Physical activity, sleep and symptoms of depression in adults – testing for mediation

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ABSTRACT

Purpose Physical activity, sleep problems and symptoms of depression contribute to overall wellbeing. The factors are reciprocally associated, but the nature of these associations remains unclear. The present study examined whether sleep problems mediated the association between physical activity and depressive symptoms.

Methods The eligible population (n = 3596) consisted of adults from the ongoing, population-based Cardiovascular Risk in Young Finns Study started in 1980. Participants' leisure-time physical activity was assessed with physical activity index (2007) and sleep problems with Jenkins' Sleep Questionnaire (JSQ) in 2007 and 2011. Depressive symptoms were measured using modified Beck Depression Inventory (BDI-II) in 2007 and 2012, from which the items reflecting sleep problems were excluded. Mediation analyses, through which the associations between the variables were examined, were adjusted for sex and a set of health-related covariates assessed in 2007 and 2011.

Results Physical activity was associated with decreased levels of sleep problems and depressive symptoms (P <0.05). The association between physical activity and depressive symptoms (b = -0.10, P < 0.01) was partly mediated by sleep problems (proportion mediated = 0.36, P < 0.01). The adjustment for depressive symptoms at baseline attenuated the mediation effect (proportion mediated= 0.30, P > 0.05).

Conclusion Physical activity's favorable contribution to depressive symptoms was mediated partly by sleep, but the mediation effect disappeared after adjusting for the previous depressive symptoms in adulthood.

Keywords Depression, sleep problems, leisure-time physical activity, causality

INTRODUCTION

Depression affects 340 million people globally, and it is one of the leading causes of disability (1). Depression is often a comorbid with other chronic medical conditions, including cardiovascular and psychiatric diseases (1, 2). Early signs of the disorder, such as depressive symptoms, associate also with somatic health outcomes and risks for future mental disorders (2). Although depression has been characterized as one of the psychological disorders that cause the greatest burden of disease worldwide (1, 3), research suggests that it is also one of the most preventable disorders (3). Studying the determinants and mechanisms through which depression develops can provide insights into better prevention of the disorder (3).

Along with genetic, psychophysiological and -social determinants, lifestyle factors are contributing to the development and progression of depression (3-5). Physical activity has been regarded as one of the most influential of these factors (5). Recent studies have also shown that approximately 30% of the world's population are physically inactive (6), and the prevalence of physical inactivity is increasing in many countries (6, 7). Studies have demonstrated that even low doses of physical activity may have a protective effect against the onset of depression (7). Literature has also shown that physical activity associates with decreased levels of depression in those with diagnosed depression (7). Some evidence, however, suggests that physical activity may not contribute favorably to depressive symptoms among individuals with a history of depressive episodes (8). To date, the potentially causal association between physical activity and depressive symptoms has not been thoroughly studied, and the importance of identifying mediators affecting the link has been highlighted (1, 4).

Sleep has been regarded as one of the most essential psychophysiological and –social factors affecting lifestyles and depression (5, 9). The reciprocal associations between physical activity, sleep problems and depressive symptoms have also been established (5). Based on diagnostic criteria, 6 to 10% of people are suffering from insomnia (9). Studies have also reported

that 9%-45% of general population are suffering from some insomnia-related symptoms or sleep problems (9, 10). These problems are increasing in many countries (11, 12). It has also been denoted that highly physically active individuals tend to have a better sleep quality, as well as lower levels of depressive symptoms comparing to physically more inactive ones (13). Previous studies have pointed out the need for targeting the potential causal processes between physical activity, sleep and depressive symptoms (13, 14).

Biological factors may partly explain the mechanisms between physical activity, sleep and depressive symptoms. For instance, it has been suggested that sleep problems may result from body temperature's inadequate downregulation, and physical exercising might help in heat acclimation which contributes to better sleep (13). Research has also denoted that physical activity contributes to homeostatic sleep control by increasing the total sleep time and intensity of slow-wave sleep (13, 14). Physically active people are also usually aware of the benefits of sleep for recovery after training sessions (13), and may therefore make efforts to control and structure their sleep patterns. Through these processes, physical activity is likely to contribute to psychological functioning and experienced wellbeing (13, 14). Furthermore, sleep may contribute to alterations in the major neuroendocrine stress system (15). Sufficient sleep may impact the secretion of cortisol (15, 16), which may lead to reduced risk at getting stress-related diseases and disorders including depression (15-17).

