Supporting Information

Efficacy of non-surgical treatments for androgenetic alopecia in men and women: a systematic review with network meta-analyses, and an assessment of evidence quality

Aditya Gupta [1,2]. Mary Bamimore[1]. Kelly Foley[1]

[1]Mediprobe Research Inc., London, Ontario, Canada.
[2]Division of Dermatology, Department of Medicine, University of Toronto School of Medicine, Toronto, Ontario, Canada

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S1 Appendix Copy of the protocol registered with PROSPERO (ID: CRD42019138703)

Note: After the protocol for our study was registered in 2019, we updated the search on January 2nd, 2020.

A systematic review and network meta-analysis of non-surgical interventions for androgenetic alopecia

Aditya K. Gupta, Mary A. Bamimore, Kelly A. Foley

Citation

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Review question

What is the relative efficacy of non-surgical treatments for androgenetic alopecia?

Searches

We will search the following electronic databases: PubMed, EMBASE, Scopus. We will also search the US National Institutes of Health Ongoing Trial Register (www.ClinicalTrials.gov). No limits will be placed on publication year.

Types of study to be included

Randomized controlled trials (RCTs) will be included in this review.

Condition or domain being studied

Androgenetic alopecia (AGA), also known as male pattern hair loss/baldness and female pattern hair loss

Participants/population

Adult men and women diagnosed clinically with androgenetic alopecia

Intervention(s), exposure(s)

Pharmacological treatments will likely include approved and off-label medications such as finasteride, dutasteride, and minoxidil. Treatments may be administered orally or topically. Non-pharamacological treatments will likely include platelet-rich plasma (PRP) therapy and low-level laser/light therapy (LLLT).

Comparator(s)/control

Compared alternatives may include placebo/vehicle/sham, no treatment, or active comparator (drug or device).

Context

Main outcome(s)

Hair density: hair per cm2

Timing and effect measures

Change in hair density from baseline will be measured at the end of treatment.

Additional outcome(s)

None

Timing and effect measures

Not applicable

Data extraction (selection and coding)

Titles, abstracts, and full-text were evaluated by MAB and KAF.

Data will be extracted from studies meeting inclusion criteria by MAB and KAF. Discrepancies identified will be resolved through discussion.

Extracted information will include: author, randomization and blinding methods, attrition data, number of recruitment centers, number of patients randomized, gender, age, severity of hair loss, interventions, dose and duration of interventions, follow-up time period, hair count and/or hair density at baseline and study end point for all interventions, change in hair density from baseline for all interventions

Risk of bias (quality) assessment

The Cochrane Risk of Bias (ROB) tool will be used to assess selection bias, performance bias, detection bias, attrition bias, and reporting bias. ROB will be assessed by two independent reviewers (MAB and KAF) and discrepancies will be resolved through discussion.

Strategy for data synthesis

Participant data will be used whenever possible. In some cases, within-participant controls (half-head) will be necessary. Data will be combined using Mantel-Haenszel random-effects models in RevMan 5.3, with effect sizes expressed as difference of means between the treatment arm vs. control/comparator.

Network meta-analyses will be performed using R. We will perform arm-based network meta-analysis under Bayesian random-effects model. We will complete relative risks and corresponding 95% credible intervals to compare treatments with each other for efficacy. We will produce rank probabilities that to estimate each treatment's surface under the cumulative ranking (SUCRA) curve.

Analysis of subgroups or subsets

If meta-analyses yield high heterogeneity (I^2 statistic greater than 75%), we will explore sources of heterogeneity. This will include, but not be limited to: age, gender, treatment duration. If possible, separate models will be created for males and females.

Contact details for further information

Aditya K. Gupta
agupta@mediproberesearch.com

Organisational affiliation of the review

Mediprobe Research

Review team members and their organisational affiliations

Dr Aditya K. Gupta. Mediprobe Research
Mary A. Bamimore. Mediprobe Research
Dr Kelly A. Foley. Mediprobe Research

Type and method of review

Network meta-analysis, Systematic review

Anticipated or actual start date

01 March 2019

Anticipated completion date

30 August 2019

Funding sources/sponsors

None

Conflicts of interest

Language

English

Country

Canada

Stage of review
Review Ongoing

Subject index terms status
Subject indexing assigned by CRD

Subject index terms
Alopecia; Humans; Network Meta-Analysis

Date of registration in PROSPERO
15 August 2019

Date of publication of this version
15 August 2019

Details of any existing review of the same topic by the same authors
This is an expansion of our earlier review/NMA due to new published studies since the last literature search (16 October 2017). In addition, the outcome measure is different and will allow a greater number of studies to be included.

The citation for the existing review is Gupta et al. JEADV. 2018;32:2112-25.

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Versions
15 August 2019

S2 Appendix. Search methodology for the identification of studies.

Identification of studies through search strategy

PubMed, EMBASE, Scopus and clinicaltrials.gov databases were independently searched—till January 2nd, 2020—by two authors, MAB and KAF.

