Physical Activity and Incident Depression: A Meta-Analysis of Prospective Cohort Studies

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Objective: The authors examined the prospective relationship between physical activity and incident depression and explored potential moderators.

Method: Prospective cohort studies evaluating incident depression were searched from database inception through Oct. 18, 2017, on PubMed, PsycINFO, Embase, and SPORTDiscus. Demographic and clinical data, data on physical activity and depression assessments, and odds ratios, relative risks, and hazard ratios with 95% confidence intervals 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.

Results: A total of 49 unique prospective studies (N=266,939; median proportion of males across studies, 47%) were followed up for 1,837,794 person-years. Compared with people with low levels of physical activity, those with high levels had lower odds of developing depression (adjusted odds ratio=0.83, 95% CI=0.79, 0.88; I^2=0.00). Furthermore, physical activity had a protective effect against the emergence of depression in youths (adjusted odds ratio=0.90, 95% CI=0.83, 0.98), in adults (adjusted odds ratio=0.78, 95% CI=0.70, 0.87), and in elderly persons (adjusted odds ratio=0.79, 95% CI=0.72, 0.86). Protective effects against depression were found across geographical regions, with adjusted odds ratios ranging from 0.65 to 0.84 in Asia, Europe, North America, and Oceania, and against increased incidence of positive screen for depressive symptoms (adjusted odds ratio=0.84, 95% CI=0.79, 0.89) or major depression diagnosis (adjusted odds ratio=0.86, 95% CI=0.75, 0.98). No moderators were identified. Results were consistent for unadjusted odds ratios and for adjusted and unadjusted relative risks/hazard ratios. Overall study quality was moderate to high (Newcastle-Ottawa Scale score, 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 physical activity can confer protection against the emergence of depression regardless of age and geographical region.

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Depressive disorders are the second leading cause of global burden of illness and account for more than 44 million years lived with disability (1). They are associated with heightened medical comorbidity (2), increased health care 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 needed (5).

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

Given these gaps, our aims were to systematically review and meta-analyze prospective cohort studies examining the role of physical activity in reducing the risk of incident depression; 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; and to evaluate the quality of the studies.

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METHOD

This review adhered to the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) (11) guidelines and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (12) statement, following a protocol defined a priori (available on request).

Search Procedure

Two researchers (F.B.S., E.S.S.) searched PubMed, Embase, PsycINFO and SPORTDiscus from database inception to Oct. 18, 2017. Searches were adapted for each database, using keywords that included a combination of terms related to physical activity, depression, and longitudinal studies. (The searches are described in detail in the data supplement that accompanies the online edition of this article.) Manual searches were conducted of the reference lists from recovered articles and other systematic reviews investigating the association between physical activity, sedentary behavior or fitness, and depression (9, 10, 13, 14).

Inclusion and Exclusion Criteria

Articles were eligible if they met the following criteria:

1. The study evaluated participants, of all ages, who were free of depression or depressive symptoms at baseline.
2. Physical activity was measured with a self-report questionnaire, such as the International Physical Activity Questionnaire (15), single or multiple questions on participation in exercise, sports, or physical activity, or objective physical activity measures (e.g., accelerometers). Physical activity was defined as any bodily movement produced by skeletal muscles and requiring energy expenditure (16).
3. The study used a prospective design with at least 1 year of follow-up. Prospective studies with less than 1 year of follow-up were excluded, as this was not considered a sufficient time frame for risk and protective factors to exert a meaningful influence on depressive symptoms (17).
4. The study evaluated incident depression as the outcome, including increased depressive symptoms, through established cutoffs of depression screening instruments (e.g., the Beck Depression Inventory [18]) or based on tertiles, quartiles, or quintiles of depressive symptoms or on presence of major depressive disorder, diagnosed using structured or semistructured diagnostic interviews (e.g., instruments using DSM [19] or ICD criteria [20]) or through a self-report of physician diagnosis of depression.
5. The study reported an adjusted or unadjusted odds ratio, hazard ratio, or relative risk and 95% confidence intervals or the raw numbers of exposed and nonexposed participants who developed depression over the course of follow-up, in a way that allows calculations of odds ratios or relative risks. In instances when data were not available, we contacted corresponding authors to request the data to enable inclusion in our meta-analysis. To compare with most of the risk measures selected for the meta-analysis, the odds ratio, relative risk, or hazard ratio of studies using the lowest physical activity 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 odds ratio, relative risk, or hazard ratio (21).

We excluded studies without primary data (reviews, commentaries, editorials); conference presentations without information about the methods or the outcomes; studies in languages other than English, Portuguese, or Spanish; and studies that evaluated physical activity as a continuous measure.

Studies of the same epidemiological cohort were included only when they reported the results in different metrics (odds ratio or relative risk/hazard ratio). For example, if one study reported odds ratio and another relative risk, each one was included in their respective analyses. 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 reported data from 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 (F.B.S., E.S.S.) independently screened titles and abstracts of all articles retrieved from the search. Afterward, the full text of potentially eligible references was reviewed in detail by the same investigators. Disagreements were resolved through discussion until consensus was achieved. A third reviewer (B.S.) was available for mediation.

Outcomes

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

Data Extraction

Five authors (F.B.S., E.S.S., M.H., J.F., and S.R.) independently extracted data, including geographical location, name of cohort, number of participants included at baseline, age at baseline, physical activity assessment (instrument or questions used, what aspects of physical activity were considered by the measure to define physical activity levels [e.g., frequency, intensity, time, type, amount of energy expended, steps, or other]), depression assessment (e.g., instrument and cutoff used, diagnostic criteria, medical records), follow-up period, odds ratio, relative risk, or hazard ratio and 95% confidence interval, and the number of covariates. The data utilized for the adjusted meta-analysis were those of the most adjusted model presented in each of the respective reports.

Study Quality

The methodological quality of studies was assessed with the Newcastle-Ottawa Scale by two authors (F.B.S. and S.R.). The

Newcastle-Ottawa Scale uses three elements to evaluate the risk of bias of prospective studies: 1) selection of participants (four items: representativeness of the exposed cohort, equal derivation between source of exposed and nonexposed participants, ascertainment of the exposure, and demonstration that the outcome of interest was not present at the start of the study); 2) comparability (one item: comparability of cohorts on the basis of the design of the analysis) (studies where the odds ratio or relative risk were calculated on the basis of the raw number of participants provided from the original reports received zero points for comparability); and 3) outcomes (three items: adequate assessment of outcome, adequate follow-up time, and adequacy of follow-up). A study can be awarded a maximum of 1 point for each numbered item within the selection and outcome categories, and a maximum of two points can be given for comparability. The maximum score on the Newcastle-Ottawa Scale is 9 (highest quality), and we assigned scores of 0–3, 4–6, and 7–9 for low, moderate, and high quality of studies, respectively (22). In case of disagreement, a consensus was reached through discussion.

