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Increasing physical activity in adult women with Prader–Willi syndrome: A transferability study

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12 **Title**

13 Increasing physical activity in adult women with Prader-Willi syndrome: a transferability
14 study

15

16 **Running Title**

17 Physical activity and Prader-Willi syndrome

18

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42

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45

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51

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58

59 **Abstract**

60

61 **Background:** We aimed 1) to objectively quantify spontaneous physical activity (PA) in
62 adult patients with Prader-Willi syndrome (PWS) and 2) to evaluate the transferability of a
63 home-based exercise training program in these patients.

64 **Method:** Physical activity was compared between 10 adult women with PWS (PWS group)
65 and 20 adult women with non-syndromic obesity (CON group, for cross-sectional
66 comparison). In the PWS group, PA, body composition, walking capacity, quality of life and
67 eating behavior were then compared before and after a 16-week supervised exercise program.

68 **Results:** The PWS group displayed lower PA and higher sedentary time compared to the
69 CON group. Median attendance to exercise sessions reached 100% (Q1-Q3: 97-100%)
70 sessions. Moderate-to-vigorous PA and walking capacity increased after the program without
71 significant effect on body composition.

72 **Conclusion:** Supervised home-based exercise sessions are an effective strategy to improve
73 PA in women with PWS who are less active than women matched for adiposity.

74

75 **Keywords:** Obesity, Prader-Willi syndrome, Physical activity, Exercise training,

76 Accelerometers

77 **Introduction**

78

79 Prader-Willi syndrome (PWS) is the most frequent genetic syndrome causing marked obesity
80 (Driscoll, 1993) with a prevalence between one in 20,000 to one in 30,000 births (Bar, 2017;
81 Lioni, 2015). PWS is a complex genetic neurodevelopmental disorder caused by an absence
82 of expression of paternal-origin imprinted alleles on chromosome 15 (Driscoll, 1993). PWS is
83 characterized by hyperphagia, hypotonia and early fat mass gain as well as decreased motor
84 competencies and physical fitness (Capodaglio, 2009; Gross, 2017; Lloret-Linares, 2013).
85 Subsequently, patients with PWS are prone to develop obesity with severe complications,
86 such as cardiac or respiratory failure as well as physical disabilities (Cassidy, 2012).
87 Behavioral approaches for the management of PWS include the promotion of physical
88 activity (PA) (Goldstone, 2008); however, day-to-day management of these patients with
89 cognitive, and sometimes psychiatric disorders, is particularly challenging and little is known
90 about PA interventions in this population.

91

92 In line with current PA guidelines for the general population (PAGAC, 2018), adult patients
93 with obesity are advised to progressively reach a minimum of 150 min of moderate-intensity
94 PA (MVPA) per week consisting of bouts of at least 10 min (Garvey, 2016; Jensen, 2014). In
95 a recent study using accelerometers for the objective assessment of PA, only 15% of adult
96 women with PWS met these recommendations (Nordstrom, 2013). This is in agreement with
97 studies that reported a high prevalence of physical inactivity in women with non-syndromic
98 obesity (Tudor-Locke, 2010). However, given that no comparison was made with a control
99 group of subjects without intellectual disability in the study by Nordstrom et al., it is unclear
100 whether PA is lower in women with PWS compared to women with non-syndromic obesity.
101 Studies conducted in children and adolescents with PWS reported 30% to 55% lower levels

102 of objectively-measured PA compared to both normal-weight and non-syndromic obese
103 controls (Castner, 2014; Eiholzer, 2003; van den Berg-Emons, 2008), suggesting that the low
104 level of PA observed in patients with PWS might be related to obesity *per se* as well as the
105 physical and intellectual disabilities associated with PWS. Additionally, patterns of MVPA
106 and sedentary behavior (i.e. performed in short or longer bouts), which have received
107 growing attention in recent years (Saint-Maurice, 2018; Shiroma, 2013), are not known in
108 adult patients with PWS. Accelerometers are currently the monitoring method of choice for
109 assessing habitual PA and sedentary (sitting) time, especially considering that PA self-
110 reporting is a complex cognitive task that is particularly challenging in patients with PWS
111 (Shephard, 2003).

