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1 **Physical activity and incident depression: A meta-analysis of prospective cohort studies**

2  
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30  
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35

36       **Abstract:**

37       **Objective:** Examine the prospective relationship between Physical activity (PA) and incident  
38 depression and explore potential moderators.

39       **Methods:** Prospective cohort studies evaluating incident depression were searched from  
40 database inception to October 18, 2017 on PubMed, PsycINFO, EMBASE and Sportsdiscuss.  
41 Demographic and clinical data, PA and depression assessment, and Odds Ratios (ORs),  
42 Relative Risks (RRs) and Hazard Ratios (HRs) and 95% confidence interval data were  
43 extracted. Random effects meta-analyses were conducted and the potential sources of  
44 heterogeneity were explored. Methodological quality was assessed using the Newcastle Ottawa  
45 Scale (NOS).

46       **Results:** A total of 49 unique prospective studies (n=266,939, median of males/females across  
47 studies=47%/53%) were followed up for 1,837,794 person-years. People with high PA (versus  
48 low PA) were at reduced odds of developing depression ((adjusted)AOR=0.83, 95%CI=0.79 to  
49 0.88, p<0.001, I<sup>2</sup>=0.00). Furthermore, PA had a protective effect upon the emergence of  
50 depression in youth (AOR=0.90, 95%CI=0.83 to 0.98), in adults (AOR=0.78, 95%CI=0.70 to  
51 0.87), and the elderly (AOR=0.79, 95%CI=0.72 to 0.86). Protective effects were found across  
52 geographical regions: Asia (AOR=0.76, 95%CI=0.68 to 0.85), Europe (AOR=0.83, 95%CI=0.73  
53 to 0.95), North-America (AOR=0.84, 95%CI=0.79 to 0.93) and Oceania (AOR=0.65,  
54 95%CI=0.48 to 0.89), and for increased incidence of positive screen for depressive symptoms  
55 (AOR=0.84, 95%CI=0.79 to 0.89) or MDD diagnosis (AOR=0.86, 95%CI=0.75 to 0.98). No  
56 moderators were identified. Results were consistent for unadjusted ORs and for adjusted and  
57 unadjusted RR/HR. Overall study quality was moderate to high (NOS=6.3). Although significant  
58 publication bias was found, adjusting for this did not change the magnitude of the associations.

59       **Conclusions:** Available evidence supports the notion that PA can confer protection against the  
60 emergence of depression regardless of age and geographical region.

61

62       **Key Words:** exercise, physical activity, depression, cohort, prevention, incidence

63

64

65

66 **Introduction**

67 Depressive disorders are the second leading cause of global burden and account for  
68 44,224.4 thousands of years lived with disability (YLDs) (1). They are associated with  
69 heightened medical comorbidity (2), increased healthcare costs (3) and premature mortality (4).  
70 Given the breadth of depressive disorders and the individual and societal burden, strategies that  
71 may reduce the onset of depression are urgently required (5).

72 One potentially modifiable risk factor for the onset of depression is low physical activity  
73 (PA) (6). People with major depressive disorder (MDD) are known to have a 50% odds of not  
74 meeting the recommended PA levels (e.g., performing > 150 minutes of moderate intensity  
75 physical activity each week), compared with people without the disorder (7). Moreover,  
76 structured PA is known to reduce depressive symptoms in those with depression (8). Previous  
77 systematic reviews suggest that PA is a protective factor for depression onset (9, 10), with even  
78 small amounts of PA (e.g., walking <150 minutes per week) decreasing the incidence of future  
79 depressive episodes (9). The studies, however, have not conducted meta-analyses to quantify  
80 the magnitude of the protective role of PA (9). Moreover, the role of moderators such as gender,  
81 and age, which may influence the relationship between PA and depression, have not been  
82 explored.

83 Given these gaps, our aims were to: (a) systematically review and meta-analyze  
84 prospective cohort studies examining the role of physical activity to reduce symptoms of  
85 depression; (b) explore potential moderators including age at baseline, geographical location,  
86 gender, length of follow-up, study quality, number of covariates used in the model, sample size  
87 of the study and total person-years; and, (c) evaluate the quality of the studies.

88

89 **Methods**

90 This review adhered to the Meta-analysis Of Observational Studies in Epidemiology  
91 (MOOSE) (11) guidelines and Preferred Reporting Items for Systematic Reviews and Meta-  
92 analyses (PRISMA) (12) statement, following an apriori defined yet unpublished protocol  
93 (available upon request).

94

95 *Search procedure*

96 Two researchers (FS, ES) searched PubMed, Embase, PsycINFO and SPORTDiscuss  
97 from database inception to October 18<sup>st</sup>, 2017. Keywords included a combination of terms  
98 related to physical activity, depression and longitudinal studies. Searches were adapted for  
99 each database and are displayed in the supplementary materials 1. Manual searches of the  
100 reference lists from recovered articles and other systematic reviews investigating the  
101 association between PA, sedentary behavior or fitness and depression were conducted (9, 10,  
102 13, 14).

