Physical Activity Protects from Incident Anxiety: A meta-analysis of prospective cohort studies

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Abstract:

Background: Prospective cohorts have suggested that physical activity (PA) can decrease the risk of incident anxiety. However, no meta-analysis has been conducted. **Aims:** To examine the prospective relationship between PA and incident anxiety and explore potential moderators. **Methods:** Searches were conducted on major databases from inception to October 10, 2018 for prospective studies (at least one year of follow-up) that calculated the odds ratio (OR) of incident anxiety in people with high PA against people with low PA. Methodological quality was assessed using the Newcastle-Ottawa Scale (NOS). A random-effects meta-analysis was conducted and heterogeneity was explored using subgroup and meta-regression analysis. **Results:** Across 14 cohorts of 13 unique prospective studies (N=75,831, median males=50.1%) followed for 357,424 person-years, people with high self-reported PA (versus low PA) were at reduced odds of developing anxiety (Adjusted OR=0.74, 95%CI=0.62, 0.88; crude OR=0.80, 95%CI=0.69, 0.92). High self-reported PA was protective against the emergence of agoraphobia (AOR=0.42, 95%CI=0.18, 0.98) and posttraumatic stress disorder (AOR=0.57, 95%CI=0.39, 0.85). The protective effects for anxiety were evident in Asia (AOR=0.31, 95%CI=0.10, 0.96) and Europe (AOR=0.82, 95%CI=0.69, 0.97); for children/adolescents (AOR=0.52, 95%CI=0.29, 0.90) and adults (AOR=0.81, 95%CI=0.69, 0.95). Results remained robust when adjusting for confounding factors. Overall study quality was moderate to high (mean NOS=6.7 out of 9). **Conclusion**: Evidence supports the notion that self-reported PA can confer protection against the emergence of anxiety regardless of demographic factors. In particular, higher PA levels protects from agoraphobia and posttraumatic disorder.

Declaration of interest: Nothing to declare.

Key words: Agoraphobia, Anxiety, Exercise, Incidence, Panic, Physical Activity, Protection, Post-traumatic stress disorder, Meta-analysis.

Introduction

Anxiety disorders are common and burdensome across the world (Baxter, Vos, Scott, Ferrari, & Whiteford, 2014; Baxter et al., 2014). The point prevalence varies across world regions, ranging between 2.1% (range: 1.8-2.5%) in East Asia up to 6.1% (range: 5.1-7.4%) in North Africa/Middle East (Baxter et al., 2014; Baxter et al., 2014). The prevalence of anxiety symptoms is even higher, at approximately 11% worldwide (Stubbs et al., 2017). Globally, anxiety disorders are the sixth leading cause of disability regarding years of life lived with disability (YLDs) across all ages, and fourth in adults (18-49 years) (Meier et al., 2016). In addition, anxiety disorders are associated with a 39% and 146% increased risk of premature mortality from natural causes and unnatural causes, respectively (Meier et al., 2016).

People with anxiety disorders are at higher risk of cardiometabolic diseases, such as diabetes and acute cardiac events (Edmondson & von Kanel, 2017; Smith, Deschenes, & Schmitz, 2018). This is potentially due to shared etiological biological factors between anxiety and cardiovascular disorders (e.g. increased inflammation and oxidative stress) (da Silva et al., 2017), but also due to modifiable risk behaviors like lower physical activity (PA) levels and increased sedentary behavior (Stubbs et al., 2017; Vancampfort, Stubbs, Herring, Hallgren, & Koyanagi, 2018). Although several previous cross-sectional studies suggest that people with anxiety disorders or higher levels of anxiety symptoms are more likely to engage in lower levels of PA (22.9% vs. 16.6%) (Dillon, McMahon, O'Regan, & Perry, 2018; Stubbs et al., 2017) and spend more time in sedentary activities when compared to people without anxiety (Dillon et al., 2018; Teychenne, Costigan, & Parker, 2015; Vancampfort et al., 2016; Vancampfort et al., 2018), PA is not always inversely associated with anxiety symptoms (Nguyen et al., 2013).

Randomized controlled trials have demonstrated that exercise, the structured and planned form of PA, has anxiolytic effects in people with and without anxiety disorders (Matthew P. Herring, Lindheimer, & O'Connor, 2014; M. P. Herring, O'Connor, & Dishman, 2010; Stubbs B et al., 2017; Davy Vancampfort et al., 2016). Previous reviews have also demonstrated that a single bout of exercise can help alleviate anxiety symptoms in people with anxiety disorders (Strohle et al., 2010). Moreover, previous systematic and non-systematic reviews (Martinsen, 2008; Teychenne et al., 2015) have suggested that higher levels of PA are linked to a decreased risk of future anxiety disorders. No study, however, performed a meta-analysis to estimate the magnitude of the effect. Whilst helpful, the lack of meta-analysis has prevented wider quantitative inferences to be made about this relationship, and reduced the ability to investigate potential

sources of heterogeneity. Thus, it remains unclear if and to what degree PA confers protection against the emergence of anxiety.