In PubMed, the following search term was used:

(((((("male pattern alopecia"[Title/Abstract] OR "female pattern alopecia"[Title/Abstract] OR "male pattern baldness"[Title/Abstract] OR "female pattern baldness"[Title/Abstract] OR "androgenic alopecia"[Title/Abstract] OR "androgenetic alopecia"[Title/Abstract] OR "hair loss"[Title/Abstract]))) AND ("treatment"[Title/Abstract] OR "treatments"[Title/Abstract] OR "therapy"[Title/Abstract] OR "therapies"[Title/Abstract] OR therap*[Title/Abstract]))) AND (effic*[Title/Abstract] OR "impact"[Title/Abstract] OR effect*[Title/Abstract])

In Scopus, the following search term was used:

(ABS ("male pattern alopecia" OR "female pattern alopecia" OR "male pattern baldness" OR "female pattern baldness" OR "androgenic alopecia" OR "androgenetic alopecia") AND ABS ("treatment" OR "treatments" OR "therapy" OR "therapies" OR therap*) AND ABS (effic* OR "impact" OR effect*))

In EMBASE, the following search terms (that were all combined with the "AND" Boolean operator) were used:

- ("male pattern baldness" or "female pattern baldness" or "androgenetic alopecia" or "androgenic alopecia" or "male pattern alopecia" or "female pattern alopecia").ab,ti.
- ("treatment" or "treatments" or "therapy" or "therapies" or therap*).ab,ti.
- (effic* or "impact" or effect*).ab,ti.

In Clinicaltrials.gov the search term "androgenetic alopecia" was used.

After search results were de-duplicated, the abstracts and titles were screened, after which full texts were reviewed. At both stages of abstract/title and full-text screens, studies were excluded if they were: non-randomized controlled trials, studies in a non-English language, extension trials, studies with no objective measure for outcome quantification, studies that were primarily investigating adverse events, and studies where combination therapy was a comparator. Any discrepancies in inclusion of studies by MAB and KAF were resolved through discussion. Data extraction were done for studies that were included after full-text screen; the extracted information were organized into spreadsheets by two authors (MAB and KAF). The outcome of interest was change in hair count from baseline in units of hair per square centimeter (hair/cm^2).

For the male and female networks, each comparison was based on a minimum of two randomized controlled trials (RCTs); therefore, any comparison that came from only one eligible study was excluded. Thirty-eight studies were eligible for network meta-analyses, and quality assessment was performed for each study.

S1 Table. The 2015 PRISMA checklist for a network meta-analysis

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Efficacy of non-surgical treatments for androgenetic alopecia in men and women: a systematic review with network meta-analyses, and an assessment of evidence quality	1
ABSTRACT			
Structured summary	2	**Background and objective:** Various treatments exist for androgenetic alopecia (AGA); we determined the relative efficacies of non-surgical AGA monotherapies separately for men and women. **Methods**: Randomized controlled trials (RCTs) were systematically searched in PubMed, EMBASE, Scopus and clinicaltrials.gov. Separate networks were used for men and women; for each network, a Bayesian network meta-analysis (NMA) of mean change in hair count from baseline (in units of hairs per squared centimetre) was done using a random effects model. **Results**: Our networks for male and female AGA included 30 and 10 RCTs, respectively. We identified the following treatments for male AGA in decreasing rank of efficacy: platelet-rich plasma (PRP), low-level laser therapy (LLLT), 0.5mg dutasteride, 1mg finasteride, 5% minoxidil, 2% minoxidil, and bimatoprost. For female AGA the following were identified in decreasing rank of efficacy: LLLT, 5% minoxidil, and 2% minoxidil. The evidence quality of the highest ranked therapies, for male and female AGA, was judged to be low. **Conclusions**: While newer treatments like LLLT are apparently more efficacious than older therapies like 5% minoxidil, the efficacy of the more recent treatment modalities needs to be further validated by future RCTs with low risk of bias.	1
INTRODUCTION			

Rationale	3	Various treatments exist for male and female androgenetic alopecia (AGA), albeit little is known about these treatments' relative effectiveness. Thus, we conducted network meta-analyses to determine the relative effectiveness of AGA therapies for men and women.	2
Objectives	4	To determine the relative efficacy of non-surgical AGA treatments on hair count (hairs/cm^2) in male and female adults (i.e., aged 18 years or above), by conducting a systematic review and network meta-analyses.	2-3
METHODS			
Protocol and registration	5	A protocol for our systematic review with network meta-analyses was registered with the International prospective register of systematic reviews (PROSPERO) database; the registration identification is CRD42019138703.	S1 Appendix (Supplementary Information)
Eligibility criteria	6	Only randomized controlled trials (RCTs) were included; studies were excluded if they were: studies in a non-English language, extension trials, studies with no objective measure for outcome quantification, studies that were primarily investigating adverse events, and studies where combination therapy was a comparator. **Patients**: men and women with androgenetic alopecia (AGA). **Intervention/Comparators**: non-surgical treatments for AGA. **Outcome**: mean change in hair count from baseline (hairs/cm^2).	S2 Appendix (Supplementary Information)
Information sources	7	PubMed, EMBASE, Scopus and clinicaltrials.gov were searched on March 27th 2019, with no date restrictions.	S2 Appendix (Supplementary Information)
Search	8	In PubMed, the following search term was used: (((((("male pattern alopecia"[Title/Abstract] OR "female pattern alopecia"[Title/Abstract] OR "male pattern baldness"[Title/Abstract] OR "female pattern baldness"[Title/Abstract] OR "androgenic alopecia"[Title/Abstract] OR "androgenetic alopecia"[Title/Abstract] OR "hair loss"[Title/Abstract]))) AND ("treatment"[Title/Abstract] OR "treatments"[Title/Abstract] OR "therapy"[Title/Abstract] OR	S2 Appendix (Supplementary Information)

