

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form ([see an example](#)) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Male Pattern Baldness and Its Association with Coronary Heart Disease: A Meta-Analysis
AUTHORS	Yamada, Tomohide; Hara, Kazuo; Umematsu, Hitomi; Kadowaki, Takashi

VERSION 1 - REVIEW

REVIEWER	Paulo A Lotufo University of Sao Paulo
REVIEW RETURNED	12-Jan-2013

GENERAL COMMENTS	No major corrections for a well presented systematic review.
-------------------------	--

REVIEWER	Dr Stephen-Mark Cooper (PhD) Reader & Graduate Studies Coordinator Cardiff School of Sport : Athrofa Prifysgol Cymru, Caerdydd Cardiff Metropolitan University : Prifysgol Fetroplitan Caerdydd There are no competing interests.
REVIEW RETURNED	15-Jan-2013

RESULTS & CONCLUSIONS	The authors need to consider the points about the table and figures I have raised in my review of the MS attached herewith.
GENERAL COMMENTS	<p>In this manuscript (MS), the authors have applied some of the most appropriate meta-analysis statistical methods to investigate the relationship between male pattern baldness and coronary heart disease (CHD) risk factors.</p> <p>The study is conducted on a large sample of subjects but unfortunately these subjects are drawn from a total of only six previously published studies.</p> <p>As I am not an expert on the body of research that is the focus of this meta-analysis I have limited myself to making general comments about the MS and its presentation, and more specifically the research design and the statistical analyses of the data. The study is well-designed, the research is well-organised, the data seem to have been collected appropriately and the data are expertly handled and analysed. As far as the methodology is</p>

concerned I am convinced that I could replicate the study based on the description the authors provide in the MS. The authors communicate their arguments in a clear and concise manner in a paper that is well crafted and skilfully written.

If I have any criticisms of the MS at all it is to do with the lack of consistency in the expression of terms; primarily the mixed-economy use of relation/relationship/association throughout when identifying the aim of the meta-analysis. 'Relation' is a term that should not be used at all but 'relationship' is acceptable as is 'association' but not the mix of terms that appears here. The authors should chose one term and be consistent with its use throughout the MS. If it is of any help, 'relationship' unusually is linked with a correlation based analysis and 'association' when a chi-squared based test has been applied. Interestingly, the authors indicate in the method section that Cochrane's χ^2 test was used to analyse data but no feedback on outcomes are recorded in the results or the discussion sections of this MS. I also found the amount of information, and the manner in which it was being expressed in the Table and in the Figures confusing. I would also like to see all statistical indices expressed in italics where appropriate (e.g. *CI*, *P*, *n*, χ^2 , I^2 etc.).

I realise that such points might seem pedantic but then ... one man's pedantry is another man's precision! Seriously, this was a really good paper, and even though I have no background in the academic area other than the research design and the statistics used, it was one which I thoroughly enjoyed reading.

My specific comments are as follows.

Abstract (page 2)

Line 12: ... so are the authors confirming 'the association' or 'the relationship' **between** (not of) male pattern baldness **and** (not with) coronary heart disease (CHD)? I'm asking for a consistent term to be used throughout the MS not the mixed-economy of terms used here.

Line 26: ... suggest ... both 'baldness' and 'coronary heart disease' and the reference lists of those studies identified were also searched.

Line 44: ... suggest ... interval (95% *CI*) were estimated using the ...

Line 53: ... suggest ... Included 850 possible studies, three cohort studies and three case-control studies (36,990 subjects).

Page 3; Line 9: (and elsewhere in the MS) ... 95%CI: 1.08 – 1.63, $P = 0.008$, $f^2 = 25\%$ (spacing, superscripting and italics)

Line 15: the same thing ... (95%CI: 1.11 – 1.86, $P = 0.006$, $f^2 = 0\%$).

Line 38: (and elsewhere in the MS) ...

Line 40: (and throughout the MS) ... **might** (not may) ...

Article summary (page 4)

Line 12: Again is it ‘the association’ or ‘the relationship’ **between** (not of) male pattern baldness (androgenetic alopecia) **and** (not with) coronary heart disease (CHD)? A consistent use of term.

Line 21: ... suggest ... studies with **a total of** 36,690 subjects ... the relationship depends **upon** the ...