Longitudinal studies are needed to test the direction of the association between physical activity and depressive symptoms, and the potential mediators affecting the association (1, 11, 18). Some previous experimental studies have been criticized for the small sample sizes and differing study protocols, and the advantages of epidemiological studies assessing large samples have been acknowledged (14). Furthermore, modern and sophisticated techniques are also needed to overcome the limitations of earlier methods assessing time dependent processes (19). As the etiology of depression is complex, taking into account the potentially confounding influences of

variety of physiological and health related factors has been accentuated (3, 4, 7). Sex, age, body mass index, health behavioral (e.g., smoking), socioeconomic (e.g., education), and social (e.g., marital status) contributors have been regarded of utmost importance in the development of depression (20-23). These factors may, for instance, affect the stability of adulthood physical activity and sleep patterns that contribute to experienced wellbeing (9, 24).

The present study examined the association between physical activity and depressive symptoms using sleep problems as a mediator among adults (aged from 30 to 50) in a prospective, community-based cohort design. Based on the literature, we hypothesized that physical activity contributes to decreased levels of depressive symptoms, and this association is mediated partly by sleep problems. The hypothesis was tested using a mediation model, a standard analyzing tool for assessing such mechanisms, within a sophisticated statistical framework (19). The baseline values of the mediator (sleep problems) and outcome (depressive symptoms), participants' age, sex (2007), body mass index, education, income, employment, marital and smoking statuses (assessed in 2007 and 2011) were controlled for to test the strength of the potential association.

METHODS

Study Design and Participants

The study participants were from the ongoing longitudinal Cardiovascular Risk in Young Finns study that began in 1980 (25). The original sample consisted of 3596 children and adolescents (83.2% of those invited, 1832 women and 1764 men) from six birth cohorts (aged 3, 6, 9, 12, 15 and 18). The sample was collected from five Finnish cities (Helsinki, Kuopio, Oulu, Tampere, and Turku), and the participants were randomly selected from nearby urban and rural areas based on their social security numbers. Informed consent was requested from each subject (or from the parents of small children). The study protocol was approved by the local ethics committees, and conducted according to Helsinki Declaration and American Psychological Association's standards.

The sample has been examined in 1980, 1983, 1986, 1989, 1992, 1997, 2001, 2007-2008, and 2011-2012, and medical, psychological and physical-activity data have been collected during these years. In the present study, participants' physical activity was assessed in 2007 and 2011, response rate ranging from 53.1% to 60.2% (n = 1910-2166) of the original study participants (Supplementary Table 1). Depressive symptoms were measured in 2007 and 2012, and the response rate ranged from 48% to 56.2% (n = 1725-2020) of the original participants (Supplementary Table 1). Participants' sleep problems were assessed in 2007 and 2011, and the response rate ranged from 55.8% to 61.9% (n = 2006-2226) of the original examinees (Supplementary Table 1). The participants were aged from 30 to 50 when the present study's data was obtained (in 2007, 2011 and 2012).

Based on our recent analyses (unpublished results) from the examination in 2011, there were no selective attrition with respect to participants' leisure-time physical activity, which is in line with previous attrition assessments (25, 26). Participants with sleep problems had discontinued the study more often than others ($P < 0.05$). Furthermore, it has also been shown that depressed examinees had discontinued the study more often than other subjects (27). Regarding the potential confounders adjusted for in the present study (unpublished studies), some selective attrition with respect to participants' age, sex, income level, employment, marital and smoking statuses was found. Younger participants, men, the ones with lower income levels and unemployment status had discontinued the study more often than others ($P < 0.05$). Furthermore, smokers and unmarried participants had dropped out of the study more often than others ($P < 0.05$).

Measures

Physical Activity

Physical activity was measured via self-administered questionnaires. Participants, from whom physical activity was assessed, were aged from 30 to 45 in 2007. The questionnaires consisted of

five questions assessing the intensity and frequency of leisure-time physical activity, hours spent on physical activity per week, average duration of a physical activity session, and participation in organized physical activity (8, 26). The answers for each question were coded into 3 ordinal categories (ranging from 1 to 3), higher scores reflecting higher physical activity. A sum score (physical activity index, PAI) of questions was created for each participant, ranging from 5 to 15 (Supplementary Table 1). Higher sum scores reflect higher levels of physical activity. The index has been found reliable and valid (8, 26, 28). Physical activity indices have shown to correlate with objective measurements (e.g., ergometer and pedometer tests), coefficients ranging from small to moderate (26, 29). The findings are in the same direction with previous literature demonstrating that self-reports correlate with objective physical activity measures (30, 31).

Sleep problems

Participants' sleep quality was measured with four items reflecting participants' experiences of sleep problems (32) in 2011 when they were aged from 34 to 49. The questions assessed troubles falling asleep, staying asleep (i.e., waking up too early and problems in getting back to sleep), waking up several times per night, and waking up after usual amount of sleep and feeling tired and worn out. The response options ranged from one to six (1 = not at all, 6 = every night). An average of the items was calculated for each participant, higher scores reflecting higher level of sleep problems. The Cronbach's α for the items was 0.77 in 2007, and 0.76 in 2011, indicating good internal consistency for the items. The measure has shown to be appropriate among patient samples as well as in observational, population-based settings (27, 32). There exists evidence indicating that subjective evaluations of sleep correlate with objective measurements (33).

