Supplementary Materials

The Benefits and Risks of Menopause Hormone Therapy for the Cardiovascular System in Postmenopausal Women: A Systematic Review and Meta-analysis

Methods S1 Search strategies(search date 15/07/2022)

Cochrane Controlled Trial Register (search date 15/07/2022)
Search Strategies
1 Mesh descriptor (estradiol) explode all trees
2 Mesh descriptor (hormone replacement therapy) explode all trees
3 menopause hormone therapy
4 hot flashes
5 menopause* or postmenopause*
6 cardiovascular
7 stroke*
8 Mesh descriptor (thromosis and embolish) explode all trees
9 cardiovascular death
10 MHT or HT or ORT or ERT or HRT
11 estrogen or oestrogen
12 hyperlipidemia*
13 (1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12)
14 Mesh descriptor (endothelium) explode all trees
15 vascular endothelium dependent relaxation
16 vasorelaxation* or vasodilatation* or vasodilation*
17 flow mediate
18 nitroglycerin* or glyceryl trinitrate* or trinitrate*
19 endothelium function
20 FMD or NMD
21 (14 or 15 or 16 or 17 or 18 or 19 or 20)
22 nitrate medidate
23 endothelial*
24 brachial artery or arteria brachialis
25 vascular effect

Cochrane Controlled Trial Register (search date 15/07/2022)
Search Strategies
26 brachial artery diameter
27 (22 or 23 or 24 or 25 or 26)
28 (13 and 21)
29 (13 and 27)

MEDLINE
Search Strategies
1 exp estradiol/
2 exp hormone replacement therapy /
3 estrogen$.mp.
4 exp menopause hormone therapy/
5 hot flashes.mp.
6 exp menopause/
7 cardiovascular.mp.
8 stroke$.mp.
9 exp thromosis/ or thromosis.mp.
10 exp embolish / or embolish.mp.
11 hyperlipidemia.mp.
12 (1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11)
13 exp endothelium/
14 vascular endothelium dependent.mp.
15 flow mediate.mp.
16 endothelium function.mp.
17 brachial.mp. or exp brachial artery/
18 endothelial$.mp.
19 (13 or 14 or 15 or 16 or 17 or 18)

MEDLINE
Search Strategies
20 (12 and 19)

EMBASE
Search Strategies
1 exp estradiol/
2 exp hormone replacement therapy /
3 estrogen.mp. or exp estrogen/
4 hot flashes.mp.
5 exp menopause/ or postmenopause.mp.
6 cardiovascular.mp.
7 stroke.mp.
8 exp thromosis/ or thromosis.mp.
9 exp embolish / or embolish.mp.
10 exp menopause hormone therapy/
11 exp hyperlipidemia/
12 cardiovascular death.mp.
13 (1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12)
14 exp endothelium/
15 nitrate medidate.mp.
16 flow mediate.mp.
17 exp endothelium function/
18 brachial.mp. or exp brachial artery/
19 endothelial.mp.
20 (14 or 15 or 16 or 17 or 18 or 19)
21 (13 and 20)

Table S1 Evaluation of evidence quality based on GRADE approach

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Menopause hormone therapy	Placebo(or NT)	Relative (95% CI)	Absolute (95% CI)		
Death(all causes)												
19	randomised trials	not serious	not serious	not serious	not serious	none	796/20565 (3.9%)	806/20348 (4.0%)	**RR 0.96** (0.85 to 1.09)	**2 fewer per 1,000** (from 6 fewer to 4 more)	⊕⊕⊕⊕ High	Important(5)
Cardiovascular events												
13	randomised trials	not serious	not serious	not serious	not serious	none	669/19331 (3.5%)	670/19039 (3.5%)	**RR 0.97** (0.82 to 1.14)	**1 fewer per 1,000** (from 6 fewer to 5 more)	⊕⊕⊕⊕ High	Important(5)
Stroke												
15	randomised trials	not serious	not serious	not serious	not serious	strong association	476/18099 (2.6%)	381/17880 (2.1%)	**RR 1.23** (1.08 to 1.41)	**5 more per 1,000** (from 1 more to 9 more)	⊕⊕⊕⊕ High	Critical(8)
Venous thrombosis												
16	randomised trials	not serious	not serious	not serious	not serious	strong association	345/20038 (1.7%)	184/19840 (0.9%)	**RR 1.86** (1.39 to 2.50)	**8 more per 1,000** (from 4 more to 14 more)	⊕⊕⊕⊕ High	Critical(8)
Flow-mediated vasodilation												
15	randomised trials	not serious	very serious[a]	not serious	not serious	strong association	340	334		SMD **1.46 higher** (0.86 higher to 2.07 higher)	⊕⊕⊕◯ Moderate	Important(4)
Nitroglycerin mediated vasodilation												
13	randomised trials	not serious	serious[b]	not serious	not serious	none	316	319		SMD **0.27 higher** (0.08 lower to 0.62 higher)	⊕⊕⊕◯ Moderate	Important(4)

CI: confidence interval; **RR:** risk ratio; **SMD:** standardized mean difference.

Explanations

a. Could be imprecise due to I2=90%, Although a large number of clinical trials have proved its strong correlation.Nevertheless,we conservatively rated down for imprecision.

b. Could be imprecise due to I2=76%, we conservatively rated down for imprecision

Table S2 PRISMA checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review and meta analysis.	1
ABSTRACT			
Structure 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; conclusions and implications of key findings.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	2-3
Objectives	4	Provide an explicit statement of the subject(s), intervention(s),outcome(s) and study design the review addresses.	4-5
METHODS			
Protocol and registration		Indicate if a review protocol exists, if and where it can be accessed, if available, provide registration information such as registration number.	5-6
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	6
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	sMethods.1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	6-7

Section and Topic	Item #	Checklist item	Location where item is reported
Data items	10	List and define all other variables for which data were sought (e.g. participant and intervention characteristics). Describe any assumptions made about any missing or unclear information.	6-7
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	8
Synthesis methods	13	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	8
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	8
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	8
RESULTS			
Study selection	16	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	9,Figure1
Study characteristics	17	Cite each included study and present its characteristics.	9,Table1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	10,sFigure1
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	10-14, Figure2(A-L),Figure3
Results of syntheses	20	Present results of all investigations of possible causes of heterogeneity among study results.	14-15, sFigure2,4
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	14-15, sFigure1,3
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	eTable1
Additional analysis		Give results of additional analysis, if done (e.g., sensitivity or subgroup analysis, meta-regression	15-17, sFigure5-7
DISCUSSION			