Line 29: ... **might** (not may) ...

Line 35: ... suggest investigated **in** further studies ...

Line 44: ... do you mean relationship or association? Not ‘relation’.

Line 50: ... spacing ... 11.0 – 14.0 years.

Line 53: ... **might** (not may) ...

Introduction (page 5)

Line 18: ... suggest ... participants in **wellbeing programmes** often also ...

Line 21: suggest ... screening **has** yet to be confirmed. Young *et al.* (2009) reported that ...

Line 27: ... suggest ... scintigraphy (3), and McEvoy *et al.* (2011) also reported that computed tomography screening ... You don’t use CT again so it should not be abbreviated here – I’m presuming it is computed tomography of course!

Line 50: ... suggest ... is a classic feature of this **thinning** condition (7).

Line 53: ... suggest ... with the risk of **CHD** (8-13).

Line 58: Is it ‘the relationship’ (or ‘the association’) between

baldness and CHD? Not 'relation'.

Page 6; line 6: ... or is it the relationship'?! Also, you could provide some examples here from the literature to illustrate how the associations/relationships vary.

Line 15: ... suggest ... a cardiac event **thereby allowing** the delivery ...

Methods (page 6)

Line 35: you are very precise about the end of the data collection (27/11/2012) but from when in 1950 did you start the data collection?

Line 38: ... suggest ... headings "baldness" (... and "coronary heart ... Also, did you put CHD into the search as well as coronary heart disease?

Line 44: ... suggest ... observational studies that **estimated** the association ... or is it 'relationship'?

Line 47: ... suggest ... The reference lists of all studies **identified** were also reviewed.

Page 7; line 6: ... involved a full-text review.

Line 9: ... association or relationship but not relation.

Line 15: ... covariates not confounders.

Line 56: ... non-randomized.

Page 8; line 6: ... (15)? Should be on previous page.

Line 27: is this the country where the study was conducted or where the article was published?

Line 38: ... covariates not confounders.

Line 41: ... (and elsewhere in the MS) you used (95%CI) previously ... be consistent. Also, you could do with a reference for the DerSimonian-Laird random effect model here.

Line 47: ... (and elsewhere in the MS) ... z-statistic test. Cochrane's χ^2 test and the I^2 test a threshold *P*-value of 0.10 (italics). Also, why was the *P*-value of 0.10 chosen – it can't be arbitrary – what type of error were you willing to make?

Page 9; line 6: you need a reference here for the Begg and Egger test. But is it not Begg's test and Egger's test (this is suggested on p.13, line 44)? In which case you need a reference for each.

Results (page 9)

Line 44: ... suggest ... used for **the present** meta-analysis.

Line 53: ... The **six** studies that were selected included **three** cohort studies and **three** case-control ...

Page 10; line 6: is this the country where the study was conducted or where the article was published?

Line 9: ... suggest ... the other **two** (8, 12) were **conducted** in the ...

Line 12: they are samples in studies not populations. Also, which study (ref) had the 1437 subjects and which study (ref) had the sample of 19112 subjects?

Line 15: ... suggest ... In **five** of the **six** studies ...

Line 21: ... suggest ... employed in **four** studies ... being used in the other **two** studies ...

Line 30: ... suggest ... original scale to the following five **categories:** ...

Line 47: ... suggest ... scales, Ford *et al.* (1996) classified ...

Line 55: ... suggest ... In the other study, Miric *et al.* (1998) ...

Page 11; line 18: ... suggest ... on all **three** cross-sectional ...

Line 24: ...suggest ... influence of **covariates**. The reports on all **three** studies ...

Line 29: ...suggest ... but the other **five** studies ...

Line 35: association or relationship?

Line 41: ...suggest ... studies used in **the present** meta-analysis ...

Line 53: ...suggest ... Among the **six** studies

Page 12; line 123: ...suggest ... In the **three** cohort ...

Line 15: (and throughout the rest of the MS) it should be f^2 throughout.

Line 21: association or relationship?

Line 27: ... suggest ... In the **three** case-control ...

Line 35: ... suggest ... was **non-significant** ...