Depressive symptoms

Participants' depressive symptoms were assessed in 2012 when they were aged from 35 to 50. Beck Depression Inventory II (BDI-II) (34), consisting of 21 symptoms with a range from 0 (no symptoms) to 3 (severe level of depressive symptoms), was used. A sum score of all items was

computed for each study subject (Supplementary Table 1), and no missing items were allowed (34). Items reflecting participants' sleeping habits ("I'm sleeping as well as before"), and feelings of fatigue ("I am not more tired than usually") were excluded from the sum score due to the overlap with the items assessing sleep problems (32). The reliability estimate (Cronbach's α) for the depressive symptom scores was 0.93 both in 2007 and 2012, indicating an excellent internal consistency for the items. BDI-II evaluates variation in symptom severity among normal population as well as in clinical samples (34, 35). The instrument has shown to correlate with other widely used scales for depression within non-clinical and clinical contexts, and it has shown to be applicable screening tool for future depressive disorder (36).

Covariates

Participants' baseline sleep problems and symptoms of depression (32, 34) assessed in 2007 were controlled for in the mediation analyses (Tables 1-2). General confounders (sex, age and body mass index), socioeconomic factors, and marital as well as smoking statuses were also adjusted for in the models (20-23) (Tables 1-2). The variables (excluding sex and age) were adjusted for in the baseline in 2007, as well as in 2011 to control for the potential time-related change within them. Participants' socioeconomic status was determined via three indices both in 2007 and 2011; educational level was assessed via a 3-category scale (1 = comprehensive school, 2 = secondary education, not academic 3 = academic education). Participants' income level was assessed with an 8-point scale (1 = <10 000 euros, 8 = >70 000 euros/ year) in 2007, and with a 13-point scale in 2011 (1 = <5 000 euros, 13=> 60 000 euros/ year). Employment status was examined with a question "Are you unemployed in the present moment?" (1 = no, 2 = yes) during the years 2007 and 2011. Participants' marital statuses were examined using a 5-category scale in 2007 (1 = widowed, 2 = unmarried, 3 = divorced/ living separately, 4 = in a civil partnership, 5 = married) and using a 6-category instrument in 2011 (1= widowed, 2 = unmarried, 3 = divorced/ living separately, 4 =

cohabiting, 5 = in a civil partnership, 6= married). Smoking status was examined via a 5-category scale (1 = smokes a cigarette per day or more, 2 = smokes once in a week, 3 = smokes less than once in a week, 4 = has quitted smoking, 5 = has never smoked) during the year 2007, and with a 6-category scale (1= smokes a cigarette per day or more, 2= smokes once in a week or more, not daily, 3= smokes less than once in a week, 4= has temporarily quitted smoking, 5= has quitted smoking, 6= has never smoked) in 2011.

Statistical Analyses

The associations between physical activity (2007), sleep problems (2011) and depressive symptoms (2012) were first examined with correlational analyses. Thereafter, the mediation analyses were conducted within a modern framework of statistical testing (19, 37, 38). We studied first the model in which physical activity was expected to contribute to decreased levels of depressive symptoms, and whether the association was mediated by sleep problems (Figure 1). The results were further examined with adjusting for the mediator's and outcome's values at baseline, participants' sex, age, body mass index, socioeconomic factors, marital and smoking statuses. We also tested which covariate(s) potentially affected the mediation by controlling for each of them separately in the model. Furthermore, we conducted the same analyses using the standardized cut off values for BDI-II (0-13 = no symptoms of depression/ minimal depression, ≥14 = mild, moderate or severe depression) (34, 35).

The mediation analysis used in this study is applicable in estimating both linear and nonlinear relationships, parametric and nonparametric models, as well as variables with different measurement scales (19, 37). The method relies on the assumption of sequential ignorability, according to which the independent variable should be ignorable of the observed pretreatment covariates, and the mediator should be independent of the observed treatment and pretreatment confounders (19, 37, 38). Conducting mediation analysis requires two models, one for the mediator

and one for the outcome. Missing values were removed from the present data before the estimation of the mediation models, as both models must have identical number of observations in the same order within the data. The potential confounding factors, which could not be regarded as perfectly valid ordinal or interval variables (sex, education, employment, marital and smoking statuses), were defined as factors (nominal variables) with the use of a reference category in the mediation models.

After fitting the models, the results were generated using the algorithm designed for parametric, semiparametric and nonparametric models (Algorithm 2) (38). This algorithm was also applied due to the potential skewness of the variables' distributions (38, 39). The algorithm is based on nonparametric bootstrap (38), which relies on random sampling with replacement method. Along with producing mediation, direct and total effects, the algorithm generates uncertainty estimates including confidence intervals and p-values. Confidence intervals were calculated using percentile method, and p-values were calculated from percentile-based confidence intervals. All the bootstrap calculations were performed with 1000 resamples (simulations).

