

## *Comparative Effectiveness Research Review Disposition of Comments Report*

### **Research Review Title:** *Effectiveness of Screening and Treatment of Subclinical Hypothyroidism or Hyperthyroidism*

Draft review available for public comment from April 16, 2010 to May 14, 2010.

**Research Review Citation:** Rugge B, Balslem H, Sehgal R, Relevo R, Gorman P, Helfand M. Screening and Treatment of Subclinical Hypothyroidism or Hyperthyroidism. Comparative Effectiveness Review No. 24. (Prepared by the Oregon Evidence-based Practice Center under Contract No. 290-2007-10057-I.) AHRQ Publication No. 11(12)-EHC033-EF. Rockville, MD: Agency for Healthcare Research and Quality. October 2011. Available at: [www.effectivehealthcare.ahrq.gov/reports/final.cfm](http://www.effectivehealthcare.ahrq.gov/reports/final.cfm).

### **Comments to Research Review**

The Effective Health Care (EHC) Program encourages the public to participate in the development of its research projects. Each comparative effectiveness research review is posted to the EHC Program Web site in draft form for public comment for a 4-week period. Comments can be submitted via the EHC Program Web site, mail or E-mail. At the conclusion of the public comment period, authors use the commentators' submissions and comments to revise the draft comparative effectiveness research review.

Comments on draft reviews and the authors' responses to the comments are posted for public viewing on the EHC Program Web site approximately 3 months after the final research review is published. Comments are not edited for spelling, grammar, or other content errors. Each comment is listed with the name and affiliation of the commentator, if this information is provided. Commentators are not required to provide their names or affiliations in order to submit suggestions or comments.

The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

Commentator	Section	Comment	Response
Peer Reviewer #2	Executive Summary	I would have listed/reviewed the criteria used to judge a screening test in the Executive Summary as you did on page 18	We have made the change suggested by the reviewer
Peer Reviewer #2	Executive Summary	The Executive Summary should probably also mention that you reviewed prior systematic reviews plus new publications and reports since January 1, 2002. I'd list the end date as well	We have made the change suggested by the reviewer
Peer Reviewer #2	Executive Summary	On page ES-4, the sentence, "Because we found no U.S. studies..." sounds prejudicial. In this case, I'd just say what you did, not why	We have made the change suggested by the reviewer
Peer Reviewer #2	Executive Summary	Do we know what proportion of primary care patients have symptoms consistent with hypo- or hyperthyroidism? My clinical experience suggests that virtually everyone over 65 has at least one symptom (e.g. dry skin, constipation, fatigue, etc.). If this is true, then the question of screening seems somewhat irrelevant and we are really talking about case finding. This has practical implications for how your results would be operationalized in the primary care setting.	We agree, these symptoms are very common. The older literature indicates that if we tested everyone in primary care, about 1% would have an overt thyroid dysfunction (e.g., an elevated TSH and low FT4), whereas when clinicians test based on clinical suspicion then 2% of the individuals are diagnosed with overt thyroid dysfunction. Because of the high frequency of nonspecific symptoms, the term "screening in asymptomatic primary care patients" makes little sense clinically--a better term would be "routine testing or case finding in primary care." (NOTE: See also response to comment #16, below).
Peer Reviewer #2	Executive Summary	The last sentence on ES-8 is a little hard to decipher. I think it suggests that many people with mildly elevated TSH have normal subsequent TSH levels without treatment, but the way the sentence is worded, it took me a few minutes to get to that conclusion.	We have changed the language here to try to address the reviewers concerns
Peer Reviewer #2	Ch. 1 Introduction	On page 2, for those of us who are prone to forget things we haven't seen or read about in awhile, if you are going to mention acute myxedema coma, please provide a little more information about what precipitates it and whether it can be precipitated in patients with subclinical hypothyroidism. Is this serious complication a reason to want to screen or treat? (This is the only sentence I could find about this in the whole manuscript.)	We added a description of myxedema coma