112

113 Exercise training programs have been found either to increase (Eiholzer, 2003; Schlumpf,
114 2006) or maintain (Rubin, 2019b) habitual PA (i.e. spontaneous PA performed independently
115 of exercise training) in children with PWS but this has not been assessed in adults. As
116 recently reviewed, different types of exercise programs have been conducted in adults with
117 PWS (Morales, 2019) and most programs were supervised and performed in a residential or
118 community setting (Cimolin, 2014; Grolla, 2011; Kaufman, 1995; Shields, 2019;
119 Silverthorne, 1993). This literature review found that residential programs that are organized
120 several times per year and include dietary restriction, a high daily amount of supervised PA
121 and a structured environment substantially reduced body mass over a long-term period
122 (Cimolin, 2014; Grolla, 2011; Kaufman, 1995). A walking program with two weekly sessions
123 for six months was also effective to reduce body mass and body fat and to improve
124 cardiorespiratory fitness (Silverthorne, 1993). Finally, a strength training program including
125 two weekly sessions increased muscle strength (Shields, 2019). Other programs that were
126 conducted at home for six months without any supervision led to improvements in gait

127 patterns but not muscle strength or balance control (Capodaglio, 2011; Vismara, 2010). So
128 far, no study has assessed the effectiveness and transferability of a home-based individually
129 supervised exercise training program in adult patients with PWS. Due to the specific
130 impairment of executive functions and psychopathological features in this syndrome,
131 integration of an exercise program as part of daily routine along with individual interaction
132 with health professionals might be especially important (Chevalere, 2015). Two case reports
133 suggested that a home-based exercise training program supervised by a PA instructor was
134 feasible and well-accepted by children with PWS, although mixed findings were reported on
135 changes in body mass and body composition, habitual PA and physical fitness (Amaro,
136 2016). A recent controlled study conducted in youth with PWS reported that a home-based
137 exercise training program facilitated by parents improved muscle strength and gross motor
138 skill proficiency and decreased body mass in subjects who experienced an increase in
139 objectively-measured MVPA (Rubin, 2019a; Rubin, 2019b).

140

141 Given the lack of data on objective PA in adults with PWS vs non-syndromic obesity and on
142 the effectiveness of home-based supervised exercise training program in adults with PWS, we
143 aimed 1) to quantify habitual PA using accelerometers, including an analysis of MVPA and
144 sedentary bouts, in adults with PWS and in a control group of patients with non-syndromic
145 obesity matched on age and adiposity; 2) to evaluate the transferability and effectiveness of a
146 home-based supervised exercise training program on habitual PA, physical fitness, and body
147 composition.

148

149 **Methods**

150

151 **Study design and participants**

152 The current observational study was conducted in a standard care setting and included 10
153 women with PWS (PWS group) and 20 women with non-syndromic obesity (CON group) to
154 serve as a cross-sectional comparison. Only the women from the PWS group took part in the
155 intervention.

156

157 Participants in the PWS group were recruited from June 2016 to January 2018 among patients
158 with PWS and referred to a reference university clinic for patients with PWS. Inclusion
159 criteria were: genetically confirmed PWS, age between 18 and 60 years, BMI ≥ 30 kg.m⁻² or
160 body fat $\geq 40\%$, no treatment modifications in the previous two months, enrollment in a
161 social security program (patient or beneficiary). Considering the low prevalence of PWS and
162 the low number of patients meeting inclusion criteria, all available patients willing to
163 participate were included in the study. No published data allowed sample size calculations
164 relevant to our hypotheses. Approval was obtained from the Ethics Committee of our
165 institution and the study was registered in the ClinicalTrials.gov Web site (Identifier:
166 NCT03673813). Informed written consent was obtained from all subjects and caregivers prior
167 to study inclusion. Participants in the CON group were recruited among bariatric surgery
168 patients with non-syndromic obesity and had been included in a previous clinical trial
169 (ClinicalTrials.gov Web site: NCT01113996). Data were collected from this group pre-
170 surgery, and details of this study, which was entirely performed at our university medical
171 center, can be found elsewhere (Oppert, 2018). Each participant of the PWS group was
172 individually matched with two control participants for gender, age and percent body fat.
173 Participants from the control group did not participate in the exercise program and their data
174 were used only for cross-sectional comparison of a given set of variables (PA, body
175 composition, handgrip strength).

176

177 To address aim 1, we performed a cross-sectional comparison between PWS and CON
178 groups for habitual PA, body composition and handgrip strength, which were measured using
179 similar procedures in participants from the PWS and CON groups. To address aim 2, we
180 compared pre- and post-interventional habitual PA, walking capacity, postural stability,
181 health-related quality of life and eating behavior in the PWS group. The primary outcomes
182 was changes in accelerometry-assessed habitual PA after the intervention. Secondary
183 outcomes included the changes in body composition, physical function, health-related quality
184 of life and eating behavior following the intervention.