Sensitivity analysis for mediation test is based on the correlation between the error for the mediation model, and the error for the outcome model (19, 37, 38). The sensitivity parameter rho (ρ) represents the model's deviance from the sequential ignorability assumption. Under sequential ignorability, ρ is zero, and nonzero values ranging from -1 to 1 indicate departures from the ignorability assumption (37, 38). The goal of sensitivity analysis is to quantify the degree to which the key identification assumption is violated (37). It has been suggested that the degree of sensitivity can be evaluated in comparison to other studies (38, 40), and in conjuction with expert opinion (38). Given the importance of sequential ignorability, it has been argued that a mediation analysis is not complete without a sensitivity assessment (38). P-values < 0.05 were considered significant. The analyses were performed via SPSS (version 24.0) and R-software (version 3.1, mediation package 4.4.6).

RESULTS

Descriptive statistics of the sample are presented in Tables 1 and 2, as well as in Supplementary Tables 1 and 2. Due to the non-normal distributions regarding depressive symptoms and sleep problems, square root transformations were conducted. Thereafter, the variables were standardized to improve the comparability of the results. Physical activity correlated negatively with sleep problems and symptoms of depression in most tests ($P < 0.05$). Positive correlations between sleep problems and depressive symptoms were found ($P < 0.05$) (Table 3).

The favorable contribution of physical activity to depressive symptoms ($b = -0.10$, $P < 0.01$) was partly mediated by sleep problems (proportion of total effect via mediation = 0.36, $P < 0.01$, $\rho = 0.36$) (Table 4, Unadjusted analyses). After adjusting for the mediator's and outcome's baseline values (2007), participants' sex, age (2007), body mass index, socioeconomic factors, marital and smoking statuses (2007 and 2011), the results turned into non-significance (proportion mediated =24.06, $P > 0.05$) (Table 4, Adjusted analyses). After testing for which of the covariates affected the mediation effect, the baseline value of depressive symptoms (2007) attenuated it (proportion mediated = 0.30, $P > 0.05$). Approximately similar results were found when the outcome, depressive symptoms assessed in 2012, was used as a dichotomized variable. Within these analyses, the contribution of physical activity to depressive symptoms ($b = -0.02$, $P < 0.01$) was partly mediated by sleep problems (proportion mediated = 0.16, $P < 0.01$). The results became nonsignificant when the covariates were controlled for (proportion mediated = 0.08, $P > 0.05$). After testing for which of the covariates affected the mediation effect, the baseline value of depressive symptoms (2007) attenuated it (proportion mediated = 0.09, $P > 0.05$).

DISCUSSION

This study examined the associations between physical activity, sleep problems and depressive symptoms, and whether the potential contribution of physical activity to depressive symptoms were

mediated by sleep problems. The results were further tested by adjusting the models for mediator's and outcome's values at baseline (2007), participants' sex, age (2007), body mass index, socioeconomic factors, marital and smoking statuses (2007 and 2011). Moreover, the mediation analyses' robustness was examined with sensitivity analyses.

The results indicated that physical activity was associated with decreased levels of sleep problems and depressive symptoms, which is in line with previous studies (4, 7). The favorable contribution of physical activity to symptoms of depression was partly mediated by sleep problems, which is in agreement with our hypothesis. When the covariates were controlled for, the significant mediation effect disappeared. Adjusting for depressive symptoms at baseline attenuated the mediation effect, whereas other potential confounders did not contribute to the tested association. As the results were approximately similar when the depressive symptoms were studied as a dichotomized outcome, we gained supportive evidence for the suggestion that the lost impact of sleep as a mediator was due to the pre-existing symptoms of depression. Furthermore, the sensitivity analyses indicated that unobserved confounding exists in the study.

It has been suggested that physical activity's favorable effects on depressive symptoms might be mediated through sleep due to physiological processes. For instance, physical activities might associate with body temperature's downregulation, which contributes to improved sleep (13). Physical activities may also boost body's catabolic activity, which facilitates body restoration during rest (14, 41). Improved sleep is likely to associate with psychological functioning and wellbeing (13, 14). Sufficiency of sleep may also contribute to hormonal balance impacting cortisol secretion associating with mood and psychological wellbeing (15-17).