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Peer Reviewer #2	Ch. 1 Introduction	On page 6 and in several other places you mention evidence that a mildly elevated TSH may be beneficial in older people. You cite 3 references. For skeptical readers, you may want to say more about the types of studies (cohort I think) that produced this finding and the strength of the evidence at this point	We have made changes to the text. The sentence was removed from page 6; the cited studies' designs are stated elsewhere in the review
Peer Reviewer #2	Ch. 1 Introduction	On page 6 under "Prevalence and Course of Mild Thyroid Dysfunction," the sentence that says, "Approximately one in four...a markedly elevated TSH (>10mIU/L)." That sentence follows a sentence that implies that you are using a definition of mild hypothyroidism based upon reference ranges. I suspect that 10 is above the upper limit of most reference ranges for TSH, making this sentence confusing	We have added language that we hope addresses the reviewers concerns
Peer Reviewer #2	Ch. 1 Introduction	On page 15, 2 <sup>nd</sup> full paragraph, first sentence, you refer (for the first time) to "the Wickham study." You need to tell us which study this is in a prior paragraph before referring to it in this way	We have added language briefly describing the Whickham study in the paragraph in which it's discussed
Peer Reviewer #2	Ch. 1 Introduction	On page 16, mid-page, in the sentence, "Finally, the study was conducted before the era of statins...." I'd include the date of the study just before "before"	We have added the dates of the study
Peer Reviewer #2	Ch. 1 Introduction	On the bottom of page 16 and top of page 17, because of the way you have worded the sentences, it seems to me that the values for blood pressure and total cholesterol levels within the parentheses should be reversed (higher numbers first).	We have made the change suggested by the reviewer
Peer Reviewer #2	Ch. 1 Introduction	In the summary paragraph on page 17, there is no mention of subclinical hyperthyroidism.	We added a summary sentence for hyperthyroidism in the draft
Peer Reviewer #2	Ch. 3 Results	On page 34, second full paragraph, first sentence, second line, I think it should be "included in the" rather than "include the."	We have corrected this
Peer Reviewer #2	Ch. 3 Results	On page 46, line 3, I think it should be "blind" rather than "blinded."	We have corrected this

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Peer Reviewer #9	General Comments	Meaningful, explicitly defined and key questions appropriate. A potential concern is the exclusion for further consideration patients detected through screening who are found to have overt hypo or hyperthyroidism. I agree that these should formally be out of the review esp. for the questions related to treatment of subclinical disease. However, as you note, an argument has been that screening (esp. among those with vague, nonspecific symptoms) may detect individuals with clinical hypo or hyperthyroidism...and by ignoring this potential benefit the review is skewed against a possible benefit. One way to address this would be to assume a benefit among all patients found to have clinical hypo or hyperthyroid but detected in a screening program that includes those with "vague symptoms"...and then evaluate population studies to see what the plausible prevalence of that might be...I imagine it is small and thus you could make some outer bounds as to greatest plausible benefit even if assuming clinical hypo/hyperthyroid patients only detected by screening. (this still excludes the "overt hypo/hyperthyroid)	We have added a sentence to the limitations section to acknowledge this issue. While AHRQ and the USPSTF defined screening for undetected overt thyroid disease as outside the scope of this review, we agree that it is an important consideration in deciding whether to test routinely. We are not sure this "skews the review" since the review is not evaluating the overall benefits and harms of screening, but rather the benefits and harms of screening to detect borderline abnormal TSH values. Especially if one believes in routine testing to detect overt thyroid dysfunction, the question of what to do for patients who have borderline test result is important. As suggested above, older literature suggests that about 1% of unselected primary care patients have symptomatic, but undetected overt thyroid disease. There is anecdotal evidence that in the absence of screening, people can be symptomatic for a long time before clinical suspicion leads to the diagnosis. While anecdotal, this notion is consistent with experience--we all know people or patients who in retrospect were symptomatic for months if not years before they were diagnosed. For these reasons, in 1990 and 1998 the ACP recommended routine testing in older female primary care patients to detect symptomatic, overt thyroid dysfunction (primarily hypothyroidism) that had escaped clinical detection.
Peer Reviewer #9	Clarity and Usability	clear and usable. nice job.	Thank you
Peer Reviewer #9	Introduction	Line 33-35 see my concerns above about vague symptoms in those with e.g. mild increase TSH and mild low T4	See our responses to Comments #5 and #16 above

