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# 1 1. Title Page

## (a) Alterations in the metabolic and cardiorespiratory response to exercise in Huntington's Disease

### (b) Authors and affiliations

*J Steventon<sup>1,2,3</sup>, J. Collett<sup>4,5</sup>, H. Furby<sup>2,3</sup>, K. Hamana<sup>6</sup>, C. Foster<sup>3</sup>, P. O'Callaghan<sup>7</sup>, A. Dennis<sup>8</sup>, R. Armstrong<sup>9</sup>, A. H. Németh<sup>9</sup>, A. E. Rosser<sup>10</sup>, K. Murphy<sup>1,3</sup>, L. Quinn<sup>11</sup>, M. Busse<sup>12</sup>, H. Dawes<sup>4,13</sup>*

1. *School of Physics and Astronomy, Cardiff University*
2. *NMHRI, School of Medicine, Cardiff University*
3. *CUBRIC, School of Psychology, Cardiff University*
4. *Centre for Movement, Occupation and Rehabilitation Sciences, OxINMAHR, Oxford Brookes University, Oxford, UK.*
5. *Faculty of Health and Life Sciences, Oxford Brookes University, Oxford, UK.*
6. *School of Healthcare Sciences, Cardiff University*
7. *Cardiology Department, University Hospital of Wales, Cardiff*
8. *FMRIB Centre, Nuffield Department of Clinical Neurosciences, John Radcliffe Hospital, University of Oxford, OX3 9DU, UK*
9. *Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK;*
10. *IPMCN, School of Medicine, Cardiff University*
11. *Department of Biobehavioral Sciences, Teachers College, Columbia University, USA.*
12. *Centre for Trials Research, Cardiff University, UK;*
13. *Department of Clinical Neurology, University of Oxford, Oxford, UK.*

(c) **Corresponding author:** *Dr Jessica Steventon, Cardiff University Brain Research Imaging Centre (CUBRIC), Maindy Road, Cardiff, UK. CF24 4HQ. Email: [steventonjj@cardiff.ac.uk](mailto:steventonjj@cardiff.ac.uk) Telephone: +44 (0) 29 206 88758*

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## 2. Abstract

### Background

Limited data suggests that an altered metabolic and cardiorespiratory exercise response may affect exercise performance in individuals with Huntington's disease (HD). There is no clear exploration of the response in individuals at different stages of the disease or in relation to genetic markers. This study aimed to examine the exercise response and recovery of HD participants, and the relationship to genetic and clinical markers.

### Method

HD gene-positive participants (n=31; 9 pre-manifest; 22 manifest HD) and a healthy control group (n=29) performed an incremental exercise test until exhaustion. Performance, cardiorespiratory, metabolic and perceptual responses to exercise were determined from a maximal cycle ergometer test throughout the exercise test and during a recovery period.

### Results

During sub-maximal exercise, metabolic (lactate levels, oxygen uptake) and cardiorespiratory markers (heart rate) were elevated in HD participants compared to controls. Lactate elevation was specific to pre-manifest HD participants. Work capacity was reduced in both pre-manifest and manifest HD participants with tests terminated with no difference in metabolic, perceptual or cardiorespiratory markers. Submaximal oxygen uptake was correlated with motor score, whilst peak measures were unrelated to genetic or clinical markers. Heart rate recovery was attenuated in pre-manifest and manifest HD participants.

### Conclusions

Our findings confirm metabolic and cardiorespiratory deficits reduce exercise performance and affect recovery from an early stage in HD, with submaximal deficits related to phenotypic expression. Exercise capacity appears to be limited by an altered movement economy, thus clinicians should consider an altered exercise response and recovery may affect prescription in HD.

### 31 3. Introduction

32 Huntington's disease (HD) is a neurodegenerative disorder caused by the expansion of a polyglutamine  
33 stretch within the Huntingtin gene<sup>1</sup>. Neuropathology causes progressive motor disturbances,  
34 cognitive dysfunction and psychiatric symptoms<sup>2</sup>. However, as the mutant Huntingtin gene is  
35 ubiquitously expressed, people with HD also experience an array of peripheral organ dysfunctions,  
36 including a severe metabolic phenotype, weight loss, abnormal fat and glucose homeostasis,  
37 cardiomyopathy, skeletal muscle wasting and reduced muscle strength<sup>3-6</sup>.