Section and Topic	Item #	Checklist item	Location where item is reported
Discussion	23	Provide a general interpretation of the results in the context of other evidence.	17-20, Figure4
Limitations	24	Discuss any limitations of the evidence included in the review.	20-21
OTHER INFORMATION			
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	21-22
Competing interests	26	Declare any competing interests of review authors.	22

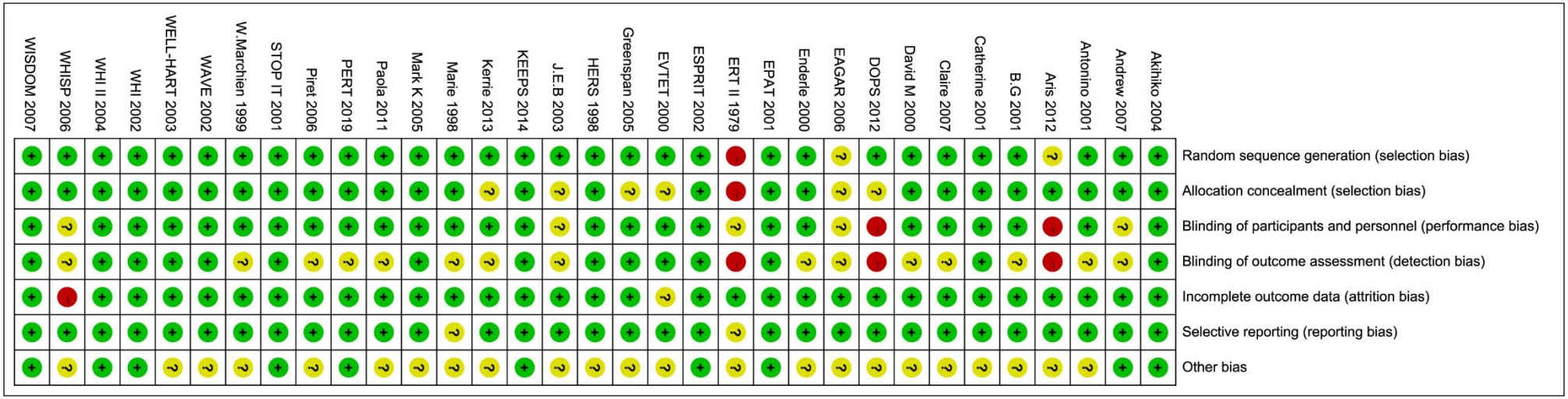
Table S3 MOOSE checklist

Recommendation	Reported on Page No
Reporting of background should include	
Problem definition	Background (Page 2)
Hypothesis statement	Introduction (Page 4-5)
Description of study outcome(s)	All-cause death, cardiovascular events, stroke, venous thromboembolism, FMD, NMD
Type of exposure or intervention used	MHT
Type of study designs used	Systematic review and Meta-analysis
Study population	Postmenopausal women
Reporting of search strategy should include	
Qualifications of searchers (eg, librarians and investigators)	Investigator (Page 6)
Search strategy, including time period included in the synthesis and key words	Eligibility criteria, information sources, search strategy (Page 6) and Methods S1
Effort to include all available studies, such as digitize and extract data if data were only presented as graphs	GetData Graph Digitizer 2.24 was applied to digitize and extract the data
Databases and registries searched	Eligibility criteria, information sources, search strategy (Page 6)
Search software used, name and version, including special features used (eg, explosion)	Review Manager (RevMan5.4.1) GetDataGraph Digitizer 2.24 TSA-0.9.5.10-Beta
Use of hand searching (eg, reference lists of obtained articles)	Eligibility criteria, information sources, search strategy (Page 6)

Recommendation	Reported on Page No
List of citations located and those excluded, including justification	Flow diagram in Figure 1
Method of addressing articles published in languages other than English	Eligibility criteria, information sources, search strategy (Page 6)
Method of handling abstracts and unpublished studies	Methods (Page 6)
Description of any method to extract data (if data were only presented as graphs)	Methods (Page 6-7)
Reporting of methods should include	
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Methods (Page 6-7)
Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	Methods (Page 6-7)
Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	Methods (Page 6-7)
Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	Methods (Page 7)
Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	Methods (Page 8)
Assessment of heterogeneity	Methods (Page 8)
Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	Methods (Page 7)
Provision of appropriate tables and graphics	Additional materials and supplementary materials

Recommendation	Reported on Page No
Reporting of results should include	
Graphic summarizing individual study estimates and overall estimate	Figure 2A-2L, Figure 3
Table giving descriptive information for each study included	Table 1
Results of sensitivity testing (eg, subgroup analysis)	Sensitivity analysis (Page 14-15)
Indication of statistical uncertainty of findings	Discussion (Page 19)
Reporting of discussion should include	
Quantitative assessment of bias (eg, publication bias)	Discussion (Page 20)
Justification for exclusion (eg, exclusion of non-English language citations)	Discussion (Page 20)
Assessment of quality of included studies	Discussion (Page 20)
Reporting of conclusions should include	
Consideration of alternative explanations for observed results	Conclusions (Page 21)
Generalisation of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	Conclusions (Page 21)
Guidelines for future research	Discussion (Page 20)
Disclosure of funding source	Grant Support (Page 22)

Figure S1 Evaluate the bias risk of trials included in the systematic review based on the bias risk assessment criteria in *Cochrane Handbook for Systematic Reviews of Interventions*



