# Impact of Male Pattern Baldness on Coronary Heart Disease: A meta-analysis

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# Impact of Male Pattern Baldness on Coronary Heart Disease: A meta-analysis

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**Abstract**

**Objective:**

To confirm the association of male pattern baldness with coronary heart disease (CHD).

**Design:**

Meta-analysis of observational studies.

**Data sources:**

Medline and the Cochrane Library were searched for articles published up to November 2012 using keywords that included both baldness and coronary heart disease, and references of the identified studies were also searched.

**Study selection:**

Observational studies were identified that reported risk estimates for CHD related to baldness. Two observers independently assessed eligibility, extracted data, and assessed the possibility of bias.

**Data synthesis:**

The adjusted relative risk (RR) and 95% confidence interval (95%CI) were calculated with the DerSimonian-Laird random-effect model.

**Results:**

From 850 possible studies, 3 cohort studies and 3 case-control studies were selected (36,990 subjects).

In the cohort studies, the adjusted RR of men with severe baldness for CHD was 1.32 (95%CI: 1.08-1.63, P=0.008, I squared=25%) versus those without baldness. Analysis of younger men (<55 or ≤60 years) showed a similar association of CHD with severe baldness (RR: 1.44, 95%CI: 1.11-1.86, P=0.006, I squared=0%).

In 3 studies employing the modified Hamilton scale, vertex baldness was associated with CHD and the relation depended on the severity of baldness (severe vertex: RR 1.48 (1.04-2.11, P=0.03); moderate vertex: RR 1.36 (1.16-1.58, P<0.001); mild vertex: RR 1.18 (1.04-1.35, P<0.001). However, frontal baldness was not associated with CHD (RR 1.11 (0.92-1.32. P=0.28)).

**Conclusion:**

Vertex baldness, but not frontal baldness, is associated with an increased risk of CHD. The association with CHD depends on the severity of vertex baldness and also exists among younger men. Thus, vertex baldness may be more closely related to atherosclerosis than frontal baldness, but the relation between male pattern baldness and CHD deserves further investigation.

**Key words**: male pattern baldness, androgenetic alopecia, coronary heart disease, relative risk, meta-analysis

**Article summary**

**Article focus:**

・The present meta-analysis aimed to confirm the association of male pattern baldness (androgenetic alopecia) with an increased risk of coronary heart disease (CHD).

**Key messages:**

・Meta-analysis of 6 observational studies with 36,690 subjects showed that vertex baldness is associated with an increased risk of CHD and that the relationship depends on the severity of baldness, while frontal baldness is not.

・Thus, vertex baldness may be a marker of CHD and is more closely associated with systemic atherosclerosis than frontal baldness.

・This potential relationship should be investigated by further studies, including well-designed prospective studies.

**Strengths and limitations of this study:**

・This was the first meta-analysis of the relation between baldness and CHD; it showed that the relationship depends on the severity of baldness.

・The cohort studies had a long follow-up period of 11.0-14.0 years.

・A weakness may be the small number of studies analyzed.

## Introduction

Coronary heart disease (CHD) is a major cause of death and disability worldwide (1). Advanced obstructive CHD can exist in patients with minimal or no symptoms and can progress rapidly (2), so early detection is extremely important. Many clinicians carry out screening for asymptomatic CHD and participants in wellness programs often also request such screening, but the usefulness of CHD screening is yet to be confirmed. It was reported that the incidence of CHD was not significantly reduced in asymptomatic diabetic patients when screening was conducted by myocardial scintigraphy (3), and it was also reported that coronary CT screening of asymptomatic patients without a history of coronary artery disease fails to prevent major cardiovascular events (4).

Male pattern baldness, also called androgenetic alopecia (AGA), is the most common cause of hair loss. It affects approximately 30 to 40% of adult men (5) and it is seen in 80% of men by the age of 80 years (6). AGA is considered to be a heritable, androgen-dependent condition that is characterized by varying degrees of thinning/hair loss primarily at the vertex and the frontal areas (temples) of the scalp. In men with AGA, the thin residual hairs tend to be of various lengths and diameters since each follicle is in a different phase of the hair cycle, so the presence of variations in hair length and texture is a classic feature of thin condition (7).

Several recent studies have shown that baldness is associated with the risk of coronary heart disease (CHD)(8-13). These studies have generally found a positive relation between baldness and CHD,

although the strength of the association has varied.

Clarifying the relationship between baldness and CHD could lead to more effective approaches to the early detection of heart disease, since it might permit the reliable identification of persons with an increased risk of suffering from a cardiac event and allow the delivery of appropriate therapy (e.g., antihypertensive or lipid-lowering therapy) to improve the prognosis of such high-risk persons. Accordingly, we performed a meta-analysis to further assess the influence of male pattern baldness (AGA) on CHD.

## Methods

### *Search strategy*

The Medline and Cochrane Library electronic databases were searched from 1950 until November 27, 2012 using the medical subject headings "Baldness" ("baldness" or "hair loss" or "alopecia") and "Coronary heart disease" ("coronary heart disease" or "cardiovascular disease" or "coronary artery disease") to identify observational studies that tested the association between baldness and CHD. The reference lists of all relevant studies were also reviewed.

### *Study selection*

We performed initial screening based on the study titles or abstracts, while the second screening

involved full-text review. Cohort studies, case-control studies, and cross-sectional studies that assessed the relation between male pattern baldness and CHD were eligible for inclusion if the following criteria were met: 1) the full text of the report was published in English, 2) the relative risk (risk ratio, hazard ratio, or odds ratio) was reported with adjustment for possible confounders (e.g. age, smoking, family history of baldness, or family history of CHD), 3) the presence and severity of male pattern baldness was reported, and 4) CHD events were reported.

***Definitions of baldness and CHD***

Baldness was defined according to the description in the history and/or on the basis of terms such as AGA and male pattern hair loss. We excluded studies that analyzed men with other types of baldness (e.g., alopecia areata or scarring alopecia). CHD was defined as including all of the following: coronary artery disease, myocardial infarction, angina pectoris, cardiomyopathy, and other types of ischemic heart disease.

***Assessment of validity***

To ascertain the validity of the eligible studies, the quality of each report was appraised with reference to the STROBE statement (14). Moreover, the Newcastle-Ottawa Scale for assessing quality of nonrandomized studies in meta-analyses was used to quantify the validity of each study

(15).

***Data extraction***

Two investigators (T.Y. and K.H.) independently reviewed each study to determine its eligibility, and then extracted and tabulated all of the relevant data. Disagreement was resolved by consensus between the two investigators.

The following information was obtained from each study: first author, year of publication, type of study, country, number of subjects, CHD events, method of assessing baldness, follow-up period, mean age, smoking, covariates used for adjustment during analysis, and severity of baldness.

***Statistical analysis***

The pooled relative risk (RR) adjusted for possible confounders and its 95% confidence interval (CI) were calculated for the risk of CHD events in each study by the DerSimonian-Laird random effect model weighted with inverse variance. Equivalence of RRs between the cohort studies and the cross-sectional studies was assessed by the z-statistic test. Cochrane's $\chi^2$ test and the $I^2$ test were used to evaluate heterogeneity among studies and a threshold P value of 0.10 was considered to be significant (16). Possible publication bias was evaluated by creating a funnel plot of the effect size for each study versus the standard error (SE). Funnel plot asymmetry was assessed by the Begg and

Egger tests. All statistical analyses were performed with Stata 12.0 software (StataCorp, College Station, TX). Results are expressed as the mean with 95%CI, unless otherwise indicated. Except for tests of heterogeneity, a P value of less than 0.05 was considered significant. All procedures were performed in accordance with the guideline published by the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group (17) and the PRISMA statement (18)**(Supplementary Data 1)**.

## Results

### *Literature search*

**Figure 1** shows a flow chart of the study selection process. We identified a total of 850 reports by searching the databases. Among these, 834 reports were excluded after review of the title and abstract, leaving 16 studies for further evaluation. Ten of these 16 studies were excluded after full text evaluation, chiefly because of the lack of pertinent data. The remaining 6 studies (8-13) fulfilled the inclusion criteria were used for this meta-analysis.

### *Study characteristics*

The 6 studies that were selected included 3 cohort studies and 3 case-control studies, and their characteristics are summarized in **Table 1**. There were moderate differences with respect to the

country of origin, number of subjects, and method of assessing baldness. The studies were published between 1993 and 2008. Four studies (9-11,13) were conducted in the USA and the other 2 (8,12) were performed in the European Union. The size of the study populations ranged from 1,437 to 19,112 subjects (mean: 6,165 subjects). In 5 of the 6 studies (8,10-13), CHD was defined as non-fatal myocardial infarction. The mean follow-up period ranged from 11 to 14 years. The method of assessing baldness varied, with a modified or simplified Hamilton scale being employed in 4 studies (8,10,11,13) and a personal scale being used in the other 2 studies (9,12).

Three studies (10,11,13) used a modified Hamilton scale that reduced the 12 categories of the original scale to the following five: no baldness (I, II); frontal baldness alone (IIa, III, IIIa, IVa); mild vertex baldness (III vertex, IV); moderate vertex baldness (V, Va); and severe vertex baldness (VI, VII). One study (8) used a simplified Hamilton scale, in which the extent of baldness was classified as follows: none; frontoparietal region (no bald triangle but >3 cm in front of the ear, or bald triangle but ≤3 cm in front of the ear); crown-top region (thick hair, partly thin hair, bald spot, or bald top and front); and combined.

Among the two studies that employed personal scales, Ford, classified baldness as none, minimum, moderate, or severe (9). Minimum baldness corresponded to no obvious baldness when the participant walked into the examining room, while moderate baldness was observable baldness at the first encounter and severe baldness was obvious at the first encounter. In the other study, Miric

classified baldness as none, frontal, parietal (vertex), or combined (12).

The RR for CHD of the subjects with baldness was adjusted for several coronary risk factors (age, smoking, diabetes, etc.) in each study, but the number of variables differed significantly among the studies.

The reports on all 3 cross-sectional studies (11-13) explicitly mentioned the limitations of a cross-sectional design (i.e., it cannot assess causality), the possible biases of each study, and the influence of confounders. The reports on all 3 cohort studies (8-10) mentioned the possibility of misclassification of the severity of baldness.

One study found that baldness was not associated with CHD (13), but the other 5 studies concluded that baldness was associated with a significantly increased risk of CHD, although the strength of the association varied.

According to the Newcastle-Ottawa quality assessment scale for observational studies, all of the studies used in this meta-analysis achieved at least six out of nine points, indicating that the overall quality of the studies was good **(Supplementary Data 2).**

***Association of baldness with CHD***

Among the 6 studies with a total of 36,990 subjects that were selected (8-13), no study showed a significant decrease in the risk of CHD for men with baldness.

**Figures 2-4** show the results obtained by combining the RRs for CHD with the random-effect model.

In the 3 cohort studies (8-10), the adjusted RR of CHD for men of all ages with severe baldness versus those without baldness was 1.32 (95%CI: 1.08-1.63; P=0.008; P for heterogeneity=0.26; I squared=25%). Analysis restricted to younger subjects (<55 years old or ≤60 years old at baseline) revealed a similar association of severe baldness with CHD (RR 1.44 (95%CI: 1.11-1.86; P=0.006; P for heterogeneity=0.59; I squared=0%)) (**Figure 2**).

In the 3 case-control studies (11-13), the adjusted RR was 1.70 (95%CI: 1.05-2.74; P=0.03; P for heterogeneity=0.01: I squared=78%) for all subjects, while the RR was 1.84 (95%CI: 1.30-2.62; P=0.001; P for heterogeneity=0.17; I squared=44%) among the younger subjects (**Figure 3**). The difference of RR values between the cohort and case-control studies was not significant (all subjects: P=0.15; patients≤60 years old: P=0.07).

