Author's response to reviews

Title: Joint association of physical activity and overweight with subsequent psychotropic medication: a register-linked follow-up study among employees

Authors:

Tiina Loponen (tiina.loponen@helsinki.fi)
Tea Lallukka (tea.lallukka@ttl.fi)
Ansku Holstila (ansku.holstila@helsinki.fi)
Jouni Lahti (jouni.mm.lahti@helsinki.fi)

Version: 2
Date: 28 August 2015

Author's response to reviews: see over
1. Numerous covariates are included in the analysis. Theoretical and data driven justification for the inclusion of covariates should be advanced.

Response: Based on previous studies (Hämäläinen et al. 2001, Simon 2002, Fryers et al. 2003, Härter et al. 2007) these covariates are associated mental health. We have added a reference to these studies in the introduction. To be able to show the more independent associations of physical activity and obesity with mental health, we aimed to control for these covariates. We have used these same covariates in our previous articles from the same data (Lahti et al. 2013, Lindholm et al. 2013).

2. It is appreciated that the author(s) make reference to Lindholm et al. (2013). The sample is similar (albeit not identical) as are the predictors. To ensure non-duplication, additional details are warranted to determine the unique contribution of this submission.

Response: We acknowledge the similarities with Lindholm et al. (2013), however, that study focused on physical and mental health functioning using self-reported SF-36 as the outcome. In the present study, we focused on mental health using register-based psychotropic medication as the outcome. Thus we don't feel that there are any problems in this sense. Furthermore, the survey-based outcome was measured in 2007, 5 to 7 years after the baseline survey, while register based follow-up began immediately after returning the baseline questionnaire and covered complete follow-up of all prescribed reimbursed medication purchases. In addition, we able to control prior medication/mental ill-health before the baseline survey in this current study.

3. It is acknowledged by the author(s) that there is not one gold-standard self-report instrument for physical activity. However there are some that have a larger history such that the wealth of validity evidence for test scores is apparent. Please specify whether the instrument to measure physical activity was developed expressly for the purposes of this study. Further to this whether there is standardized scoring protocol to facilitate interpretation. So, for example, the classification of inactive, moderate physical activity differs
Response: We used a series of questions on leisure-time physical activity based on Kujala et al. (1998). These questions (compared with detailed interview) are a reasonably valid measure of the volume (METs) of leisure time and commuting physical activity (Waller et al. 2008). Lindholm et al. (2013) were especially interested in those who are not physically active at all (MET<7). This explains the difference between lower boundaries of moderate physically active group. We decided to use MET value 14 as boundary between physically inactive and moderately active because it corresponds to approximately 1000kcal, which is enough activity to offset health risks, related to inactivity and corresponds to a minimum of physical activity recommendations i.e. 2.5 hours of brisk walking.

4. Please provide reference support for "...this is a minor problem" (Page 13; line 328)

Response: We revised this sentence (Page 14; line 358). It’s commonly known fact that BMI is problematic measure of body composition in young people, especially young males. Our study population is comprised of about midlife adults, dominated by women. Therefore, in this study, a higher BMI likely reflects overweight status (and not fat free mass). Furthermore, our earlier study showed both measured and self-reported BMI similarly predict medically certified sickness absence (Korpela et al. 2013). While self-reported BMI is somewhat underreported, these earlier results suggest that can be used to examine associations between BMI and health outcomes, as predictive value is likely not affected by reporting bias.

5. Spelling mistake (Page 20; Model 3). Please change the spelling of "sosioeconomic"

Response: Change according to this suggestion has been made.

**Reviewer Name Marie-Eve Mathieu**

This paper presents a combined approach to highlight how baseline body weight status and physical activity level are associated to the incidence of psychotropic medication. A workplace sample of over
6,000 responders was followed over 7 years and is revealed that both reduced adiposity and high activity status at baseline do contribute to lower prescription of psychotropic medication with an advantage for the active lifestyle. The current work conducted in non-clinical settings contributes to the understanding of primary prevention for mental health beyond the impact of factors independently.

Major Compulsory Revisions

1. Main document – introduction and discussion: The mechanisms underlying the use of psychotic medication, excess body weight and inactivity should be presented. The discussion on why the physical activity level ends up being more important and body weight is currently too limited and could use this mechanistic approach (e.g. Reference 6, among others, might be discussed in greater details).

Response: Many studies have earlier focused on the association between obesity and poorer mental health, but the joint associations of obesity and physical activity have been less studied, particularly regarding mental health. Regarding somatic outcomes, physical activity appears to reduce the risk of heart failure among both normal and overweight adults (Hu et al. 2010). Thus, it could be assumed that physical activity could shape the risk found between obesity and mental health, or help counteract the risks related to obesity.

In line with the assumed prospective effects of physical activity, a recent study (Becofsky et al. 2015) showed that cardiorespiratory fitness is more important than fatness preventing depressive symptoms. We have now added discussion on page 12.

2. The follow-up period is substantial with 7.8 years and the approach is based on the incidence of psychotropic used. While this represents interesting information, complementary information such as the number of different medication used (apart from the two subcategories), duration of treatment and doses are not presented. A partial profile is present in the 1st paragraph of the result section (descriptive), but not linked to the 6 subgroups. More details would strengthen the understanding of the disease state and help distinguish for example an acute condition of impaired mental health to chronic and more serious conditions.
Response: We agree, however, the first purchase is our choice of outcome reflecting the onset of mental health problem. We have used the same protocol with the outcome as in our previous studies using psychotropic medication as the outcome (Mauramo et al. 2012, Lahti et al. 2013, Haaramo et al. 2014). In addition, we have made sensitivity analyses using e.g. 365DDD as the outcome reflecting more severe problems in mental health. However, this made but a minor contribution to the results. We have added discussion on page 14.