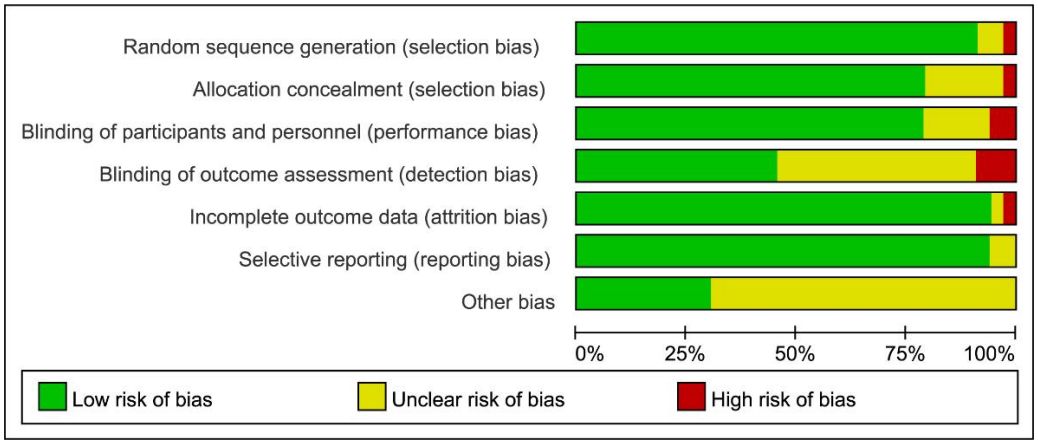
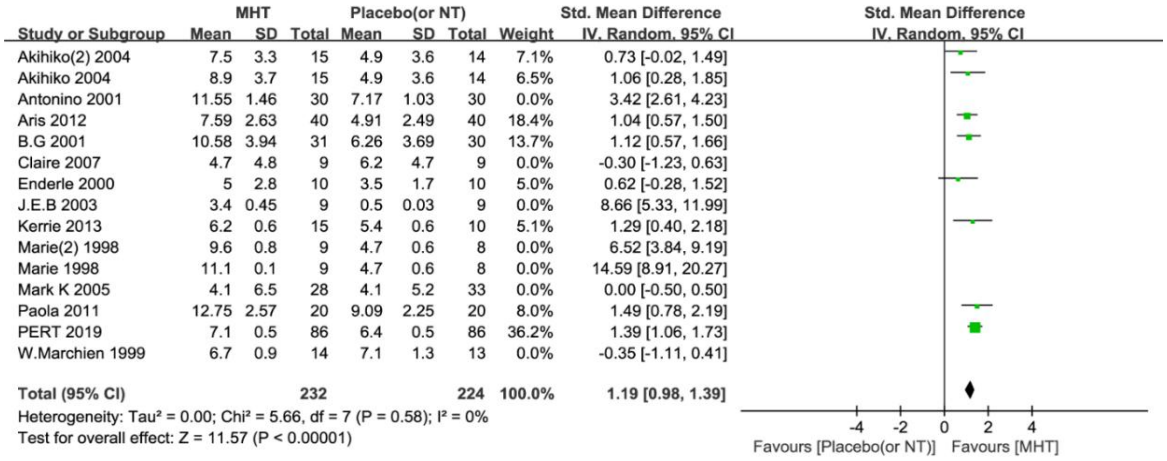


Figure S2 Sensitivity Analysis (leave one-out method)

(A)



(B)