The existing literature has not been, however, able to fully explain the sleep-promoting efficacy of physical activities (14). As adjusting for the baseline of depressive symptoms attenuated the sleep problems' mediating effect in the relation between physical activity and depressive symptoms, it seems possible that physical activity's favorable effect on mood mediated

by sleep disappears in people who have pre-existing symptoms of depression. Previous research has also shown that physical activity is not associated with progression of depression in adulthood (8). Depressed people often experience feelings of sadness, failure, quilt, disappointment and irritation (33). They also tend to suffer from a lack of healthy appetite, self-belief, motivation and ability to start and maintain distinct activities (33). Thus, it is possible that depressed people's psychophysiological and behavioral predispositions mismatch with those that are needed in getting interested and engaging in physical activities. It is is also possible that pre-existing depressive symptoms associate with difficulties with sleep regulation (4). Such difficulties may hamper body restoration during rest, and hinder physical activity's favorable effects on mood mediated by sleep. Thus, it is possible that the pre-existing symptoms of depression predispose an individual to such psychophysiological conditions and behaviors that may not contribute to physically active lifestyle and related benefits as good sleep through which the favorable effects of physical activity on psychological wellbeing could partly come.

Limitations

Proportion of total effects via mediation was quite large (36%) in the unadjusted model in which BDI-II was used as continuous variable, although the results were not perfectly robust (ρ=0.36). We cannot perfectly determine whether the potential mediator-outcome confounding, exposure-mediator interaction, or mediator-outcome confounding affected by the exposure introduced bias into our data (42), but the sensitivity analyses gave us the possibility to evaluate the degree to which the unobserved confounding might have affected the results. Unobserved confounding's existence is, however, unavoidable especially in observational studies where the study designs are not randomized (37, 38). Furthermore, we were able to adjust for the baseline values of the mediator and outcome variables along with other covariates with this observational design, but even after

controlling for the potential time-related change within these variables our possibility to consider causality is limited. Furthermore, participants did not provide information regarding each variable across the measurement years, which diminished the sample size to some degree. Sample attrition can be regarded as a major limitation of the study as it can contribute to both under- and overestimation of the associations. The study was also non-experimental. Due these reasons, the results should be interpreted with caution. Finally, the assessments concerning the participants' physical activity, sleep problems and symptoms of depression were self-reported, and therefore the possibility of subjective bias cannot be perfectly excluded. Self-reports have, however, shown to be correlated with objective measurements and diagnoses (29-31, 33-35).

Strengths

The study's strengths were its prospective and population-based design. Validated and clinically relevant measures (26, 32, 34) were used, and a set of relevant covariates were controlled for. Furthermore, the mediation analyses were conducted within a modern and sophisticated framework of causal inference (37, 38).

Conclusions

This population-based, prospective study showed that the association between physical activity and decreased levels of depressive symptoms was mediated partly by sleep problems in adults. However, controlling for the pre-existing depressive symptoms attenuated this finding. Thus, physical activity's favorable contribution to depressive symptoms was mediated partly by sleep, but the mediation effect disappeared after adjusting for the previous depressive symptoms in adulthood.

REFERENCES

1. Dinas P, Koutedakis Y, Flouris A. Effects of exercise and physical activity on depression. *Ir J Med Sci.* 2011;180(2):319-325.

2. Aalto-Setälä T, Marttunen M, Tuulio-Henriksson A, Poikolainen K, Lönnqvist J. Depressive symptoms in adolescence as predictors of early adulthood depressive disorders and maladjustment. *Am J Psychiatr.* 2002;159(7):1235-1237.

3. Muñoz R, Cuijpers P, Smit F, Barrera A, Leykin Y. Prevention of major depression. *Ann Rev Clin Psychol.* 2010;6:181–212.

4. Lopresti A, Hood S, Drummond P. A review of lifestyle factors that contribute to important pathways associated with major depression: Diet, sleep and exercise. *J Aff Dis.* 2013;148(1):12-27.

5. World Health Organization. *Global recommendations on physical activity for health.* Switzerland: World Health Organization; 2010. 60 p.

6. Dumith S, Hallal P, Reis R, Kohl H. Worldwide prevalence of physical inactivity and its association with human development index in 76 countries. *Prev Med.* 2011;53(1-2):24-28.

7. Teychenne M, Kylie B, Salmon J. Physical activity and likelihood of depression in adults: a review. *Prev Med.* 2008;46(5):397-411.

8. Kaseva K, Rosenström T, Hintsa T, et al. Trajectories of Physical Activity Predict the Onset of Depressive Symptoms but Not Their Progression: A Prospective Cohort Study. *J Sports Med.* 2016; 8947375.

9. Roth T. Insomnia: definition, prevalence, etiology, and consequences. *J Clin Sleep Med.* 2007;3(5):S7-S10.

10. Kronholm E, Partonen T, Härmä M, et al. Prevalence of insomnia-related symptoms continues to increase in the Finnish working-age population. *J Sleep Res.* 2016;25(4):454-457.

11. Stranges S, Tigbe W, Gómez-Olivé F, Thorogood M, Kandala M. Sleep problems: An emerging global epidemic? Findings from the INDEPTH WHO-SAGE Study Among More Than 40,000 Older Adults From 8 Countries Across Africa and Asia. *Sleep.* 2012;35(8):1173-1181.