Considering the aforementioned gaps in the literature, our aim was to systematically review and meta-analyze prospective cohort studies examining the role of PA in reducing the risk of incident anxiety. We also aimed to explore potential moderators, including age at baseline, geographical location, sex, length of follow-up, study quality, number of covariates used in the model, study sample size, and total person-years.

Methods

This review was conducted following the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) (Stroup et al., 2000) guidelines and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher, Liberati, Tetzlaff, & Altman, 2009) statement. In order to eliminate researcher bias, the search strategy, inclusion criteria and data extraction, as well as the overall and pre-planned subgroup analyses, strictly adhered to those adopted in a previous systematic review of physical activity as a protective factor for incident for depression (Schuch et al., 2018). The protocol was not registered in PROSPERO but is available upon request.

Search procedure

Four researchers (AH, FS, SH, PZ) searched PubMed, Embase, Web of Science and SPORTDiscus from database inception to October 10, 2018 for eligible studies. Keywords included a combination of terms related to PA, anxiety, anxiety disorders and longitudinal design studies, adapted for each database. Full details of the searches and terms used are displayed in 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 anxiety disorders were conducted (Teychenne et al., 2015).

Inclusion and exclusion criteria

Articles were eligible if they met the following criteria: (1) Evaluated participants, of any age, free from anxiety at baseline; (2) Measured PA with a self-report questionnaire (SRQ) such as the International Physical Activity Questionnaire (IPAQ) (Craig et al., 2003), single or multiple questions of exercise, sports

or PA participation, or any objective PA measures (e.g. pedometers, accelerometers). PA definition used in the present study was: any bodily movement produced by skeletal muscles and which requires energy expenditure (Caspersen, Powell, & Christenson, 1985). Only evaluations of high versus low PA, using any criterion, were eligible; (3) Used a prospective cohort study design with a follow-up period of one-year or longer. Prospective cohort studies with less than one year follow up were not included since it may not be considered a sufficient period for risk and protective factors to exert a meaningful influence on mental health symptoms (Cairns, Yap, Pilkington, & Jorm, 2014); (4) Evaluated incident (new cases from baseline to follow-up) anxiety as the outcome, namely increased anxiety symptoms identified via established cut-offs of anxiety screening instruments (e.g. Hospital Anxiety and Depression Scale, Beck Anxiety Scale) (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961); or anxiety disorders, diagnosed using structured or semi-structured diagnostic interviews (e.g. instruments using DSM (American Psychiatric Association, 2013) or ICD criteria (World Health Organisation, 1993)). For the present meta-analysis, we included posttraumatic stress disorder (PTSD) in the analysis as PTSD was considered an anxiety disorder until the DSM-IV; (5) Report an adjusted or non-adjusted odds ratio (OR) and 95% confidence intervals or the raw numbers of exposed and non-exposed participants who developed anxiety at follow-up in a way that allows calculation of OR. In instances where data were not available or additional information was needed, we contacted the corresponding authors up to three times (or until the data were provided, whichever came first) over a 4-week period to request the data to enable inclusion in the present analysis (see acknowledgments).

Excluded were: (1) reviews, commentaries, editorials or any other study without primary data; (2) conference or congress presentations without clear information about the design, methods or the outcomes; (3) studies written in languages other than Dutch, English, French, German, Portuguese or Spanish.

Studies of the same epidemiological cohort were included in different analyses when they reported the results with different metrics (i.e, adjusted and non-adjusted OR). When two or more studies reported 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, four authors (FS, SH, AH, PZ) independently screened titles and abstracts of all articles retrieved from the search in duplicate. Afterward, the full-text of potentially eligible

references were reviewed in detail by the same investigators. Disagreements were resolved through discussion until consensus was achieved.

Outcomes

The primary outcome was the adjusted odds ratio (AOR) for incident anxiety or anxiety disorders and 95% confidence interval (CI).

Data extraction

One author extracted (FS) and a second cross-checked (SH) the data including geographical location, name of cohort, number of participants included at baseline, age at baseline, % of females, 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]), anxiety assessment (e.g. instrument and cut-off used, diagnostic criteria, medical records), follow-up period, odds ratio and 95% confidence interval, and covariates. Data from figures were extracted using GetData Graph Digitizer (version 2.26).

Study quality

The Newcastle-Ottawa Scale (NOS) was used to assess the methodological quality of studies by two authors (FS and JM). The NOS scale evaluates the risk of bias of prospective studies with three domains: (a) selection of participants, with four items assessing (a.1) representativeness of the exposed cohort, (a.2) same derivation between source of exposed and non-exposed participants, (a.3) ascertainment of the exposure and (a.4) demonstration that the outcome of interest was not present at the baseline, (b) comparability, with one item regarding comparability of cohorts on the basis of the design of the analysis; studies where the OR were calculated on the basis of the raw number of participants provided from the original papers or did not present adjusted analyses received zero points for comparability, and (c) outcomes, with three items regarding (c.1) adequate assessment of the outcome of interest, (c.2) adequate duration of follow-up and (c.3) adequacy of follow-up. A study can be awarded a maximum of one point for each numbered item within the selection (a), and outcome (c) categories and a maximum of two stars can be given for comparability. The maximum score according to the NOS scale is 9 (highest quality).