***Stratified analysis***

All three studies that assessed the severity of baldness by using the modified Hamilton scale (10,11,13) showed that vertex baldness was associated with CHD and that this association was dependent on the severity of baldness. In subjects with severe vertex baldness, the RR was 1.48 (95%CI: 1.04-2.11; P=0.03; P for heterogeneity=0.02; I squared=75%), while the RR was 1.36

(95%CI: 1.16-1.58; P<0.001; P for heterogeneity=0.95; I squared=0%) for moderate vertex baldness and 1.18 (95%CI: 1.04-1.35; P<0.001; P for heterogeneity=0.35; I squared=4%) for mild vertex baldness. In contrast, there was no significant association of frontal baldness with CHD and the RR was only 1.11 (95%CI: 0.92-1.32; P=0.28; P for heterogeneity=0.24; I squared=30%) (**Figure 4**).

Because the method of assessing baldness was not homogenous, we also performed a sensitivity analysis of the studies that used personal scales to classify baldness into 4 grades (none, frontal, crown-top, or combined) (8,12). Similar results were obtained showing that the association with CHD depended on the severity of baldness, with an RR of 1.69 (95%CI: 1.28-2,23; P<0.001; P for heterogeneity=0.97; I squared=0%) for combined baldness, an RR of 1.52 (95%CI: 0.97-2.39; P=0.07; P for heterogeneity=0.001; I squared=91%) for crown-top baldness, and an RR of 1.22 (95%CI: 0.70-2.14; P=0.49; P for heterogeneity=0.05; I squared=73%) for frontal baldness.

***Publication bias***

The funnel plot, Begg's test, and Egger's test were used to evaluate the potential influence of publication bias on the association between baldness and CHD. The funnel plot did not show an asymmetric pattern, while Egger's test and Begg's test revealed no significant publication bias (all P≥0.05).

**Discussion**

The present meta-analysis of 6 studies from the USA and Europe demonstrated that vertex baldness was associated with an increased risk of CHD among subjects of all ages and also among younger men. Interestingly, frontal baldness was not associated with CHD.

When baldness was classified by the Hamilton-Norwood scale, which is the most commonly used classification of male pattern baldness worldwide (19), the relation of CHD with baldness was shown to be dependent on the severity of baldness.

These findings support the hypothesis that vertex baldness is a local manifestation of factors promoting systemic atherosclerosis, such as metabolic syndrome, hypertension, and smoking.

Minoxidil (Rogaine) is one of the most popular drugs for the treatment of male pattern baldness. Minoxidil was originally developed as an antihypertensive agent (vasodilator) and it is thought to improve the blood flow and the supply of oxygen and nutrients to the hair follicles by dilating vessels in the scalp and opening potassium channels. This may lead to shedding of hairs in the telogen phase, which are then replaced by thicker hairs in the anagen phase (20).

Minoxidil is only indicated for vertex baldness and is ineffective for frontal baldness (21), which supports our finding that vertex baldness is more closely related to atherosclerosis than frontal baldness.

*Mechanism of the relation between baldness and CHD*

The reason for the association between baldness and CHD is unclear. It has been suggested that classical coronary risk factors (e.g., age, hypertension, dislipidemia, and smoking) might influence both conditions, so that baldness is a marker of atherosclerosis. In fact, previous studies have demonstrated a positive association between male pattern baldness and insulin resistance (22), metabolic syndrome (23), and hypertension (24). It has also been postulated that baldness is linked to CHD by mechanisms such as hyperinsulinemia, chronic inflammation, and increased peripheral sensitivity to androgens, and these are briefly discussed below.

1) Hyperinsulinemia/insulin resistance is the central factor in metabolic syndrome and it promotes intolerance of carbohydrates and the development of central (abdominal) obesity. Insulin resistance has also been shown to cause vasoconstriction and impairs the supply of nutrients to the hair follicles of the scalp, as well as enhancing the influence of dihydro-testosterone (DHT) on follicular miniaturization (25,26).

2) A proinflammatory state could increase the levels of inflammatory cytokines in the arterial walls (27) and hair follicles (28). High-sensitivity C-reactive protein is a marker of inflammation and is also a good predictor of future cardiovascular disease (29), so chronic inflammation could be related to both CHD and baldness.

3) Male pattern baldness may be caused by increased peripheral sensitivity to androgens, since bald

men show an increase of androgen receptors in the scalp (30) and have higher serum levels of both total and free testosterone (31). Free testosterone is converted to DHT by 5a-reductase, leading to miniaturization of hair follicles. It has been reported that 5a-reductase exists in the blood vessels and the heart, as does the DHT receptor, which is involved in vascular smooth muscle proliferation that represents a fundamental feature of arteriosclerosis along with the deposition of lipids (32).

***Strengths and Limitations***

The strengths of this meta-analysis were as follows. First, our analysis included several large cohort and case-control studies, with a total of 36,990 subjects. Second, the cohort studies had a long follow-up period (11.0-14.0 years). In all of the studies, analyses were adjusted for various classical coronary risk factors, such as age, smoking, hypertension, dyslipidemia, and body mass index.

However, this meta-analysis also had several limitations. First, we only reviewed English-language reports, which could have led to selection bias. Our analyses of publication bias did not suggest that unpublished results had been missed, but these analyses might have been underpowered due to the small effect sizes. Second, although most factors showed no significant between-study heterogeneity, it was significant for some factors, suggesting that differences of epidemiological characteristics (e.g., the rate of severe baldness or CHD) or different diagnostic criteria (for baldness and/or CHD) contributed to heterogeneity to some extent.

Unlike the results of the other studies, the effect sizes reported by Lesko (11) varied widely and even changed the sign when different patterns of baldness were compared (Fig. 4). This study had the lowest validity score (6/9 points on the Newcastle-Ottawa scale) among the six studies included in our meta-analysis (**Supplementary Data 2**). Lesko et al. contacted the coronary care units of participating hospitals to identify potential subjects with their first myocardial infarction and to obtain permission to conduct an interview. Thus, details about CHD were not obtained in this study, which might have led to bias and influenced the effect size.

Moreover, as alredy reported by Rebora et al. (33), Lotufo et al. (10) relied on each patient's memory of a condition that had developed up to 40 years before, which might have led to recall bias. These two studies would have a higher risk of misclassification bias that could lead to underestimating the strength of the association between baldness and CHD, since it is often considered shameful to admit to the existence of baldness.

The third limitation was incomplete information about the use of medications such as anticoagulants, anticonvulsants, beta-blockers, antidepressants, and hormone replacement therapy that may have contributed to baldness (34).

Fourth, the methods used to assess baldness varied between studies, which meant that we could not rule out other local causes of diffuse hair loss (alopecia areata or nonscarring alopecia), as well as possible systemic causes (e.g., thyroiditis, iron deficiency (35,36), trauma, excessive dieting, or

debilitating diseases).

Even with such limitations, the present meta-analysis provided useful evidence regarding the potential influence of baldness on CHD. Patients and physicians should consider the possibility that baldness is associated with an increased risk of CHD.

***Conclusions***

In the present meta-analysis, vertex baldness was associated with an increased risk of CHD among younger men as well as among all subjects, and the relation was dependent on the severity of baldness. These findings suggest that vertex baldness is more closely associated with systemic atherosclerosis than frontal baldness. Thus, cardiovascular risk factors should be reviewed carefully in men with vertex baldness, especially younger men, and they should be encouraged to improve their cardiovascular risk profile.

In addition, the relationship between baldness and CHD should be investigated by further studies, including well-designed and controlled cohort studies, in order to confirm whether persons with male pattern baldness (especially severe vertex baldness) have an increased risk of CHD.

*Contributors*

TY, KH and TK conceived the idea of the study and were responsible for the design of the study. TY and KH were responsible for undertaking for the data analysis and produced the tables and figures. TY and KH provided input into the data analysis. The initial draft of the manuscript was prepared by TY and KH and then circulated repeatedly among all authors for critical revision. TY was responsible for the acquisition of the data and TY, KH and TK contributed to the interpretation of the results.

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*Competing Interests*

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare:

no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

***Ethical approval***

Not needed.

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## *Supplementary Data*

**Supplementary Data 1. PRISMA Checklist.**

**Supplementary Data 2. Newcastle-Ottawa quality assessment scale for observational studies**

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**Figure legends**

**Figure 1**. **Flow diagram of study selection.**

**Figure 2. Association of baldness with CHD in the 3 cohort studies.**

The forest plot shows the association between male pattern baldness and the risk of coronary heart disease (CHD). CI=confidence interval; RR=relative risk.

**Figure 3. Association of baldness with CHD in the 3 case-control studies.**

The forest plot shows the association between male pattern baldness and the risk of coronary heart disease (CHD). CI=confidence interval; RR=relative risk.

**Figure 4. Association of baldness with CHD in studies using the modified Hamilton scale.**

The forest plot shows the association between male pattern baldness and the risk of coronary heart disease (CHD). CI=confidence interval; RR=relative risk

Table 1. Summary of studies evaluating the association between baldness and coronary heart disease

| First author, year | Type of study | Country | Subjects | CHD (events) | Assessment of baldness | Follow-up (years) | Covariates used for adjustment |
|---|---|---|---|---|---|---|---|
| Schnohr, 1995 (8) | Cohort | Denmark | 5837 | Myocardial infarction (750) | Simplified Hamilton (None, Frontoparietal, Crown-top, Combined) | 12.0 | Age, smoking, systolic blood pressure, cholesterol, triglycerides, physical activity, BMI, family history of MI, marital status, education, economic status, diabetes, and alcohol consumption |
| Ford, 1996 (9) | Cohort | USA | 3994 | Ischemic heart disease (965) | Personal scale (None, Minimum, Moderate, Severe) | 14.0 | Age, age squared, race, education, systolic blood pressure, antihypertensive medication, cholesterol, smoking, BMI, and diabetes mellitus |
| Lotufo, 2000 (10) | Cohort | USA | 19112 | Nonfatal MI, angina, coronary revascularization (1446) | Modified Hamilton (None, Frontal, Mild vertex, Moderate vertex, Severe vertex) | 11.0 | Age, aspirin assignment, beta carotene assignment, BMI, height (cm), hypertension, hypercholesterolemia, diabetes, parental history of MI, physical activity, smoking, and alcohol use. |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Lesko, 1993 (11) | Case-control | USA | 1437 | Non-fatal Myocardial infarction (665) | Modified Hamilton (None, Frontal only, Mild vertex, Moderate vertex, Severe vertex) | - | Age, race, religion, years of education, BMI, use of alcohol and cigarettes, family history of myocardial infarction, personal history of angina, hypertension, diabetes, hypercholesterolemia, gout, exercise, personality, and number of doctor visits in the past year. |
| Miric, 1998 (12) | Case-control | Croatia | 1554 | Non-fatal Myocardial infarction (842) | Personal score ( None, Any, Frontal, Parietal, Fronto-parietal) | - | Age, family history of MI, hypertension, hypercholesterolemia, BMI, diabetes, and smoking. |
| Shahar, 2008 (13) | Case-control | USA | 5056 | Non-fatal Myocardial infarction (767) | Modified Hamilton ( None, Frontal, Mild vertex, Moderate vertex, Severe vertex) | - | Age, smoking, BMI, race-center, cholesterol-lowering medication, antihypertensive medication, HDL, diabetes, educational level, and family history of MI. |

CHD, coronary heart disease; BMI, body mass index; MI, myocardial infarction; AGA, androgenic alopecia; HDL, high density lipoprotein;