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Peer Reviewer #9	Methods	Search date only through June 2009 (?UPdate...nearly 1 year old). See my potential concerns for not providing some estimates of % patients with "clinical hypo/hyperthyroid" detected only through screening program	We have indicated that we have updated the search through June 2010
Peer Reviewer #9	Methods	See my potential concerns for not providing some estimates of % patients with "clinical hypo/hyperthyroid" detected only through screening program	See our response to Comment #16 above
Peer Reviewer #9	Results	Detail good and adequate. P 22 line 25-28. Important to highlight that this led to no change in health risk	Have added language that we hope addresses this concern
Peer Reviewer #9	Results	p 23 line 47: a figure showing changing prevalence by TSH level would be helpful to illustrate the issue	We feel that the text adequately addresses this issue.
Peer Reviewer #9	Results	p24 line 45: change "markedly" to e.g. moderately elevated (you use mildly elevated for TSH < 10 but then use "markedly" for a value of e.g. 10.1 P 29 line 3 and p 31 line 50-57: these points as noted above should be addressed hopefully with some prevalence data	We have modified Table 2 to explicitly define Marked and Mildly elevated to help clarify these definitions
Peer Reviewer #9	Results	P32: there was a recent patient level meta-analysis from 6 cohorts of risk of cardiac events and mortality by TSH values according to age etc...Presented as oral presentation at 2010 SGIM by Rodondi PD Nicolas that is quite interesting. He might be willing to share data and this would be useful. nicolas.rodondi@jpspvd.ch Additionally Doug Bauer at UCSF is planning a pilot grant on screening for thyroid disease...talking with him and obtaining their protocol could be useful to determine if it is likely to address gaps...	We have e-mailed Dr. Rodondi and ask him; awaiting a response. We have had conversations with Doug Bauer in August of 2009 as part of our Technical Expert Panel
Peer Reviewer #9	Results	p50 table 7 provides some additional information regarding overdetected and treatment as well as likely "false +" ... if one assumes reversion to normal is a false +...I think this is quite valuable and could be additionally highlighted P 55 and P 66. Please check direction of arrows in tables: the text statements suggest they lower t chol, LDL and BP for Razvi and Yonem but the arrows go in the opposite direction...I like the arrows but this seems confusing	We have been unable to identify the section of the report referred to by the reviewer.
Peer Reviewer #9	Results	Please check direction of arrows in tables: the text statements suggest they lower t chol, LDL and BP for Razvi and Yonem but the arrows go in the opposite direction...I like the arrows but this seems confusing	We have added a footnote to the figure that we hope clarifies this.
Peer Reviewer #9	Results	p74: line 39: these harms are important and could be additionally highlighted	Although we can't identify the passage mentioned by the reviewer, we believe that our discussion of harms has been thorough.