Meta-Analysis

A random-effects meta-analysis was conducted investigating the relationship between baseline physical activity level and incident depression. Procedures included first pooling data across all studies comparing the incident depression in the highest physical activity level group (the group with greater frequency, intensity, volume, energetic expenditure, or other, from each study, as defined by the study authors) and the lowest physical activity level group (reference group). Analysis for adjusted odds ratio, crude odds ratio, adjusted relative risk/hazard ratio, and crude relative risk/hazard ratio were conducted separately. Specifically, adjusted odds ratio, odds ratio, relative risk/hazard ratio, adjusted relative risk/hazard ratio, and 95% confidence intervals were calculated for incident depression. For the adjusted odds ratio and adjusted relative risk/hazard ratio, 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 physical activity levels were assessed (e.g., asking about intensity, frequency, volume [time spent in physical activity], or composite variables including two or more variables, and studies using metabolic equivalents as units were classified together with the metabolic equivalents category); 3) the mean age of the sample at baseline (e.g., children and adolescents [<18 years of age], adults [ages 18–65], or elderly persons [over age 65]; 4) the use of self-report questionnaires or objective measures to assess physical activity; 5) depression assessment method, including screening instruments, major depression diagnosis, assessed by structured or semistructured diagnostic instruments, or self-report of physician diagnosis of major depression; and 6) the adjustment for potential confounders (age and sex, body mass index, smoking, and baseline depressive symptoms; age and sex and one more of the other three; and age and sex and two of the other three). Third, we evaluated potential moderators: percentage of males (only for crude odds ratio and relative risk/hazard ratio), length of follow-up, year of publication, person-years, total number of participants at baseline, study quality according to the Newcastle-Ottawa Scale score, and the score for the selection of participants, outcome, and comparability (only for adjusted analyses), and the number of covariates included in the model (only for adjusted odds ratio and adjusted relative risk/hazard ratio, to evaluate whether studies using more covariates are more likely to find significant or stronger effects) (23) through meta-regression analysis. Lastly, we evaluated publication bias using the Begg and Mazumdar (24) and Egger tests (25) and corrected for this using the Duval and Tweedie trim and fill method (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 studies was performed to assess whether they had an impact on 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 statistics, 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, version 3.

RESULTS

Search Results

The initial search yielded 13,474 results. After the removal of duplicates and exclusion at the level of titles and abstracts, 10,099 abstracts were considered. At the full-text review stage, 430 studies were considered; 383 studies were subsequently excluded, and two additional studies were identified in the references of other included articles. Therefore, 49 unique studies were included in the review (29–77). (A flowchart [Figure S1] and a list of excluded articles are provided in the online data supplement.)

Studies and Participant Characteristics

Across the 49 unique prospective studies, 266,939 individuals were included, with nearly equal sex distribution (47% males), followed up for an average of 7.4 years. The total person-years was 1,837,794. Of these, 36 cohorts from 34 unique studies provided data for adjusted odds ratio, 19 cohorts from 18 studies provided for odds ratio, 18 cohorts from 12 studies provided for adjusted relative risk, and 17 cohorts from 15 studies provided for relative risk. Table 1 lists the studies included in each analysis. Only one study used objective measures to evaluate physical activity. Fifteen studies evaluated major depression using structured or semistructured diagnostic instruments or self-reported

TABLE 1. Description of Studies in a Meta-Analysis of Physical Activity and Incident Depression[a]

Study Authors, Year, Reference	Study Name	Country	N	Follow-Up (years)	Persons-Years	Male (%)
Almeida et al., 2006 (29)[b,c,d]	None	Australia	601	4.8	2,884	100.0
Augestad et al., 2008 (30)[e]	Nord-Trøndelag Health Survey (HUNT)	Norway	6,660	11	73,271	49.6
Baumeister et al., 2017 (31)[e,f,g]	Study of Health in Pomerania (SHIP)	Germany	1,952	4.5	8,784	49.7
Beard et al., 2007 (32)[c]	Northern Rivers Mental Health Study (NoRMHS)	Australia	968	2	1,936	43.3
Brown et al., 1996 (33)[b,c,h]	National Health and Nutrition Examination Survey (NHANES I)	United States	1,132	7–9 (8 used)	9,056	45.0
Cabello et al., 2017 (34)[d,e]	WHO Study on Global Ageing and Adult Health (SAGE)	Ghana, India, Mexico, and Russian Federation	4,888	3 (computed)	14,664	34.5
Chang et al., 2016 (35)[e]	Age Gene/Environment Susceptibility–Reykjavik Study	Iceland	4,140	25	103,500	55.4
Chang et al., 2016 (36)[b,c,d,f,h]	Nurses' Health Study (NHS) Waves 2000–2010	United States	21,728	10	217,280	0.0
Chen and Millar, 1999 (37)[b,c,d,h,i]	National Population Health Survey (NPHS 1994/1995–1996/1997)	Canada	7,593	2	15,186	46.2
Choi et al., 2015 (38)[c,d,e]	Korean Longitudinal Study of Aging (KLoSA)	South Korea	5,327	4	21,308	47.4
Clark et al., 2007 (39)[d,e]	East London Adolescents: Community Health Survey (RELACHS)	England	1,170	2	2,340	49.5
Collard et al., 2015 (40)[d,f]	Invecchiare in Chianti (Aging in the Chianti Area) (InCHIANTI)	Italy	699	9	6,291	50.0
Cooper-Patrick et al., 1997 (41)[b,d,f]	Precursors Study	United States	752	15	11,280	92.0
Da Silva et al., 2012 (42)[c,e]	Whitehall II Study	United Kingdom	9,309	8	74,472	68.5
España-Romero et al., 2013 (43)[e]	Aerobic Center Longitudinal Study (ACLS)	United States	5,110	6.1	31,171	79.6
Farmer et al., 1988 (44)[d,e]	National Health and Nutrition Examination Survey (NHANES I) augumentation group (1975)	United States	1,163	7–9 (8 used)	9,304	48.5
Gallegos-Carrillo et al., 2013 (45)[e]	Health Worker Cohort Study (HWCS)	Mexico	1,047	6	6,282	22.5
García-Peña et al., 2013 (46)[e]	Integrated Study of Depression Among the Elderly	Mexico	7,449	2	14,898	48.85
Giltay et al., 2006 (47)[b,c,h]	Zutphen Elderly Study	Netherlands	464	15	6,960	100.0
Groffen et al., 2013 (48)[d,f]	Health, Aging, and Body Composition (Health ABC) Study	United States	2,694	9	24,246	49.7
Hiles et al., 2015 (49)[e,g]	Hunter Community Study	Australia	1,410	4	5,640	49.6
Jerstad et al., 2010 (50)[e,g]	None	United States	496	6	2,976	0.0
Jonsdottir et al., 2010 (51)[b,f]	None	Sweden	2,818	2	5,636	13.0