185

186 **Habitual physical activity measurement**

187 PA and sedentary time were measured using a tri-axial GT3x Actigraph accelerometer
188 (Manufacturing Technology, Inc., FL, USA), as previously described (Oppert, 2018).
189 Participants were asked to wear the accelerometers at the hip using an elastic belt for seven
190 consecutive days during all waking hours except during water-based activities. To assess
191 habitual PA, accelerometers were worn before and after the end of the intervention, outside of
192 the exercise training program. Therefore, exercise sessions were not included in the
193 measurement of habitual PA. Data were considered valid when the accelerometer was worn
194 for at least three days for at least eight hours each day. Freedson cutpoints were used to
195 quantify sedentary behavior ($<100 \text{ counts}\cdot\text{min}^{-1}$), light-intensity PA (100 to $1951 \text{ counts}\cdot\text{min}^{-1}$)
196 and moderate-to-vigorous PA (MVPA, $\geq 1952 \text{ counts}\cdot\text{min}^{-1}$) (Freedson, 1998). Because
197 wear time differed between PWS and CON groups, the time spent in each intensity category
198 was expressed as the percentage of total wear time. Thus, the sum of sedentary time, light-
199 intensity PA and MVPA equal to 100% of total wear time.

200 MVPA and sedentary bouts were defined as follows: MVPA bouts of one to 4 four min
201 ($\text{MVPA}_{1-4 \text{ min}}$), five to nine min ($\text{MVPA}_{5-9 \text{ min}}$) and at least 10 min ($\text{MVPA}_{\geq 10 \text{ min}}$); and

202 sedentary bouts of one to nine min ($SED_{1-9 \text{ min}}$), 10 to 29 min ($SED_{10-29 \text{ min}}$) and of at least 30
203 min ($SED_{\geq 30 \text{ min}}$). MVPA $_{\geq 10 \text{ min}}$ bouts were defined as a minimum of 10 consecutive min
204 above 1952 counts.min⁻¹ with allowance of two min below this threshold (Saint-Maurice,
205 2018; Tudor-Locke, 2012). $SED_{\geq 30 \text{ min}}$ bouts were defined as a minimum of 30 consecutive
206 min below 100 counts.min⁻¹ (Tremblay, 2017). Participants reaching 150 min per week of
207 MVPA in ≥ 10 -min bouts were considered compliant with PA guidelines (PAGAC, 2018).

208

209 **Anthropometry and body composition measurement**

210 Body composition was estimated by whole-body fan-beam DXA scanning (Hologic QDR
211 2000, Hologic, France), as previously described (Oppert, 2018). Fat mass index and fat-free
212 mass index were calculated as fat mass and lean body mass, respectively, divided by height
213 squared (kg.m⁻²) (Schutz, 2002).

214

215 **Physical function measurement**

216 Walking capacity was assessed with the six-min walk-test. The test was performed according
217 to the American Thoracic Society recommendations (American Thoracic Society, 2003), with
218 the exception of more frequent encouragements, as previously described in patients with
219 PWS (Nordstrom, 2013). Participants were asked to walk for six min and to cover as much
220 ground as possible between two cones positioned 30 m apart. Handgrip strength was
221 measured with a handgrip dynamometer (Jamar, Sammons Preston Rolyan, Bolingbrook,
222 Canada). Participants sat in a chair with arms close to their sides and elbow flexed at 90° and
223 were asked to provide 5 maximal attempts with each hand (Roberts, 2011). The highest value
224 obtained was kept for analyses. Static balance control was assessed using an unipedal stance
225 test. Participants were asked to stand barefoot on one leg for as long as possible, with the
226 eyes open and the other limb raised (Springer, 2007). Participants performed 3 trials on each

227 leg and the best trial was recorded. For consistency, all tests were undertaken by the same
228 investigator (AB) for participants in the PWS group.

229

230 **Quality of life, eating behavior assessment in patients with PWS**

231 Health-related quality of life was assessed with the 12-item short-form (SF-12) questionnaire
232 and was summarized in a physical and mental component score ranging from zero (poor) to
233 100 (good) (Gandek, 1998). Eating behavior was assessed with the Hyperphagia
234 questionnaire, a tool specifically designed for assessing eating behavior in patients with PWS
235 (Dykens, 2007).

