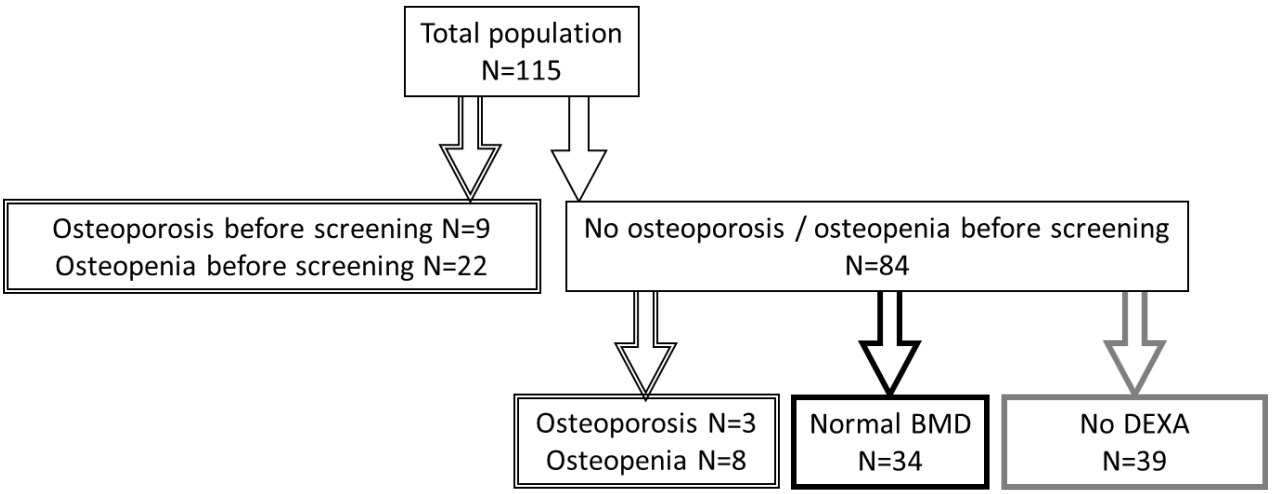
Figure S1. Sleep apnea: clinical data and poly(somno)graphy results



Abbreviations: CSA (central sleep apnea), PG (polygraphy), PSG (polysomnography), OSA (obstructive sleep apnea).

Legens: Grey arrows and squares represent patients in which polygraphy was not performed. Double lined arrows and squares represent patients that were diagnosed with sleep apnea. Bold arrows and squares represent patients in which sleep apnea was excluded.

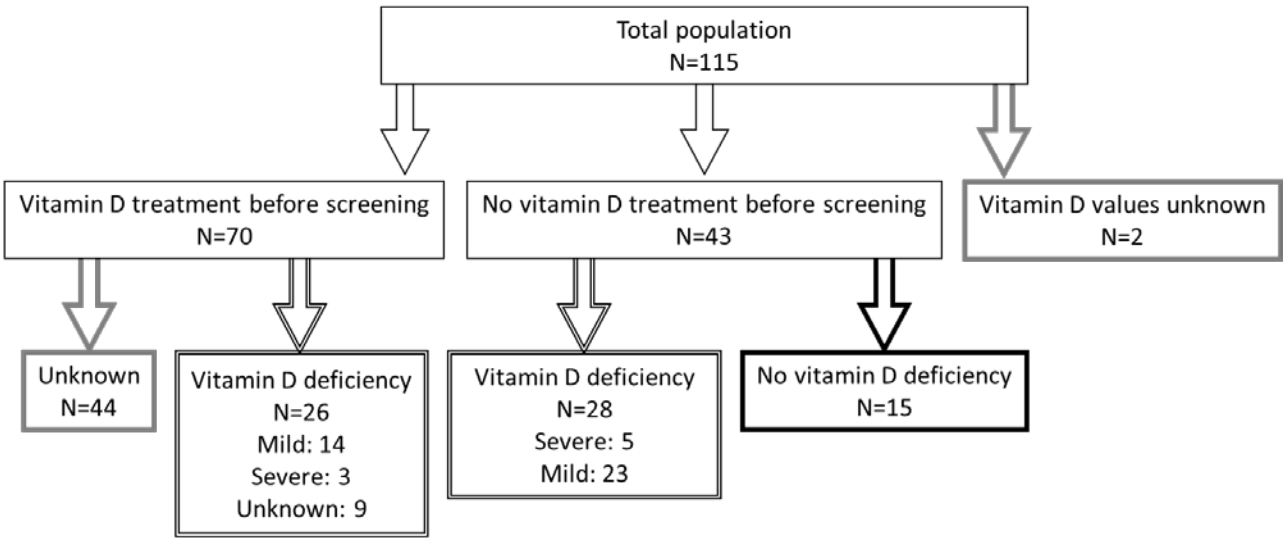
Figure S2. Osteopenia and osteoporosis



Abbreviations: BMD (bone mineral density), DEXA (dual energy X-ray absorptiometry).

Legens: The grey arrow and square represent patients in which DEXA was not performed. Double lined arrows and squares represent patients that were diagnosed with osteoporosis or osteopenia. The bold arrow and square represent patients in which osteoporosis and osteopenia were excluded.

Figure S3. Vitamin D deficiency



Legens: The grey arrow and square represent patients that received vitamin D supplementation before screening for unknown reasons. Double tined arrows and squares represent patients that were diagnosed with vitamin D deficiency. The bold arrow and square represent patients in which vitamin D deficiency was excluded.