103

#### 104 *Inclusion and exclusion criteria*

105 Articles were eligible if they met the following criteria: (1) evaluated participants, of all  
106 ages, free from depression/depressive symptoms at baseline. (2) PA was measured with a self-  
107 report questionnaire (SRQ) such as the International Physical Activity Questionnaire (IPAQ)  
108 (15), single or multiple questions of exercise, sports or PA participation, or objective PA  
109 measures (e.g. accelerometers). PA was defined as any bodily movement produced by skeletal  
110 muscles and which requires energy expenditure (16). (3) Used a prospective study design with  
111 at least one-year period of follow-up duration. Prospective studies with less than one year follow  
112 up were not included, as this was not considered a sufficient time frame for risk and protective  
113 factors to exert a meaningful influence on depressive symptoms (17). (4) Evaluated incident  
114 depression as the outcome including increased depressive symptoms, through established cut-  
115 offs of depression screening instruments (e.g. Beck Depression Inventory (BDI) I or II) (18) or  
116 based on tertiles, quartiles or quintiles of depression symptoms, major depressive disorder  
117 (MDD), diagnosed using structured or semi-structured diagnostic interviews (e.g. instruments  
118 using DSM (19) or ICD criteria (20)) or through a self-report of physician diagnosis of  
119 depression (5). Reported an adjusted or non-adjusted odds ratio (OR), hazard ratio (HR) or  
120 relative risk (RR) and 95% confidence intervals or the raw numbers of exposed and non-  
121 exposed participants who developed depression at follow-up, in a way that allow calculations of  
122 ORs or RRs. In instances when data were not available we contacted corresponding authors at  
123 least three times over a 3-week period to request the data to enable inclusion in our meta-  
124 analysis (see acknowledgments). To compare with most of the risk measures selected to the  
125 meta-analysis, the OR, RR or HR of studies using the lowest PA group as the reference group

126 had to be inverted. Likewise, the limits of the corresponding confidence intervals were also  
127 inverted, giving rise to the limits of the confidence intervals to the reciprocal of the OR, RR or  
128 HR (21) .

129 Excluded were: (1) studies without primary data (reviews, commentaries, editorials); (2)  
130 conference presentations without information about the methods or the outcomes; (3) studies in  
131 languages other than English, Portuguese or Spanish; (4) studies that evaluated PA as a  
132 continuous measure.

133 Studies of the same epidemiological cohort were included only when they report the  
134 results in different metrics (OR or RR/HR). For example, if one study is reporting OR and other  
135 RR, each one was included in its analysis. This strategy allows the inclusion of the greatest  
136 number of studies without counting the same participants twice in each meta-analysis. When  
137 two or more studies report data of the same cohort, we selected the most recently published.  
138 Studies reporting subsamples of cohorts were excluded.

139

#### 140 *Study selection*

141 In the first stage of study selection, two authors (FS, ES) independently screened titles and  
142 abstracts of all articles retrieved from the search. Afterwards, the full-text of potentially eligible  
143 references were reviewed in detail by the same investigators. Disagreements were resolved  
144 through discussion until consensus was achieved. A third reviewer (BS) was available for  
145 mediation.

146

#### 147 *Outcomes*

148 The primary outcome was the adjusted odds ratio (AOR) for incident diagnosed depression or  
149 depressive symptoms and 95% confidence interval (CI).

150

#### 151 *Data extraction*

152 Five authors (FS, ES, MH, JF and SR) independently extracted data including geographical  
153 location, name of cohort, number of participants included at baseline, age at baseline, PA  
154 assessment (instrument or questions used, what aspects of PA were considered by the  
155 measure to define PA levels (e.g. frequency, intensity, time, type, energetic amount expended,

156 steps, or other)), depression assessment (e.g. instrument and cut-off used, diagnostic criteria,  
157 medical records), follow-up period, odds ratio OR/RR/HR and 95% confidence interval and the  
158 number of covariates. The data utilized for the adjusted meta-analysis was the most adjusted  
159 model presented in each of the respective papers.

160

#### 161 *Study quality*

162 The methodological quality of studies was assessed with the Newcastle-Ottawa Scale (NOS) by  
163 two authors (FS and SR). The NOS scale evaluates the risk of bias of prospective studies with  
164 three elements: (a) selection of participants, four items (representativeness of the exposed  
165 cohort, equal derivation between source of exposed and non-exposed participants,  
166 ascertainment of the exposure, demonstration that the outcome of interest was not present at  
167 the start of the study), (b) comparability, one item (comparability of cohorts on basis of the  
168 design of the analysis); Studies where the OR or RR were calculated on the basis of the raw  
169 number of participants provided from the original papers received zero points for comparability,  
170 and (c) outcomes, three items (adequate assessment of outcome, adequate time of follow-up  
171 and adequacy of follow-up). A study can be awarded a maximum of one point for each  
172 numbered item within the selection and outcome categories and a maximum of two stars can be  
173 given for comparability. The maximum score of the NOS is 9 (highest quality) and we assigned  
174 scores of 0–3, 4–6 and 7–9 for the low, moderate and high quality of studies, respectively  
175 (22). In case of disagreement, a consensus was reached through a discussion.