continued

Age at Baseline	Depression Definition	Physical Activity Measure	Physical Activity Parameters
Older	GDS-15 >5	Single question on physical activity intensity	Intensity
Adults	HADS-D >8	Physical activity questions used in HUNT study	Composite/metabolic equivalents
Adults	BDI-II ≥12 or M-CIDI	Baecke questionnaire	Frequency
Adults	CIDI or DIS	Physical activity questionnaire (not specified)	Volume
Adults	CES-D ≥16	Two questions on level of activity	N/A
Adults	CIDI-based algorithm	IPAQ	Composite/metabolic equivalents
Older	GDS-15 >6	Two questions on regularity and time spent in physical activity	Volume
Older	Self-report of physician-diagnosed major depression or depressive symptoms, use of antidepressants, MHI-5 <52, CES-D10 ≥16 or GDS-15 >6 (2000–2010)	Questions on hours per week of moderate to vigorous exercise	Volume
Adults	CIDI	Questions on frequency and duration of different physical activities	Composite/metabolic equivalents
Adults	CES-D10 ≥4	Single question on exercise	Frequency
Children/ adolescents	SMFQ ≥8	Question on physical activity/exercise	Unclear
Older	CES-D ≥20	Unclear	Unclear
Adults	Self-report on annual morbidity questionnaires and by review of medical records, using DSM-IV criteria	Harvard Alumni Physical Activity Questionnaire	Frequency
Adults	GHQ (four items for depression) ≥ 4	Two questions on time and intensity of physical activity	Composite/metabolic equivalents
Adults	CES-D ≥8	Participation in recreational physical activity	Composite/metabolic equivalents
Adults	CES-D ≥16	Two questions on level of activity	N/A
Adults	CES-D ≥16	Questionnaire assessing time and intensity spent in different recreational physical activities	Composite/metabolic equivalents
Older	GDS-30 >11	Single question on regular exercise	Unclear
Older	ZSDS ≥50	Questionnaire on total minutes per week	Volume
Older	CES-D10 >10 or use of antidepressant medication	Adapted Minnesota Leisure Time Physical Activity Questionnaire	Composite/metabolic equivalents
Older	CES-D ≥16	Pedometer	Volume
Children/ adolescents	K-SADS	Past Year Activity Scale	Volume
Adults	HADS-D > 10	Adapted Saltin-Grimby scale	Intensity

continued

TABLE 1, *continued*

Study Authors, Year, Reference	Study Name	Country	N	Follow-Up (years)	Persons-Years	Male (%)
Joshi et al., 2016 (52)[e,g]	New York City Neighborhood and Mental Health in the Elderly Study II	United States	2,355	3	7,065	40.1
Koster et al., 2006 (53)[d,f]	Longitudinal Aging Study Amsterdam (LASA)	Netherlands	2,153	9	19,377	50.8
Ku et al., 2009 (54)[e,g]	Taiwan's Health and Living Status of the Elderly Survey	Taiwan	3,778	7	26,446	53.9
Kuwahara et al., 2015 (55)[b,f]	None	Japan	29,802	6.4	190,732	84.8
Mckercher et al., 2014 (56)[b,c,f,h]	Childhood Determinants of Adult Health Study	Australia	1,630	20	32,600	46.5
Messier et al., 2013 (57)[b,c,d,e,h]	Montreal Diabetes Health and Well-Being Study	Canada	1,868	1	1,868	46.4
Mihrshahi et al., 2015 (58)[c,e]	Australian Longitudinal Study on Women's Health (ALSWH), waves 2004–2010	Australia	5,117	6	30,702	0.0
Mikkelsen et al., 2010 (59)[b,f,g]	Copenhagen City Heart Study	Denmark	18,146	26	471,796	44.1
Mobily et al., 1996 (60)[e]	Iowa 65+ Rural Health Study	United States	1,926	10	19,260	38.6
Park et al., 2015 (61)[b,c,e,h]	Yeoncheon Elderly Depression and Dementia Study	South Korea	340	5	1,700	61.2
Pasco et al., 2011 (62)[e]	Geelong Osteoporosis Study (GOS)	Australia	547	4.1	2,242	56.0
Rius-Ottenheim et al., 2013 (63)[b,c,e,h]	Alpha Omega Trial (AOT)	Netherlands	445	4.3	1,913	81.3
Roh et al., 2015 (64)[e]	None	Korea	15,146	3	45,438	44.5
Sanchez-Villegas et al., 2008 (65)[e]	SUN study	Spain	10,381	6	62,286	N/A
Sanchez-Villegas et al., 2016 (66)[d,f]	SUN study	Spain	11,800	14	165,200	N/A
Smith et al., 2010 (67)[c,e]	Honolulu-Asia Aging Study	United States	1,417	8	11,336	100.0
Strawbridge et al., 2002 (68)[d,e]	Alameda County Study (waves 1994–1999)	United States	1,651	5	8,255	N/A
Strohle et al., 2007 (69)[e]	Early Developmental Stages of Psychopathology Study (EDSP)	Germany	2,458	4	9,832	50.9
Ten Have et al., 2011 (70)[e]	Netherlands Mental Health Survey and Incidence Study (NEMESIS)	Netherlands	4,796	3	14,388	50.6
Tsai et al., 2013 (71)[e]	Taiwan Longitudinal Survey on Aging (TLSA)	Taiwan	2,145	8	17,160	53.2
Tsutsumimoto et al., 2017 (72)[b,c,d,e,h]	Obu Study of Health Promotion for the Elderly (OSHPE)	Japan	3,053	15	45,795	49.7
Veronese et al., 2017 (73)[c,d,e]	English Longitudinal Study of Ageing (ELSA)	United Kingdom	4,077	2	8,154	47.0