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Peer Reviewer #9	Results	p81 line 8: I do not agree with the term watchful waiting...to me it should be screen or don't screen...watchful waiting is more typically used for someone with a diagnosed condition who you are evaluating by just asking them periodically if they have progression of a specific issue relevant to their diagnosed disease...I am not aware that the default here would be to routinely ask individuals: are you fatigued, cold intolerant, having weight gain, losing hair...etc or other issues to "assess" presence of overt thyroid disease...recommend changing	Correct, the text is confusing, we made changes to the text to clarify the the following: - there are two questions -- 1. to screen or not to screen -- our review finds no evidence to support screening -- 2. to treat vs. watchful waiting once an individual is found to have sub-clinical thyroid disease; the question then is to treat or "wait watchfully" -- our review finds no compelling reason to treat vs. wait watchfully.
Peer Reviewer #9	Results	p87 line 33: emphasize at least theoretic benefit of not screening esp. elderly where given the noted findings of overtreatment (and subsequent harms related to this)...less is more.	We feel that this issue has been adequately addressed.
Peer Reviewer #9	Discussion/ Conclusion	So...given the relative rarity, frequent overdetection and overdiagnosis, the very long interval from subclinical to overt disease and the findings from smaller trials indicating little to know impact on intermediate markers is it closer to say likelihood of benefit is no greater than small and would require at least decades to determine?	We agree that this might be the case, but we would need future research to confirm and have briefly discussed this in the Future Research section.
Peer Reviewer #7	Discussion/ Conclusion	The recent ecological studies of TSH in the elderly begs the question of what the actual treatment studies included in the review found for this subgroup, recognizing that the numbers included are sure to be small-. Could the EPC comment on the numbers of elders in the trials, and if there were any trials primarily of the elderly, whether the results differed?	We agree. The studies of TSH in the elderly do highlight the importance of understanding how TSH varies with age, what the effect of that variation is on health and health-related outcomes, and whether the effect of treatment varies by age. Unfortunately, the main focus of our review is the effectiveness of treatment, and treatment studies have not addressed this issue. Ages in the subclinical hypothyroidism treatment studies ranged from 30 - 64 for the studies of subclinical hypothyroidism. Studies of treatment for subclinical hyperthyroidism included patients ranging in age from 33 to 59. While some studies reported how treatment differed for subjects with different TSH levels, none reported the effects of treatment by age, and the studies were not long enough in duration or large enough to be helpful with respect to the findings of the recent ecological studies.

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Peer Reviewer #4	General Comments	The authors, and most clinicians, realize that thyrotropin and TSH is the same thing. BUT, I think that the use of both terms is confusing for other audiences and would recommend using one or the other after including information that they are the same. I'd recommend saying "TSH" because it is more commonly used and more descriptive. So, it would look something like: ". . . TSH (also called thyrotropin) . . .". Making sure, of course, to spell out what TSH stands for at the first use.	We have made the change suggested by the reviewer
Peer Reviewer #4	Introduction	Suggest that where ever MS says "physician" (as at line 28 on p.1) that "clinician" be substituted.	We have made this change
Peer Reviewer #4	Introduction	Line 10, p. 2, insert "overt" before hypothyroidism	We have made the change suggested by the reviewer
Peer Reviewer #4	Introduction	Table 2, p. 3, line 53--the word "Some" in the comment column is not clear. Some what?	We have modified the language
Peer Reviewer #4	Introduction	p. 6, line 40--specify the ref range to which this refers	We have added the cutoff for this reference range
Peer Reviewer #4	Introduction	line 47--this needs a reference	We have added this reference
Peer Reviewer #4	Introduction	p. 7, line 7--how low? needs ref	We have added this reference
Peer Reviewer #4	Introduction	line 27--the NHANES study needs a ref cited	We have added the reference
Peer Reviewer #4	Introduction	p. 9, line 21--suggest adding "and primary care based" between recent and data	We have made the change suggested by the reviewer
Peer Reviewer #4	Introduction	p. 12, table 3--add date (2004)	We have made the change suggested by the reviewer

