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DOI:

[10.1176/appi.ajp.2018.17111194](https://doi.org/10.1176/appi.ajp.2018.17111194)

Document Version

Peer reviewed version

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Citation for published version (APA):

Felipe B. Schuch, Davy Vancampfort, Joseph Firth, Simon Rosenbaum, Phillip B. Ward, Edson S. Silva, Mats Hallgren, Antonio Ponce De Leon, Andrea L. Dunn, Andrea C. Deslandes, Marcelo P. Fleck, Andre F. Carvalho, & Brendon Stubbs (2018). Physical Activity and Incident Depression: A Meta-Analysis of Prospective Cohort Studies. *American Journal of Psychiatry*, 175(7), 631-648. <https://doi.org/10.1176/appi.ajp.2018.17111194>

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

2
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28 **Word count (excluding abstract, references, acknowledgements, tables and figures): 3462**

29 **Tables=3, Figures=1, Supplementary files=3.**

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, I²=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 18st, 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 I² 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

400 Acknowledgments

401 The authors would like to thank to the following authors: Anne Sund, Backmand Heli, Coen van
402 Gool, Emina Hadzibajramovic, Ian Colman, Ingborn Jonsdotirr, Jane Tolstrup, Kylie Ball, Ku-
403 Powen, Kuwahara Keisuke, Lisa Cooper, Magdalena Cerdá, Ness Kiri, Sarah Hiles, Sarah
404 Jerstad, Sebastian Baumeister, Seppo Sarna, Stine Shou Mikkelsen, for the time and effort
405 spent providing the additional information and/or data for this study. BS is supported by the
406 National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health
407 Research and Care South London at King's College Hospital NHS Foundation Trust. The views
408 expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the
409 Department of Health.

410

411 Conflict of interest

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

413

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