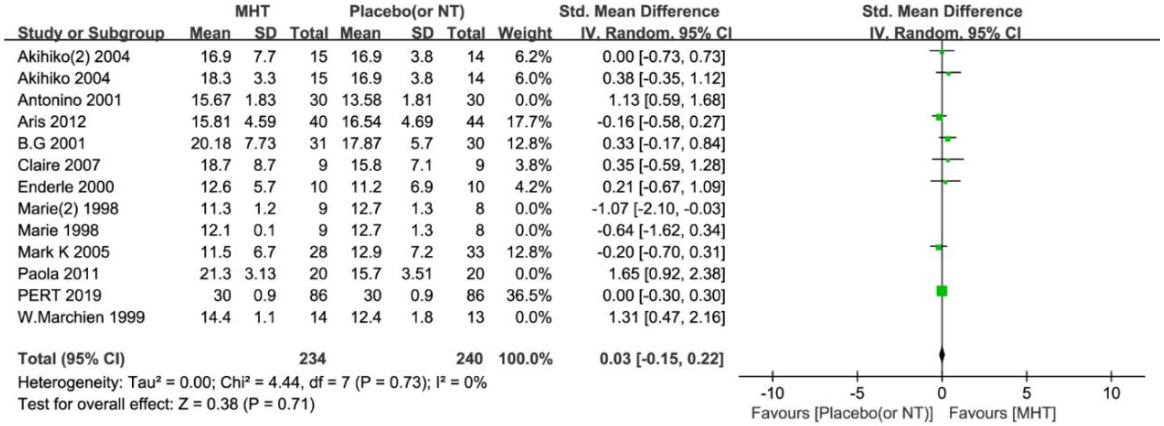


Figure S2A: FMD sensitivity analysis; Figure S2B: NMD sensitivity analysis

Figure S3 Funnel plots

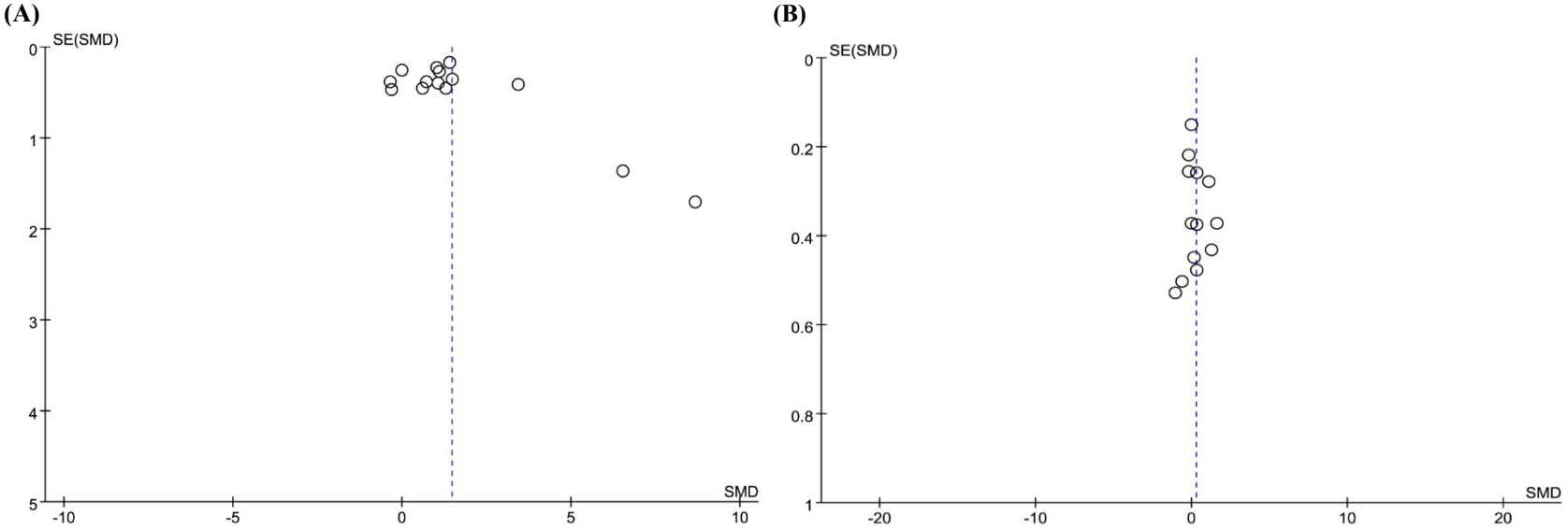
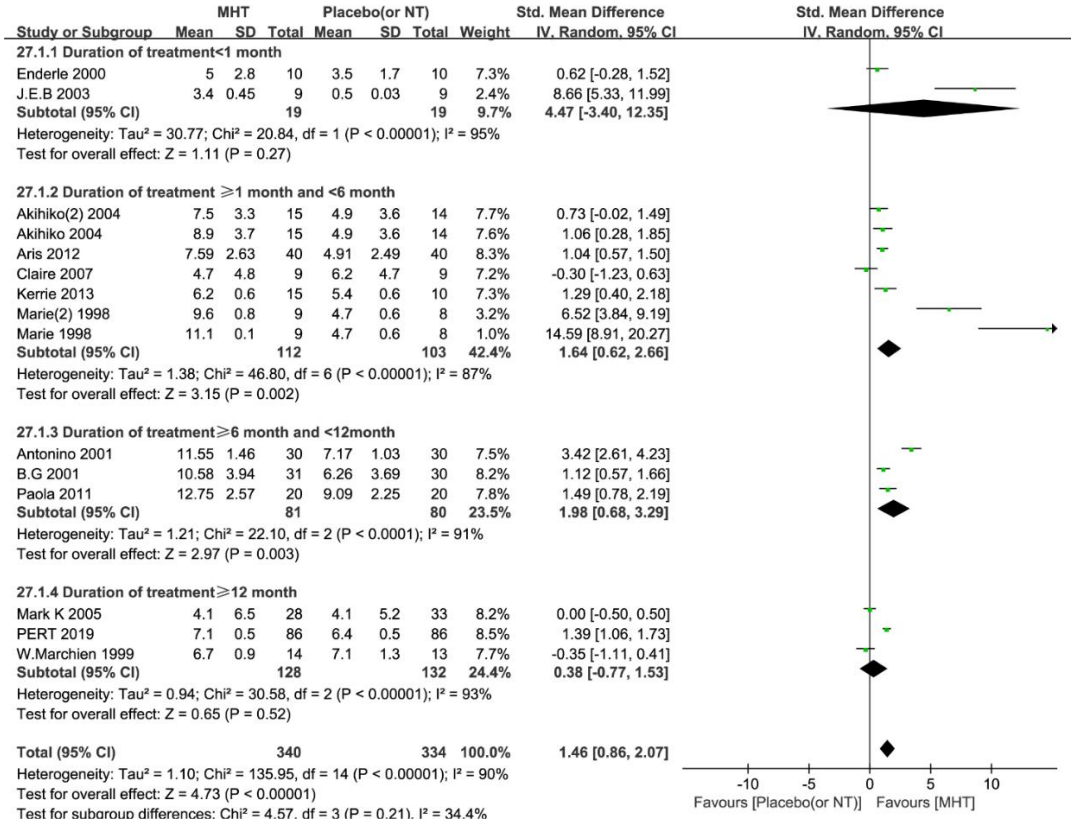


Figure S3A: FMD funnel plot; Figure S3B: NMD funnel plot

Figure S4 Subgroup analysis of different MHT treatment durations

(A)



(B)