	<p>Line 50: association or relationship?</p> <p>Page 13; line 12: ... suggest ... there was a non-significant (association or relationship)</p> <p>Line 21: ... suggest ... baldness into four grades ...</p> <p>Lines 23 & 47: association or relationship?</p> <p>Line 50: ... suggest ... revealed non-significant ... <i>P</i> ≥ 0.05. Italics and spacing.</p> <p>Discussion (page 14)</p> <p>Line 9: ... suggest ... The present meta-analysis of six studies ...</p> <p>Line 12: ... suggest ... was significantly associated (or related) with ...</p> <p>Line 15: ... suggest ... was non-significantly associated (or related) with ...</p> <p>Line 21: ... suggest ... the relationship between CHD and baldness was ...</p> <p>Line 32: is it Regaine?</p> <p>Line 41: ... suggest ... This might lead to the shedding ...</p> <p>Page 15; line 18: association or relationship?</p> <p>Line 56: ... suggest ... baldness might be caused ...</p> <p>Page 16; line 24: ... suggest <i>Strengths and limitations</i></p> <p>Line 26: ... suggest ... The strengths of the present meta-analysis ...</p> <p>Line 38: ... suggest ... However, the present meta-analysis ...</p> <p>Line 47: ... suggest ... factors showed non-significant ...</p> <p>Line 55: ... suggest ... contributed to the heterogeneity ...</p> <p>Page 17; line 6: ... suggest ... Lesko <i>et al.</i> (1993) ...</p> <p>Line 15: ... suggest ... Lesko <i>et al.</i> (1993) ...</p> <p>Lines 21 & 22: why does the font change here?</p> <p>Line 27: already (spelling)</p> <p>Line 27: according to the reference list the Rebera article only has the one author so <i>et al.</i> is not needed but the date needs to be</p>
--	---

appended ... by Rebora (2001, 33), Lotufo *et al.* (2000, 10) ...

Line 35: association or relationship?

Line 44: **might** not may

Conclusions (page 18)

Line 23: ... suggest ... baldness was **significantly** associated (or related?) with ...

Line 26: ... suggest ... and the **relationship** (or association) was dependent ...

Line 29: association or relationship?

Line 33: ... suggest ... than **with** frontal ...

Line 41: association or relationship? Also, ... suggest ... investigated **in** further ...

Table 1 (page 27)

This is certainly a 'busy' table but it is necessary in the context of the research design and the analysis. In the legend decide if it is an 'association' or a 'relationship'. In the column titles is it the 'year' of publication that is meant? What does 'country' relate to – where the study was conducted or where the article was published? Do you mean the *n* of 'subjects'?

Figure 1 (page 29)

On the copy I downloaded for review this Figure was overtyped with standard BMJ information.

Figures 2, 3 & 4 (pages 30, 31 & 32)

These were confusing figures. It was not clear what was trying to be

	illustrated here. The numerics were fine but I was unsure what the schematics were meant to portray. f^2 not I squared.
--	---

REVIEWER	Shih-Ying Lee. MD Director in Department of Neurology, West Garden Hospital, Taiwan.
REVIEW RETURNED	25-Jan-2013

GENERAL COMMENTS	<p>There are several points need to be clarified as listed in the followings:</p> <ol style="list-style-type: none"> 1. There were several occasions in this paper mentioned of younger men (55 or ≤ 60 years), but in Fig. 2&3, they used ≤ 60 years (Check Page 3, line 9-12; page 12, line 18 & 36-39). They might need an explanation or to be more consistent on the range of age. 2. Page 3, line 27, at the end: (0.92-1.32, P=0.28) should be (0.92-1.32, P=0.28). 3. Page 5, line 52-55: Since the result of ref. 13 did not support baldness associated with risk of coronary heart disease (CHD), it should be (8-12) instead of (8-13). (check page 11, line 30); Also, page 12, line 48-51: "All three studies (10,11,13)..." needs to be rephrased. 4. Page 16, line 18: By "arteriosclerosis", did you mean atherosclerosis? 5. There are several articles emphasized on early onset androgenetic alopecia like ref. 22, 25, 28 of this article, and "Early onset of androgenetic alopecia (AGA) associated with early severe coronary heart disease: a population-based case control study. By Matilainen VA, et al. J of cardiovascular Risk, 2001, Vol; 8(3): 147-151.". It would be nice to add some concept of early onset AGA to the risk of CHD in the discussion and in the weakness of this article.
-------------------------	---

VERSION 1 – AUTHOR RESPONSE

1. 'Impact of' in the title seems to conflict with the study aim which to assess the 'association', not 'impact'.