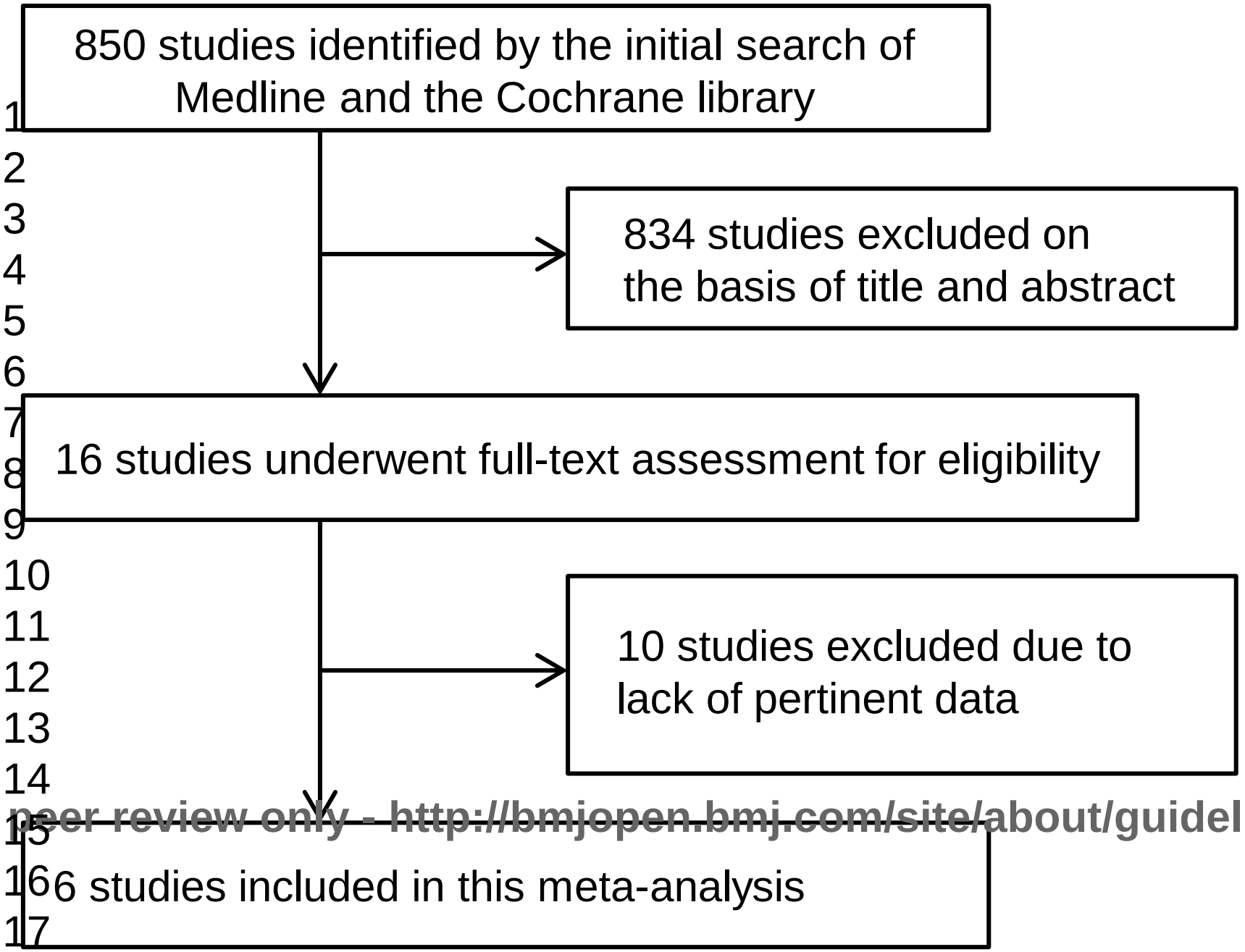


Fig. 2

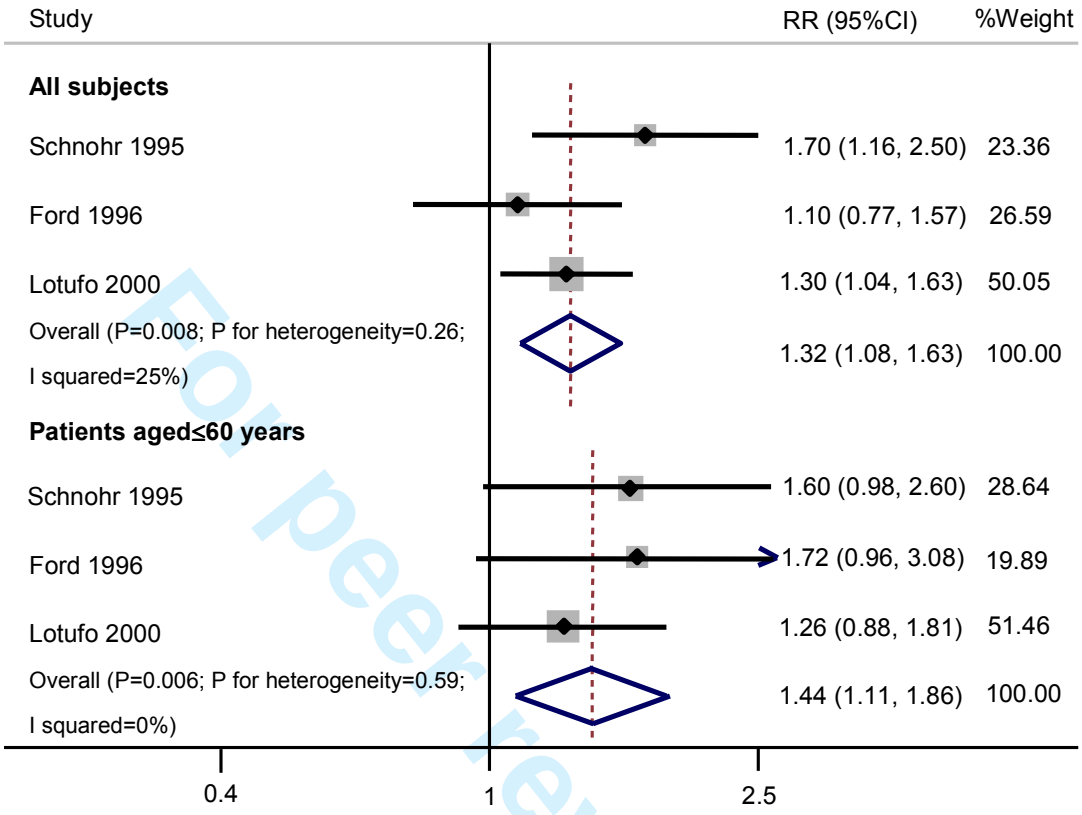


Fig. 3

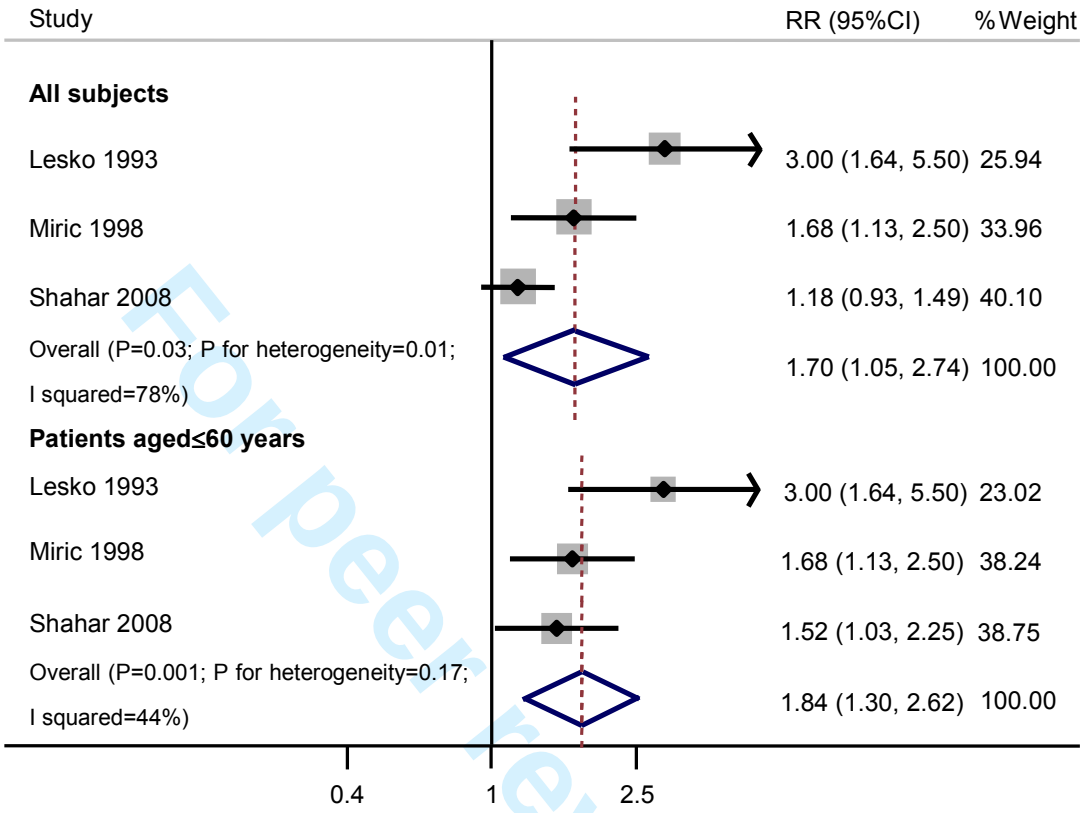
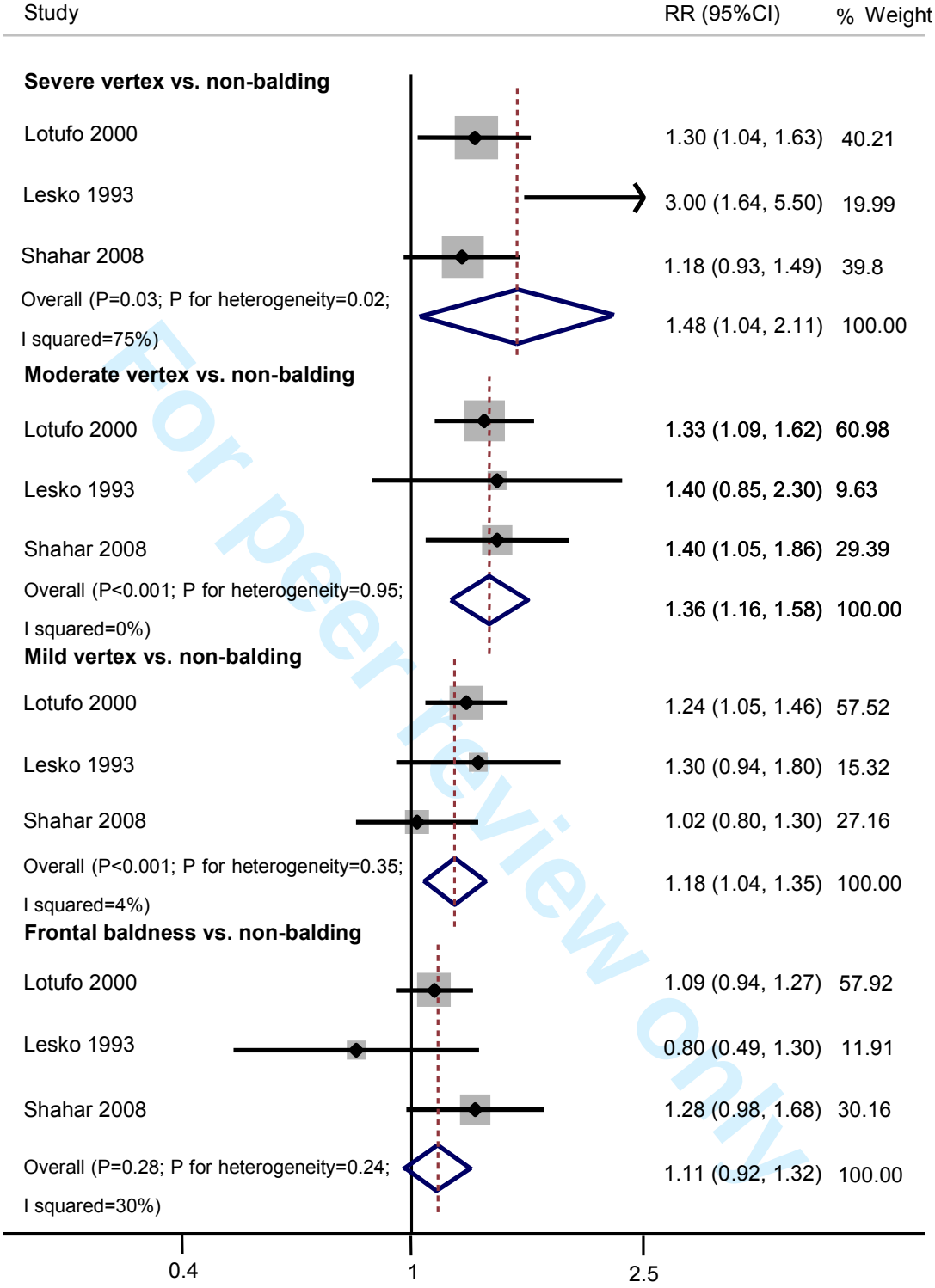


