

1 Objectively measured physical activity levels and sedentary time in  
2 children and adolescents with sickle cell anemia

3 Short Title: Physical activity levels in sickle cell anemia

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31 **Abstract:**

32 The aim of this study was to identify the levels of physical activity and sedentary  
33 behaviour of children and adolescents with sickle cell disease (SCA) compared  
34 to healthy individuals. A cross-sectional study with a quantitative approach was  
35 performed at a reference center for the treatment of patients with  
36 hemoglobinopathies in northeastern Brazil. Patients were recruited between  
37 October 2015 and January 2017. Eligible participants answered a Physical  
38 Activity Questionnaire for Older Children and Adolescents (PAQ-C) and were  
39 instructed to use an ActiGraph wGT3X-BT triaxial accelerometer for seven  
40 consecutive days. The analysis of the results was performed using the SPSS  
41 software (version 13.0). Differences between means were analysed using the  
42 Mann-Whitney U test and the chi-square test was used to evaluate the  
43 proportions of occurrence of categorical variables, comparing patient and  
44 controls groups. Among the 352 patients in the follow-up, 64 met the inclusion  
45 criteria and agreed to participate. Of those, 14 did not use the accelerometer  
46 during the 7 consecutive days and were excluded. 50 patients (and their 50  
47 controls) were then evaluated. We observed a statistically significant difference  
48 between cases and controls in the variables "total time of moderate and vigorous  
49 physical activity" ( $p=0.009$  and  $p=0.0001$ , respectively) and "daily mean of  
50 moderate and vigorous physical activity" ( $p=0.005$  and  $p=0.003$ ). There was also  
51 a significant difference among cases and controls in the following variables:  
52 "metabolic equivalent" (MET), with  $p=0.04$ , total of steps ( $p=0.04$ ) and "total  
53 caloric expenditure" ( $p=0.0001$ ), with the worst performances for the group of  
54 patients with SCA. Children and adolescents with SCA presented lower levels of  
55 physical activity than healthy children and adolescents, both when evaluated by

56 the PAQs or by the accelerometer. The results suggest the need to develop  
57 specific programs aimed at promoting physical activity levels and reducing  
58 sedentary behaviour among young individuals with SCA.

59 **Keywords:** Exercise; Motor Activity; Sickle cell anemia; Physical Exertion.

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## 61 **Author Summary**

62 Sickle cell anemia is a hereditary and hematological disease that occurs due to  
63 the abnormal production of red blood cells. On the other hand, childhood physical  
64 activity has beneficial effects on health, both in the short and long terms, and may  
65 reduce risk factors for chronic diseases. The aim of this study was to identify the  
66 levels of physical activity and sedentary behaviour of children and adolescents  
67 with sickle cell disease compared to healthy individuals. Participants answered a  
68 Physical Activity Questionnaire for Older Children and Adolescents (PAQ-C) and  
69 were instructed to use an ActiGraph wGT3X-BT triaxial accelerometer for seven  
70 consecutive days. We observed children and adolescents with sickle cell anemia  
71 presented lower levels of physical activity than healthy children and adolescents,  
72 both when evaluated by the PAQs or by the accelerometer. The results suggest  
73 the need to develop specific programs aimed at promoting physical activity levels  
74 and reducing sedentary behaviour among young individuals with sickle cell  
75 anemia.

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## 82           **Introduction**

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84           Sickle cell anemia (SCA) is a neglected tropical disease [1] characterized  
85 by a point mutation in the  $\beta$ -chain hemoglobin (Hb) gene. When deoxygenated,  
86 HbS, the Hb resulting from the mutation, polymerises, resulting in a change in the  
87 red blood cells and assuming a sickle shape. The falcized red blood cells can  
88 obstruct the microcirculation, resulting in ischemia-reperfusion injury, with  
89 inflammatory cytokines, pain and functional impairment, particularly in the  
90 musculoskeletal system [2], which can lead to defensive sedentary behaviour  
91 even among young patients.