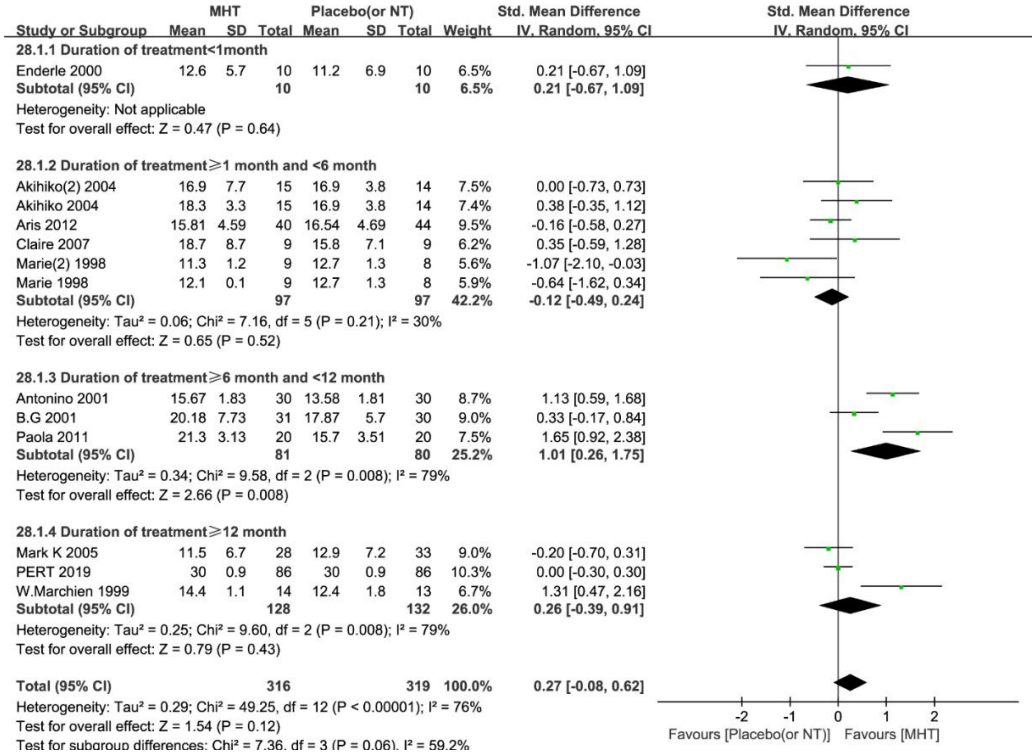
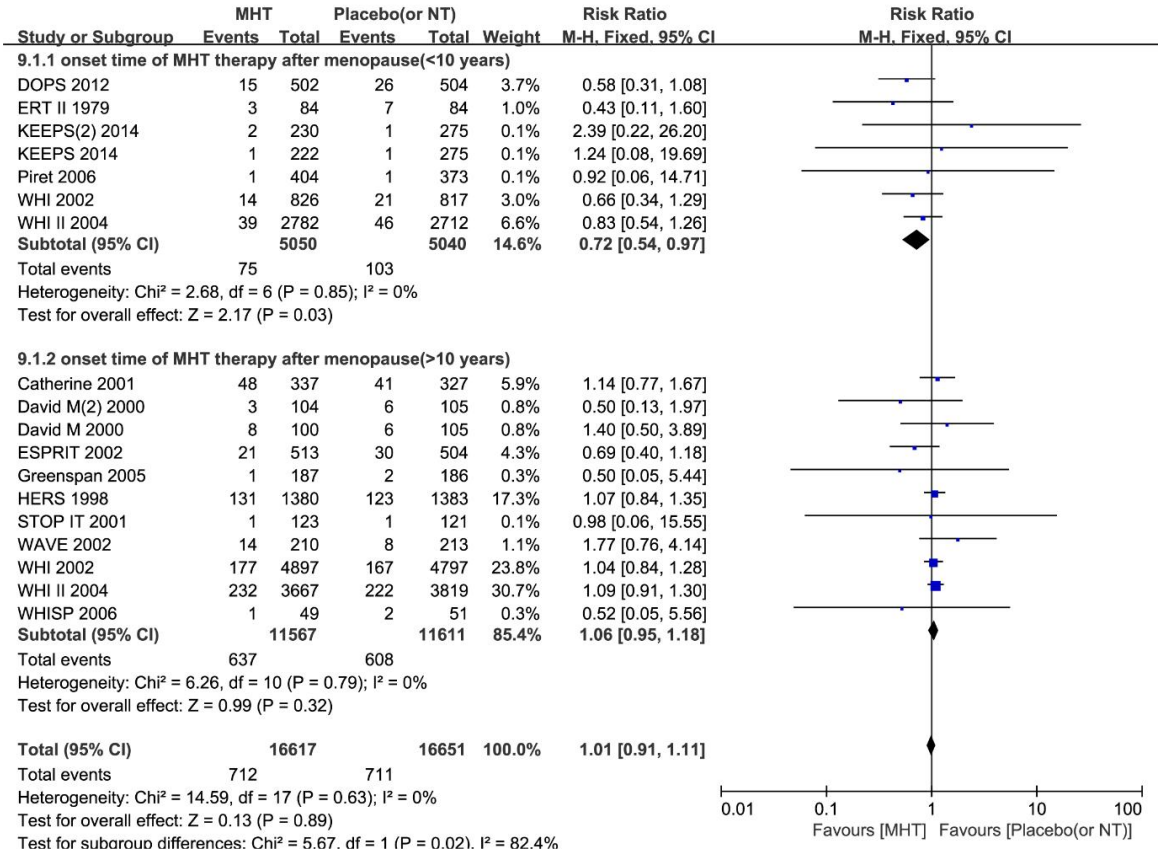


Figure S4A: Effect of different MHT treatment durations on FMD; Figure S4B: Effect of different MHT treatment durations on NMD

Figure S5 Subgroup analysis of MHT onset time

(A)



(B)

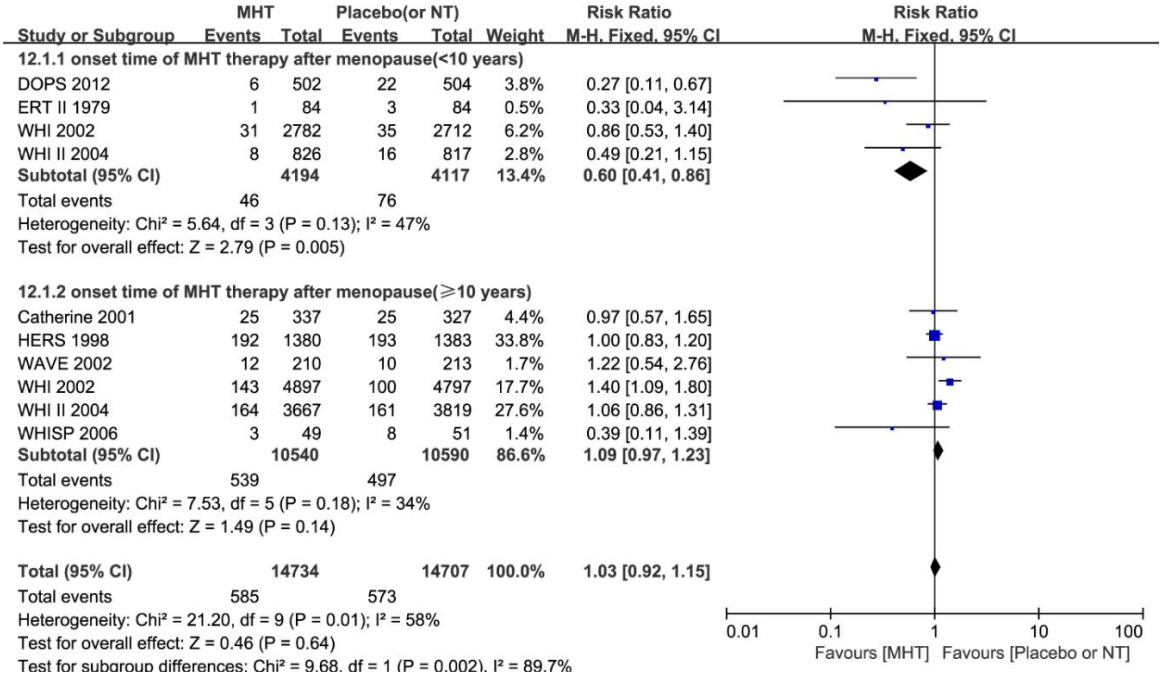
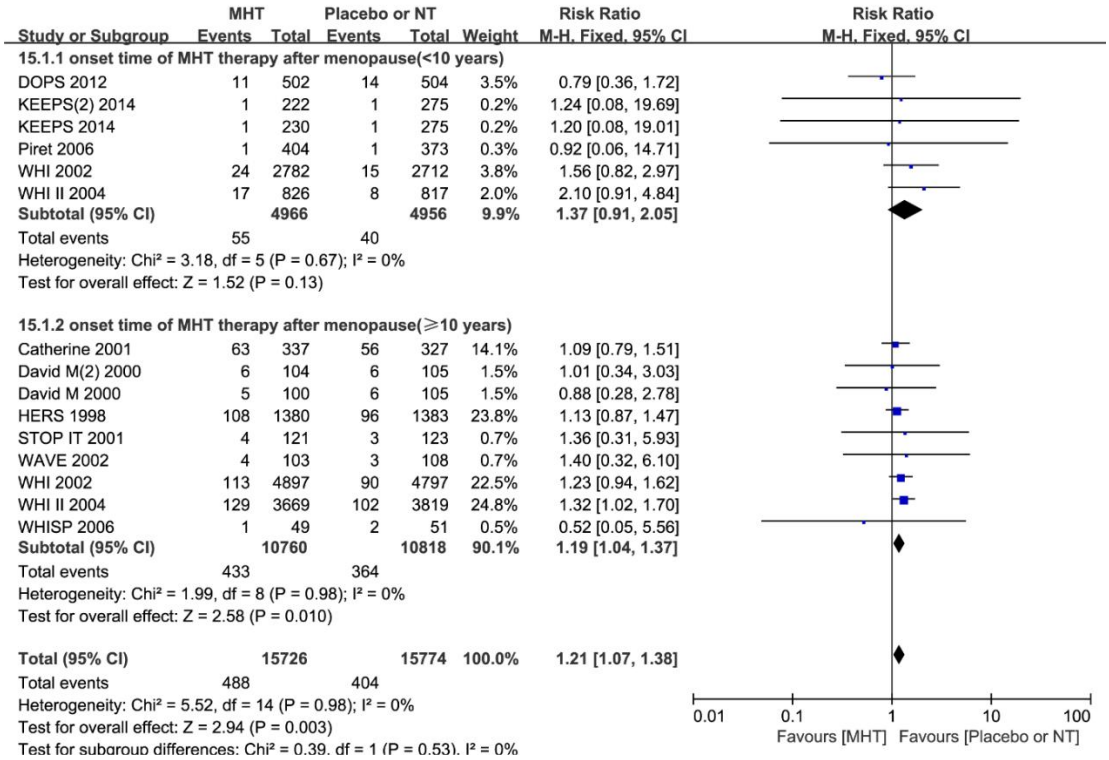