236

237 **Exercise training program in patients with PWS**

238 Patients with PWS participated in a 16-week exercise training program. The program was
239 conceived and implemented in partnership with Siel Bleu, a non-profit organization
240 specialized in delivering PA intervention to patients with chronic diseases and older adults
241 (El-Khoury, 2015). The program included two exercise sessions per week, conducted at home
242 on an individual basis and supervised by a specifically trained PA instructor. Patients were
243 supervised by the same instructor throughout the program. As recommended in PA guidelines
244 for adults with disabilities available at the time the study was designed, exercise sessions
245 were based on a combination of endurance-based and muscle-strengthening activities of
246 moderate intensity (Department of Health and Human Services, 2008). Each training session
247 lasted one hour and included 10 min of a light endurance warm-up, 30 min of moderate-
248 intensity endurance training, 15 min of strength training, and five min of stretching and
249 cooling down. To make training sessions more enjoyable and improve adherence, endurance
250 activities varied along the program and included walking, Nordic walking, orienteering,
251 running, step or stair climbing, ball games (football, basketball, volleyball) and racket games

252 (badminton, tennis table). To supervise intensity, PA instructors regularly asked patients to
253 rate their level of effort and verified that patients were able to talk while performing the
254 activity (PAGAC, 2018). Strength exercises targeting major muscle groups were performed
255 with training equipment such as free weights or elastic bands (sit-to-stand transitions, squats,
256 biceps and triceps curls with free weights, or rowing with an elastic band). Exercises were
257 performed either indoors or outdoors close to home, depending on weather conditions. In
258 addition to the training program, patients and their families were encouraged to increase
259 habitual PA. The program was provided free of charge to the participants.

260

261 **Transferability of the exercise training program**

262 Transferability was assessed using the RE-AIM framework (Glasgow, 1999), as used
263 previously by our research group in a French setting (Bellicha, 2016). The following
264 dimensions were described: Reach (participation to exercise sessions), Effectiveness (patient
265 and family satisfaction assessed with a five-point scale and potential adverse consequences,
266 e.g. injuries, temper outbursts, behavioral changes), Adoption (perception of PA instructors
267 involved in the study), Implementation (the extent to which the program was delivered as
268 intended), and Maintenance (the number of participants who maintained the exercise sessions
269 after the end of the study).

270

271 **Procedures**

272 For the women from the PWS group, all the measures were implemented prior to the
273 intervention and within 2 weeks following the intervention. For the control group, data were
274 collected at a single time point, during the pre-operative visit at our university clinic, as part
275 of standard care.

276

277 **Statistical analysis**

278 Given the limited sample size and the non-normality of most variables, data are presented as
279 median (25th-75th percentile) and non-parametric tests were used. To address aim 1,
280 characteristics of participants in the PWS and CON groups were compared with Mann-
281 Whitney test for continuous variables and with Chi-Square test for categorical variables. To
282 address aim 2, characteristics of participants in the PWS group before and after the exercise
283 training program were compared with Wilcoxon test (continuous variables) and with
284 McNemar test (categorical variables). Pre- to post-intervention changes were expressed as
285 mean (SD). The null hypothesis was rejected at $p < 0.05$. Analyses were performed using R
286 version 3.4.3 (R Core Team, 2017).

287

288 **Results**

289

290 **Aim 1: Comparing clinical characteristics, physical activity and sedentary behavior**
291 **between women with PWS and women with non-syndromic obesity**

292 As expected, patients with PWS were comparable to patients from the CON group in terms of
293 age and percentage body fat but were shorter and had lower BMI, lean body mass and
294 handgrip strength (all $P < 0.05$) (Table 1). Nine participants were given replacement therapy
295 for gonadotropin deficiency and 3 participants for thyrotropin deficiency. Four participants
296 had received growth hormone (GH) treatment during childhood, however, ~~and~~ none had
297 received GH treatment in adulthood.

298

299 The accelerometer was worn during seven days in both groups for a median duration of 12.1
300 hours. d^{-1} in the PWS group and 13.5 hours. d^{-1} in the CON group ($P < 0.001$) (Table 2).

301 Median activity counts were 37% lower in the PWS group compared to CON group ($P < 0.05$).

302 Sedentary time was higher in the PWS group while light-intensity PA was lower in patients
303 with PWS (both $P < 0.001$). Duration of MVPA was not significantly different between
304 groups, although it tended to be lower in the PWS group ($P = 0.11$). $MVPA_{\geq 10 \text{ min}}$ was low in
305 both groups, with no significant difference between groups. Only two participants in the PWS
306 group and one participant in the CON group were compliant with PA guidelines ($P = 0.52$).

