Author's response to reviews

Title: Japan Diabetes Outcome Intervention Trial-1 (J-DOIT1), a nationwide cluster randomized trial of type 2 diabetes prevention by telephone-delivered lifestyle support for high-risk subjects detected at health checkups: Rationale, design, and recruitment

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Author's response to reviews: see over
Reviewer's report

Title: Japan Diabetes Outcome Intervention Trial-1 (J-DOIT1), a nationwide trial of type 2 diabetes prevention by telephone-delivered lifestyle support for high-risk subjects detected at health checkups: Rationale, design, and recruitment

Version: 1 Date: 12 March 2012

Reviewer: Patty Chondros

Dear reviewers,

Thank you very much for your comments. A number of problems were pointed out in our old manuscript. We tried to make our revised paper clear as much as possible.

Here are our point-by-point responses to your comments.

Major compulsory revisions

Although some sections of the paper are clearly described, overall the paper lacks clarity and details about the study design. The manuscript needs to be revised considerably and needs extra information about the study design. Some reorganisation of the flow of information may help improve the clarity.

Some of the issues identified are as follows:

Study design and recruitment

1) A brief description of the health care system in Japan is needed to provide the reader unfamiliar with the health care system in Japan with the context and a better understanding of the clusters. For instance: What are health care divisions in companies/communities? What is their function? Do they differ between the companies and communities? Are the health check-ups conducted through the health care divisions? Can individuals attend more than one division? Do they need to be registered with the health care division?

2) Health check-ups – are these part of routine health care in Japan? Do all individuals have an annual health checkup?

We added the brief description of the health care system in Japan in the revised manuscript [page 3, lines 15-32 for 1) and 2)].

There could be some disparities in health care services each health care division provides, but its basic functions are not different between communities and workplaces. Guidelines for health check implementation were announced in
2004 based on the Health Promotion Law

3) What are lifestyle support centres? Were they set up for the study itself or are they existing organisations. How are they funded / formed? Similarly, data management center – need more information on their exact role.

In this study we outsourced some parts of the works to existing private companies. Tokio Marine & Nichido Medical Service Co., Ltd., National Education Association, INC. VISIT HEALTH Co., Ltd., and Meiji Yasuda System Technology Co., Ltd., Japan are all from health-related industries and run lifestyle supporting business utilizing public health nurses and dieticians. They take part in this study as a lifestyle support center, taking charge of the recruitment and enrollment of study subjects and the lifestyle intervention [page 6, lines 21-28 and page 8, line 6-8].
Data collection and management were outsourced to CIMIC Co.Ltd, a contract research organization offering clinical research management services [page 8, lines 35 – page 9, line 1].

Randomisation
4) More detail is needed on the randomisation process. For instance, how was the randomisation sequence generated? Type of randomisation (stratification, minimisation, matching)? If so, details on the approach need to be described? Who and how was the random allocation sequence generated and how was it implemented?

Stratified block randomization was used to randomly allocate the clusters to an intervention (n=22) or control (n=21) arm of the study. The clusters were stratified based on their size, location (urban or rural), and setting (companies setting or communities setting) [page 5, line 15-18].

Recruitment
5) More detail is needed about how the clusters were identified and recruited. Were the clusters identified first and then the individuals? Who recruited the clusters and participants? How were the clusters formed from the 17 health check up divisions?
One of the key issues for the success would be how many participants we can recruit for the study. We thought it would be easier to recruit health care divisions first rather than recruiting individual participants. Eligible subjects, identified in each cluster, were then enrolled.

We added the sentence [page 5, line 2-15].

6) If the intervention is delivered through the life support centres, why did you choose cluster randomisation by health care division rather than individual randomisation? Eg was it to avoid individuals sharing information when working in the same workplace or community?

Since study subjects in each health care division are working at the same workplaces or living in the same communities, to avoid potential contamination of interventional effects, we chose cluster randomization by health care division rather than individual randomization. The cluster randomization design has also advantages of administrative convenience and ease of obtaining the cooperation from staff in the health care division [page 3, line 36 – page 4, line 2].

Blinding
7) Who was blinded to the study arm status?

Blinding
The study participants and the staff members in each cluster are not blinded. The analysts who perform final analysis will be blinded to the study arm status [pages 9, lines 5-7].

Eligibility criteria
8) What were the inclusion and exclusions criteria for the clusters?

We added the inclusion and exclusion criteria for the clusters (health care divisions) [page 5, line 4-10].

