Leisure time physical activity and incident use of prescription tranquilizers: a longitudinal population-based study

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Citation:

Sheikh, M.A., 2018. Leisure time physical activity and incident use of prescription tranquilizers: a longitudinal population-based study. *Journal of Affective Disorders* 238, 327-335. doi: 10.1016/j.jad.2018.06.010

Running title: Physical activity and use of tranquilizers

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Acknowledgments: I am thankful to Brendon Stubbs and Davy Vancampfort.

Conflict of interest: None

Financial disclosure: Mashhood Ahmed Sheikh has no financial disclosures.

Abstract

Objective: Physical inactivity is a major public health problem associated with an increased risk of several psychiatric and physical conditions. This study investigated the association between leisure time physical activity (PA) and incident use of prescription tranquilizers in a regionally representative and prospective cohort. **Methods:** A total of 4043 men and women (mean age: 61.3 years; 57% women) from the Tromsø Study were followed for six years. Leisure time PA was captured at baseline. Psychiatric morbidity was measured by use of prescription tranquilizers, captured at both baseline and follow-up. Leisure time PA at baseline was used as a predictor of subsequent (incident) use of prescription tranquilizers. We used multinomial regression models and Poisson regression models to estimate relative risk-ratios (RRRs), and relative risks (RRs), respectively, and their corresponding 95% confidence intervals (CIs). **Results:** In the fully-adjusted model, accounting for socio-demographic factors, parental history of psychopathology, years of education, smoking, respondent's psychopathology at baseline, and occupational PA, a lower leisure time PA conferred a 41% increased risk of incident use of prescription tranquilizers at follow-up (RR= 1.41, 95% CI: 1.09, 1.83; p=0.010). **Conclusions:** These findings suggest that physical inactivity increases the risk of psychiatric morbidity (albeit, measured via use of prescription tranquilizers). Future regionally representative and longitudinal research is required to confirm/refute our findings and explore underlying mechanisms.

Keywords: physical activity; tranquilizer; psychotropic; psychiatric morbidity

Highlights

• Leisure time physical activity conferred protection against incident use of tranquilizers.

• Lower leisure time physical activity is associated with increased incident use of tranquilizers six years later.

• Physical activity in late–midlife can be important for preventing mild psychiatric morbidity in early old age.

Introduction

Previous evidence suggests that leisure time physical activity (PA) plays a protective role for burnout, psychological distress, depression, and anxiety (Gerber et al., 2013; Gudmundsson et al., 2015; Josefsson et al., 2014; Lindwall et al., 2014; Perales et al., 2014; Sheikh et al., 2018; Teychenne et al., 2008). However, a paucity of regionally representative, prospective studies have assessed the association between leisure time PA and psychiatric morbidity (Sheikh et al., 2018).

The Tromsø Study is a longitudinal population-based study of the general population, representative of adults in corresponding age groups in the Tromsø region, Norway (Jacobsen et al., 2012). Although no validated instruments for psychiatric diagnosis were included in the surveys, questions on use of prescription medication were included. Psychotropic medication, such as tranquilizers and sedatives, are prescribed for several psychopathologies and psychiatric disorders, including depression, dysthymia, phobias, PTSD, anxiety disorders, and mood disorders (Lahti et al., 2013; Sanchez-Villegas et al., 2008; Stubbs et al., 2017; Waller et al., 2016). Therefore, a longitudinal association between a lower leisure time PA and incident use of prescription tranquilizers may suggest that a lower leisure time PA is associated with an increased risk of psychiatric morbidity (Sanchez-Villegas et al., 2008). This assumption underlies this study.

In this study, we set out to assess the longitudinal association between leisure time PA and *incident* use of prescription tranquilizers. The influence of prior use of prescription tranquilizer medication and other key covariates at baseline such as age, gender, parental history of psychopathology, years of education, marital status, smoking, psychological distress, psychiatric problems, insomnia, and occupational PA were also examined, because

they have been associated with psychiatric morbidity in previous studies (Lahti et al., 2013; Sheikh, 2018a, b; Sheikh et al., 2018; Stubbs et al., 2017; Waller et al., 2016).

Methods

Study population

The Tromsø Study is a representative, prospective cohort study of the adult population residing in the municipality of Tromsø, Norway (Jacobsen et al., 2012). Between 1974 and 2007–2008, six waves of the Tromsø Study were conducted (referred to as Tromsø I–VI) (Jacobsen et al., 2012). The present study has a two-wave design. To be eligible for the present analyses, participants had to have attended both Tromsø V (2001–02) and Tromsø VI (2007–08) (N = 4630). The study sample included respondents aged 30–81 (mean: 61.3) at Tromsø V, and 36–87 (mean: 67.3) at Tromsø VI.

Study variables

Leisure time physical activity (Tromsø V)

Measurement of self-reported leisure time PA is expected to be valid in population-based studies in Norway (Aires et al., 2003; Kristin B Borch et al., 2012). Leisure time PA was measured with a question on a four-point Likert scale: "How has your physical activity (sweating/out of breath) in leisure time been during this last year? Think of your weekly average hours/week for the year. Time spent going to work counts also as leisure time" (Sheikh, 2018f; Sheikh et al., 2018). The response alternatives were: "none", "less than 1", "1–2", and "3 or more' hours/week". The scores were inverted, so that a higher score represents lower leisure time PA.