Table 1 Psychotropic medication purchases and DDDs among those who had psychotropic medication (percents counted individually for each category)

<table>
<thead>
<tr>
<th></th>
<th>Any (%)</th>
<th>Antidepressants (%)</th>
<th>Sedatives (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 to 2 purchases</td>
<td>37.1</td>
<td>33.3</td>
<td>57.3</td>
</tr>
<tr>
<td>3 or more purchases</td>
<td>62.9</td>
<td>66.7</td>
<td>42.7</td>
</tr>
<tr>
<td>DDD 1 to 365</td>
<td>63.7</td>
<td>59.6</td>
<td>81.9</td>
</tr>
<tr>
<td>DDD over 365</td>
<td>36.3</td>
<td>40.4</td>
<td>18.1</td>
</tr>
</tbody>
</table>

3. The use of only baseline profile of independent variables (i.e. body weight status and physical activity level) is problematic. Changes in anthropometric profile as well as lifestyle habits are expected over a 7-year period but not accounted for in current analysis.

Response: We agree that weight and physical activity may change during follow-up. The study of the same data (Roos et al. 2015) showed that obesity and weight gain are associated with sickness absence especially among women, however; also weight loss was associated with sickness absence of all lengths. In addition, increasing physical activity at midlife is associated with lower sickness absence (Lahti et al. 2012). However, examining combined effect of changes is beyond of the scope of this study, and would make interpretations of the results complex.

Moreover, it needs to be noted that mean time to the first purchase was much shorter than the time between the surveys, or the maximum follow-up time in this study. Thus, the 7-year period mainly reflects the follow-up time for those with no psychotropic medication, while those who purchased psychotropic medication were censored after the first purchase. Changes in the exposure variables and other
covariates are likely minor during the shorter time. We have added discussion about this matter to the discussion (Page 15; lines 371-374).

4. The use of MET hours as physical activity units is a strength compared to approaches using only total time or time in moderate-to-vigorous physical activity. In fact, low intensity activities are interesting for mental health. A reference could strengthen the methods and/or discussion section on this aspect

Response: We agree that there are different aspects of physical activity that are interesting for mental health. In this study we focused on recommended levels of physical activity accounting wide range of activities from walking to running. We have added references to the methods section (Page 6; lines 140 and 143).

- Minor Essential Revisions

1. Please specify in the abstract and main document how the questionnaire was administered.

Response: The questionnaires were send to the employees by mail. We have clarified this in the text (Page 5; line 113).

2. Abstract: The sentence « No gender interaction was found » might be removed from the method section.

3. Abstract: please define HR.

Response: Changes according to these suggestions have been made.

4. Main document – psychotropic medication and covariates: Please indicate the source of the information regarding the first medication purchase or death as well as the variables used as covariates.

Response: We have clarified the text accordingly (Page 7; lines 164, 171-180). The data on mortality were derived from the register of Statistics Finland. Covariates were derived from the baseline questionnaire except the information on socioeconomic position, was derived from the employer’s register, and prior medication, from Social Insurance
Institution of Finland.


Response: We have detailed the information of the software (Page 9; line 212).

6. *Main document – Results: The fact that only baseline anthropometric and PA profiles are used should be present in the result section.*

Response: We have stated this in methods section and thus we think that it is redundant to repeat this in the results section. However, we added some points about baseline to the results section, as suggested.

7. *Main document – Discussion: The follow-up period presented is shorter in the discussion (6 vs. 7.8 years). A comparison of the medication use in the current study with a reference population is needed. In the 2nd paragraph, the authors mention that the diagnosis underlying the prescription was not known. The presentation of which common conditions and treatment protocols used in Finland leading to the medication investigated here would strengthen the paper. The 7th paragraph highlight the fact that not all prescriptions are used or that medication is not always used by patients. Given the importance of this statement for the current study, references and specific numbers should be presented.*

Response: We have corrected the time of follow-up period to the discussion.

We were actually interested in the need of psychotropic medication (reflected by the prescription from a physician) rather than if the participants had used the medication purchased (although most reimbursed medication is assumed to be also used). When doctors prescribe medication, they have done an estimation of the need of medication. In Finland psychiatrists are not the only doctors who prescribe psychotropic medication, furthermore, general practitioners and occupational health care doctors are in key position prescribing psychotropic medication. In Finland, basically all employees are entitled to occupational health care, and as we focus on an occupational cohort, all our participants had access to occupational health care. We have added discussion (Page 15; lines 368-370).
Abstract: Add « level » to physical activity (1st sentence).
Main document: some numbers are not separated from the units (ex. 25kg/m2).
Table 1: use 2 instead of 2 for BMI units; A capital should be used at the beginning of each line (ex. in the weight/activity groups subgroups presentation); present n(%) at the top of the table; are gender differences tested?
Table 2: Capitalize 1st letter of each line;
Tables: The grey/white background brings more confusion to distinguish the various subgroups.

Response: Changes according to these suggestions have been made. Gender differences were tested and there were no significant differences between genders (p-value 0.44).

References


