Author's response to reviews

Title: A cluster-randomised, controlled trial to assess the impact of a workplace osteoporosis prevention intervention on the dietary and physical activity behaviours of working women: study protocol

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Author's response to reviews: see over
Cover Letter

Thank you the opportunity to revise and resubmit our manuscript. We respond to the reviewer point by point below, referring to corresponding changes in the manuscript by page numbers, with changes in the manuscript marked by yellow highlighting in the manuscript text. We have also included a reference list specifically for this document (page 9).

Author's response to address Reviewer's comments

Major Essential Revision

1. Reviewer's comment:
   *Abstract: please provide information on the critical parameter of interest in the power calculation (average, sd, change) and the ICC used, otherwise the sentence is not informative at all.*

   Author's response:
   Parameters that were used to calculate sample size for calcium intake have been added to the abstract (limited by word length).

2. Reviewer’s comment:
   *Abstract: what is the content of the intervention?*

   Author's response:
   We have revised the abstract to include a brief description of the intervention strategies and the type of activities (limited by word length).

3. Reviewer's comment:
   *Abstract: what is measured when, follow-up period etc?*

   Author's response:
   We have revised the abstract to indicate that the outcome measures are calcium intake (milligrams per day) and physical activity level (duration in minutes per week) and the follow up periods were at baseline, four weeks and six months post intervention.

4. Reviewer’s comment:
   *Introduction: There is a huge body of scientific literature on workplace interventions on PA. It is of paramount importance to first briefly summarize the essential guidance from these studies, and then subsequently address the issue whether the interventions conducted in this target population present different results because (a)*
these interventions did not incorporate the effective elements, or (b) the target population is really different and, thus, required a different approach.

Author's response:
This study did not aim to address general physical activity, but a subset of physical activity that is able to impact on bone mineral density and hence the risk of osteoporosis. Load bearing physical activities of moderate to vigorous intensity have been recognised to be of value in maintaining and even increasing bone turnover and bone mass. There is limited evidence on behaviour change interventions addressing this subset of physical activity to reduce osteoporosis risk. Conventional workplace physical activity intervention should not be used to guide the intervention in our study as it does not address the component of physical activity that is relevant for preventing osteoporosis.

A unique approach was required to build participant's knowledge and capacity to increase and/or to change their physical activity behaviour sufficiently so as to have an impact on their bone health. This study should be guided by interventions that are carried out in the context of bone health and osteoporosis prevention. Unfortunately, such interventions are limited.

We have added a sub-section "Limitations in current evidence base" (pages 4 to 5) under the "Background" section. This sub-section presents the limitation in the available evidence.

We have also added a sub-section "Importance of this study for osteoporosis prevention at population level" (pages 6 to 7) to detail how this study proposed to develop an improved intervention design for osteoporosis prevention.

We have added descriptions of the targeted physical activities under the sub-section "Intervention strategy development for physical activity", paragraph 3 (page 22). This additional information should enable readers to clearly differentiate the type of physical activity behaviour that our study is targeting.

5. Reviewer's comment:
The rationale should be strengthened: how much change in PA and calcium intake is needed to prevention how much osteoporosis? In other words, when PA is a low population attributable fraction and intervention will introduce a modest change, then the intervention will not contribute to prevention much.

Author's response:
We thank the reviewer for this valuable comment. We have identified and added relevant evidence on population attributable risk derived from observational studies (under "Background" section, Paragraph 2, line 3-9).

"Evidence suggests that the modifiable risk factors of physical activity and calcium intake can affect not just bone mineral density, but also risk of osteoporotic fractures
Prospective longitudinal studies have estimated that 23% of osteoporosis is attributable to physical inactivity [1]. Data from another study has allowed us to estimate that nearly 10% of osteoporosis is attributable to low dietary calcium intake [2].

This demonstrates that there are substantial preventable fractions on the order of 10% - 20% for osteoporosis and osteoporotic fractures, and that efforts to develop intervention strategies to achieve this are warranted.

6. **Reviewer’s comment:**
   Aims: why is aim 2 only addressing self-efficacy, which is only one element in behavioural models?

   **Author’s response:**
   We used Bandura’s self-efficacy model to guide the intervention. Self-efficacy is the proposed mediator of both behaviour change outcomes in this intervention (i.e. self-efficacy is an intermediate outcome), hence only self-efficacy was addressed.