Scores of 0–3, 4–6 and 7–9 were assigned for the low, moderate and high quality of studies, respectively (Wu et al., 2015). 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 anxiety. First, we pooled data across all studies comparing incident anxiety (henceforth overall analysis) 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 (reference group). Analysis for adjusted (AOR) and crude OR were conducted separately. For the AOR we pooled the estimates using the model with the greatest number of covariates presented by the authors. Second, subgroup analyses were conducted investigating the protective effects of PA on different anxiety classifications (anxiety symptoms only, any diagnosed anxiety disorders, and specific anxiety disorders, whenever data were available), continents, age groups of the sample at baseline (e.g. children/adolescents [<18 years], adults [18-65 years] or elderly [>65 years]), PA assessments (e.g. comparison of high and low PA-based on intensity, frequency, volume [time spent in PA] or a composition of two or more variables including metabolic equivalents [METS] units), and adjustments for potential confounders in AOR analysis (age and sex, body mass index [BMI] and, smoking, age and sex and either BMI or smoking, and age and sex and both BMI and smoking). Third, we evaluated potential moderators through meta-regression for AOR. The moderators tested were, length of follow-up, person-years, total number of participants at baseline, study quality according to the NOS overall score, and the individual NOS scores for the selection of participants, outcome and comparability, and the number of covariates included in the model. The covariates tested were chosen based on previous studies to evaluate whether studies with greater sample size, length of follow-up or greater person-years were more powered to detect stronger effects, and to understand if studies with lesser bias risk or more adjusted for potential covariates are more likely to find significant or larger effects (Schuch et al., 2018; Thompson & Higgins, 2002). Fourth, we evaluated the publication bias using the Begg and Mazumdar (Begg & Mazumdar, 1994) and Egger tests (Egger, Smith, Schneider, & Minder, 1997) and corrected through the Duval and Tweedie trim and fill procedure (Duval & Tweedie, 2000). To maximize statistical power, studies pooling participants with incident anxiety disorders along with incident depressive disorders were included in the main analysis. However, a sensitivity analysis excluding those papers was performed to evaluate

whether they influenced the obtained results. The Q and I^2 statistic were used to assess and to quantify the heterogeneity, respectively. Scores of <25%, 25-50% and >50% indicated low, moderate and high heterogeneity, respectively (Higgins, Thompson, Deeks, & Altman, 2003). 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 (Rosenthal, 1979). All analyses were performed using Comprehensive Meta-Analysis software (version 3).

Results

Search results

The initial search identified 9,966 titles. After the removal of duplicates, 7,382 abstracts were considered. At the full-text review stage, 93 studies were assessed for eligibility and 80 were subsequently excluded (see supplementary figure 1 for the flowchart and supplementary material 2 for a list of excluded articles). One study was found using the reference lists of previously published studies. In total, 14 cohorts of 13 unique prospective studies were included in this review (Baumeister et al., 2017; Beard, Heathcote, Brooks, Earnest, & Kelly, 2007; Cynthia et al., 2011; Da Silva et al., 2012; Jonsdottir, Rodjer, Hadzibajramovic, Borjesson, & Ahlborg, 2010; Kang et al., 2015; McDowell et al., 2018; McDowell, Gordon, Andrews, MacDonncha, & Herring, 2018; Muller, Ganeshamoorthy, & Myers, 2017; Pasco et al., 2011; Sanchez-Villegas et al., 2008; Strohle et al., 2007; Ten Have, de Graaf, & Monshouwer, 2011; Zainal & Newman, 2018).

Studies and participants characteristics

Across the 14 cohorts of 13 unique prospective studies, 75,831 individuals were included, with nearly equal sex distribution (median 50.1% males; interquartile range (IQ) = 43.72 to 65.37), followed up for a median of 3.5 years (IQ = 2.0 to 6.5). The total person-years was 357,424. Eleven cohorts provided data for AOR (n=69,037) and six cohorts provided for OR (n=22,902). No study used an objective measure to evaluate PA. Across the 14 cohorts, ten studies evaluated anxiety disorders using structured or semi-structured diagnostic instruments or self-reported physician diagnosis of anxiety disorders, and four used cut-offs of anxiety screening instruments. A description of the included studies can be found in table 1. Detailed information on PA classification within studies can be seen at supplementary table 1.

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Study quality

The mean (SD) NOS score was 6.71 (0.9), which is suggestive for a moderate to high methodological quality and a low risk of bias of the included studies. More detailed information about the quality assessment of the studies included in this meta-analysis can be seen in the supplementary table 2.