307

308 MVPA patterns did not differ between PWS and CON groups (Fig. 1). In the PWS group,
309 $MVPA_{1-4 \text{ min}}$ represented on average 61% of total MVPA, $MVPA_{5-9 \text{ min}}$ represented 21% of
310 total MVPA and $MVPA_{\geq 10 \text{ min}}$ represented 18% of total MVPA (vs. 60%, 27% and 14% in the
311 CON group, respectively). Sedentary patterns differed between groups (Fig. 2): $SED_{1-9 \text{ min}}$
312 bouts were lower in the PWS group (31% of total sedentary time vs. 44% in the CON group,
313 $P < 0.001$) and $SED_{\geq 30 \text{ min}}$ were higher (41% of total sedentary time vs. 18% in the CON
314 group, $P < 0.001$).

315

316 **Aim 2: Assessing the effectiveness and transferability of the exercise training program** 317 **in women with PWS**

318 After the exercise training program, walking capacity increased by mean (SD) 29 (37) m ($P =$
319 0.02) and stance time increased by 4 (6) s ($P = 0.02$) (Table 2) although no effect was found
320 on body weight and composition (Table 1). Total MVPA increased by 11 (13) $\text{min}\cdot\text{d}^{-1}$ ($P <$
321 0.05) and $MVPA_{\geq 10 \text{ min}}$ by 86 (97) $\text{min}\cdot\text{week}^{-1}$ ($P = 0.03$). After the program, three
322 participants (43%) were compliant with PA guidelines. The percentage of MVPA
323 accumulated in $MVPA_{\geq 10 \text{ min}}$ increased to 36% of total MVPA ($P = 0.03$) while MVPA
324 accumulated in $MVPA_{5-9 \text{ min}}$ tended to decrease ($P = 0.05$) (Fig. 1). The physical component
325 of quality of life tended to increase after the program but no effect was found on, sedentary
326 patterns or eating behaviour.

327

328 Patient participation in exercise sessions was very good, with a median (25th-75th percentile)
329 number of exercise sessions attended of 32 (31-32) sessions. Participants and their families
330 were very satisfied with the program as participants scored their satisfaction 4.4 (4.0-5.0) on
331 a five-point scale and their relatives scored their's 4.8 (4.1-5.0). No adverse events occurred
332 during the program. All of the five PA instructors who participated in the program had at
333 least two years of experience with the management of patients with chronic diseases and
334 physical and/or intellectual disability, and all received a specific training on PWS before the
335 program. The main difficulties reported by instructors were related to psychological disorders
336 associated with PWS (emotional lability and immaturity, mental rigidity), physical disorders
337 (increased fatigability, balance disorders and reduced motor skills), and a lack of motivation.
338 One-to-one sessions were seen as an important aspect to personalize exercises and general
339 advice about PA and to improve the patient-care provider relationship. All instructors
340 declared that they sometimes had to adapt the exercise sessions according to the patient's
341 motivation, mood, or fatigue. Mainly, the type of endurance-based activities performed was
342 chosen by the instructor in agreement with the patient to make the sessions more enjoyable
343 and to increase motivation. The most frequently performed activities were walking (66%
344 sessions), Nordic walking (19% sessions), ball games (12% sessions), racket games (6%
345 sessions), step or stair climbing (4%), orienteering (3% sessions), cycling (3% sessions), and
346 running (2% sessions). Finally, three participants continued exercise sessions (two to two
347 weekly sessions) at their own expense with the same organization after the end of the study,
348 i.e. from 4 four months after the end of the program.

349

350 **Discussion**

351 This study provides a detailed analysis of habitual PA and sedentary patterns in adult women
352 with PWS. Compared to control women matched for age and adiposity, total PA assessed
353 with accelerometers was lower and sedentary time was higher in patients with PWS. Our data
354 also demonstrate the effectiveness and feasibility of an exercise program including one-on-
355 one sessions of endurance and strength exercises for patients with PWS, when conducted at
356 the participant's home or community setting and supervised by the same PA instructor
357 throughout the program.

358

359 In our sample of participants with PWS, the amount of PA assessed as accelerometer counts
360 per min was found to be 37% lower in patients with PWS compared to the CON group.
361 Sedentary time accounted for almost two-quarters of accelerometer wear time, which was
362 comparable to values previously reported in adult women with PWS (Nordstrom, 2013). This
363 was, however, higher than values obtained in our CON group or previously reported in
364 subjects with severe obesity (King, 2015). Participants in the PWS group were also
365 characterized by more prolonged, uninterrupted sedentary bouts. Prolonged bouts of 30 min
366 or longer accounted for more than 40% of total sedentary time, more than two-fold the values
367 obtained in the CON group. We found no other study examining PA in PWS to compare
368 these data to. The increase in sedentary time in the PWS group was mainly explained by a
369 decrease in light-intensity PA, and to a lesser extent, by a decrease in MVPA. Previous
370 studies have reported a lower duration of light-intensity PA in youth with PWS and a trend
371 for a lower duration of MVPA (Castner, 2014; Rubin, 2018).