continued

Age at Baseline	Depression Definition	Physical Activity Measure	Physical Activity Parameters
Older	PHQ-9 ≥10	PASE	Composite/metabolic equivalents
Older	CES-D ≥16	Question on number of activities in past week	Frequency
Older	CES-D10 ≥10	Single question on frequency of leisure-time physical activity	Frequency
Adults	Adapted CES-D ≥16	Questions on regularity, frequency, and time spent in 20 physical activities	Composite/metabolic equivalents
Children/ adolescents	CIDI-Auto	Questions on frequency and time spent on physical activity	Composite/metabolic equivalents
Adults	PHQ-9 (one of the first two symptoms and five of the others)	Question on the frequency of sports participation	Frequency
Adults	CES-D10 ≥10	Questionnaire based on Australian recommendations for physical activity	Composite/metabolic equivalents
Adults	Record of major depression in Danish hospital discharge register or Danish psychiatric hospital (ICD-8 codes 296, 298, or 300 or ICD-10 codes F32, F33)	Single question on intensity and frequency	Composite/metabolic equivalents
Older	CES-D11 ≥15	Single question on walking frequency	Frequency
Older	SGDS-K ≥8	IPAQ	Composite/metabolic equivalents
Older	SCID-I/NP	PASE	Composite/metabolic equivalents
Older	GDS-15 ≥4	PASE	Composite/metabolic equivalents
Older	SGDS-K ≥8	Two questions on frequency and duration of moderate to vigorous physical activity "in a week"	Frequency
Adults	Self-report of physician diagnosis of depression	Questionnaire assessing time spent per week in 17 physical activities	Composite/metabolic equivalents
Adults	Self-report of physician diagnosis of depression	Questionnaire assessing time spent per week in 17 physical activities	Composite/metabolic equivalents
Older	CES-D11 ≥9	Single question on distance walked per day	Volume
Older	DSM-12D	Four questions evaluating the usual frequency of physical exercise, taking part in active sports, taking long walks, and swimming	Frequency
Children/ adolescents	CIDI	Four questions on physical activity frequency	Frequency
Adults	DSM-III-R	Single question on hours per week of exercise	Volume
Older	CES-D ≥10	Three questions on frequency, time, and intensity of exercise	Composite/metabolic equivalents
Older	GDS-15 >6	IPAQ	Volume
Older	CES-D8 ≥4	Three questions on frequency of participation in light, moderate, or vigorous physical activity	Intensity

continued

TABLE 1, *continued*

Study Authors, Year, Reference	Study Name	Country	N	Follow-Up (years)	Persons-Years	Male (%)
Wang et al., 2011 (74)[d,f]	National Population Health Survey (NPHS waves 1994–1995 to 2004–2005)	Canada	15,201	6	91,206	54.4
Weyerer, 1992 (75)[d,e]	Upper Bavarian Field Study	Germany	1,233	5	6,165	46.8
Wise et al., 2006 (76)[b,c,e]	Black Women's Health Study	United States	35,224	2	70,448	0.0
Yoshida et al., 2015 (77)[c,d,e]	None	Japan	680	1	680	42.5

[a] BSI=Brief Symptom Inventory; BDI-II=Beck Depression Inventory–II; CES-D, CES-D8, CES-D10, CES-D11=Center for Epidemiologic Studies Depression Scale, 20, 8, 10, and 11 item; CIDI=Composite International Diagnostic Interview; CIDI-Auto=Composite International Diagnostic Interview–computerized; CIS=Clinical Interview Schedule; DIS=Diagnostic Interview Schedule; DSM-12D=12-item scale for DSM depression; GDS-15, GDS-30=Geriatric Depression Scale, 15 and 30 item; GHQ=General Health Questionnaire; HADS-D=Hospital Anxiety and Depression Scale, depression subscale; IPAQ=International Physical Activity Questionnaire; K-SADS=Schedule for Affective Disorders and Schizophrenia for School-Age Children; M-CIDI=Munich–Composite International Diagnostic Interview; MDI=Major Depression Inventory; MHI-5=Mental Health Index–5; N/A=not available; PASE=Physical Activity Scale for the Elderly; PHQ-9=Patient Health Questionnaire–9; SCID-I=Structured Clinical Interview for DSM-IV Axis I Disorders; SCID-I/NP=Structured Clinical Interview for DSM-IV Axis I Disorders, Non-Patient Edition; SGDS-K=adapted Korean version of the GDS; SMFQ=Short Mood and Feelings Questionnaire; WHO=World Health Organization; ZSDS=Zung Self-Rating Depression Scale.
[b] Unadjusted relative risk/hazard ratio.
[c] Unadjusted odds ratio.
[d] Data inverted using antilog procedures.
[e] Adjusted odds ratio.
[f] Adjusted relative risk/hazard ratio.
[g] Data supplied by study author.
[h] Data were calculated using raw numbers.
[i] The Chen and Millar study (37) used moderate physical activity as the reference group for adjusted odds ratio but was included in our adjusted odds ratio analysis because of the nondifference between moderate and high physical activity levels (odds ratio=1).

physician diagnosis of major depression only. The details of the included studies are summarized in Table 1. The list of included studies is provided in the online data supplement.

Study Quality

The mean study quality score of the studies was 6.34 (SD=0.8) out of 9 on the Newcastle-Ottawa Scale, representing moderate to high methodological quality. A detailed quality assessment is presented in Table S1 in the data supplement.

Physical Activity and Incident Depression

Highest versus lowest physical activity. People with higher physical activity levels were at reduced odds of incident depression when compared with people with lower physical activity levels in adjusted (adjusted odds ratio=0.83, 95% CI=0.79, 0.88, $p<0.001$; $I^2=0.00$, Q=25.93, N=36) (Figure 1) and crude odds ratio analyses (odds ratio=0.59, 95% CI=0.51, 0.68, $p<0.001$; $I^2=52.38$, Q=37.80, N=19) and had decreased risks on adjusted and crude relative risk analyses (adjusted relative risk=0.83, 95% CI=0.76, 0.90, $p<0.001$; $I^2=0.00$, Q=14.86, N=18; relative risk=0.68, 95% CI=0.60, 0.78, $p<0.001$; $I^2=33.40$, Q=24.02, N=17). The plots for odds ratio, adjusted relative risk, and relative risk are provided in Figures S2, S3, and S4 in the data supplement, and the incidence rates are listed in Table S3 in the data supplement. Publication bias was evidenced for adjusted odds ratio (Egger's intercept= −0.65, p=0.002), adjusted relative risk (Egger's intercept= −1.25, $p<0.001$; Begg and Mazumdar tau=−0.43, p=0.01). The Duval and Tweedie trim and fill technique adjusted the effects to an adjusted odds ratio of 0.85 (95% CI=0.81, 0.89), an odds ratio of 0.63 (95% CI=0.54, 0.74), an adjusted relative risk of 0.86 (95% CI=0.78, 0.96), and a relative risk of 0.80 (95% CI=0.69, 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 physical activity on incident depression for adjusted odds ratio, odds ratio, adjusted relative risk, and relative risk analyses, respectively.