Physical activity and incident anxiety

Highest versus lowest PA

Higher self-reported PA levels were associated with decreased incident anxiety when compared to lower PA levels in adjusted (AOR=0.74, 95% CI=0.62, 0.88, p=0.001, I^2=23.96, Q-value=13.15 p=0.21, N=11, n=69,037) (figure 1) and crude odds ratio analyses (OR=0.80, 95% CI=0.69, 0.92, p=0.002, I^2=0.00, Q-value=3.78, p=0.57, N=7, n=22,902) (supplementary figure 2). Publication bias was evident for the AOR analysis in the Egger's (intercept=-1.61, p=0.01) but not in the Begg and Mazumdar (Tau=-0.21, p=0.35) test. Both Egger's (intercept=-1.29, p=0.05) and the Begg and Mazumdar (Tau=-0.66, p=0.06) are suggestive of publication bias for crude odds ratio analysis. The adjusted values, according to the Duval and Tweedie trim and fill technique remained significant: AOR=0.86 (95% CI=0.69, 0.99) and OR=0.83 (95% CI=0.72, 0.95). The number of studies with negative results required to nullify the effects of PA on incident anxiety were 40 and 13, in AOR and OR analyses, respectively.

Subgroup analyses

Subgroup analyses were performed in order to explore the effects of self-reported PA on incident anxiety symptoms only, on anxiety disorders, excluding anxiety symptoms, on specific disorders (posttraumatic stress disorder [PTSD], obsessive-compulsive disorder [OCD], generalized anxiety disorder [GAD], social phobia, panic, agoraphobia) and, exploring potential differences across different geographical regions, age groups, PA assessments, completers of the public health recommended dose of PA, and the use of potential confounders. Subgroup analyses were performed both for adjusted and crude analysis. The results are briefly summarized below and the detailed results of subgroups analyses can be seen in table 2. The detailed list of studies included in each analysis can be seen in supplementary table 3 for AOR and supplementary 4 for OR.

Analysis of adjusted data reported in studies

Higher self-reported PA levels decreased the risk of incident anxiety disorders (AOR=0.62, 95% CI=0.62, 0.88). PA had significant protective effects against the development of agoraphobia (AOR=0.42, 95% CI=0.18, 0.98) and PTSD (AOR=0.57, 95% CI=0.39, 0.88), with no significant effects among the other analyzed anxiety disorders, including phobias, panic and generalized anxiety disorder. The protective effects were significant across two continents: Asia (AOR=0.31, 95% CI=0.10, 0.96), and Europe (AOR=0.82, 95% CI=0.69, 0.97); for children/adolescents (AOR=0.52, 95% CI=0.29, 0.90) and adults (AOR=0.81, 95% CI=0.69, 0.95). Instruments assessing PA according to different intensities (AOR=0.58, 95% CI=0.40, 0.83), or METS (AOR=0.77, 95% CI=0.59, 1.00) found that higher intensity or energetic expenditure during PA were significantly associated with reduced incident anxiety. Also, completing the recommendation of 150 minutes of moderate/vigorous PA was associated with a lower risk of incident anxiety (AOR=0.71, 95% 0.54, 0.94). Analyses adjusting for age and sex, BMI, or combining age, sex, with BMI or smoking were significant.

Analysis of crude data reported in studies

In non-adjusted analyses, higher levels of self-reported PA conferred protective effects on the emergence of anxiety symptoms (OR=0.74, 95% CI=0.59, 0.92). There were no studies presenting crude ORs for specific anxiety disorders. Effects were only significant for studies in Europe (OR=0.75, 95% CI=0.59, 0.94) and those that included older adults at baseline (OR=0.73, 95% CI=0.58, 0.92). Studies that established PA using questions on measures based in METS or combined intensity, frequency or volume of PA found significant effects (OR=0.83, 95% CI=0.71, 0.96). Performing at least 150 minutes of moderate or vigorous PA per week conferred protective effects (OR=0.77, 95% CI=0.60, 0.97).

Sensitivity analysis

One study (Pasco et al., 2011) pooled data for the incidence of depression and anxiety disorders together and one study used self-report of physician diagnosis of anxiety as the outcome measure (Sanchez-Villegas et al., 2008). Sensitivity analyses removing the study that pooled depression and anxiety together (AOR=0.75, 95% CI=0.63, 0.90), or the study that used self-report of physician diagnosis of anxiety as the outcome measure did not change the findings (AOR=0.73, 95% CI=0.60, 0.90), or removing both (AOR=0.74, 95% CI=0.60, 0.91) have not changed the protective effects of PA on incident anxiety.

Meta-regression

We explored the potential moderating role of sample size at baseline, the length of follow-up, individual study person-years, the % of males, the number of covariates used in each study for adjusted analyses and the study quality according to the NOS scale. All variables tested were used as continuous variables. No significant moderators were identified via meta-regression (table 3).