Intervention
9) Why is the implementation of the intervention not standardised across the three life support centres? How will this impact of the effectiveness of the intervention?
We outsource the lifestyle intervention by telephone to existing private companies (Tokio Marine & Nichido Medical Service Co., Ltd., National Education Association, INC. VISIT HEALTH Co., Ltd., and Meiji Yasuda System Technology Co., Ltd., Japan). Because the sample size is large, we use three companies. Each company has its own intervention schedule approved by the study group (Table 1). We do not standardize the intervention program. As shown in the Table 1, there are considerable differences in the quantity of services among the companies. However, for public health nurses and dieticians in those companies, we will hold educational sessions on diabetes and its prevention and for training skills of telephone counseling with motivational interviewing [page 8, lines 8-11]. It would be of interest to see how these differences could affect the results.

Follow-up and outcome
10) Page 6, lines 23 and 24: It is confusing why the individual where CPG was measured diabetes is defined as a secondary outcome. Do you mean that it was used as an alternative outcome measure when FPG was not available?

At the health checkups during the follow-up period blood is withdrawn after 8 hours of fasting. Before blood sampling, participants are asked if they have fasted (≥ 8 hours) or not. If they have not, they are asked to have a blood sample taken on a different day. This rule, however, could not be applied to the 2006 checkups, which we used for screening high-risk individuals. At the 2006 checkups blood was not always withdrawn after 8 hours of fast. Therefore, in those cases where FPG was not available, plasma glucose concentrations (casual plasma glucose, CPG) of 118 ≤ CPG < 144mg/dl were considered eligible. Thus 57 subjects (2%) were enrolled with 118 ≤ CPG < 144mg/dl. We cannot apply our definition of "development of diabetes" to those subjects, since they do not have a baseline FPG value. As the reviewer pointed out this is very confusing. We rewrote this part as shown in the revised manuscript [page 6, line 7-13].

Sample size
11) Need more information on how the sample size of 1100 individuals was
calculated assuming an individually randomised trial. Based on the assumptions
given in the manuscript, the remainder of the sample size calculations that allow
for the clustering effect and drop-out are correct.

We added the some more information in the revised manuscript [page 9, line
7-25].

12) Does the sample size allow for testing the interaction between T2DM and
metabolic syndrome in IFG subjects (sub-analysis)?

We did not estimate the sample size for testing the interaction between T2DM
and metabolic syndrome in IFG subjects.

Statistical analysis
13) How will the clustering effect be taken into account in the main outcome
analysis? The statistical analysis on individual level data needs to allow for the
clustering effect due to randomising the clusters instead of individuals.

Taking account of clustering effect we will use the LWA model (Lee, Wei and
Amato) in the main outcome analysis. We will also do some explanatory data
analysis using this model [page 9, line 35 – page 10, line2].

14) Do you plan on adjusting for any other possible risk factors or stratification
factors? If so, this analysis should be stated in the study protocol.

We plan on adjusting for any other possible risk factors or stratification factors
using the multivariate Cox regression analysis [page 10, line 2-7].

15) Are there any secondary outcomes? If there are secondary outcomes, how
will these be analysed?

Other outcomes are changes in body weight, BMI, plasma glucose, blood
pressure, serum lipids, HbA1c, the percentage of subjects with the Metabolic
Syndrome, lifestyle, and the development of cardiovascular diseases. We add
the statistical analysis [page 9, line 29-34].
16) P-values reported for the baseline comparisons reported Table 2 are unnecessary (See Schulz and Grimes: Allocation concealment in randomised trials: defending against deciphering. Lancet 2002; 359: 614–18)

As suggested, we deleted P-values in Table 2.

Minor essential revisions

Results

17) Report average and range of cluster sizes for each study arm. Also, cluster characteristics (if applicable) by study arm status should also be reported to assess for chance imbalance between the study arms of cluster characteristics.

We added the results and in the abstract. There is no difference in cluster size between groups [page 10, line 25-28].

18) If information is available, include a table comparing the characteristics of participants that were invited to participate but declined and those that were included in the study to help assess the generalisability of your sample to the intended population.

We are sorry that we could not collect any data from those who were invited to participate but declined.

Grammar and spelling

19) There are inconsistencies in the tenses and typographical errors in the manuscript that need to be corrected.

As suggested, we corrected.

Discretionary revisions

Include the rationale for cluster randomisation to be included in the background section (as described in discussion, pg 9 of the manuscript).

We added the rationale for cluster randomization in the background section.

Report the intra-cluster correlation of the main outcome at baseline and participant characteristics.
We added the ICC in the results section [page 10, line 30-31].

Is the use of “casual plasma glucose” an internationally recognised term for measuring glucose sugar levels?