92           Previously, it has been demonstrated that childhood physical activity (PA)  
93 has beneficial effects on health, both in the short and long terms, and may reduce  
94 risk factors for chronic diseases [3]. More recently, one study concluded that  
95 moderate physical exercise is not harmful for patients with SCA [4], and, in an  
96 animal model (rats with SCA), it is suggested that PA could be beneficial in the  
97 clinical course of the disease [5].

98           The evaluation of PA is complex due to its multi-dimensional  
99 characteristics. Questionnaires that use semi-quantitative scales, such as the  
100 Physical Activity Questionnaire for Older Children and Adolescents (PAQ-C),  
101 have the advantage of easier applicability, but they are influenced by the  
102 interviewee's perception of their level of physical activity. Thus, objective methods  
103 are preferable and the accelerometer is an instrument that generates quantitative  
104 results and thus confers objectivity to the assessment of BP in children and  
105 adolescents [6].

106 Thus, this study aimed to evaluate the level of PA and sedentary behaviour  
107 of children and adolescents with SCA compared to healthy individuals.

## 108 **Methods**

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### 110 **Design**

111 This is a cross-sectional study carried out at the outpatient clinic of a  
112 university center in the northeast of Brazil, which is a regional reference for the  
113 treatment of patients with SCD. After initial screening, eligible patients and  
114 healthy controls completed the Physical Activity Questionnaire for Older Children  
115 and Adolescents (PAQ-C) [7,8]. Subsequently, participants and their caregivers  
116 were instructed on how to properly use the ActiGraph wGT3X-BT triaxial  
117 accelerometer and to use it for seven consecutive days.

### 118 **Population**

119 Patients were recruited between October 2015 and January 2017. Among  
120 the patients with SCA (homozygous for HbS) confirmed by hemoglobin  
121 electrophoresis, individuals who were between 6 and 18 years of age and in a  
122 stable clinical condition were considered eligible, if they had not received blood  
123 transfusions in the last three months and if they were without acute complications  
124 for at least one month, before being included in this study. Patients with  
125 neurological or orthopedic impairment were excluded.

126 The control group consisted of healthy children and adolescents recruited  
127 at a local public school and matched for age and sex with the patients.

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130 **Ethics Statement**

131 This study was approved by the Research Ethics Committee involving  
132 Human Beings of the Federal University of Sergipe (protocol:  
133 30661314.0.0000.5546). All guardians responsible for the patients and controls  
134 signed a free and informed consent form.

135 **Laboratory tests**

136 The results of hematological examinations (hemoglobin, hematocrit,  
137 erythrocyte counts, platelets, leukocytes, neutrophils, reticulocytes, indirect  
138 bilirubin, mean corpuscular volume, lactate dehydrogenase) and hemoglobin  
139 electrophoresis (fetal hemoglobin and hemoglobin S) were obtained  
140 retrospectively from a database especially created for this research. Laboratory  
141 tests were performed under stable clinical conditions within four weeks prior to  
142 the application of the accelerometer. All the exams were performed at the Central  
143 Laboratory located at the service itself, using the same standardised techniques  
144 and equipment.

145 **Medication use**

146 All patients were using folic acid supplements (2 mg/day). Patients on  
147 hydroxyurea received an initial dose of 15 mg/kg/day and were currently using  
148 the standard dose (20 to 35 mg/kg/day) for at least 12 months [9].

149 **Physical activity questionnaire for older children and adolescents (PAQ-C)**

150 All patients included in this study completed the Brazilian version of PAQ-  
151 C [8], composed of nine questions about sports, games, and other physical  
152 activities at school and at leisure activities. This questionnaire aims to provide a  
153 complete picture of the type and amount of PA that the participant had been

154 performing in the last seven days prior to the interview. Each question was scored  
155 on a scale of 1 to 5, being: very sedentary (1), sedentary (2), moderately active  
156 (3), active (4) or very active (5). In order to determine the final score, the mean of  
157 all responses was calculated.