Fig. 4



# PRISMA 2009 Checklist

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 |
| **ABSTRACT** | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 2-3 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 5-6 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 5-6 |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | 6 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 6 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 6-7 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | 6 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 6-7 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 6-7 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 7 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 7 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 7-8 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | 7-8 |

# PRISMA 2009 Checklist

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 7-8 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 7-8 |
| **RESULTS** | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 9, Fig 1 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 9, Table 1 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 9, Table 1 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 9-10, Table 1, Fig 2-4 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | 10-12, Fig 2-4 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | 10-12 Suppl.2 |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | 11-13 |
| **DISCUSSION** | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 14-15 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 16-18 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 18 |
| **FUNDING** | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 19-20 |

*From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097.

# PRISMA 2009 Checklist

doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Supplementary Data 2. Newcastle-Ottawa quality assessment scale for observational studies

| Study reference (author, year) | Selection | Comparability | Outcome/Exposure |
|---|---|---|---|
| Cohort studies | | | |
| Schnohor, 1995 (8) | *** | ** | *** |
| Ford, 1996 (9) | *** | ** | *** |
| Lotufo, 2000 (10) | *** | ** | *** |
| Case-control studies | | | |
| Lesko, 1993 (11) | ** | ** | ** |
| Miric, 1998 (12) | *** | ** | ** |
| Shahar, 2008 (13) | **** | ** | ** |

# Male Pattern Baldness and Its Association with Coronary Heart Disease: A Meta-Analysis

| | |
|---|---|
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| Manuscript ID: | bmjopen-2012-002537.R1 |
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| Complete List of Authors: | Yamada, Tomohide; University of Tokyo, Department of Diabetes and Metabolic Diseases<br>Hara, Kazuo; University of Tokyo, Department of Diabetes and Metabolic Diseases<br>Umematsu, Hitomi; University of Tokyo, Department of Diabetes and Metabolic Diseases<br>Kadowaki, Takashi; University of Tokyo, Department of Diabetes and Metabolic Diseases |
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| Keywords: | Coronary heart disease < CARDIOLOGY, Ischaemic heart disease < CARDIOLOGY, Adult dermatology < DERMATOLOGY, Dermatological epidemiology < DERMATOLOGY, EPIDEMIOLOGY |
| | |

# Male Pattern Baldness and Its Association with Coronary Heart Disease: A Meta-Analysis

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**Brief title**: Male pattern baldness and CHD

**Word count**: 3691 words

**Abstract**

**Objective:**

To confirm the association between male pattern baldness and coronary heart disease (CHD).

**Design:**

Meta-analysis of observational studies.

**Data sources:**

Medline and the Cochrane Library were searched for articles published up to November 2012 using keywords that included both 'baldness' and 'coronary heart disease' and the reference lists of those studies identified were also searched.

**Study selection:**

Observational studies were identified that reported risk estimates for CHD related to baldness. Two observers independently assessed eligibility, extracted data, and assessed the possibility of bias.

**Data synthesis:**

The adjusted relative risk (RR) and 95% confidence interval (95%CI) were estimated using the DerSimonian-Laird random-effect model.

**Results:**

Included 850 possible studies, three cohort studies and three case-control studies were selected (36,990 subjects).

In the cohort studies, the adjusted RR of men with severe baldness for CHD was 1.32 (95%CI: 1.08 - 1.63, $P$ = 0.008, $I^2$ = 25%) versus those without baldness. Analysis of younger men (<55 or ≤60 years) showed a similar association of CHD with severe baldness (RR: 1.44, 95%CI: 1.11 - 1.86, $P$ = 0.006, $I^2$ = 0%).

In 3 studies employing the modified Hamilton scale, vertex baldness was associated with CHD and the relation depended on the severity of baldness (severe vertex: RR 1.48 (1.04 - 2.11, $P$ = 0.03); moderate vertex: RR 1.36 (1.16 - 1.58, $P$ < 0.001); mild vertex: RR 1.18 (1.04 - 1.35, $P$ < 0.001). However, frontal baldness was not associated with CHD (RR 1.11 (0.92 - 1.32, $P$ = 0.28)).

**Conclusion:**

Vertex baldness, but not frontal baldness, is associated with an increased risk of CHD. The association with CHD depends on the severity of vertex baldness and also exists among younger men. Thus, vertex baldness might be more closely related to atherosclerosis than frontal baldness, but the association between male pattern baldness and CHD deserves further investigation.

**Key words**: male pattern baldness, androgenetic alopecia, coronary heart disease, cardiovascular disease, relative risk, meta-analysis

**Article summary**

**Article focus:**

・The present meta-analysis aimed to confirm the association of male pattern baldness (androgenetic alopecia) with an increased risk of coronary heart disease (CHD).

**Key messages:**

・Meta-analysis of 6 observational studies with a total of 36,690 subjects showed that vertex baldness is associated with an increased risk of CHD and that the relationship depends upon the severity of baldness, while frontal baldness is not.

・Thus, vertex baldness might be a marker of CHD and is more closely associated with systemic atherosclerosis than frontal baldness.

・This potential relationship should be investigated in further studies, including well-designed prospective studies.

**Strengths and limitations of this study:**

・This was the first meta-analysis of the association between baldness and CHD; it showed that the relationship depends on the severity of baldness.

・The cohort studies had a long follow-up period of 11.0 - 14.0 years.

・A weakness might be the small number of studies analyzed.

## Introduction

Coronary heart disease (CHD) is a major cause of death and disability worldwide (1). Advanced obstructive CHD can exist in patients with minimal or no symptoms and can progress rapidly (2), so early detection is extremely important. Many clinicians carry out screening for asymptomatic CHD and participants in wellbeing programs often also request such screening, but the usefulness of CHD screening has yet to be confirmed. Young et al. (2009) reported that the incidence of CHD was not significantly reduced in asymptomatic diabetic patients when screening was conducted by myocardial scintigraphy (3), and McEvoy et al. (2011) also reported that coronary computed tomography screening of asymptomatic patients without a history of coronary artery disease fails to prevent major cardiovascular events (4).

Male pattern baldness, also called androgenetic alopecia (AGA), is the most common cause of hair loss. It affects approximately 30 to 40% of adult men (5) and it is seen in 80% of men by the age of 80 years (6). AGA is considered to be a heritable, androgen-dependent condition that is characterized by varying degrees of thinning/hair loss primarily at the vertex and the frontal areas (temples) of the scalp. In men with AGA, the thin residual hairs tend to be of various lengths and diameters since each follicle is in a different phase of the hair cycle, so the presence of variations in hair length and texture is a classic feature of this thinning condition (7).

Several recent studies have shown that baldness is associated with the risk of CHD (8-12). These

studies have generally found a positive association between baldness and CHD, although the strength of the association has varied (8-13).

Clarifying the relationship between baldness and CHD could lead to more effective approaches to the early detection of heart disease, since it might permit the reliable identification of persons with an increased risk of suffering from a cardiac event thereby allowing the delivery of appropriate therapy (e.g., antihypertensive or lipid-lowering therapy) to improve the prognosis of such high-risk persons. Accordingly, we performed a meta-analysis to further assess the influence of male pattern baldness (AGA) on CHD.

## Methods

### *Search strategy*

The Medline and Cochrane Library electronic databases were searched from January 1, 1950 until November 27, 2012 using the medical subject headings "Baldness" ("baldness" or "hair loss" or "alopecia") and "Coronary heart disease" ("coronary heart disease" or "cardiovascular disease" or "coronary artery disease") to identify observational studies that estimated the association between baldness and CHD. The reference lists of all studies identified were also reviewed.

### *Study selection*

We performed initial screening based on the study titles or abstracts, while the second screening involved a full-text review. Cohort studies, case-control studies, and cross-sectional studies that assessed the association between male pattern baldness and CHD were eligible for inclusion if the following criteria were met: 1) the full text of the report was published in English, 2) the relative risk (risk ratio, hazard ratio, or odds ratio) was reported with adjustment for possible covariates (e.g. age, smoking, family history of baldness, or family history of CHD), 3) the presence and severity of male pattern baldness was reported, and 4) CHD events were reported.

***Definitions of baldness and CHD***

Baldness was defined according to the description in the history and/or on the basis of terms such as AGA and male pattern hair loss. We excluded studies that analyzed men with other types of baldness (e.g., alopecia areata or scarring alopecia). CHD was defined as including all of the following: coronary artery disease, myocardial infarction, angina pectoris, cardiomyopathy, and other types of ischemic heart disease.

***Assessment of validity***

To ascertain the validity of the eligible studies, the quality of each report was appraised with reference to the STROBE statement (14). Moreover, the Newcastle-Ottawa Scale for assessing

quality of non-randomized studies in meta-analyses was used to quantify the validity of each study (15).

***Data extraction***

Two investigators (T.Y. and K.H.) independently reviewed each study to determine its eligibility, and then extracted and tabulated all of the relevant data. Disagreement was resolved by consensus between the two investigators.

The following information was obtained from each study: first author, year of publication, type of study, country where the study was conducted, number of subjects (all subjects who participated in the study), CHD events, method of assessing baldness, follow-up period, mean age, smoking, covariates used for adjustment during analysis, and severity of baldness.

***Statistical analysis***

The pooled relative risk (RR) adjusted for possible covariates and its 95% confidence interval (95%CI) were calculated for the risk of CHD events in each study by the DerSimonian-Laird random effect model weighted with inverse variance (16). Equivalence of RRs between the cohort studies and the cross-sectional studies was assessed by the z-statistic test. Cochrane's $\chi^2$ test and the $I^2$ test were used to evaluate heterogeneity among studies (17). Possible publication bias was

evaluated by creating a funnel plot of the effect size for each study versus the standard error (SE). Funnel plot asymmetry was assessed by the Begg (18) and Egger tests (19). All statistical analyses were performed with Stata 12.0 software (StataCorp, College Station, TX). Results are expressed as the mean with 95%CI, unless otherwise indicated. A *P* value of less than 0.05 was considered significant. All procedures were performed in accordance with the guideline published by the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group (20) and the PRISMA statement (21)**(Supplementary Data 1)**.

## Results

### *Literature search*

**Figure 1** shows a flow chart of the study selection process. We identified a total of 850 reports by searching the databases. Among these, 834 reports were excluded after review of the title and abstract, leaving 16 studies for further evaluation. Ten of these 16 studies were excluded after full text evaluation, chiefly because of the lack of pertinent data. The remaining 6 studies (8-13) fulfilled the inclusion criteria were used for the present meta-analysis.