Figure S5A: Effect of MHT onset time on all-cause death; Figure S5B: Effect of MHT onset time on cardiovascular events

(C)



(D)

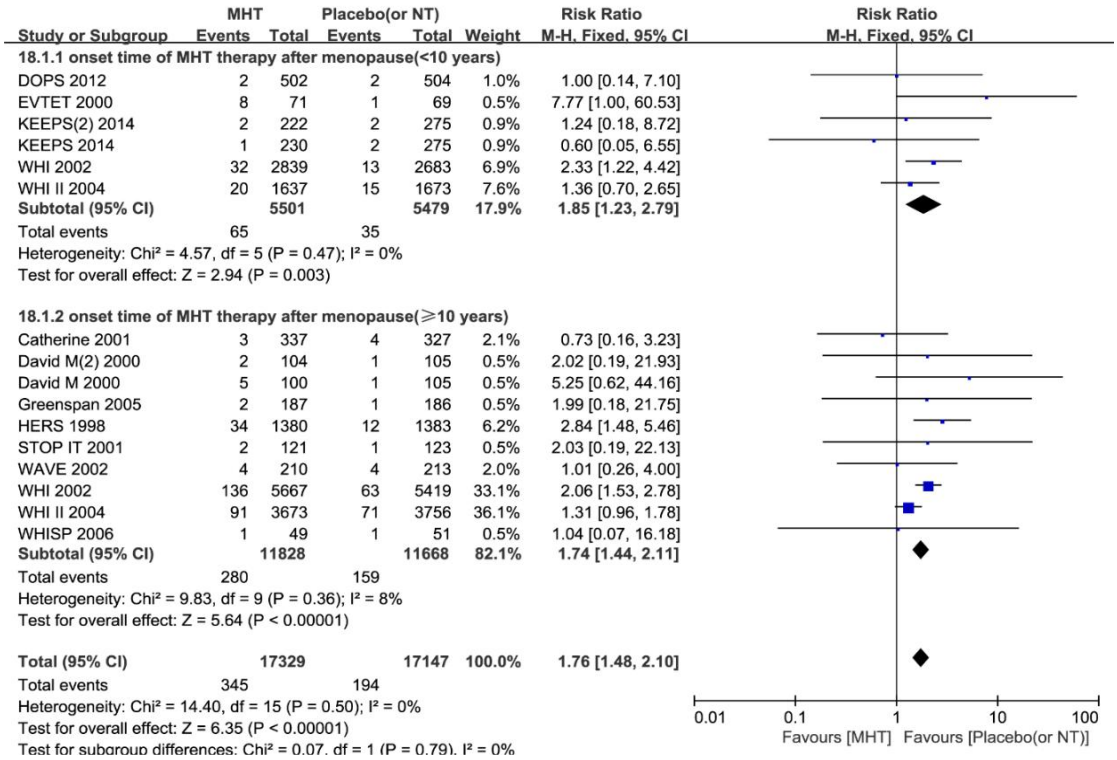
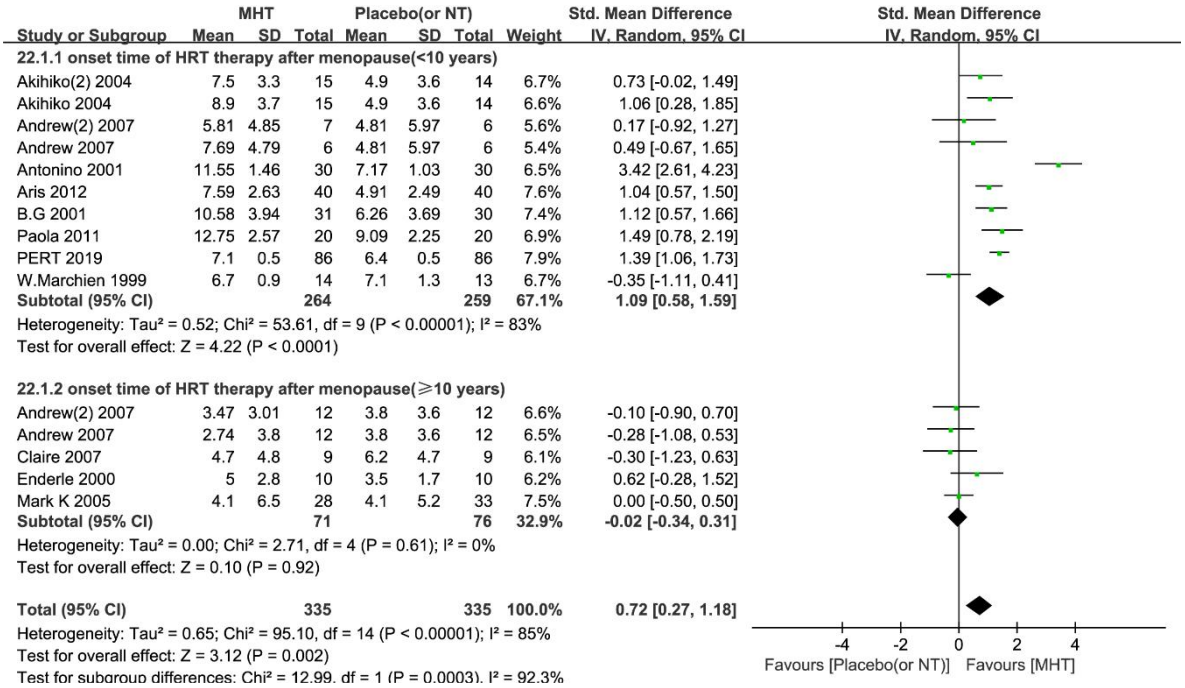