Discussion

To the best of our knowledge, this is the first meta-analysis demonstrating that higher levels of self-reported PA are associated with a decreased risk of both anxiety symptoms and anxiety disorders in people free of anxiety at baseline. This protective effect of self-reported PA was evident across Asia and Europe, children/adolescents and adults, regardless of how self-reported PA was captured and after the adjustment for publication bias and other confounders such as age, sex, smoking, and BMI. Specifically, our data suggest that people with higher levels of self-reported PA have a 27% and 21% lower risk for developing anxiety when compared to people with lower levels of self-reported PA, even after adjusting for potential confounders, in AOR and OR analyses respectively.

The protective effects of self-reported PA on anxiety development are in line with previous cross-sectional studies showing that lower PA levels are associated with current anxiety symptoms (da Silva et al., 2014), and that exercise training has anxiolytic effects in people with and without anxiety disorders (Herring et al., 2014; Herring et al., 2010; Stubbs et al., 2017). In the present study, we have found initial evidence that PA has potential protective effects on incident-specific anxiety disorders, such as agoraphobia and PTSD. No protective effects on another diagnosis, such as panic, OCD, social phobia, specific phobias or GAD were found. Previous cohorts have found the existence of disorder-specific risk factors (Blanco et al., 2014). For instance, early parental loss is a protective factor for panic (OR=0.9, 95%CI=0.7-1.0), but a risk factor for PTSD (OR=1.2, 95%CI 1.0-1.4) (Blanco et al., 2014). Although we have found effects only for PTSD and agoraphobia, due to the small number of studies included in subgroup analysis, only 2 studies provided data for incident agoraphobia (Strohle et al., 2007; Ten Have et al., 2011), PTSD (LeardMann et al., 2011; Strohle et al., 2007), panic (Strohle et al., 2007; Ten Have et al., 2011), OCD (Strohle et al., 2007; Ten Have et al., 2011), social phobia (Strohle et al., 2007; Ten Have et al., 2011) and specific phobias (Strohle et al., 2007; Ten Have et al., 2011), and four for GAD (McDowell et al., 2018; Strohle et al., 2007; Ten Have et al., 2011; Zainal & Newman, 2018), it is

precocious to determine whether these effects are common to all anxiety disorders or are disorder-specific and more research is needed to adequately address this point.

The potential mechanisms that may underlie the protective effects of self-reported PA on incident anxiety are unclear. From a biological perspective, self-reported PA influence some of the core biological processes thought to be involved in the onset of anxiety; for instance, habitual self-reported PA may promote neuroregeneration, as shown by increased levels of neuroregeneration markers, such as brain-derived neurotrophic factor (Szuhany, Bugatti, & Otto, 2015) or the balance between inflammatory/anti-inflammatory (Gleeson et al., 2011) and oxidative/anti-oxidative markers (Bogdanis et al., 2013; Schuch et al., 2014). Research in healthy adults has shown that higher levels of PA can reduce IL-6 and this may be the mechanism through which it exerts its protective effect (Jankord & Jemiolo, 2004). From a psychological perspective, self-reported PA can reduce anxiety sensitivity (Asmundson et al., 2013), which is the main focus in the genesis and maintenance of panic and other anxiety disorders (Paulus, Gallagher, Bartlett, Tran, & Vujanovic, 2018). Also, engaging in PA, particularly structured exercise, may directly improve psychological factors such as increasing self-efficacy regarding the ability to exert control over potential threats (Anderson & Shivakumar, 2013), thereby reducing the risk of developing anxiety. The role of self-reported PA in anxiety may also not necessarily be causal, but pleiotropic, with common genetic factors underlying both propensity to exercise and mental health problems (De Moor, Beem, Stubbe, Boomsma, & De Geus, 2006).

The present study is, however, not free from limitations. First, evidence of publication bias was encountered both for adjusted and crude analysis. Nonetheless, the analyses remained significant after adjusting for publication bias, trimming three studies in each analysis: AOR=0.80 (95% CI=0.66 to 0.98) and OR=0.82 (95% CI=0.70 to 0.95). The publication bias found is at best modest and have not changed the overall effect size significantly. Second, we have included only 11 studies that provided effects adjusting for relevant covariates and 6 studies that provided crude OR and the results should be read with this limitation in consideration. The small number of studies also affects the subgroup analyses for many of the potential moderators, that should be considered in light of a potential lack of statistical power to drawn definitive conclusions. Similarly, given the few numbers of studies that could be included, we were likely underpowered to detect significant linear moderators of the relationship between PA on anxiety. Third, the included studies assessed self-reported PA levels in a time frame of days or weeks. Thus, it is not clear whether being engaged in higher levels of self-reported PA for longer periods implies greater

