| Project Name: Lifestyle Interventions for Four Conditions: Type 2 Diabetes, Metabolic Syndrome, Breast Cancer, and Prostate Cancer | | | |
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| Project ID: LFST1209 | | | |
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| Table 1: Invited Peer Reviewer Comments | | | |
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| Reviewer[1] | Section[2] | Reviewer Comments | Author Response[3] |
| 1 | General | The authors have provided a thorough and well-documented review | Thank you for your comment |
| 1 | General | For example, the most common sources of bias (page 23) were unclear sequence generation, inadequate allocation concealing, and inadequate blinding. Where possible, it would have been helpful to have sensitivity analyses to estimate the direction and extent of bias rather than just noting the potential bias., e.g. would these potential biases have changed the conclusions of the study? | Where feasible, we conducted sensitivity analyses for studies with high vs unclear risk of bias. They did not change the results or our conclusions. |
| 1 | General | Perhaps more important, data on compliance with the interventions is lacking. Without data on compliance it is not possible to know whether an intervention failed because its components, even if fully implemented, were not effective against the disease process or whether an intervention failed because it was not implemented as planned. Although the "number of dropouts/withdrawals was used as a surrogate measure for compliance," (p 56 and 73) dropout rates are not as informative as some measure of how well the study subjects complied with the regimens. Although the abstraction form includes a space for the author's statement on success/maintenance/failure of diet uptake (e.g. page 140) I could not find a summary of these findings in the report. Further, when effects seen at the end of the intervention disappeared with time, was this because the study subjects no longer complied with their diet and exercise? It is possible that this information was not available from the publications resulting from the studies, but it might be possible to get some information | It was decided a priori that we would use withdrawal and dropout rates as a surrogate measure for compliance. Where data on adherence were reported, we extracted them; however, adherence was poorly and inconsistently reported |

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| | | from the authors directly. As an example, the Ornish study (p.22) reports an intervention using a vegan diet. Is there a theoretical basis that justifies a diet that is potentially so difficult to follow? | |
| 1 | General | In addition, much more detail on the "usual care" (control) groups is needed. To be included in this structured review, the intervention group had to receive 3 or more interventions (diet, exercise and one other). This decision should be justified more fully. Within these studies, the control group could have had one or both of the diet/exercise interventions or something else. (pages 37-38) Thus, usual care could mean very different things in different studies. It is possible that both the intervention and control groups could have had diet and exercise components, potentially obscuring the effect of a diet/exercise intervention. | Additional information about "usual care" has been added to tables describing the interventions. |
| 1 | General | What would be considered a strong enough intervention to have an effect on the specified outcomes? The statistically significant differences between the intervention and control groups reported by some studies do not necessarily point to a meaningful clinical effect. This should be discussed further. Given the expense and difficulty of mounting intervention trials, each should contribute as much information as possible. | This is an excellent point. Determining clinical significance can be difficult, particularly for outcomes including changes in weight & metabolic markers. This is why we determined to make our primary outcomes clinical outcomes including progression to micro and macrovascular outcomes. Arguably any improvement in these is significant. With regards to secondary outcomes, in many instances the evidence is too limited to identify a truly clinically relevant endpoint. We added more about this in the discussion |
| 1 | General | Further, although observational studies fall lower in the hierarchy of valid research designs, many analytic techniques are available to minimize bias and confounding. To the extent that such studies can shed light on the effectiveness of lifestyle interventions, they should be used to the fullest before conclusions are reached. The authors acknowledge this point on page 26. | Thank you for your comment; no change. |

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| 1 | Executive summary | The Executive Summary is clearly written and reinforces many of the points mentioned above. The authors note that future studies should assess components that may improve adherence, that information on optimal interventions is needed, and that studies of long-term sustainability are needed. (p. 27) | Thank you for your comment |
| 1 | Methods | The methods are well described. | Thank you for your comment |
| 1 | Methods | The Data Analysis section, page 39, states that for continuous variables like BMI, the MD (or SMD where appropriate) would be used but for dichotomous outcomes like death the RR would be used. However, the tables and, to some extent, the figures contain errors regarding the summary measures used. On many occasions, RR (for relative risk) is erroneously used when MD (mean difference) is correct. The calculations as presented appear appropriate but the measure of effect is not a RR. Some examples are: page 17 under changes in body composition and metabolic variables; pages 18 and 22, cholesterol, triglycerides, blood pressure, and again on page 95, 96, 100. The authors need to check the report thoroughly for the many instances in which RR is used incorrectly. I have only provided some examples. Note that in Figures 4 – 14 the correct summary measures are used. | These errors were corrected. |
| 1 | Results | See above for errors in the tables and figures. | These errors were corrected. |
| 1 | Discussion/ conclusion | The discussion and conclusions are relevant and thoughtful. | Thank you for your comment |
| 1 | Discussion/ conclusion | Unfortunately, Key Question 3 asked whether specific components of the intervention, composition of the team and/or patient characteristics contributed to better outcomes, but the analysis could not address this as there was insufficient data (p91). Observational studies may have data on some of these factors and should be considered. | No change. The decision to include RCTs was made a priori in consultation with the Agency for Health Research Quality (AHRQ) and the Centers for Medicare and Medicaid Services (CMS). This is because RCTs are considered the highest level of evidence to evaluate the effectiveness of an intervention. |

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| 1 | Tables | See above for summary measures | We have corrected the summary measures as noted above. |
| 1 | Figures | Summary figures are very nice | Thank you for your comment |
| 2 | General | This is a comprehensive review that aimed to assess outcomes on conditions relevant to patients suffering from major health problems | Thank you for your comment |
| 2 | General | The abbreviation EPC should be defined in the list of abbreviations. | Change made. |
| 2 | General | Under 'Limitations of the existing evidence', the language restriction to English literature should be included. Also, include this in the discussion. | A sentence was added in the limitations section. |
| 2 | Introduction/ background | There is still a live controversy on whether the metabolic syndrome may be considered as a useful clinical entity. Further, there are different definitions of this condition that are not concordant and it is not clear whether the MS has any additional value in terms of cardiovascular risk assessment from its individual components. It is probably worthwhile to comment on this issue. | The decision to list metabolic syndrome in the key questions was made in consultation with the Centers for Medicare and Medicaid Services (CMS) and AHRQ. Due the evolving definition of metabolic syndrome as well as the debate regarding its ability to predict CVD and type 2 diabetes over abnormal blood glucose levels alone, we created an operational definition. Our operational definition of metabolic syndrome included metabolic syndrome, insulin resistance, prediabetes, impaired glucose tolerance, syndrome X, dysmetabolic syndrome X, and Reaven syndrome. |
| 2 | Introduction/ background | The term 'insulin dependent diabetes' should be avoided here and throughout the whole review. This is the term that was used for type 1 diabetes in a former classification of diabetes mellitus. It may be more appropriate to use the term 'insulin treated diabetes'. | Change made. 'Insulin dependent diabetes" changed to "insulin treated diabetes". |
| 2 | Introduction/ background | It is not stated that studies including participants with inclusion criteria other than the metabolic syndrome were included. Actually, only the study by Bo et al. included participants with this condition; the rest of studies included under the 'Metabolic syndrome' included participants that | The decision to list metabolic syndrome in the key questions was made in consultation with the Centers for Medicare and Medicaid Services (CMS) and AHRQ. Due the evolving definition of metabolic syndrome as well as the debate regarding its ability to |

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| | | were at high risk of type 2 diabetes development because of other conditions, mainly impaired glucose tolerance and/or obesity. | predict CVD and type 2 diabetes over abnormal blood glucose levels alone, we created an operational definition. Our operational definition of metabolic syndrome included metabolic syndrome, insulin resistance, prediabetes, impaired glucose tolerance, syndrome X, dysmetabolic syndrome X, and Reaven syndrome. |
| 2 | Introduction/ background | For type 2 diabetes, although few studies assess them, it would be important in terms of relevance for type 2 diabetic patients to include the quality of life and, probably, the satisfaction with treatment. Also, hypoglycemia is a relevant outcome (adverse event associated with pharmacological treatment) for these subjects. | No change. |
| 2 | Results | Literature search: Every effort should be made to retrieve the four studies not available through the University of Alberta library. Important information may be missed.<br>Were there any disagreements between those authors that selected the studies?<br>Please, it is necessary to define 'wrong publication type' | No change. Every effort was made to retrieve these articles; however, they did not arrive prior to our predetermined cut-off date.<br><br>Reviewers reached consensus for all studies included in the review.<br>Wrong publication type has been more clearly defined as "abstract or protocol only" in both the flow diagram and the Appendix D: Excluded studies |
| 2 | Results | Key question: There is a major issue in this section concerning the validity of at least 2 studies for answering the Key question. The studies by Gaede et al (Steno-2) and Menard et al are randomized controlled trials that include intensive multifactorial interventions as compared to usual care. Lifestyle interventions were just one of the components of these interventions. Unfortunately, there are sufficient data published by the Steno-2 investigators that show that lifestyle intervention had little or no effect, as mentioned in the review. It is very relevant to note that both trials had different goals of treatment (glycemic control, blood pressure, lipid targets) in the two arms of the trials. This implies also the utilization of different medications in each arm. The results of these two trials do not allow to | Medication use was one of the accepted third components of the lifestyle interventions. However, we conducted a series of post hoc sensitivity analyses comparing studies that had medication use as part of their intervention versus those that did not. The reviewer is correct in noting that the 'lifestyle' intervention per se often had little effect on outcomes. We have revised our results and conclusions based on these sensitivity analyses. |

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| | | assess what is the individual effect of lifestyle interventions on the outcomes assessed by the review (complications, metabolic variables, blood pressure, progression of treatment). Certainly, I would not include these 2 studies in the review. | |
| 2 | Results | Metabolic syndrome: As mentioned above, there is only 1 trial dealing with participants with the metabolic syndrome. The other included studies were carried out in subjects at high-risk of developing type 2 diabetes, mainly those with impaired glucose tolerances and/or obesity. The inclusion criteria in these latter trials did not comprise the metabolic syndrome. This should be clearly stated and the corresponding sections modified. | The decision to list metabolic syndrome in the key questions was made in consultation with the Centers for Medicare and Medicaid Services (CMS) and AHRQ. Due the evolving definition of metabolic syndrome as well as the debate regarding its ability to predict CVD and type 2 diabetes over abnormal blood glucose levels alone, we created an operational definition. Our operational definition of metabolic syndrome included metabolic syndrome, insulin resistance, prediabetes, impaired glucose tolerance, syndrome X, dysmetabolic syndrome X, and Reaven syndrome. |
| 2 | Results | Metabolic syndrome: The study by Pinkston 2006 compared two groups: a waiting list group and an intervention that combined orlistat and lifestyle measures. Therefore, this trial design does not allow to draw any conclusions on the individual effect of lifestyle measures. Thus, I would not include this trial. | We conducted sensitivity analyses to determine if the use of orlistat resulted in different effect size estimates for Pinkston vs other studies. There was no difference. We have added this statement to the results section for metabolic syndrome. |
| 2 | Discussion/ Conclusion | The following systematic review may be useful to the authors for revision and discussion:<br>Orozco LJ, Buchleitner AM, Gimenez-Perez G, Roque-Figuls M, Richter B, Mauricio D. Exercise or exercise and diet for preventing type 2 diabetes mellitus. Cochrane Database of Systematic Reviews 2008, Issue 3. Art. No.: CD003054. | Thank you for your comment. We reviewed reference lists of several relevant systematic reviews. |
| 2 | Discussion/ Conclusion | This section may be modified if the previous comments are taken into account by the authors. | Any changes made to the report will be addressed accordingly in the discussion/conclusion section. |
| 3 | General | The report needs to be carefully proofread as discrepancies between text and tables, typos, missing words, and missing references are found in various sections. | Any discrepancies or errors will be adjusted for the final draft. |
| 3 | Key | KQ1: As stated, it is unclear what the focus of the report is | The key questions were developed a priori in |

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| | Questions | in terms of the effectiveness of lifestyle interventions, i.e., whether it is on the prevention of incident cases of the four disease conditions in at-risk populations or on the management of disease progression among individuals who already have any of the diseases. The question should be revised to state clearly that it asks what the evidence is on the effectiveness of lifestyle interventions [to prevent disease progression and/or recurrence among individuals with] type 2 diabetes mellitus, metabolic syndrome, breast cancer, or prostate cancer. Please also see comments below on the Methods section regarding the selection of primary outcomes | consultation with both AHRQ and CMS. We have reworded the objectives in the structured abstract to make this more clear. |
| 3 | Key Questions | KQ2: It is implied by this question and by the relevant text in the report that age was used as the only determining factor for assessing generalizability to the Medicare population. Obviously, findings from studies in populations younger than 65 years are not generalizable to older populations. But, just because a study included or even exclusively targeted those older than 65 years, would the findings be automatically generalizable to the Medicare population? Age is not the only defining characteristic of the Medicare population. | In KQ2, age (>65 years) was identified as the subgroup of the Medicare population that we were interested in. |
| 3 | Key Questions | KQ3: To date, few behavioral intervention trials are designed to test the comparative efficacy or effectiveness of different components of a multifaceted intervention or different compositions of the team delivering the intervention. The sample sizes and associated resources that would be required to conduct such trials would likely be prohibitive due to the projected modest effect sizes, especially if the primary endpoint were to be a clinical outcome such as disease progression or recurrence. The practical and policy implications of testing a small intervention effect that may have limited clinical relevance are questionable. It is no surprise that the authors were unable to address this question due to insufficient, or essentially no data. It is unclear that there would ever be sufficient evidence to address the part of this question | None of the included studies presented moderation or regression analyses examining differences in intervention effects among the subgroups defined a priori for Key Question 3. These subgroups included particular components of the lifestyle intervention and who delivered them. |

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| | | about specific components of the interventions and composition of the team. In terms of the impact of patient characteristics on outcomes, it is increasingly common that behavioral intervention trials report on moderation analyses examining differences in intervention effects among subgroups defined a priori. It is surprising that the report presented no data in this regard.<br><br>The overall conceptual framework for defining lifestyle interventions is that the intervention had to include a diet component, an exercise component, and at least one other component. Descriptions given for the other component are inconsistent and confusing. In Tables 2, 5 and 7, the "other" components listed mostly include modality of contact (e.g., individual or group counseling, telephone or face-to-face), intensity and/or frequency of contact (e.g., number of counseling sessions, time intervals), and type of intervention personnel (e.g., nutritionists, case managers, physicians). It would be more helpful to revise the conceptualization of the lifestyle interventions to articulate the content of intervention (diet, exercise, and other) and the other features of intervention format and structure as noted above. It would also be important to describe the theoretical basis, if any, of the intervention tested in a given study and whether and how the study measured the core constructs of the theory. | We deconstructed the interventions in table format so that readers could see a description of each intervention component and could compare components across studies. We were deliberate in this presentation and believe this is the best way to summarize very complicated and varied interventions. |
| 3 | Executive summary | The ES will need to be revised in accordance with any changes made in response to the general comments and to comments on the main body of the report. Minor comments on the ES specifically are as follows: | The executive summary has been revised to correspond with any changes made in the main body of the report. |
| 3 | Executive summary | Pg ES-2, it is unclear why the trial by Ornish et al. was mentioned in the Background about prostate cancer. | We have removed this reference in the introduction. |
| 3 | Executive summary | No citations were provided on pages ES-4 through ES-12. | It is a summary so we did not feel it was important to cite all of the studies here. All studies are cited when they are described in the main report. |
| 3 | Executive summary | Pg ES-12, last paragraph, first line, the citations needs reformatting. | Change made. |

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| 3 | Executive summary | Pg ES-15, last sentence, "we may ~~not~~ have missed some studies…" | Change made. |
| 3 | Executive summary | Pg ES-16, under Future Research, the 2nd bullet states that "future research should seek to minimize risk of bias by blinding study participants…" It needs to be acknowledged that, by design, treatments are typically identifiable to participants in behavioral intervention trials, even if an active placebo intervention is employed. Nevertheless, blinding of the data collection, outcome event adjudication, and data analysis remains possible and should be ensured. | Comments were noted and added into the document. |
| 3 | Executive summary | The 3rd bullet states that "…information on optimal exercise and dietary interventions is needed." It is unclear how "optimal" would be defined or assessed. Accumulating evidence suggests that there is no "one size fits all" when it comes to exercise and dietary interventions. Tailoring and individualization are critical in order to be effective. Also, the efficacy (and safety) of any lifestyle intervention depends not only on the mix of supposedly active components but on the setting, population, and other contextual factors as well. | We have reworded some of the bullets in the future research section to address these points. |
| 3 | Executive summary | The last bullet states that "research to assess the most effective delivery setting is needed…" No one setting would be "most effective." Instead, to stem the tide of chronic diseases that are largely preventable non-communicable conditions associated with lifestyle and behaviors will require interventions in the settings where individuals live, work and play through partnerships among all stakeholders. | We have reworded this point to clarify. |
| 3 | Introduction/ background | Pg 1, no citation was provided for the statement "Despite the demonstrated benefit of improved diet and physical activity in the prevention of certain chronic diseases…" | This statement has been removed. |
| 3 | Introduction/ background | Pg 5, as in the ES, it is unclear why the trial by Ornish et al. was described in the Background when it is one of the studies reviewed and presented in the results. | We have removed this reference in the introduction. |
| 3 | Introduction/ background | Pg 6, it is stated that "adverse reactions are unlikely but are included..." It needs to be recognized that exercise-related adverse events are not uncommon in interventions that involve increased physical activity, esp. in habitually | No studies reported any adverse events directly attributed to physical activity. We changed the sentence to "Adverse reactions directly related to the lifestyle intervention are unlikely but are included in the |