Subgroup and sensitivity analysis. Significant protective associations of physical activity on incident depression were found across the four continents (Asia, Europe, North America, and Oceania) with available data for adjusted odds ratio and relative risk analyses. Protective effects were found for Asia, North America, and Oceania for odds ratio analysis, and for Europe, North America, and Oceania in adjusted relative risk analysis. Significant associations of high physical activity were found in all analyses for studies that assessed physical activity levels in terms of different volumes and composite/metabolic equivalents. Higher frequency of physical activity provided protective effects in adjusted odds ratio and odds ratio analyses, but not in adjusted relative risk or relative risk analyses. Higher intensity was significantly associated with lesser incident depression in all but adjusted odds ratio analysis. Protective effects were found for adults and older persons in all analyses and for children in adjusted odds ratio and relative risk analyses. Significant associations were found for studies assessing depressive symptoms across

Age at Baseline	Depression Definition	Physical Activity Measure	Physical Activity Parameters
Adults	CIDI	Questions on frequency and duration of engagement in different physical activities	Composite/metabolic equivalents
Adults	CIS	Single question on exercise frequency	Frequency
Adults	CES-D ≥16	Questionnaire on number of hours spent in walking for exercise and vigorous exercise	Volume
Older	GDS-15 >6	Questions about participants' engagement in physical activity and weekly frequency	Frequency

the four analyses. Physical activity was protective for major depression diagnosis in adjusted odds ratio, odds ratio, and relative risk analyses. Completing 150 minutes per week of moderate to vigorous physical activity was protective for incident depression in adjusted odds ratio and adjusted relative risk analyses. Lastly, subgroup analyses of studies that adjusted for age and sex, body mass index, smoking, baseline depressive symptoms, or age and sex and one more confounder, or age and sex and two more confounders were all significant in adjusted odds ratio analyses. Adjusted relative risk analyses adjusting for age and sex, body mass index, smoking, or age and sex and one more confounder were all significant. The details of the subgroup analyses are summarized in Table 2.

We performed sensitivity analyses (available on request) removing the study that pooled participants with anxiety disorders together with those with depression both in the overall analysis and in major depression only (78), excluding the study that used objectively measured physical activity (49). The results remained significant for all analyses.

Meta-Regressions

Sample size at baseline, year of publication, length of follow-up, individual study person-years, percentage of males, number of covariates used in each study for adjusted analyses (the list of the covariates used is provided in Table S2 in the data supplement), and the study quality according to the Newcastle-Ottawa Scale were investigated as potential moderators through meta-regression analysis. None of the investigated moderators significantly explained the variance of the effects of physical activity on depression onset in any of the analyses. The detailed results of the meta-regressions are summarized in Table 3 (plots are available on request).

DISCUSSION

To our knowledge, this is the first study to meta-analyze the relationship between physical activity levels and incident depression. Study findings indicate that across 49 studies, higher physical activity levels are 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 physical activity offer a protective effect on future development of depression for people of all ages (youths, working-age adults, elderly persons), and this finding is robust across geographical regions around the world.

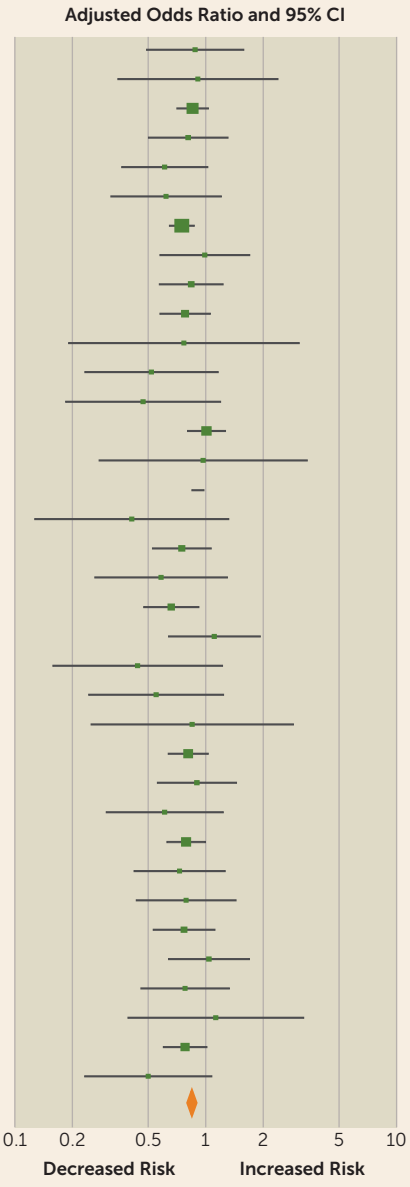
Previous narrative systematic reviews have suggested that physical activity can be protective against the development of depression (9, 10). Our study advances the field by conducting the first pooled meta-analysis investigating this relationship, which allows a clearer understanding of a true association between an exposure and outcome, rather than when studies are considered separately, as in previous reviews (79). Recently, a meta-analysis including 11 prospective studies found that sedentary behavior is associated with an increased incident depression at follow-up (relative risk=1.14, 95% CI=1.06, 1.21) (14). While sedentary behavior and physical activity are related constructs—with the former existing at the low end of the physical activity spectrum—it is of clinical relevance to quantify the pooled relationships of physical activity with subsequent depression onset independently of sedentary behavior.

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

Our meta-analysis suggests that physical activity is associated with a decrease in the risk of developing depression, which raises an inevitable question: How might physical activity offer protection against depression onset? It is likely

FIGURE 1. Forest Plot of Studies Examining the Association Between Physical Activity and Incident Depression[a]