The term of “Casual plasma glucose” is not internationally used. A CPG $\geq 11.1$ mmol/l (200 mg/dl) indicates diabetic type of glucose tolerance according to the report of the committee on the classification and diagnostic criteria of diabetes mellitus. A CPG is also used as the risk assessment for cardiovascular disease in Japan [page 6, line 8-13].

Dropout and discontinuance - Pg 6, line 36
Participants who have developed diabetes are the individuals where the event has occurred (outcome), thus they are still part of the study and contribute to the analysis. Consider moving point (1) “participants who have developed diabetes” from this section. Suggest moving elsewhere in document, with an explanation that when the event occurred the participants were not followed up any further.

As suggested, we deleted (1) and moved it to page 4, line 34-35.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Not suitable for publication unless extensively edited

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:
'I declare that I have no competing interests'
Reviewer's report
Title: Japan Diabetes Outcome Intervention Trial-1 (J-DOIT1), a nationwide trial of type 2 diabetes prevention by telephone-delivered lifestyle support for high-risk subjects detected at health checkups: Rationale, design, and recruitment
Version: 1 Date: 2 March 2012
Reviewer: Karen Walker

Dear reviewers,
Here are our responses to the reviewer comments.
We believe the revised manuscript is now much better than the previous one. Thank you very much for your comments and suggestions. They were really helpful and useful for us in revising the manuscript.

- Major Compulsory Revisions
1. Page 3 lines 14-15: The Introduction poses the question – ‘What are effective and efficient methods to identify subjects at risk for diabetes?’ However, the paper then describes how participants were selected for J-DOIT1 based where possible on a fasting plasma glucose of 100-125 mg/dL (5.6-6.9 mmol/L) (page 4, line 31). Only one criterion has been used to identify most subjects at risk and the comparison of screening methods posited in the Introduction is not addressed by outcomes presented. The text in the Introduction should be refocussed.

   We have deleted the sentence ‘What are effective and efficient methods to identify subjects at risk for diabetes? ’ from the Introduction. This is not main subject of the present study. We identified subjects at risk based on results obtained at annual health checkups. Only fasting plasma glucose value was available.

2. Page 3 lines 33 to 35- presumably the clusters of 200-300 participants all came from the same area or community or company setting. Or was the cluster based on the lifestyle support centre that was closest? The nature of the cluster needs to emerge more clearly here.

   Clusters were formed within the same community or the same company. So
individuals in the same cluster came from the same area or community or company settings. First we recruited 17 health care divisions, having 2,000 or more examinees annually, from communities and companies across the country. Many of them were large organizations with a large number of examinees of health checkups. In addition, health care divisions of a large company usually have branches covering different areas spreading widely. Therefore, for administrative convenience, the health care division was divided into clusters, each having approximately 200-300 subjects, as the unit of randomization. A total of 43 clusters were formed from 17 health care divisions. These are described in Methods-Recruitment of health care divisions and cluster randomization [page 5, line 2-15].

3. The abstract states that 'A large cohort was successfully randomised' but in discussing recruitment and allocation of clusters, no detail is provided on the method used for randomisation (page 3, lines 34-35). Were the clusters stratified by setting and then randomised?

The clusters were stratified by setting and then randomized. Details are provided on the method used for randomization in the revised manuscript [page 5, line 15-18].
We deleted the sentence, "A large cohort was successfully randomized".

4. Page 4, Health check-ups. The information provided on anthropometric and biochemical methods appears unnecessarily brief. Who carried out the anthropometric assessments and what equipment was used? Calculation of BMI might be mentioned. If blood was withdrawn from people who had not fasted how are these data treated?

As suggested, we added the following sentences. Height was measured in the standing position by public health nurses or industrial nurses. Weight is measured without shoes or heavy clothes to the nearest 0.1 kg using standard calibrated scales. Body mass index (BMI: kg/m$^2$) was calculated as body weight (kg) divided by square of body height (m$^2$). Systolic and diastolic blood pressure values were measured in the sitting position. If blood was withdrawn from people who had not fasted, blood glucose data was treated as casual plasma glucose and triglycerides values were omitted from the
analysis [page 5, line 28- page 6, line 1].

5. Participant eligibility- could be based on fasting plasma glucose or on casual plasma glucose. How many participants were enrolled based on the latter criterion? Also page 4 line 34- if correct- it should be stated rather than inferred that women with a history of gestational diabetes could be enrolled.

57 participants were allocated to control or intervention group, but all of them were excluded in Figure 1. We changed the sentence. Woman with a history of gestational diabetes could be enrolled [page 6, line 14-15].