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| | | sedentary, high-risk populations. | framework." |
| 3 | Introduction/ background | Pg 7, Figure 1, for the long-term health outcomes, clarify that it is progression [of metabolic syndrome] to diabetes, health disease or stroke and development of [diabetes] complications or comorbidities. | Changes have been made. |
| 3 | Introduction/ background | The background clearly highlights obesity and its relationships with each of the four disease conditions. However, no information was given on the relationships between eating patterns or dietary constituents or physical activity and any of the disease conditions. | We address this in the background section of the introduction. |
| 3 | Methods | Pg 10, the primary outcomes for type 2 diabetes are "progression to additional medication or insulin, or progression to cardiovascular problems, hypertension or neuropathies." Rarely, if ever, is progression to additional medication or insulin measured assessed as a primary outcome in trials of type 2 diabetes. Why was it chosen as one of the primary outcomes in the review? The "cardiovascular problems" of interest need to be clearly defined. Hypertension is a common comorbid CVD risk factor in diabetic patients. Changes in blood pressure are commonly evaluated in diabetes trials but no studies have assessed "progression to hypertension" as a primary outcome. No microvascular complications of diabetes other than neuropathy are listed among the primary outcomes. | In light of some evidence that lifestyle interventions resulted in decreased medication intake, we felt this would be an important variable to assess. Unfortunately, as some interventions included medication as part of the intervention, the results cannot be reliably interpreted. This is included in the discussion. |
| 3 | Methods | It is unclear how the primary outcomes in each individual study included in the review correspond to the primary outcomes chosen for the review. Is this what the "directness" domain was supposed to reflect for assessing the level of evidence? | The primary outcomes for the included studies were not necessarily the primary outcomes of the review.<br><br>The "directness" domain was a reflection of whether the evidence linked the intervention directly to the health outcome. Most outcomes in the review were indirect because they were intermediate or surrogate outcomes instead of primary outcomes. |
| 3 | Methods | Changes in body composition (primarily weight and BMI) are included among secondary outcomes. However, most of the lifestyle interventions included in the review did not specifically target weight loss. Weight loss is difficult to achieve and even harder to maintain; sustained, targeted | The primary outcomes for the included studies were not necessarily the primary outcomes of the review. Change in body composition was an intermediate outcome in our analytical framework, and a surrogate measure for our primary outcomes. |

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| | | intensive interventions are required to be effective. So, negative findings should not be taken to suggest ineffectiveness of the intervention when the intervention was not designed to affect the outcome in the first place. | |
| 3 | Methods | Pg 10, third line under "Methodological Quality," should "'other' sources of data" be "'other' sources of bias"? No rationale was provided for rating the quality of the studies included in the review as "high," "low," or "unclear," as opposed to using the Jadad score. | We have made this change.<br><br>The Risk of Bias tool is recommended by the Cochrane Collaboration and is based on empirical evidence for potential sources of bias in RCTs. |
| 3 | Methods | Pg 11, under "Grading the Body of Evidence," it is stated that "…four major domains were examined for each outcome: risk of bias (rated as low, medium, or high)…" The ratings given for risk of bias are low, high, or unclear. No definition or criteria were presented for the consistency, directness, and precision domains. | We added a short description of the domains. The reference was provided for further information on the AHRQ GRADE approach |
| 3 | Methods | Pg 12, it is stated that "when no studies were available for an outcome, the evidence was graded as insufficient." But, for a number of outcomes across the disease conditions, the evidence was graded as insufficient even when one or more studies were available for the outcome (Appendix E). | We removed this sentence. There were other criteria that resuted in an assessment of "insufficient". |
| 3 | Results | Pg 15, the description of the lifestyle interventions lacks structure and does not appear to have any theoretical grounding. | Beyond the requirement for a lifestyle intervention to have diet, exercise and at least one additional component, we did not have an all encompassing description or theoretical grounding for the lifestyle interventions. Lifestyle intervention, as defined by the study authors, is described in the tables in the main part of the report. |
| 3 | Results | Pg 15, under "Methodological Quality," it is unclear whether the study by Kirkman et al. (ref 148) was included in the review? It is referenced on page 15 but not included in any of the tables. | We have made this correction. |
| 3 | Results | It is unclear why the Diabetes Prevention Program is mentioned on pages 15-16. "One study[124] stated that the allocation to metformin or placebo was double blinded; however, we did not extrapolate this double blinding to the diet and exercise components of the intervention." The DPP included individuals free of diabetes at baseline. | Change made, this sentence was moved from the diabetes section to metabolic syndrome section. |

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| 3 | Results | Data at four years from the Look AHEAD trial need to be included in the review. | The 4 year data have been added. |
| 3 | Results | Pg 26, data on medication use are provided. However, it is unclear how medication use was assessed in the studies this was measured. It was presented as though less medication use in the intervention group in some of the studies were an unfavorable outcome. However, this may reflect more intensive treatment or greater patient compliance as a result of the intervention. | It is possible that it may reflect more intensive treatment or greater patient compliance. However, we only reported what the study said about the number of people who took medication or the number of medications used. None reported on compliance. We have added a comment in the discussion about this. |
| 3 | Results | Pg 62, "For our secondary outcomes, we believe that the results should be generalizable to individuals aged 65 or older." The basis is for this judgment needs be provided and justified. | We have added a sentence to this section to clarify. |
| 3 | Discussion/ conclusion | Comments provided above on "Future Research" in the Executive Summary need be addressed as well for the Discussion/Conclusion. | Any changes made in the "future research section" of the executive summary have been addressed accordingly in the discussion/conclusion sections of the main report. |
| 3 | Tables | The primary outcome(s) of the individual studies included in the review need to be presented in the tables. | Since the description of studies and baseline characteristic tables were already quite lengthy and complicated, we made the pragmatic decision to focus on descriptions of interventions and study/population characteristics rather than results. |
| 3 | Tables | The "risk of bias" tables list the ratings as "yes" or "no," which is confusing. Need to be consistent with the descriptions given in the Methods and use "high" or "low" instead. As noted above, the decision to use this categorical classification instead of the Jadad score needs to be justified. | We have made this change. |
| 3 | Figures | References need to be provided in the figures. | No change. The software we used to generate the metagraphs is not compatible with the cite-while-you-write feature that was used to generate bibliographic information in the rest of the report. |
| 3 | Appendices | Appendix B.1, fasting glucose $\geq$110 mg/dL is used for defining metabolic syndrome, but the current guidelines recommend using 100 mg/dL as the threshold. | This was originally based on the 2005 American Heart Association/National Heart, Lung and Blood Institute scientific statement Executive Summary. We changed this to 100mg/dL which is from the 2006 statement. |
| 3 | Appendices | Appendix B.1, the rationale is unclear for why the review | We were interested in the effectiveness of lifestyle |

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| | | excluded studies in which the comparator group was a less intensive intervention, as opposed to usual care. | interventions compared with usual care. It was beyond the scope of the review to examine a dose-response relationship for different levels of lif style interventions. |
| 3 | Appendices | Appendix B.2, the study objectives listed under item 3 do not include any of the primary outcomes chosen for the review. As noted above, the primary outcomes of the individual studies need to be presented, and how (dis)concordance between these and the chosen primary outcomes in the review is factored into the evaluation of the strength of evidence needs to be clarified. | As stated earlier, the primary outcomes for our review may have been different than the primary outcomes for the included studies. This is not unusual in the conduct of systematic reviews. Where data for our primary objectives were reported, we extracted them. Where data for other outcomes were reported and were considered relevant to this report (through discussion with the clinical and methodological leads), we extracted the data. |
| 3 | Appendices | Appendix B.2, the table headings in 7a and 7b in this appendix and in Tables 2, 5, and 7 make it appear that end/duration of study/trial was used to refer to end/duration of intervention. These are two distinct concepts and end/duration of intervention should be clearly labeled as such. | The data on duration of the intervention were extracted and interpreted correctly. All data extraction was verified by a second reviewer. |
| 3 | Appendices | Appendix B.2, 7a, is energy intake the only relevant data item extracted for “diet related” from studies? | Many more outcomes were extracted into our Excel database which was used after the creation of this data extraction form. These outcomes are reported in the body of this review. |
| 3 | Appendices | Appendix B.2, 7b, the examples given in parentheses for adverse clinical events are actually primary outcomes chosen for type 2 diabetes trials for the review. How the information extracted for the adverse clinical events was used in the review/meta-analysis needs be clarified. | We have taken out these examples on the data extraction form. Our criteria for adverse events were any adverse events, side effects, or harms described by the authors of the individual studies. These examples were not part of the Excel database, which was used by reviewers to extract data. |
| 3 | References | The references appear to be complete and up to date, except that the publication on the 4 years data from Look AHEAD needs to be added. As noted above, citations are missing in different sections of the report. | The 4 year data have been added. |
| 4 | General | This is a carefully conducted systematic review on lifestyle interventions on health outcomes among patients with four conditions: type 2 diabetes, metabolic syndrome, breast cancer and prostate cancer. The methodology for | Thank you for your comment |

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| | | systematic reviews and quantitative meta-analysis is generally sound. | |
| 4 | General | The data are appropriately interpreted. | Thank you for your comment |
| 4 | General | The conclusions are consistent with the data. | Thank you for your comment |
| 4 | General | The main issue is that only three small studies were included for patients with prostate or breast cancer. The limited literature does not permit any meaningful meta-analysis or drawing any useful conclusions. Although this is an inherent limitation of the literature, a question is raised whether the inclusion criteria are so rigid that some meaningful studies were excluded from the analyses. | No change made. An a priori decision was made in consultation with AHRQ and CMS to include RCTs (considered the highest level of evidence to evaluate the effectiveness of an intervention) and lifestyle interventions that had exercise and diet and at least one other component which allowed us to assess multifaceted interventions. |
| 4 | General | According to the report, the lifestyle intervention had to include an exercise component, a diet component, and at least one other component (e.g., counseling, smoking cessation, behavior modification). This inclusion criterion led to exclusion of some important studies that were focused on only diet or exercise. For example, the WHEL study (diet intervention among breast cancer survivors) was not included. Similarly, the Women's Nutrition Intervention Study (WINS) was also excluded. One can argue that these studies are as important as those that include multiple components of interventions. For dietary intervention, counseling, behavioral modifications, and lifestyle changes need to be involved. Thus, these interventions can be considered as "lifestyle interventions." | No change made. The decision regarding our inclusion criteria for lifestyle interventions were made in consultation with AHRQ and CMS. |
| 4 | Executive summary | It should be pointed out that most of the intervention studies were not designed or powered to examine the effects of lifestyle intervention on hard endpoints such as cardiovascular events, total or cause-specific mortality. | We agree and have acknowledged this in the discussion section. |
| 4 | Executive summary | It is also important to point out that the interventions in different studies are not exactly comparable because of different delivery methods, different settings, and different goals. | No change. We acknowledge that the interventions were variable. |
| 4 | Introduction/ Background | Nicely written | Thank you for your comment |
| 4 | Introduction/ Background | It would be useful to discuss economical consequences of the diseases and common underlying risk factors (e.g. | We addressed many of the risk factors for these conditions in the introduction. There are many |

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| | | obesity and unhealthy diet and lifestyle) for these conditions. | consequences of the diseases that could have been discussed (including economic). We chose to focus on morbidity and mortality. |
| 4 | Introduction/ Background | The report needs to provide justifications why only these four conditions were considered in the analyses and why CVD or other cancer (e.g., colorectal) patients were not included in the review. | The scope of the review (i.e. diseases included) was determined by CMS and their needs. |
| 4 | Methods | As discussed above, the authors may need to reconsider the inclusion criteria. The exclusion of important studies that were only focused on diet or exercise led to a very narrow selection of literature, which prevents the meta-analysis from drawing meaningful conclusions on diet and lifestyle modifications on cancer-related outcomes. | The inclusion criteria and operational definition of a lifestyle intervention were developed in consultation with CMS and AHRQ. |
| 4 | Results | For metabolic syndrome outcomes, the report included several well-known diabetes prevention studies such as DPP, Finish Diabetes Prevention Project, and Chinese Da Qing Diabetes Study. Although all the participants had impaired glucose tolerance due to the inclusion criterion, many of them did not have the metabolic syndrome according to NIH or WHO criteria. Thus, the findings from these studies cannot be used as evidence to suggest that diet and lifestyle interventions are effective in preventing diabetes among those with the metabolic syndrome. Also, none of the studies were powered to examine hard endpoints. | The decision to list metabolic syndrome in the key questions was made in consultation with the Centers for Medicare and Medicaid Services (CMS) and AHRQ. Due the evolving definition of metabolic syndrome as well as the debate regarding its ability to predict CVD and type 2 diabetes over abnormal blood glucose levels alone, we created an operational definition. Our operational definition of metabolic syndrome included metabolic syndrome, insulin resistance, prediabetes, impaired glucose tolerance, syndrome X, dysmetabolic syndrome X, and Reaven syndrome.<br>We have added some information to the introduction to address the controversy. |
| 4 | Discussion/ Conclusion | It should be pointed out that the Steno-2 trial included not only lifestyle modifications, but also diabetes management through medications and supplements. This is different from other trials in which only behavioral interventions were employed. | We have conducted sensitivity analyses to assess the impact of medication vs. no medication as part of the lifestyle intervention. We have revised our results and conclusions to reflect these analyses. |
| 4 | Discussion/ Conclusion | It is important to point out that no meaningful conclusions can be drawn on cancer-related outcomes because of the limited literature that was considered in the meta-analysis. | We agree. This was stated in our results section. For both cancers we state that the strength of evidence is insufficient. |

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| 4 | Tables | Generally sound | Thank you for your comment |
| 4 | Figures | Generally sound | Thank you for your comment |
| 4 | Appendices | Generally sound | Thank you for your comment |
| 4 | References | Generally sound | Thank you for your comment |
| | | | |
| [1] Peer reviewers are not listed in alphabetical order. | | | |
| [2] If listed, page number, line number, or section refers to the draft report. | | | |
| [3] If listed, page number, line number, or section refers to the final report. | | | |

Project Name: Lifestyle Interventions for Four Conditions: Type 2 Diabetes, Metabolic Syndrome, Breast Cancer, and Prostate Cancer
Project ID:

Table 2: Public Review Comments

| Reviewer Name[1] | Reviewer Affiliation[2] | Section[3] | Reviewer Comments | Author Response[4] |
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| Anonymous | American College of Cardiology | | Overall, the draft report appears well-done and thoroughly researched. | Thank you for your comment |
| | American College of Cardiology | | The data analyzed include data from as far back as 1980. The ability to include data from that broad a time span is remarkable with one concern: the current definitions for diabetes and metabolic syndrome have lower thresholds; thus, the diagnosis pooling may have a margin of error from then to now. The diagnostic criteria for diabetes, metabolic syndrome and hypertension have been downgraded, so the prevalence statistics are subject to an error when data from different decades are combined into one analysis | We looked for studies dating as far back as 1980 in order to capture long-term studies. The oldest study that met our inclusion criteria was published in 1992. |
| | American College of Cardiology | | It is not always possible to separate diabetes from metabolic syndrome. Given the tremendous overlap between the two conditions, it is important that the point be emphasized. | The studies we included were all very clear on their differentiation between patients with type 2 diabetes and metabolic syndrome. |
| | American College of Cardiology | | Additionally, the term “lifestyle changes” has not been clearly defined in a standard manner. Because of this, there is no commonality among the various studies as to what actions were precisely taken or what they accomplished. Quantifying those lifestyle changes would be of great help. However, today, it is generally a mixture of a variety of methods. It becomes unclear as to | We agree that ‘lifestyle change’ was defined in various ways across the studies. Where there were data for our primary and secondary outcomes, we extracted and analyzed them, regardless of whether it was the primary or secondary outcome for the individual studies. |

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| | | | whether the goals were achieved at all in the studies where there was no benefit from lifestyle changes. Was it a failure of intervention or did that intervention not really take place? Advising weight loss is one thing, while achieving weight loss is another. Thus, it becomes a question as to whether the patients achieved the intent at all or if they were merely counseled? This means that a negative or insufficient study may not be that negative at all if the objectives were achieved. Also, in many studies cited by the draft, lifestyle changes were recommended along with pharmacological treatment, and it is not always possible to separate the effects of the lifestyle changes from those of the pharmaceuticals. This information, if available, should be discussed. | We conducted sensitivity analyses to examine the effect estimates for studies with versus studies without pharmacological treatment as part of the lifestyle intervention. We have revised our conclusions as appropriate. |
| | American College of Cardiology | | One way of quantifying the effects of lifestyle changes would be to assess correlations between the amount of lifestyle changes achieved and a fall in metrics used to diagnose diabetes and metabolic syndrome. These include blood sugar, HgB A1c, blood pressure, and lipids. It would also be helpful to track the uniformity of participants? ability to sustain lifestyle changes. | We used these metabolic variables as one way to measure the effect of the lifestyle interventions.<br><br>We looked at the ability to sustain lifestyle changes by looking at longest postintervention timepoint measurement available for each outcome. |
| | American College of Cardiology | | Diet is one of the key lifestyle changes discussed in studies. However, this term is never defined in the studies analyzed. It would be useful for this term to be defined in studies. If it is defined in the studies, the definition should be included in the assessment. Additionally, the assessment should examine more closely the differences in evidence regarding the effects of dietary changes based on effectiveness of those diet and exercise changes. The research seems robust regarding the decrease in events and | Diet was a necessary component of a lifestyle intervention in order for a study to be included in our review. For each study we describe the diet component in the tables in the main body of the report. There were insufficient data to determine whether particular diets were more or less effective for our outcomes of interest. |

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| | | | disease progression as a result of effective diet and exercise. Unfortunately, when the studies are examined further, it appears as those people were not truly effective at dietary and exercise changes, which affected their ability to lose weight. Thus, it is critical that the point be made that the basics of weight loss are critical in attempts to make major lifestyle changes, such as diet and exercise and that despite setbacks, these methods can still work without the need for pharmaceutical intervention. | |
| | American College of Cardiology | | Similar to the problems with the term lifestyle changes, “physical activity” as used by various studies is seldom defined or quantified. If definitions of “physical activity” are available, the draft should provide that information.<br>Additionally, it should include a discussion of patient views of their fitness and changes in their exercise endurance. A clearer objective measure of physical activity, not just counseling, should be cleared, as well as any differences between individuals who are fit versus those who are not. | We described the physical activity components of the lifestyle intervention in the study description tables.<br>There were no subgroup analyses provided for patients who were fit versus those who were not. |
| | American College of Cardiology | | The draft assessment seems to neglect discussion of two critical points: the effect of lifestyle interventions on prevention of a disease and the effects of withdrawal or cessation of those interventions. Research seems to indicate that the greatest benefit of lifestyle changes may be in preventing the transformation of impaired glucose tolerance to diabetes and from pre-hypertension to hypertension. However, the draft assessment does not address this point, that is, whether a clinical disorder in the early stages was aborted as a result of intervention. Additionally, it does not address the effects of withdrawal or cessation of lifestyle changes on the re-emergence of cardiometabolic risk profile. In other words, if the patient ceases the lifestyle interventions and reverts to his or her | It was beyond the scope of the review to address the impact of interventions on primary prevention of a disease.<br><br>It was beyond the scope of this review to determine if risk profiles reverted once a patient ceased the lifestyle intervention and reverted back to his/her previous lifestyle. |