Use of prescription tranquilizers (Tromsø VI)

Self-reported use of prescription tranquilizers is expected to be reliable and valid (Haapea et al., 2010; Hafferty et al., 2018; Rauma et al., 2013). Use of prescription tranquilizer medication was asked in the Tromsø VI (2007–08) questionnaire as: "How often have you used prescription tranquilizers during the last four weeks?" The response alternatives were: "not used" (n=4069); "less frequently than every week" (n=110); "every week, but not daily" (n=62), and; "daily" (n=76) (Sheikh, 2018d). Those reporting any of the last three categories were classified as using prescription tranquilizers (n=248).

In order to assess the influence of leisure time PA at baseline on *incident* use of prescription tranquilizers at follow-up, and to avoid the effect of prior psychiatric morbidity on leisure time PA (reverse causality) and subsequent psychiatric morbidity (confounding), we excluded respondents that reported using prescription tranquilizers at baseline (n=182), had a clinically significant level (HSCL-10 score ≥ 18.5) of psychological distress (Sheikh et al., 2018; Strand et al., 2003) at baseline (n=211), and reported psychiatric problems (Sheikh, 2018a, f) at baseline (n=351). In the remaining study sample of 4043 participants, there were 111 incident users of prescription tranquilizers at follow-up (Table 1). The five-category variable was used for analysis with multinomial regression models, while the binary variable was used for analysis with Poisson regression models (see Table 4).

Confounding variables (Tromsø V)

Confounding variables derived from the baseline questionnaire (Tromsø V) included age, gender, parental history of psychopathology, years of education, smoking, marital status (single, married or registered partnership, widow/widower, divorced or separated), occupational PA, prevalence of psychiatric problems, psychological distress, insomnia and use of prescription tranquilizers at baseline. Previous evidence has shown age (Simoni-

Wastila, 2000; The ESEMeD Mhedea investigators et al., 2004), and psychological distress (Myhrene Steffenak et al., 2012) are positively associated with use of prescription tranquilizers; while education (The ESEMeD Mhedea investigators et al., 2004) is negatively associated with use of prescription tranquilizers. Other studies have shown that age is negatively associated with leisure time PA (Sheikh et al., 2018). A higher proportion of women use prescription tranquilizers than men (Myhrene Steffenak et al., 2012; Norris et al., 2011; Ohayon et al., 1998; Quintana et al., 2013; The ESEMeD Mhedea investigators et al., 2004). Numerous studies have shown that smoking is associated with leisure time PA (Laaksonen et al., 2001; Løchen and Rasmussen, 1992; Morseth et al., 2016; Sheikh et al., 2018) and mental health outcomes (Ekblad et al., 2011; Hansen and Jacobsen, 1989; Sheikh et al., 2018). Similarly, several studies have shown that education is positively associated with leisure time PA (Morseth et al., 2016; Seiluri et al., 2011; Sheikh et al., 2018) and negatively associated with a wide range of mental health outcomes (Sheikh, 2018b; Sheikh et al., 2018).

Valid information on age and gender was obtained from Statistics Norway, using the unique personal identification number of each respondent. Mother's/father's history of psychopathology was measured as: “Does your mother/father have/has your mother/father ever had psychiatric problems?” (yes, no). The test-retest reliability of mother's history of psychopathology and father's history of psychopathology in the Tromsø Study were Kappa: 0.57 (95% CI: 0.52–0.62) and Kappa: 0.61 (95% CI: 0.53–0.69), respectively (Sheikh, 2018c). Participants reported years of education in Tromsø V (mean = 10.50, 95% CI: 10.39, 10.61). The test-retest reliability of self-reported education was very good (Kappa: 0.91, 95% CI: 0.91, 0.92) in the Tromsø Study (Sheikh, 2018e). Smoking was measured by the question, “Do you smoke?” (yes, daily /yes, sometimes/no, never). Occupational PA was measured by the question “If you have paid or unpaid work, how would you describe your

work?". The response alternatives were 1=Mostly sedentary work (e.g. office work, mounting); 2=Work that requires a lot of walking (e.g. shop assistant, light industrial work, teaching); 3=Work that requires a lot of walking and lifting (e.g. Postman, nursing, construction); and, 4=Heavy manual labour (e.g. forestry, heavy farm-work, heavy construction). The test-retest reliability of occupational PA was good in this sample [weighted Kappa coefficient (**κ**=0.74, 95% CI: 0.71-0.75); Polychoric correlation coefficient (**ρ**=0.82, p<0.001)]. Prevalence of psychiatric problems at baseline was measured by the question: "Do you have, or have you had psychiatric problems for which you sought help?" (0=no, 1=yes) (Sheikh, 2018f). Psychological distress was measured using the 10-item Hopkins Symptom Checklist (HSCL-10), which has been shown to have an acceptable degree of internal consistency in the Tromsø Study (Cronbach's alpha: 0.90, mean inter-item correlation: 0.42, McDonald's omega coefficient for composite reliability: 0.91) (Sheikh, 2018d). The 10 items in the HSCL-10 are rated by the respondent on a four-point scale, ranging from *not at all* (1) to *extremely* (4) (Sheikh, 2018d). A HSCL-10 score was calculated by summing the score of all 10 items, thus possible scores ranged from 10 to 40, with 40 representing the highest and 10 representing the lowest psychological distress (mean: 12.67, SD: 3.29). Insomnia was measured by the question: "How often do you suffer from sleeplessness?" (1=never, or just a few times a year, 2=1-3 times a month, 3=approximately once a week, 4=more than once a month) (Sheikh, 2018d). Use of prescription tranquilizer medication was also asked in the Tromsø V (2001-02) questionnaire as: "How often have you used prescription tranquilizers during the last four weeks?" The response alternatives were: "not used"; "less frequently than every week"; "every week, but not daily", and; "daily".