7. **Reviewer’s comment:**
   Power calculations: this is confusing:
   - what is effect size (not the often used Cohen’s d value)
   - what is average in the normal population?
   - when using a change of 0.4 SD for PA, and ICC 0.05, the number of required participants is over far over 1000 in my calculations

   **Author’s response:**
   First, we apologise for failing to specify the number "20" in the following paragraph under "Sample size calculation" section in the original submission (page 13):

   "The design effect was calculated based on a within-cluster sample size of 20 and the intracluster correlation coefficient (ICC) using the formula: Design Effect = 1 + (within cluster sample size -1) X ICC."

   The number was accidentally deleted in the original submission. It is an important figure in the sample size calculation and a regrettable omission.

   In rechecking our sample size calculations, we discovered an error in the final step of our sample size calculations: we failed to double the sample size calculation that yielded the number of required subjects per arm (for this two-arm study). Hence the correct sample size, roughly consistent with the reviewer’s estimate, is 960.

   Having acknowledged the error, we have added an explanation in the paper under "Sample size calculation" section, paragraph 3 (Page 12). The sample size calculation, however, used very conservative ICC estimates and the study was
expected to be overpowered despite the omission of this step. We still have 90% power to detect 355 milligrams increase in calcium intake and 85 minutes increase in moderate to vigorous intensity physical activity with 16 clusters of 20 participants per cluster.

Full details of the sample size calculation for this study are detailed in an Appendix at the end of this document.

8. 
**Reviewer's comment:**
The description of the intervention does not reflect on available evidence from literature what change is expected based on previous RCTs

**Author's response:**
We thank the reviewer for this valuable comment. The following additions and amendments have been made:

i) A new section "Specification of intervention targets" (page 8 to 11) presents the rationale for our effect size for both calcium intake and physical activity.

ii) We have expanded the following sub-sections "Intervention strategy development for calcium intake" (paragraph 1, page 21) and "Intervention strategy development for physical activity" (paragraph 3, 5 and 6, page 22 to 23) to describe how the intervention contents are supported by previous randomised controlled trials.

9. 
**Reviewer's comment:**
The analysis should be intention-to-treat. Also, a simple t-test is not enough, as a repeated measurement design is required.

**Author's response**
The analysis approach is intention to treat as stated in the first line in the first paragraph of the "Proposed Data Analysis" section (page 25).

"All analyses will follow intention-to-treat principles when comparing intervention and control".

We agree with the reviewer's comment that a simple t-test is not sufficient and a repeated measure design is required. We have revised the “Proposed Data Analysis section to clarify this.

A new sub-section "Cluster level analysis that adjusts for individual covariates and baseline measures" was added (page 25 to 26) to describe how repeated measures is incorporated into this two-stage covariate adjusted cluster-level analysis described by Hayes and Moulten (2009, pp182-184) [3]. This is analysis is recommended over analysis at individual level due to the small number of clusters.
Minor Essential Revision

1. The workplaces invited have active policies in place, it seems. How about co-interventions other than the one mentioned taking place in these companies? Will it reduce the contrast between intervention and control arm?

Author's response
Our study addresses this potential concern in two ways. First, the within-cluster recruitment process excluded employees who were participating or planned to participate in any dietary and/or physical activity interventions. Second, random assignment of sites/clusters to intervention nor control should results in equal probability of sites being affected by non-intervention influences, hence the issue is also addressed by study design.

During the course of the study, the principal investigator would be physically present at the workplace and would be aware of any co-interventions.
Appendix

Sample size calculation

Sample size calculation took into consideration the cluster randomisation design of the study. The intracluster correlation coefficient (ICC) was used in the calculation of the inflation factor, or design effect for cluster study design. Sample size estimates were based on the following outcome measures:

1. Calcium intake (mg per day)
2. Physical activity duration (minutes per week)

The calculations for each outcome measure are detailed below.

1. Sample size calculation based on calcium intake as outcome measure

Published ICC for changes in calcium or other nutrient intake was not available at the time of the study. Simpson et al (2000) based their sample size calculation for a worksite dietary and physical activity intervention on an ICC value of 0.03 to 0.05 reported by Gomel et al in 1997 [4, 5]. However, this ICC estimate might be too low for a conservative estimate in the current study and the nutritional outcome measures was fat and fibre intake and not calcium intake.

The mean calcium intake for Singaporean females was reported in the 1998 National Nutrition Survey to be 458 mg with standard error of mean (SEM) of 8.1 [6]. This was based on survey sample (n) of 1284 females. The standard deviation (SD) was estimated to be 290mg [6].