### *Study characteristics*

The six studies that were selected included three cohort studies and three case-control studies, and

their characteristics are summarized in **Table 1**. There were moderate differences with respect to the country, number of subjects, and method of assessing baldness. The studies were published between 1993 and 2008. Four studies (9-11,13) were conducted in the USA and the other two (8,12) were conducted in the European Union. The size of the study populations ranged from 1,437 (11) to 19,112 (10) subjects (mean: 6,165 subjects). In five of the six studies (8,10-13), CHD was defined as non-fatal myocardial infarction. The mean follow-up period ranged from 11 to 14 years. The method of assessing baldness varied, with a modified or simplified Hamilton scale being employed in four studies (8,10,11,13) and a personal scale being used in the other two studies (9,12).

Three studies (10,11,13) used a modified Hamilton scale that reduced the 12 categories of the original scale to the following five categories: no baldness (I, II); frontal baldness alone (IIa, III, IIIa, IVa); mild vertex baldness (III vertex, IV); moderate vertex baldness (V, Va); and severe vertex baldness (VI, VII). One study (8) used a simplified Hamilton scale, in which the extent of baldness was classified as follows: none; frontoparietal region (no bald triangle but >3 cm in front of the ear, or bald triangle but ≤3 cm in front of the ear); crown-top region (thick hair, partly thin hair, bald spot, or bald top and front); and combined.

Among the two studies that employed personal scales, Ford et al. (1996) classified baldness as none, minimum, moderate, or severe (9). Minimum baldness corresponded to no obvious baldness when the participant walked into the examining room, while moderate baldness was observable

baldness at the first encounter and severe baldness was obvious at the first encounter. In the other study, Miric et al. (1998) classified baldness as none, frontal, parietal (vertex), or combined (12).

The RR for CHD of the subjects with baldness was adjusted for several coronary risk factors (age, smoking, diabetes, etc.) in each study, but the number of variables differed significantly among the studies.

The reports on all three cross-sectional studies (11-13) explicitly mentioned the limitations of a cross-sectional design (i.e., it cannot assess causality), the possible biases of each study, and the influence of covariates. The reports on all three cohort studies (8-10) mentioned the possibility of misclassification of the severity of baldness.

One study found that baldness was not associated with CHD (13), but the other five studies concluded that baldness was associated with a significantly increased risk of CHD, although the strength of the association varied.

According to the Newcastle-Ottawa quality assessment scale for observational studies, all of the studies used in the present meta-analysis achieved at least six out of nine points, indicating that the overall quality of the studies was good **(Supplementary Data 2).**

***Association of baldness with CHD***

Among the six studies with a total of 36,990 subjects that were selected (8-13), no study showed a

significant decrease in the risk of CHD for men with baldness.

**Figures 2-4** show the results obtained by combining the RRs for CHD with the random-effect model.

In the three cohort studies (8-10), the adjusted RR of CHD for men of all ages with severe baldness versus those without baldness was 1.32 (95%CI: 1.08 - 1.63; $P = 0.008$; $P$ for heterogeneity = 0.26; $I^2 = 25\%$) with non-significant heterogeneity. Analysis restricted to younger subjects (<55 years old or ≤60 years old at baseline) revealed a similar association of severe baldness with CHD (RR 1.44 (95%CI: 1.11 - 1.86; $P = 0.006$; $P$ for heterogeneity = 0.59; $I^2 = 0\%$)) with non-significant heterogeneity (**Figure 2**).

In the three case-control studies (11-13), the adjusted RR was 1.70 (95%CI: 1.05 - 2.74; $P = 0.03$; $P$ for heterogeneity = 0.01: $I^2 = 78\%$) for all subjects, while the RR was 1.84 (95%CI: 1.30 - 2.62; $P = 0.001$; $P$ for heterogeneity = 0.17; $I^2 = 44\%$) among the younger subjects (**Figure 3**). The difference of RR values between the cohort and case-control studies was non-significant (all subjects: $P = 0.15$; patients≤60 years old: $P = 0.07$).

***Stratified analysis***

In the three studies that assessed the severity of baldness by using the modified Hamilton scale (10,11,13), two studies (10,11) showed that vertex baldness was associated with CHD and that this

association was dependent on the severity of baldness. In subjects with severe vertex baldness, the RR was 1.48 (95%CI: 1.04 - 2.11; $P = 0.03$; $P$ for heterogeneity = 0.02; $I^2 = 75\%$), while the RR was 1.36 (95%CI: 1.16 - 1.58; $P < 0.001$; $P$ for heterogeneity = 0.95; $I^2 = 0\%$) for moderate vertex baldness and 1.18 (95%CI: 1.04 - 1.35; $P < 0.001$; $P$ for heterogeneity = 0.35; $I^2 = 4\%$) for mild vertex baldness. In contrast, there was non-significant association of frontal baldness with CHD and the RR was only 1.11 (95%CI: 0.92 - 1.32; $P = 0.28$; $P$ for heterogeneity=0.24; $I^2 = 30\%$) **(Figure 4)**.

Because the method of assessing baldness was not homogenous, we also performed a sensitivity analysis of the studies that used personal scales to classify baldness into four grades (none, frontal, crown-top, or combined) (8,12). Similar results were obtained showing that the association with CHD depended on the severity of baldness, with an RR of 1.69 (95%CI: 1.28 - 2.23; $P < 0.001$; $P$ for heterogeneity = 0.97; $I^2 = 0\%$) for combined baldness, an RR of 1.52 (95%CI: 0.97- 2.39; $P = 0.07$; $P$ for heterogeneity = 0.001; $I^2 = 91\%$) for crown-top baldness, and an RR of 1.22 (95%CI: 0.70 - 2.14; $P = 0.49$; $P$ for heterogeneity = 0.05; $I^2 = 73\%$) for frontal baldness.

***Publication bias***

The funnel plot, Begg's test, and Egger's test were used to evaluate the potential influence of publication bias on the association between baldness and CHD. The funnel plot did not show an

asymmetric pattern, while Egger's test and Begg's test revealed non-significant publication bias (all $P \geq 0.05$).

## Discussion

The present meta-analysis of six studies from the USA and Europe demonstrated that vertex baldness was significantly associated with an increased risk of CHD among subjects of all ages and also among younger men. Interestingly, frontal baldness was non-significantly associated with CHD.

When baldness was classified by the Hamilton-Norwood scale, which is the most commonly used classification of male pattern baldness worldwide (22), the relationship between CHD and baldness was shown to be dependent on the severity of baldness.

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 (23-26).

These findings support the hypothesis that vertex baldness is a local manifestation of factors promoting systemic atherosclerosis, such as metabolic syndrome, hypertension, and smoking.

Minoxidil (Rogaine/Regaine) is one of the most popular drugs for the treatment of male pattern baldness. Minoxidil was originally developed as an antihypertensive agent (vasodilator) and it is

thought to improve the blood flow and the supply of oxygen and nutrients to the hair follicles by dilating vessels in the scalp and opening potassium channels. This might lead to the shedding of hairs in the telogen phase, which are then replaced by thicker hairs in the anagen phase (27). Minoxidil is only indicated for vertex baldness and is ineffective for frontal baldness (28), which supports our finding that vertex baldness is more closely related to atherosclerosis than frontal baldness.

***Mechanism of the relation between baldness and CHD***

The reason for the association between baldness and CHD is unclear. It has been suggested that classical coronary risk factors (e.g., age, hypertension, dislipidemia, and smoking) might influence both conditions, so that baldness is a marker of atherosclerosis. In fact, previous studies have demonstrated a positive association between male pattern baldness and insulin resistance (23), metabolic syndrome (29), and hypertension (30). It has also been postulated that baldness is linked to CHD by mechanisms such as hyperinsulinemia, chronic inflammation, and increased peripheral sensitivity to androgens, and these are briefly discussed below.

1) Hyperinsulinemia/insulin resistance is the central factor in metabolic syndrome and it promotes intolerance of carbohydrates and the development of central (abdominal) obesity. Insulin resistance has also been shown to cause vasoconstriction and impairs the supply of nutrients to the hair follicles

of the scalp, as well as enhancing the influence of dihydro-testosterone (DHT) on follicular miniaturization (24,31).

2) A proinflammatory state could increase the levels of inflammatory cytokines in the arterial walls (32) and hair follicles (25). High-sensitivity C-reactive protein is a marker of inflammation and is also a good predictor of future cardiovascular disease (33), so chronic inflammation could be related to both CHD and baldness.

3) Male pattern baldness might be caused by increased peripheral sensitivity to androgens, since bald men show an increase of androgen receptors in the scalp (34) and have higher serum levels of both total and free testosterone (35). Free testosterone is converted to DHT by 5a-reductase, leading to miniaturization of hair follicles. It has been reported that 5a-reductase exists in the blood vessels and the heart, as does the DHT receptor, which is involved in vascular smooth muscle proliferation that represents a fundamental feature of atherosclerosis along with the deposition of lipids (36).

***Strengths and limitations***

The strengths of the present meta-analysis were as follows. First, our analysis included several large cohort and case-control studies, with a total of 36,990 subjects. Second, the cohort studies had a long follow-up period (11.0-14.0 years). In all of the studies, analyses were adjusted for various classical coronary risk factors, such as age, smoking, hypertension, dyslipidemia, and body mass

index.

However, the present meta-analysis also had several limitations. First, we only reviewed English-language reports for inclusion in this meta-analysis and we might possibly have overlooked some non-English literature, which could have led to selection bias. However, we also investigated all of the references in each study as far as possible. Also, our analyses of publication bias did not suggest that unpublished results had been missed, but these analyses might have been underpowered due to the small effect sizes. Second, although most factors showed non-significant between-study heterogeneity, it was significant for some factors, suggesting that differences of epidemiological characteristics (e.g., the rate of severe baldness or CHD) or different diagnostic criteria (for baldness and/or CHD) contributed to the heterogeneity to some extent.

Unlike the results of the other studies, the effect sizes reported by Lesko et al. (1993) (11) varied widely and even changed the sign when different patterns of baldness were compared (Fig. 4). This study had the lowest validity score (6/9 points on the Newcastle-Ottawa scale) among the six studies included in our meta-analysis **(Supplementary Data 2)**. Lesko et al. contacted the coronary care units of participating hospitals to identify potential subjects with their first myocardial infarction and to obtain permission to conduct an interview. Thus, details about CHD were not obtained in this study, which might have led to bias and influenced the effect size.

Moreover, as already reported by Rebora (2001)(37), Lotufo et al. (2000)(10) relied on each

patient's memory of a condition that had developed up to 40 years before, which might have led to recall bias. These two studies would have a higher risk of misclassification bias that could lead to underestimating the strength of the association between baldness and CHD, since it is often considered shameful to admit to the existence of baldness.

The third limitation was incomplete information about the use of medications such as anticoagulants, anticonvulsants, beta-blockers, antidepressants, and hormone replacement therapy that might have contributed to baldness (38).

Fourth, the methods used to assess baldness varied between studies, which meant that we could not rule out other local causes of diffuse hair loss (alopecia areata or nonscarring alopecia), as well as possible systemic causes (e.g., thyroiditis, iron deficiency (39,40), trauma, excessive dieting, or debilitating diseases).

Even with such limitations, the present meta-analysis provided useful evidence regarding the potential influence of baldness on CHD. Patients and physicians should consider the possibility that baldness is associated with an increased risk of CHD.

***Conclusions***

In the present meta-analysis, vertex baldness was significantly associated with an increased risk of CHD among younger men as well as among all subjects, and the association was dependent on the

severity of baldness. These findings suggest that vertex baldness is more closely associated with systemic atherosclerosis than with frontal baldness. 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. 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).

In addition, the association between baldness and CHD should be investigated in further studies, including well-designed and controlled cohort studies, in order to confirm whether persons with male pattern baldness (especially severe vertex baldness) have an increased risk of CHD.

***Contributors***

TY, KH, HU and TK conceived the idea of the study and were responsible for the design of the study. TY and KH were responsible for undertaking for the data analysis and produced the tables and figures. TY and KH provided input into the data analysis. The initial draft of the manuscript was

prepared by TY and KH and then circulated repeatedly among all authors for critical revision. TY was responsible for the acquisition of the data and TY, KH and TK contributed to the interpretation of the results.