Figure S5C: Effect of MHT onset time on stroke; Figure S5D: Effect of MHT onset time on venous thromboembolism

(E)



(F)

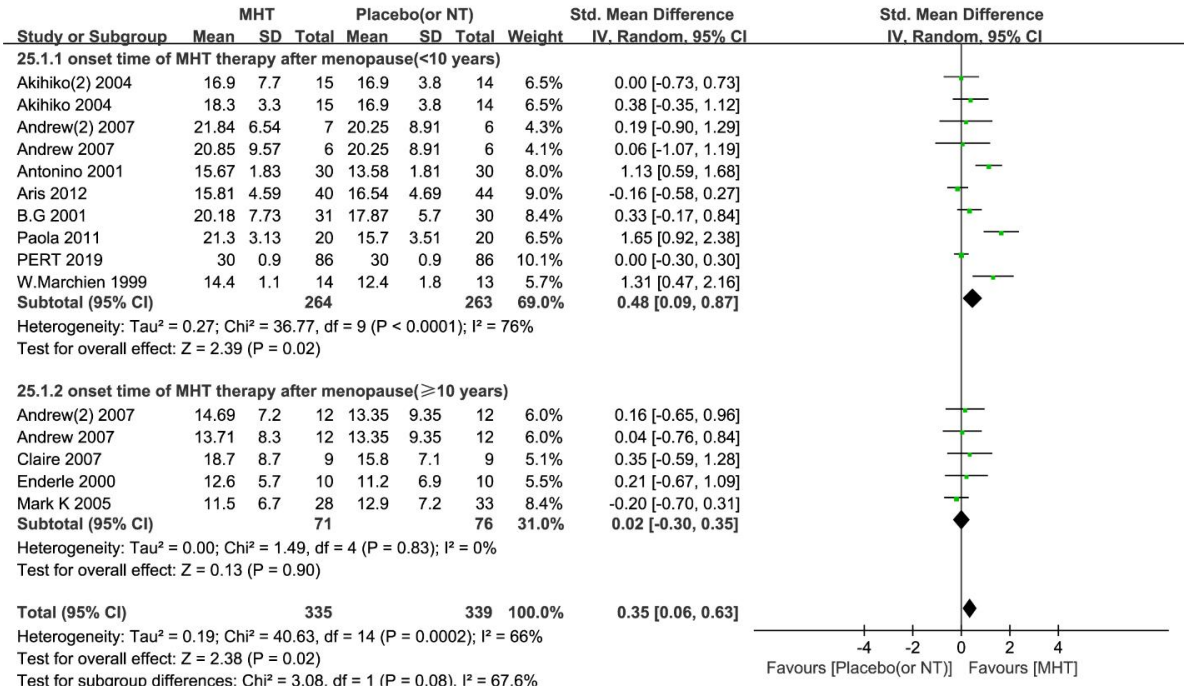
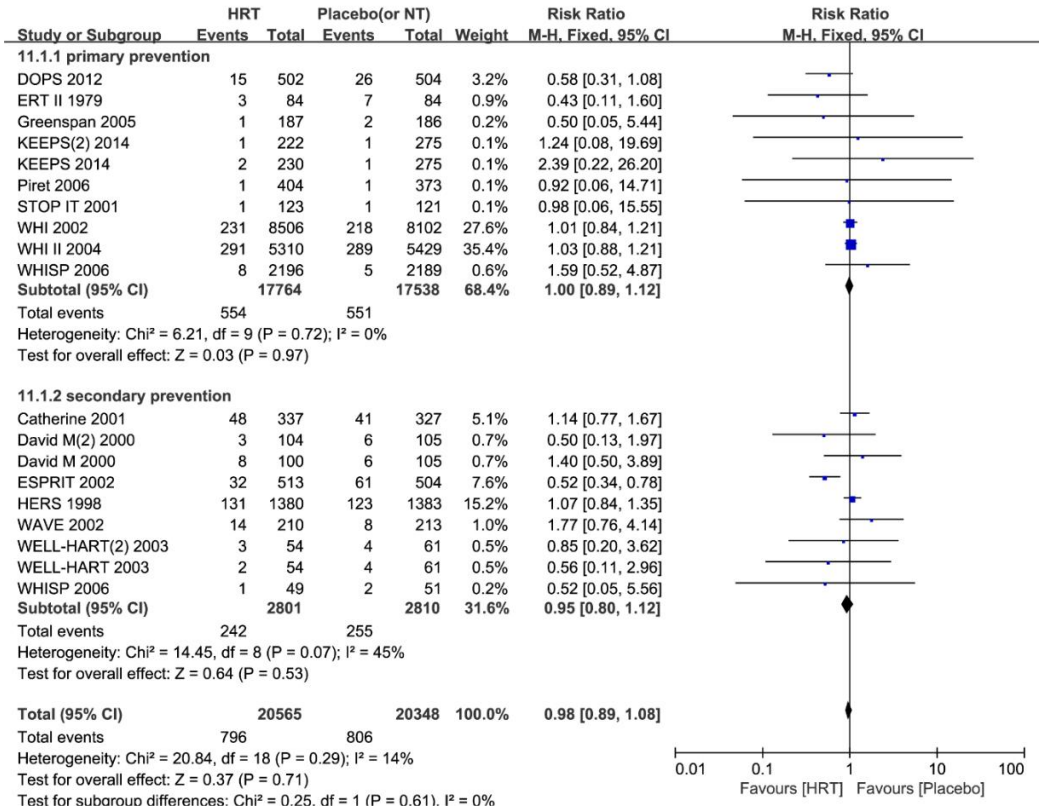