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| | | | previous lifestyle, will the risk profile revert, as well? | |
| | American College of Cardiology | | We would also encourage the drafters to consider improved blood pressure levels as a result of lifestyle changes more closely. While some of the studies cited improvement in blood pressure levels with lifestyle changes, it is important to note that blood pressure measurement is more accurate with a reduction in the arm width, regardless of cuff size. Thus, when a patient loses weight and experiences a reduction in arm width, corresponding reductions in blood pressure may be the result of more accurate measurement, rather than the lifestyle change. | No studies reported a change in arm width so we are unable examine this association. |
| Anonymous | American Medical Association | General | While the report had a narrow objective to synthesize the evidence of lifestyle interventions to control progression and/or prevent recurrence for the four medical conditions, it also shines an important spotlight on other important healthy outcomes from behavioral changes. | Thank you for your comment. |
| Anonymous | American Medical Association | General | Moreover, the conclusions of the AHRQ report are also consistent with recommendations of the 2008 HHS Physical Activity Guidelines Advisory Committee Report, the 2005 U.S. Department of Agriculture Dietary Guidelines for Americans, and Healthy People 2010.<br>We note that the AHRQ report is also consistent with the AMA's position that patients should be committed to health maintenance through health-enhancing behavior. | Thank you for your comment. |
| Anonymous | American Medical Association | Outcomes | The report does not identify evidence about which interventional strategy would be most successful in inducing and maintaining behavioral change or improving patient-oriented outcomes. | Since no two interventions were exactly the same and given the small number of studies, we were unable to determine which strategy was the most successful in inducing and maintaining behavioral change. |
| Bruce Blehart | American Academy of | General | Our concern with the draft TA is its limited focus. By only looking at the relationship between physical | The scope of the report was determined in consultation with AHRQ and CMS. Sleep |

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| | Sleep Medicine | | activity and diet as modifiable risk factors that may impact onset or progression of disease, this detailed assessment totally ignored the well-established relationship between sleep and diabetes and metabolic syndrome. We hope to have an opportunity to work with the Agency to expand this TA to include the third arm of prevention: effective sleep. | management may have been part of some lifestyle interventions (as the 3rd component) and if so, would have been identified in the tables summarizing the interventions in the main report. |
| Bruce Blehart | American Academy of Sleep Medicine | General | A study that was published in the current issue of Sleep, Sleep Symptoms Predict the Development of Metabolic Syndrome (Sleep, Vol.33. No. 12, 2010), supports "a directional link between commonly reported sleep symptoms, including difficulty falling asleep and loud snoring, and development of metabolic syndrome." This study built on previous research that showed a clear linkage between self-reported sleep duration and sleep-disordered breathing with the development of various components of metabolic syndrome, including diabetes, hypertension and obesity.<br>The AASM strongly encourages consideration of sleep modification as an integral lifestyle element that needs to be incorporated in this TA and added as a related topic for future research. As the Agency works to complete this TA, the Academy will be pleased to provide further information on the value of sleep as a key component of a healthy lifestyle. Please contact Richard Rosenberg, PhD, at RRosenberg@AASMnet.org to discuss this further and to be connected with the researchers who completed the previously cited and other relevant studies. | No change made. Sleep management may have been part of some lifestyle interventions (as the 3rd component) and if so, would have been identified in the tables summarizing the interventions in the main report. |
| Jeanne Blankenship | American Diabetic Association | Methods | Methodological limitations of the systematic review with restricting research to RCT and with some of the other specific inclusion/exclusion criteria. Inherent limitations in the studies that were selected for inclusion, e.g., terms and concepts not clearly | In consultation with AHRQ and CMS, an a priori decision was made to include only RCTs. The other limitations have been noted in the discussion section of the report. |

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| | | | delineated for components of interventions (group/individual, counseling/education) reported and potential for impact of the type of healthcare professional delivering the intervention. Additional recommendations for future research to include cost and testing of impact of evidence-based guidelines/protocols | |
| Jeanne Blankenship | American Diabetic Association | Methods | While randomized controlled trials (RCT) are the type of scientific experiment most commonly used in testing the efficacy or effectiveness of healthcare services or health technologies, limiting the review of the evidence to only these trials may not allow for full exploration of the research that addresses a topic. A body of research can only be understood after a full evaluation of research studies not just RCTs. Essentially, this report considered only one kind of evidence while acknowledging that other types of evidence are needed and, in our opinion, should have been considered.<br><br>Blumberg et al1 noted in their review that the inherent complexity of dietary interactions will sometimes not be adequately addressed through one type of research design, such as the RCT, which is only one approach to understanding the efficacy of dietary interventions. Because of the limitations inherent in RCTs, Blumberg et al suggest that dietary recommendations and policy decisions be made using the totality of the available evidence. They concluded that advancing evidence-based nutrition will need to rely on research approaches that supplement RCTs. | In consultation with AHRQ and CMS, an a priori decision was made to include only RCTs. In the discussion and future research sections, we have noted that well designed observational studies may provide evidence for the long-term outcomes. |
| Jeanne Blankenship | American Diabetic Association | Study design | Other types of study design, such as observational studies, may have more potential for new discoveries.[2] RCTs may not be needed in assessing treatments that deliver strong and rapid effects compared to a stable or progressively worse natural | See previous comment |

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| | | | course of a treated condition, such as cancer.[3, 4] | |
| Jeanne Blankenship | American Diabetic Association | Study design | When performing evaluations of scientific evidence, one must consider the drawbacks of RCTs.[3, 5] The extent to which RCT results are applicable outside the parameters of the RCT varies; thus the external validity may be limited.[3,6] Factors that can affect RCTs' external validity include location of RCT, characteristics of the patients, study procedures, outcome measures, and incomplete reporting of adverse effects.[6, 7] Additionally, RCTs do not allow study of rare events and uncommon adverse outcomes. In order to study these situations, extremely large sample sizes would be necessary, and are, therefore, best assessed by observational studies.[3] Finally, it is costly to maintain RCTs for the years or decades that would be ideal for evaluating some interventions.[3, 5] | See previous comment |
| Jeanne Blankenship | American Diabetic Association | Study design | Studies have assessed the relative importance of RCTs and observational studies. Two studies found that observational studies and RCTs overall produced similar results.8, 9 Concato et al concluded that well-designed observational studies (cohort or case-control design) do not systematically overestimate the magnitude of treatment effects as compared with RCTs on the same topic.9 Their assessment demonstrated that the average results of observational studies were remarkably similar to those of RCTs, as did the study by Benson et al.8 These assessments challenge the assumption that observational studies have less validity associated with overestimation of treatment effects than do RCTs. Therefore, the assumption that observational studies should not be used for defining evidence-based medical care and that RCT results are always evidence of the highest grade should be reconsidered based on these studies. | See previous comment |
| Jeanne | American | Study design | The current AHRQ report notes that the provision of | See previous comment |

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| Blankenship | Diabetic Association | | long term comparative data from studies comparing an active treatment with an active control may not be feasible. As such, the authors suggest that observational studies are needed to provide data on patients using different interventions over several years to determine the comparative benefits of these interventions. However, the current AHRQ report only includes RCTs. The report does acknowledge that studies examining long term sustainability of lifestyle interventions over the course of several years are needed. We would agree, but these studies would likely not be feasible in an RCT form; thus, observational studies can be useful to follow populations and the effectiveness of interventions over time. | |
| Jeanne Blankenship | American Diabetic Association | Bias (blinding) | The current AHRQ report excludes studies due to inadequate blinding. Blinding is sometimes inappropriate or impossible to perform in an RCT; for example, if an RCT involves a treatment in which active participation of the patient is necessary (e.g., lifestyle intervention), participants cannot be blinded to the intervention. The AHRQ report recognizes that it is not feasible to blind subjects in studies using lifestyle intervention, while it is possible to blind to the hypothesis, provide treatment to the control group (usual care), and blind those assessing data, yet studies were excluded based on lack of blinding in this evidence-based analysis. | We did not exclude studies that had inadequate blinding. We assessed blinding as one of the domains in the risk of bias tool. |
| Jeanne Blankenship | American Diabetic Association | Conclusion | The current AHRQ report concludes that there is insufficient evidence to demonstrate an effect of lifestyle interventions for the treatment of type 2 diabetes, metabolic syndrome, breast cancer, and prostate cancer. However, ADA would suggest caution in this conclusion and recommends that AHRQ further refine this report through review of additional studies that are well designed but lack randomization. The report overlooks key | See above comment regarding RCT.<br>Our search strategies were comprehensive captured the terms suggested by this reviewer.<br>We did not exclude studies on the basis of reported outcomes. |

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| | | | information, since not all the studies evaluated were specifically designed to answer the questions proposed for this evidence-based analysis. Additionally, the report only includes studies with intervention components of diet, exercise and one other behavior modification. Additional terms could have been considered within lifestyle intervention definition, such as, nutrition therapy, food, nutrition, food/eating patterns, and physical activity. Further, the selection criteria used would have excluded studies which measured functional outcomes, i.e., LEAD and RENEW studies, which are important cost:benefit factors to consider, particularly in older, Medicare populations. | |
| Jeanne Blankenship | American Diabetic Association | Limitations | The AHRQ evidence analysis focus on only RCTs may have resulted in the underestimation of the effect of lifestyle interventions for the treatment of type 2 diabetes, metabolic syndrome, breast cancer, and prostate cancer. | See previous comment on RCTs |
| Jeanne Blankenship | American Diabetic Association | Limitations | The definition of the "diet component" in the studies varies greatly, making it difficult to compare across studies. Some studies provided food, group counseling, and nutrition education, while other studies lacked these elements. These dissimilarities make it difficult to formulate a clear conclusion. | We agree and we have noted this in our report. This is why under "future research" we state, "Standardization of lifestyle interventions would allow for improved reporting and comparison of interventions in the medical literature." |
| Jeanne Blankenship | American Diabetic Association | Limitations | Diet and/or nutrient intake is limited to saturated fat and energy intakes in the studies evaluated. Studies reporting other nutrients, such as carbohydrate, total fat (and types of fats), protein, and fiber intakes, would provide a better understanding of the relationship between total macronutrient intake and effectiveness of lifestyle interventions on body composition and metabolic parameters. | Nutrients such as carbohydrates, proteins, fruits and vegetables and fiber were considered during data extraction. However, fat and energy intakes were the most commonly reported. The other outcomes were not reported enough to have any meta-analyses performed. |
| Jeanne Blankenship | American Diabetic Association | Limitations | Reporting change in behavioral outcomes would also be beneficial for determining the effects of lifestyle interventions. For example, blood glucose monitoring is a key intervention for improving A1C. | We reported A1C outcomes as a measure of glucose control. Self-monitoring of blood glucose may have been part of the 3rd component of the lifestyle intervention and |

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| | | | As noted by the ADA systematic review, Sixteen type 2 diabetes studies that involved self-monitoring of blood glucose and glycemic control were reviewed. Self-monitoring of blood glucose, compared to non-self-monitoring of blood glucose, is associated with greater improvement in A1C when it is a part of a structured education program where subjects use the information to make changes in their diabetes self-management program. Evidence on frequency and duration of self-monitoring of blood glucose is inconclusive. Grade II.?[10] The addition of these studies to the evidence analysis would require a broader search term list. | would have been included in the summary tables describing the interventions. |
| Jeanne Blankenship | American Diabetic Association | Limitations | It was noted in the report that eight of the 10 diabetes intervention studies reported dietitian involvement (Christian et al, 2008 and Menard et al, 2005 did not), and five of the six metabolic syndrome studies had dietitian involvement (Pan et al did not). It may be misleading to compare a nutrition intervention with a registered dietitian (RD) as part of the multidisciplinary team to one without RD involvement. In some studies, the nutrition education or nutrition counseling was performed by an RD, while in other studies other health care professionals delivered this service. The systematic review by ADA indicates, "Nine studies demonstrate that the inclusion of nutrition interventions and counseling, when provided by a registered dietitian as part of a healthcare team, resulted in significant improvements in weight and BMI, A1C, blood pressure and serum lipids. The majority of these studies took place in primary care settings. Grade I."[11] | Thank you for your comment. However our inclusion criteria focused on the intervention components and not who delivered the intervention. There were insufficient data to examine the impact of specific elements of the lifestyle interventions, such as involvement of a RD. |
| Jeanne Blankenship | American Diabetic Association | Recommendations for future | We agree with the future research suggestions outlined in the AHRQ report, particularly related to testing guidelines for chronic disease. The report | We changed the wording to "Information regarding the benefit of individual components of lifestyle interventions is needed. |

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| | | research and recommended guidelines | notes that many chronic disease guidelines now recommend healthy dietary and exercise behaviors; thus, studies that are designed to assess components that may improve adherence to guidelines would be beneficial. The report also notes that lifestyle interventions need to be standardized. However, we would contend that, just as there is often no one medication or regimen for a particular disease/condition, a single approach does not exist for lifestyle interventions or medical nutrition therapy/nutrition counseling. Nutrition education and counseling needs to be sensitive to the personal needs and preferences of the individual and his/her willingness and ability to make lifestyle changes. | Determination of the benefit of individual components would allow for standardization of these interventions in the literature, improve reporting, and facilitate comparisons across populations." |
| Jeanne Blankenship | American Diabetic Association | Recommendations for future research and recommended guidelines | The American Dietetic Association (ADA) Diabetes Mellitus (DM) Type 1 and 2 Evidence-based Nutrition Practice Guideline for Adults (2008) outlines several key objectives of nutrition protocols for diabetes with the overall objective of providing Medical Nutrition Therapy (MNT) guidelines for DM that assist in the normalization and maintenance of glycemia, lipid profiles, and blood pressure.[12] The Evidence-Based Nutrition Practice Guideline (EBNPG) is based on the synthesis of the best available research and identifies the expected outcomes based on previous research results.[13-16] ADA's method for creating Evidence Based Guidelines is built upon ADA's Evidence Analysis Process. This method collects evidence and follows a series of clearly defined steps. A complete review of literature is implemented using a very strident methodology for assessing and summarizing evidence. Once this process is completed, guidelines are developed and published on ADA's web site. National guidelines, such as ADA Diabetes Type 1 and 2 Evidence-based Nutrition | Thank you for your comment. |

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| | | | Practice Guidelines for Adults (2008), are the standards used by the Centers for Medicare and Medicaid Services (CMS) and many other insurers to define nutrition interventions in clinical practice.[17, 18] | |
| Jeanne Blankenship | American Diabetic Association | Recommendations for future research and recommended guidelines | With the review of 18 published studies, the ADA Diabetes Type 1 and 2 Evidence-based Nutrition Practice Guidelines (EBNPG) for Adults indicates, "Medical nutrition therapy resulted in reductions in HbA1c, ranging from 0.25%-2.9%, depending on the type and duration of diabetes. Multiple encounters and a variety of nutrition therapy interventions were employed. Also reported are improvements in other outcomes, such as lipids, blood pressure, weight management, decreased need for medications and reduced risk for onset and progression of comorbidities."[19] The recommendation of multiple encounters is critical in order to reinforce lifestyle changes, to evaluate and monitor outcomes that indicate the need for changes in nutrition therapy or medication(s), and to determine whether additional medical nutrition therapy encounters are needed. It is unrealistic that one nutrition therapy intervention (or lifestyle intervention or one set of interventions) is expected to last indefinitely without further interventions because there is no end of the active management of chronic diseases. Further, diseases such as type 2 diabetes are progressive; therefore, changes in medical and nutritional therapies are necessary over the course of the disease. | We agree with your comment. We state in the discussion section "There is currently no consensus on optimal behavioral regimens. In addition, it remains unclear which interventions are sustainable over the long term. There was limited success in the achievement of permanent lifestyle changes. Long term change is dependent on a number of factors including patient motivation and compliance. In our review we measured compliance by the number of withdrawals. Overall, there were more withdrawals in the lifestyle group, although this was not statistically significant. A true measure of compliance with lifestyle intervention, however; is complex, particularly when a number of trials rely on self reported data. One of the central objectives of therapeutic lifestyle interventions is to modify and shape healthy lifestyle behaviors long term. Improved measurement and reporting of this outcome would be beneficial for the development of future interventions. |
| Jeanne Blankenship | American Diabetic Association | Recommendations for future research and recommended guidelines | Registered dietitians in the Diabetes Control and Complications Trial (DCCT) described the benefits of an expanded role for RDs, including their close alliance with team members and active involvement in monitoring glucose levels and adjusting insulin dose.20 Three studies by investigators Lemon et al, Kulkarni et al and Franz et al, were completed prior | We planned to do a subgroup analysis looking at the evidence on whether specific components of the interventions, composition of the team, and/or patient characteristics contribute to better outcomes (KQ3). However there were insufficient data to conduct these analyses. |

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| | | | to the publication of ADA's Type 2 DM EBNPG for Adults (2008) and still serve as preliminary data to indicate that the guidelines have the ability to inform the practice of the RD and result in identifiable outcomes.13,15-16 Lemon et.al.16 provided excellent support for improved outcomes in patients for whom evidence-based guides were implemented, including food and meal planning topics, knowledge of potential food/drug interaction, and physical activity. In a study by Kulkarni et al13, RDs administering nutrition practice guidelines with patients who had type 1 diabetes, scored significantly higher with regard to glycemic control goals than did those providing usual care. Similar data were gathered by Franz et al15, who reported that increases in the number of visits by patients and in the amount of total contact time with RDs who followed the practice guidelines, in conjunction with the modified pattern of nutrition care, led to better outcomes than usual care. The correlation between increased attention to glycemic control goals by RDs following practice guidelines and the greater improvement in A1C levels achieved by their patients suggests a potential relationship. Additionally, the National Health and Nutrition Study (1999-2004) for adults with type 2 DM and those without diabetes, the Wolf study, and the LOOK AHEAD studies, while not specifically using the ADA guidelines, did utilize dietary interventions with similar modifications. 21-23 | |
| Jeanne Blankenship | American Diabetic Association | Recommendations for future research and recommended guidelines | Mazze et al24, in a study comparing practice guidelines for nutrition care and basic nutrition care, demonstrated the consequences of a reported outcome measure on cost effectiveness. Fasting plasma glucose, A1C, and costs from the field test on patients with non-insulin dependent diabetes mellitus (NIDDM) were assessed to | Thank you for your comment. The scope of our review did not include cost-effectiveness. |