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***Competing Interests***

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

***Ethical approval***

Not needed.

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***Supplementary Data***

**Supplementary Data 1. PRISMA Checklist.**

**Supplementary Data 2. Newcastle-Ottawa quality assessment scale for observational studies**

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**Figure legends**

**Figure 1**. **Flow diagram of study selection.**

**Figure 2. Association of baldness with CHD in the 3 cohort studies.**

The forest plot shows the association between male pattern baldness and the risk of coronary heart disease (CHD). CI=confidence interval; RR=relative risk.

**Figure 3. Association of baldness with CHD in the 3 case-control studies.**

The forest plot shows the association between male pattern baldness and the risk of coronary heart disease (CHD). CI=confidence interval; RR=relative risk.

**Figure 4. Association of baldness with CHD in studies using the modified Hamilton scale.**

The forest plot shows the association between male pattern baldness and the risk of coronary heart disease (CHD). CI=confidence interval; RR=relative risk

| First author, | Type of | Country | Subjects | CHD | (events) | Assessment of baldness | Follow-up | Covariates used for adjustment |
|---|---|---|---|---|---|---|---|---|



Table 1. Summary of studies evaluating the association between baldness and coronary heart disease

| year of publication | study | | | | | (years) | |
|---|---|---|---|---|---|---|---|
| Schnohr, 1995 (8) | Cohort | Denmark | 5837 | Myocardial infarction (750) | Simplified Hamilton (None, Frontoparietal, Crown-top, Combined) | 12.0 | Age, smoking, systolic blood pressure, cholesterol, triglycerides, physical activity, BMI, family history of MI, marital status, education, economic status, diabetes, and alcohol consumption |
| Ford, 1996 (9) | Cohort | USA | 3994 | Ischemic heart disease (965) | Personal scale (None, Minimum, Moderate, Severe) | 14.0 | Age, age squared, race, education, systolic blood pressure, antihypertensive medication, cholesterol, smoking, BMI, and diabetes mellitus |
| Lotufo, 2000 (10) | Cohort | USA | 19112 | Nonfatal MI, angina, coronary revascularization (1446) | Modified Hamilton (None, Frontal, Mild vertex, Moderate vertex, Severe vertex) | 11.0 | Age, aspirin assignment, beta carotene assignment, BMI, height (cm), hypertension, hypercholesterolemia, diabetes, parental history of MI, physical activity, smoking, and alcohol use. |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Lesko, 1993 (11) | Case-control | USA | 1437 | Non-fatal Myocardial infarction (665) | Modified Hamilton (None, Frontal only, Mild vertex, Moderate vertex, Severe vertex) | - | Age, race, religion, years of education, BMI, use of alcohol and cigarettes, family history of myocardial infarction, personal history of angina, hypertension, diabetes, hypercholesterolemia, gout, exercise, personality, and number of doctor visits in the past year. |
| Miric, 1998 (12) | Case-control | Croatia | 1554 | Non-fatal Myocardial infarction (842) | Personal score ( None, Any, Frontal, Parietal, Fronto-parietal) | - | Age, family history of MI, hypertension, hypercholesterolemia, BMI, diabetes, and smoking. |
| Shahar, 2008 (13) | Case-control | USA | 5056 | Non-fatal Myocardial infarction (767) | Modified Hamilton ( None, Frontal, Mild vertex, Moderate vertex, Severe vertex) | - | Age, smoking, BMI, race-center, cholesterol-lowering medication, antihypertensive medication, HDL, diabetes, educational level, and family history of MI. |

CHD, coronary heart disease; BMI, body mass index; MI, myocardial infarction; AGA, androgenic alopecia; HDL, high density lipoprotein;

# Male Pattern Baldness and Its Association with Coronary Heart Disease: A Meta-Analysis

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**Brief title**: Male pattern baldness and CHD

**Word count**: 3691 words

**Abstract**

**Objective:**

To confirm the association between male pattern baldness and coronary heart disease (CHD).

**Design:**

Meta-analysis of observational studies.

**Data sources:**

Medline and the Cochrane Library were searched for articles published up to November 2012 using keywords that included both 'baldness' and 'coronary heart disease' and the reference lists of those studies identified were also searched.

**Study selection:**

Observational studies were identified that reported risk estimates for CHD related to baldness. Two observers independently assessed eligibility, extracted data, and assessed the possibility of bias.

**Data synthesis:**

The adjusted relative risk (RR) and 95% confidence interval (95%CI) were estimated using the DerSimonian-Laird random-effect model.

**Results:**

Included 850 possible studies, three cohort studies and three case-control studies were selected (36,990 subjects).

In the cohort studies, the adjusted RR of men with severe baldness for CHD was 1.32 (95%CI: 1.08 - 1.63, $P = 0.008$, $I^2 = 25\%$) versus those without baldness. Analysis of younger men (<55 or ≤60 years) showed a similar association of CHD with severe baldness (RR: 1.44, 95%CI: 1.11 - 1.86, $P = 0.006$, $I^2 = 0\%$).

In 3 studies employing the modified Hamilton scale, vertex baldness was associated with CHD and the relation depended on the severity of baldness (severe vertex: RR 1.48 (1.04 - 2.11, $P = 0.03$); moderate vertex: RR 1.36 (1.16 - 1.58, $P < 0.001$); mild vertex: RR 1.18 (1.04 - 1.35, $P < 0.001$). However, frontal baldness was not associated with CHD (RR 1.11 (0.92 - 1.32, $P = 0.28$)).

**Conclusion:**

Vertex baldness, but not frontal baldness, is associated with an increased risk of CHD. The association with CHD depends on the severity of vertex baldness and also exists among younger men. Thus, vertex baldness might be more closely related to atherosclerosis than frontal baldness, but the association between male pattern baldness and CHD deserves further investigation.

**Key words**: male pattern baldness, androgenetic alopecia, coronary heart disease, cardiovascular disease, relative risk, meta-analysis

**Article summary**

**Article focus:**

・The present meta-analysis aimed to confirm the association of male pattern baldness (androgenetic alopecia) with an increased risk of coronary heart disease (CHD).

**Key messages:**

・Meta-analysis of 6 observational studies with a total of 36,690 subjects showed that vertex baldness is associated with an increased risk of CHD and that the relationship depends upon the severity of baldness, while frontal baldness is not.

・Thus, vertex baldness might be a marker of CHD and is more closely associated with systemic atherosclerosis than frontal baldness.

・This potential relationship should be investigated in further studies, including well-designed prospective studies.

**Strengths and limitations of this study:**

・This was the first meta-analysis of the association between baldness and CHD; it showed that the relationship depends on the severity of baldness.

・The cohort studies had a long follow-up period of 11.0 - 14.0 years.

・A weakness might be the small number of studies analyzed.

## Introduction

Coronary heart disease (CHD) is a major cause of death and disability worldwide (1). Advanced obstructive CHD can exist in patients with minimal or no symptoms and can progress rapidly (2), so early detection is extremely important. Many clinicians carry out screening for asymptomatic CHD and participants in wellbeing programs often also request such screening, but the usefulness of CHD screening has yet to be confirmed. Young et al. (2009) reported that the incidence of CHD was not significantly reduced in asymptomatic diabetic patients when screening was conducted by myocardial scintigraphy (3), and McEvoy et al. (2011) also reported that coronary computed tomography screening of asymptomatic patients without a history of coronary artery disease fails to prevent major cardiovascular events (4).

Male pattern baldness, also called androgenetic alopecia (AGA), is the most common cause of hair loss. It affects approximately 30 to 40% of adult men (5) and it is seen in 80% of men by the age of 80 years (6). AGA is considered to be a heritable, androgen-dependent condition that is characterized by varying degrees of thinning/hair loss primarily at the vertex and the frontal areas (temples) of the scalp. In men with AGA, the thin residual hairs tend to be of various lengths and diameters since each follicle is in a different phase of the hair cycle, so the presence of variations in hair length and texture is a classic feature of this thinning condition (7).

Several recent studies have shown that baldness is associated with the risk of CHD (8-12). These

studies have generally found a positive association between baldness and CHD, although the strength of the association has varied (8-13).

Clarifying the relationship between baldness and CHD could lead to more effective approaches to the early detection of heart disease, since it might permit the reliable identification of persons with an increased risk of suffering from a cardiac event thereby allowing the delivery of appropriate therapy (e.g., antihypertensive or lipid-lowering therapy) to improve the prognosis of such high-risk persons. Accordingly, we performed a meta-analysis to further assess the influence of male pattern baldness (AGA) on CHD.

## Methods

### *Search strategy*

The Medline and Cochrane Library electronic databases were searched from January 1, 1950 until November 27, 2012 using the medical subject headings "Baldness" ("baldness" or "hair loss" or "alopecia") and "Coronary heart disease" ("coronary heart disease" or "cardiovascular disease" or "coronary artery disease") to identify observational studies that estimated the association between baldness and CHD. The reference lists of all studies identified were also reviewed.

### *Study selection*

We performed initial screening based on the study titles or abstracts, while the second screening involved a full-text review. Cohort studies, case-control studies, and cross-sectional studies that assessed the association between male pattern baldness and CHD were eligible for inclusion if the following criteria were met: 1) the full text of the report was published in English, 2) the relative risk (risk ratio, hazard ratio, or odds ratio) was reported with adjustment for possible covariates (e.g. age, smoking, family history of baldness, or family history of CHD), 3) the presence and severity of male pattern baldness was reported, and 4) CHD events were reported.

***Definitions of baldness and CHD***

Baldness was defined according to the description in the history and/or on the basis of terms such as AGA and male pattern hair loss. We excluded studies that analyzed men with other types of baldness (e.g., alopecia areata or scarring alopecia). CHD was defined as including all of the following: coronary artery disease, myocardial infarction, angina pectoris, cardiomyopathy, and other types of ischemic heart disease.

***Assessment of validity***

To ascertain the validity of the eligible studies, the quality of each report was appraised with reference to the STROBE statement (14). Moreover, the Newcastle-Ottawa Scale for assessing

quality of non-randomized studies in meta-analyses was used to quantify the validity of each study (15).

***Data extraction***

Two investigators (T.Y. and K.H.) independently reviewed each study to determine its eligibility, and then extracted and tabulated all of the relevant data. Disagreement was resolved by consensus between the two investigators.

The following information was obtained from each study: first author, year of publication, type of study, country where the study was conducted, number of subjects (all subjects who participated in the study), CHD events, method of assessing baldness, follow-up period, mean age, smoking, covariates used for adjustment during analysis, and severity of baldness.

***Statistical analysis***

The pooled relative risk (RR) adjusted for possible covariates and its 95% confidence interval (95%CI) were calculated for the risk of CHD events in each study by the DerSimonian-Laird random effect model weighted with inverse variance (16). Equivalence of RRs between the cohort studies and the cross-sectional studies was assessed by the z-statistic test. Cochrane's $\chi^2$ test and the $I^2$ test were used to evaluate heterogeneity among studies (17). Possible publication bias was

evaluated by creating a funnel plot of the effect size for each study versus the standard error (SE). Funnel plot asymmetry was assessed by the Begg (18) and Egger tests (19). All statistical analyses were performed with Stata 12.0 software (StataCorp, College Station, TX). Results are expressed as the mean with 95%CI, unless otherwise indicated. A *P* value of less than 0.05 was considered significant. All procedures were performed in accordance with the guideline published by the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group (20) and the PRISMA statement (21)**(Supplementary Data 1)**.

## Results

### *Literature search*

**Figure 1** shows a flow chart of the study selection process. We identified a total of 850 reports by searching the databases. Among these, 834 reports were excluded after review of the title and abstract, leaving 16 studies for further evaluation. Ten of these 16 studies were excluded after full text evaluation, chiefly because of the lack of pertinent data. The remaining 6 studies (8-13) fulfilled the inclusion criteria were used for the present meta-analysis.