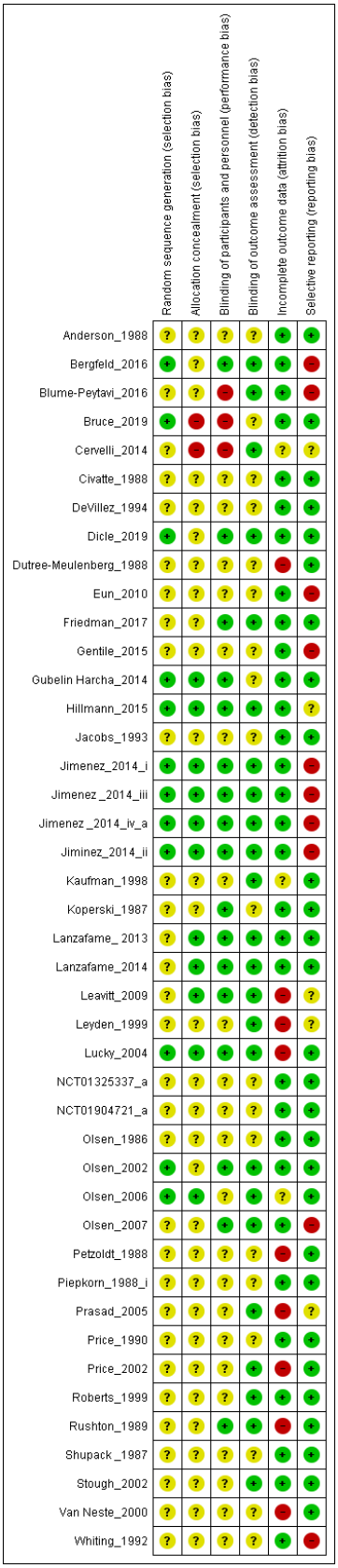
		"therapies"[Title/Abstract] OR therap*[Title/Abstract]))) AND (effic*[Title/Abstract] OR "impact"[Title/Abstract] OR effect*[Title/Abstract]) In Scopus, the following search term was used: (ABS ("male pattern alopecia" OR "female pattern alopecia" OR "male pattern baldness" OR "female pattern baldness" OR "androgenic alopecia" OR "androgenetic alopecia") AND ABS ("treatment" OR "treatments" OR "therapy" OR "therapies" OR therap*) AND ABS (effic* OR "impact" OR effect*)) In EMBASE, the following three search terms were used: • ("male pattern baldness" or "female pattern baldness" or "androgenetic alopecia" or "androgenic alopecia" or "male pattern alopecia" or "female pattern alopecia").ab,ti • ("treatment" or "treatments" or "therapy" or "therapies" or therap*).ab,ti. • (effic* or "impact" or effect*).ab,ti. [all three were combined with the 'AND' Boolean operator]	
Study selection	9	After search results were de-duplicated, the abstracts and titles were screened, after which full texts were screened; the eligibility criteria (i.e., item 6 in this PRISMA checklist) were used for both screens. For the male and female networks, each comparison was based on a minimum of two RCTs; therefore, any comparison that came from only one eligible study was excluded.	S2 Appendix (Supplementary Information), Figure 1
Data collection process	10	Two authors (MAB and KAF) extracted information from eligible studies and organized the data into spreadsheets. The outcome of interest was mean change in hair count from baseline and standard deviation (±SD); when the point estimate (i.e., mean change) and measure of variability (i.e., ±SD) were not given, we estimated the two through various procedures.	4-5, S2 Appendix (Supplementary Information)
Data items	11	For each study that were included after full-text review, we extracted/estimated the following information: author name(s), article's title, mean change in hair count from baseline (±SD) in hairs/cm^2, proportion of participants who are male, mean age (±SD), dose and duration of comparator.	Table 1

Geometry of the network	**S1**	We conducted separate network meta-analysis for the male and female population. Network plots were used to depict the network for men and women. Network plots are constituted of nodes and edges; each therapy is represented by a node, and an edge refers to the line between each node, where the two treatments were directly compared in a head-to-head trial. An edge's thickness corresponds to the number of direct comparisons between the respective nodes.	6
Risk of bias within individual studies	12	Risk of bias within individual studies was assed using Cochrane Collaboration's risk of bias assessment table in Review Manager 5.3 software.	5
Summary measures	13	• Our point estimate of interest was mean change in hair count from baseline (in units of hairs/cm^2), and our measure of variability was the standard deviation (±SD). • Rank probabilities were generated and were used to estimate each treatment's surface under the cumulative ranking curve (SUCRA). • Forest plots (generated by RevMan software) were used to present results from meta-analyses of pair-wise comparison.	6
Planned methods of analysis	14	After eligible studies were identified for the male and female population, network meta-analyses commenced. We carried out an arm-based NMA under a Bayesian random-effects model that assumed normal likelihood and used uniform priors. We used four Markov Chain Monte Carlo (MCMC) chains that each had 20,000 iterations. Relative effects between treatments were quantified as average change in hair count, and 95% credible intervals (CrIs) were computed for each mean. Rank probabilities were generated and were used to estimate each treatment's surface under the cumulative ranking curve (SUCRA).	6
Assessment of Inconsistency	**S2**	For each network, node-splitting analysis was done to assess inconsistency between direct and indirect evidence.	6
Risk of bias across studies	15	Assessment of risk of bias across studies was done using GRADEpro.	5
Additional analyses	16	None.	
RESULTS			