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| | | | measure relative cost per unit of outcome between options, i.e., practice guidelines for nutrition care versus basic nutrition care. This study showed that the cost ratios were higher in the basic nutrition care group than for the group following practice guidelines for nutrition care. Further, there are several studies to support the cost-effectiveness, cost benefit or economic savings of lifestyle interventions for diabetes prevention. An ADA systematic review explains, “Compared with pharmacotherapy or no intervention, lifestyle interventions for diabetes prevention were cost-effective in terms of cost per quality-adjusted life years gained, based on six cost-effectiveness analyses. Grade I”.25 | |
| Jeanne Blankenship | American Diabetic Association | Recommendations for future research and recommended guidelines | While medical professionals have been involved in efforts to define quality care in terms of practice guidelines, quality care does not stand alone. There is a need for data on the outcomes of effectiveness and costs of treatment. Achieving high quality, cost effective care requires: 1) developing standardized evidence-based nutrition practice guidelines and protocols and 2) evaluating patient-centered services based on a thorough knowledge of patient problems, provider interventions, and the time and cost associated with achieving optimal patient outcomes.26 | Thank you for your comment. The scope of our review did not include cost-effectiveness. |
| Jeanne Blankenship | American Diabetic Association | Recommendations for future research and recommended guidelines | In closing, ADA urges AHRQ to further evaluate this topic through expansion of search terms and a more complete review of research findings beyond RCTs for lifestyle intervention. ADA strongly objects to the use only of this type of research methodology when important data and information can be gathered through other well accepted research methods that may be more practical in certain clinical situations. Often the presence of disease requires intervention that does not afford the opportunity to risk the health | Thank you for your comment and offer of assistance. We will forward it to AHRQ. |

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| | | | and well-being of a individual by placing him or her in a treatment arm of a research study that may result in sub-standard or unknown treatment efficacy. Certainly, human protection often defines the ethical methodology that can be used to conduct clinical research. This warrants consideration in reviewing lifestyle interventions. ADA offers our assistance to AHRQ for further analysis of this topic and can provide research findings and analysis from our Evidence Analysis Library. | |
| Sharon McCauley | American Dietetic Association | Discussion/ conclusion | The American Dietetic Association agrees with the conclusions that comprehensive lifestyle interventions appear to have a position impact on behavioral outcomes including exercise and dietary intake. | Thank you for your comment |
| Sharon McCauley | American Dietetic Association | Discussion/ conclusion | Research needs to continue on outcomes when more than one type of intervention - nutrition education and nutrition counseling, exercise and promoting physical activity, and life style modification - is applied within a single encounter or in sequential encounters by qualified registered dietitians. The qualified registered dietitians through nutrition counseling provides supportive process, characterized by a collaborative counselor-patient relationship, sets priorities, establish goals, and creates individualized action plans that acknowledge and foster responsibility for self-care in treating an existing condition and promote health. It is the qualified registered dietitian's standardized consistency in dietetics practice that must be incorporated within the intervention plans of these four conditions: Type 2 Diabetes, Metabolic Syndrome, Breast Cancer, and Prostate Cancer. | We planned to do a subgroup analysis looking at the evidence on whether specific components of the interventions, composition of the team, and/or patient characteristics contribute to better outcomes (KQ3). However there were insufficient data to conduct these analyses. |
| Sharon McCauley | American Dietetic Association | Discussion/ conclusion | A supportive process, characterized by a collaborative counselor-patient relationship, to set priorities, establish goals, and create individualized action plans that acknowledge and foster | Thank you for your comment. |

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| | | | responsibility for self-care to treat an existing condition and promote health provides standardized consistency in dietetics practice by qualified registered dietitians. | |
| Anonymous | No commercial affiliations | Executive summary | The style of reporting the results does not conform to current standards (see references below).<br>References:<br>1. CONSORT Statement 2010 (CONsolidated Standards of Reporting Trials): http://www.consortstatement.org/consort-statement/.<br>2. Bailar JC III and Mosteller F, Guidelines for statistical reporting in articles for medical journals. Annals Intern. Med., 1988; 108:266-73.<br>3. Gardner MJ and Altman DG, Confidence intervals rather than p values: estimation rather than hypothesis testing. BMJ, 1986; 292:746-50. | The style of the reporting for this review complies with AHRQ guidelines. |
| Anonymous | No commercial affiliations | Results | The actual result (the difference between groups or effect size) is not reported, only whether it was statistically significant or not. While this type of reporting was common in the medical literature in the past, it is no longer acceptable, even in abstracts and executive summaries. Such abbreviated reporting places undue importance on the secondary activity of estimating the random error, while totally omitting the actual primary data, the effect size. The preferred approach is to report the effect size, which allows an assessment of the clinical and practical significance, along with a confidence interval, which allows assessment of the random error. While this information is give correctly in the tables, failure to report effect sizes in the text renders it a waste of time to read, as it is devoid of any meaningful interpretable results. | We have added the effect estimates to the summary tables. |
| Anonymous | No commercial affiliations | Tables | In the tables no units are provided for the mean differences. For the benefit of non-specialists in these fields, some idea of the accepted benchmarks | In the “Description of studies and baseline characteristics or participants” tables, we have added the units in column headings. We also |

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| | | | for normal and diseased conditions should be given for each type of unit. This is particularly important for standardized measures such as BMI and SMD, and for technical measures such as HbA1c and PSA. | added the units in the text as well as the metagraph titles. |
| Anonymous | No commercial affiliations | General | While some of this information is provided in the internal results sections (and some is not), many consumers and even clinicians from other specialties will not read beyond the Executive Summary, particularly if even in summarized form the information is cryptic and opaque and in specialist and methodologist jargon. It is well to remember that consumers pay for this information and their support is necessary for the continuation of these activities. | This is a technical report which is by its nature complicated. We reviewed the entire Executive Summary and removed as much jargon and extraneous information as we felt feasible. |
| Anonymous | None stated | General | Many people will just read the Abstract and Executive Summary, and additional clarity is needed in those sections.<br>See specifics below. | See comment above. |
| Anonymous | None stated | Executive summary | It is not clear why one would require another component to be added to exercise and diet in order to define “lifestyle intervention”. Either exercise or diet alone, or both together, are considered lifestyle interventions. Also, it is not clear whether the studies examined needed to include both exercise and diet. | The decision to require diet, exercise, and at least one other component was made in consultation with AHRQ and CMS. We included the third component because we wanted to assess multifaceted lifestyle interventions that included more than just exercise and diet. |
| Anonymous | None stated | Abstract | The abstract does not define the outcomes prespecified to be examined. Specifically, it does not make clear what are primary and what are secondary outcomes, as it presents all results as if they are equal: morbidity/mortality outcomes (e.g., subsequent events, like strokes), changes in the lifestyle behaviors (e.g., diet and physical activity), and changes in the condition being examined (e.g., changes in physical components of MetSyn). It | These details are included in the executive summary and the full report. The word count limit for the abstracts forces us to make difficult decisions about what to include. We feel the abstract is an acceptable summary of our findings. |

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| | | | would be much clearer if under each topic there were one sentence for primary outcomes, and another for secondary outcomes (and this is indicated). | |
| Anonymous | None stated | Abstact | The objective of the report would be more clearly stated as examining the RCT evidence. | "RCT" was added into the objective of the abstract. |
| Anonymous | None stated | Executive summary | The Key Questions are not written in PICO format (population, intervention, comparator, outcome), so it is not clear what the exact research questions were. Key question #1, for example, would be clearer if it were something like this: Are lifestyle interventions effective in improving morbidity and mortality in people with existing metabolic syndrome or type 2 diabetes, or who are survivors of breast of prostate cancer, compared with usual care or other control group? Such wording would make it clearer that the population being studied has the disease(s) of interest and that primary outcomes were those as stated in the "Study Selection" section. | No change. These key questions were decided a priori after consultation AHRQ and CMS. |
| Anonymous | None stated | Executive summary | The abstract states that meta-analyses were done, so one would expect quantitative results in the abstract and executive summary. It was not clear where quantitative meta-analytic results were in these sections. There were no quantitative results in the Abstract. If there were 6 RCTs in a summary table, for example, do the RR and 95% CI for that row indicate meta-analytically combined estimates? | These details are included in the executive summary and the full report. The word count limit for the abstracts forces us to made difficult decisions about what to include. We feel the abstract is an acceptable summary of our findings. |
| Anonymous | None stated | Executive summary | One would not expect "changes to be sustained following the end of the active intervention." We do not require that situation when we treat medical conditions with medicines, so why would one expect sustained changes after cessation of lifestyle interventions? For example, we treat blood pressure with medications, and do not expect the BP to remain low when the medications are discontinued. | We included studies that had a followup to see whether the effects observed during active intervention were sustained after the cessation of the intervention. |
| Anonym | None stated | Executive | The tables in the executive summary are not very | According to AHRQ's December 10, 2010 |

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| ous | | summary | useful, as the studies are not referenced. | publishing guidelines, the Executive Summary does not need citations as they can be found in the rest of the report. |
| Bruce Wolfe, MD | American Society for Metabolic and Bariatric Surgery (president) | Results | The current draft AHRQ technology assessment identifies 4 randomized controlled trials (RCT), all assessed as having a high risk of bias, meeting inclusion criteria and supporting the conclusion that comprehensive lifestyle interventions are effective in decreasing the risk for developing type 2 diabetes in high risk patients. In contrast, 10 RCT were identified in which comprehensive lifestyle interventions were evaluated in patients with an existing diagnosis of type 2 diabetes. Despite more studies meeting inclusion criteria in this group, evidence for benefit of comprehensive lifestyle interventions on patient oriented outcomes is less clear. A single trial of high risk diabetic patients suggests long-term benefit on microvascular and macrovascular outcomes in diabetic patients. Beyond that, a number of studies reported positive effects for lifestyle interventions on changes in body composition, metabolic variables, physical activity, and dietary intake; however the results were not always statistically significant and were not always sustained. | Appears to be a summary of results. No change. |
| Bruce Wolfe, MD | American Society for Metabolic and Bariatric Surgery (president) | Results | Comprehensive lifestyle interventions included dietary changes, exercise, and at least one other element, such as counseling, stress management, behavior modification, weight loss, smoking cessation, physician care, or risk factor modulation. Remarkably, weight loss was not uniformly accomplished, or even the primary objective of dietary change in diabetic subjects, despite strong evidence that weight loss improves control of hyperglycemia. Weight loss in individuals with type 2 diabetes is known to significantly reduce a number of cardiovascular disease (CVD) risk factors. | We did not require weight loss to be an outcome; we were interested in change in weight and that is what was reported. |

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| | | | Furthermore, reductions in weight significantly decrease premature mortality in diabetic patients. Failure to reliably accomplish sustained weight loss by dietary change is an altogether too common scenario in the treatment of both type 2 diabetes and metabolic syndrome, and it is likely that mandating weight loss as an endpoint would have excluded even the few studies that met inclusion criteria for this review. | |
| Bruce Wolfe, MD | American Society for Metabolic and Bariatric Surgery (president) | Results | Among the list of other mentioned components of comprehensive lifestyle interventions, metabolic surgery is notably absent. The term metabolic surgery provides an acronym for surgical intervention for the purpose of improving metabolic diseases including type 2 diabetes and the metabolic syndrome. Although metabolic surgery's roots derive from bariatric surgery, it represents an evolution of the original focus on weight loss limited to the morbidly obese toward a focus on the metabolic benefits observed in many studies over several decades. A growing body of literature supports the high level of effectiveness accompanying metabolic surgical interventions in type 2 diabetics and patients with metabolic syndrome who do not meet criteria for morbid obesity. While some degree of weight loss usually accompanies metabolic surgery, metabolic benefits (particularly reduced insulin resistance) commonly precede significant degrees of weight loss after several operations, notably gastric bypass, sleeve gastrectomy, and biliopancreatic diversion, suggesting that the mechanisms are at least somewhat independent of a reduction in the degree of obesity. Pair fed and surgical controls in diabetic animal models confirm a likely physiologic mechanism arising from the anatomic changes induced by gut bypass, particularly involving the | Metabolic surgery was beyond the scope of this report. |

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| | | | duodenum, or by undigested food making contact with the distal small intestine (by ileal interposition or malabsorptive bypass). Novel surgical approaches designed to impact hyperglycemic control while minimizing weight loss have been reported with increasing frequency in the world literature. | |
| Morgan Downey | Downey Obesity Report | General | This is a very impressive review of the literature | Thank you for your comment |
| Morgan Downey | Downey Obesity Report | Abstract | I have questions about the abstract, particularly the Conclusions. This section, which is likely to be the most that many people see, seems far rosier than the text or the Results section. I think the limited basis for the Conclusions section should be highlighted | We have revised this sentence. |
| Molly Choate Summers | Finger Relief | General | As the 175 page study does not mention breast self examination, or co morbidities such as carpal tunnel or arthritis, the study should make it clear, early on, and in the Executive summary, that the life style changes were not intended to be comprehensive, nor did the report consider comorbidities such as carpal tunnel syndrome which affect diagnosis stage. One source of information on these comorbidities are patents which are available at USPTO.gov. | We describe all of the components of each lifestyle intervention in the tables. We did not make an assessment of whether they were “comprehensive”. |
| Betty C Jung | NR | General | Overall, this document will be very useful for practitioners involved in developing interventions for addressing these chronic diseases. I like the systematic approach used for gathering and evaluating the studies. Will serve as a good foundation with which to evaluate future interventions in these areas. | Thank you for your comment. |
| Rena Wing PhD | Look AHEAD | Corrections | On page 16 of the report, you incorrectly indicate that Look AHEAD (reference 114) did not have government funding. The Look AHEAD study was supported by the Department of Health and Human | We have changed this to read “government funding with in-kind support from industry.” |

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| | | | Services through cooperative agreements from the NIH. | |
| Rena Wing PhD | Look AHEAD | Corrections | The drop out rate is described on page 28 as higher in ILI than DSE. This is INCORRECT. The flow chart in reference #114 in your report shows that 97.1% of ILI participants and 95.7% of DSE attended the year 1 exam. Data for subsequent years is provided in the Archives paper (Wing, R.R., Arch Intern Med. **170**(17): p. 1566-75.) Thus there is a slightly lower dropout rate in ILI (versus the statement in the report of higher attrition.) Moreover, we feel that it is important to report the absolute differences in retention, not the relative rate – with a sample as large as Look AHEAD and with such high levels of retention, even minor differences reach statistical significance and using relative rate may exaggerate their potential impact. | Thank you for pointing out this error, we have made the correction. However, we believe that relative risk is the appropriate way to report withdrawal and dropout rates. |
| Rena Wing PhD | Look AHEAD | Corrections | A recent publication on the 4 year outcomes of Look AHEAD clearly show—in the largest, longest study to date—that the effects are maintained through at least 4 years (Wing, R.R., Long-term effects of a lifestyle intervention on weight and cardiovascular risk factors in individuals with type 2 diabetes mellitus: four-year results of the Look AHEAD trial. Arch Intern Med. 170(17): p. 1566-75.) Of note, at 4 years, participants in the lifestyle intervention had significantly greater percent weight losses, greater improvements in cardiovascular fitness, and greater improvements in glycemic control, HDL-cholesterol, and systolic blood pressure than the control group. The failure to include this recent publication in the AHRQ report leads to a serious misrepresentation of the benefits of lifestyle intervention for individuals with type 2 diabetes. | This data has been added into the review. At the time of the original literature search, this study had not been published and was therefore not included. |
| Rena Wing PhD | Look AHEAD | Additional data | We have recently published the 4 year results of Look AHEAD (Arch Intern Med, 2010, 170 (17), 1566-75). This manuscript provides data on | Please refer to the previous comment. |

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| | | | changes in weight, fitness, cvd risk factors, and medication use for the intensive lifestyle intervention (ILI) versus the control group (DSE) at years 1, 2, 3, and 4. (See attached.) In addition, we have published the 1 year changes in physical activity from Look AHEAD in the International Journal of Obesity (Jakicic, J.M., et al., Effect of a lifestyle intervention on change in cardiorespiratory fitness in adults with type 2 diabetes: results from the Look AHEAD Study. Int J Obes (Lond), 2009. **33**(3): p. 305-16.) Additional details on the impact of the Look AHEAD intervention on medication use appears in Diabetes Care (Redmon, J.B., et al., Effect of the look AHEAD study intervention on medication use and related cost to treat cardiovascular disease risk factors in individuals with type 2 diabetes. Diabetes Care. **33**(6): p. 1153-8.) These additional publications from Look AHEAD should be added to this report. | |
| Rena Wing PhD | Look AHEAD | Additional data | On pages 16-17 of the report, the Look AHEAD study is not included in the discussion or table of the effects of the lifestyle intervention on body weight. Reference #114 in your report includes data on changes in percent body weight. (Note since the baseline weight of participants is approximately 100 kg, the percent weight loss and the kg weight loss is almost identical in this trial. The absolute weight changes at year 1 are provided in another paper by Wadden (Wadden, T.A., et al., One-year weight losses in the Look AHEAD study: factors associated with success. Obesity (Silver Spring), 2009. **17**(4): p. 713-22.) Specifically, the ILI group lost 8.6 +/- 8.2 kg and DSE lost 0.7 +/- 5.0 kg at 1 year. Percent changes in body weight are provided for year 1-4 in the Archives paper (Wing, R.R., Arch Intern Med. **170**(17): p. 1566-75.) | Data on weight at both 1 and 4 years have been added to the report. |
| Rena | Look AHEAD | Additional | These papers could also be used to add information | We did not report all of the timepoints. In |