## 158 **PA measurements**

159 The ActiGraph GT3X Accelerometer (ActiGraph LLC, Pensacola, FL,  
160 USA) was used to objectively monitor the time spent in PA and sedentary  
161 behaviour. The accelerometer was worn on an elastic belt and participants were  
162 instructed to position it on the hip line of their dominant side. Participants used  
163 the device for 7 consecutive days, including two weekend days for at least 10  
164 hours a day [10,11]. The study team instructed and monitored the children and  
165 their caregivers to remove the monitor during aquatic activities and during sleep.  
166 The accelerometer was initialised by the researcher responsible for the study  
167 through the manufacturer's software (ActiLife version 6). In order to record the  
168 movement in counts per minute, the count was set to 60 second epochs. The  
169 time of sedentary behaviour was defined by <100 count per minute [12,13].

170 Values between 100 and 1999 counts per minute were recorded as light  
171 PA (LPA) [13]. The time spent on moderate PA (MPA) and vigorous PA (VPA)  
172 was calculated based on cutoffs of 2000 and 4000 counts per minute,  
173 respectively [14]. The PA of each individual was categorised in the three intensity  
174 levels (LPA, MPA and VPA) and the average daily sedentary time had been  
175 recorded. The time spent in moderate/vigorous PA (MVPA) was calculated as the  
176 sum of MPA and VPA.

177           The daily percentage of all PA intensity levels was calculated based on the  
178 time spent at each intensity level, including sedentary time [15]. For comparison,  
179 the children were considered to be in accordance with the recommendations of  
180 the AP when the mean MPVA over all measured days was 60 min or more [16].  
181 The mean time measured for both weekdays and weekends was calculated by  
182 summarising the sedentary time and the time spent at different BP intensities.

### 183 **Statistical analysis**

184           The data analysis was performed using SPSS version 13.0 for Windows  
185 (SPSS, Inc., Chicago, IL, USA). Quantitative variables were described as means  
186 and standard deviations. All variables were checked for normality prior to analysis  
187 using the Kolmogorov-Smirnov test. Differences between means were analysed  
188 using the Mann-Whitney U test and the chi-square test was used to evaluate the  
189 proportions of occurrence of categorical variables, comparing patient and control  
190 groups. Differences in time spent at different PA intensities and the mean times  
191 measured on weekdays and weekends were analysed by using the t-test for  
192 paired samples. The chi-square test was used to determine differences in the  
193 percentage of time spent at different PA intensities. The significance level used  
194 was 5% ( $p < 0.05$ ).

### 195 **Results**

196           We accessed a registry of patients with SCA who regularly attended the  
197 outpatients' clinic in the study institution (352 children and adolescents). 288  
198 patients did not meet the inclusion criteria. 64 patients were considered eligible,  
199 but 14 were later excluded because they did not use the accelerometer for seven  
200 consecutive days. Thus, 50 patients were included in this study, of which 60%  
201 were male with a mean age of  $12.02 \pm 3.6$  years.



202 The control group was selected from a public school located in the same  
 203 city. The students were asked to participate with consent of their guardians and,  
 204 if they did not have any relatives diagnosed with SCA and if they had no chronic  
 205 disease nor acute disease during the days of using the accelerometer, were  
 206 paired to patients with SCA according to sex and age.

207 Table 1: Characterization of study participants

Variables	SCA children and adolescents (n=50)	Range	Controls (n=50)	Range	p
Height (m)	1.41 ± 0.17	1.13 – 1.77	1.47 ± 0.16	1.2 – 1.81	0.092
Weight (kg)	34.20 ± 12.92	17.2 – 66.1	47.26 ± 16.45	20.7 – 78.2	0.0001
BMI (kg/m <sup>2</sup> )	16.38 ± 2.4	13.01 – 23.48	21.07 ± 4.5	14.37 – 30.26	0.0001
Age (yrs)	12.02 ± 3.6	6 – 18	11.02 ± 3.44	6 – 18	0.147
Sex male (%)	60	-	58	-	
Hb (g/100mL)	8.1 ± 1.1	5.03 – 12.1	-		
Hematocrit (%)	22.4 ± 3.8	14.2 – 38.1	-		
RBC (10 <sup>12</sup> /L)	2.4 ± 0.7	1.6 – 5.18	-		
Platelets (10 <sup>9</sup> /L)	419.7 ± 123.2	109 – 878	-		
Leukocytes (10 <sup>9</sup> /L)	11.7 ± 2.9	4.1 – 20.7	-		
Neutrophils (%)	47.7 ± 8.9	30 – 78	-		
Reticulocytes (%)	9.1 ± 4.7	07 – 19.2	-		
Indirect bilirubin (mg/dL)	2.8 ± 2.7	03 – 17.09	-		
MCV (fL)	86 ± 17	31.07 – 125	-		
LDH (U/L)	957.4 ± 480	100 – 2127	-		
Hydroxyurea therapy (HU) (number of patients, %)	24; 48	-	-		
HbF (%)	11.1 ± 7.3	1.9 – 31.7	-		
HbS (%)	74.3 ± 14.2	34.4 – 95	-		