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Peer Reviewer #4	Introduction	p. 13, line 22--since scope excludes pregnant women why mention this at all?	We agree, but we also wanted to include the major guidelines in the background. Indirectly, the statement indicates that ACOG did not make a recommendation for nonpregnant women.
Peer Reviewer #4	Introduction	p. 14, line 3--suggest inserting "of screening" between harms and of	We have made the change suggested by the reviewer
Peer Reviewer #4	Introduction	p. 14, line 29--unclear sentence, probably should read "One meta-analysis included six . . . "	We have made the change suggested by the reviewer
Peer Reviewer #4	Introduction	line 32 & 34--spurious precision. Cut down to no more than 2 places to the right of the decimal.	We have made these changes.
Peer Reviewer #4	Introduction	p. 14, line 43--on the third review, state number and type of studies	We have added this description
Peer Reviewer #4	Introduction	p. 14, line 53--what type of studies were the 15 "studies"	We have added this description
Peer Reviewer #4	Introduction	page 15, line 8--don't give a p value when you've given the CI	We have removed the p value when we provide CIs
Peer Reviewer #4	Introduction	page 15, line 12--here and elsewhere, be consistent with how CIs are expressed. Are they always in (parens) or are they in [brackets] if inside parens? Make it clear that this is a 95% CI (if indeed it is)	We have standardized the way CIs are reported in the report
Peer Reviewer #4	Introduction	page 15, line 53--add "95% CI" and nix the p value and same comment on p. 16 at line 3	We have removed the p value when we provide CIs
Peer Reviewer #4	Introduction	p. 16, line 8--"two" not 2	We have made this change
Peer Reviewer #4	Introduction	p. 16, lines 18-25--prime example of an overly long sentence (see general comments to editor)	We have broken this into two sentences which we hope addresses the reviewers concerns here.
Peer Reviewer #4	Introduction	p. 16, line 47--suggest edit to read "The 2004 AHRQ review by Helfand and colleagues . . . "	We have added the language suggested by the reviewer

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Peer Reviewer #4	Introduction	p. 17, line 14--consistency, is the suprascript references supposed to be inside or outside the final punctuation in your template? don't care, just make it the same throughout	We have corrected this according to the AHRQ EHCP Style Guide.
Peer Reviewer #4	Methods	Were non-English studies excluded? Not explicit on that point.	Non-English studies were not excluded. Our original search found a total of 948 individual articles published from 2002 to 2009. After selection of articles for review, we found that no foreign language articles had been included. To ensure that we had not erred in our selection of articles we re-reviewed the abstracts of foreign language articles from the original search and expanded our search to include CINAHL and the WHO Global Health Library, databases with broader indexing of foreign-language journals.
Peer Reviewer #4	Methods	Did you search initially only for U.S. done studies (ES-4, line 33). This line makes me think that, but wouldn't recommend that unless there is a good reason that is explained fully.	We have modified the language to clarify that our search was not restricted to English-language studies.
Peer Reviewer #4	Methods	p. 22--line 37--specify language restrictions (see also p. 23 line 5)	There were no language restrictions. We have revised the text and hope this is now clearer.
Peer Reviewer #4	Methods	p. 30--line 10--U.S. rather than US	We have made this change
Peer Reviewer #4	Results	Table 7, p. 32--formatting issues: put the suprascript ref number in after citation; under sample size column center number; quality score column appears to be not needed for this table? why studies not rated?	We have included citations in all tables and centered the sample size column