Study selection	17	After 4,213 articles were retrieved, 1,576 were excluded after deduplication. Thus, 2,637 underwent title and abstract screen. Full text review was done for 286 studies; 30 studies were included in our network for male AGA, while 10 studies were included in our network for female AGA.	Fig 1
Presentation of network structure	**S3**	The male and female networks are presented in Figures 2 and 3	Figs 2 and 3
Summary of network geometry	**S4**	The female network constituted 10 studies while the male network constituted 30 studies.	7
Study characteristics	18	Table 1 presents the characteristics of the 40 studies (i.e., 30 and 10 trials of the networks for male and female AGA, respectively). In total, the female network had four comparators (low-level laser therapy, 5% minoxidil, 2% minoxidil and placebo/sham); the male network had eight comparators (platelet-rich plasma (PRP), low-level laser therapy (LLLT), 0.5mg dutasteride, 1mg finasteride. 5% minoxidil, 2% minoxidil, bimatoprost, and placebo/sham).	Table 1
Risk of bias within studies	19	Figure S1 presents risk of bias within studies.	S1 Figure
Results of individual studies	20	In Table 1, the mean change in hair count from baseline is presented.	Table 1
Synthesis of results	21	Relative effectiveness of non-surgical AGA treatments for men and women are presented in Tables 3 and 4, respectively; Tables 5 and 6 present the SUCRA values for non-surgical male and female AGA treatments, respectively. Forest plots for the female and male AGA treatments, are presented in Appendices S4 and S5, respectively.	Tables 3-6, S4 and S5 Appendices
Exploration for inconsistency	**S5**	Given that a node-splitting analysis of consistency is predicated on a network having a closed loop, we could not assess inconsistency in the network for men as it had no closed loop (Fig. 2). The network for the female population had a closed loop, and thus we were able to conduct an inconsistency analysis—the results of which are presented in Table 2. We failed to reject the null hypothesis that there is no inconsistency as the point estimates from indirect and direct comparisons were not significantly different from each other (Table 2). Notwithstanding that our network for men could not be statistically assessed for consistency, we argue that	Table 2

		this network did not violate the assumption of transitivity as we did not perceive any discrepancy between relevant effect modifiers.	
Risk of bias across studies	22	The summary of findings (SoF) tables presents the risk of bias across studies.	S3 Appendix
Results of additional analyses	23	Not applicable.	
DISCUSSION			
Summary of evidence	24	As per SUCRA values, LLLT and PRP were ranked the most effective non-surgical treatment for AGA in women and men, respectively.	Tables 5, 6
Limitations	25	Deciding the most effective treatment should never be solely based on SUCRA rankings as such metrics do not incorporate the certainty level (i.e., evidence quality); thus, interpretations based merely on SUCRA rankings are inconclusive. Low certainty level of the evidence for treatments' effectiveness increases the likelihood that their ranks are due to chance. So, while LLLT and PRP had the highest SUCRA values for women and men, respectively, their evidence quality is low.	11
Conclusions	26	Findings from the current study make a case for the conduct of more randomized controlled trials that investigate the effects of newer AGA treatments, such as LLLT and PRP, with low risk of bias.	12
FUNDING			
Funding	27	None.	

S1 Fig. Risk of bias assessment for individual studies



S3 Appendix. Summary of Findings (SoF) tables

Herein, a summary of findings (SoF) table was produced, by GRADEpro software, for each comparison.

Summary of findings:

0.5 mg Dutasteride compared to Placebo for men with androgenetic alopecia

Patient or population: men with androgenetic alopecia

Intervention: 0.5 mg Dutasteride

Comparison: Placebo

Outcomes	**Anticipated absolute effects** (95% CI) **Risk with 0.5 mg Dutasteride**	№ of participants (studies)	Certainty of the evidence (GRADE)
0.5mg Dutasteride vs. Placebo in men	MD **17.55 hairs per square centimeter higher** (7.95 higher to 27.15 higher)	764 (3 RCTs)	⨁⨁⨁◯ MODERATE [a]

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Downgraded by one because of significant heterogeneity (I^2 =92%)

Summary of findings:

1 mg Finasteride compared to Placebo for men with androgenetic alopecia

Patient or population: men with androgenetic alopecia

Intervention: 1 mg Finasteride

Comparison: Placebo

Outcomes	**Anticipated absolute effects** (95% CI) **Risk with 1 mg Finasteride**	№ of participants (studies)	Certainty of the evidence (GRADE)
1mg Finasteride vs. Placebo in men	MD **15.9 higher** (11.23 higher to 20.57 higher)	2368 (7 RCTs)	⨁⨁◯◯ LOW [a,b]

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Downgraded by one because, in all studies, there is an unclear risk of bias for randomization and allocation concealment

b. Downgraded by one because of serious heterogeneity (I^2= 82%)

Summary of findings:

2% Minoxidil compared to 5% Minoxidil for women with androgenetic alopecia

Patient or population: women with androgenetic alopecia

Intervention: 2% Minoxidil

Comparison: 5% Minoxidil

Outcomes	**Anticipated absolute effects** (95% CI) **Risk with 2% Minoxidil**	№ of participants (studies)	Certainty of the evidence (GRADE)
2% Minoxidil vs. 5% Minoxidil in women	MD **1.81 hairs per square centimeter lower** (5.83 lower to 2.2 higher)	476 (2 RCTs)	⨁⨁⨁◯ MODERATE [a]

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Downgraded by one because, out of the two studies that the meta-analysis was based on, one (i.e., 50% of the studies), one of them had a high risk of bias for blinding of participants and study personnel

Summary of findings:

2% Minoxidil compared to Placebo for women and men with androgenetic alopecia

Patient or population: women and men with androgenetic alopecia

Intervention: 2% Minoxidil

Comparison: Placebo

Outcomes	**Anticipated absolute effects** (95% CI) **Risk with 2% Minoxidil**	№ of participants (studies)	Certainty of the evidence (GRADE)
2% Minoxidil vs. Placebo in women	MD **14.07 hairs per square centimeter higher** (7.44 higher to 20.69 higher)	717 (4 RCTs)	⨁⨁⨁◯ MODERATE [a]
2% Minoxidil vs. Placebo in men	MD **8.1 hairs per square centimeter higher** (5.8 higher to 10.39 higher)	1207 (10 RCTs)	⨁⨁⨁◯ MODERATE [a]

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Downgraded by one because majority of the studies had unclear risk of bias for randomization, and allocation concealment

Summary of findings:

5% Minoxidil compared to Placebo for women and men with androgenetic alopecia

Patient or population: women and men with androgenetic alopecia

Intervention: 5% Minoxidil

Comparison: Placebo

Outcomes	**Anticipated absolute effects** (95% CI) **Risk with 5% Minoxidil**	№ of participants (studies)	Certainty of the evidence (GRADE)
5% Minoxidil vs. Placebo in women	MD **11.74 hairs per square centimeter higher** (5.9 higher to 17.57 higher)	476 (2 RCTs)	⨁⨁⨁⨁ HIGH
5% Minoxidil vs. Placebo in men	MD **14.89 hairs per square centimeter higher** (11.37 higher to 18.41 higher)	598 (3 RCTs)	⨁⨁⨁⨁ HIGH

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Summary of findings:

Bimatoprost compared to Placebo for men with androgenetic alopecia

Patient or population: men with androgenetic alopecia

Intervention: Bimatoprost

Comparison: Placebo

Outcomes	**Anticipated absolute effects*** (95% CI) **Risk with Bimatoprost**	№ of participants (studies)	Certainty of the evidence (GRADE)
Bimatoprost vs. Placebo in men	MD **4.65 hairs per square centimeter higher** (0.62 higher to 8.69 higher)	428 (2 RCTs)	⨁⨁⨁◯ MODERATE [a]

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Downgraded by one because, in all studies, there was unclear risk of bias for randomization and allocation concealment

Summary of findings:

Low level laser therapy compared to Placebo for women and men with androgenetic alopecia

Patient or population: women and men with androgenetic alopecia

Intervention: Low level laser therapy

Comparison: Placebo

Outcomes	**Anticipated absolute effects** (95% CI) **Risk with Low-level laser therapy**	№ of participants (studies)	Certainty of the evidence (GRADE)
LLT vs. Placebo in women	MD **18.84 hairs per square centimeter higher** (14.7 higher to 22.97 higher)	204 (4 RCTs)	⨁⨁◯◯ LOW [a,b]
LLT vs. Placebo in men	MD **20.72 hairs per square centimeter higher** (13.26 higher to 28.18 higher)	254 (4 RCTs)	⨁◯◯◯ VERY LOW [a,b,c]

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Downgraded by one because half the studies had high risk of bias for selective reporting, and half the studies had unclear risk of bias for randomization

b. Downgraded by one because the total sample size was well below 400

c. Downgraded by one because of significant heterogeneity (I^2=71%)

Summary of findings:

Change in hair count from baseline in men (measured in hairs per square centimetre) compared to placebo for AGA

Patient or population: AGA

Intervention: Change in hair count from baseline in men (measured in hairs per square centimetre)

Comparison: placebo

Outcomes	**Anticipated absolute effects*** (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with Change in hair count from baseline in men (measured in hairs per square centimetre)		
PRP vs. Placebo	MD **33.58 higher** (9.91 higher to 57.25 higher)	85 (3 RCTs)	⨁⨁⨁◯ MODERATE [a,b]

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Downgraded by one because sample size was well below 400

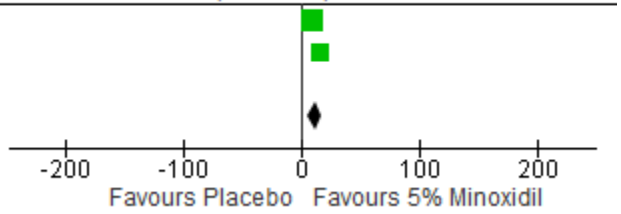
b. Downgraded by one because the funnel plot of the three studies seemed asymmetrical

S4 Appendix Forest plots for pair-wise comparisons of non-surgical treatments for female AGA

S4A Fig. Forest plot for 5% Minoxidil vs. Placebo for women

Study or Subgroup	Experimental Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Bergfeld_2016	13.4	21.92	159	4.3	15.99	165	56.1%	9.10 [4.91, 13.29]
Lucky_2004	24.5	21.9	101	9.4	14.6	51	43.9%	15.10 [9.24, 20.96]
Total (95% CI)			**260**			**216**	**100.0%**	**11.74 [5.90, 17.57]**

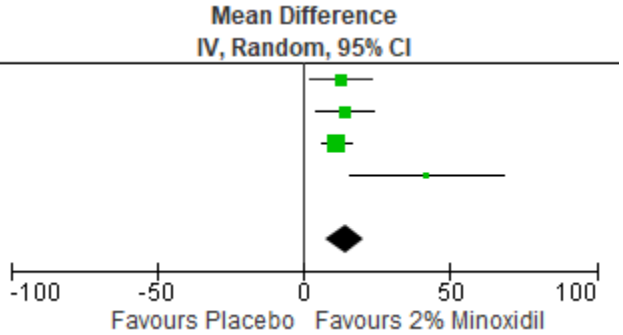
Heterogeneity: Tau² = 11.25; Chi² = 2.67, df = 1 (P = 0.10); I² = 63%
Test for overall effect: Z = 3.94 (P < 0.0001)