176

#### 177 *Meta-analysis*

178 A random-effects meta-analysis was conducted investigating the relationship between  
179 baseline PA and incident depression. Procedures included first pooling data across all studies  
180 comparing the incident depression in highest PA levels group (the group of greater frequency,  
181 intensity, volume, energetic expenditure or other, from each study, as defined by the authors)  
182 versus the lowest PA level group (reference group). Analysis for adjusted (AOR), crude OR,  
183 adjusted relative risks/hazard ratio (RR/HR) and crude RR/HR were conducted separately.  
184 Specifically, AOR, OR, ARR/AHR or HR/RR and 95% CI were calculated for incident  
185 depression. For the AOR and ARR/AHR, we pooled the estimates using the model with the

186 greatest number of covariates presented by the authors. Second, subgroup analyses were  
187 performed investigating the relationship between: 1) different geographical regions (different  
188 continents); 2) how PA levels were assessed (e.g. asking about intensity, frequency, volume  
189 (time spent in PA) or composite variables including two or more variables, and studies using  
190 metabolic equivalents [METs] as units were classified together with the METs category); 3)  
191 the mean age of the sample at baseline (e.g. children or adolescents (<18 years), adults (18-  
192 65 years) or elderly (>65 years)); 4) the use of SRQ or objective measures to assess PA; 5)  
193 depression assessment method including screening instruments, MDD diagnosis, assessed  
194 by structured or semi-structured diagnostic instruments, or self-report (SR) of physician  
195 diagnosis of MDD; and, 6) the adjustment for potential confounders (age and sex, body mass  
196 index, smoking and baseline depressive symptoms, age and sex and more one of the three  
197 others, and age and sex and more two of the three others). Third, we evaluated potential  
198 moderators (% of males (only for crude OR and RR/HR), length of follow-up, year of  
199 publication, person-years, total number of participants at baseline, study quality according to  
200 the NOS scale overall score, and the score for the selection of participants, outcome and  
201 comparability (only for adjusted), and the number of covariates included in the model (only for  
202 AOR and ARR/AHR, to evaluate whether studies using more covariates are more likely to find  
203 significant or stronger effects) (23) through meta-regression analysis. Lastly, we evaluated  
204 the publication bias using the Begg and Mazundar (24) and Egger tests (25) and corrected for  
205 this using the Duval and Tweedie trim and fill (26). To maximize statistical power, studies  
206 pooling participants with incident depressive disorders along with incident anxiety disorders  
207 were included in the main analysis. However, a sensitivity analysis excluding those papers  
208 were performed to evaluate whether they impacted the results obtained. Sensitivity analyses  
209 were also performed excluding studies of the same cohorts that have any potential sample  
210 overlapping. Heterogeneity was quantified using the Q and I<sup>2</sup> statistic, with scores of <25%,  
211 25-50% and >50% indicating low, moderate and high heterogeneity, respectively (27). Finally,  
212 the fail-safe number of negative studies that would be required to nullify (i.e. make p>0.05) the  
213 effect size was calculated (28). All analyses were performed using Comprehensive Meta-  
214 Analysis software (version 3).

215



## 216 **Results**

### 217 *Search results*

218 The initial search yielded 13,474 results. After the removal of duplicates and exclusion  
219 at the title/abstract level, 10,099 abstracts were considered. At the full-text review stage, 430  
220 studies were considered, and 383 studies were subsequently excluded, and two were identified  
221 in the references of other included articles (see supplementary figure 1 for the flowchart and  
222 supplementary material 2 for a list of excluded articles). Therefore, 49 unique studies were  
223 included in the review.

224

### 225 *Studies and participants characteristics*

226 Across the 49 unique prospective studies, 266,939 individuals were included, with  
227 nearly equal gender distribution (47% males), followed up for an average of 7.4 years. The total  
228 person-years was 1,837,794. Of these, 39 cohorts from 36 unique studies provided data for  
229 AOR, 19 cohorts from 18 studies provided for OR, 18 cohorts from 15 studies provided for ARR  
230 and 15 cohorts from 13 studies for RR. Table 1 indicates the studies included in each analysis.  
231 Only one study used objective measures to evaluate PA. Fifteen studies evaluated MDD using  
232 structured or semi-structured diagnostic instruments or SR physician diagnosis of MDD only.  
233 The description in details of the included studies are summarized in table 1. The list of included  
234 studies is provided on supplementary material.