38 In healthy people, exercise interventions reduce all-cause mortality and are beneficial for  
39 cardiorespiratory fitness, muscle strength, mental health and cognition<sup>7-10</sup>. Exercise prescription has  
40 also been shown to be safe, feasible and in some cases, beneficial for motor symptoms in HD<sup>11-13</sup>.  
41 However, results have been variable and detrimental effects of exercise training have also been  
42 reported<sup>4,14</sup>. These conflicting and variable findings may reflect an altered physiological and  
43 perceptual response to exercise in HD<sup>15</sup> which may consequentially affect exercise prescription  
44 outcomes. Importantly, the variability in the response to exercise suggests that targeted exercise  
45 prescription may be required for people with HD.

46 In order to develop targeted approaches, it is necessary to understand what factors affect the  
47 pathophysiological response to exercise. The current study was designed to improve knowledge on  
48 who may benefit from exercise prescription by understanding individual exercise responses. Previous  
49 work has found manifest HD participants experience an early increase in blood lactate and a reduced  
50 work capacity and peak oxygen consumption, with no abnormalities in peak cardiac and ventilatory  
51 performance<sup>16</sup>. Cardiac alterations and differences in perceived exertion were also found at lower  
52 exercise intensities in HD participants prior to commencing an exercise intervention<sup>15</sup>, and an  
53 increased oxygen cost of exercise has been demonstrated<sup>11</sup>.

54 Previous studies in HD showing an altered exercise response were measured at a distinct  
55 exercise stage, most commonly the response to maximal exercise intensity<sup>11,17</sup>, whilst  
56 cardiorespiratory and metabolic recovery after exercise has not been previously studied in HD. Here,  
57 we measured the incremental response to exercise across the entirety of a cardiopulmonary test and  
58 recovery period. We hypothesised that the physiological responses to the submaximal, maximal and  
59 recovery phases may differ between controls and HD participants, which may relate to clinical and  
60 genetic disease markers.

## 61 4. Methods

### 62 **Participants**

63 Thirty-one HD participants (22 manifest, 9 pre-manifest) were recruited from specialist HD clinics in  
64 Cardiff, UK and Oxford, UK. Twenty-nine gene-negative controls were matched for age, gender and  
65 self-reported physical activity levels. Demographic and clinical data are shown in Table 1. Data was  
66 collected with ethical approval and participants gave informed consent.

### 67 **Exercise protocol**

68 Participants completed an incremental cycle ergometer exercise test<sup>18</sup> (Excalibur Sport, Lode,  
69 Netherlands) involving two minutes of rest, two minutes of unloaded cycling, followed by 25-watt  
70 increments every two minutes, starting at 50-watts (Supplementary Figure 1). The exercise test was  
71 symptom limited; individuals pedalled at 50 revolutions/minute until discomfort or fatigue due to  
72 effort prevented them from maintaining the work rate. A 10-point Borg Scale measured perceived  
73 exertion, fatigue in the legs and dyspnea. At 2 minute intervals, Borg ratings were collected along with  
74 whole blood capillary lactate concentration (Lactate pro, UK).

75 Pulmonary gas exchange was measured on a breath-by-breath basis (MetaMax 3B, Cortex  
76 Biophysik GmbH, Leipzig, Germany) and averaged every 30-seconds. Direct measurements of oxygen  
77 consumption ( $O_2$ ), carbon dioxide production ( $CO_2$ ), minute ventilation (VE), and derived variables  
78 including the respiratory exchange ratio (RER, i.e.,  $O_2/CO_2$ ), oxygen pulse ( $O_2/HR$ ) and the ventilatory  
79 equivalents for oxygen ( $VE/O_2$ ) and carbon dioxide ( $VE/CO_2$ ) were obtained. Heart rate was  
80 continuously recorded using short-range telemetry (Polar S810, Finland).

81 After reaching exhaustion, participants cycled at an unrestrained speed at 25-watts for 2  
82 minutes. Participants then transferred to a seated position and heart rate, blood pressure, lactate and  
83 Borg ratings were recorded every 2-minutes for 10-minutes. Additional protocol details can be found  
84 in the supplementary information.

### 85 **Clinical and genetic measures**

86 The motor component (TMS) of the UHDRS and the Total Functional Capacity (TFC)<sup>19</sup> score were  
87 recorded. Self-reported physical activity levels were recorded using the International Physical Activity  
88 Questionnaire [IPAQ]<sup>20</sup>. CAG repeat length data was available for 19 HD participants. To assess

89 baseline cognition, participants completed the Trail Making Test (part B) and The Symbol Digit  
90 Modalities Test (SDMT).