Study Authors, Year, Reference	Odds Ratio	Lower Limit	Upper Limit	p
Augestad et al., 2008 (30) (men)	0.880	0.484	1.599	0.675
Augestad et al., 2008 (30) (women)	0.910	0.343	2.415	0.850
Baumeister et al., 2017 (31)	0.854	0.699	1.044	0.124
Cabello et al., 2017 (34)	0.810	0.496	1.322	0.399
Chang et al., 2016 (36)	0.610	0.359	1.036	0.068
Chen and Millar, 1999 (37)	0.620	0.315	1.221	0.167
Choi et al., 2015 (38)	0.750	0.639	0.881	0.000
Clark et al., 2007 (39)	0.990	0.570	1.720	0.972
Da Silva et al., 2012 (42)	0.840	0.566	1.247	0.387
España-Romero et al., 2013 (43)	0.780	0.570	1.068	0.121
Farmer et al., 1988 (44) (men)	0.769	0.189	3.123	0.713
Farmer et al., 1988 (44) (women)	0.520	0.230	1.175	0.116
Gallegos-Carrillo et al., 2013 (45)	0.470	0.183	1.209	0.117
Garcia-Pena et al., 2013 (46)	1.010	0.795	1.283	0.935
Hiles et al., 2015 (49)	0.970	0.274	3.440	0.962
Jerstad et al., 2010 (50)	0.910	0.837	0.990	0.028
Joshi et al., 2016 (52)	0.410	0.126	1.335	0.139
Ku et al., 2009 (54)	0.750	0.521	1.080	0.122
Messier et al., 2013 (57) (remained active)	0.584	0.260	1.313	0.193
Mihrshahi et al., 2015 (58)	0.660	0.468	0.930	0.018
Mobily et al., 1996 (60)	1.110	0.631	1.951	0.717
Park et al., 2015 (61)	0.440	0.157	1.237	0.120
Pasco et al., 2011 (62)	0.550	0.241	1.254	0.155
Rius-Ottenheim et al., 2013 (63)	0.850	0.248	2.910	0.796
Roh et al., 2015 (64)	0.810	0.629	1.043	0.102
Sanchez-Villegas et al., 2008 (65)	0.900	0.553	1.466	0.672
Smith et al., 2010 (67)	0.610	0.298	1.249	0.176
Strawbridge et al., 2002 (68)	0.790	0.620	1.007	0.057
Strohle et al. 2007 (69)	0.730	0.417	1.278	0.271
Ten have et al., 2011 (70)	0.790	0.428	1.457	0.450
Tsai et al., 2013 (71)	0.770	0.525	1.129	0.181
Tsutsumimoto et al., 2017 (72)	1.040	0.632	1.713	0.878
Veronese et al., 2017 (73)	0.780	0.453	1.344	0.371
Wereyer, 1992 (75)	1.130	0.388	3.295	0.823
Wise et al., 2006 (76)	0.780	0.593	1.026	0.075
Yoshida et al., 2015 (77) (maintenance)	0.500	0.230	1.089	0.081
Summary effect size estimate	0.837	0.794	0.883	0.000



[a] Random-effects modeling was employed. The square size is proportional to the individual studies' sample size, and the diamond represents the summary effect size estimate.

that no single mechanism can explain this relationship. A range of biochemical and psychosocial factors are likely responsible, including biological mechanisms through which exercise increases neurogenesis and reduces inflammatory and oxidant markers (80) and activates the endocannabinoid system (81). People with depression have decreased hippocampal volumes and levels of markers of neurogenesis, and increased levels of inflammatory (e.g., interleukin-6) (82) and oxidant markers (82). Physical activity may regulate these abnormalities, increasing hippocampal volume (83) and neurogenesis levels (84), as well as adjusting the imbalance between anti- and proinflammatory (85) and oxidant markers (86, 87). Also, physical activity may directly increase psychological factors such as self-esteem or perceptions of physical competence. Finally, an improved level of fitness leads to both subjective and objective improvements in physical health status (88). 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

Our meta-analysis has some limitations. First, most of the studies analyzed used self-report questionnaires to measure

TABLE 2. Subgroup Analysis Exploring the Effects of Physical Activity on Incident Depression in Different Continents, Physical Activity Assessment Unity, Presence of Diagnosed Depression, and Age[a]

Analysis	Number of Cohorts (Arms)	Meta-Analysis			Heterogeneity		Trim and Fill Method		Adjusted Studies	Classic Fail Safe N
Studies with adjusted odds ratio		Adjusted odds ratio	95% CI	p	I^2	Q	Effect size	95% CI	N	N
Overall	36	0.837	0.794, 0.883	<0.0001	0.00	25.93	0.85	0.81, 0.89	10	380
Continent										
Asia	7	0.765	0.682, 0.859	<0.0001	0.00	3.97	0.77	0.69, 0.87	2	26
Europe	12	0.836	0.732, 0.954	0.008	0.00	2.53	0.72	0.72, 0.94	1	6
North America	13	0.864	0.796, 0.937	<0.0001	4.28	12.53	0.88	0.79, 0.97	6	54
Oceania	3	0.658	0.484, 0.895	0.008	0.00	0.54	0.64	0.47, 0.86	1	1
Physical activity assessment unit										
Composite/ metabolic equivalents	14	0.746	0.648, 0.858	<0.0001	0.00	5.83	0.75	0.66, 0.87	2	50
Frequency	10	0.789	0.718, 0.866	<0.0001	0.00	4.85	Unchanged			39
Intensity	1	0.780	0.453, 1.344	0.371	0.00	0.00	N/A			N/A
Volume	7	0.888	0.822, 0.960	0.003	0.00	4.71	0.89	0.83, 0.97	2	9
150 minutes of moderate to vigorous physical activity per week	4	0.780	0.617, 0.986	0.038	0.00	1.33	0.77	0.61, 0.97	2	1
Depression assessment										
Depressive symptoms	28	0.844	0.798, 0.892	<0.0001	0.00	23.22	0.85	0.81, 0.90	7	245
Major depression	10	0.862	0.757, 0.981	0.024	0.00	5.29	0.89	0.79, 1.00	3	7
Age at baseline										
Adults	16	0.787	0.707, 0.877	<0.0001	0.00	5.85	0.79	0.71, 0.88	1	57
Older	16	0.794	0.726, 0.868	<0.0001	0.00	13.13	0.80	0.74, 0.88	4	85
Children/ adolescents	3	0.907	0.836, 0.985	0.021	0.00	0.68	Unchanged			0
Adjustments										
Age and sex	32	0.836	0.791, 0.883	<0.0001	0.00	20.92	0.85	0.80, 0.90	10	310
a. Baseline depressive symptoms	3	0.897	0.829, 0.970	0.007	0.00	0.99	Unchanged			3
b. Body mass index	12	0.871	0.810, 0.937	<0.0001	0.00	8.18	0.90	0.81, 1.00	5	34
c. smoking	12	0.748	0.647, 0.865	<0.0001	0.00	6.37	0.75	0.65, 0.87	1	32
Age and sex and one other (a, b, or c)	17	0.865	0.800, 0.928	<0.0001	0.00	12.38	0.88	0.80, 0.97	6	66
Age and sex and two others (a+b, a+c, or b+c)	8	0.836	0.749, 0.934	0.001	9.23	7.71	0.90	0.79, 1.03	5	26
Studies with crude odds ratio		Odds ratio	95% CI	p	I^2	Q	Effect size	95% CI	N	N
Overall	19	0.591	0.510, 0.685	<0.0001	52.38	37.80	0.63	0.54, 0.74	4	519
Continent										
Asia	4	0.657	0.577, 0.749	<0.0001	0.00	2.01	0.66	0.58, 0.75	1	24
Europe	4	0.546	0.286, 1.040	0.065	75.01	12.00	0.37	0.19, 0.73	2	13
North America	6	0.644	0.496, 0.835	0.001	63.94	13.86	Unchanged			52
Oceania	5	0.480	0.405, 0.568	<0.0001	0.00	0.07	0.48	0.40, 0.56	1	35