protection in comparison to shorter periods, nor whether increasing or decreasing PA over the years would alter the protective effects. Fourth, no studies applied objective measures of PA, which makes the present analyses more vulnerable to recall biases, potentially resulting in over or even under estimations when compared to objective measures (Dyrstad, Hansen, Holme, & Anderssen, 2014). Also, only 5 of the included studies used validated PA measures and PA characterization differed across instruments. Fifth, studies included in this meta-analysis did not specifically exclude people with incident depression from analysis, which is highly comorbid with anxiety and also associated with low PA. Previous meta-analytic evidence demonstrates that PA is protective against depression, with a slightly higher AOR than observed here for anxiety (AOR=0.83, 95% CI=0.79, 0.88; I^2=0.00, N=49) (Schuch et al., 2018). Although it is possible that the effect of PA on anxiety is in part mediated through the effect of PA on depression, previous research that effects of exercise on anxiety are equal to and independent of effects of exercise on depression (Hiles, Lamers, Milaneschi, & Penninx, 2017). Sixth, it is unclear whether the use of psychotropic medications, particularly the off-label use influence this relationship (Bernard & Carayol, 2015). Last, two studies identified in our screening presented their results in risk ratio or hazard ratio (Brunes, Gudmundsdottir, & Augestad, 2015; Yu, Ter Riet, Puhan, & Frei, 2017), and one using a referent group different than the lower or the higher self-reported PA levels (Harvey et al., 2017), could not be included in the meta-analysis. Of these, two studies, are in accordance with the findings of the present meta-analysis (Brunes et al., 2015; Yu et al., 2017), and one not (Harvey et al., 2017).

In light of these limitations, we propose that: 1) further well-designed prospective studies using nationally representative samples and validated and objective PA measures are warranted; 2) the effects of different PA types and 'dosages' on subsequent risk for anxiety and anxiety disorders should be investigated; 3) 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 anxiety.

Anxiety is a highly prevalent disorder and one of the leading causes of global burden and our data suggests that higher levels of PA may confer protection against new cases in the general population. Given the established health benefits of PA more broadly, our data add further evidence to the growing calls for the necessity to promote PA at the population-level. This goal is facilitated by multiple layers of intervention – from individual-level healthcare, workplace and education-based health behaviour change or PA programs, to broad-scale national policy change including urban planning to create PA-promoting,

accessible and clean environments. Increasing PA should be considered a priority on preventing mental and physical chronic conditions and reducing overall mortality.

Conclusion

Higher levels of self-reported PA are associated with lower odds of developing future anxiety and anxiety disorders. Our data further emphasize the importance of policies targeting increased PA levels to reduce incident anxiety.

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Conflict of Interest:

The authors declare no conflict of interest.

Authors contribution:

FS and BS designed the protocol of the study. FS, AH, SH and PZ performed the searches within the this found. FS and SH extracted the data from the studies. FS and JM evaluated the quality of the studies. All authors have read and contributed with the interpretation of the results, and with the elaboration of the text.

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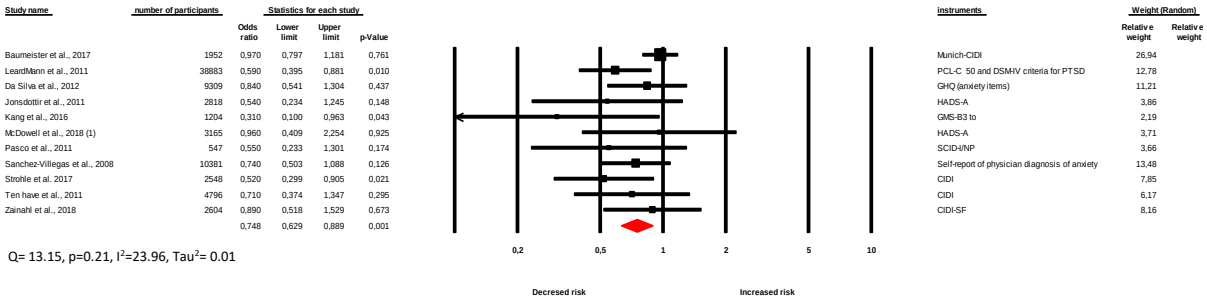

Figure 1. Forest plot using random effect model of studies examining the impact of PA on incident anxiety. Effect size estimates are based on adjusted odds ratios (AORs) and 95% confidence intervals (CI) reported by studies.