## 91 **Statistical analyses**

92 HD participants were stratified according to disease stage (see Table 1; manifest HD participants = TFC  
93 score < 13 and TMS >18, Supplementary Figure 2 shows TFC range in manifest group).

94 As sample size differed across test stages due to different termination points, multiple univariate  
95 analyses of variance (ANOVA's) assessed group differences at each test stage (rest, submaximal stages  
96 [50-, 75-, 100- and 125-watts], and peak performance), using SPSS software [IBM, version 23]. Multiple  
97 comparisons were corrected for using the false discovery rate (FDR) at  $p < 0.05$ . Where results survived  
98 the FDR correction, Bonferroni-adjusted post-hoc pairwise analyses examined group differences.  
99 Multivariate ANOVA's were conducted for the recovery measures with post-hoc Bonferroni-adjusted  
100 analyses.

101 Where group differences were found, the relationship with clinical and genetic data was tested using  
102 a Pearson's correlation analysis.

103 A slope analysis assessed the relationship between physiology measures and work rate, from rest to  
104 peak. The oxygen uptake efficiency slope (OUES)<sup>21</sup>, was determined from rest to peak using the  
105 following equation:

$$106 \quad \dot{V}O_2 = a \log \dot{V}E + b;$$

107 *Where a represents the OUES, the rate of increase in  $\dot{V}O_2$  in response to  $\dot{V}E$ .*

108

109 *[Table 1 here]*

## 110 **5. Results**

111 Despite no significant difference in age, BMI, and IPAQ score between control and HD participants  
112 overall (all  $p > 0.05$ ), manifest HD participants were significantly older than pre-manifest HD and  
113 controls participants, thus age was included as a covariate in all analyses.

### 114 **Exercise protocol compliance**

115 Four HD participants were excluded from the analysis as they were unable to achieve the required  
116 speed of 50 revolutions/min (see Supplementary Table 1). One HD participant experienced syncope  
117 following maximal exertion.

118 **Resting measures**

119 Resting VO<sub>2</sub>, heart rate, RER, mean arterial blood pressure (MAP) and lactate levels did not differ  
120 between HD participants and controls ( $p > 0.05$ , Figure 1). Perceptually, there was no difference in  
121 resting ratings of fatigue ( $p > 0.05$ ).

122 **Submaximal exercise function**

123 Exercise parameters across test stages are shown in Figure 1.

124 **Physiology.** VO<sub>2</sub> was elevated in manifest HD participants compared to controls at 50 watts (33%  
125 increase,  $F_{2,50} = 5.42$ ,  $p = 0.006$ ) and 75 watts (24.3% increase,  $F_{2,50} = 3.45$ ,  $p = 0.035$ ) with no  
126 differences between pre-manifest and control participants ( $p > 0.05$ ). Similarly, heart rate was  
127 elevated in manifest HD participants compared to controls at 50 and 75 watts ( $F_{2,49} = 5.54$  and 6.47  
128 respectively,  $p < 0.05$ ). In pre-manifest participants, heart rate was elevated compared to controls at  
129 75 watts only ( $p = 0.024$ ).

130 There was a main effect of group (HD vs. controls) on lactate levels at 50 watts ( $F_{1,37} = 5.36$ ,  $p = 0.035$ ),  
131 75 watts ( $F_{1,35} = 8.21$ ,  $p = 0.028$ ) and 100 watts ( $F_{1,34} = 5.90$ ,  $p = 0.034$ ). Lactate was higher in pre-  
132 manifest HD participants compared to controls, surviving Bonferroni correction at 75 and 100 watts ( $p$   
133  $= 0.014$  and  $0.039$ ) but not 50 watts (controls vs. manifest HD,  $p = 0.053$ ). The difference between  
134 controls and manifest HD participants was significant at 50 and 75 watts ( $p = 0.027$  and  $0.049$   
135 respectively) before age was accounted for, however with age as a covariate, this difference was not  
136 significant.

137 Results from the slope analysis are shown in Supplementary Table 2. There was no difference in the  
138 OUES nor the relationship between work rate and VO<sub>2</sub>, heart rate and lactate between control and HD  
139 participants (all  $p > 0.05$ ).

140 **Perceptual responses.** There were no group difference in perceived exertion ratings at any workload  
141 between 50 and 125 watts ( $p > 0.05$ ).

