Author’s response to reviews

Title: Cost-effectiveness of the SLIMMER diabetes prevention intervention in Dutch primary health care: economic evaluation from a randomised controlled trial

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Rebuttal letter

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Title: Cost-effectiveness of the SLIMMER diabetes prevention intervention in Dutch primary health care: economic evaluation from a randomised controlled trial

We thank the editor and the reviewers for their careful examination of the manuscript and useful suggestions to improve the quality of the paper. It was a pleasure to reply to the comments, as given below. Please note that the page numbers and line numbers mentioned in the authors’ reply refer to the revised manuscript. All changes in the paper have been marked in yellow.

Reviewer #1 (Andres Berruti)

* Comment 1: The manuscript is clear and well written.
Authors’ reply 1: We thank the reviewer for his careful reading of this manuscript and provision of helpful feedback. We will address the reviewer’s comments below.

* Comment 2: Consider using a comma after i.e...

Authors’ reply 2: The sentence containing “i.e.” has been changed and does not contain this abbreviation anymore.

* Comment 3: Consider using commas instead of parentheses once parentheses has been used. Too many levels of parentheses is confusing.

Authors’ reply 3: In line with the reviewer’s comment, we used commas instead of parentheses to prevent confusion (see page 3, line 59; page 6, line 99; and page 8, lines 161-162).

* Comment 4: Please consider describing why that methodology was selected. (method section 2.6.4 intervention cost)

Authors’ reply 4: Bottom-up micro-costing approach was chosen because this is generally considered the gold standard when (large) differences in costs between individuals are to be expected. All relevant resources are identified and every single resource is valued for individual patients, leading to detailed cost estimates. As the micro-costing method is advised in health economic guidelines all over the world, we choose not to explain specifically why we used this method. Instead, we now mention that this method is advised in health economic guidelines and refer to the Dutch health economic guidelines. We adapted the text of the paper as follows: “Bottom-up micro-costing analysis was used to estimate intervention costs as this method is advised in health economic guidelines [15]” (page 8, lines 172-173).

* Comment 5: Are there any other cost that are not included (e.g., transportation, communication, building, etc.)? If yes, please indicate why they are not included. (method section 2.6.4 intervention cost)

Authors’ reply 5: As mentioned in the discussion section, participant time investment was not taken into account. We now added a clarification to this issue in the discussion section as follows: “Second, besides monetary investments, participants have to make a time investment, which was not taken into account in the current analysis as this is considered to be captured in the assessment of the quality of life [26].” (see pages 13, lines 310-312). Furthermore, costs of transportation were not included; this is now added to the discussion section as follows: “Furthermore, costs of transportation were not included because the intervention was delivered in participants’ neighbourhoods; therefore distances were short and costs negligible” (see pages 13, lines 312-314).
* Comment 6: Were all the participants arrive at the beginning of the intervention or during the time of the intervention? Please make sure that the numerator is comparable with the denominator (i.e., flow vs stock variable). (method section 2.6.4 intervention cost)

Authors’ reply 6: After baseline measurement, 316 participants were randomly allocated to the intervention group or to the control group. Thereafter, physical activity training groups were formed and complete, and thereby efficient, groups then started the intervention programme. This information was added to the methods section on lifestyle intervention as follows: “Physical activity training groups were formed after randomisation, based on day and time preferences of participants and availability of physiotherapists. Groups with a minimum number of four participants then started the intervention programme.” (page 7, lines 136-138).

Information on realistic estimation of intervention costs was added as follows: “Intervention costs were estimated in a realistic way by dividing total costs over those who completed the programme.’ (see page 8, lines 173-174).

* Comment 7: In Table 1, please describe what is included in the education levels.

Authors’ reply 7: Information on the education levels is added as a footnote to Table 1: “Education level was based on the highest level of education completed and divided in three categories: low (no, primary or lower secondary school), middle (higher secondary school or intermediate vocational school), and high (higher professional education or university level)” (see page 21, lines 475-477).