continued

TABLE 2, *continued*

Analysis	Number of Cohorts (Arms)	Meta-Analysis			Heterogeneity		Trim and Fill Method		Adjusted Studies	Classic Fail Safe N
Studies with crude odds ratio		Odds ratio	95% CI	p	I^2	Q	Effect size	95% CI	N	N
Physical activity assessment unit										
Composite/ metabolic equivalents	4	0.574	0.402, 0.819	0.002	52.52	6.31	Unchanged			33
Frequency	3	0.662	0.580, 0.755	<0.0001	0.00	0.36	0.66	0.58, 0.75	1	17
Intensity	2	0.303	0.198, 0.462	<0.0001	0.00	0.53	N/A			N/A
Volume	8	0.628	0.487, 0.810	<0.0001	48.49	13.59	0.64	0.51, 0.80	2	56
150 minutes of moderate to vigorous physical activity per week	3	0.704	0.477, 1.038	0.077	8.38	2.18	Unchanged			1
Depression assessment										
Depressive symptoms	14	0.618	0.568, 0.674	<0.0001	58.44	31.28	0.66	0.54, 0.80	3	281
Major depression	5	0.511	0.429, 0.608	<0.0001	0.00	2.79	0.48	0.40, 0.58	2	32
Age at baseline										
Adults	8	0.662	0.550, 0.979	<0.0001	62.10	18.47	0.63	0.54, 0.74	1	190
Older	9	0.496	0.399, 0.616	<0.0001	21.79	10.22	0.45	0.36, 0.57	2	112
Children/ adolescents	2	0.496	0.208, 1.186	<0.0001	0.00	0.05	N/A			N/A
Studies with adjusted relative risk/hazard ratio (ARR/AHR)		ARR/AHR	95% CI	p	I^2	Q	Effect size	95% CI	N	N
Overall	18	0.832	0.762, 0.909	<0.0001	0.00	14.86	0.86	0.78, 0.96	8	102
Continent										
Asia	1	0.950	0.777, 1.162	0.611	0.00	0.00	N/A			N/A
Europe	8	0.773	0.660, 0.906	0.001	21.92	8.99	0.84	0.70, 1.01	4	31
North America	7	0.811	0.673, 0.978	0.028	0.00	2.19	0.86	0.73, 1.02	3	4
Oceania	2	0.502	0.241, 1.045	0.0001	0.00	0.01	N/A			N/A
Physical activity assessment unit										
Composite/ metabolic equivalents	12	0.832	0.741, 0.935	0.002	0.00	8.72	0.88	0.79, 0.98	6	35
Frequency	3	0.873	0.755, 1.010	0.062	0.00	0.61	0.89	0.77, 1.02	2	0
Intensity	1	0.290	0.104, 0.805	0.017	0.00	0.00	N/A			N/A
Volume	1	0.815	0.815, 1.331	0.413	0.00	0.00	N/A			N/A
150 minutes of moderate to vigorous physical activity per week	4	0.689	0.498, 0.951	0.024	0.00	0.53	Unchanged			2
Depression assessment										
Depressive symptoms	11	0.845	0.766, 0.932	0.001	0.12	10.03	0.88	0.78, 1.00	6	57
Major depression	8	0.873	0.748, 1.108	0.082	10.78	7.84	0.93	0.77, 1.13	4	6

continued

TABLE 2, *continued*

Analysis	Number of Cohorts (Arms)	Meta-Analysis			Heterogeneity		Trim and Fill Method		Adjusted Studies	Classic Fail Safe N
Studies with adjusted relative risk/hazard ratio (ARR/AHR)		ARR/AHR	95% CI	p	I^2	Q	Effect size	95% CI	N	N
Age at baseline										
Adults	9	0.863	0.776, 0.960	0.007	7.53	8.65	0.89	0.78, 1.02	4	20
Older	7	0.703	0.567, 0.879	0.001	0.00	1.27	Unchanged			12
Children/ adolescents	0	N/A	N/A	N/A	N/A	N/A	N/A			0
Adjustments										
Age and sex	18	0.832	0.762, 0.909	<0.0001	0.00	14.86	0.86	0.78, 0.96	8	102
a. Baseline depressive symptoms	1	0.950	0.777, 1.162	0.618	0.00	0.00	N/A			N/A
b. Body mass index	10	0.821	0.714, 0.945	0.006	14.28	10.50	0.88	0.74, 1.04	5	28
c. smoking	4	0.694	0.505, 0.953	0.024	0.00	1.24	Unchanged			1
Age and sex and (a, b, or c)	11	0.833	0.734, 0.946	0.005	0.39	10.50	0.88	0.75, 1.04	5	29
Age and sex and two others (a+b, a+c, or b+c)	4	0.823	0.648, 1.045	0.109	13.25	11.23	Unchanged			1
Studies with crude relative risk/hazard ratio (RR/HR)		RR/HR	95% CI	p	I^2	Q	Effect size	95% CI	N	N
Overall	17	0.687	0.601, 0.786	<0.0001	33.40	24.02	0.80	0.69, 0.94	9	210
Continent										
Asia	3	0.821	0.688, 0.980	0.029	0.00	1.00	0.84	0.72, 0.99	2	2
Europe	5	0.593	0.439, 0.801	0.001	0.00	3.10	0.55	0.42, 0.72	1	11
North America	6	0.681	0.537, 0.865	0.002	66.23	14.80	Unchanged			49
Oceania	3	0.513	0.270, 0.974	0.041	0.00	0.07	0.49	0.27, 0.91	1	0
Physical activity assessment unit										
Composite/ metabolic equivalents	5	0.774	0.653, 0.916	0.003	0.00	3.11	0.84	0.69, 1.01	3	9
Frequency	2	0.705	0.440, 1.129	0.146	0.00	0.00	N/A			N/A
Intensity	2	0.336	0.157, 0.718	0.005	0.00	0.48	N/A			N/A
Volume	6	0.695	0.538, 0.898	0.005	66.50	14.92	0.71	0.55, 0.90	1	40
150 minutes of moderate to vigorous physical activity per week	2	0.635	0.368, 1.096	0.103	0.00	0.10	N/A			N/A
Depression assessment										
Depressive symptoms	9	0.811	0.729, 0.920	<0.0001	0.00	7.38	0.83	0.72, 0.95	5	36
Major depression	8	0.575	0.502, 0.660	<0.0001	0.00	1.63	0.55	0.48, 0.63	3	63
Age at baseline										
Adults	9	0.764	0.667, 0.876	<0.0001	16.01	9.52	0.82	0.69, 0.96	5	51
Older	6	0.588	0.509, 0.678	<0.0001	0.00	2.99	0.56	0.48, 0.64	2	34
Children/ adolescents	2	0.537	0.250, 1.149	0.109	0.00	0.03	N/A			N/A

[a] N/A=not available.