142 *[Figure 1 here]*

143

144

145 **Peak exercise capacity**

146

147

148

149 Figure 2 shows the individual and group data at exhaustion. Age-adjusted marginal means are shown  
150 in Supplementary Table 3.

151 **Performance.** Volitional exhaustion occurred at a lower working capacity ( $W_{peak}$ ) in HD participants  
152 ( $F_{1,53} = 11.26$ ,  $p = 0.001$ , Figure 2A). Pre-manifest and manifest participants had a lower  $W_{peak}$   
153 compared to controls ( $p = 0.049$  and  $0.026$  respectively); there was no difference in  $W_{peak}$  between  
154 pre-manifest and manifest HD participants ( $p > 0.05$ ).

155 **Physiology.** There were no differences in  $\dot{V}O_2$  peak, heart rate, oxygen pulse, RER, VE,  $VE/VCO_2$   
156 (controls =  $28.9 \pm 0.8$ ; pre-manifest =  $30.7 \pm 1.4$ ; manifest HD =  $30.0 \pm 1.0$ ),  $VE/O_2$  (controls =  $35.5 \pm$   
157  $1.4$ ; pre-manifest =  $33.2 \pm 2.1$ ; manifest HD =  $34.9 \pm 1.6$ ) at exhaustion between HD and control  
158 participants ( $p > 0.05$ ).

159 Blood lactate production was 25.3% lower in HD participants at exhaustion compared to controls ( $F_{1,40}$   
160 =  $9.37$ ,  $p = 0.004$ , Figure 2E) and was lower in manifest HD participants compared to controls ( $p =$   
161  $0.032$ ). Pre-manifest HD participants did not differ from controls. To determine the effect of  $W_{peak}$   
162 on lactate production, peak lactate levels were normalised by  $W_{peak}$ . There was no difference in  
163 normalised peak lactate between control and HD participants (controls =  $0.057 \pm 0.003$ ; pre-manifest  
164 HD =  $0.060 \pm 0.004$ ; manifest HD =  $0.050 \pm 0.003$ ,  $p > 0.05$ ).

165 **Perceptual responses.** There were no differences in perceived exertion ratings between HD  
166 participants and control participants at volitional exhaustion ( $p > 0.05$ ).

167

*[Figure 2 here]*

## 168 **Exercise recovery**

169 **Physiology.** On a group level, heart rate did not differ between HD and control participants (Figure  
170 3A). To examine individual variability in heart rate recovery (HRR), the change in heart rate from peak  
171 was calculated. HRR was slower in HD participants compared to controls ( $F_{10,70} = 1.98$ ,  $p < 0.05$ , Figure  
172 3B). HRR was higher in controls compared to manifest HD participants at 2-minutes post exercise ( $p =$   
173  $0.011$ ), whereas after 4-minutes, HRR was higher in controls compared to pre-manifest and manifest  
174 participants ( $p = 0.038$  and  $0.007$  respectively). At 6-, and 8-minutes post exercise, HRR remained  
175 higher in controls compared to pre-manifest participants ( $p = 0.016$  and  $0.021$  respectively). There

176 were no differences in HRR between manifest and pre-manifest HD participants. Ten minutes  
177 following exercise, the difference between HRR in pre-manifest participants and controls was not  
178 significant ( $p = 0.07$ ).

179 Lactate levels were reduced in manifest HD participants compared to controls at 2- and 4-minutes  
180 post exercise ( $p = 0.012$  and  $0.034$  respectively, Figure 3C), with no differences between control and  
181 pre-manifest HD participants, and pre-manifest and manifest HD participants. To account for peak  
182 lactate levels, lactate change (from peak) was calculated. There were no differences between control  
183 and HD participants in lactate change during recovery ( $p > 0.05$ , Figure 3D).

184 **Perceptual response.** Self-reported ratings of fatigue during the recovery phase did not differ  
185 between HD and control participants (Figure 3,  $p > 0.05$ ).

186 *[Figure 3 here]*

187

### 188 **Relationship between exercise measures and genetic and phenotypic HD expression**

189 UHDRS TMS, where a higher score indicates greater movement disorder, was correlated with  $VO_2$  at  
190 50 watts ( $r = 0.49$ ,  $p = 0.032$ ), and 75 watts ( $r = 0.44$ ,  $p = 0.041$ , Supplementary Figure 3). There was no  
191 correlation between submaximal  $VO_2$  and UHDRS TFC or CAG repeat length (all  $p > 0.05$ ). Heart rate  
192 at 50- and 75-watts, and lactate levels at 50-, 75- and 100-watts were not correlated with cUHDRS  
193 TMS and TFC or CAG repeat length, all  $p > 0.05$ .