Ethical approval

This investigation was carried out in accordance with the latest version of the Declaration of Helsinki. The Tromsø Study has been approved by the Regional Committee for Medical and Health Research Ethics, the Data Inspectorate, and the Norwegian Directorate of Health. Written informed consent was obtained from all individual participants included in the study.

Statistical analysis

All analyses were conducted using Stata version 15 (StataCorp LLC). Baseline characteristics of the study sample were determined with means (standard error), and proportions (Table 1). Missing values were generated with multiple imputation with chained equations. A comparison between the complete-case (excluding missing) and the imputed dataset is presented with proportions (%), and mean (standard error) (Table 1). Concordance between use of prescription tranquilizers at baseline (Tromsø V), and follow-up (Tromsø VI) was assessed with Kappa statistic (**κ**) (Sheikh et al., 2016) and Polychoric correlation (**ρ**) (Kolenikov and Angeles, 2004). Established benchmarks for rating the strength of Kappa concordance as poor (<0.20), fair (>0.20 to ⩽0.40), moderate (>0.40 to ⩽0.60), good (>0.60 to ⩽0.80), and very good (>0.80 to ⩽1.00) were used (Sheikh et al., 2016). We estimated Pearson product-moment correlations between all binary, ordinal or continuous variables in this study (Table 2).

We assessed the association between all covariates and prevalent use of prescription tranquilizers at follow-up (binary variable) with Poisson regression models (Table 3). Relative risks (RRs) were estimated, and both unadjusted (crude) and adjusted estimates from multivariable regression model are presented (Table 3). Leisure time PA was modelled as a continuous variable in the regression analysis. To assess the linear trend of association between insomnia and prevalent use of prescription tranquilizers at follow-up, insomnia was

modelled as a continuous variable. No statistically significant multiplicative interactions between leisure time PA and confounding variables were observed. Error variance was derived with first-order Taylor-series linearization method (Huber, 1967; White, 1980) in Stata, and 95% confidence intervals (CIs) are presented.

We used multinomial regression models and Poisson regression models to assess the association between leisure time PA and incident use of prescription tranquilizers at follow-up (Table 4). Relative risks (RRs), and relative risk ratios (RRRs) were estimated (Table 4). Five-category variable of incident use of prescription tranquilizers was used as dependent variable in multinomial regression model (reference=not used prescription tranquilizers), while binary variable (0=not used, 1=used prescription tranquilizers) was utilized as the dependent variable in Poisson regression models (Table 4). We used an Ordinary Least Square regression (OLS) model to assess the linear trend of association between leisure time PA and *frequency* of incident use of prescription tranquilizers. To assess the collinearity of regressors, we estimated variance inflation factors (VIFs) in Stata (-vif-) (Hamilton, 2013). In the fully-adjusted model, mean VIF was 1.29, and none of the individual regressors' VIF (binary or continuous variables) were greater than 1.33 (VIF for age and psychological distress). Similarly, in the complete-case analysis, we observed that fully-adjusted regression models (OLS and Poisson) were correctly specified (Stata command –linktest–). The –linktest– is based on the idea that if a regression model is properly specified, one should not be able to find any additional independent variables that are statistically significant except by chance (Pregibon, 1980; Tukey, 1949).

Results

The distribution of variables was similar in the complete-case dataset (excluding those with missing values) and the imputed datasets (Table 1). Women were more likely to have missing value on leisure time PA ($p<0.001$), prevalent use of prescription tranquilizers at follow-up ($p<0.001$), and incident use of prescription tranquilizers at follow-up ($p<0.001$). Missing values on leisure time PA were associated positively with age ($p<0.001$), and psychological distress ($p=0.007$); while years of education ($p<0.001$) were associated negatively. A higher age ($p<0.001$), father's history of psychopathology ($p=0.027$), being single ($p=0.023$), and a lower education ($p=0.001$) were associated with missing values on prevalent use of prescription tranquilizers at follow-up. Similarly, a higher age ($p<0.001$), father's history of psychopathology ($p=0.019$), a higher psychological distress ($p=0.015$), being single ($p=0.019$), and a lower education ($p=0.004$) were associated with missing values on incident use of prescription tranquilizers at follow-up.

