DOI:
10.1176/appi.ajp.2018.17111194

Document Version
Peer reviewed version

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

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

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

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Abstract:

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

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

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

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

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

Introduction

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

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

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

Methods

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

Search procedure

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

Inclusion and exclusion criteria

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

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

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

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

Study selection

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

Outcomes

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

Data extraction

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

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

Study quality

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

Meta-analysis

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

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

Results

Search results

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

Studies and participants characteristics

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

Study quality

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

Physical activity and incident depression

Highest versus lowest PA

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

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

Subgroup and sensitivity analysis

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

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

Meta-regressions

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

Discussion

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

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

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

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

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

Limitations and future research

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

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

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

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

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

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

Conclusion

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

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

Acknowledgments

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

Conflict of interest

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

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