194 No correlations were found between clinical data (UHDRS TMS and TFC), CAG repeat length and peak  
195 lactate or  $W_{peak}$ , all  $p > 0.05$ .

196 The correlation between HRR at 4- and 6-minutes post exercise and the UHDRS TMS ( $r = -0.40$  and -  
197  $0.40$ ,  $p = 0.039$  and  $0.041$  uncorrected) and UHDRS TFC ( $r = 0.38$  and  $0.46$ ,  $p = 0.053$  and  $0.017$   
198 uncorrected) was not significant after multiple comparison adjustments.

199

## 200 **6. Discussion**

201 This study shows an altered exercise response in people with HD during a graded exercise test. Despite  
202 normal resting physiology, upon initiation of low intensity exercise, heart rate, lactate, and oxygen  
203 uptake were elevated in HD participants compared to controls, suggestive of a movement economy

204 deficit and altered metabolism. The early elevation in lactate was observed in pre-manifest HD  
205 participants specifically, suggesting that abnormal oxidative metabolism in skeletal muscle may be an  
206 early feature of HD prior to functional decline. In contrast, elevated oxygen uptake at low intensities  
207 was related to greater motor dysfunction in HD participants. In agreement with previous work<sup>16</sup>,  
208 volitional exhaustion occurred at a lower working capacity in HD participants and both pre-manifest  
209 and manifest HD participants produced less lactate at maximal effort. Almost one fifth of manifest HD  
210 participants were unable to maintain the required cycling speed, highlighting an altered exercise  
211 tolerance and physical ability in HD.

212           The altered cardiorespiratory and metabolic response to exercise may account for the variable  
213 responses to exercise prescription previously reported in HD<sup>17</sup>. The relationship between oxygen  
214 uptake during submaximal exercise and motor functioning suggest some of the variability can be  
215 accounted for by phenotypic disease expression, however metabolic differences were not accounted  
216 for by genetic load or phenotype, and were evident in pre-manifest HD participants, suggesting a  
217 complex physiological response to exercise in HD.

218           Notably, these novel findings provide support for individualised exercise prescription, and  
219 suggest that the effect of long-term exercise training may vary between individuals based on the  
220 prescribed exercise intensity and their subsequent physiological response. Further studies measuring  
221 the response to exercise are therefore recommended throughout the prescription period in order to  
222 understand if disturbances in exercise response interact with exercise prescription outcomes. In  
223 addition, it would be valuable to measure creatine kinase following exercise to explore muscle cell  
224 disturbance in HD and to further explore autonomic functioning.

225           Whereas previous work has shown a reduced  $\dot{V}O_2$  peak in manifest HD<sup>16</sup>, we failed to replicate  
226 this. The discrepancy is most likely explained by the inclusion of age as a covariate in this study; when  
227  $\dot{V}O_2$  was measured as a percent of theoretical maximum capacity according to age, body type, and sex,  
228 differences due to HD were no longer observed<sup>16</sup>. In line with previous work<sup>16</sup>, HD participants had a  
229 normal ventilatory response to maximal exercise and both clinical data and genetic data did not  
230 predict peak measures. CAG repeat length was also not predictive of the submaximal physiological  
231 response, suggesting that genetic markers are insensitive to exercise response in HD. The rate of  $\dot{V}O_2$   
232 may be affected by how effectively oxygen is delivered to the muscles (respiratory and cardiovascular  
233 systems), how it is utilised (metabolic systems) and how hard the muscles are working (neuromuscular  
234 systems). We propose that higher  $\dot{V}O_2$  at submaximal exercise and not at peak may be due to muscles  
235 working harder in people with HD due to chorea and/or poor co-ordination which requires greater

236 oxygen use. At peak exercise, aerobic metabolism is limited due to issues with bioenergetics and  
237 mitochondrial functioning in the HD group.