12. Ford E, Wheaton A, Cunningham T, Giles W, et al. Trends in outpatient visits for insomnia, sleep apnea, and prescriptions for sleep medications among US adults: findings from the National Ambulatory Medical Care Survey 1999–2010. *Sleep.* 2014;37(8):1283–1293.

13. Brand S, Gerber M, Beck J, Hatzinger M, Pühse U, Holsboer-Trachsel E. High exercise levels are related to favorable sleep patterns and psychological functioning in adolescents: a comparison of athletes and controls. *J Adolesc Health.* 2010;46(2):133-141.

14. Driver H, Taylor S. Exercise and Sleep. *Sleep Med Rev.* 2000;4(4):387-402.

15. Meerlo P, Sgoifo A, Suchecki D. Restricted and disrupted sleep: effects on autonomic

function, neuroendocrine stress systems and stress responsivity. *Sleep Med Rev*. 2008;12(3):197-210.

16. Kumari M, Badrick E, Ferrie J, Perski A, Marmot M, Chandola T. Self-reported sleep duration and sleep disturbance are independently associated with cortisol secretion in the Whitehall II study. *J Clin Endocrinol Metab.* 2009;94(12):4801-4809.

17. Stokes P. The potential role of excessive cortisol induced by HPA hyperfunction in the pathogenesis of depression. *Eur Neuropsychopharmacol.* 1995;5:77-82.

18. Penedo F, Dahn J. Exercise and well-being: a review of mental and physical health benefits associated with physical activity. *Curr Op Psych*. 2005;18(2):189-193.

19. Tingley D, Yamamoto T, Hirose K, Keele L, Imai K. Mediation: R package for causal mediation analysis. *Journal of Statistical Software* 2014;59(5):1-38.

20. Allgöwer A, Wardle J, Steptoe A. Depressive symptoms, social support, and personal health behaviors in young men and women. *Health Psychol.* 2001;20(3):223–227.

21. Luppino F, de Wit L, Bouvy P, et al. Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. *Arch Gen Psychiatry*. 2010;67(3):220–229.

22. Galobardes B, Shaw M, Lawlor D, Lynch J, Smith D. Indicators of socioeconomic position (part 1). *J Epidemiol Community Health.* 2006;60:7-12.

23. Inaba A, Thoits P, Ueno K, Gove W, Evenson R, Sloan M. Depression in the United States and Japan: gender, marital status, and SES patterns. *Soc Sci Med*. 2005;*61*(11):2280-2292.

24. Hirvensalo M, Lintunen T. Life-course perspective for physical activity and sports participation. *Eur Rev Aging Phys Act.* 2011;8(1):13-22.

25. Raitakari O, Juonala M, Rönnemaa T, et al. Cohort profile: the cardiovascular risk in Young Finns Study. *Int J Epidemiol.* 2008;37(6):1220-1226.

26. Telama R, Yang X, Viikari J, et al. Physical activity from childhood to adulthood - A 21-year

tracking study. *Am J Prev Med.* 2005;28(3):267–73.

27. Rosenström T, Jokela M, Puttonen S, et al. Pairwise measures of causal direction in the epidemiology of sleep problems and depression. *PLoS One.* 2012;7:e50841.

28. Yang X, Kaseva K, Keltikangas-Järvinen L, et al. Does Childhood Temperamental Activity Predict Physical Activity and Sedentary Behavior over a 30-Year Period? Evidence from the Young Finns Study. *Int J Behav Med.* 2017;24(2):171-179.

29. Kari J, Pehkonen J, Hirvensalo M, et al. Income and Physical Activity among Adults: Evidence from Self- Reported and Pedometer-Based Physical Activity Measurements. *PloS One.* 2015;10:e0135651.

30. Mansikkaniemi K, Juonala M, Taimela S, et al. Cross-sectional associations between physical activity and selected coronary heart disease risk factors in young adults. The Cardiovascular Risk in Young Finns Study. *Ann Med.* 2012;44(7):733-744.

31. Tudor-Locke C, Williams J, Reis J, Pluto D. Utility of pedometers for assessing physical activity: construct validity. *Sports Med.* 2004;34(5):281-291.

32. Jenkins C, Stanton B, Niemcryk S, et al. A scale for the estimation of sleep problems in clinical research. *J Clin Epidemiol.* 1988;41(4):313-321.

33. Armitage R, Trivedi M, Hoffmann R. Relationship between objective and subjective sleep measures in depressed patients and healthy controls. *Depress Anxiety.* 1997;5(2):97-102.

34. Beck A, Steer R, Brown G. *Manual for the Beck Depression Inventory-II*. San Antonio, TX: Psychological Corporation; 1996. 38p.