The concordance of use of prescription tranquilizers between Tromsø V (2001–02) and Tromsø VI (2007–08) was moderate [Kappa coefficient (κ=0.48, 95% CI: 0.42, 0.54); weighted Kappa coefficient (κ=0.46, 95% CI: 0.36, 0.50); Pearson's correlation (r=0.47, $p<0.001$) (Table 2); Polychoric correlation (ρ=0.78, $p<0.001$)]. A higher age and female gender were associated ($p<0.001$) with a lower leisure time PA in MI dataset (Table 2). Similarly, in the complete-case analysis, women reported lower leisure time PA than men [$t(3720) = 11.58$, $p < 0.001$]. A lower education level and a lower occupational PA were

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PA was associated ($p<0.001$) with a higher psychological distress and insomnia at baseline (Table 2). A higher age ($p<0.001$), female gender ($p<0.001$), mother's history of psychopathology ($p<0.01$), and a lower education ($p<0.001$) were associated with prevalent use of prescription tranquilizers at baseline and follow-up (Table 2). Psychiatric problems at

baseline, a higher psychological distress, and insomnia were associated (p<0.001) with prevalent use of prescription tranquilizers at baseline, and follow-up (Table 2). Moreover, a lower leisure time PA was associated with prevalent use of prescription tranquilizers at baseline, and follow-up (Table 2).

Association between covariates (at baseline) and prevalent use of prescription tranquilizers at follow-up

Two estimates are presented in Table 3 for each covariate: crude (unadjusted), and estimates adjusted for all other covariates. In the fully-adjusted model, a higher age (RR=1.02, 95% CI: 1.01, 1.04; p=0.003), mother's history of psychopathology (RR=1.35, p=0.079), a lower education (RR=0.93, 95% CI: 0.90, 0.97; p=0.001), daily smoking (reference=never smoking) (RR=1.26, p=0.081), psychiatric problems at baseline (RR=1.93, 95% CI: 1.38, 2.71; p<0.001), insomnia at baseline (*p* for linear trend=0.042), a lower leisure time PA (RR=1.19, 95% CI: 1.04, 1.35; p=0.010), and use of prescription tranquilizers at baseline (p<0.001) were associated with prevalent use of prescription tranquilizers at follow-up (Table 3).

Association between leisure time PA and incident use of prescription tranquilizers

When incident use of prescription tranquilizers at follow-up was modelled as a continuous variable (i.e., without collapsing into a binary variable) in an OLS regression model, the test for linear trend for the estimate of leisure time PA was statistically significant, but the estimate was close to null (β_{PA} = 0.01, p=0.038). Consequently, when a multinomial regression model was used to assess the association between leisure time PA and incident use of prescription tranquilizers at follow up, the estimates did not show a clear linear trend in the

expected direction (Table 4). With *no incident prescription tranquilizer use* as the reference (n=3658) in the fully-adjusted multinomial regression model, a lower leisure time PA was associated with 60% increased risk of using prescription tranquilizers *less frequently than every week* (RRR=1.60, 95% CI: 1.12, 2.28; p=0.010); a 14% increased risk of using prescription tranquilizers *every week, but not daily* (RRR=1.14, 95% CI: 0.63, 2.06; p=0.667); and a 47% increased risk of using prescription tranquilizers *daily* (RRR=1.47, 95% CI: 0.82, 2.65; p=0.192) (Table 4). This trend may suggest that leisure time PA is most effective for mild psychiatric morbidity [reflected by category *incident use of prescription tranquilizers less frequently than every week*]. Moreover, when binary variable was used as an outcome, a lower leisure time PA conferred a 41% increased risk of incident use of prescription tranquilizers at follow-up (RR= 1.41, 95% CI: 1.09, 1.83; p=0.010) (Table 4).

Discussion

Our objective was to examine the relationship between leisure time PA and subsequent psychiatric morbidity, measured via use of prescription tranquilizers in a regionally representative, prospective cohort in Norway. To the best of our knowledge, the current study is the first to explore the longitudinal relation between leisure time PA and use of prescription tranquilizers. In summary, our results suggest that leisure time physical activity conferred protection against incident use of prescription tranquilizers. Although the point estimates of the RRRs went in a similar direction, statistically non-significant differences were observed for frequent (incident) use of prescription tranquilizer at follow-up. A lower leisure time PA was not significantly associated with *severity* of psychiatric morbidity (expressed via *frequent* incident use of prescription tranquilizers). We observed weaker and statistically non-significant associations among *more frequent than every week* incident users of prescription tranquilizers at follow-up, compared to non-users. The lowest RRR was seen among *every week, but not daily* incident users of prescription tranquilizers at follow-up in fully-adjusted model. However, the association was strongest when the analysis included the respondents who only used prescription (incident) tranquilizers "less frequently than every week". This pattern of findings indicate that physical inactivity is significantly associated with less severe psychiatric morbidity, as expressed by 'less frequently than every week' use of prescription tranquilizers, but not with more severe psychiatric morbidity, as implied by a need for more frequent use of prescription tranquilizers. Other studies have also found a similar trend (Teychenne et al., 2008; Waller et al., 2016).