235

### 236 *Study quality*

237 The mean (SD) study quality score of the studies was 6.34 (0.8) out of 9 on the NOS  
238 scale, representing moderate to high methodological quality. The detailed quality assessment is  
239 presented in supplementary table 1.

240

### 241 *Physical activity and incident depression*

#### 242 ***Highest versus lowest PA***

243 People with higher PA levels were at reduced odds of incident depression when  
244 compared to people with lower PA levels in adjusted (AOR=0.83, 95% CI=0.79 to 0.88,  
245  $p<0.001$ ,  $I^2=0.00$ ,  $Q\text{-value}=25.93$ ,  $N=36$ ) (figure 1) and crude odds ratio analyses (OR=0.59,

246 95% CI=0.51 to 0.68,  $p<0.001$ ,  $I^2=52.38$ ,  $Q\text{-value}=37.80$ ,  $N=19$ ) and with decreased risks on  
247 adjusted (ARR=0.83, 95% CI=0.76 to 0.30,  $p<0.001$ ,  $I^2=0.00$ ,  $Q\text{-value}=14.86$ ,  $N=18$ ) and crude  
248 relative risks analyses (RR=0.68, 95% CI=0.60 to 0.78,  $p<0.001$ ,  $I^2=33.40$ ,  $Q\text{-value}=24.02$ ,  
249  $N=17$ ). The plots for OR, ARR and RR can be seen at supplementary figures 2, 3 and 4,  
250 respectively, and the incidence rates can be seen at supplementary tables 3. Publication bias  
251 were evidenced for AOR (Egger's intercept=-0.65,  $p=0.002$ ), ARR (Egger's intercept=-1.25,  
252  $p<0.001$ ; Begg and Mazundar Tau=-0.43,  $p=0.01$ ). The Duval and Tweedie trim and fill  
253 technique adjusted the effects to: (1) AOR=0.85 (95% CI=0.81 to 0.89), (2) OR=0.63 (95%  
254 CI=0.54 to 0.74), (3) ARR=0.86 (95% CI=0.78 to 0.96); and (4) RR=0.80 (95% CI=0.69 to 0.94).  
255 The classic fail-safe n test revealed that 380, 519, 102 and 210 studies with negative results  
256 would be required to nullify the protective effect of PA on incident depression for AOR, OR,  
257 ARR and RR analyses respectively.

258

### 259 ***Subgroup and sensitivity analysis***

260 Significant protective associations of PA on incident depression were found across the  
261 four continents (Asia, Europe, North America and Oceania) with available data for AOR, and RR  
262 analysis. Protective effects were found for Asia, North America and Oceania for OR and for  
263 Europe, North America and Oceania in ARR analysis. Significant associations of high PA was  
264 found in all analysis for studies assessing PA levels considering different volumes and  
265 composed/METS. Higher frequency of PA provided protective effects in AOR and OR analysis,  
266 but not in ARR or RR. Higher intensity was significantly associated with lesser incident  
267 depression in all but AOR analysis. Protective effects were found for adults and older in all  
268 analyses and for children in AOR and RR. Significant associations were found for studies  
269 assessing depressive symptoms across the four analyses. PA was protective for MDD  
270 diagnosis in AOR, OR, and RR analyses. Significant reduction of 150 min of moderate/vigorous  
271 on the incident depression in AOR and ARR analyses. Lastly, subgroup analyses of studies that  
272 have adjusted for age and sex, body mass index, smoking, baseline depressive symptoms, or  
273 age and sex one more, or age and sex two more confounders are all significant in AOR. For  
274 ARR, adjusting for age and sex, body mass index, smoking, or age and sex and one more  
275 confounder. Details of the subgroup analyses can be seen in table 2.

276 We performed sensitivity analyses removing the study that pooled participants with  
277 anxiety disorders together with depression both in the overall analysis (available upon request)  
278 and in MDD only (available upon request) (29), excluding the study that used objectively  
279 measured PA (available upon request) (30),. The results remained significant for all analyses.

280

#### 281 *Meta-regressions*

282 Sample size at baseline, year of publication, the length of follow-up, individual study person-  
283 years, the % of males, the number of covariates used in each study for adjusted analyses (the  
284 list of the covariates used can be seen in the supplementary table 2) and the study quality  
285 according to the NOS scale were investigated as potential moderators through meta-  
286 regressions analysis. None of the investigated moderators significantly explained the variance  
287 of the effects of PA on depression onset in any of the analyses. Detailed results of meta-  
288 regressions can be seen at table 3 (plots available upon author request).

289

#### 290 **Discussion**

291 To the best of our knowledge, the current paper is the first to meta-analyze the  
292 relationship between PA levels and incident depression. Study findings indicate that across 52  
293 studies, higher PA is associated with a decreased odds of developing future depression. The  
294 results remained robust after adjustment for potential publication bias. Moreover, our results  
295 indicate that higher levels of PA offer a protective effect on future development of depression for  
296 people of all ages (youth, working age adults, elderly) and this finding is robust across  
297 geographical regions around the world.