372

373 After the exercise training program, total MVPA increased by more than two-fold and MVPA
374 spent in bouts of ≥ 10 min increased from five to 90 min per week. Despite this substantial
375 increase in MVPA, more than half of the participants remained insufficiently active.

376 Sedentary time and patterns, as well as light-intensity PA, did not change after the program.
377 Growing evidence suggests that breaking prolonged sedentary bouts with short bouts of light-
378 intensity PA elicits cardiometabolic benefits (Duvivier, 2018). Interestingly, the
379 cardiometabolic risks associated with an increase in sedentary time might be higher in
380 subjects with lower levels of MVPA (Biswas, 2015). Improvements in cardiometabolic
381 factors have been reported after a PA intervention in patients with PWS (Kaufman, 1995;
382 Rubin, 2018). It should be noted, however, that the study by Kaufman et al. (1995) also
383 included a nutritional intervention, and the study by Rubin et al. (2018) reported higher
384 metabolic benefits in patients who experienced no gain or a decrease in body fat. Thus, the
385 cardiometabolic benefits described cannot be attributed solely to the PA program. More
386 studies are needed to better understand the contribution of PA to the cardiometabolic health
387 of patients with PWS.

388
389 Another important objective of this study was to assess the transferability of a four-month
390 exercise training program in participants with PWS. Participation in exercise sessions was
391 excellent, as well as the satisfaction from both participants and their families. Studies that
392 implemented home-based exercise training programs, either supervised or non-supervised,
393 usually reported high participation in exercise sessions compared to programs based outside
394 the home (Amaro, 2016; Capodaglio, 2011; Rubin, 2019b). Instructors involved in this
395 program reported they had to adapt to the participants' psychological and cognitive disorders
396 and physical limitations associated with PWS, and sometimes to patients' fatigue and lack of
397 motivation. Individual interaction was found to be very important to build-up confidence,
398 improve the patient-health professional relationship, and promote self-esteem in these very
399 sensitive patients. This study showed the potential of transferability of a home-based
400 supervised exercise training program in patients with PWS, even though the sample size was

401 rather small. The data also suggest the need to involve experienced PA instructors with a
402 well-developed capacity to adapt exercise programs and make the sessions enjoyable with
403 these patients.

404

405 The program was effective to improve physical function although no change in body weight
406 or body composition was found. Previous studies that reported significant weight loss after a
407 PA intervention in adult patients with PWS also included a dietary intervention (Cimolin,
408 2014; Grolla, 2011). Given the major importance of restricting food intake for obtaining
409 negative energy balance, the expected benefit of PA alone should not be to lose weight but
410 rather to focus on improving physical function or metabolic outcomes. A significant 30-m
411 improvement in walking distance was observed after the program, which is consistent with
412 studies that previously examined a three- to four-month exercise training programs in
413 subjects with severe obesity (Baillot, 2014; Marcon, 2017). This suggests that exercise
414 training could be equally effective to increase walking capacity in patients with PWS or with
415 common obesity. To increase the generalizability of such findings, future research should
416 investigate whether this type of home-based supervised exercise training program is effective
417 in adult patients with other forms of genetic (e.g. Bardet-Biedl) or hypothalamic lesional (e.g.
418 craniopharyngioma) obesity, who represent up to five percent of obesity cases (Huvenne,
419 2016), and more broadly in individuals with intellectual disabilities, who often present with
420 overweight or obesity (Flygare Wallen, 2018).

421

422 **Study strengths and limitations**

423 The strengths of this study include the objective monitoring of habitual PA by accelerometers
424 over a relatively long (more than six days) period in a group of adult women with PWS and
425 in a control group of subjects with non-syndromic obesity carefully matched on gender, age