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Peer Reviewer #4	Results	p. 33, line 41--uncertain why you would include studies which included pts with known thyroid disease. Doesn't that defeat the SUB clinical part of this review?	We did not include any original articles with patients with known thyroid disease. However, because of the paucity of studies on asymptomatic individuals screened in primary care settings we felt it necessary to include studies of patients with subclinical thyroid disease, without history of known overt thyroid disease, drawn from settings other than primary care. Our limitations section discusses issues raised by including previous systematic reviews that did include patients with known thyroid disease in this report.
Peer Reviewer #4	Results	p. 37, table 8a--formatting issue, would be better to move the N column to left of each thyroxine column and placebo columns	Ns are provided in Table 8. For consistence with the other detail tables 8b - 8g, we have removed the columns of Ns from Table 8a
Peer Reviewer #4	Results	p. 38, table 8b--move quality rating to far right. having it on the far left is confusing. also consider adding N to the right of the citation; similar comment for Tables 8c-e, 9a-b	In the main quality tables-- 8 and 9-- and the summary table--10-- we list quality on the right, but we could not find a way to do that legibly in the subtables (Tables 8b-g and Tables 9a-d).
Peer Reviewer #4	Results	p. 42, table 8f--add duration to dosage column header; on the Nagasaki study I'm unclear whether you are saying that after 5 months it was clear what dose? or whether the duration was 5 months for the whole study and the dose wasn't stated	We have added Duration to the column head and corrected the information on dosage for Nagasaki.
Peer Reviewer #4	Results	p.45 and other spots with results variously in mg/dL would be helpful to have an appendix with conversion to mmol/L units too	We have added this to Appendix A1 and included a reference to the conversion table in the report
Peer Reviewer #4	Results	p.47, line 12--alternating assignment isn't an RCT and shouldn't be classed as such. It is a controlled clinical trial.	This study was described as a controlled trial not a randomized controlled trial.
Peer Reviewer #4	Results	p.56--blank page makes me think that something is missing. Start Benefits section on this page.	This has been corrected
Peer Reviewer #4	Results	p. 57, table 10A--some subtables are Xa and some XA--be consistent. On 10A Risk of Bias column why are some N/A and one rated Fair?	Risk of bias was marked "N/A" when no studies were available for that particular outcome

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Peer Reviewer #4	Discussion/Conclusion	Limitations, p. 66, line 40--studies of abnl TSH, but also a "normal" T4	We have made the correction suggested by the reviewer
Peer Reviewer #4	Discussion/Conclusion	Expansion of Discussion to include the following issues that need to be address in future studies may be beneficial:	Good suggestion, this section was revised to incorporate this suggestion
Peer Reviewer #4	Discussion/Conclusion	--primary care identification and treatment of pts as opposed to the (mostly) specialist nature of these studies in current review	Good suggestion, this section was revised to incorporate this suggestion
Peer Reviewer #4	Discussion/Conclusion	--must be powered to detect harms	Good suggestion, this section was revised to incorporate this suggestion
Peer Reviewer #4	Discussion/Conclusion	--need sufficient time to detect potential harms which may be a role for large database studies such as UKGP database	Good suggestion, this section was revised to incorporate this suggestion
Peer Reviewer #4	Discussion/Conclusion	--what are the key outcomes which should be studied? if any of these are subject to interpretation and use different measures (e.g. QOL) then MS should recommend particular measures and instruments for use to standardize results across future studies	Good suggestion, this section was revised to incorporate this suggestion
Peer Reviewer #4	Clarity and Usability	MS needs general copy editing. There are some typos. Too many sentences are over-long and/or run on. This makes the report harder to read than it needs to be. There are also many inconsistencies in style, formatting and some in spelling. Throughout the paper there are inconsistencies about spelling out numbers below 10.	We have edited the document and hope that the revisions address the reviewers concerns.
Peer Reviewer #4	Executive Summary	ES-6 through ES-8 are landscape and should be portrait orientation.	This has been corrected
Peer Reviewer #12	General Comments	The report is clinically relevant based on the potential prevalence of subclinical hypothyroidism in the general population. Key questions are appropriate.	Thank you
Peer Reviewer #12	Introduction	Introduction provides an excellent review of thyroid functioning, screening parameters, clinical outcomes and potential benefits and harms.	Thank you
Peer Reviewer #12	Methods	Inclusion and exclusion criteria are appropriate. I especially like the analytic framework which was very comprehensive. There is limited data for statistical analyses.	Thank you – no response required
Peer Reviewer #12	Results	The results section is complete. There are few results given the paucity of studies, particularly RCTs, in this area.	Thank you – no response required