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| Wing PhD | | data | about changes in lipids, blood pressure, and glycemic control at years 2, 3, and 4 in Look AHEAD to the previously reported year 1 data. (Wing, R.R., Arch Intern Med. **170**(17): p. 1566-75.) | general, we reported data at baseline, immediate postintervention, and the longest followup timepoint. |
| Rena Wing PhD | Look AHEAD | Additional data | The use of medications for glycemic control, lipids and blood pressure at baseline and year 1 is included in the paper you cite (#114). Additional data for years 2, 3, and 4 are provided in the Archives article (Wing, R.R., Arch Intern Med. **170**(17): p. 1566-75.) See, also, Redmon et al. Diab Care 2010;33:1153-8. | Data were added for both 1 and 4 years. |
| Rena Wing PhD | Look AHEAD | Additional data | The paper by Jakicic et al (Jakicic, J.M., et al., Int J Obes (Lond), 2009. **33**(3): p. 305-16.) provides data on changes in physical activity at year 1 in Look AHEAD. | These data were added to the review. |
| Rena Wing PhD | Look AHEAD | Clarifications | We note, on Table 3, several attributions to Look AHEAD that may not be accurate. The table is titled "Risk of bias assessment for studies of type 2 diabetes." Look AHEAD is recorded as being at risk due to "sequence generation." This is incorrect. The Look AHEAD randomization protocol meets the criteria for having adequate sequence generation (Schultz KF, et al. Empirical evidence of bias. JAMA 1995;273:408-412) because this was done with a computer random number generator in a sequence that was concealed from study staff (https://www.lookaheadtrial.org/public/home.cfm and our design paper in Cont Clin Trials 2003;24:610-628). | Your interpretation of "yes" in the table is incorrect; rather it means there was correct sequence generation. However, we have changed the risk of bias tables to make it clear what is meant. |
| Rena Wing PhD | Look AHEAD | Clarifications | Allocation concealment is listed as "unclear." Look AHEAD allocation was masked to all staff involved with the measurement and assessment of outcomes, as noted in Arch Intern Med 2010;170:1566-1575. Necessarily, no clinical trial of a behavioral intervention can be double-blind; by conducting outcome assessment in a masked | "Masked to all staff" is insufficient to gain low risk of bias rating. Therefore this rating will not be changed. |

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| | | | manner, Look AHEAD meets the standard for allocation concealment. | |
| Rena Wing PhD | Look AHEAD | Clarifications | The blinding of self-reported outcomes for Look AHEAD is reported as "unclear." These were recorded by staff persons who were masked to intervention assignment, as noted in the above reference. | Staff members were only reported as being blinded to the objective outcomes. This is insufficient to receive a low risk of bias rating for self-reported outcomes. |
| Rena Wing PhD | Look AHEAD | Clarifications | Look AHEAD is listed as having "incomplete outcome data." This may be a reference to the ongoing status of Look AHEAD: data on its primary outcomes related to CVD events have not been reported. However, Look AHEAD has a remarkable retention rate (93-94% at 4 years and reported in the 2010 Arch Intern Med article, so that the completion rates of follow-up and data collection are superb. | Your interpretation of "yes" in the table is incorrect; rather it means there was correct sequence generation. However, we have changed the risk of bias tables to make it clear what is meant. |
| Rena Wing PhD | Look AHEAD | Clarifications | Look AHEAD is reported as being "unclear" with respect to "selective outcome reporting." Look AHEAD publications are guided by its protocol and publication process and reporting is thus "pre-specified." The timing of the reporting of outcomes has been defined to protect the integrity of the trial with respect to its primary outcomes. | We have changed our assessment from "unclear" to "low risk of bias". |
| Rena Wing PhD | Look AHEAD | Clarifications | Look AHEAD is listed as having a "baseline imbalance." This is incorrect. There are no meaningful differences in any baseline characteristic between intervention groups, as is expected from random allocation and a sample size greater than 5,000. None of the Look AHEAD publications describe any imbalances of any consequence. Based on the above points, we respectfully argue that Look AHEAD has very low overall risk of bias and should be listed as such. | Your interpretation of "yes" in the table is incorrect; rather it means there was correct sequence generation. However, we have changed the risk of bias tables to make it clear what is meant. |
| Rena Wing PhD | Look AHEAD | Clarifications | For the diet component, the table should state:<br>▪ Minimum wt loss of ≥ 7% in 1st yr, encouraged wt loss of ≥ 10%<br>▪ Caloric restriction, portion control, meal | We have incorporated these changes. |

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| | | | replacements, increased fruit and vegetable intake, lower fat diet<br>▪ Toolbox options for sub-optimal weight loss, including: written behavioral contracts; additional funds to promote adherence to behavioral goals (e.g, gym membership, cooking classes, pre-packaged meals); weight loss medication orlistat. | |
| Rena Wing PhD | Look AHEAD | Clarifications | For the Counseling or other Components section, the table should state:<br>▪ Group and individual behavioral program (with curriculum similar to DPP) delivered by lifestyle counselor<br>▪ Group counseling done in 3 phases; 3 visits/mo. for mo. 1-6; 2 visits/mo. for mo. 7-12; intermittent group sessions thereafter (typically 6-8 wk session offered 2-3 times/yr).<br>▪ One individual counseling visit/mo provided throughout the study by lifestyle counselor. | Suggested changes have been incorporated. |
| Rena Wing PhD | Look AHEAD | General | Thus in conclusion, we recognize that writing this report was an ambitious project. However, there are serious errors of interpretation and omission of key articles and data that seriously affect the conclusions that are derived. We implore the writers of the report to correct these errors and reconsider their conclusions before actual publication of this report. | We carefully reviewed all of your comments and suggestions and have made any necessary changes. |
| Mark S. McIntosh MD, MPH | | General | While the Assessment takes an important first step by evaluating lifestyle intervention effectiveness, I am concerned that the scope of the investigation was not sufficient to provide conclusive or, in many respects, even useful answers to the “Key Questions”. How can such important questions be answered with evidence from only 20 randomized controlled trials (RCTs), particularly where substantial additional evidence exists, but has not | The decision to include RCTs was made a priori in consultation with AHRQ and CMS This is because RCTs are considered the highest level of evidence to evaluate the effectiveness of an intervention. |

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| | | | been considered? I find it surprising that, although 802 lifestyle intervention citations were identified, after accounting for duplicates, the Assessment was nevertheless limited to just the 20 unique RCTs. | |
| Mark S. McIntosh MD, MPH | | General | This leads me to conclude that the study inclusion criteria were overly strict and that, as a result, the Assessment simply failed to include the full spectrum of the existing evidence supporting lifestyle interventions. For example, in light of the overwhelming public health crisis posed by metabolic syndrome and other chronic diseases, I was disappointed that the Assessment did not consider any non-RCT evidence. The decision to exclude non-RCT evidence across-the-board was, in my view, a poor one, as even the Assessment recognized that additional types of studies may be necessary and entirely appropriate in attempting to understand, for instance, the comparative benefits of intervention components. | The decision to include RCTs was made a priori in consultation with AHRQ and CMS. This is because RCTs are considered the highest level of evidence to evaluate the effectiveness of an intervention. We have indicated in the discussion and future research sections that well conducted observational studies may be appropriate to provide evidence for some outcomes. |
| Mark S. McIntosh MD, MPH | | General | Additionally, it appears that the Assessment's definition of "intervention" was too rigid. By requiring a diet component, an exercise component, and some third component in one "intervention," the Assessment both eliminated many useful studies and was unable to assess the effects of individual components of lifestyle intervention programs. As a result, the Assessment missed an important opportunity to evaluate individual components in isolation in order to determine if simpler and less costly intervention components are effective. | We were interested in examining the effect of multifaceted lifestyle interventions. The decision to require interventions to have exercise, diet, and at least one additional component was made in consultation with AHRQ and CMS. |
| Mark S. McIntosh MD, MPH | | General | Moreover, consideration of the evidence that focuses on assessing the effectiveness of individual components of lifestyle intervention programs is likely necessary to address the unanswered Key Question as to whether the lifestyle intervention programs are generalizable or relevant to the Medicare population. An aged population may be | The DPP study included participants up to 85 years of age at baseline. There was no comment regarding their inability or difficulty participating in the multifaceted lifestyle interventions.<br><br>There were insufficient data to evaluate the |

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| | | | less capable of multi-dimensional interventions and may, for instance, be more dependent on diet and nutritional elements of a program, at least initially. Evaluation of specific lifestyle intervention components in isolation could help to identify which component interventions best address different subpopulations and their specific needs. This in turn would encourage flexibility in establishing insurance coverage for programs and program components. | specific components of the lifestyle interventions included in our review. |
| Mark S. McIntosh MD, MPH | | General | Results from a multicenter clinical study for which I was a Principal Investigator should be considered as part of the Assessment. The study was sponsored by Metagenics, Inc. Although it has not yet been published, the study demonstrated that diet modification alone significantly reduced cardiometabolic symptoms in adults with metabolic syndrome. The study consisted of a 12-week, randomized, controlled trial investigating the efficacy of a medical food as part of a diet modification program. At the end of the study, all participants had reduced waist circumference, blood pressure, and plasma triglycerides. Participants in the medical food arm additionally had decreased levels of LDL-C, non-HDL-C, apolipoprotein B, and homocysteine. Over 44% of participants in the medical food arm and almost 32% of participants in the control arm no longer met criteria for diagnosis of metabolic syndrome at the end of the study.<br>Equally as important were the observations that I made about the impact of environmental cues on intervention effectiveness. Study participants were motivated to engage in a long-term weight management program, although they faced many obstacles to success. Through my interactions with patients, several trends contributing to the outcome of the intervention became apparent: | Thank you for the information on your study. According to the information you have provided, the study would not have met our inclusion criteria. |

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| | | | - Busy schedules and long working hours require effective time management skills to accommodate preparation of healthy meals and regular exercise programs.<br>- Patient education about healthy, affordable food selection and preparation addresses resource limitations, while allowing the participant to be in control of their meal planning.<br>- Supportive home and work environments are keys to long-term success.<br>- Psychological counseling about lifestyle modification and stress reduction are important for sustained success.<br>Many people's poor eating habits are mood driven and socially reinforced, and require ongoing support to effect permanent change.<br>Given the vast array of potential obstacles that may limit the success of lifestyle intervention programs, the value of personalized lifestyle interventions along with clinical monitoring is clear and contributes to long-term success. This, again, underscores that the Assessment should take a broader approach to evaluating the effectiveness of lifestyle intervention programs by examining components in isolation. I recommend that, in light of the serious issues presented by the current draft Assessment, that a new analysis be undertaken with a new set of study selection criteria. If the intention is to evaluate all available data in order to make sound recommendations to policy makers, then the task should be undertaken in a manner that will, in fact, consider all of the available and useful information. | |
| Deanna Minich, | Metagenics, Inc | General | We agree with the Technology Assessment that chronic diseases, including type 2 diabetes and | The decision to require a postintervention followup period was made in consultation with |

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| Ph.D. | | | metabolic syndrome, pose an overwhelming public health crisis warranting urgent and targeted actions. The Technology Assessment's methods for selection and review of studies demonstrating the effectiveness of lifestyle interventions poorly realized the TA's commendable objectives to identify and synthesize the "available" evidence. The criteria used for the selection of studies were excessively stringent and the definition of intervention was too narrow, resulting in consideration of only 20 randomized controlled trials (RCTs) and a failure to consider most of the "available" evidence. The requirement for post-intervention follow-up as part of RCTs precluded the consideration and evaluation of the effectiveness of lifestyle interventions as reflected in multiple well-designed studies. Clinical research from Metagenics demonstrates that a physician-supervised lifestyle intervention program was effective for managing metabolic syndrome and reducing cardiovascular disease risk factors in adults up to 80 years of age, and should be included in the AHRQ analysis. Unpublished data from Metagenics indicate the long-term effectiveness for up to 2 years of a lifestyle intervention program that includes a physician supervised, active maintenance phase for managing metabolic syndrome. Assessment of individual components of lifestyle interventions should be included in the AHRQ report in order to address a key question raised in the Technology Assessment but left unaddressed because of the methods selected. Clinical research from Metagenics suggests that the dietary component of a lifestyle intervention by itself has a significant impact on modifying cardiometabolic risk factors in metabolic syndrome patients. | AHRQ and CMS We were interested in seeing whether outcomes were sustained either a minimum of 12 months or after cessation of an active intervention. |
| Deanna | Metagenics, | General | The impact of type 2 diabetes, metabolic syndrome, | The scope of the review including study |

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| Minich, Ph.D. | Inc. | | and cancer to our society is severe, and the toll it places on our health systems, especially Medicare, should not be underestimated. In light of the information about these chronic conditions summarized below, included in the Technology Assessment “Lifestyle Interventions for Four Conditions: Type 2 Diabetes, Metabolic Syndrome, Breast Cancer, and Prostate Cancer? (the TA, report, or analysis) itself and supplemented by additional sources, we believe that the TA’s methodology should have been expanded to address the reality more fully. | designs to include, and definition and duration of “lifestyle intervention” were decided a priori in consultation with AHRQ and CMS. |
| Deanna Minich, Ph.D. | Metagenics, Inc. | General | Metabolic syndrome presents another alarming health concern. The TA acknowledges that metabolic syndrome directly promotes the development of cardiovascular disease and type 2 diabetes. Moreover, the National Heart Lung and Blood Institute reports that almost 25 percent of adults in the United States have metabolic syndrome, and the number continues to grow. [6] It is predicted that “metabolic syndrome may overtake smoking as the leading risk factor for heart disease.” [7] A study published in 2002 states that the prevalence of metabolic syndrome is 43.5 percent for adults ages 60-70, and 42.0 percent for those age 70 and older. [8] Another recently published study conducted in 2003-2005 concluded that the average annual health utilization costs for an individual with metabolic syndrome as compared to an individual without metabolic syndrome differed by a magnitude of 1.6. [9] Accordingly, for each additional risk factor, costs rise an average of 24 percent. [10] | Comment noted. |
| Deanna Minich, Ph.D. | Metagenics, Inc. | General | Breast cancer and prostate cancer also pose significant health concerns, as the TA acknowledges. The National Cancer Institute estimates that in 2010, there were 209,060 new | Comment noted. |

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| | | | diagnoses of breast cancer and 40,230 deaths, as well as 217,730 new diagnoses of prostate cancer and 32,050 deaths. [11] Furthermore, the National Cancer Institute reports that from 2003-2007, the median age at diagnosis was 61 years for breast cancer, and 67 years of age for prostate cancer clearly impacting the Medicare population. [12] | |
| Deanna Minich, Ph.D. | Metagenics, Inc. | Methods | We commend the Agency for Healthcare Research and Quality (AHRQ) for commissioning the Technology Assessment "Lifestyle Interventions for Four Conditions: Type 2 Diabetes, Metabolic Syndrome, Breast Cancer, and Prostate Cancer" (the TA, report, or analysis) because it reflects an appreciation of the enormous public health threats posed by diabetes and metabolic syndrome. The TA authors are clearly aware that "type 2 diabetes is a major cause of morbidity and mortality", and that metabolic syndrome, affecting more than 25% of adults in the US, "directly promote[s] the development of CVD and type 2 diabetes". Unfortunately, we are concerned that the methods employed in the TA do not accord with the urgency of the public health crises acknowledged in the TA. Given the prevalence of type 2 diabetes and metabolic syndrome in the United States, the TA did not realize its stated objective to consider all of the "available" evidence related to these pressing public health crises. One of the "key" questions referenced in the draft report broadly asks "what is the evidence for the effectiveness of lifestyle interventions ?"[13] It does not ask the narrower question of what "RCT-based evidence" exists. Similarly, in framing its objective, the draft report broadly states that the "objective" was to identify and synthesize the available evidence regarding the effect of lifestyle interventions?. [14] | The key questions were developed in consultation with AHRQ and CMS. While it is true that the key questions are broad, a detailed description of the inclusion criteria can be found in the methods section of the executive summary, the main report, and Appendix B.<br><br>We have restated the objective in the abstract to specify that we only looked for RCTs. |
| Deanna | Metagenics, | Methods | Despite these broad statements about the nature | The scope of the review including study |

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| Minich, Ph.D. | Inc. | | and scope of the TA, the criteria for study inclusion in the AHRQ analysis were so stringent that only a fraction of the "available" evidence was ultimately considered.<br>As the draft TA states, the "filters" used to eliminate "available" evidence meant that only "20 unique RCTs" were selected from among the many studies performed and reflected in more than 1,287 citations. [15] While we understand the rigorous standards set forth by the authors, the exclusion of a wide array of available studies prevented a fair evaluation of the "available" evidence in a manner reflective of the urgency of the health care crises and the urgent needs of the policy, medical, and provider communities. The circumstances call for a wider perspective. As the prior AHRQ (formerly the Agency for Health Care Policy and Research) Administrator John Eisenberg, M.D., said:<br>"Those who conduct technology assessments should be as innovative in their evaluations as the technologies themselves. There is little argument that the randomized clinical trial is an accepted high standard for testing effectiveness under ideal circumstances, but it may not be the best way to evaluate all the interventions and technologies that decisions makers are considering." [16] | designs to include, and definition and duration of "lifestyle intervention" were decided a priori in consultation with AHRQ and CMS. |
| Deanna Minich, PhD. | Metagenics, Inc. | Methods | Although we appreciate the value of RCTs, the exclusion of non-RCT evidence is inconsistent with the objectives of the report and the TA itself. As the report states: "[p]roviding long-term comparative data or studies comparing an active treatment with an active control may not be feasible. As such, observational studies are needed to provide data on patients using different interventions over several years to determine the comparative benefits of these interventions." [17] Later, the report acknowledges that "evidence from retrospective | See previous comment |