Thank you for your numerous valuable comments about our paper. The title has been changed as follows in response to your advice: "Male Pattern Baldness and Its Association with Coronary Heart Disease: A Meta-Analysis".

2. A limitation is that you only looked at English language studies;

We only searched English studies for inclusion in this meta-analysis and we might possibly have overlooked some non-English literature, which might have resulted in a selection bias. However, we also investigated all of the references in each study as far as possible. Also, there was no significant publication bias, and the fact was added to the Discussion. Page 17/Lines 9-24.

3. We would also think you should provide a more balanced message in you conclusion. At present you say younger men with vertex baldness should be encouraged to increase their cvd profile, but we think this needs to be balanced against the potential for over-medicalising - after all male pattern baldness affects 30-40% of adult men.

The sentence starting with "Thus, cardiovascular risk factors~" in Conclusions was toned down to

"Thus, cardiovascular risk factors should be reviewed carefully in men with vertex baldness, especially younger men, and they probably should be encouraged to improve their cardiovascular risk profile". The following sentence was also added: "However, the usefulness of CHD screening in asymptomatic populations is yet to be elucidated, so the screening method (e.g., exercise ECG, coronary computed tomography, or scintigraphy) employed should be practicable in terms of its advantages/disadvantages and cost performance, and patients should be evaluated for eligibility before screening to avoid possible over- medicalization since male pattern baldness affects 30-40% of adult men (5)". Page 19/Lines 9-29.

Dear Dr. Lotufo,

1. No major corrections for a well presented systematic review.

Thank you for reviewing our manuscript and we appreciate your kind comments.

Dear Dr. Cooper

Thank you for your valuable advice. We were deeply impressed by your encouragement.

We are convinced that our report has been improved thanks to your detailed and accurate comments.

We have revised the text based on a total of 85 specific comments.

Replies to other questions are shown below.

1. If I have any criticisms of the MS at all it is to do with the lack of consistency in the expression of terms; primarily the mixed-economy use of relation/relationship/association throughout when identifying the aim of the meta-analysis.

In response to the advice of Dr. Richard Sands, the managing editor, and Dr Alison Walker, Associate editor, the title of the study was changed to "Male Pattern Baldness and Its Association with Coronary Heart Disease: A Meta-Analysis". The term "association" has now been used throughout the text to maintain consistency with the title.

2. 'Interestingly, the authors indicate in the method section that Cochrane's χ^2 test was used to analyse data but no feedback on outcomes are recorded in the results or the discussion sections of this MS.

The results of Cochrane's test for heterogeneity have been added to the Results section. The figures were also corrected. Page 12/Lines 15-30.

3. I would also like to see all statistical indices expressed in italics where appropriate (e.g. CI, P, n, χ^2 , I² etc.).

"I squared" was changed to "I²" throughout the text.

4. Methods (page 6)Line 35: you are very precise about the end of the data collection (27/11/2012) but from when in 1950 did you start the data collection?

We started the data collection on January 1, 1950. This has been added to the "Methods" section. Page 6/Line 38.

5. Methods Line 38: ... suggest ... headings "baldness" (... and "coronary heart ... Also, did you put CHD into the search as well as coronary heart disease?

We did not put CHD into the search because it is an abbreviation and was not likely to be in the title of a paper or abstract. We searched again using CHD just for confirmation, but the number of papers

retrieved was nearly the same and did not affect the number of papers included in the present meta-analysis.

6. Methods Line 27: is this the country where the study was conducted or where the article was published?

The country where the study was conducted. This has been added to the "Methods" section. Page 8/Lines 29-32.

7. Methods Line 41: you could do with a reference for the DerSimonian-Laird random effect model here.

"DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986 Sep; 7(3): 177-88." was added to the list of references (Ref #16). Page 8/Lines 49.

8. Methods Line 47: ... (and elsewhere in the MS) ... z-statistic test. Cochrane's χ^2 test and the I2 test ... a threshold P-value of 0.10 (italics). Also, why was the P-value of 0.10 chosen – it can't be arbitrary – what type of error were you willing to make?