* Comment 8: In Table 1, please consider changing the word ethnicity for word that more appropriately describe the variables.

Authors’ reply 8: In line with the reviewer’s comment, in Table 1 we changed the word ‘ethnicity’ in ‘cultural background’ (see page 20, Table 1).

* Comment 9: In Table 1, do you mean full time job by paid job? Please clarify.

Authors’ reply 9: By paid job we mean both full time and part time jobs. We added this information to Table 1 as follows: “Paid job includes both full time and part time jobs” (see page 21, line 478).

Reviewer #2

* Comment 1: This manuscript evaluates the cost-effectiveness of the SLIMMER intervention. Overall, this is a well written and conducted study. Below are specific points that I think would improve the manuscript.
Authors’ reply 1: We thank the reviewer for his/her careful reading of this manuscript and provision of helpful feedback. We will address the reviewer’s comments below.

* Comment 2: The abstract should state the country in which the study was conducted.

Authors’ reply 2: The country (The Netherlands) was added to the background section of the abstract: “The aim of this study is to assess the cost-effectiveness of the SLIMMER lifestyle intervention targeted at patients at high risk of developing type 2 diabetes compared with usual health care in a primary care setting in the Netherlands.” (see page 3, lines 41-43).

* Comment 3: I recognize that the full details of the trial are published elsewhere but the current manuscript still should provide sufficient detail to understand the design of the study. The authors note that this is a pragmatic trial; however, from the description of the trial this is not apparent. More detail as to what makes the trial pragmatic would be helpful and a greater description of how training was conducted would be helpful.

Authors’ reply 3: The SLIMMER study was designed as a pragmatic trial, aimed to evaluate the (cost-)effectiveness of the intervention programme in real-life routine practice conditions. The intervention programme was implemented in Dutch primary health care, involving GPs and their practice nurses, dieticians, physiotherapists, and local sports clubs. Additional information on these real-life conditions was added as follows: “The existing structure of GPs, having natural referral lines with dieticians and physiotherapists, was used for implementation of the SLIMMER intervention.” (see page 6, lines 104-106).

Furthermore, the cost-effectiveness evaluation was also performed in a pragmatic way by estimating intervention costs in a realistic way, i.e., total costs were divided over those who completed the programme. (see author’s reply to reviewer #1 comment 6, and page 8, lines 173-174).

Furthermore, information on the training of health care professionals was added as follows: “The SLIMMER intervention conformed regular functioning and professional performance of Dutch GPs, practice nurses, dieticians, and physiotherapists. Minimal training and a detailed manual were provided during a two-hour SLIMMER kick-off training for health care professionals.” (see page 7, lines 128-130).

* Comment 4: It would be beneficial to have more information on what happened during the different aspects of the intervention. For example, what happened during the dietician meeting and what was actually involved in the case management meeting.

Authors’ reply 4: More detailed information on the intervention programme is added as follows: “The dietary intervention consisted of five to eight individual consultations and one group session with a dietician during 10 months. Tailored dietary advice was given on a sustainable healthy dietary pattern and during the group session participants shared experiences, motivated
each other, and discussed the topic of label reading. The physical activity intervention was
delivered by physiotherapists as weekly group-based training sessions for 10 months and
consisted of both aerobic and resistance exercise. Furthermore, case management was performed
by practice nurses and consisted of keeping in contact with both health care professionals and
intervention participants throughout the intervention period, to detect and solve problems, and to
motivate and support participants.” (see page 7, lines 130-141).

* Comment 5: Please clarify that the intervention group also received usual care.