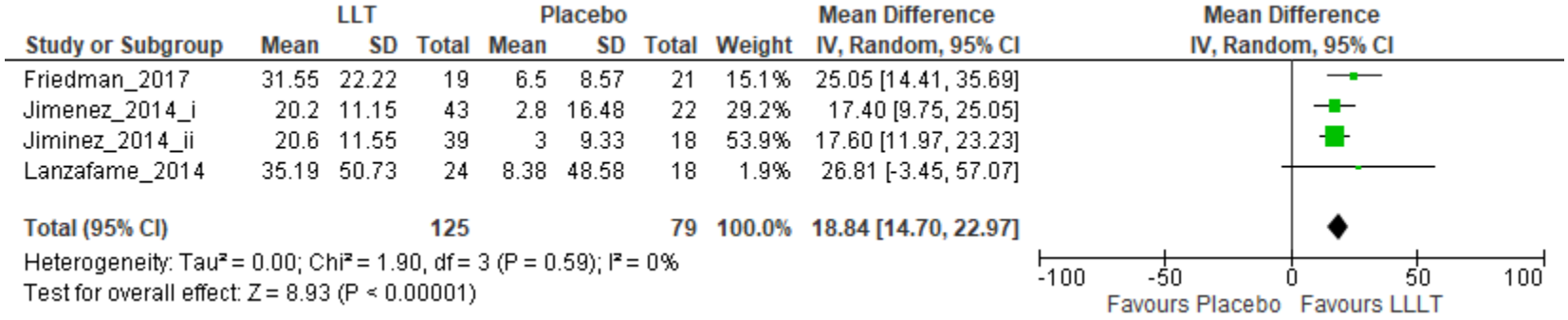
S4B Fig. Forest plot for 2% Minoxidil vs. Placebo for women

Study or Subgroup	2% Minoxidil Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
DeVillez_1994	22.7	48.63	128	10.1	38.67	128	23.5%	12.60 [1.84, 23.36]
Jacobs_1993	33.1	41	155	19.1	46	139	25.7%	14.00 [3.99, 24.01]
Lucky_2004	20.7	17.6	108	9.4	14.6	51	45.0%	11.30 [6.10, 16.50]
Price_1990	38.75	24.8	4	-3.25	10.24	4	5.8%	42.00 [15.71, 68.29]
Total (95% CI)			**395**			**322**	**100.0%**	**14.07 [7.44, 20.69]**

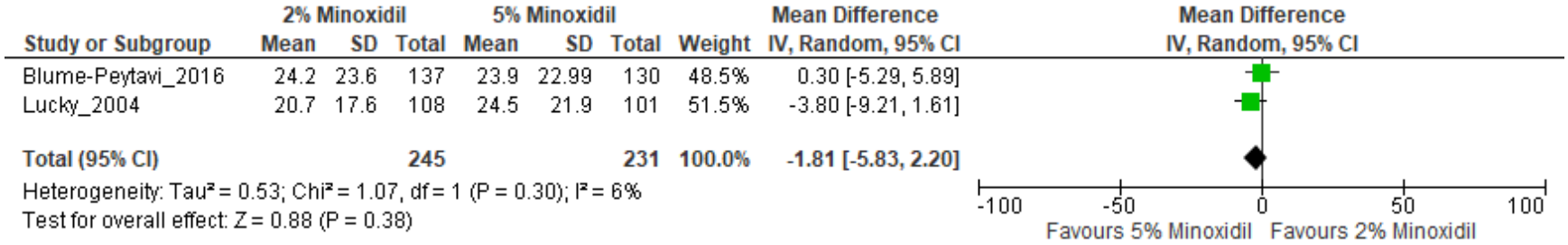
Heterogeneity: Tau² = 18.35; Chi² = 5.11, df = 3 (P = 0.16); I² = 41%
Test for overall effect: Z = 4.16 (P < 0.0001)



S4C Fig. Forest plot for LLLT vs Placebo for women



S4D Fig. Forest plot for 2% Minoxidil vs 5% Minoxidil for women

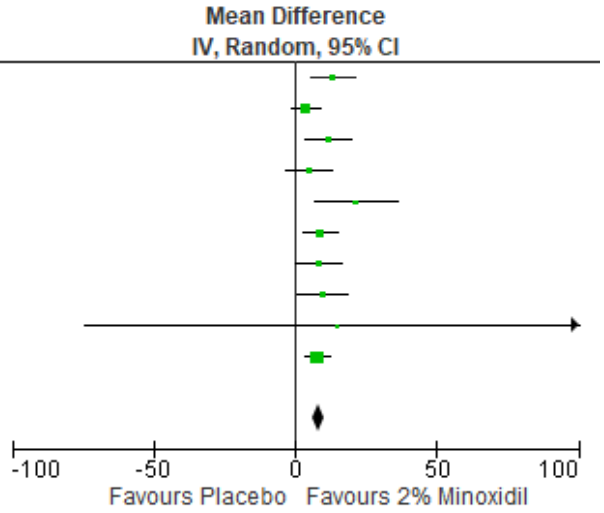


S5 Appendix Forest plots for pair-wise comparisons of non-surgical treatments for male AGA