208 Results are expressed as mean, standard deviation and range unless otherwise indicated. *BMI*:  
 209 Body mass index, *Hb*: hemoglobin, *RBC*: Red blood cells, *MCV*: Mean corpuscular volume,  
 210 *LDH*: Lactate Dehydrogenase, *HbF*: Fetal hemoglobin, *HbS*: hemoglobin S.

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212 All 50 patients and 50 controls used the accelerometer for seven  
 213 consecutive days without any complications. The clinical characteristics of both

214 groups (patients with SCA and healthy controls) are described in Table 1. The  
 215 groups were similar in terms of age and distribution by sex, meeting the pairing  
 216 criteria, but presented a statistically significant difference in the means of body  
 217 mass and body mass index (BMI), with  $p=0.0001$ .

218 Table 2: Physical Activity and Sedentary Behavior Variables

Variables	SCA children and adolescents (n=50)	Range	Controls (n=50)	Range	p
Sedentary Time (min)	2918.12 ± 848.3	1271 – 5208	2865.5 ± 914.4	1363 – 6682	0.775
Sedentary Time (min/day)	416.87 ± 106.03	158.87 – 651	409.35 ± 114.3	170.37 – 835.25	0.639
Sedentary Time (%)	56.84 ± 13.92	30.66 – 95.54	52.54 ± 11.76	32.71 – 77.46	0.453
Light PA (min)	2279.04 ± 913.51	740 – 5208	2359.84 ± 751.95	880 – 3517	0.630
Light PA (min/day)	325.57 ± 114.18	92.5 – 651	337.12 ± 93.99	110 – 439.62	0.237
Light PA (%)	42.96 ± 10.77	22.98 – 95.54	47.73 ± 14.84	20.14 – 59.79	0.424
Moderate PA (min)	134.9 ± 95.5	15 – 447	190.18 ± 110.9	6 – 498	0.009
Moderate PA (min/day)	19.27 ± 11.94	1.87 – 59.62	27.16 ± 13.87	0.75 – 62.25	0.005
Moderate PA (%)	2.66 ± 1.8	0.35 – 8.31	3.51 ± 1.93	0.15 – 8.3	0.368
Vigorous PA (min)	25.76 ± 33.05	0 – 202	54.94 ± 59.85	0 – 370	0.0001
Vigorous PA (min/day)	3.68 ± 4.13	0 – 25.25	7.84 ± 7.48	0 – 46.25	0.003
Vigorous PA (%)	0.51 ± 0.61	0 – 3.52	1.11 ± 0.93	0 – 5.03	0.351
MPVA (min)	160.66 ± 148.88	30 – 752	245.12 ± 538.05	20 – 1014.83	0.712
MPVA (min/day)	22.95 ± 18.6	3.7 – 94	35.01 ± 66.6	2.5 – 306.2	0.705
MPVA (%)	3.17 ± 4.35	0.47 – 9.12	4.62 ± 2.49	0.53 – 11.25	0.423
MET	1.71 ± 0.4	1.17 – 2.45	1.87 ± 0.39	1.12 – 2.57	0.04
Current PA recommendations	8	-	30	-	
Kcal total	1015.73 ± 516.83	701.56 – 2659.73	2404.31 ± 1308.22	806.23 – 5178.81	0.0001
Sitting (%)	18.3 ± 5.17	7 – 32	19.16 ± 5.83	11 – 36	0.153
Standing (%)	24.94 ± 7.34	6 – 40	25.64 ± 7.43	10 – 39	0.682
Lying (%)	5.12 ± 3.8	0 – 19	6.24 ± 5.75	0 – 28	0.254
Total steps	51010.52 ± 19600.13	16057 – 120567	59105.40 ± 22650.89	20583 – 137817	0.04

219 Results are expressed as mean, standard deviation and range unless otherwise indicated. PA:  
 220 physical activity, MPVA: moderate-to-vigorous physical activity.