Authors’ reply 5: For clarification reasons, we first describe the control group before we describe
the intervention group. We added information on the reason for giving usual health care to both
the intervention and control group as follows: “At the time of the study, all Dutch patients with
impaired fasting glucose or an elevated/high risk of type 2 diabetes received usual health care
from their GPs and/or practice nurses. This was conform the standard for prevention of type 2
diabetes in primary health care, developed by the Dutch College of General Practitioners [12].
Therefore, the control group received this usual health care, consisting of yearly monitoring of
blood glucose.” (see page 6, lines 117-121); and “Besides usual health care provided by GPs
and/or practice nurses, the intervention group received the SLIMMER lifestyle intervention. This
intervention resembled the SLIM intervention [3] and consisted of a dietary and physical activity
intervention, including case management and a maintenance programme.” (see page 6, lines 125-
128).

* Comment 6: Please specify the look back period for the resource utilization questions. Did you
ask people about their consumption in the previous 18 months?

Authors’ reply 6: Self-reported data on resource utilisation was collected intermittently to
prevent recall bias. This was specified as follows: “Data on volumes of health care utilisation
(general practitioner, dietician, physiotherapist, consultations at outpatient clinic, and
hospitalisation), use of medication, and participant out-of-pocket costs (sports club memberships
and sports equipment) were obtained from participant questionnaires that were collected
intermittently (at baseline, 12 and 18 months) with a 3-month recall period.” (see page 8, lines
157-160).

* Comment 7: Please clarify the reason for reporting costs in 2012 units. This is a bit dated and I
presume the willingness to pay threshold is in 2017 or 2018 units?

Authors’ reply 7: Costs were reported in 2012 units because the intervention programme was
delivered mainly in 2012. This information is added as follows: “We used 2012 price levels,
since the intervention was delivered mainly in 2012, and indexed prices when necessary using
the consumer price indices from Statistics Netherlands [14].” (see page 8, lines 166-167). Indeed,
the willingness to pay threshold is the one currently in use, but this has not been changed in the
Netherlands since 2002. Hence, comparing the ICER based on 2012 cost levels to the WTP
threshold of 2018 does not introduce further bias, the threshold would have been similar in 2012.
* Comment 8: Page 11 line 257. It seems odd to report median ICERS. We are generally interested in the means. Please report the mean if it is available. Also, please clarify that the ICER reported on page 11 line 258 is in the same year of costs as the current study.

Authors’ reply 8: The systematic review we refer to reported only the median ICER (based on 16 studies) as a summary measure (Li et al., 2015), therefore we included this measure in our manuscript. The median ICER from the review that was reported in the discussion is based on the cost level of 2013, while our ICER, apparently based on the mean of bootstraps samples, is based on 2012 cost data. As the Dutch consumer price index reports a 2.5% increase of prices between 2012 and 2013 only, we feel confident that the comparison of our ICER with the ICER from the systematic review does not reflect an entirely different price level. We now included information on the year of cost in the systematic review as follows: “Recently, a systematic review found a median ICER for diet and physical activity programmes of $13,761/QALY (2013 price levels), from a healthcare perspective [2]” (see page 12, lines 275-276).

* Comment 9: In the discussion, it would be helpful to comment on the large degree of uncertainty associated with the ICER being cost-effective. Can you please discuss why this is the case.

Authors’ reply 9: The degree of uncertainty for the intervention to be cost-effective that is reported in the discussion (i.e., the range of 43-70% and 56-81%) is related to the fact that two different threshold values are quoted in the Netherlands, a lower one of €20,000 and a higher one of €80,000 per QALY. The Figures 2 and 3 enable to read what the exact probability is at both thresholds. Hence, the uncertainty is more related to the issue what threshold value applies in the case of an intervention such as SLIMMER, than to uncertainty per se. To make this more clear, we have now specified this in the discussion, as follows: “From a societal perspective, the ICER was €28,094/QALY, reflecting a relatively low probability of cost-effectiveness of 43% at a WTP of €20,000/QALY and a higher probability of 70% at a WTP of €80,000/QALY.” (see page 11, lines 268-270).

* Comment 10: The discussion would also benefit with contrasting and comparing results to the SLIM cost-effectiveness intervention described in the introduction.