S5A Fig. Forest plot for 2% Minoxidil vs Placebo for men

Study or Subgroup	2% Minoxidil Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Anderson_1988	25.35	26.05	75	12.14	23.97	76	8.1%	13.21 [5.22, 21.20]
Civatte_1988	13.31	26.95	196	9.67	23.85	188	19.5%	3.64 [-1.45, 8.73]
Dutree-Meulenberg_1988	17.49	22.9	74	5.9	26.12	70	8.0%	11.59 [3.55, 19.63]
Koperski_1987	12.38	15.15	23	7.35	12.37	21	7.8%	5.03 [-3.11, 13.17]
Olsen_1986	37.26	26.67	19	15.89	18.63	19	2.4%	21.37 [6.74, 36.00]
Olsen_2002	12.7	20.7	141	3.9	21.7	71	13.8%	8.80 [2.70, 14.90]
Petzoldt_1988	10.81	28.34	80	2.53	23.71	83	8.0%	8.28 [0.24, 16.32]
Piepkorn_1988_i	22.66	12.2	21	13.12	12.73	11	6.2%	9.54 [0.38, 18.70]
Rushton_1989	9.83	81.46	11	-5.18	93.83	6	0.1%	15.01 [-74.18, 104.20]
Shupack _1987	10.61	6.22	11	2.95	3.99	11	26.1%	7.66 [3.29, 12.03]
Total (95% CI)			**651**			**556**	**100.0%**	**8.10 [5.80, 10.39]**

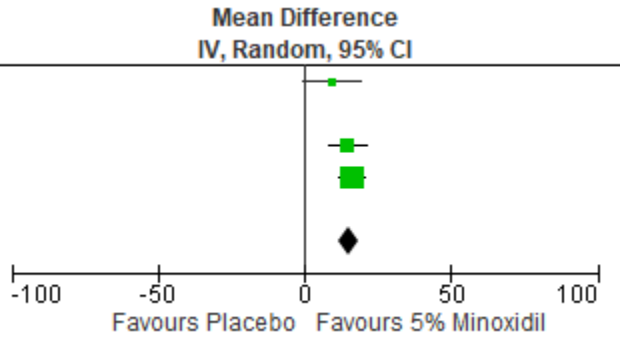
Heterogeneity: Tau² = 0.26; Chi² = 9.17, df = 9 (P = 0.42); I² = 2%
Test for overall effect: Z = 6.93 (P < 0.00001)



S5B Fig. Forest plot for 5% Minoxidil vs Placebo for men

Study or Subgroup	5% Minoxidil Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Hillmann_2015	7.8	24.1	31	-1.5	15	34	12.8%	9.30 [-0.57, 19.17]
NCT01325337_a	21.9	19.3	61	4.1	15.59	61		Not estimable
Olsen_2002	18.6	25.4	139	3.9	21.7	71	28.7%	14.70 [8.12, 21.28]
Olsen_2007	20.9	22.5	167	4.7	19.7	156	58.6%	16.20 [11.60, 20.80]
Total (95% CI)			**337**			**261**	**100.0%**	**14.89 [11.37, 18.41]**

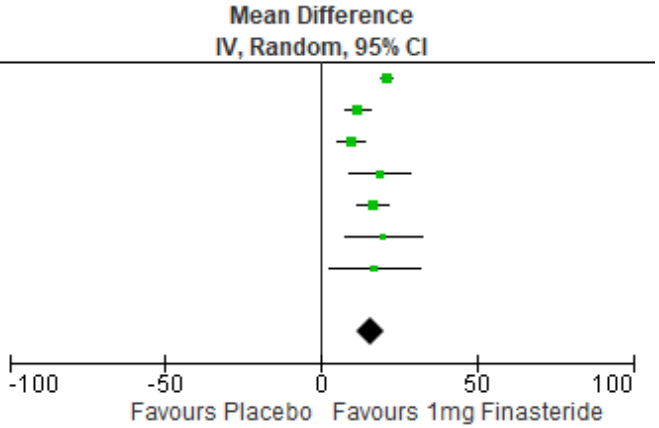
Heterogeneity: Tau² = 0.00; Chi² = 1.55, df = 2 (P = 0.46); I² = 0%
Test for overall effect: Z = 8.28 (P < 0.00001)



S5C Fig. Forest plot for 1mg Finasteride vs Placebo for men

Study or Subgroup	1mg Finasteride Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Kaufman_1998	16.87	18.61	779	-4.12	18.55	774	20.6%	20.99 [19.14, 22.84]
Leyden_1999	9.6	18.25	148	-2.06	17.62	138	18.2%	11.66 [7.50, 15.82]
Prasad_2005	6.55	7.23	23	-3.05	7.05	16	17.7%	9.60 [5.05, 14.15]
Price_2002	23.98	21.5	28	5.23	14.45	27	11.1%	18.75 [9.10, 28.40]
Roberts_1999	13.53	18.89	117	-2.95	20.08	117	17.1%	16.48 [11.48, 21.48]
Stough_2002	16	11.3	8	-4	15	9	8.4%	20.00 [7.46, 32.54]
Van Neste_2000	7.4	51.12	93	-9.6	49.64	91	6.9%	17.00 [2.44, 31.56]
Total (95% CI)			**1196**			**1172**	**100.0%**	**15.90 [11.23, 20.57]**

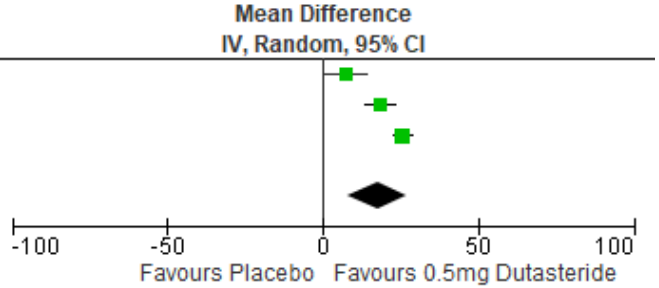
Heterogeneity: Tau² = 26.74; Chi² = 32.57, df = 6 (P < 0.0001); I² = 82%
Test for overall effect: Z = 6.67 (P < 0.00001)