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Peer Reviewer #12	Discussion/ Conclusion	The implications of the lack of data are clearly stated- essentially that we are unable to make any change in the current recommendations.	Thank you – no response required
Peer Reviewer #12	Clarity and Usability	It would be helpful to include an outline of studies that need to be performed. It would also be useful to list them in order of priority. Such a list, I believe would inform AHRQ on potential funding priorities in this field.	Good suggestion, this section was revised to incorporate this suggestion
Peer Reviewer #6	General Comments	The report is very well done and I have relatively few suggestions. The rationale, methods and results are nicely described and clear. The tone and inferences of the report are generally balanced, with several some exceptions noted below. The significant issues which deserve additional consideration are:	Thank you.
Peer Reviewer #6	General Comments	Screening for TSH abnormalities vs. the timing of treatment of TSH abnormalities. The report should clarify how these two differ conceptually and practically, since key questions 1 and 2 specifically relate to screening and key questions 3 and 4 relate to the benefits and harms of early treatment. I think it is important to point out somewhere that the results of screening vs. no Screening trials could differ from the results obtained from trials of early vs. late treatment of TSH abnormalities. This could occur if TSH abnormalities did cause harm but such harms were only found when TSH progressed to some level as bad as or worse than the threshold for treatment with delayed therapy. For example, if only individuals with TSH>10 benefited from treatment, trials of immediate vs. expectant treatment of those with TSH>5 would show no difference if everyone in the expectant arm was treated when TSH reached 10, while under the same hypothetical circumstances screening trials might show a benefit to those who are screened compared to those who are not screened because some of those who aren't screened will progress to TSH>10.	We agree that the results of the trials of screening could differ from the results of trials of treatment. Changes to the future research section were made to incorporate this suggestion.
Peer Reviewer #6	General Comments	Review of harms associated with subclinical thyroid dysfunction. I realize that this was not a specific aim of the review, but there are new published data relating clinical heart failure outcomes with subclinical hypothyroidism that should be included. Specifically, subclinical hypothyroidism is associated with an increased risk of clinical heart failure in two prospective cohorts (Health ABC and CHS), and future studies should include heart failure outcomes.	Edits were made to incorporate these studies and this comment.

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Peer Reviewer #6	Executive Summary	ES-6, Key Question 2. I would delete the last sentence (line 29-30) as the two studies cited are problematic (one did not require subclinical disease for at least 3 months before enrollment and one only enrolled individuals >85).	Some of our reviewers felt that we should have given more emphasis to these studies, some thought that we made too much of them. We reviewed our discussion of these studies and agree that these studies are not ideal to answer this question. We acknowledge that, in fact we did not assign a quality rating to these studies, because they only indirectly shed light on this issue. We feel that our discussion in the report regarding this issue is balanced. .
Peer Reviewer #6	Executive Summary	ES-8, Key Question 4. Again the last sentence (line 12-14) is problematic as this is not referenced or further discussed in the report. Overtreatment" is a poor choice of words as it implies over replacement and I believe the authors intended to say "unnecessary treatment."	This line was deleted from the report.
Peer Reviewer #6	Introduction	Table 1 should be labeled "Symptoms and Signs of Overt Thyroid Dysfunction."	We have made the revision suggested by the reviewer.
Peer Reviewer #6	Introduction	Page 3, line 27. I think the authors should comment that the threshold of TSH>10 is completely arbitrary and probably represents digit preference rather than any real biologic differences.	Text edits have been made to address this comment
Peer Reviewer #6	Introduction	Page 5, line 38-49. It is probably relevant to describe the growing literature that demonstrates differences in CV and skeletal outcomes even within the "normal range" of TSH.	While we appreciate that this research is important in understanding the effects of thyroid hormone, it is outside the scope of this review.
Peer Reviewer #6	Introduction	Page 6, line 9-10. There is no evidence that treatment of subclinical hypothyroidism is associated with worse outcomes in the elderly and to pose this is pure conjecture.	these sentences were deleted
Peer Reviewer #6	Introduction	Page 8, line 9. Would add a subheading "Subclinical Hypothyroidism" here, and I would point out that existing management strategies are based on expert opinion not trials.	We have added the subheading.
Peer Reviewer #6	Introduction	Page 14, line 14. Prevention of heart failure is also a potential reason for treatment.	We added text to address this concern