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| | | | chart reviews and observational studies suggests that reductions in weight significantly decrease premature mortality in diabetic patients." [18]<br>Despite these acknowledgements, the TA excludes from consideration anything other than a small subset of RCTs. Although the fact that certain evidence was not obtained in an RCT bears on the strength of the evidence, non-RCT evidence must be considered if the stated objective is to evaluate and synthesize all of the "available" evidence. | |
| Deanna Minich, PhD. | Metagenics, Inc. | Methods | Significantly, this report is to be provided to the Centers for Medicare and Medicaid Services (CMS) and the MedCAC for possible consideration in the development of coverage policy. As AHRQ is aware, it is common for CMS and, indeed, all payors to provide coverage where there are no RCTs that support coverage. For instance, under Part B, a hierarchy of evidence may support coverage. Specifically, local coverage determinations should be based on, in order of preference:<br>Published authoritative evidence derived from definitive randomized clinical trials or other definitive studies,<br>And general acceptance by the medical community (standard of practice), as supported by sound medical evidence based on:<br>- Scientific data or research studies published in peer-reviewed medical journals;<br>- Consensus of expert medical opinion (i.e., recognized authorities in the field); or<br>- Medical opinion derived from consultations with medical associations or other health care experts. [19]<br><br>Accordingly, although we understand the strict approach taken by the authors, we are concerned that if this report is used as the basis for a CMS or | See previous comment |

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| | | | MedCAC determination, the strict approach taken would effectively create a new, higher standard for coverage than that which is provided by law and supports coverage for many items and services under Medicare and other health care insurance systems. | |
| Deanna Minich, PhD | Metagenics, Inc. | Methods | We are also very concerned that the term "intervention" was narrowly defined to require only those interventions that included exercise, diet, and at least one other component. This extremely narrow definition of an intervention unnecessarily excluded much of the "available" evidence and does not comport with the clinical dimension of the underlying public health challenge. In addition, the diversity of "third components" among the selected studies prevents direct comparison, and provides sub-optimal information about the common features of an effective lifestyle intervention program. | The scope of the review including study designs to include, and definition and duration of "lifestyle intervention" were decided a priori in consultation with AHRQ and CMS. |
| Deanna Minich, PhD. | Metagenics, Inc. | Methods | Further, the TA's decision to exclude intervention studies that do not have at least three elements is inconsistent with the TA's own observation that it is important to address the contribution that individual components of a particular lifestyle intervention make to overall effectiveness. As the report concludes, "[i]n particular, specific information on optimal exercise and dietary interventions is needed." [20] Because of the TA's narrow definition of an intervention (which required the presence of at least three components), the TA did not assess the effects of individual program components. In other words, the methodology of the report itself prevented this question (Key Question 3, a specific objective of the TA) from being addressed. As a policy matter, we should focus on individual components in an effort to determine if less extensive (and thereby less costly) interventions will be effective. | We were interested in assessing multifaceted lifestyle interventions that included more than just exercise and diet. The definition and duration of "lifestyle intervention" were decided a priori in consultation with AHRQ and CMS. |

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| Deanna Minich, PhD. | Metagenics, Inc. | Methods | We respectfully disagree with the decision to disregard even RCTs, if they had no post-intervention follow-up of a minimum of 6 months. We do not believe that a review of the "available" evidence should exclude RCTs, properly conducted, because of the absence of this one selection criterion. Although post-intervention follow-up data are important as a part of the "available" evidence, those data are not critical to a determination of the effectiveness of the treatment itself, which is the central issue in the stated objective. The intervention period alone provides an ample basis for determining the effectiveness of the intervention. Beyond that, we believe that the post-intervention follow-up criterion reflects, ultimately, an unreasonable bias in the TA itself. It appears to be based on the assumption that lifestyle interventions can only be deemed "effective" when the interventions sustain results for a year or more after the intervention has ended, without the benefit of any subsequent intervention, support, or maintenance. In our view, this is an unreasonably rigorous standard, the application of which would increase the likelihood that the incidence of diabetes and metabolism syndrome will continue to increase. | We agree and that is why we made a post hoc decision to include studies that were at least one year in duration but had no postintervention followup. We stated this in the methods section of our executive summary as well as the study selection section in our methods chapter. |
| Deanna Minich, PhD. | Metagenics, Inc. | Methods | The notion that interventions must be evaluated on the basis of their effectiveness a year or more after they have ended ignores the fact that lifestyle interventions are largely behavioral modification programs, and learning or breaking habits is a complex phenomenon. [21] It may be that some or even a majority of patients may not be able to maintain the gains secured from lifestyle interventions for long periods after those interventions have ended without some measure of on-going support. A need for maintenance or other on-going support would not render a program | As noted above, we made the post hoc decision to include long-term studies that had no postintervention followup. We also included studies that had long-term maintenance of intervention and/or followup. This enabled us to assess the impact of maintenance or other ongoing support in sustaining behavior changes and/or results. |

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| | | | ineffective. It would simply mean that on-going support should be an element in this type of program, with provisions for coverage. We see no basis to exclude otherwise valid data from a review of the “available” evidence simply because it does not include a post-intervention period.<br><br>In fact, the TA itself recognizes that it would be inappropriate to refuse consideration of all studies that do not have a post-intervention follow-up period of analysis. The report’s authors acknowledge making “a post hoc modification to include RCTs in which the duration of the lifestyle intervention was at least 1 year but without a 6 month postintervention follow-up.” [23] The narrowness of this exception is not justified, in our view. For instance, if a study of a specific intervention demonstrates greater impact from a 12 week intervention than a different intervention undertaken for a 1 year period, why would we exclude the 12 week study, such that it is not even considered? We appreciate that the 1 year study will provide some data regarding a longer period than the 12 week study, but, by the same token, the 12 week intervention may suggest a more promising approach than the 1 year study. Both should be considered. The purpose of a metaanalysis is to consider the “available” evidence, weigh that evidence, and come to a judgment based on it.<br>Given the enormous burden of type 2 diabetes, metabolic syndrome, and cancer on the health-care system, and the potential benefits derived from the widespread practice of lifestyle medicine, all well-designed lifestyle intervention studies should be considered. When the task of assessing effectiveness of interventions is aligned with the urgency of the situation, it is clear that some studies | |

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| | | | were excluded unnecessarily.<br>The importance of evaluating the effectiveness of lifestyle intervention programs is one that cannot be overestimated. The urgency of the current public health crisis makes it imperative to produce a useful assessment in a timely manner. In light of the variety of clinical research studies in the area of lifestyle medicine, we believe that the stated objective of the report can only be accomplished by a meta-analysis that considers the available data. | |
| Deanna Minich, PhD. | Metagenics, Inc. | Results | Analysis of well-designed studies that did not include post-intervention follow-up would yield a more comprehensive assessment of lifestyle intervention programs. For instance, one of the lifestyle intervention studies excluded due to absence of post-intervention follow-up was the study reported in Lerman et al., 2008 [ref 20]. This study was a 12-week, randomized, controlled trial in overweight and obese men and women aged 25 to 80 with metabolic syndrome. Importantly, it included Medicare beneficiary subjects. The goal of this study was to investigate whether a phytochemical-enriched diet would improve cardiometabolic risk factors as part of a physician-supervised lifestyle intervention; thus it would provide data about specific interventions as called for by Key Question 3.<br><br>The results of the study demonstrated that all study participants benefitted from a lifestyle intervention that included modification of exercise and diet. At 12 weeks, subjects in both study arms lost an average of 13 lbs and had significant reductions in mean waist circumferences. Additionally, subjects in the treatment arm experienced improvements that were significantly different from baseline and from control for measures of total cholesterol, triglycerides (TG), | The scope of the review including definition and duration of “lifestyle intervention” were decided a priori in consultation with AHRQ and CMS. This study did not meet our inclusion criteria. |

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| | | | and non-high-density lipoprotein (non-HDL). Significant improvements within the treatment arm were observed for blood pressure, HDL, low-density lipoprotein (LDL), apolipoprotein (apo) B, fasting insulin, and glycosylated hemoglobin (HbA1c). The calculated Framingham 10-year CVD risk score decreased 5.7% in the treatment arm and 2.9% in the control arm. At the end of the study, 43% of the subjects in the treatment arm and 22% of the subjects in the control arm no longer met criteria for metabolic syndrome. In a sub-analysis of high-risk individuals with metabolic syndrome and elevated LDL from the same study, the investigators observed that significant benefit was derived from lifestyle intervention as measured by reductions in risk factors for CVD (LDL, total cholesterol, non-HDL, apoB, homocysteine, and LDL/HDL particle number). [24] These results demonstrate a profound impact of lifestyle intervention on the reduction of cardiovascular risk factors. The study lends support to the effectiveness of lifestyle medicine interventions, and should be considered for inclusion in the AHRQ analysis. | |
| Deanna Minich, Ph.D. | Metagenics, Inc. | Results | Additional research from our group is consistent with previously described results supporting the effectiveness of lifestyle change interventions. Metagenics developed a 12-week, physician-based therapeutic lifestyle change program, called FirstLine Therapy (FLT), which includes diet modification, aerobic exercise, stress reduction, and diet counseling. While randomized, controlled, clinical studies have not been performed on this program, we have collected data (unpublished) indicating the long-term effectiveness of this lifestyle intervention program. In a 12-month, open-label study without a control arm, effectiveness of FLT on cardiometabolic risk factors was examined in 8 | Thank you for your suggestion however this study does not meet our inclusion criteria. |

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| | | | participants ages 21 to 75 with metabolic syndrome. After completion of the 12-week intervention, patients continued on a maintenance program, under supervision of a physician. Clinical laboratory tests were performed on blood samples taken every three months. Results demonstrated that triglycerides, fasting serum insulin, and very low-density lipoprotein (VLDL) levels were significantly reduced at 3 months and throughout the duration of the study. At the end of the study, 7 out of 8 TG levels were in the normal range. Fasting serum glucose levels trended toward a reduction over the 12 month study, although values at all time points were not significantly different from baseline. In our view, these data underscore the importance of including a physician-supervised maintenance program following the lifestyle intervention for long-term effectiveness. In several clinics using the FLT program nationwide, retrospective chart reviews on patients aged 22 to 77 receiving the FLT lifestyle intervention for over 2 years have been performed. Analyses of 38 patient charts revealed that patients using the FLT program experienced significant improvements in the first year in body weight, BMI, blood pressure, total cholesterol, LDL, and HDL. Patients in the second year retained significant improvements in body weight, BMI, and HDL. Results were variable for other clinical outcomes, although trends were observed for improvements in TG, fasting serum glucose, and HbA1c levels. Findings from these chart reviews support the longterm effectiveness of a comprehensive, physician-supervised, lifestyle medicine intervention to clinically manage metabolic syndrome.<br>Results from our research demonstrate that lifestyle intervention is effective for reducing risk factors for type 2 diabetes and CVD in patients with metabolic | |

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| | | | syndrome. Statistically significant effects of the interventions on body composition and metabolic variables align with the secondary outcomes established in the AHRQ analysis, and results from our studies are consistent with those included in the AHRQ report. Furthermore, as noted before, our studies included participants up to 80 years old, indicating the applicability of this lifestyle intervention to the Medicare population. | |
| Deanna Minich, PhD. | Metagenics, Inc. | General | As we discussed above and as the report itself states, an important issue to address is what contribution individual components of a particular lifestyle intervention have on overall effectiveness. Unfortunately, the scope of study selection criteria did not allow for assessment of the effects of individual program components, so this question (Key Question 3) remains unaddressed in the draft report. In addition to data regarding effects of specific program components, information regarding optimal exercise and dietary interventions also will be important for determining the best practice for lifestyle interventions, as was acknowledged in the report's recommendations for future research.<br>A recently completed clinical trial investigating the effects of diet on cardiometabolic risk factors illuminates the importance of considering single components of lifestyle intervention. Not yet published, a 12-week, multicenter, randomized, controlled trial in women ages 20 to 75 with metabolic syndrome and hypercholesterolemia (n=89) was conducted to examine the effects of diet only (low-glycemic-load, Mediterranean-style diet ? phytochemical-enriched medical food), without any exercise component. At study conclusion, reductions from baseline in waist circumference ($P < 0.001$), systolic and diastolic blood pressure ($P < 0.001$) and plasma triglycerides ($P < 0.0001$) | We were interested in assessing the effectiveness of multifaceted lifestyle interventions. The decision to require exercise, diet and at least one more component was made in consultation AHRQ and CMS. |

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| | | | occurred in all subjects with no differences between arms. However, plasma LDL, non-HDL, total cholesterol, apoB, and apo B/apo A1 were further reduced in the intervention arm only ($P < 0.05$), indicating that the medical food had significant effect in altering lipoprotein metabolism. The intervention arm also experienced a reduction in plasma homocysteine ($P < 0.01$) compared to the control arm. These results support the effectiveness of diet modification and nutrition counseling for improving cardiometabolic risk factors. | |
| Deanna Minich, PhD. | Metagenics, Inc. | General | We commend the AHRQ and the authors of the TA for their recognition of the health care crisis posed by diabetes and metabolic syndrome and the pressing need for a meta-analysis of the available evidence. We believe, unfortunately, the TA does not achieve its objective. We urge the authors to revise the report in light of the significant concerns and the important suggestions that we have offered. | See previous comments. |
| David M. Nathan, M.D. | DPP | Results | The meta-analysis that you have undertaken is daunting and we commend EPC for approaching such a complex set of diverse studies to arrive at evidence-based conclusions. | Thank you for your comment |
| David M. Nathan, M.D. | DPP | General | However, many of the important details that characterize the different studies, and our study in particular, have been lost, making the description of the combined study results less than the sum of the total. The relative size and duration of studies, differences in study cohorts, and other important features of the individual studies that are particularly relevant to the application of interventions in the US are often lost in these types of summary analyses. In reviewing the AHRQ report, we feel that we should be as critical of the quality of the reporting as the authors were in reviewing the studies. We have discovered numerous inaccuracies in the descriptions of the studies and their results that | Any inaccuracies in the descriptions of studies and their results have been corrected. |

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| | | | must be corrected. | |
| David M. Nathan, M.D. | DPP | Population | One of the most glaring issues is the description of diabetes prevention studies under the rubric of "Metabolic Syndrome". The report describes in detail the origin and elements of the metabolic syndrome (introduction, page 3), but neglects to note that the majority of the studies cited did not aim to recruit subjects with metabolic syndrome. For example, the eligible participants in the DPP, again the largest of the clinical trials by far, were recruited as being at high risk to develop diabetes on the basis of having impaired glucose tolerance (IGT) and elevated fasting glucose levels and being overweight. Only 53% of them coincidently had metabolic syndrome, as reported by our group (Orchard T et al- reference 169 in the AHRQ report). Similarly, most of the other studies in the "Metabolic Syndrome" category recruited patients with IGT and/or increased fasting glucose levels. Subjects were, in general, not selected on the basis of having metabolic syndrome by any of the current definitions. The apparent failure to recognize or understand the populations being studied results in questions and conclusions that are not accurate, for example: "KQ1. What is the evidence of the effectiveness of lifestyle interventions for metabolic syndrome?" Oddly, the differences between metabolic syndrome and IGT are briefly mentioned, for the first time, in the discussion (page 70) suggesting that different authors wrote different sections of the report and didn't coordinate their efforts. The statement that "patients with metabolic syndrome are at higher risk of progression to type 2 diabetes than those diagnosed with IGT" (page 70) is unreferenced, simplistic and not very helpful. | The decision to list metabolic syndrome in the key questions was made in consultation with the Centers for Medicare and Medicaid Services (CMS) and AHRQ. Due the evolving definition of metabolic syndrome as well as the debate regarding its ability to predict CVD and type 2 diabetes over abnormal blood glucose levels alone, we created an operational definition. Our operational definition of metabolic syndrome included metabolic syndrome, insulin resistance, prediabetes, impaired glucose tolerance, syndrome X, dysmetabolic syndrome X, and Reaven syndrome.<br><br>Comments have been included in the introduction and discussion to address this controversy. |
| David M. Nathan, | DPP | Risk of bias | The "high risk of bias" that has been assigned to the DPP was predicated, at least in part, on our | Based on the additional information provided by the authors, we have reassessed our |

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| M.D. | | | apparent failure to describe the method of randomization, conceal allocation, and blind assessors to treatment allocation. (The AHRQ authors recognize that complete double-blinding is problematic- in fact, practically impossible- in studies that include lifestyle intervention). However, randomization was described in our design paper and in our on-line protocol that is referenced repeatedly in our publications. For example, in the design paper (The Diabetes Prevention Program Research Group. The Diabetes Prevention Program: Design and methods for a clinical trial in the prevention of type 2 diabetes. *Diabetes Care*. 1999 Apr;22(4):623-34) we note: "To ensure balance among the three treatment groups with respect to anticipated differences in the participant populations and possible differences in participant management, adaptive randomization is stratified by clinical center. An adaptive randomization procedure provides a high probability of balance in treatment assignments and is unpredictable by adjusting the treatment group allocation probabilities according to the actual imbalance in the numbers of participants assigned to the groups." The online DPP protocol (http://www.bsc.gwu.edu/dpp/PROTOCOL.PDF, Chapter 5.4.2 Randomization Method) describes the randomization method in further detail: "There are several alternative methods to assign the participants randomly within clinical center (e.g., simple randomization or permuted block designs). The urn method of randomization provides a high probability of balance in treatment assignments, is unpredictable in unmasked studies, and allows an explicit randomization analysis to be conducted with relative ease (Wei and Lachin, 1988). For these reasons, the urn method will be used to randomly | conclusions regarding several of the domains included in the risk of bias tool.<br><br>For blinding, we gave studies a "low" risk of bias if there was blinding of study participants to the hypothesis and blinding of those involved in outcome assessment and data analysis to the treatment allocation |