Table 1. Description of studies

Study	Acronym	n	Follow-up (years)	Persons-years	Country	National representative	% males	Age group at baseline	Anxiety/stress disorder definition	PA measure	PA parameters
Baumeister et al., 2017 [1]‡	Study of Health in Pomerania (SHIP)	1952	4.5	8784	Germany	No	49.7	adults	Munich-CIDI	Baecke questionnaire	frequency
Beard et al., et al., 2007 [2]	Northern Rivers Mental Health Study (NoRMHS)	968	2	1936	Australia	No	43.3	adults	CIDI OR DIS	PA questionnaire (not specified)	volume
Da Silva et al., 2012 [1,2]	The Whitehall II study	9309	8	74472	UK	No	68.5	adults	GHQ (five items for anxiety scores >= 8)	Two questions on time and intensity of PA	METS/Composed
Jonsdottir et al., 2010 [1,2]	-	2818	2	5636	Sweden	No	13	adults	HADS-A > 10	Adapted Santin and Grimby scale	intensity
Kang et al., 2016 [1,2]*	-	745	2	1490	Korea	No	48.5	older adults	GMS-B3 together with the AGECAT	Active versus inactive lifestyle “estimated by measuring work and leisure activities”	?
LeardMann et al., 2011 [1]	The Millennium Cohort Study	30218	3	90654	US	No	77.7	adults	PCL-C ≥ 50 and DSM-IV criteria for PTSD	Questions on average number of minutes/day and days/week in strength training, vigorous physical activity, and moderate or light physical activity.	METS/Composed
McDowell et al., 2018 (1) [1,2]	The Irish Longitudinal Study on Ageing (TILDA)	3165	2	6330	Ireland	No	?	older adults	HADS-A >= 8	IPAQ	METS/Composed

McDowell et al., 2018 (2)	The Irish Longitudinal Study on Ageing (TILDA)	3236	2	6472	Ireland	No	43.8	older adults	CIDI-SF	IPAQ	METS/Composed
Muller et al., 2017 [2,*]	Veterans Exercise Testing Study (VETS)	5826	9.6	55929	US	No	96.4	adults	PTSD (ICD-9-CM 309.81) as diagnosed and recorded electronically by the patient's primary care physician	One question on engagement in moderate to vigorous PA, at least 3 times per week	?
Pasco et al., 2011 [2]	Geelong Osteoporosis Study (GOS)	547	4.1	2242	Australia	No	56	older adults	SCID-I/NP	PASE	METS/Composed
Sanchez-Villegas et al., 2008 [1]	The SUN study (Seguimiento University of Nav arra)	10381	6	62286	Spain	No	?	adults	Self-report of physician diagnosis of anxiety	Questionnaire assessing time spent in 17 PA per week	METS/Composed
Strohle et al., 2007 [1]	Early Developmental Stages of Psycho-pathology (EDSP)	2501	4	9832	Germany	Yes	50.9	children/adolescents	CIDI	Four questions on PA frequency	frequency
Ten Have et al., 2011 [1]	Netherlands Mental Health Survey and Incidence Study (NEMESIS)	4796	3	14388	Netherlands	Yes	50.6	adults	CIDI	Single question on hours per week of exercise	volume
Zainal et al., 2018	Midlife Development in the United States (MIDUS)	2605	9	23445	US	Yes	43.7	adults	CIDI-SF	Unclear	?

Key: [1] = adjusted Odds Ratio (OR); [2] = crude OR; ‡ = Data sent by the author; * = Data were calculated using raw numbers; AGECAT= Automated Geriatric Examination for Computer-Assisted Taxonomy algorithm; CIDI= World Mental Health Composite International Diagnostic Interview; DIS= Diagnostic Interview Schedule; DSM=Diagnostic and Statistical Manual for Mental Disorders; GHQ=General Health Questionnaire; GMS-B3 = Geriatric Mental State Schedule; HADS-A= Hospital Anxiety and Depression Scale; ICD=International Classification of Disease; IPAQ=International Physical Activity Questionnaire; METS=Metabolic equivalents; PA=Physical Activity; PCL-C=PTSD Checklist Civilian Version; PASE=Physical Activity Scale for the Elderly; SCID-I/NP=**Structured Clinical Interview for DSM-IV Axis I Disorders, non-patient version; UK = United Kingdom; US = United States**.

Table 2. Subgroup analysis exploring the effects of PA on incident anxiety in different continents, physical activity assessment unity, presence of diagnosed depression and age.

Analysis			Meta-analysis				Heterogeneity			Classic fail safe N
Studies with adjusted odds ratio (AOR)	**Number of cohorts (arms)**	**Number participants**	**AOR**	**95% CI**		**P value**	**I^2**	**Q**	**P value**	
Overall	11	69,037	0.748	0.629	0.889	**0.001**	23.96	13.15	0.21	40
Diagnosis										
Any disorder	8	56,236	0.748	0.608	0.921	**0.006**	35.83	9.35	0.18	17
Anxiety symptoms	4	16,037	0.711	0.483	1.046	0.083	13.77	3.47	0.32	1
Agoraphobia	2	7,297	0.426	0.185	0.988	**0.047**	0.00	0.14	0.70	n/a
Panic	2	7,317	0.417	0.141	1.222	0.111	0.00	0.76	0.38	n/a
OCD	2	7,333	1.002	0.213	4.714	0.998	0.00	0.12	0.73	n/a
PTSD	2	32,753	0.579	0.393	0.855	**0.006**	0.00	0.12	0.72	n/a
Social phobia	2	7,220	0.790	0.411	1.506	0.473	0.00	0.79	0.37	n/a
Specific phobia	2	7,076	0.653	0.401	1.048	0.074	0.00	0.14	0.70	n/a
GAD	4	13,164	0.768	0.488	1.209	0.255	0.00	1.18	0.75	0
Continent										
Asia	1	745	0.310	0.100	0.963	**0.043**	0.00	0.00	0.00	n/a
North America	2	32,823	0.695	0.468	1.031	0.071	30.12	1.43	0.23	n/a
Europe	7	34,922	0.821	0.692	0.976	**0.025**	11.36	6.77	0.34	8
Oceania	1	547	0.555	0.233	1.301	0.174	0	0	0.00	n/a
Age at baseline										