Calculation:
SEM = SD/square root of n
Estimated SD = Square root of 1284 x 8.1 = 290

The variance, which is the square of SD, was estimated to be 84100
In the absence of reference ICC value for calcium intake, this study made a conservative assumption that ICC will be large. Assuming that the variance between cluster and within was the same, the ICC was estimated to be 0.5

Calculation:
ICC = variance between cluster/(variance between cluster + variance within cluster)
ICC = 84100/84100+84100 = 0.5

Hence the Design Effect = 1 + (20-1) 0.5 = 10.5
The effect size was set at 250mg
Normal sample size calculation = 21 x Square of SD / Square of effect size
= 21 x 84100/62500 = 28

at 5% level of significance and 90% power.

The sample size required for cluster design was 10.5 times of 28 = 294
With 20 subjects in each cluster, the numbers of workplaces/clusters required = 14.7
Assuming that the attrition rate in each cluster is 30%, a total of 30 women need to be recruited in each cluster.
Using calcium intake as the outcome measure, the recommended cluster size was 16 with 30 subjects in each cluster.
Total number of subjects = 480

There was an error in the final step of this study's sample size calculations. The calculation did not double the sample size calculation that yielded the number of required clusters per arm (for this two-arm study).

Based on the above acknowledged error, this would double to 32 clusters and a total of 960 subjects. Nevertheless, we still have 90% power to detect 355 milligrams increase in calcium intake with 16 clusters of 20 participants per cluster.

2. Sample size calculation based on physical activity duration as an outcome measure

The ICC of 0.05 was reported in Simpson et al (2000) [4] and the empirical ICC estimate taken from the University of Aberdeen ICC Estimate database.
Hence the Design Effect = 1 + (20-1) 0.05 = 1.95

The effect size was set at 60 minutes. Standard deviation (SD) for physical activity level of local population is not available. According to a 2001 study on physical activity of Singaporeans by Teh et al (2004), the mean duration of physical activity per week was 457 minutes, however the standard deviation was not published [7]. Standard deviations ranging from 115-174 minutes were published by studies that reported on baseline physical activity duration [8, 9]. The average standard deviation reported is 152.3 minutes per week. Hence, the following calculation used the SD of 150 minutes.

Normal sample size calculation = 21x Square of SD / Square of effect size
= 21X 22500/3600 = 131
at 5% level of significance and 90% power .

The sample size required for cluster design is 1.95 times of 131 = 255

With 20 subjects in each cluster, the numbers of workplaces/clusters required = 13

Assuming that the attrition rate in each cluster is 30%, a total of 30 women need to be recruited in each cluster.

Using physical activity as the outcome measure, the recommended cluster size was 14 with 30 subjects in each cluster.
Total number of subjects = 420

Using calcium intake as the outcome measure, the recommended cluster size was 16 with 30 subjects in each cluster.
Total number of subjects = 480
There was an error in the final step of this study's sample size calculations. The calculation did not double the sample size calculation that yielded the number of required clusters per arm (for this two-arm study).

Based on the above acknowledged error, this would double to 26 clusters and a total of 520 subjects. Nevertheless, we still have 90% power to detect 85 minutes increase in moderate to vigorous intensity physical activity with 16 clusters of 20 participants per cluster.

Table 1: Summary of parameters used in the sample size calculation

<table>
<thead>
<tr>
<th>Outcome measures and mediators</th>
<th>Effect size</th>
<th>Intraclass Correlation Coefficient used in sample size calculation</th>
<th>Standard deviation used in sample size calculation</th>
<th>Design effect</th>
<th>Number of clusters</th>
<th>Total subjects to be recruited Before factoring in 30% attrition</th>
<th>After factoring in 30% attrition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium intake (milligrams per day)</td>
<td>250 milligrams</td>
<td>0.5*</td>
<td>290 milligrams***</td>
<td>10.5</td>
<td>14.7</td>
<td>294</td>
<td>480</td>
</tr>
<tr>
<td>Physical activity duration (minutes per week)</td>
<td>60 minutes</td>
<td>0.05**</td>
<td>150 minutes****</td>
<td>1.95</td>
<td>13</td>
<td>255</td>
<td>420</td>
</tr>
</tbody>
</table>

***Based on estimates from published studies [4, 5]
*****Based on estimates from published studies [8, 9]

The sample size for this study was determined based on the largest sample size required for any of the outcome measures. The calcium intake outcome measure required the largest sample size, hence the recommended sample size for this study was 16 clusters (8 intervention, 8 control), with 30 subjects in each cluster.

As stated previously, there was an error in the final step of this study's sample size calculations. The calculation did not double the sample size calculation that yielded the number of required subjects per arm (for this two-arm study). The sample size calculation, however, was very conservative with the ICC estimates and the study was expected to be overpowered despite the omission of this step.

We still have 90% power to detect 355 milligrams increase in calcium intake and 85 minutes increase in moderate to vigorous intensity physical activity with 16 clusters of 20 participants per cluster.
References