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| | | | assign participants to the three treatment groups. A sequence of randomization numbers within a clinical center will be constructed of the form XXYZZZ, where XX is the clinical center number, Y is a number that indicates assignment to either the intensive lifestyle intervention or pharmacological treatment, and ZZZ is a three digit sequence number within each XXY combination. The DPP Coordinating Center will prepare the master randomization list with assignments to the three treatment groups within a clinical center using the standard urn design. The sequence of pharmacological randomization numbers within a clinical center with the specific pharmacological treatment assignment (i.e., metformin or placebo) will be forwarded, in confidence, to the drug distribution center for drug labeling and distribution. Pharmacological treatment assignment to the sequence of pharmacological randomization numbers will be known only by the staff of the DPP Coordinating Center and the drug distribution center."<br><br>While it is true that DPP was not completely blind (it's impossible to blind participants or investigators to the lifestyle intervention), the main outcomes assessments were not subject to investigator bias. For example, all major outcome measurements were performed in central laboratories that were masked to randomized treatment group. | |
| David M. Nathan, M.D. | DPP | Population | In several sections (KQ2-generalizability, ES-14, page 62), the age range of the prevention studies is noted to be up to age 75. In the DPP, there was no upper age limit and we purposefully aimed to recruit at least 20% of our study population to be older than age 60. DPP had participants who were as old as 85 at baseline (reported by Crandall J, reference | This was adjusted in the review. |

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| | | | 165 in your report). | |
| David M. Nathan, M.D. | DPP | Results | The report states in at least two places (page 37 and 45) that we did not report use of diabetic medications. However, we did report the use of diabetic medications in our recent 10-year follow-up report (DPP Research Group, Lancet. Reference 166 in your report, figure 5). | We have added this information. |
| David M. Nathan, M.D. | DPP | Results | The report notes in several sections an apparent distinction between metabolic variables and outcomes and the diagnosis of diabetes and appears to focus on fasting glucose levels and HbA1c values, ignoring the oral glucose tolerance testing that was used in many of the studies, including ours. Since the diabetic state is currently recognized to include abnormalities in all three measurements of dysglycemia, each of which may carry different risk implications for long-term complications, the failure to note the results of oral glucose tolerance testing seems odd. | In light of the multitude of variables that could be reported, we made an a priori decision to report a representative sample of measures of glucose control. |
| David M. Nathan, M.D. | DPP | Results | Table 4 (page 48) attempts to include a lot of data describing the baseline characteristics of the trial cohorts (again, mislabeled as "metabolic syndrome"). In the absence of adequate footnotes, it is difficult to understand the data presented. However, it appears as if a substantial number of withdrawals occurred in our study (for example, 441 of 1079 in the "I" group (presumably the lifestyle intervention) and 447 of 1073 in the "C" group (presumably control). ("Grp3" is probably our metformin-assigned treatment group.) Of course, the number of "withdrawals" in our study was miniscule (with total loss to follow-up <5% during the DPP and far fewer "withdrawals" if you mean withdrawn consent) and we have no idea what the numbers in the table refer to. Similarly, the values reported for "Insulin resistance" are unintelligible. We have reported blood pressure results in several | The decision to list metabolic syndrome in the key questions was made in consultation with the Centers for Medicare and Medicaid Services (CMS) and AHRQ. Due the evolving definition of metabolic syndrome as well as the debate regarding its ability to predict CVD and type 2 diabetes over abnormal blood glucose levels alone, we created an operational definition. Our operational definition of metabolic syndrome included metabolic syndrome, insulin resistance, prediabetes, impaired glucose tolerance, syndrome X, dysmetabolic syndrome X, and Reaven syndrome.<br><br>We mistakenly used DPPOS end of intervention numbers instead of DPP |

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| | | | publications: 1) Ratner R, Goldberg R, Haffner S, Marcovina S, Orchard T, Fowler S, Temprosa M, Diabetes Prevention Program Research Group. Impact of intensive lifestyle and metformin therapy on cardiovascular disease risk factors in the diabetes prevention program. Diabetes Care. 2005 Apr;28(4):888-94. 2) Goldberg RB, Temprosa M, Haffner S, Orchard TJ, Ratner RE, Fowler SE, Mather K, Marcovina S, Saudek C, Matulik MJ, Price D, Diabetes Prevention Program Research Group. Effect of progression from impaired glucose tolerance to diabetes on cardiovascular risk factors and its amelioration by lifestyle and metformin intervention: The diabetes prevention program randomized trial by the diabetes prevention program research group. Diabetes Care. 2009 Apr;32(4):726-32. 3) Lancet paper, Reference 166 in your report, table 4). | numbers. We have made the correction.<br><br>For the remaining baseline characteristics and/or outcomes, we made the necessary corrections where data were available. |
| David M. Nathan, M.D. | DPP | Results | Similarly, Table 5 which purports to describe the lifestyle interventions, is grossly inaccurate. You have recorded the duration of the study (and we can only assume that you mean the DPP and not DPPOS here) as 1 year, when the mean study duration of the DPP was 2.8 years (range 1.8 to 4.6 years) as noted in the main results manuscript (N Engl J Med 2002;346:393-403). Perhaps more importantly, your description of the intervention ("counseling") ignores the behavioral modification approach that was taken and which we continue to think was central to the effectiveness of the intervention. | This refers to the duration of the intervention and we have made the change to the headings of the tables summarizing the lifestyle interventions.<br><br>We feel that the summary tables provide sufficient information to give a sense of what the different lifestyle interventions involved. |
| David M. Nathan, M.D. | DPP | Results | We have not checked the values reported for the other trials; however, if the reporting of the DPP results is emblematic of the reporting of the other studies, fact-checking needs to be performed for all of the tables. | |
| David M. | DPP | Abstract | Finally, the structured abstract, which is likely to be | The decision to list metabolic syndrome in the |

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| Nathan, M.D. | | | the most frequently read part of this lengthy and detailed report, is not particularly well written. It continues to mischaracterize studies that predominantly focused on impaired glucose tolerance and dysglycemia as "metabolic syndrome". In addition, the results section summarizes the studies as showing that the "positive effects for change in body composition, metabolic variables, physical activity and dietary intake" were not "always sustained following the end of the active intervention", neglecting to mention any sustained effects on diabetes or glycemia (the primary outcome for most of the studies). On the other hand, the conclusion states that the "Comprehensive lifestyle interventions … are effective in decreasing the incidence of type 2 diabetes mellitus in high risk patients and the benefit extends beyond the active intervention phase". Both of these statements are accurate, but disjointed. | key questions was made in consultation with the Centers for Medicare and Medicaid Services (CMS) and AHRQ. Due the evolving definition of metabolic syndrome as well as the debate regarding its ability to predict CVD and type 2 diabetes over abnormal blood glucose levels alone, we created an operational definition. Our operational definition of metabolic syndrome included metabolic syndrome, insulin resistance, prediabetes, impaired glucose tolerance, syndrome X, dysmetabolic syndrome X, and Reaven syndrome.<br><br>We don't isolate glycemia, rather we include it in metabolic outcomes. While it is the primary outcome in many included studies, our primary outcomes were clinical outcomes.<br><br>The first sentence relates to DM progression, the following one in the conclusion refers to metabolic syndrome. |
| David M. Nathan, M.D. | DPP | Abstract | The statement in the last paragraph of the Metabolic Syndrome part of the Introduction (page 3, last paragraph) also seems to be at odds with the conclusion in the abstract quoted above: "The benefit of lifestyle interventions has shown *early* promise ….". The sentence goes on to note that further study is required to determine the benefits of lifestyle intervention on cardiovascular risk factors (evidence of a salutary effect has already been shown in the DPP/DPPOS long-term follow-up paper- your reference 166). While we agree that the ultimate, long-term benefit of diabetes prevention on cardiovascular disease requires further investigation, this sentence appears to ignore the | Sentence deleted in introduction for metabolic syndrome. Our original intention was to provide rationale for this systematic review. |

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| | | | potent effects of lifestyle intervention on the development of diabetes (58% reduction in the DPP and FDPS) which, in and of itself, is a major public health benefit. The abstract and perhaps other parts of the document require further editing to be accurate and internally consistent. | |
| Paul Meissner | Montefiore Medical Center | Key Question | The review would benefit from a discussion of comparative effectiveness with respect to these conditions. The question would be: what do lifestyle interventions add to clinical interventions? | The Key Questions and scope were determined a priori in consultation with AHRQ and CMS. |
| Paul Meissner | Montefiore Medical Center | Conclusion | The conclusion would also benefit from discussion of recommendations other than RCTs as appropriate methods for generating future research findings. | In the discussion section we have indicated that a review of observational studies is needed to provide data on patients using different interventions over several years to determine the comparative benefits these interventions. |
| Lynda Szczech, MD | National Kidney Foundation | Additional studies | In addition to the Steno-2 trial, we would like to draw your attention to additional publications that could be considered in this technical assessment. For example, please see: "A Meta-Analysis of the Effects of Dietary Protein Restriction on the Rate of Decline in Renal Function," (Kasiske, et al., American Journal of Kidney Diseases, Vol 31, No 6 (June) 1998: pp 954-961.) Of the 13 randomized controlled trials included in this meta-analysis four investigations had been limited to participants with diabetes. (Of those four, judging from their titles, two involved only individuals with type 1diabetes. The other two studies cited are: BH Brouhard et al., "Effect of dietary protein restriction on functional renal reserve in diabetic nephropathy," Am J Med 89:427-431, 1990; and FJ Raal, et al. "Effect of dietary protein restriction on the progression of overt diabetic nephropathy: A 6-month prospective study." Am J Clin Nutrition 60:579-585, 1994.) Dr. Kasiske found that the | Thank you for your suggestions. These RCTs focused on dietary interventions rather than a multifaceted lifestyle intervention and therefore would not meet our inclusion criteria. |

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| | | | pooled results from 13 randomized controlled trials, along with 11 other nonrandomized, controlled trials, showed a relatively greater effect of dietary protein restriction on decline in kidney function among patients with diabetes than among those without diabetes. | |
| Lynda Szczech, MD | National Kidney Foundation | Additional studies | A comprehensive review of the literature was published last month in the Journal of the American Dietetic Association: "The Evidence for Medical Nutrition Therapy for Type 1 and Type 2 Diabetes in Adults," Volume 110, Issue 12 , Pages 1852-1889, December 2010. Various studies that explore the impact of protein restriction on albumin excretion rate and kidney function are described. A 4-month study reported improvements in albumin excretion rate and kidney function in patients with macroalbuminuria from a lower protein diet (0.8 g/kg/day), but no changes in either metric in patients with normo- or microalbuminuria (Velezquez LL, Sil AMJ, Goycochea RMV, Torres TM,Castaneda LR. Effect of protein restriction diet on renal function and metabolic control in patients with type 2 diabetes: A randomized clinical trial. Nutr Hosp. 2008;23:141-147). Long-term consumption of soy protein compared to no soy protein in low protein diets (0.8 g/kg/day) led to improvements in kidney-related biomarkers (proteinuria and urinary creatinine) and cardiovascular risk factors (Azadbakht L, Atabak S, Esmaillzadeh A. Soy protein intake, cardiorenal indices, and C-reactive protein in type 2 diabetes with nephropathy. Diabetes Care. 2008;31:648-654). The article in the Journal of the American Dietetic Association also mentions a Cochrane Review (Robertson L, Waugh N, Robertson A. Protein restriction for diabetic renal disease. (Cochrane Database Syst Rev. 2007;4:CD002181) and a meta-analysis of low-protein diets for diabetic | Thank you for your comment. |

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| | | | nephropathy (Pan Y, Guo LL, Jin HM. Low-protein diet for diabetic nephropathy: A meta-analysis of randomized controlled trials. Am J Clin Nutr 2008;88:660-666). The Cochrane Review included 12 studies. The authors concluded that reducing protein intake appears to slightly slow progression to renal failure but is not statistically significant. The meta-analysis found that low-protein diets (prescribed 0.6 to 0.8 g/kg/day; actual average intake 0.9 g/kg/day) compared to the normal-protein diets (1.3 g/kg/day) were not significantly associated with change in kidney function or creatinine clearance rate, but did result in a decline in urinary protein excretion. | |
| Jonathan W. Simons, MD | Prostate Cancer Foundation | General | It follows that in underscoring the paucity of data assessing the usefulness of lifestyle interventions for prostate cancer patients, the Report cannot serve as a source for information for healthcare decision-making or set policy for our national coverage decisions for the Medicare program as well as to provide information to Medicare carriers. Instead, it is our hope that the findings of this Report may serve as the platform for a future public-private initiative where AHRQ, the EPCs, NIH, NCI, CMS, PCF, and the extramural research community could form a research partnership together to fast-forward collaborative investigation on the role of lifestyle interventions as they relate to reducing the substantial public health burden that prostate cancer now poses. | Comment noted. |
| Jonathan W. Simons, MD | Prostate Cancer Foundation | Analytic framework | Our assessment is that the analytical framework requiring the three specific interventions (diet, exercise and at least one additional) in combination should be clearly stated in the abstract. The logic behind these specifications should be communicated as well. Although, to our knowledge there are no randomized clinical trials investigating | The definition of lifestyle interventions (including diet, exercise and at least one additional) is included in the abstract. The actual analytic framework is found in the introduction. |

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| | | | independent lifestyle intervention components that meet the strict criteria of this review, it could be useful to state in the conclusion that research on independent lifestyle interventions could be as relevant as combinatorial interventions.<br>For example, we found 10 randomized control studies evaluating diet with or without nutrition supplements in men with prostate cancer. | |
| Jonathan W. Simons, MD | Prostate Cancer Foundation | Population | The methods state that only men successfully treated for prostate cancer were included. This should be explicitly defined. Over 70,000 U.S. prostate cancer survivors per year are treated with androgen deprivation therapy and should be included in the study population. We recognize that there are currently no randomized control studies investigating lifestyle intervention in men on ADT that meet the requirements of this study. Regardless, this population of men is critical for CMS and the research community at large to consider in the future. | Comment noted; no change. |
| Jonathan W. Simons, MD | Prostate Cancer Foundation | General | We respectfully suggest you consider re-structuring the report. Each chapter might address the three key questions for each disease independently. This way the references would correspond to each disease. Currently, the references for a specific disease are difficult to locate for analysis. | We used the format required by AHRQ. |
| Jonathan W. Simons, MD | Prostate Cancer Foundation | Future research | We commend the authors for the section entitled "Future Research" (page 79). These general recommendations might represent the foundation for a new set of guidelines on designing lifestyle intervention trials in the future. Such guidelines would ensure that any investment made would return sufficient and conclusive data on the value of lifestyle interventions on a clinically important outcome. | Thank you for your comment. |
| Jonathan W. | Prostate Cancer | Additional research | We are enclosing a table that details PCF's $2.2 million investment in 20 lifestyle intervention studies | Thank you for this information. |

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| Simons, MD | Foundation | | conducted by 7 investigators at 4 institutions over the past 17 years. This table is essentially a roster of national experts working on lifestyle intervention questions for prostate cancer patients. We hope these PCF-funded experts can serve as a resource alongside the Report in shaping a direction for future hypothesis-driven endeavors that could become building blocks for health care quality improvement projects throughout the Nation. | |
| Sam | www.qualifacts.com | General | I enjoyed reading about the TA Program and appreciate its efforts towards pubic transparency. Thank you. | Thank you for your comment |
| Ed Greissing | Sanofi-aventis US (VP) | General | Overall, sanofi-aventis believes this document presents a useful survey of the literature on randomized controlled trials (RCTs) that have examined the efficacy of lifestyle interventions in slowing the progression or preventing the recurrence of the four studied conditions. The report also provides the beneficial service of analyzing the strength of the evidence provided in the studied RCTs, pointing out their limitations, and suggesting directions for future research. | Thank you for your comment. |
| Ed Greissing | Sanofi-aventis US (VP) | Study design | We believe that the exclusive focus on RCTs in the literature review omits an important and substantively different body of evidence -- high-quality observational studies. Moreover, we believe that high-quality observational studies can complement RCT evidence by addressing many of the limitations pointed out in the report. In particular, high-quality observational studies offer the possibility for long-term follow-up and the analysis of diverse subpopulations of interest. This makes high-quality observational studies a potentially illuminating direction for future research. Many researchers consider RCTs the gold-standard approach for causal inference in biomedicine. This is undoubtedly true insofar as the RCT accurately | The decision to include RCTs was made a priori in consultation with AHRQ and CMS. This is because RCTs are considered the highest level of evidence to evaluate the effectiveness of an intervention. We have indicated in the discussion and future research sections that well conducted observational studies may be appropriate to provide evidence for some outcomes. |

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| | | | gauges the causal impact of the treatment administered in the RCT, on the population participating in the RCT. However, the appropriateness of RCT evidence ultimately rests on the ability to generalize from the population and treatment used in the trial to the patients and treatments administered in real-world clinical settings. While the evidence generalizes in many respects, it is not without its limitations.<br><br>While issues such as length of follow-up, generalizability, and representativeness are inherent to many types of RCTs, there is reason to believe that these limitations are particularly salient when the treatment in question is a lifestyle intervention. By their very nature, lifestyle interventions require major changes to patients' lifestyles, and thus are typically difficult to sustain. On top of this, the effects of lifestyle interventions typically require a great deal of time to become apparent. For these reasons, the highly controlled environment of the RCT presents a less than ideal setting in which to evaluate lifestyle interventions, as adherence is often achieved through extraordinary means and length of follow-up is often relatively short. As a result of these limitations, insufficient RCT evidence is not bulletproof evidence of poor efficacy.<br>In itself, a critique of RCTs is worth little without a strategy for addressing the gaps in RCT evidence. As a result, we also discuss what the current body of observational studies on lifestyle interventions to treat the four studied conditions has to offer, and where it falls short. In general, well-designed observational studies -- using the latest advances in causal inference from econometrics and statistics – can complement RCTs and fill gaps in inference that | |

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| | | | may result from imperfect generalizability to real-world patients and treatments.<br>At present, there exists a large body of observational studies examining the relationship between lifestyle intervention and the incidence and severity of type 2 diabetes, metabolic syndrome, prostate cancer, and breast cancer. Such studies typically do find that diet and exercise have large and significant protective effects against these conditions. However, in an observational study, the potential for unobserved patient characteristics to confound the analysis and bias the results must always be considered. Some studies do a better job of controlling for this potential bias than others, and for this reason, the quality of observational studies is of paramount importance.<br>Despite the challenges involved, the potential for high-quality observational studies to complement and expand the RCT literature on lifestyle interventions is great. By their nature, lifestyle interventions require a considerable length of time to demonstrate an effect and vary considerably in their ease of adoption outside the clinical setting. Observational studies observe participants passively (for example, through surveys or claims data), enabling them to conduct their lives in a realistic setting and to provide long-term follow-up without proving overly intrusive. In addition, well-designed observational studies can potentially include large enough groups of patients to stratify the analysis by subpopulations of interest and by specific treatment regimens, something that is often prohibitively costly when conducting RCTs.<br>Our comments proceed as follows:<br>1. We discuss the limitations of RCTs, with special reflection on how these issues may be particularly relevant in the case of lifestyle | |