S5D Fig. Forest plot for 0.5mg Dutasteride vs Placebo for men

Study or Subgroup	0.5mg Dutasteride Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Eun_2010	12.2	23.6	70	4.7	16.8	73	31.1%	7.50 [0.76, 14.24]
Gubelin Harcha_2014	18.1	21.27	153	-0.3	22.29	157	33.5%	18.40 [13.55, 23.25]
Olsen_2006	18.97	14.61	153	-6.59	11.85	158	35.4%	25.56 [22.60, 28.52]
Total (95% CI)			**376**			**388**	**100.0%**	**17.55 [7.95, 27.15]**

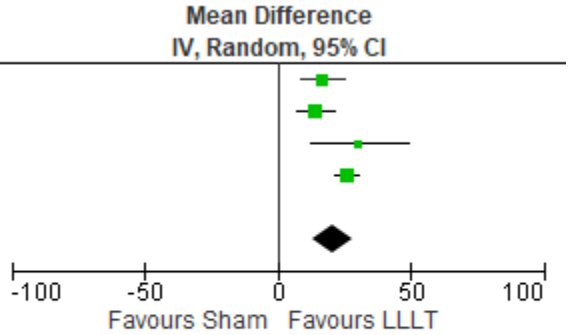
Heterogeneity: Tau² = 65.44; Chi² = 25.35, df = 2 (P < 0.00001); I² = 92%
Test for overall effect: Z = 3.58 (P = 0.0003)



S5E Fig. Forest plot for LLLT vs Placebo for men

Study or Subgroup	LLT Mean	LLT SD	LLT Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Jimenez _2014_iii	18.4	16.6	24	1.6	8.6	14	26.6%	16.80 [8.78, 24.82]
Jimenez _2014_iv_a (1)	23.36	15.6	43	9.4	12.94	22	28.4%	13.96 [6.82, 21.10]
Lanzafame_ 2013	30.42	31.29	22	-0.1	28.83	19	11.5%	30.52 [12.11, 48.93]
Leavitt_2009	17.3	11.9	71	-8.9	11.7	39	33.5%	26.20 [21.60, 30.80]
Total (95% CI)			**160**			**94**	**100.0%**	**20.72 [13.26, 28.18]**

Heterogeneity: Tau² = 37.73; Chi² = 10.50, df = 3 (P = 0.01); I² = 71%
Test for overall effect: Z = 5.44 (P < 0.00001)

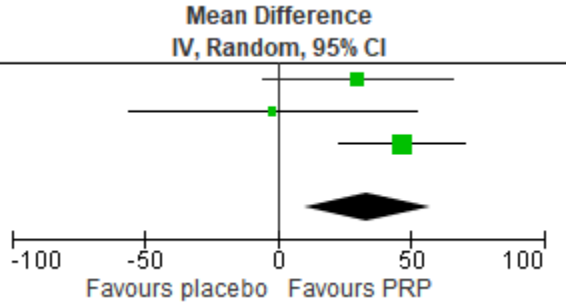


Footnotes
(1) The value reproted for outcome is an average estimate

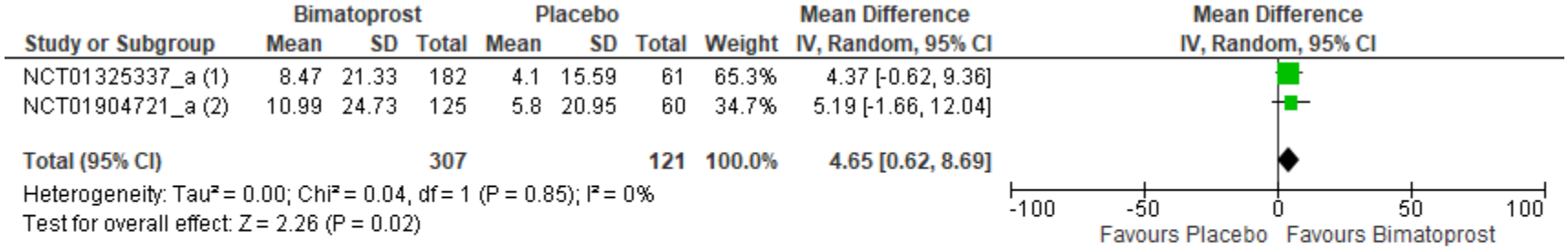
S5F Fig. Forest plot for PRP vs Placebo for men

Study or Subgroup	PRP Mean	PRP SD	PRP Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Cervelli_2014	27	50	10	-3	28.55	10	31.3%	30.00 [-5.69, 65.69]
Dicle_2019	2.3	72.3	10	4.3	59.85	15	16.3%	-2.00 [-56.09, 52.09]
Gentile_2015	51.7	42.4	20	4.9	33.14	20	52.4%	46.80 [23.22, 70.38]
Total (95% CI)			**40**			**45**	**100.0%**	**33.58 [9.91, 57.25]**

Heterogeneity: Tau² = 133.79; Chi² = 2.81, df = 2 (P = 0.25); I² = 29%
Test for overall effect: Z = 2.78 (P = 0.005)



S5G Fig. Forest plot for Bimatoprost vs. Placebo for men



Footnotes

(1) The value reprorted for outcome is an average estimate

(2) The value reproted for outcome is an average estimate