35. Wang Y, Gorenstein C. Psychometric properties of the Beck Depression Inventory-II: a comprehensive review. *Revista Brasileira de Psiquiatria* 2013;35(4):416–431.

36. Karsten J, Hartman C, Smit J, et al. Psychiatric history and subthreshold symptoms as predictors

of the occurrence of depressive or anxiety disorder within 2 years. *Br J Psych.* 2011;198(3):206-212.

37. Imai K, Keele L, Tingley D, Yamamoto T. *Causal mediation analysis using R.* In: Vinod H, Editor. Advances in Social Science Research Using R. New York: Springer; 2010, p. 129–154.

38. Imai K, Tingley D, Keele L. A general approach to causal mediation analysis. *Psychol Methods.* 2010;15(4):309-334.

39. Mackinnon D, Lockwood C, Williams, J. Confidence limits for the indirect effect: Distribution of the product and resampling methods. *Multivariate Behavioral Research.* 2004;39(1):99–128.

40. Rosenbaum P. Covariance adjustment in randomized experiments and observational studies: Rejoinder. *Stat Sci.* 2002;17(3):286–327.

41. Adam K, Oswald I. Protein synthesis, bodily renewal and the sleep-wake cycle. *Clin Sci.* 1983;65(6):561–567.

42. Richiardi L, Bellocco R, Zugna D. Mediation analysis in epidemiology: methods, interpretation and bias. *Int J Epidemiol.* 2013;42(5):1511–1519.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare. The results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation. The results of the study do not constitute endorsement by American College of Sports Medicine.

Figure 1. Sleep problems mediating the association between physical activity and depressive symptoms

Table 1. Descriptive statistics for the complete sample (*n* = 1018).

Variables		Mean/SD/ *n* (%)	Range
Confounding factors[1]			
	Sex (1980)		0-1
	Females	601 (59.0)	
	Males	417 (40.9)	
	Age, years (2007)	38.1±5.0	30-45
	Body mass index (2007)	25.8±4.7	16.6-58.8
	Body mass index (2011)	26.3±4.9	17.0-58.5
	Education (2007)[2]	2.2±0.5	1-3
	Education (2011)	2.3±0.5	1-3
	Income (2007)	3.5±1.5	1-8
	Income (2011)	7.3±3.0	1-13
	Employment status (2007)		0-1
	Employed	987 (97.0)	
	Not employed	31 (3.0)	
	Employment status (2011)		0-1
	Employed	973 (95.6)	
	Not employed	45 (4.4)	
	Marital status (2007)[3]	4.2±1.1	1-5
	Marital status (2011)[4]	4.9±1.5	1-6
	Smoking status (2007)[5]	4.0±1.4	1-5
	Smoking status (2011)[6]	4.9±1.7	1-6
	Sleep problems (2007)	1.5±0.3	1-2.5
	Depressive symptoms (2007)	1.6±1.4	0-6.2
Independent/ mediator/ dependent variables			
	Physical activity index (2007)	8.9±1.8	5-15
	Sleep problems (2011)	1.5±0.3	1-2.5
	Depressive symptoms (2012)	1.4±1.3	0-7.2
	Depressive symptoms (dichotomized scores) (2012)		0-1
	No depression/ minimal depression	955 (93.8)	
	Mild, moderate or	63 (6.2)	

severe depression

[1]The dichotomized variables are dummy coded (0-1).
[2]1= comprehensive school, 3= academic education both in 2007 and 2011
[3]1= widowed, 5= married
[4]1= widowed, 6= married
[5]1= smokes a cigarette per day or more, 5=has never smoked
[6]1= smokes a cigarette per day or more, 6= has never smoked

Table 2. Descriptive Z-statistics for the complete sample (n = 1018).[1]

Variables		Range
Confounding factors		
	Sex (1980)	-0.98-1.02
	Age, years (2007)	-1.49-1.51
	Body mass index (2007)	0.83-1.99
	Body mass index (2011)	0.82-1.88
	Education (2007)	-2.36-1.58
	Education (2011)	-2.44-1.58
	Income (2007)	-1.60-2.89
	Income (2011)	-2.06-1.81
	Employment status (2007)	-0.21 4.82
	Employment status (2011)	-0.24 4.18
	Marital status (2007)	-2.85 0.74
	Marital status (2011)	-2.53 0.75
	Smoking status (2007)	-1.84-0.78
	Smoking status (2011)	-2.03-0.71
	Sleep problems (2007)	-1.42-2.89
	Depressive symptoms (2007)	-1.19-2.89
Independent/ mediator/ dependent variables		
	Physical activity index (2007)	-2.10-3.41
	Sleep problems (2011)	-1.47-3.04
	Depressive symptoms (2012)	-1.10-4.15

[1]Excluding the dichotomized scores for depressive symptoms (presented in Table 1), the scores are standardized with a mean of 0 and standard deviation of 1

Table 3. Correlation coefficients between physical activity, sleep problems and symptoms of depression (*n* = 1365-2161).