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| | | | interventions.<br>2. We discuss how high-quality observational studies can address these potential shortcomings.<br>1. We examine the existing body of observational evidence on the effect of lifestyle interventions on type 2 diabetes, metabolic syndrome, prostate cancer, and breast cancer.<br>2. We conclude by discussing the limitations of the existing observational studies and suggesting how AHRQ might provide guidance to researchers weighing the evidence from existing observational studies and contemplating the design of new ones.<br>Will refer to attached PDFs for the above | |
| Roberta Madej | Tethys Bioscience | Results | Tethys was encouraged that the conclusions of the TA stated “overall, comprehensive lifestyle interventions that include exercise, dietary changes, and at least one other component are effective in decreasing the incidence of type 2 diabetes mellitus in high risk patients and the benefit extends beyond the active intervention phase.” (ES-16 and pg 79) This is an important finding and consistent with current work in the field of diabetes prevention as demonstrated by the studies you evaluated and supporting evidence in observational and longitudinal studies. However, the clarity of this finding, which is found in the middle of the Executive Summary and in the detailed Metabolic Syndrome sections, does not appear to translate to your overall conclusions in the abstract, and may be misrepresented by the title of the section. This finding is critical, especially in light of the estimate by the Centers for Disease Control and Prevention that if current trends continue, as many as 1 in 3 Americans could have type 2 diabetes by 2050 (http://www.cdc.gov/media/pressrel/2010/r101022.html); and by findings that only 4.8% - 7% of pre-diabetics are even aware of their status or risk. | We have modified the ‘conclusion’ in the abstract. |

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| | | | Further, these researchers find that the majority of people at risk for the development of type 2 diabetes are untreated with interventions (Geiss, et al., 2010; Karve & Hayward, 2010). | |
| Roberta Madej | Tethys Bioscience | Strength of evidence | The dilution of evidential strength could be due to the assessment of metabolic syndrome as the "condition" studied for the outcomes of CVD, stroke or type 2 diabetes. While it is understandable that policy makers wish to examine this broad category, the evolving definition of metabolic syndrome (Alberti, et al, 2009; Cameron, 2009) and its application to this TA may have confused and biased the stated effects. Metabolic syndrome is a heterogeneous grouping of factors and the risk of developing type 2 diabetes in individuals varies substantially, depending on which components of metabolic syndrome are present (Nichols & Moler, 2009). The studies that "survived" the selection process in the TA methodology were weighted towards RCTs with participants having impaired glucose metabolism - not necessarily meeting the criteria for metabolic syndrome. In addition, they were not all aligned with the ADA's definition of persons with pre-diabetes (ADA, 2010). To consolidate the findings with respect to the outcome of type 2 diabetes by combining studies, each meeting different aspects of the criteria for metabolic syndrome or pre-diabetes, may obscure the actual effects of the intervention evaluated. Tethys realizes our remarks are focused on the effect that the methodology and terminology may have on the findings regarding the progression to diabetes, but it is expected that those expert in the progression to CVD and stroke may also express concern. | The decision to list metabolic syndrome in the key questions was made in consultation with the Centers for Medicare and Medicaid Services (CMS) and AHRQ. Due the evolving definition of metabolic syndrome as well as the debate regarding its ability to predict CVD and type 2 diabetes over abnormal blood glucose levels alone, we created an operational definition. Our operational definition of metabolic syndrome included metabolic syndrome, insulin resistance, prediabetes, impaired glucose tolerance, syndrome X, dysmetabolic syndrome X, and Reaven syndrome. |
| Roberta Madej | Tethys Bioscience | Results | Further, since the TA also found (in the Type 2 Diabetes section) that "in patients who have already | We have repeated our conclusions in the abstract, in the conclusion section of the |

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| | | | been diagnosed with type 2 diabetes, evidence for benefit of comprehensive lifestyle interventions on patient oriented outcomes is less Clear" (ES017) the distinction between the effects of lifestyle intervention on the prevention of diabetes in high risk individuals and on the progression of those already diagnosed with type 2 diabetes is critical. There is a difference between preventing the onset of the disease altogether and reducing the consequences of type 2 diabetes. The public health and policy implications are not trivial. An unintended consequence of the TA as it currently reads, with progression-to-diabetes findings in the Metabolic Syndrome section, is that one just reading specific summaries or sections may only read the Type 2 Diabetes section for information regarding this disease - and may miss the important conclusions for the prevention of diabetes.<br><br>In order to make it clear to readers that the TA includes information regarding the progression to diabetes, Tethys suggests that the concluding statements regarding the impact of lifestyle interventions on those at risk for developing diabetes should also appear in the Type 2 Diabetes section with a reference to the full discussion in the Metabolic Syndrome section.<br><br>In summary, we are encouraged by the finding that lifestyle intervention plays a role in the prevention of diabetes for those patients with metabolic syndrome but are concerned that the conclusions might be misleading or missed based on the co-mingling of studies with heterogeneous conditions and the dispersed placement of all the findings relating to Diabetes. We further believe that the distinction between the use of lifestyle interventions in the | executive summary and the main report. We do not think it necessary to include the conclusions regarding metabolic syndrome in the section addressing patients who have already been diagnosed with type 2 diabetes. |

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| | | | progression to diabetes and diabetes disease is an important one that needs to be clearer in the summary parts of the assessment.<br>Additionally, Tethys supports the need for more research in this area and encourages the TA to also recommend the continued use of well designed behavioral observational and longitudinal studies in addition to RCTs pertaining to this issue. | |
| Wendy Demark-Wahnefried | University of Alabama at Birmingham | Intervention | One concern lies in the complexity of how "lifestyle interventions" were defined, and the criteria which specified that diet, exercise and at least one other intervention component was necessary to warrant consideration in this report. Indeed, the number of interventions which have combined both diet and exercise components is already very small; however, the number of trials which have at least three components is even more limited. Perhaps more expansive criteria should be considered, especially for cancer where the number of multi-component interventions is exceptionally small. | We were interested in multifaceted lifestyle interventions, which defined as diet, exercise and at least one other component. This definition was developed in consultation with AHRQ and CMS. |
| Wendy Demark-Wahnefried | University of Alabama at Birmingham | Intervention | Another concern regarding interventions in cancer survivors or other high risk cancer populations is the relatively long lead time required to either manifest a second primary, cancer recurrence, or cancer progression (particularly for the two cancers selected for this report - breast and prostate cancer). While the authors acknowledge this as an issue, there is limited discussion as to appropriate intermediate endpoints, and the fact that some of the endpoints used to define "success" for other diseases in this report, e.g., blood pressure, etc. may not be informative for cancer. Given that cancer survivors are at increased risk for comorbidity and functional decline, which are exceedingly costly issues among older adults, it would be helpful if such endpoints also were included (or at least mentioned) in this report, | Thank you. We included some comments reflecting these ideas in the discussion section for breast and prostate cancer. |

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| | | | particularly given its intended use in making Medicare decisions. | |
| Wendy Demark-Wahnefried | University of Alabama at Birmingham | General | Since consensus has been reached regarding the treatment of obesity (see citation below), at least some mention of these guidelines seems appropriate in order to keep the science and policy moving forward.<br>http://www.cdc.gov/obesity/resources.html | Thank you. We do not feel it necessary to include additional information about obesity in the introduction. Obesity is not the focus of the report. |
| Wadie Najm | University of California, Irvine | Study design | Despite recognizing the immediate public health crises posed by chronic diseases and the potential benefit of lifestyle interventions in preventing the progression of chronic diseases, the Report used methods that failed to adequately consider the full body of evidence available on the effectiveness of lifestyle interventions. As a consequence, I believe that the Report failed to appreciate the full value of lifestyle interventions and the strength of the existing evidence supporting those interventions. Although the Report clearly stated that its "objective" was to identify and synthesize the available evidence regarding the effect of lifestyle interventions",[2] the methods used clearly prevented the authors from considering much, even most, of the available evidence.<br><br>In part, this was the result of the inclusion criteria being so strict that the Report inevitably only assessed a small portion of the "available" evidence. Even though 1,287 lifestyle intervention references were initially identified, after AHRQ applied its overly stringent study inclusion criteria, mere 20 unique randomized controlled trials (RCTs) were included in the review. This systematic failure to even consider most of the available evidence is particularly disappointing in light of the nature of the health care crisis that our society faces and the expected, dramatic increase in the number of | The scope of the review as well as the decision to include only RCTs was decided upon a priori in consultation AHRQ and CMS. |

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| | | | affected diabetic and metabolic syndrome patients expected in the near term. | |
| Wadie Najm | University of California, Irvine | Intervention | In addition, I am concerned that much of the "available" evidence was excluded due to the narrow definition of the term "intervention." The Report's definition required an "intervention" to include exercise, diet, and at least one other component. However, by requiring three components, the Report failed to evaluate the effects of specific components of these broad interventions as required by "Key Question 3."[4] Assessment of individual components of lifestyle interventions is extremely valuable because it can help determine if less extensive and less costly interventions are effective. The Report's design and methods made this unfortunate shortcoming a foregone conclusion. | The scope of the review as well as the decision to assess multifaceted lifestyle interventions was decided a priori in consultation AHRQ and CMS. |
| Wadie Najm | University of California, Irvine | Follow-up | I was also concerned by the AHRQ's decision to exclude RCTs which did not conduct a post-intervention follow-up at a minimum of 6 months. While, as a practicing physician, I understand the importance of follow-up data, the absence of that data should not exclude otherwise well-designed RCTs from being evaluated for effectiveness of the lifestyle intervention. Effects achieved during the intervention period alone should be evaluated for determining effectiveness of the intervention.<br><br>Moreover, making a post-intervention follow-up a necessary requirement for study inclusion may unfairly bias the AHRQ's assessment of lifestyle interventions. From my perspective as a physician, it is unreasonable to assume that interventions can only be considered effective if the intervention results are sustained for a considerable amount of time after the intervention has ended without any additional intervention or support. The goal of | The scope of the review as well as the decision to require long-term interventions (>12 mo.) or > 6 mo followup was decided in consultation AHRQ and CMS. |

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| | | | lifestyle interventions is to modify behavior and breaking old habits and learning new habits is clearly a complicated process. Some patients may require additional support in order to maintain the benefits from a lifestyle intervention and this need has no bearing on the effectiveness of the initial intervention. As such, otherwise valid data should not be excluded from the review of available evidence just because it did not include a post-intervention follow-up.<br>If the Report included well-designed studies without post-intervention follow-ups, it would be able to more comprehensively assess lifestyle intervention programs. For example, the clinical study I conducted, sponsored by Metagenics, Inc., was a 12-week, randomized, controlled trial investigating the efficacy of a medical food as part of a diet modification program. At the end of the study, all participants had reduced waist circumference, blood pressure, and plasma triglycerides. Participants in the medical food arm additionally had decreased levels of LDL-C, non-HDLC, apolipoprotein B, and homocysteine. Over 44% of participants in the medical food arm and almost 32% of participants in the control arm no longer met criteria for diagnosis of metabolic syndrome at the end of the study. I believe that consideration of this study and many other available studies would add to the Report and the quality of the review. | |
| Wadie Najm | University of California, Irvine | Future research | Therapeutic lifestyle change has been recommended as the first line of therapy for metabolic syndrome by the American Heart Association. Results from our study underscore the tremendous clinical value of diet modification alone for management of metabolic syndrome. Paired with exercise, our diet modification program would be an excellent lifestyle intervention for patients at risk for | Comment noted. |

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| | | | heart disease and type 2 diabetes. | |
| Wadie Najm | University of California, Irvine | Conclusion | In the Report, analyses of the effectiveness of lifestyle interventions were based on too few studies to be an informative report or to provide a meaningful meta-analysis. The Report largely ignores a vast body of medical literature supporting the benefits of lifestyle medicine in managing chronic disease. Lifestyle medicine has the potential to slow or reverse the escalating incidence of metabolic syndrome and diabetes in the U.S. Immediate goals should be to increase access for patients to lifestyle medicine programs and to facilitate the physician's role in managing patients with lifestyle medicine. An appropriate meta-analysis of all available evidence is a time-sensitive first step in that process. This Report does not take that first step. | The scope of the review as well as the decision to include only RCTs was decided a priori in consultation with AHRQ and CMS. |
| David Williamson, PhD | Rollins School of Public Health, Emory University | Population | I do not agree with this report's use of the term "metabolic syndrome" to designate a "chronic disease", especially since the basic concept of "metabolic syndrome" has been severely critcised by a number of health scientists, including the originator of the concept Dr. Gerald Reaven. Dr. Reaven concludes that the metabolic syndrome does no better than fasting plasma glucose in predicting the onset of type 2 diabetes, and is inferior to the Framingham Risk Score in predicting onset of CVD (see most recently: Reaven GM. The metabolic syndrome: time to get off the merry-goround? J Intern Med 2010; doi:10.1111/j.1365-2796.2010.02325.x.). The RCTs that were designed to demonstrate the impact of structured lifestyle intervention on the incidence of type 2 diabetes should not be portrayed as trials to prevent the development of so-called metabolic sydrome. This is highly misleading, even though the lifestyle trials generally improved blood pressure, | The decision to list metabolic syndrome in the key questions was made in consultation with the Centers for Medicare and Medicaid Services (CMS) and AHRQ. Due the evolving definition of metabolic syndrome as well as the debate regarding its ability to predict CVD and type 2 diabetes over abnormal blood glucose levels alone, we created an operational definition. Our operational definition of metabolic syndrome included metabolic syndrome, insulin resistance, prediabetes, impaired glucose tolerance, syndrome X, dysmetabolic syndrome X, and Reaven syndrome. |

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| | | | lipoproteins, blood glucose, BMI, and abdominal obesity -- all components of the metabolic syndrome. | |
| David Williamson, PhD | Rollins School of Public Health, Emory University | Risk of bias | The idea that RCTs of structured lifestyle intervention are at "high risk" of bias because of "inadequate blinding" is deeply flawed. First, it is not possible to design a double-blind RCT of a lifestyle intervention. Even if the investigators are "blinded" to the intervention arm a participant has been randomized to, the participant surely knows if they are in a lifestyle intervention! Unless the investigators are truly blind and never see the participants they will often notice the weight loss and other physical changes lifestyle participants undergo during the trial.<br><br>Do the authors of this report seriously believe that the diagnosis of diabetes based on oral glucose tolerance tests, as employed in the Finnish and US DPP trials, is biased in these trials because those in the lifestyle intervention were not blinded to the intervention they were receiving? Given that the blood testing results were performed by a central laboratory (in the case of the DPP) which was blinded to participants' intervention status, the whole idea that these RCTs are at "high risk" of bias verges on the ludicrous. | We understand that it is difficult if not impossible to design a double-blind RCT of a lifestyle intervention. For blinding, we gave studies a “low” risk of bias if there was blinding of study participants to the hypothesis and blinding of those involved in outcome assessment and data analysis to the treatment allocation<br><br>We separated our blinding ratings for objective and self-reported outcomes. Blinding for objective outcomes was assessed as having a low risk of bias. |
| David Williamson, PhD | Rollins School of Public Health, Emory University | Results | The authors of this report need to explain why they come to different conclusions regarding the impact of lifestyle intervention on body weight vs. BMI. They appear to conclude that lifestyle intervention was less effective on weight loss and more effective on reduction in BMI. Given that BMI is simply weight adjusted for height, AND, that height is unlikely to change in adults during the 3-6 years of most RCTs, their separate conclusions regarding weight loss vs. BMI loss are nonsensical. | In the diabetes studies, only one study (the POWER study) reported both changes in BMI and body weight. The remaining studies reported either BMI or weight change and not both. The studies that favor lifestyle intervention are not the same studies that favor the usual care.<br><br>The results were more consistent in the metabolic syndrome and cancer studies. |

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| David Williamson, PhD | Rollins School of Public Health, Emory University | Results | The report's conclusion that "... at 6 month followup, there was no difference between groups..." in weight loss is surely wrong. It is well documented in the voluminous weight loss literature that it is at about 6 months that the majority of participants approach their peak weight loss! This was certainly true in the DPP and other diabetes prevention trials that employed lifestyle intervention. | This was changed from “no difference” to “no statistically significant difference between groups”. While one study reported 4 year followup data that significantly favored the lifestyle intervention, the one study with 6 month followup data reported that the usual care was favored though not significantly. |
| David Williamson, PhD | Rollins School of Public Health, Emory University | Results | On page ES-10, Table ES2, the report gives evidence about RCTs which employed lifestyle intervention for the reduction in incidence of type-2 diabetes. In the table evidence for 3 RCTs of 1-6 year duration is given as "moderate" and evidence for 2 RCTs of 4-10 year duration as low. Given that these two groups of RCTs have over-lapping durations, why were they separated? It is also noteworthy that both groups of RCTs achieved the same summary RR for diabetes incidence attributable to lifestyle intervention of 0.44.<br><br>Therefore, the reader is left with the impression that the evidence that lifestyle intervention reduces incidence of type 2 diabetes as only "modest -to-limited", even though the report summarizes the magnitude of the reduction in incidence across all 5 RCTs as -56%! (100%-44%). | We included the results for each timepoint in the summary tables to clarify. For the followup timepoints, the results are based on one study for each timepoint, which reduces our confidence in their conclusions. |
| David Williamson, PhD | Rollins School of Public Health, Emory University | General | I believe that this report -- at least regarding the efficacy of lifestyle intervention for reduction of diabetes incidence -- gives an overly pessimistic view, and is thus biased to the null in its conclusions. | We stand by our conclusions regarding the strength of evidence for this outcome. |

[1] Names are alphabetized by last name. Those who did not disclose name are labeled

"Anonymous Reviewer 1," "Anonymous Reviewer 2," etc.

[2] Affiliation is labeled "NA" for those who did not disclose affiliation.

[3] If listed, page number, line number, or section refers to the draft report.

[4] If listed, page number, line number, or section refers to the final report.