298 Previous narrative systematic reviews have suggested that PA can be protective  
299 against the development of depression (9, 10). Our study advances the field by conducting the  
300 first pooled meta-analysis investigating this relationship, which enables a clearer understanding  
301 of a true association between an exposure and outcome, rather than when studies are  
302 considered separately as in previous reviews (34). Recently, a meta-analysis including 11  
303 prospective studies found that sedentary behavior (SB) is associated with an increased incident  
304 depression at follow-up (RR=1.14, 95%CI=1.06 to 1.21) (14). While sedentary behaviour and  
305 PA are related constructs - with the former existing at the low end of the PA spectrum – it is of

306 clinical relevance to quantify the pooled relationships of PA with subsequent depression onset  
307 independently of sedentary behaviour.

308 Mammen and Faulkner reported previously that gender might modify the effect of PA on  
309 incident depression (9). This assumption was not supported in our meta-regression analysis,  
310 suggesting that the potential protective association of PA is similar for men and women. Also,  
311 we demonstrated that PA has protective effects on depression across different geographical  
312 regions, and for people of all ages. Importantly, PA was assessed by different parameters such  
313 as frequency, intensity, volume and type that can be captured to discriminate different PA  
314 levels. Our subgroup analyses demonstrated that the protective effects of PA are found in  
315 studies in which the different aspects of PA (intensity, frequency, volume) were measured  
316 individually or when two or more (METS/composed) were considered.

317 Our meta-analysis suggests that PA is associated with a decrease in the risk of  
318 developing depression, which raises an inevitable question; how might PA offer protection  
319 against depression onset? It is likely that no single mechanism can explain this relationship. A  
320 range of biochemical and psychosocial factors are likely responsible including biological  
321 mechanisms showing that exercise increases neurogenesis and reduces inflammatory and  
322 oxidant markers (35) and activate the endocannabinoid system (36). People with depression  
323 have decreased hippocampal volumes and levels of markers of neurogenesis, and increased  
324 levels of inflammatory (e.g: interleukin-6) (37) and oxidant markers (37). Physical activity, in  
325 turn, may regulate these abnormalities increasing hippocampal volume (38) and neurogenesis  
326 levels (39), as well as, adjusting the imbalance between anti- and proinflammatory (40) and  
327 oxidant markers (41, 42). Also, physical activity may directly increase psychological factors such  
328 as increased self-esteem or perceptions of physical competence. Finally, an improved level of  
329 fitness leads to both subjective and objective improvements in physical health status (43).  
330 Productive areas of future research include physical activity interventions to prevent symptoms  
331 of depression and the underlying biological and psychological mechanisms.

332

### 333 *Limitations and future research*

334 Some limitations were present in our meta-analysis. First, the use of SRQs to measure  
335 the exposure factor and the outcome. While common in the PA literature, SRQs are associated

336 with recall biases. However, only one of the included studies used an objective measure  
337 (pedometer) (30) to evaluate PA, thus precluding exploration as to results were different with  
338 SRQs compared to objective measures. Also, subgroup analyses showed that PA decreased  
339 the risk of developing depression, regardless of whether this was based on self-report  
340 measures or MDD diagnosis from structured clinical diagnostic interviews (e.g.: MINI, CIDI,  
341 SCID). Second, we found some evidence of publication bias, in AOR and ARR. Nonetheless,  
342 adjusting for publication bias, after trimming 10 studies for AOR and 8 studies for ARR, resulted  
343 in smaller but still significant associations (AOR=0.85; 95% CI=0.81 to 0.89; ARR=0.86; 95%  
344 CI=0.78 to 0.96). Therefore, the primary results of our analyses are not altered by considering  
345 the potential number of unpublished studies. Third, it should be noted that we only included  
346 studies in which there were no depressed participants at baseline, which minimizes the risk of  
347 selection bias. Despite this, the risk of selection bias was not entirely excluded since depression  
348 is a recurrent disorder and previous depressive episodes were not well-documented in the  
349 studies we investigated. Fourth, we were able to perform subgroup analyses including studies  
350 that evaluated the protective effect of 150 minutes of moderate to vigorous PA per week.  
351 However, these analyses included a small number of studies. Also, in all the other studies, the  
352 definition of low or high PA, as well as what aspects of PA (intensity, frequency, volume or two  
353 or more) that were captured by each instrument varied largely. These limitations prevent the  
354 present review from establishing the "minimum" or the "optimal" dose of PA necessary to  
355 decrease the odds of incident depression. However, we can conclude that people with higher  
356 levels of PA have a lower risk of developing depression than those with lower levels of PA. Fifth,  
357 seven of our subgroup analyses were non-significant. It should be considered that those  
358 analyses included a small number of studies and potentially are underpowered. Lastly, the  
359 included studies have assessed PA participation using questionnaires over the preceding days  
360 or weeks. Thus, it is not possible to evaluate whether being engaged in higher levels of PA for  
361 longer periods confers greater protection in comparison to shorter periods.