426 and adiposity. Accelerometer data processing was performed using the same procedures,
427 increasing the comparability of data between groups. The min-by-min analysis of
428 accelerometer data provided new insights about MVPA and sedentary patterns in patients
429 with PWS, highlighting the added value of objective measure of PA for improving our
430 understanding of PA patterns and guiding patient management. However, the cutpoints used
431 to define sedentary time and light-, moderate- and vigorous-intensity PA were initially
432 validated in young and non-obese individuals (Freedson, 1998), and have not been validated
433 in patients with PWS. According to previous reports (Agiouvasitis, 2011), the relation
434 between counts per min and oxygen consumption differs in patients with intellectual
435 disabilities, suggesting that traditional cutpoints might not be adapted to these subjects. More
436 research is needed to validate specific intensity cutpoints in patients with PWS, and more
437 broadly in patients with intellectual disabilities (Leung, 2017). In addition, the sample size
438 was limited and only women were included in the analyses, which prevents us from
439 extrapolating results to all patients with PWS. Finally, the control group did not receive the
440 intervention and was not used as a control group to compare the effectiveness of the exercise
441 program in PWS vs non syndromic obesity. Hence, although unlikely, we cannot exclude that
442 the improvements observed in the PWS group after the intervention might have been due to
443 other factors.

444

445 **Conclusion**

446 This study shows substantially lower objectively-measured total PA and higher sedentary
447 time, especially in uninterrupted bouts of 30 min or longer, in women with PWS compared to
448 control subjects with common obesity. Participation in the home-based supervised exercise
449 training program was very high, showing the feasibility and transferability potential of such
450 programs in patients with PWS. The 16-week program was found to be effective to in

451 increasing habitual MVPA and improving walking capacity, although body weight and body
452 composition were not changed. This increase in PA is likely to have beneficial health effects
453 over time, showing the adjunct value of including a specifically-designed PA program in the
454 clinical management and rehabilitation of patients with PWS.

455

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647

648

649 **Figures legend**

650

651 **Figure 1**

652 **Title:** Distribution of MVPA in very short, short and prolonged bouts

653 **Legend:** * In the PWS group, significantly different after the program compared to ~~baseline~~
654 pre-intervention values ($P < 0.05$, P-value from Wilcoxon test).

655 Abbreviations: PWS group, patients with Prader-Willi syndrome; CON group, control group;

656 MVPA= moderate-to-vigorous physical activity

657

658 **Figure 2**

659 **Title:** Distribution of sedentary time in very short, short and prolonged bouts

660 **Legend:** * Significantly different from the CON group ($P < 0.001$, P-value from Mann-
661 Whitney test).

662 Abbreviations: PWS group, patients with Prader-Willi syndrome; CON group, control group;

663 SED= sedentary time

664

665 **Table 1- Body composition, quality of life and eating behavior in patients with Prader-**
666 **Willi syndrome before and after the exercise program and in controls**

667

	CON group (N=20)	PWS group Pre-intervention (N=10)	P- value ¹	PWS group Post-intervention (N=10)	P- value ²
Age, years	30 (26-36)	28.8 (24.2-33.0)	0.25	--	--
Height, cm	165 (158-168)	151 (143-156)	<0.001	--	--
Body weight, kg	121.2 (106.6-133.9)	82.3 (74.3-107.8)	0.002	84.5 (73.3-99.0)	0.15
BMI, kg.m⁻²	43.4 (40.9-48.3)	37.2 (34.3-45.8)	0.05	37.1 (34.5-42.0)	0.16
Waist circumference, cm	--	106.0 (94.3-116.4)	--	106 (89-106)	0.47
Body fat, %	52.4 (50.1-53.7)	51.9 (49.2-54.7)	0.42	52.8 (49.4-54.2)	0.42
Fat mass, kg	62.9 (56.0-70.4)	40.2 (39.3-58.6)	0.004	41.3 (36.8-55.2)	0.15
Lean body mass, kg	57.8 (51.2-62.2)	50.1 (34.1-46.8)	<0.001	41.1 (33.2-42.8)	0.50
Fat mass index, kg.m⁻²	22.2 (21.3-25.0)	19.8 (16.8-25.0)	0.08	19.2 (16.9-23.4)	0.13
Lean body mass index, kg.m⁻²	21.2 (18.3-22.7)	17.0 (16.4-18.7)	0.006	17.2 (16.3-18.2)	0.46
Quality of life					
Physical score	--	49.6 (48.5;53.5)	--	54.1 (51.5-56.3)	0.06
Mental score	--	51.6 (41.8;58.2)	--	55.3 (42.2;60.4)	0.50
Dykens questionnaire*					
Hyperphagic behavior	--	8.5 (6.0;10.8)	--	7.0 (6.0-7.75)	0.08
Hyperphagic drive	--	7.5 (6.0;11.8)	--	9.0 (6.8;11.0)	0.39
Hyperphagic severity	--	3.0 (3.0;4.0)	--	3.0 (2.0;5.0)	0.50