Authors’ reply 10: Information on the cost-effectiveness of SLIM is added to the discussion section as follows: “The Dutch SLIM study which formed the basis of our intervention programme revealed an ICER of €3,900-€5,500 [4]. Results, however, are difficult to compare due to methodological differences, such as the use of a lifetime horizon and modelling with SLIM, and the different years of cost.” (see page 12, lines 282-285).

* Comment 11: If the authors are going to discuss the willingness to pay findings in the discussion then they need to provide more detail in the methods and results about how these questions were delivered and how the data were analyzed. Otherwise, the willingness to pay data should not be reported.
Authors’ reply 11: We decided to not report data on the willingness to pay. Therefore, we deleted these lines in the discussion section: “Out-of-pocket costs were €48 higher in the intervention group than in the control group. We separately asked participants about their willingness to pay for the intervention. On average, they reported that they would be willing to pay €97 (data not shown). The additional out-of-pocket costs of €48 therefore appear to be acceptable for participants.” (see page 13, line 302).

* Comment 12: Table 1. For education, it is unclear as to the meaning of low, middle, and high.

Authors’ reply 12: Information on the education levels is added as a footnote to Table 1: “Education level was based on the highest level of education completed and divided in three categories: low (no, primary or lower secondary school), middle (higher secondary school or intermediate vocational school), and high (higher professional education or university level)” (see page 21, lines 475-477).

* Comment 13: Table 2. Please clarify that the costs represent 18-month cumulative costs.

Authors’ reply 13: A footnote was added to Table 2: “Total costs represent costs over the total 18-month study period.” (see page 24, line 481).

* Comment 14: Figures 2 and 3 need titles.

Authors’ reply 14: In line with the journal’s Submission Guidelines, the titles of the figures are stated after the References, namely: “Figure 2. Cost-effectiveness acceptability curve of the SLIMMER intervention compared to usual health care, from a societal perspective” and “Figure 3. Cost-effectiveness acceptability curve of the SLIMMER intervention compared to usual health care, from a health care perspective” (see page 19, lines 462-466).

* Comment 15: Some of the language in the introduction is awkward.

Authors’ reply 15: The text in the introduction has been checked by a native speaker, and has been adapted as follows: “Nowadays, diabetes is recognised as a major public health problem as it leads to a high disease and economic burden. In 2013 alone, diabetes accounted for 5.1 million deaths and a global health expenditure of USD 548 billion (11% of total health expenditure) [1]. Diabetes is associated with an unhealthy lifestyle characteristics, including obesity, poor diet, and physical inactivity [1]. Although evidence is accumulating that lifestyle modification may be cost-effective in patients with prediabetes, information is limited on the cost-effectiveness of interventions implemented in public health and primary health care settings [2]. Evidence from well-conducted pragmatic trials is needed to gain insight into the realistic cost-effectiveness of diabetes prevention interventions in real-world settings. The Dutch SLIM intervention, which led to a 47% diabetes risk reduction amongst study participants [3], has proven to be cost-effective [4]. The SLIM intervention was subsequently translated from the experimental setting into a real-
world intervention, called SLIMMER [5-7]. The aim of the current study is to assess the cost-effectiveness of the SLIMMER lifestyle intervention compared with usual health care in a primary care setting. We recently reported the effects of the SLIMMER intervention, including improvements in anthropometry, glucose metabolism, dietary intake, physical activity, and quality of life. These improvements were more significant amongst the intervention group than in the control group, both at 12 and at 18 months [8]. Here, we report on the cost-effectiveness analysis conducted alongside this pragmatic randomised trial.” (see page 5, lines 73-89).

In line with this, we adapted the text in the abstract: “Although evidence is accumulating that lifestyle modification may be cost-effective in patients with prediabetes, information is limited on the cost-effectiveness of interventions implemented in public health and primary health care settings.” (see page 3, lines 37-39).