Adults	7	62,079	0.815	0.695	0.957	**0.013**	12.18	6.83	0.33	11
Children/adolescents	1	2,051	0.520	0.299	0.901	**0.021**	0.00	0.00	0.00	n/a
Older	3	4,457	0.593	0.324	1.083	0.089	20.21	2.50	0.28	n/a
PA assessment										
Frequency	2	4,453	0.751	0.412	1.370	0.351	76.87	4.32	0.03	n/a
Intensity	2	33,036	0.580	0.405	0.830	**0.003**	0.00	0.03	0.85	n/a
METS/composed	4	23,402	0.772	0.594	1.000	0.050	0.00	1.03	0.79	0
Volume	1	4,796	0.710	0.374	1.347	0.295	0.00	0.00	0.00	n/a
150 min mod/vig PA per week	3	42,692	0.717	0.542	0.949	**0.020**	0.00	1.85	0.70	n/a
Adjustment										
Age and sex	10	68,292	0.779	0.667	0.910	**0.002**	13.75	10.43	0.31	27
BMI	5	36,188	0.680	0.541	0.851	**0.001**	0.00	2.14	0.71	10
smoking	5	45,191	0.810	0.639	1.028	0.083	32.60	5.93	0.20	2
Age and sex + (BMI or smoking)	7	51,686	0.795	0.656	0.963	**0.019**	20.96	7.59	0.27	9
Age and sex + BMI + smoking	5	45,191	0.810	0.639	1.028	0.083	32.60	5.93	0.20	2
Studies with crude odds ratio (OR)			**OR**	**95% CI**		**P value**	**I^2**	**Q**		
Overall	6	22,902	0.804	0.699	0.924	**0.002**	0.00	3.798	0.57	13
Diagnosis										
Any disorder	3	10,030	0.676	0.361	1.269	0.223	38.76	3.26	0.19	n/a
Anxiety symptoms	4	16,037	0.741	0.597	0.920	**0.007**	0.00	0.86	0.75	4
Continent										
Asia	1	745	0.650	0.320	0.920	0.234	0.00	0.00	0.00	n/a
North America	1	5,826	0.910	0.707	1.171	0.464	0.00	0.00	0.00	n/a
Europe	3	15,292	0.751	0.599	0.943	**0.014**	0.00	0.72	0.60	2
Oceania	1	968	0.470	0.119	1.858	0.282	0.00	0.00	0.00	n/a
Age at baseline										
Adults	4	18,921	0.850	0.712	1.014	0.072	0.00	2.63	0.45	1
Older	2	3,910	0.735	0.587	0.921	**0.007**	0.00	0.18	0.22	n/a
PA assessment										

Intensity	1	2,818	0.550	0.242	1.248	0.153	0.00	0.00	0.00	n/a
METS/composed	3	18,300	0.833	0.719	0.965	**0.015**	0.00	1.37	0.50	n/a
Volume	1	968	0.470	0.094	2.358	0.359	0.00	0.00	0.00	n/a
150 min mod/vig PA per week	2	12,474	0.771	0.609	0.977	**0.031**	0.00	0.11	0.64	n/a

Key: AOR= Adjusted odds ratio; BMI=Body mass index; CI=Confidence interval; n/a= Not available; GAD=Generalized Anxiety Disorder; METS/Composed=Metabolic equivalents; OCD=Obsessive Compulsive Disorder; OR=Odds Ratio; PA=Physical activity; PTSD=Post-traumatic Stress Disorder.

Table 3: Univariate meta-regression of moderators of the effects of PA on incident anxiety for overall analyses at a time.

Moderator	Number cohorts	β	95% CI		P value	R^2
Studies presenting AOR						
Sample size	11	<-0.001	<-0.001	<0.001	0.23	0.45
Length of follow up	11	0.048	-0.043	0.139	0.30	0.00
Person-years	11	<0.001	<-0.001	<0.001	0.62	0.00
Number of covariates	9	-0.010	-0.054	0.032	0.62	0.11
% of dropout	8	<-0.001	<-0.026	0.020	0.80	0.00
Study quality	11	-0.100	-0.522	0.321	0.64	0.00
Study quality (selection of participants)	11	0.091	-0.385	0.567	0.95	0.00
Study quality (comparability)	11	0.410	-0.203	1.023	0.19	0.41
Study quality (outcome)	11	-0.568	-1.084	0.052	0.06	1.00

Key: AOR= Adjusted odds ratio; CI=Confidence interval; PA=Physical activity