668 Data are median (25th;75th percentile).

669 *Dykens questionnaires were obtained before and after the program in 8 participants

670 ¹ P-value from Mann-Whitney test for cross-sectional comparison of characteristics between the PWS group and
671 the control group

672 ² P-value from Wilcoxon test for comparison of the PWS group before vs. after the PA program

673 Abbreviations: PWS group, patients with Prader-Willi syndrome; CON group, control group

674 **Table 2- Objectively-measured physical activity and physical function in patients with**
 675 **Prader-Will syndrome before and after the exercise program and in controls**

676

	CON group (N=20)	PWS group Pre-intervention (N=10)	P- value ¹	PWS group Post-intervention (N=10)	P- value ²
<u>Physical function</u>					
6-min walk test distance, m	--	398 (366-484)	--	450 (378-509)	0.02
Handgrip strength, kgF	33 (28-38)	15 (13-18)	<0.001	15 (14-18)	0.48
Stance test, eyes open, s	--	8 (3-28)	--	9 (5-33)	0.02
<u>Physical activity*</u>					
Activity counts, counts.min⁻¹	334 (292-384)	211 (141-333)	0.02	311 (188-361)	0.11
Sedentary time, % wear time	58 (53-64)	72 (69-75)	<0.001	68 (67-75)	0.41
Light-intensity PA, % wear time	38 (32-45)	24 (23-28)	<0.001	26 (21-29)	0.34
MVPA, % wear time	3.2 (2.6-4.5)	1.7 (0.8-5.0)	0.11	4.0 (1.1-6.1)	0.02
MVPA in 10-min bouts, min.wk⁻¹	20 (0-68)	5 (0-101)	0.38	90 (21-238)	0.03

677

678 Data are median (25th;75th percentile). MVPA= moderate-to-vigorous physical activity

679 * Physical activity data were obtained in 7 participants in the PWS group after the exercise program

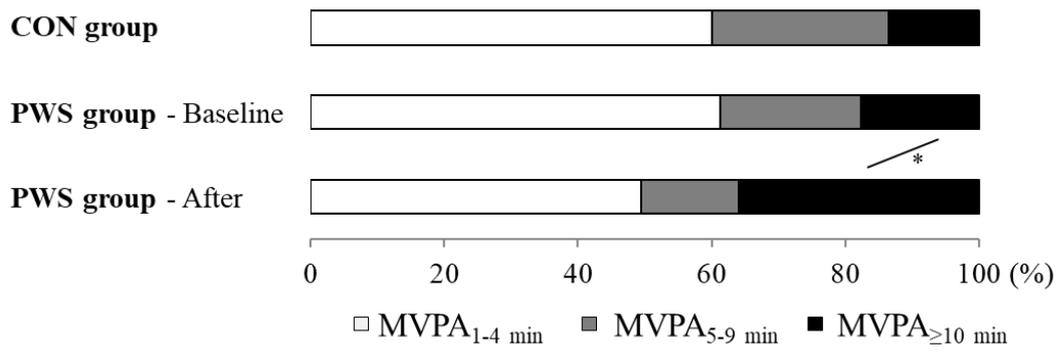
680 ¹ P-value from Mann-Whitney test for cross-sectional comparison of characteristics between the PWS group and

681 the control group

682 ² P-value from Wilcoxon test for comparison of the PWS group before vs. after the PA program

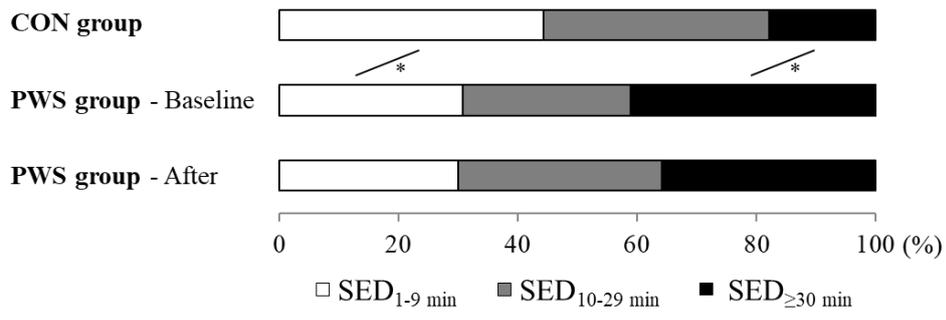
683 Abbreviations: PWS group, patients with Prader-Willi syndrome; CON group, control group

684



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Figure 1



688
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Figure 2