	1.	2.	3.	4.
1. Physical activity (2007)				
2. Sleep problems (2007)	-0.04			
3. Sleep problems (2011)	-0.08**	0.54**		
4. Depressive symptoms (2007)	-0.09**	0.41**	0.37**	
5. Depressive symptoms (2012)	-0.09**	0.30**	0.35**	0.62**

P < 0.05*
P < 0.01**

Table 4. Sleep problems mediating the association between physical activity and depressive symptoms (unadjusted analyses, *n* = 1270; adjusted analyses, *n* = 1018).

	Unadjusted analyses				Adjusted analyses[1]			
	b/ Prop. Med.	95%CI[2]	*P*-value	*ρ* (ACME)[3]	*b*/ Prob. Med.	95%CI	*P*-value	*ρ* (ACME)
ACME[4]	-0.03	-0.06 to -0.02	<0.01	0.36	-0.00	-0.01 to 0.00	0.29	0.19
ADE[5]	-0.06	-0.11 to -0.01	0.02		0.00	-0.05 to 0.05	0.90	
Total Effect	-0.10	-0.15 to -0.04	<0.01		-0.00	-0.05 to 0.05	0.99	
Proportion Mediated	0.36	0.18 to 0.76	<0.01		24.06	-3.77 to 2.46	0.93	

[1] The analyses were adjusted for mediator and outcome variables' baseline values, participants' sex, age, body mass index, socioeconomic factors, marital and smoking statuses
[2] Nonparametric bootstrap confidence intervals with the percentile method were examined
[3] Rho, sensitivity parameter
[4] ACME, average causal mediation effect
[5] ADE, average direct effect

Supplementary Table 1. Descriptive statistics for the original sample's continuous variables (*n* = 1725-3596).

Variables		All[1] *n*	Mean/ SD	Range
Confounding factors				
	Age, years (2007)	3596	37.4±5.0	30-45
	Body mass index 2007	2170	26.0±4.8	16.6-58.8
	Body mass index 2011	2049	26.5±5.1	16.2-58.5
	Income (2007)	2146	3.5±1.6	1-8
	Income (2011)	1941	7.4±3.1	1-13
	Sleep problems (2007)	2226	2.3±1.1	1-6
	Depressive symptoms (2007)	2020	4.5±5.9	0-40
Independent/ mediator/ dependent variables				
	Physical activity index (2007)	2166	8.8±1.8	5-15
	Sleep problems (2011)	2006	2.3±1.0	1-6
	Depressive symptoms (2012)	1725	4.2±5.9	0-52

Supplementary Table 2. Descriptive statistics for the original sample's categorical variables (*n*=1725-3596).

Variables		All *n*	Variables' categories	Variables' categories' *n* (%)	Range
Confounding factors					
	Sex (1980)	3596	Females Males	1832 (50.9) 1764 (49.1)	1-2
	Education (2007)	2228	Comprehensive school Secondary education Academic	110 (4.9) 1569 (70.4) 549 (24.6)	1-3
	Education (2011)	2002	Comprehensive school Secondary education Academic	78 (3.9) 1415 (70.7) 509 (25.4)	1-3
	Employment status (2007)	2182	Employed Not employed	2092 (95.9) 90 (4.1)	1-2
	Employment status (2011)	1957	Employed Not employed	1851 (94.6) 106 (5.4)	1-2
	Marital status (2007)	2223	Widowed Unmarried Divorced/ living separately In a civil partnership Married	6 (0.3) 347 (15.6) 138 (6.2) 497 (22.4) 1235 (55.6)	1-5
	Marital status (2011)	2000	Widowed Unmarried Divorced/ living separately Cohabiting In a civil partnership Married	8 (0.4) 269 (13.5) 151 (7.6) 346 (17.3) 38 (1.9) 1188 (59.4)	1-6
	Smoking status (2007)	2224	Smokes a cigarette per day or more	411 (18.5)	1-5

			Smokes once in a week	91 (4.1)	
			Smokes less than once in a week	110 (4.9)	
			Has quitted smoking	511 (23.0)	
			Has never smoked	1101 (49.5)	
	Smoking status (2011)	1999	Smokes a cigarette per day or more	306 (15.3)	1-6
			Smokes once in a week or more, not daily	58 (2.9)	
			Smokes less than once in a week	87 (4.4)	
			Has temporarily quitted smoking	28 (1.4)	
			Has quitted smoking	502 (25.1)	
			Has never smoked	1018 (50.9)	
Dependent variable					
	Depressive symptoms (dichotomized scores) (2012)	1725	No symptoms of depression/ minimal depression	1592 (92.3)	0-1
			Mild, moderate or severe depression	133 (8.8)	