A P value of <0.05 was also made significant for the test of heterogeneity and the text has been corrected accordingly. Page 9/Lines 15-18.

9. Methods Page 9; line 6: you need a reference here for the Begg and Egger test. But is it not Begg's test and Egger's test (this is suggested on p.13, line 44)? In which case you need a reference for each.

References to both the Begg test (Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics*. 1994 Dec; 50 (4): 1088-101.) and the Egger test (Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997 Sep 13; 315 (7109): 629-34) have been added (Ref #18,19). Page 9/Line 9.

10. Results (page 9); Line 12: they are samples in studies not populations. Also, which study (ref) had the 1437 subjects and which study (ref) had the sample of 19112 subjects?

Lesko (Ref 11) had a sample size of 1,437 subjects and Lotufo (Ref 10) had a sample size of 19,112 subjects. This information has been added. Page 10/Lines 15-18.

11. Discussion (page 14); Line 32: is it Regaine?

Yes. The brand name of minoxidil is Regaine in Europe and Asia, but it is Rogaine in the U.S. and Canada. Both Rogaine/Regaine are listed now. Page 14/Line 52.

12. Figure 1 (page 29): On the copy I downloaded for review this Figure was overtyped with standard BMJ information.

As you pointed out, the PDF file for peerreview was overtyped with BMJ information. However, the original PowerPoint file doesn't include this information. I will check this during proofread process. Thank you.

13. Table 1 (page 27)

This is certainly a 'busy' table but it is necessary in the context of the research design and the

analysis. In the legend decide if it is an 'association' or a 'relationship'. In the column titles is it the 'year' of publication that is meant? What does 'country' relate to – where the study was conducted or where the article was published? Do you mean the n of 'subjects'?

"Year" means the year of publication and the "country" refers to the country where the study was conducted. "Subjects" mean all subjects who participated in the study and the text has been corrected accordingly. Page 8/Lines 29-32.

14. Figures 2, 3 & 4 (pages 30, 31 & 32)

These were confusing figures. It was not clear what was trying to be illustrated here. The numerics were fine but I was unsure what the schematics were meant to portray. I² not I squared.

The statement "RR for presence of male pattern baldness" has been added to the RR section of the Forest Plot. Results of the test of heterogeneity have also been added. As instructed, "I squared" was changed to "I²".

Dear Dr. Lee

Thank you for reviewing our manuscript and we appreciate your kind comments.

1. There were several occasions in this paper mentioned of younger men (55 or ≤ 60 years), but in Fig.2&3, they used ≤ 60 years (Check Page 3, line 9-12; page 12, line 18 & 36-39). They might need an explanation or to be more consistent on the range of age.

"Patients aged ≤ 60 years" in Figs. 2 and 3 was corrected to "Patients aged < 55 or ≤ 60 years".

2. Page 3, line 27, at the end: (0.92-1.32. P=0.28) should be (0.92-1.32, P=0.28).

3. Page 5, line 52-55: Since the result of ref.13 did not support baldness associated with risk of coronary heart disease (CHD), it should be (8-12) instead of (8-13). (check page 11, line 30); Also, page 12, line 48-51: "All three studies (10,11,13)..." needs to be rephrased.

Corrections were made as instructed.

4. Page 16, line 18: By "arteriosclerosis", did you mean atherosclerosis?

This was corrected to "atherosclerosis".

5. There are several articles emphasized on early onset androgenetic alopecia like ref.22,25,28 of this article, and "Early onset of androgenetic alopecia (AGA) associated with early severe coronary heart disease: a population-based case control study. By Matilainen VA, et al. J of cardiovascular Risk, 2001, Vol; 8(3): 147-151.". It would be nice to add some concept of early onset AGA to the risk of CHD in the discussion and in the weakness of this article.

Thank you for this very useful advice. An addition was made to the Discussion as follows: "Our meta-analysis of young men alone also showed a significant relationship between androgenetic alopecia (AGA) and the risk of CHD like that revealed by the meta-analysis of men of all ages (Figs. 2,3). The results were consistent with those of many studies published so far, which have shown that early onset of AGA is related to a risk of early severe CHD and its risk factors (23,24,25,26)". The paper of Dr. Matilainen was also added (Ref #26).Page 14/Lines 35-44.