### *Study characteristics*

The six studies that were selected included three cohort studies and three case-control studies, and

their characteristics are summarized in **Table 1**. There were moderate differences with respect to the country, number of subjects, and method of assessing baldness. The studies were published between 1993 and 2008. Four studies (9-11,13) were conducted in the USA and the other two (8,12) were conducted in the European Union. The size of the study populations ranged from 1,437 (11) to 19,112 (10) subjects (mean: 6,165 subjects). In five of the six studies (8,10-13), CHD was defined as non-fatal myocardial infarction. The mean follow-up period ranged from 11 to 14 years. The method of assessing baldness varied, with a modified or simplified Hamilton scale being employed in four studies (8,10,11,13) and a personal scale being used in the other two studies (9,12).

Three studies (10,11,13) used a modified Hamilton scale that reduced the 12 categories of the original scale to the following five categories: no baldness (I, II); frontal baldness alone (IIa, III, IIIa, IVa); mild vertex baldness (III vertex, IV); moderate vertex baldness (V, Va); and severe vertex baldness (VI, VII). One study (8) used a simplified Hamilton scale, in which the extent of baldness was classified as follows: none; frontoparietal region (no bald triangle but >3 cm in front of the ear, or bald triangle but ≤3 cm in front of the ear); crown-top region (thick hair, partly thin hair, bald spot, or bald top and front); and combined.

Among the two studies that employed personal scales, Ford et al. (1996) classified baldness as none, minimum, moderate, or severe (9). Minimum baldness corresponded to no obvious baldness when the participant walked into the examining room, while moderate baldness was observable

baldness at the first encounter and severe baldness was obvious at the first encounter. In the other study, Miric et al. (1998) classified baldness as none, frontal, parietal (vertex), or combined (12).

The RR for CHD of the subjects with baldness was adjusted for several coronary risk factors (age, smoking, diabetes, etc.) in each study, but the number of variables differed significantly among the studies.

The reports on all three cross-sectional studies (11-13) explicitly mentioned the limitations of a cross-sectional design (i.e., it cannot assess causality), the possible biases of each study, and the influence of covariates. The reports on all three cohort studies (8-10) mentioned the possibility of misclassification of the severity of baldness.

One study found that baldness was not associated with CHD (13), but the other five studies concluded that baldness was associated with a significantly increased risk of CHD, although the strength of the association varied.

According to the Newcastle-Ottawa quality assessment scale for observational studies, all of the studies used in the present meta-analysis achieved at least six out of nine points, indicating that the overall quality of the studies was good **(Supplementary Data 2).**

***Association of baldness with CHD***

Among the six studies with a total of 36,990 subjects that were selected (8-13), no study showed a

significant decrease in the risk of CHD for men with baldness.

**Figures 2-4** show the results obtained by combining the RRs for CHD with the random-effect model.

In the three cohort studies (8-10), the adjusted RR of CHD for men of all ages with severe baldness versus those without baldness was 1.32 (95%CI: 1.08 - 1.63; $P = 0.008$; $P$ for heterogeneity = 0.26; $I^2 = 25\%$) with non-significant heterogeneity. Analysis restricted to younger subjects (<55 years old or ≤60 years old at baseline) revealed a similar association of severe baldness with CHD (RR 1.44 (95%CI: 1.11 - 1.86; $P = 0.006$; $P$ for heterogeneity = 0.59; $I^2 = 0\%$)) with non-significant heterogeneity (**Figure 2**).

In the three case-control studies (11-13), the adjusted RR was 1.70 (95%CI: 1.05 - 2.74; $P = 0.03$; $P$ for heterogeneity = 0.01: $I^2 = 78\%$) for all subjects, while the RR was 1.84 (95%CI: 1.30 - 2.62; $P = 0.001$; $P$ for heterogeneity = 0.17; $I^2 = 44\%$) among the younger subjects (**Figure 3**). The difference of RR values between the cohort and case-control studies was non-significant (all subjects: $P = 0.15$; patients≤60 years old: $P = 0.07$).

***Stratified analysis***

In the three studies that assessed the severity of baldness by using the modified Hamilton scale (10,11,13), two studies (10,11) showed that vertex baldness was associated with CHD and that this

association was dependent on the severity of baldness. In subjects with severe vertex baldness, the RR was 1.48 (95%CI: 1.04 - 2.11; $P = 0.03$; $P$ for heterogeneity = 0.02; $I^2 = 75\%$), while the RR was 1.36 (95%CI: 1.16 - 1.58; $P < 0.001$; $P$ for heterogeneity = 0.95; $I^2 = 0\%$) for moderate vertex baldness and 1.18 (95%CI: 1.04 - 1.35; $P < 0.001$; $P$ for heterogeneity = 0.35; $I^2 = 4\%$) for mild vertex baldness. In contrast, there was non-significant association of frontal baldness with CHD and the RR was only 1.11 (95%CI: 0.92 - 1.32; $P = 0.28$; $P$ for heterogeneity=0.24; $I^2 = 30\%$) **(Figure 4)**.

Because the method of assessing baldness was not homogenous, we also performed a sensitivity analysis of the studies that used personal scales to classify baldness into four grades (none, frontal, crown-top, or combined) (8,12). Similar results were obtained showing that the association with CHD depended on the severity of baldness, with an RR of 1.69 (95%CI: 1.28 - 2.23; $P < 0.001$; $P$ for heterogeneity = 0.97; $I^2 = 0\%$) for combined baldness, an RR of 1.52 (95%CI: 0.97- 2.39; $P = 0.07$; $P$ for heterogeneity = 0.001; $I^2 = 91\%$) for crown-top baldness, and an RR of 1.22 (95%CI: 0.70 - 2.14; $P = 0.49$; $P$ for heterogeneity = 0.05; $I^2 = 73\%$) for frontal baldness.

***Publication bias***

The funnel plot, Begg's test, and Egger's test were used to evaluate the potential influence of publication bias on the association between baldness and CHD. The funnel plot did not show an

asymmetric pattern, while Egger's test and Begg's test revealed non-significant publication bias (all $P \geq 0.05$).

**Discussion**

The present meta-analysis of six studies from the USA and Europe demonstrated that vertex baldness was significantly associated with an increased risk of CHD among subjects of all ages and also among younger men. Interestingly, frontal baldness was non-significantly associated with CHD.

When baldness was classified by the Hamilton-Norwood scale, which is the most commonly used classification of male pattern baldness worldwide (22), the relationship between CHD and baldness was shown to be dependent on the severity of baldness.

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 (23-26).

These findings support the hypothesis that vertex baldness is a local manifestation of factors promoting systemic atherosclerosis, such as metabolic syndrome, hypertension, and smoking.

Minoxidil (Rogaine/Regaine) is one of the most popular drugs for the treatment of male pattern baldness. Minoxidil was originally developed as an antihypertensive agent (vasodilator) and it is

thought to improve the blood flow and the supply of oxygen and nutrients to the hair follicles by dilating vessels in the scalp and opening potassium channels. This might lead to the shedding of hairs in the telogen phase, which are then replaced by thicker hairs in the anagen phase (27). Minoxidil is only indicated for vertex baldness and is ineffective for frontal baldness (28), which supports our finding that vertex baldness is more closely related to atherosclerosis than frontal baldness.

***Mechanism of the relation between baldness and CHD***

The reason for the association between baldness and CHD is unclear. It has been suggested that classical coronary risk factors (e.g., age, hypertension, dislipidemia, and smoking) might influence both conditions, so that baldness is a marker of atherosclerosis. In fact, previous studies have demonstrated a positive association between male pattern baldness and insulin resistance (23), metabolic syndrome (29), and hypertension (30). It has also been postulated that baldness is linked to CHD by mechanisms such as hyperinsulinemia, chronic inflammation, and increased peripheral sensitivity to androgens, and these are briefly discussed below.

1) Hyperinsulinemia/insulin resistance is the central factor in metabolic syndrome and it promotes intolerance of carbohydrates and the development of central (abdominal) obesity. Insulin resistance has also been shown to cause vasoconstriction and impairs the supply of nutrients to the hair follicles

of the scalp, as well as enhancing the influence of dihydro-testosterone (DHT) on follicular miniaturization (24,31).

2) A proinflammatory state could increase the levels of inflammatory cytokines in the arterial walls (32) and hair follicles (25). High-sensitivity C-reactive protein is a marker of inflammation and is also a good predictor of future cardiovascular disease (33), so chronic inflammation could be related to both CHD and baldness.

3) Male pattern baldness might be caused by increased peripheral sensitivity to androgens, since bald men show an increase of androgen receptors in the scalp (34) and have higher serum levels of both total and free testosterone (35). Free testosterone is converted to DHT by 5a-reductase, leading to miniaturization of hair follicles. It has been reported that 5a-reductase exists in the blood vessels and the heart, as does the DHT receptor, which is involved in vascular smooth muscle proliferation that represents a fundamental feature of atherosclerosis along with the deposition of lipids (36).

***Strengths and limitations***

The strengths of the present meta-analysis were as follows. First, our analysis included several large cohort and case-control studies, with a total of 36,990 subjects. Second, the cohort studies had a long follow-up period (11.0-14.0 years). In all of the studies, analyses were adjusted for various classical coronary risk factors, such as age, smoking, hypertension, dyslipidemia, and body mass

index.

However, the present meta-analysis also had several limitations. First, we only reviewed English-language reports for inclusion in this meta-analysis and we might possibly have overlooked some non-English literature, which could have led to selection bias. However, we also investigated all of the references in each study as far as possible. Also, our analyses of publication bias did not suggest that unpublished results had been missed, but these analyses might have been underpowered due to the small effect sizes. Second, although most factors showed non-significant between-study heterogeneity, it was significant for some factors, suggesting that differences of epidemiological characteristics (e.g., the rate of severe baldness or CHD) or different diagnostic criteria (for baldness and/or CHD) contributed to the heterogeneity to some extent.

Unlike the results of the other studies, the effect sizes reported by Lesko et al. (1993) (11) varied widely and even changed the sign when different patterns of baldness were compared (Fig. 4). This study had the lowest validity score (6/9 points on the Newcastle-Ottawa scale) among the six studies included in our meta-analysis **(Supplementary Data 2)**. Lesko et al. contacted the coronary care units of participating hospitals to identify potential subjects with their first myocardial infarction and to obtain permission to conduct an interview. Thus, details about CHD were not obtained in this study, which might have led to bias and influenced the effect size.

Moreover, as already reported by Rebora (2001)(37), Lotufo et al. (2000)(10) relied on each

patient's memory of a condition that had developed up to 40 years before, which might have led to recall bias. These two studies would have a higher risk of misclassification bias that could lead to underestimating the strength of the association between baldness and CHD, since it is often considered shameful to admit to the existence of baldness.

The third limitation was incomplete information about the use of medications such as anticoagulants, anticonvulsants, beta-blockers, antidepressants, and hormone replacement therapy that might have contributed to baldness (38).

Fourth, the methods used to assess baldness varied between studies, which meant that we could not rule out other local causes of diffuse hair loss (alopecia areata or nonscarring alopecia), as well as possible systemic causes (e.g., thyroiditis, iron deficiency (39,40), trauma, excessive dieting, or debilitating diseases).

Even with such limitations, the present meta-analysis provided useful evidence regarding the potential influence of baldness on CHD. Patients and physicians should consider the possibility that baldness is associated with an increased risk of CHD.

***Conclusions***

In the present meta-analysis, vertex baldness was significantly associated with an increased risk of CHD among younger men as well as among all subjects, and the association was dependent on the

severity of baldness. These findings suggest that vertex baldness is more closely associated with systemic atherosclerosis than with frontal baldness. 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. 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).

In addition, the association between baldness and CHD should be investigated in further studies, including well-designed and controlled cohort studies, in order to confirm whether persons with male pattern baldness (especially severe vertex baldness) have an increased risk of CHD.