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Commentator	Section	Comment	Response
Peer Reviewer #6	Introduction	Page 8, line 18. Again, a treatment threshold of TSH>10 is arbitrary and not based on evidence.	Changes to text addresses this concern
Peer Reviewer #6	Introduction	Page 16, line 38-42. Since the re-analysis of the Whickham study adjusted for lipids at baseline and relatively little lipid lowering therapy was prescribed during the study interval, it seems unlikely that the potential effects of subclinical hypothyroidism are mediated by lipids or that that treatment with statins would have much effect.	Our discussion said that the reanalysis was better evidence than we had before, but would not meet the standard we used for novel CV risk factors. We disagree that treatment with statins would not have an effect.
Peer Reviewer #6	Introduction	Page 17, line 17. Would add a subheading "Subclinical Hyperthyroidism."	We have added the subheading.
Peer Reviewer #6	Introduction	Page 17, line 31-40. The summary does not reflect the preceding paragraphs. I would say the best study suggests a substantial increase in CV risk with subclinical hypothyroidism, and other studies suggest that the association may be stronger in those <65.	In the context of our previous work on CV risk factors, we don't feel that the evidence about subclinical hypothyroidism is as clear as the reviewer suggests. We reviewed our discussion of this issue but feel the current wording : "Epidemiologic data suggest that subclinical hypothyroidism is associated with cardiovascular disease in subjects younger than 65 years, but the magnitude of risk is low." accurately describes the literature
Peer Reviewer #6	Methods	This section is excellent.	Thank you
Peer Reviewer #6	Results	Page 33, line 10-26. As noted above, these two studies are problematic and there is no evidence to support a 1-2 year observation period. Where did that come from???	we accurately describe the studies and are up front that are indirectly related to the key question. We removed the "1-2 year" from the sentence
Peer Reviewer #6	Results	Table 10AB is great, except line 32 on page 57 says "coronary heart failure"	We have corrected this.
Peer Reviewer #6	Discussion/ Conclusion	Page 62, line 17. Omission of data on heart failure is problematic.	we feel the term "cardiovascular" includes both, CAD and CHF.
Peer Reviewer #6	Discussion/ Conclusion	Page 62, line 32. Lipid treatment may be unrelated to the effect of subclinical thyroid dysfunction.	See answer to Comment #94 – we do not feel that subclinical thyroid dysfunction meets the standard we used for novel CV risk factors.

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Commentator	Section	Comment	Response
Peer Reviewer #6	Discussion/Conclusion	Page 62, line 38-43. I am not sure such pessimism is warranted without better data: it is possible that the population attributable risk is substantial.	Edits were made based on this comment --
Peer Reviewer #6	Discussion/Conclusion	Page 67, line 25. I think the preponderance of the evidence, and the Wickham reanalysis, shows that subclinical hypothyroidism is associated with a small increase in CHD events.	See response to comment #96. We do not feel that the evidence fully supports this assertion
Peer Reviewer #6	Discussion/Conclusion	Page 67, line 36. This is just plain wrong and is clearly biased. The natural history is not well studied.	edits were done based on this comment
Peer Reviewer #6	Discussion/Conclusion	Page 67, line 45. We don't know that unnecessary treatment is associated with serious harms unless there is over-replacement!	We agree with the reviewer, but don't feel that the language in the report suggests otherwise.
Peer Reviewer #6	Discussion/Conclusion	Page 69, line 10-14. Would replace "power" with some other term, such as "internal validity." It is not at all clear that including subjects with serologic evidence of autoimmunity is necessary or helpful.	edits were made based on these comments
Peer Reviewer #6	Clarity and Usability	The report is clear and usable.	Thank you
Peer Reviewer #1		Well done	Thank you
Public Comment	Executive Summary	All well done	Thank you

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