Consistent with previous studies, age (Simoni-Wastila, 2000; The ESEMeD Mhedea investigators et al., 2004) was positively associated with use of prescription tranquilizers. Similarly, consistent with previous studies (Kim et al., 2008), occupational PA was not related to subsequent psychiatric morbidity. This study is in line with two previous studies

from Finland in which leisure time PA was associated with decreased risk for using psychotropic medications (Lahti et al., 2013; Stubbs et al., 2017). However, our study used specific data on the use of prescription tranquilizers only. To our knowledge, no longitudinal studies on the association between leisure time PA and use of prescription tranquilizers (alone) have been conducted.

The results of this study suggest that leisure time PA in late–midlife may be important in the prevention of relatively mild psychiatric morbidity in early old age. One possibility is that psychopathology at baseline mediates the association between leisure time PA at baseline and incident psychiatric morbidity at follow-up (expressed via incident use of prescription tranquilizers). We explored this mediation mechanism, and the indirect effect was statistically significant (p=0.045; data not shown). However, since leisure time PA and indicators of psychopathology at baseline were measured at the same point in time, the temporality between them cannot be ascertained in this study.

Several potential mechanisms may explain the association between PA and psychiatric morbidity (Ma, 2008). PA increases several neurotransmitters, such as serotonin, dopamine, glutamate, and acetylcholine, which may protect against depression and other mood disorders (Deslandes et al., 2009; Szuhany et al., 2015). Given the established links between both psychological well-being (Goldman-Mellor et al., 2010; Wium-Andersen et al., 2013), mood disorders (Kohler et al., 2017) and PA (Gleeson et al., 2011) with inflammatory pathways (Vogelzangs et al., 2012), it is plausible to hypothesize that a better mental health experienced by physically active individuals might be partly explained by underlying inflammatory mechanisms, in particular a c-reactive protein pathway (Johnson et al., 2013; Vogelzangs et al., 2012). Moreover, recent advances in exercise neuroscience using rodent models (Duman et al., 2008; Fulk et al., 2004; Greenwood et al., 2012; Sciolino and Holmes, 2012) have shed new light on the neural mechanisms by which PA produces long-term

adaptations in brain circuits implicated in stress-related disorders (Holmes, 2014). This literature reveals that the most significant impact of PA on stress may not pertain to regulating transient states occurring in the presence of the stressor, but rather on moderating the long-term impact that acute stress may incur on subsequent stress events (Holmes, 2014). Much work has already demonstrated the capacity for PA to induce a variety of trophic factors in the brain and periphery, such as brain-derived neurotrophic factor (BDNF) (Szuhany et al., 2015), insulin-like growth factor, and vascular endothelial growth factor, but most of this previous research has focused on BDNF signaling in the hippocampus (Brown et al., 2014; Holmes, 2014; Ma, 2008; Voss et al., 2013). There is also evidence to suggest that the pro-inflammatory cytokines impair some of the growth factor signaling pathways in the brain, thus anti-inflammatory actions of exercise may again be important (Cotman and Berchtold, 2007; Cotman et al., 2007; Knaepen et al., 2010).

To the extent that use of prescription tranquilizers serves as a surrogate marker for underlying psychiatric morbidity (Sanchez-Villegas et al., 2008), these findings are consistent with the reported association of leisure time PA and mental health (Sheikh et al., 2018). This is encouraging, particularly given the multiple side effects associated with use of prescription tranquilizers and sedatives (Correll et al., 2015; Cuerda et al., 2013; Grundy et al., 2014; Hulkko et al., 2017; Kelly and Pawson, 2015). The potential cardiovascular effects of tricyclic tranquilizers are well known (Hamer et al., 2011; Licht et al., 2009). They can cause orthostatic hypotension, slowed cardiac conduction, and increased heart rate, and are therefore best avoided in patients with pre-existing cardiovascular disease (Mago et al., 2014). Use of tricyclic tranquilizers can also cause metabolic syndrome (Van Reedt Dortland et al., 2010), orthostatic hypotension, slowed cardiac conduction, increased heart rate (Mago et al., 2014), high diastolic and systolic blood pressures and hypertension (Licht et al., 2009). Among patients with high risk factors, SSRIs (i.e., citalopram) may be associated with

(modest) QTc prolongation (Beach et al., 2014). Serotonin-norepinephrine reuptake inhibitors (SNRIs) are associated with a small, but increased incidence of cardiovascular adverse events (hypertension, tachycardia and orthostatic hypotension) (Mago et al., 2014). Similarly, use of prescription tranquilizers is also associated with an increased risk of diabetes (Pan et al., 2010; Rubin et al., 2008; Yoon et al., 2013). Moreover, a few studies found that use of prescription tranquilizers might also increase the risk of atrial fibrillation (Blanchette et al., 2008; Cohen et al., 2000; Coupland et al., 2011; Hippisley-Cox et al., 2001; Tata et al., 2005), hemorrhagic and fatal stroke (Smoller et al., 2009).