362 Despite the robustness of our findings across age ranges, geographical regions, and  
363 the different aspects of PA (frequency, intensity, time, type), some caution is required given that  
364 there may be a number of covariates that were not assessed. For example, some evidence  
365 suggests that the protective effects of PA seems to be greater in the non-carriers of the E type 4

366 allele of the apolipoprotein E (APOE) gene (45), and that carriers of the Met allele of the brain-  
367 derived neurotrophic factor (BDNF) gene are more likely to experience greater benefits for  
368 somatic symptoms from exercise interventions (46). Also, the effects of PA in people with  
369 increased risk for depression, such as people with a familial history of depression, was not yet  
370 examined.

371 Differences in the assessment of depressive symptoms at baseline across studies is  
372 also a limitation. It is possible that the inclusion of participants who exhibited subthreshold  
373 symptoms depressive symptoms at baseline could have influenced the likelihood to develop  
374 depression at follow-up not only due to a lower engagement in physical activity but also to an  
375 inherently higher risk to develop full-blown depression. Nonetheless, significant associations  
376 between high PA and lower development of depression has been reported by included studies  
377 which controlled for baseline depressive symptom severity in subgroup analysis for AOR thus  
378 showing the protective effect of PA also in people with sub-threshold depressive symptoms.  
379 Only one study have adjusted for depressive symptoms at baseline for ARR and found no  
380 significant associations, but it should be considered that it this analysis is based on a single  
381 study. Also, people with lower PA levels may have other risk factors for depression, as such as  
382 obesity, poor diet, use of tobacco and other clinical comorbidities. Therefore, due to the  
383 observational nature of the included studies, it is possible that these other correlated factors  
384 contributed to increased risk of incident depression among those with low PA.

385 Further studies are warranted to evaluate the minimum PA levels required, as well as,  
386 the effects of different PA types and 'dosages' on subsequent risk for depression. Also, further  
387 studies accounting for genetic variations and assessing people with increased risk for  
388 depression are required. Lastly, considering the burden of disease and the global impact of  
389 mental illness, further studies should evaluate the cost-effectiveness of PA in the prevention of  
390 depression.

391

## 392 **Conclusion**

393 Higher levels of physical activity are consistently associated with a lower odds of  
394 developing future depression. The protective effects of PA were observed regardless of gender  
395 and age, and was significant across all geographical regions. Our data further emphasize the

396 importance for policies targeting increased PA levels. Future randomised controlled trials are  
397 required to address whether or not physical activity can prevent the development of depression  
398 in those at high risk.

399

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410

#### 411 Conflict of interest

412 None of the authors declares have conflict of interest to declare.

413

#### 414 References

- 415 1. CGBD 2016 Disease and Injury Prevalence Collaborators. Global, regional, and national  
416 incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015:  
417 a systematic analysis for the Global Burden of Disease Study 2015. *The Lancet*. 2016;388:1545-  
418 1602.
- 419 2. Vancampfort D, Correll CU, Galling B, Probst M, De Hert M, Ward PB, Rosenbaum S,  
420 Gaughran F, Lally J, Stubbs B. Diabetes mellitus in people with schizophrenia, bipolar disorder  
421 and major depressive disorder: a systematic review and large scale meta-analysis. *World*  
422 *Psychiatry*. 2016;15:166-174.
- 423 3. Chisholm D, Sweeny K, Sheehan P, Rasmussen B, Smit F, Cuijpers P, Saxena S. Scaling-up  
424 treatment of depression and anxiety: a global return on investment analysis. *The Lancet*  
425 *Psychiatry*. 2016;3:415-424.
- 426 4. Walker ER, McGee RE, Druss BG. Mortality in mental disorders and global disease burden  
427 implications: a systematic review and meta-analysis. *JAMA Psychiatry*. 2015;72:334-341.
- 428 5. Cuijpers P, Beekman AT, Reynolds CF. Preventing depression: a global priority. *Jama*.  
429 2012;307:1033-1034.
- 430 6. Hallgren M, Stubbs B, Vancampfort D, Lundin A, Jääkallio P, Forsell Y. Treatment guidelines  
431 for depression: Greater emphasis on physical activity is needed. *European Psychiatry*.  
432 2017;40:1-3.