238 After reaching exhaustion, heart rate recovery was attenuated in HD participants. This is a  
239 novel finding; impaired heart rate recovery is an independent predictor of mortality in healthy  
240 populations<sup>22</sup>. The fall in heart rate immediately after exercise is a function of the reactivation of the  
241 parasympathetic nervous system, mediated by vagal reactivation in the first two minutes of  
242 recovery<sup>23</sup>. It is not clear whether vagal reactivation continues to mediate heart rate recovery for the  
243 eight minutes observed here, or whether other mechanisms drive the slowed response. Due to the  
244 cool-down protocol used, it is not possible to compare heart rate recovery with normative data  
245 attained immediately after exhaustive exercise cessation, however our findings complement work  
246 showing reduced cardiovagal modulation in middle-stage HD<sup>24,25</sup>. The elevated heart rate observed  
247 during submaximal exercise in HD participants replicates Dawes et al.<sup>15</sup> and increases the robustness  
248 of the observation that people with HD do not reach steady heart rates when initiating low-intensity  
249 exercise. This is informative for exercise prescription; applying objective submaximal markers as  
250 opposed to training intensities based on maximal measures (e.g. heart rate, VO<sub>2</sub>), and measuring  
251 exercise recovery as an indicator of intervention effectiveness may be more appropriate.

252 The difference observed in peak lactate is most likely driven by differences in task  
253 performance. Working capacity was reduced in HD participants, and when peak lactate was  
254 normalised for maximal work rate, the lactate differences were no longer significant. This suggests  
255 that HD participants were unable to work as hard on the exercise test which contributed to the lower  
256 lactate levels and is supported by previous work showing a reduced work capacity in manifest  
257 participants<sup>16</sup>. The reduced working capacity in pre-manifest HD participants suggests an underlying  
258 energy deficit rather than reduced muscle bulk.

259 Altered metabolism was also evident during submaximal exercise. The failure of oxidative  
260 mechanisms can affect lactate production and clearance and previous work has shown elevated  
261 lactate production in symptomatic HD participants during a cardiopulmonary test at 50 watts and 75  
262 watts<sup>16</sup>. We replicated this finding, however, lactate was also significantly higher in pre-manifest HD  
263 participants compare to controls at 75 and 100 watts, whereas the difference between controls and  
264 manifest HD participants was not significant after accounting for age. The discrepancy in the results  
265 may be partly explained by higher fitness levels in the current cohort and a broader symptomatic HD  
266 group.

267 A common limitation in clinical exercise research is the physiological effect of medication.  
268 Participants in this study were prescribed a diverse range of medications which alter metabolic

269 pathways<sup>26</sup>. It is not known if observed metabolic and cardiac deficits are a cause or consequence of  
270 HD toxicity, and/or mediated by medication. A comprehensive large-scale study is required to unpick  
271 medication effects, with the metabolic consequences of drugs in the same sub-class varying  
272 substantially due to differences in receptor pharmacology. Metabolic deficits observed in animal  
273 models and cell cultures of HD suggest that observed effects are not purely driven by medication<sup>27,28</sup>,  
274 however they may account for some variability in exercise prescription responses.

275 Overall, we have demonstrated that metabolic and cardiorespiratory deficits contribute towards a  
276 reduced exercise performance and affects recovery in HD. Autonomic dysfunction has been reported  
277 in a variety of neurodegenerative dementias<sup>29,30</sup> and further work is required to elucidate whether  
278 deficits are a direct consequence of peripherally expressed mutant huntingtin protein, or secondary  
279 to a general decline in health or neurological dysfunction. This knowledge will be crucial for targeted  
280 exercise prescription in HD and for determining outcome measures.

281

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288

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## 361 8. Figure Legends

362

363 *Figure 1 Response to submaximal exercise. Results are marginal means adjusted for age, error bars = standard errors of the*  
364 *mean. RER: Respiratory exchange rate. RPE: Ratings of perceived exertion. \* p < 0.05 Bonferroni-adjusted. † unadjusted p <*  
365 *0.05. preHD: pre-manifest, HD: manifest HD.*

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367

368 *Figure 2 Peak exercise response at test termination. Black line represents mean; grey box depicts 95% CI. RER: respiratory*  
369 *exchange ratio (VCO<sub>2</sub>: VO<sub>2</sub>); RPE: Rating of perceived exertion. PreHD: pre-manifest HD participants. HD: Manifest HD*  
370 *participants. P-values are Bonferroni- adjusted.*

371

372 *Figure 3 Recovery response [B] & [D] show absolute change from peak. Results are marginal means adjusted for age. Error*  
373 *bars = standard errors of the mean. RPE: rating of perceived exertion. HR: heart rate (beats/minute). \* p < 0.05, \*\* p < 0.01.*