It is important to highlight that the present findings should be interpreted with caution because of some limitations in our data. There is substantially heterogeneity in the study sample as it is population-based. Indeed, there may be differences between respondents via unaccounted-for covariates, which in turn may moderate the association between physical inactivity and incident use of prescription tranquilizers. However, among the measured covariates, no statistically significant multiplicative interactions were observed. Whilst the results of this study imply that leisure time PA is associated with lower risk of psychiatric morbidity, this study lacks specificity as information on specific psychopathologies and psychiatric disorders was not measured in the questionnaire. Indeed, the use of prescription tranquilizers may not be considered as a direct measure of psychiatric morbidity. Tranquilizers are mostly prescribed for depressive disorders, but they are also used to treat anxiety disorders, obsessive-compulsive disorders, and pain disorders. Accordingly, this study does not provide evidence on the association of leisure time PA with any specific psychopathology or psychiatric disorder. Moreover, we were not able to explore differences between the different tranquilizer medication classes (including tricyclic or tetracyclic tranquilizers; selective serotonin reuptake inhibitors, and serotonin norepinephrine reuptake inhibitors) and the duration of tranquilizer agent exposure. Information on specific

medications were not measured in the questionnaire, which raises the concern that respondents may not have understood the question in same manner. Indeed, this raises the concern that the association between physical inactivity and incident use of prescription tranquilizers may be driven by measurement error. Another limitation of this study was that apolipoprotein E (ApoE) haplotypes and genotypes were not measured and controlled-for in this study. For instance, previous evidence suggests that the association between physical inactivity and dementia is more pronounced among ApoE-epsilon4 (ApoE-ε4) carriers than non-carriers (Rovio et al., 2005). This effect may be due to inefficient neural repair mechanisms in ApoE-ε4 carriers, which render them more dependent on lifestyle-related factors to protect against dementia. Indeed, another seminal study showed that the presence of copies of ApoE-ε4 leads to cumulative decreased participation in physical activities for patients with Alzheimer's dementia (Oliveira Fabricio et al., 2014). A further limitation of the study is that we did not have information about diagnoses of psychiatric disorders at baseline, and therefore these individuals could not be excluded from the study. However, we had information about use of prescription tranquilizers at baseline, clinically significant psychological distress at baseline, and self-reported psychiatric problems at baseline, and we were able to exclude all of these respondents from the analyses. The concordance between use of prescription tranquilizers at Tromsø V and Tromsø VI was moderate, which suggests both possibilities that (i) a substantial number of cases may have recovered from psychiatric morbidity; and (ii) a substantial number of new cases may have emerged over the course of six years, as reflected in number of *incident* users (n=111) of prescription tranquilizers in this study.

All variables, except age and gender are self-reported; therefore, the possibility of reporting errors cannot be ruled out (Sheikh, 2018d). Leisure time PA was measured with a single item; accordingly, it is likely that there is considerable non-differential measurement

error, which would lead to under-estimation of its association with use of prescription tranquilizers. Simple questions measuring leisure time PA are generally accepted as adequate in population-based surveys (Westerterp, 2009). Moreover, no single instrument for measurement of self-reported leisure time PA has been proven as better than the others (van Poppel et al., 2010). Other evidence from Norway suggests that measurement of self-reported leisure time PA in population-based surveys is valid (Kristin B Borch et al., 2012). Lastly, the association between physical inactivity and psychiatric morbidity is likely to be reciprocal (Stubbs et al., 2017) and in our study, we only examined the physical inactivity to psychiatric morbidity pathway.

The current study has a number of strengths. We utilized a prospective design, and a regionally representative sample of general population in Norway. One previous study (Stubbs et al., 2017) did not adjust for prevalent psychopathology at baseline. A longitudinal association between leisure time PA and psychiatric morbidity is likely confounded by respondent's psychopathology at the time of reporting leisure time PA (Sheikh et al., 2018). Indeed, without controlling for psychopathology at baseline, either by adjustment or by removal of prevalent cases from the analysis, the longitudinal association between leisure time PA and psychiatric morbidity remains questionable (Sheikh et al., 2018). Moreover, other studies (Lahti et al., 2013; Sanchez-Villegas et al., 2008; Stubbs et al., 2017; Waller et al., 2016) did not account for occupational PA in the analysis. Leisure time PA comprises only a fraction of total daily/weekly PA, and without controlling for occupational PA, the association between leisure time PA and psychiatric morbidity (measured via use of prescription tranquilizers) is likely to be over-estimated (Sheikh et al., 2018). In this study, we were able to control for a wide range of important confounding variables including parental history of psychopathology, occupational PA, and respondent's psychopathology at baseline via several indicators.

We examined the longitudinal relationship between leisure time PA and use of prescription tranquilizers and found that a lower leisure time PA is associated with an incident use of prescription tranquilizers after adjusting for pertinent confounding variables. Given these findings, our data suggest that leisure time PA has an important role in maintaining psychological well-being (Sheikh et al., 2018) and reducing the need for prescription tranquilizers. Promoting leisure time PA in adulthood may prove useful for preventing subsequent mild psychiatric morbidity. We conclude that leisure time PA in late–midlife can buffer against mild psychiatric morbidity in early old age.

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Table 1. General characteristics of the study sample (N=4630).