- 433 7. Schuch F, Vancampfort D, Firth J, Rosenbaum S, Ward P, Reichert T, Bagatini NC, Bgeginski  
434 R, Stubbs B. Physical activity and sedentary behavior in people with major depressive disorder:  
435 A systematic review and meta-analysis. *Journal of Affective Disorders*. 2017;210:139-150.
- 436 8. Schuch FB, Vancampfort D, Richards J, Rosenbaum S, Ward PB, Stubbs B. Exercise as a  
437 treatment for depression: a meta-analysis adjusting for publication bias. *Journal of psychiatric*  
438 *research*. 2016;77:42-51.
- 439 9. Mammen G, Faulkner G. Physical activity and the prevention of depression: a systematic  
440 review of prospective studies. *American journal of preventive medicine*. 2013;45:649-657.
- 441 10. Teychenne M, Ball K, Salmon J. Physical activity and likelihood of depression in adults: a  
442 review. *Preventive medicine*. 2008;46:397-411.
- 443 11. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ,  
444 Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for  
445 reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *Jama*.  
446 2000;283:2008-2012.
- 447 12. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic  
448 reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6:e1000097.
- 449 13. Schuch FB, Vancampfort D, Sui X, Rosenbaum S, Firth J, Richards J, Ward PB, Stubbs B. Are  
450 lower levels of cardiorespiratory fitness associated with incident depression? A systematic  
451 review of prospective cohort studies. *Preventive Medicine*. 2016;93:159-165.
- 452 14. Zhai L, Zhang Y, Zhang D. Sedentary behaviour and the risk of depression: a meta-analysis.  
453 *British journal of sports medicine*. 2015;49:705-709.
- 454 15. Craig CL, Marshall AL, Sjostrom M, Bauman AE, Booth ML, Ainsworth BE, Pratt M, Ekelund  
455 U, Yngve A, Sallis JF, Oja P. International physical activity questionnaire: 12-country reliability  
456 and validity. *Med Sci Sports Exerc*. 2003;35:1381-1395.
- 457 16. Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness:  
458 definitions and distinctions for health-related research. *Public health reports*. 1985;100:126.
- 459 17. Cairns KE, Yap MBH, Pilkington PD, Jorm AF. Risk and protective factors for depression that  
460 adolescents can modify: A systematic review and meta-analysis of longitudinal studies. *Journal*  
461 *of Affective Disorders*. 2014;169:61-75.
- 462 18. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring  
463 depression. *Arch Gen Psychiatry*. 1961;4:561-571.
- 464 19. Association AP: Diagnostic and statistical manual of mental disorders. 5th Edition ed.  
465 edition t, editor. Arlington, American Psychiatric Association; 2013.
- 466 20. organisation Wh: The ICD-10 Classification of Mental and Behavioural Disorders –  
467 Diagnostic Criteria for Research. 1993.
- 468 21. Bland JM, Altman DG. The odds ratio. *BMJ : British Medical Journal*. 2000;320:1468-1468.
- 469 22. Wu W, Tong Y, Zhao Q, Yu G, Wei X, Lu Q. Coffee consumption and bladder cancer: a  
470 meta-analysis of observational studies. *Scientific reports*. 2015;5.
- 471 23. Thompson SG, Higgins J. How should meta-regression analyses be undertaken and  
472 interpreted? *Statistics in medicine*. 2002;21:1559-1573.
- 473 24. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication  
474 bias. *Biometrics*. 1994;50:1088-1101.
- 475 25. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple,  
476 graphical test. *BMJ*. 1997;315:629-634.
- 477 26. Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and  
478 adjusting for publication bias in meta-analysis. *Biometrics*. 2000;56:455-463.
- 479 27. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-  
480 analyses. *BMJ (Clinical Research Ed)*. 2003;327:557-560.
- 481 28. Rosenthal R. The file drawer problem and tolerance for null results. *Psychological bulletin*.  
482 1979;86:638.