6. Page 6 lines 25 and 26: CPG # 144 mg/dL (8.0 mmol/L) . If symptoms are not present, it can be questioned whether this definition includes many people who do not actually have diabetes? Was their status confirmed by a second test?

All biochemical data we could use for the study were those obtained from health checkup sites. We did not do any other additional tests such as oral glucose tolerance test [page 5, line 28-page 6, line 1]. We also discussed our definition of development of diabetes in the Discussion.

7. Page 8 line 5 and Figure 1. As participants were screened for eligibility after they were enrolled, the number of people considered ineligible might differ a great deal between clusters. What was the range in cluster size before and after screening for eligibility? Did cluster size differ between the control group and the intervention group?

We added the range in cluster size before and after screening for eligibility. The median (interquartile range) of the cluster size in the control group before and after screening for eligibility was 301 (200-442) and 61 (35-88), respectively and those in the intervention group was 313 (158-587) and 60 (41-94), respectively. There is no difference in cluster size between groups [page 10, line 25-31 and abstract].

8. Page 8, line 8 and Table 2. Earlier (page 7, line 30) it is stated that all analysed variables are non-parametric. How was this tested? Where measures
given in Table 2 are parametric they should be provided as mean ± Sd and where they are non-parametric they can then be given as the median (interquartile range). Where these data are non-parametric use of a t-test for group comparisons is not appropriate and the relevant non-parametric test should be applied.

As suggested, we corrected the statistical analysis [page 9, line 29 – page 10, line 7] and Table 2.

9. In the discussion of the relatively low incidence of high BMI in this Japanese population it would be useful here to comment on the utility of a waist circumference in detecting abdominal adiposity in Asian populations and an explanation might be given here as to why this measure was not employed.

As suggested, Japanese are prone to accumulate visceral adipose tissue and the utility of a waist circumference in detecting abdominal adiposity is important. However, it was April 2008 when the Occupational Safety and Health Act of Japan included measurement of waist circumference as a mandatory item. Since our baseline data were from year 2006 health checkups, we could not include measurement of waist circumference in our study.

10. Page 11 line 7: add to the discussion a comment on strategies that might be used to capture women more equally in studies of this type.

About 80% of the study subjects were male. This is due to that health care divisions were recruited more from workplace setting than community setting in this study. There are much more male than female employees in many companies in Japan. We did not succeed in recruiting more health care divisions from communities [page 13, line13-17].

- Minor Essential Revisions
Page 3, lines 25026: Where is this Ethics Committee based?
Tokyo, Japan [page 4, line 11-13].

As suggested, we changed the term and sentence, and deleted.
Page 3 line 32: ‘being 2000 or more examinees annually’ rewrite for better clarity
The unit of cluster is 2,000 to 3,000 examinees annually. In the case of large health checkup division with several branches, those are divided into adequate size of clusters.

Page 4 lines 34-35: Why is an HbA1c of #6.5% equivalent to #6.1%? This seems a confusing statement.

As suggested, we deleted the sentence.

Page 5 line 4- was this a medical history questionnaire forming part of the baseline questionnaire? Clearer here if explicitly stated.

This questionnaire was made by the study group.

Page 5 lines 17-19: use SI units here also.

As suggested, we added SI unit also.

Page 6 line 7 and Table 1: it would be useful to include the number of participants counselled by each of these three groups

As suggested, we added the number of participants counseled by each lifestyle support centers.

The number of participants counselled by the National Education Association, the Meiji Yasuda Technology, and the Tokio Marines & Nichido Medical Service are 595, 413, 328, respectively. We added the number in Table 1.

Page 8 line 7: state proportion who gave consent in control group and percent who gave consent in the intervention group.

As suggested, we added the proportion.

The proportion who gave consent in the control and intervention group was 20.1% and 19.1%, respectively.

Table 3 first column on left-hand side: correct ‘Mets rsik’

We corrected the term.

- Discretionary Revisions

Page 3, line 20 ‘from the thoughts that as a national project’ is clumsily worded.

We changed the sentence [page 4, line 7].
Page 4, lines 17-18 “The lifestyle support centers…” This sentence might be better earlier when initially describing the centers.

As suggested, we moved the sentence [page 4, line 30-36].

Page 6 lines 19-20: consider use of # and also lines 25, 26
As suggested, we used of #.

Figure 1: In boxes headed ‘Exclude (n=5851)’ and ‘Exclude (n=5488)’ it would be useful to add in numbers who met exclusion criteria versus numbers who were eligible but refused.

We are sorry that we could not collect any data from those who were invited to participate but declined.

Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.
Declaration of competing interests:
I declare that I have no competing interests