		Complete-case data		Imputed data	
		Mean (SE)	n (%)	Mean (SE)	%
Age		61.25 (0.15)	-	-[b]	-
Gender	Male	-	1896 (40.9)	-	-[b]
	Female	-	2734 (59.1)	-	-[b]
History of psychopathology, mother	Yes	-	273 (5.9)	-	-[b]
History of psychopathology, father	Yes	-	117 (2.5)	-	-[b]
Years of education		10.53 (0.06)	-	10.50 (0.06)	-
Smoking [a]	Never smoker	-	2986 (69.9)	-	69.9
	Occasional smoker	-	282 (6.6)	-	6.6
	Daily smoker	-	1003 (23.5)	-	23.5
Marital status [a]	Single	-	433 (9.4)	-	9.4
	Married or registered partnership	-	3149 (68.0)	-	68.0
	Widowed, divorced or separated	-	1046 (22.6)	-	22.6
Occupational physical activity [a]		1.81 (0.02)	-	1.81 (0.02)	-
	Mostly sedentary work	-	1265 (47.2)	-	47.0
	Work that requires a lot of walking	-	783 (29.2)	-	29.1
	Work that requires a lot of walking and lifting	-	513 (19.1)	-	19.3
	Heavy manual labour	-	121 (4.5)	-	4.6
Psychiatric problems	Yes	-	351 (7.8)	-	7.9
Psychological distress (HSCL-10)		12.22 (0.05)	-	12.67 (0.06)	-
Insomnia [a]		1.58 (0.02)	-	1.58 (0.02)	-
	Never, or just a few times a year	-	2955 (70.2)	-	70.1
	1-3 times a month	-	556 (13.2)	-	13.2
	Approximately once a week	-	215 (5.1)	-	5.1
	More than once a week	-	484 (11.5)	-	11.6
Leisure time physical activity (hours/week) [a]		2.11 (0.02)	-	2.09 (0.02)	-
	None	-	1306 (35.1)	-	36.0
	Less than 1	-	1095 (29.4)	-	29.4
	1-2	-	923 (24.8)	-	24.4
	3 or more	-	398 (10.7)	-	10.3
Use of prescription tranquilizers at baseline (Tromsø V) [a]		1.08 (0.01)	-	1.09 (0.01)	-
	Not used	-	3874 (95.5)	-	95.1
	Less frequently than every week	-	85 (2.1)	-	2.2
	Every week, but not daily	-	48 (1.2)	-	1.3

	Daily	-	49 (1.2)	-	1.4
Prevalent use of prescription tranquilizers at follow-up (Tromsø VI) [a]		1.11 (0.01)	-	1.11 (0.01)	-
	Not used	-	4069 (94.3)	-	93.9
	Less frequently than every week	-	110 (2.6)	-	2.7
	Every week, but not daily	-	62 (1.4)	-	1.5
	Daily	-	76 (1.8)	-	1.9
Incident use of prescription tranquilizers at follow-up (Tromsø VI) [c]		1.05 (0.01)	-	1.06 (0.01)	-
	Not used	-	3658 (97.1)	-	96.8
	Less frequently than every week	-	62 (1.6)	-	1.7
	Every week, but not daily	-	22 (0.6)	-	0.7
	Daily	-	27 (0.7)	-	0.8

[a] The numbers for some variables do not add up to 4630 due to missing values.
[b] There were no missing values, so no imputations were made for these variables.
[c] The numbers do not add up to 4043 due to missing values.
SE: standard error; HSCL-10: Hopkins Symptom Check List-10.

Table 2. Bivariate Pearson product-moment correlations between variables (n=4630)

	1	2	3	4	5	6	7	8	9	10	11	12
	r	r	r	r	r	r	r	r	r	r	r	r
1. Age	1.00											
2. Gender	0.02	1.00										
3. History of psychopathology, mother	-0.07 [d]	-0.03 [a]	1.00									
4. History of psychopathology, father	-0.08 [d]	-0.01	0.02	1.00								
5. Years of education	-0.39 [d]	0.03 [b]	0.04 [c]	0.07 [d]	1.00							
6. Occupational physical activity	0.01	0.02 [a]	0.01	-0.02	-0.22 [d]	1.00						
7. Psychiatric problems	-0.02	-0.08 [d]	0.13 [d]	0.06 [d]	0.04 [c]	-0.02 [b]	1.00					
8. Psychological distress (HSCL-10)	0.01 [c]	-0.18 [d]	0.10 [d]	0.02	-0.07	0.02	0.33 [d]	1.00				
9. Insomnia	0.11 [d]	-0.19 [d]	0.06 [d]	-0.01	-0.08 [d]	-0.03 [b]	0.14 [d]	0.43 [d]	1.00			
10. Leisure time physical activity	0.11 [d]	-0.19 [d]	-0.03 [b]	0.01	-0.13 [d]	-0.11 [d]	-0.01	0.07 [d]	0.09 [d]	1.00		
11. Use of prescription tranquilizers (baseline)	0.08 [d]	-0.07 [d]	0.03 [a]	-0.01	-0.08 [d]	-0.01 [a]	0.29 [d]	0.31 [d]	0.18 [d]	0.06 [d]	1.00	
12. Prevalent use of prescription tranquilizers (follow-up)	0.09 [d]	-0.08 [d]	0.05 [c]	0.02	-0.10 [d]	-0.01	0.26 [d]	0.25 [d]	0.15 [d]	0.07 [d]	0.47 [d]	1.00

[a] $p<0.1$
[b] $p<0.05$
[c] $p<0.01$
[d] $p<0.001$

Table 3. Association between covariates and prevalent use of prescription tranquilizers at follow-up (N=4630).