TABLE 3. Meta-Regression of Moderators of the Effects of Physical Activity on Incident Depression

Moderator	Number of Cohorts	β	95% CI	p	R^2
Studies presenting adjusted odds ratio					
Sample size	36	<−0.0001	<−0.001, <0.001	0.44	0.00
Year of publication	36	−0.0035	<−0.015, <0.008	0.55	0.00
Length of follow-up	36	0.0001	−0.018, 0.018	0.99	0.00
Person-years	36	<−0.0001	<−0.001, <0.001	0.13	0.00
Number of covariates	34	−0.0183	−0.035, <0.001	0.05	0.00
Percent dropout	29	−0.0027	−0.007, 0.001	0.23	0.00
Study quality	36	0.0105	−0.067, 0.088	0.78	0.00
Study quality (selection of participants)	36	0.0657	−0.161, 0.293	0.57	0.00
Study quality (comparability)	36	0.0080	−0.185, 0.201	0.93	0.00
Study quality (outcome)	36	0.0777	−0.039, 0.194	0.19	0.00
Studies presenting crude odds ratio					
Sample size	19	<−0.0001	<−0.001, <0.001	0.31	0.00
Year of publication	19	−0.0251	−0.049, <0.001	0.05	0.00
Length of follow-up	19	−0.0025	−0.035, 0.030	0.87	0.02
Person-years	19	<−0.0001	<−0.001, <0.001	0.48	0.00
Percent males	19	0.0002	−0.003, 0.003	0.88	0.00
Percent dropout	16	−0.0034	−0.014, 0.007	0.52	0.00
Study quality	19	−0.1168	−0.409, 0.175	0.43	0.02
Study quality (selection of participants)	19	−0.0705	−0.450, 0.309	0.71	0.00
Study quality (outcome)	19	−0.1364	−0.601, 0.328	0.56	0.00
Studies presenting adjusted relative risk/adjusted hazard ratio					
Sample size	18	<0.0001	<−0.001, <0.001	0.13	0.00
Year of publication	18	0.0207	−0.008, 0.049	0.16	0.00
Length of follow-up	18	−0.0132	−0.028, 0.001	0.08	0.00
Person-years	18	<0.0001	<−0.001, <0.001	0.59	0.00
Number of covariates	18	0.0195	−0.009, 0.048	0.19	0.00
Percent dropout	15	−0.0036	−0.020, 0.013	0.67	0.00
Study quality	18	−0.0139	−0.132, 0.104	0.81	0.00
Study quality (selection of participants)	18	0.0010	−0.268, 0.270	0.99	0.00
Study quality (comparability)[a]	—	—	—	—	—
Study quality (outcome)	18	−0.0214	−0.141, 0.098	0.72	0.00
Studies presenting crude relative risk/hazard ratio					
Sample size	17	<0.0001	<−0.001, <0.001	0.06	0.82
Year of publication	17	−0.0036	−0.026, 0.018	0.75	0.04
Length of follow-up	17	−0.0124	−0.029, 0.004	0.14	0.58
Person-years	17	<−0.0001	<−0.001, <0.001	0.70	0.07
Percent males	17	0.0010	−0.002, 0.004	0.57	0.00
Percent dropout	13	−0.0083	−0.019, 0.003	0.15	0.00
Study quality	17	−0.0580	−0.134, 0.018	0.13	0.30
Study quality (selection of participants)	17	0.1204	−0.059, 0.300	0.19	0.43
Study quality (outcome)	17	−0.1033	−0.362, 0.155	0.43	0.00

[a] Not available due collinearity.

the exposure factor and the outcome. While common in the physical activity literature, self-report questionnaires are associated with recall bias. However, only one of the included studies used an objective measure (pedometer) (49) to evaluate physical activity, thus precluding exploration of whether results were different with self-report questionnaires compared with objective measures. Also, subgroup analyses showed that physical activity decreased the risk of developing depression, regardless of whether this was based on self-report measures or major depression diagnosis from structured clinical diagnostic interviews. Second, we found some evidence of publication bias in adjusted odds ratio and adjusted relative risk analyses. Nonetheless, adjusting for publication bias, after trimming 10 studies for adjusted odds ratio and eight studies for adjusted relative risk, resulted in smaller but still significant associations (adjusted odds ratio=0.85; 95% CI=0.81, 0.89; adjusted relative risk=0.86; 95% CI=0.78, 0.96). Therefore, the primary results of our analyses were not altered by considering the potential number of unpublished studies. Third, it should be noted that

we included only 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 physical activity per week. However, these analyses included a small number of studies. Also, in all the other studies, the definition of low or high physical activity, as well as the aspects of physical activity that were captured by each instrument (intensity, frequency, volume, or two or more) varied widely. These limitations prevent us from establishing a "minimum" or an "optimal" dosage of physical activity necessary to decrease the odds of incident depression. However, we can conclude that people with higher levels of physical activity have a lower risk of developing depression than those with lower levels of physical activity. Fifth, seven of our subgroup analyses were nonsignificant. It should be considered that those analyses included a small number of studies and potentially are underpowered. Lastly, the included studies assessed physical activity participation using questionnaires referring to the preceding days or weeks. Thus, it is not possible to evaluate whether being engaged in higher levels of physical activity 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 physical activity (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 effect of physical activity seems to be greater in the noncarriers of the E type 4 allele of the apolipoprotein E (APOE) gene (89), 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 (90). Also, the effects of physical activity in people with increased risk for depression, such as people with a familial history of depression, has not yet been examined.

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

Further studies are warranted to evaluate the minimum physical activity levels required as well as the effects of different physical activity 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 physical activity in the prevention of depression.

CONCLUSIONS

Higher levels of physical activity are consistently associated with a lower odds of developing future depression. The protective effects of physical activity were observed regardless of age and sex and were significant across all geographical regions. Our data further emphasize the importance of policies targeting increased physical activity levels. Randomized controlled trials are required to address whether or not physical activity can prevent the development of depression in those at high risk.

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