***Contributors***

TY, KH, HU and TK conceived the idea of the study and were responsible for the design of the study. TY and KH were responsible for undertaking for the data analysis and produced the tables and figures. TY and KH provided input into the data analysis. The initial draft of the manuscript was

prepared by TY and KH and then circulated repeatedly among all authors for critical revision. TY was responsible for the acquisition of the data and TY, KH and TK contributed to the interpretation of the results.

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***Competing Interests***

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

***Ethical approval***

Not needed.

***Funding statement***

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***Supplementary Data***

**Supplementary Data 1. PRISMA Checklist.**

**Supplementary Data 2. Newcastle-Ottawa quality assessment scale for observational studies**

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**Figure legends**

**Figure 1**. **Flow diagram of study selection.**

**Figure 2. Association of baldness with CHD in the 3 cohort studies.**

The forest plot shows the association between male pattern baldness and the risk of coronary heart disease (CHD). CI=confidence interval; RR=relative risk.

**Figure 3. Association of baldness with CHD in the 3 case-control studies.**

The forest plot shows the association between male pattern baldness and the risk of coronary heart disease (CHD). CI=confidence interval; RR=relative risk.

**Figure 4. Association of baldness with CHD in studies using the modified Hamilton scale.**

The forest plot shows the association between male pattern baldness and the risk of coronary heart disease (CHD). CI=confidence interval; RR=relative risk

| First author, | Type of | Country | Subjects | CHD (events) | Assessment of baldness | Follow-up | Covariates used for adjustment |
|---|---|---|---|---|---|---|---|



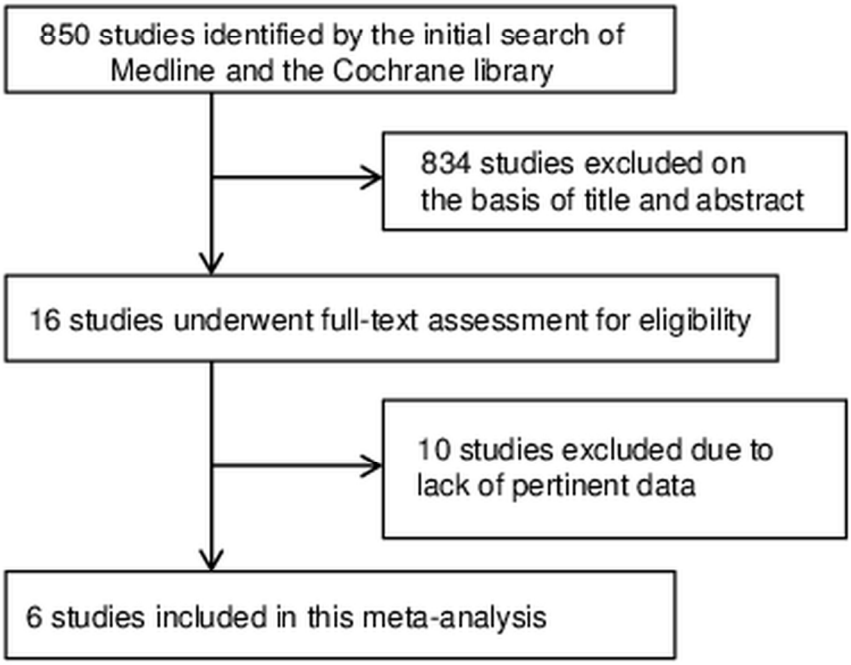
Table 1. Summary of studies evaluating the association between baldness and coronary heart disease

| year of publication | study | | | | | (years) | |
|---|---|---|---|---|---|---|---|
| Schnohr, 1995 (8) | Cohort | Denmark | 5837 | Myocardial infarction (750) | Simplified Hamilton (None, Frontoparietal, Crown-top, Combined) | 12.0 | Age, smoking, systolic blood pressure, cholesterol, triglycerides, physical activity, BMI, family history of MI, marital status, education, economic status, diabetes, and alcohol consumption |
| Ford, 1996 (9) | Cohort | USA | 3994 | Ischemic heart disease (965) | Personal scale (None, Minimum, Moderate, Severe) | 14.0 | Age, age squared, race, education, systolic blood pressure, antihypertensive medication, cholesterol, smoking, BMI, and diabetes mellitus |
| Lotufo, 2000 (10) | Cohort | USA | 19112 | Nonfatal MI, angina, coronary revascularization (1446) | Modified Hamilton (None, Frontal, Mild vertex, Moderate vertex, Severe vertex) | 11.0 | Age, aspirin assignment, beta carotene assignment, BMI, height (cm), hypertension, hypercholesterolemia, diabetes, parental history of MI, physical activity, smoking, and alcohol use. |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Lesko, 1993 (11) | Case-control | USA | 1437 | Non-fatal Myocardial infarction (665) | Modified Hamilton (None, Frontal only, Mild vertex, Moderate vertex, Severe vertex) | - | Age, race, religion, years of education, BMI, use of alcohol and cigarettes, family history of myocardial infarction, personal history of angina, hypertension, diabetes, hypercholesterolemia, gout, exercise, personality, and number of doctor visits in the past year. |
| Miric, 1998 (12) | Case-control | Croatia | 1554 | Non-fatal Myocardial infarction (842) | Personal score ( None, Any, Frontal, Parietal, Fronto-parietal) | - | Age, family history of MI, hypertension, hypercholesterolemia, BMI, diabetes, and smoking. |
| Shahar, 2008 (13) | Case-control | USA | 5056 | Non-fatal Myocardial infarction (767) | Modified Hamilton ( None, Frontal, Mild vertex, Moderate vertex, Severe vertex) | - | Age, smoking, BMI, race-center, cholesterol-lowering medication, antihypertensive medication, HDL, diabetes, educational level, and family history of MI. |

CHD, coronary heart disease; BMI, body mass index; MI, myocardial infarction; AGA, androgenic alopecia; HDL, high density lipoprotein;

Fig. 1

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# PRISMA 2009 Checklist

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 |
| **ABSTRACT** | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 2-3 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 5-6 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 5-6 |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | 6 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 6 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 6-7 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | 6 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 6-7 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 6-7 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 7 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 7 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 7-8 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | 7-9 |

# PRISMA 2009 Checklist

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 7-9 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 7-9 |
| **RESULTS** | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 9, Fig 1 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 9, Table 1 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 9, Table 1 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 9-10, Table 1, Fig 2-4 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | 10-12, Fig 2-4 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | 10-13 Suppl.2 |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | 11-14 |
| **DISCUSSION** | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 14-15 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 16-18 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 18-19 |
| **FUNDING** | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 19-21 |

*From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097.

# PRISMA 2009 Checklist

doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Supplementary Data 2. Newcastle-Ottawa quality assessment scale for observational studies

| Study reference (author, year) | Selection | Comparability | Outcome/Exposure |
|---|---|---|---|
| Cohort studies | | | |
| Schnohor, 1995 (8) | *** | ** | *** |
| Ford, 1996 (9) | *** | ** | *** |
| Lotufo, 2000 (10) | *** | ** | *** |
| Case-control studies | | | |
| Lesko, 1993 (11) | ** | ** | ** |
| Miric, 1998 (12) | *** | ** | ** |
| Shahar, 2008 (13) | **** | ** | ** |

Fig. 2

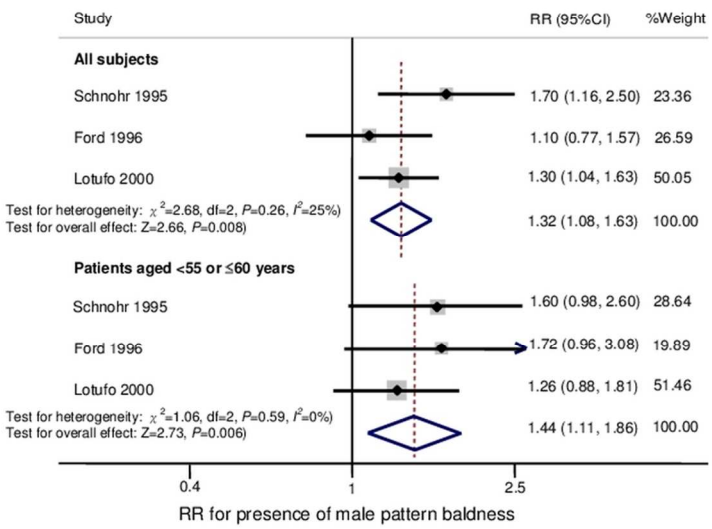


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Fig. 3

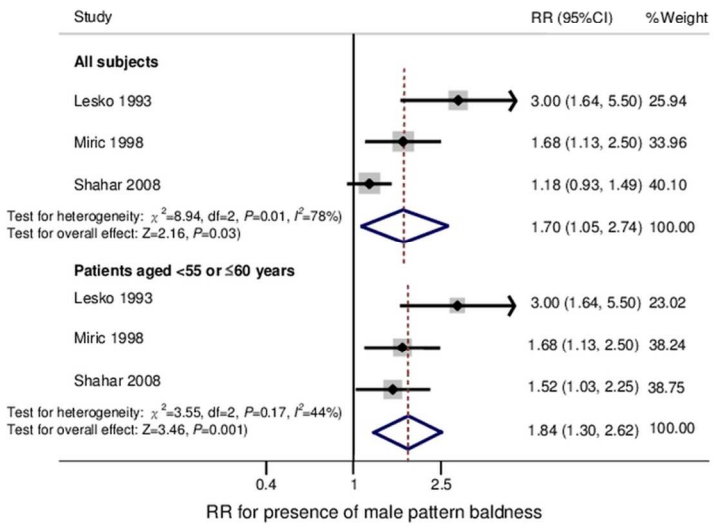


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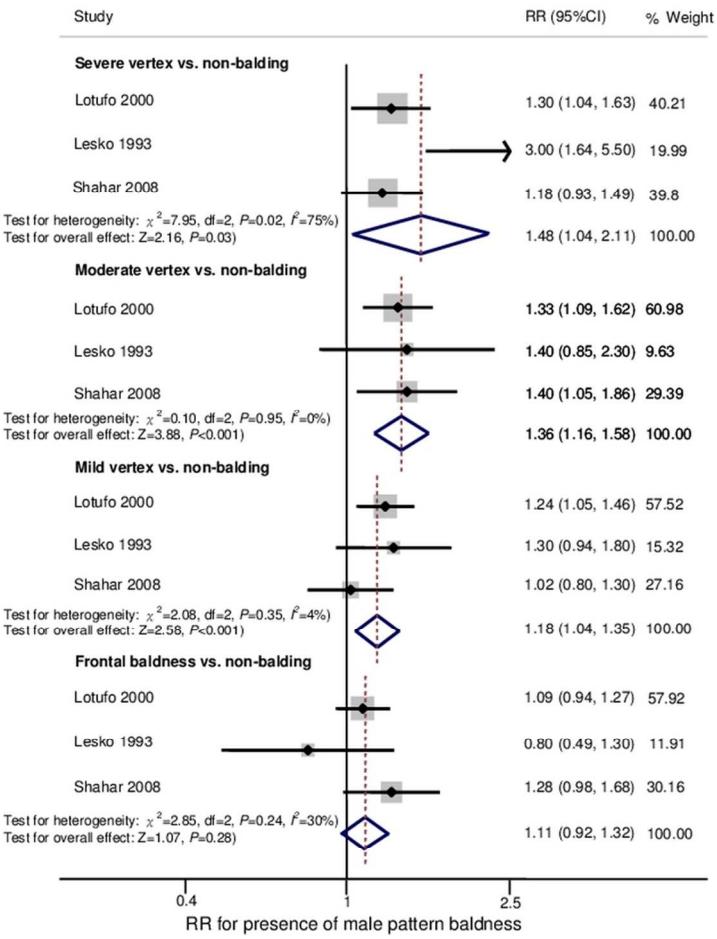
Fig. 4

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