- 483 29. Pasco JA, Williams LJ, Jacka FN, Henry MJ, Coulson CE, Brennan SL, Leslie E, Nicholson GC,  
484 Kotowicz MA, Berk M. Habitual physical activity and the risk for depressive and anxiety  
485 disorders among older men and women. *International psychogeriatrics*. 2011;23:292-298.
- 486 30. Hiles SA, Baker AL, de Malmanche T, McEvoy M, Boyle M, Attia J. Unhealthy lifestyle may  
487 increase later depression via inflammation in older women but not men. *Journal of psychiatric*  
488 *research*. 2015;63:65-74.
- 489 31. Camacho TC, Roberts RE, Lazarus NB, Kaplan GA, Cohen RD. Physical activity and  
490 depression: evidence from the Alameda County Study. *American journal of epidemiology*.  
491 1991;134:220-231.
- 492 32. Hamer M, Molloy GJ, de Oliveira C, Demakakos P. Leisure time physical activity, risk of  
493 depressive symptoms, and inflammatory mediators: the English Longitudinal Study of Ageing.  
494 *Psychoneuroendocrinology*. 2009;34:1050-1055.
- 495 33. Lucas M, Mekary R, Pan A, Mirzaei F, O'Reilly EJ, Willett WC, Koenen K, Okereke OI,  
496 Ascherio A. Relation between clinical depression risk and physical activity and time spent  
497 watching television in older women: A 10-year prospective follow-up study. *American journal*  
498 *of epidemiology*. 2011;174:1017-1027.
- 499 34. Ioannidis JP. Integration of evidence from multiple meta-analyses: a primer on umbrella  
500 reviews, treatment networks and multiple treatments meta-analyses. *Canadian Medical*  
501 *Association Journal*. 2009;181:488-493.
- 502 35. Schuch FB, Deslandes AC, Stubbs B, Gosmann NP, Silva CT, Fleck MP. Neurobiological  
503 effects of exercise on major depressive disorder: A systematic review. *Neuroscience &*  
504 *Biobehavioral Reviews*. 2016;61:1-11.
- 505 36. Brellenthin AG, Crombie KM, Hillard CJ, Koltyn KF. Endocannabinoid and Mood Responses  
506 to Exercise in Adults with Varying Activity Levels. *Med Sci Sports Exerc*. 2017;49:1688-1696.
- 507 37. Lindqvist D, Dhabhar FS, James SJ, Hough CM, Jain FA, Bersani FS, Reus VI, Verhoeven JE,  
508 Epel ES, Mahan L, Rosser R, Wolkowitz OM, Mellon SH. Oxidative stress, inflammation and  
509 treatment response in major depression. *Psychoneuroendocrinology*. 2017;76:197-205.
- 510 38. Erickson KI, Leckie RL, Weinstein AM. Physical activity, fitness, and gray matter volume.  
511 *Neurobiology of aging*. 2014;35 Suppl 2:S20-S28.
- 512 39. Szuhany KL, Bugatti M, Otto MW. A meta-analytic review of the effects of exercise on  
513 brain-derived neurotrophic factor. *Journal of Psychiatric Research*. 2015;60:56-64.
- 514 40. Toups MSP, Rethorst C, Carmody T, Trivedi MH. Cytokines in the relationship between  
515 exercise treatment and anhedonia and changes in arousal in depressed subjects. *Biological*  
516 *Psychiatry*. 2014;75:48S.
- 517 41. Schuch FB, Vasconcelos-Moreno MP, Borowsky C, Zimmermann AB, Wollenhaupt-Aguiar  
518 B, Ferrari P, de Almeida Fleck MP. The effects of exercise on oxidative stress (TBARS) and BDNF  
519 in severely depressed inpatients. *European archives of psychiatry and clinical neuroscience*.  
520 2014;264:605-613.
- 521 42. Lavebratt C, Herring MP, Liu JJ, Wei YB, Bossoli D, Hallgren M, Forsell Y. Interleukin-6 and  
522 depressive symptom severity in response to physical exercise. *Psychiatry Res*. 2017;252:270-  
523 276.
- 524 43. Cairney J, Faulkner G, Veldhuizen S, Wade TJ. Changes over time in physical activity and  
525 psychological distress among older adults. *The Canadian Journal of Psychiatry*. 2009;54:160-  
526 169.
- 527 44. De Moor MH, Boomsma DI, Stubbe JH, Willemsen G, de Geus EJ. Testing causality in the  
528 association between regular exercise and symptoms of anxiety and depression. *Archives of*  
529 *General Psychiatry*. 2008;65:897-905.
- 530 45. Ku PW, Steptoe A, Chen LJ. Prospective associations of exercise and depressive symptoms  
531 in older adults: the role of apolipoprotein E4. *Quality of Life Research*. 2017:1-10.
- 532 46. Dotson VM, Hsu FC, Langae TY, McDonough CW, King AC, Cohen RA, Newman AB,  
533 Kritchevsky SB, Myers V, Manini TM, Pahor M. Genetic Moderators of the Impact of Physical  
534 Activity on Depressive Symptoms. *The Journal of frailty & aging*. 2016;5:6-14.

- 535 47. Jerstad SJ, Boutelle KN, Ness KK, Stice E. Prospective reciprocal relations between physical  
536 activity and depression in female adolescents. *Journal of consulting and clinical psychology*.  
537 2010;78:268-272.
- 538 48. Roh HW, Hong CH, Lee Y, Oh BH, Lee KS, Chang KJ, Kang DR, Kim J, Lee S, Back JH, Chung  
539 YK, Lim KY, Noh JS, Kim D, Son SJ. Participation in physical, social, and religious activity and risk  
540 of depression in the elderly: A community-based three-year longitudinal study in Korea. *PloS*  
541 *one*. 2015;10 (7) (no pagination).
- 542 49. Veronese N, Solmi M, Maggi S, Noale M, Sergi G, Manzato E, Prina A, Fornaro M, Carvalho  
543 AF, Stubbs B. Frailty and incident depression in community-dwelling older people: Results from  
544 the elsa study. *International journal of geriatric psychiatry*. 2017:No Pagination Specified.

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