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222           There was a statistically significant difference between the groups in the  
223 variables "total time of moderate and vigorous PA" ( $p=0.009$  and  $p=0.0001$ ,  
224 respectively) and "daily mean of moderate and vigorous physical activity"  
225 ( $p=0.005$  and  $p=0.003$ ), with patients performing worse than the control group  
226 (Table 2).

227           There was a statistically significant difference between groups in the  
228 "Metabolic Equivalent" (MET) variables, with  $p=0.04$ , "Total Steps" ( $p=0.04$ ) and  
229 "total energy expenditure" ( $p=0.0001$ ), with the lower values always occurring in  
230 the patients group (Table 2). In the studied sample, 8% of patients with SCA and  
231 30% of controls complied with the current recommendations of PA, which is 60  
232 minutes or more of moderate or vigorous PA (MVPA) per day [17].

233           There was no statistically significant difference in the average time of  
234 sedentary activity (neither in total or in the daily average), but these values were  
235 always lower in the control group.

236           The questionnaire (PAQ-C) was applied to all participants. The mean  
237 score obtained by the patients was  $1.65 \pm 0.4$  and the mean score by the controls  
238 was  $3.39 \pm 0.38$ . 62% of the patients with SCA were categorised as very  
239 sedentary and the remaining 38% were sedentary (Table 3). Among the controls,  
240 11% were classified as sedentary, 75% as moderately active, and 14% were  
241 active.

242           Table 3 presents the comparison of the PA level in the different activity  
243 categories evaluated by PAQ-C and shows that patients with SCA reported lower  
244 PA levels in all categories compared to healthy controls.

245

246 Table 3: Comparison of physical activity levels in different categories assessed  
247 by the PAQ-C between patients and controls.

Variables	SCA children and adolescents (n=50)	Range	Controls (n=50)	Range	p
Spare-time activity	0.75 ± 0.3	0 – 1.6	2.48 ± 0.61	1.4 – 3.7	0.0001
Activity during PEC	1.74 ± 0.6	1 – 3	3.36 ± 0.6	2 – 5	0.0001
Break-time Activity	1.6 ± 0.69	1 – 3	3.64 ± 0.59	2 – 5	0.0001
Lunch-time Activity	1.42 ± 0.53	1 – 3	3.32 ± 0.71	2 – 5	0.0001
After school Activity	1.8 ± 0.98	1 – 4	3.38 ± 0.56	2 – 4	0.0001
Evening Activity	1.7 ± 0.8	1 – 4	3.58 ± 0.7	2 – 5	0.0001
Weekend Activity	2.08 ± 0.75	1 – 3	3.63 ± 0.7	2 – 5	0.0001
AF during the last 7days	2.32 ± 0.81	1 – 4	3.72 ± 0.5	3 – 5	0.0001
AF during each day last week	1.62 ± 0.53	0.1 – 3	3.37 ± 0.58	2.5 – 4.3	0.0001
Score total	1.65 ± 0.4	0.8 – 2.3	3.39 ± 0.38	2.7 – 4.2	0.0001

248 *PEC*: Physical Education Classes; *AF*: Activity frequency; Data expressed as mean ± standard deviation and  
249 range (minimum and maximum). Independent t-test and Mann-Whitney U test were used to compare the two  
250 groups when the variables presented parametric and non-parametric distribution, respectively.  
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## 252 Discussion

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254 To the authors' knowledge, this study presents the first results on  
255 sedentary time and the intensity level of PA of children and adolescents with SCA  
256 in Brazil. The results demonstrate increased sedentary behaviour and less  
257 intense PA levels in children and adolescents with SCA compared to healthy  
258 controls. These results are of particular importance when considering the  
259 beneficial effects on the oxidative stress damages, previously identified in a study  
260 which used an animal model [5]. The authors of that study proposed that an

261 exercise program could be useful for controlling clinical complications due to SCA  
262 [5].