		Prevalent use of prescription tranquilizers [g]	
		Unadjusted	Adjusted[e]
		RR (95% CI)	RR (95% CI)
Age [f]		1.05 (1.03, 1.06)[d]	1.02 (1.01, 1.04)[c]
Gender [f]	Male (reference=female)	0.48 (0.36, 0.63)[d]	0.82 (0.62, 1.08)
History of psychopathology, mother [f]	Yes (reference=no)	1.82 (1.26, 2.64)[c]	1.35 (0.97, 1.90)[a]
History of psychopathology, father [f]	Yes (reference=no)	1.73 (0.99, 3.05)[a]	1.61 (0.85, 3.02)
Years of education [f]		0.87 (0.84, 0.90)[d]	0.93 (0.90, 0.97)[d]
Smoking [f]	Never smoker	1.00	1.00
	Occasional smoker	1.40 (1.09, 1.81)[c]	1.26 (0.97, 1.63)[a]
	Daily smoker	0.87 (0.51, 1.50)	1.12 (0.67, 1.87)
Marital status [f]	Single	1.00	1.00
	Married or registered partnership	1.38 (0.84, 2.26)	1.00 (0.65, 1.54)
	Widowed, divorced or separated	2.14 (1.28, 3.58)[c]	1.11 (0.70, 1.77)
Occupational physical activity [f]		0.95 (0.78, 1.15)	0.94 (0.81, 1.10)
Psychiatric problems [f]	Yes (reference=no)	5.89 (4.67, 7.42)[d]	1.93 (1.38, 2.71)[d]
Psychological distress (HSCL-10) [f]		1.14 (1.13, 1.16)[d]	1.01 (0.99, 1.04)
Insomnia [f]	Never, or just a few times a year (reference)	1.00	1.00
	1-3 times a month	2.20 (1.56, 3.10)[d]	1.44 (1.03, 2.00)[b]
	Approximately once a week	3.35 (2.22, 5.05)[d]	1.39 (0.89, 2.18)
	More than once a week	3.94 (2.99, 5.18)[d]	1.40 (1.00, 1.95)[a]
Leisure time physical activity (hours/week) [f]		1.46 (1.24, 1.71)[d]	1.19 (1.04, 1.35)[c]
Use of prescription tranquilizers at baseline (Tromsø V) [f]	Not used (reference)	1.00	1.00
	Less frequently than every week	14.52 (10.93, 19.29)[d]	8.17 (5.70, 11.70)[d]
	Every week, but not daily	19.85 (15.25, 25.84)[d]	8.76 (5.76, 13.32)[d]
	Daily	15.81 (11.69, 21.39)[d]	6.31 (3.84, 10.37)[d]

[a] $p<0.1$
[b] $p<0.05$
[c] $p<0.01$
[d] $p<0.001$
[e] mutually adjusted for all covariates
[f] Covariates were measured in 2001-02 (Tromsø V)
[g] Prevalent use of prescription tranquilizers was measured in 2007-08 (Tromsø VI)
RR: relative risk; CI: confidence interval; HSCL-10: Hopkins Symptom Check List-10.

Table 4. Association between leisure time physical activity and incident use of prescription tranquilizers at follow-up (N=4043).

		Incident use of prescription tranquilizers [f]			
		Not used (n=3658) RRR (95% CI)	less frequently than every week (n=62) RRR (95% CI)	Every week, but not daily (n=22) RRR (95% CI)	Daily (n=27) RRR (95% CI)
Leisure time physical activity (hours/week) [e]	Unadjusted	1.00 (reference)	1.83 (1.31, 2.55) [c]	1.54 (0.84, 2.84)	1.79 (1.02, 3.14) [a]
	Adjusted [d]	1.00 (reference)	1.60 (1.12, 2.28) [b]	1.14 (0.63, 2.06)	1.47 (0.82, 2.65)
		Not used (n=3658) RR (95% CI)		Used (n=111) RR (95% CI)	
Leisure time physical activity (hours/week) [e]	Unadjusted	1.00 (reference)		1.72 (1.31, 2.25) [c]	
	Adjusted [d]	1.00 (reference)		1.41 (1.09, 1.83) [a]	

[a] $p<0.05$
[b] $p<0.01$
[c] $p<0.001$
[d] Adjusted for age, gender, parental history of psychopathology, years of education, smoking, marital status, occupational PA, psychological distress and insomnia.
[e] Leisure time PA were measured in 2001-02 (Tromsø V)
[f] Incident use of prescription tranquilizers was measured in 2007-08 (Tromsø VI)
RRR: relative risk ratio; RR: relative risk; CI: confidence interval.