263 The effects of an exercise program applied to heterozygous carriers for  
264 HbS (sickle cell trait) were previously evaluated and a study reported beneficial  
265 results on endothelial function, including reduction of oxidative stress markers  
266 and antioxidant enhancement (increased activity and NO availability) [18]. There  
267 is evidence that sedentary behaviour is associated with adverse health effects in  
268 groups of individuals with various chronic diseases [19], but patients with SCA  
269 have never been evaluated until now.

270 Impairment of nutritional status and growth retardation in children and  
271 adolescents with SCA are associated with resting energy expenditure 10-20%  
272 higher than that observed in healthy individuals, which is at least partially due to  
273 the higher cardiac output, such as mechanisms of compensation for moderate or  
274 severe and chronic anemia [20]. The present study showed a statistically  
275 significant difference in the MET variable, which reinforces the findings of a  
276 previous study [21]. In order to maintain their total daily energy expenditure at the  
277 same level as healthy adolescents, patients with SCA reduce their energy  
278 expenditure in PA [22].

279 Previous studies have evaluated the activity of the autonomic nervous  
280 system in patients with SCA and have identified an imbalance caused by  
281 parasympathetic activity at rest [22] and deficiency of autonomic reactivity [23].  
282 Furthermore, the degree of impairment is associated with clinical severity [24].  
283 The present study did not evaluate the activity of the autonomic nervous system.  
284 However, in healthy individuals, the energy expended with PA is positively  
285 associated with the activity of the autonomic nervous system, especially the

286 activity of the parasympathetic nervous system [25]. Regular PA increases the  
287 activity of the parasympathetic nervous system, which has a protective effect on  
288 the cardiovascular system [26], whilst sedentary behaviour leads to an imbalance  
289 in the autonomic nervous system activity, which may favour the development of  
290 cardiovascular diseases [27], a condition that is particularly detrimental to the  
291 patients with SCA.

292 The present study identified low PA levels and low energy expenditure in  
293 patients with SCA compared with healthy individuals, corroborating previous  
294 studies [19]. Various factors, such as muscular hypotrophy, pulmonary and  
295 cardiac complications, may explain these findings [5].

296 However, intense physical exercise induces metabolic and physiological  
297 changes that may be detrimental to individuals with SCA [5] and there is no  
298 consensus on the maximum intensity of safe exercise that these patients can  
299 tolerate. In addition, due to the limitations imposed by the disease and its frequent  
300 acute interurrences, parents of children and adolescents with SCA may  
301 discourage them from engaging in physical activities [28], which may explain the  
302 low energy expenditure and physical activity in the sample studied.

303 A previous study identified positive effects in MVPA for patients with SCA  
304 [29] and considered this practice to be safe. Considering the findings of this study,  
305 future objectives are to identify which training modalities would be better tolerated  
306 and could provide the greatest health benefits to patients. Given the findings, it is  
307 suggested that the evaluation of PA should be part of the outpatient follow-up for  
308 patients with SCA, being an important tool to determine the severity of the  
309 disease and to suggest a possible strategy to prevent clinical complications.

310 We identified a limitation of the present study: the use of the accelerometer  
311 was voluntarily and in the absence of acute interurrences. Thus, it is possible  
312 that patients with more severe forms of SCA have not been included. However,  
313 given the results obtained, it is assumed that the inclusion of patients with greater  
314 frequency or intensity of symptoms would result in less PA and a more sedentary  
315 lifestyle.

## 316 **Conclusion**

317 Children and adolescents with SCA were assessed for PA, assessed  
318 subjectively by the PAC-C and objectively by the accelerometer, resulting in  
319 values lower than that of healthy children and adolescents.

320 The results indicate that programs with a focus on promoting optimal PA  
321 levels and on reducing sedentary behaviour in this population are necessary.  
322 These efforts must be intensified.

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331 project and their parents.

332

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