Figure S5E: Effect of MHT onset time on FMD; Figure S5F: Effect of MHT onset time on NMD

Figure S6 Subgroup analysis of primary prevention and secondary prevention of MHT

(A)



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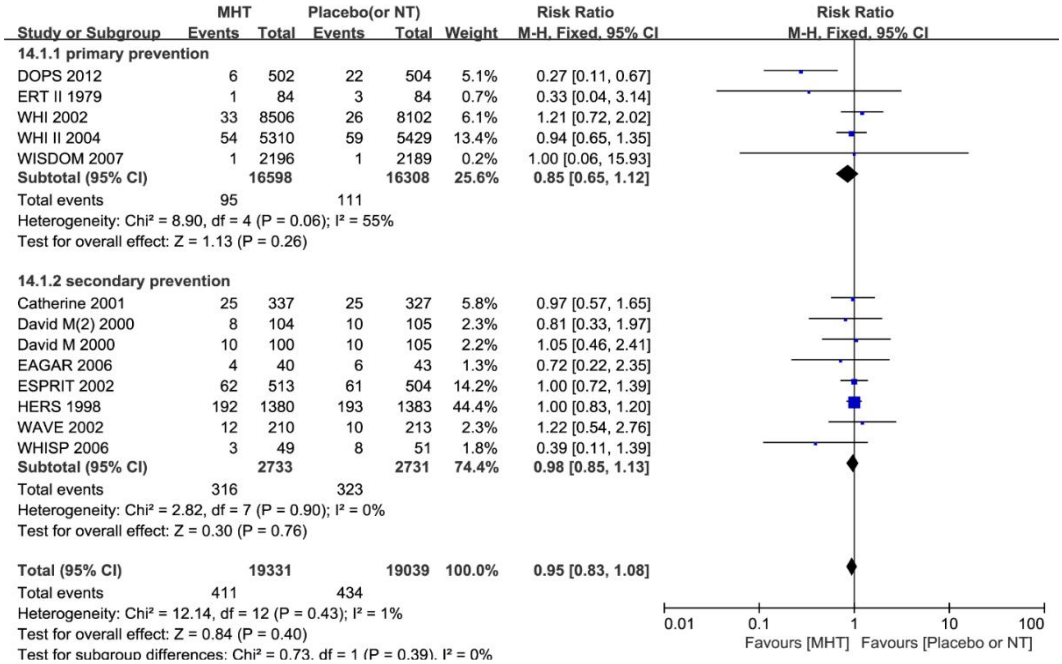
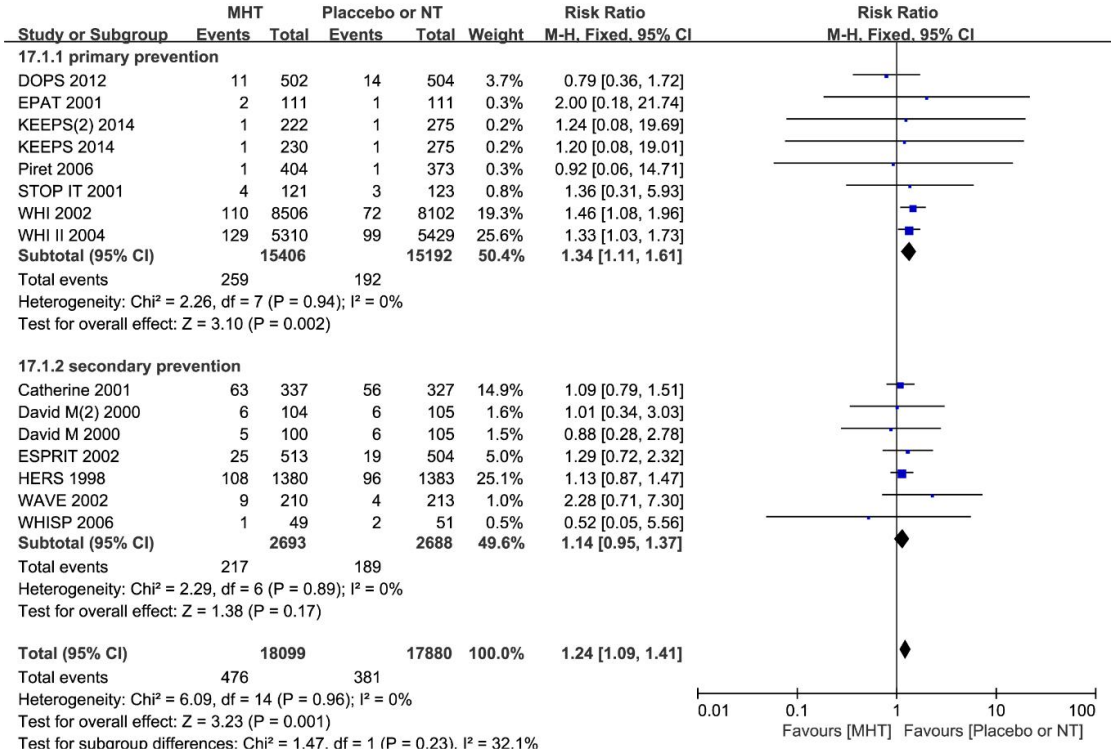


Figure S6A: Effect of different MHT prevention modes on all-cause death; Figure S6B: Effect of different MHT prevention modes on cardiovascular events

(C)



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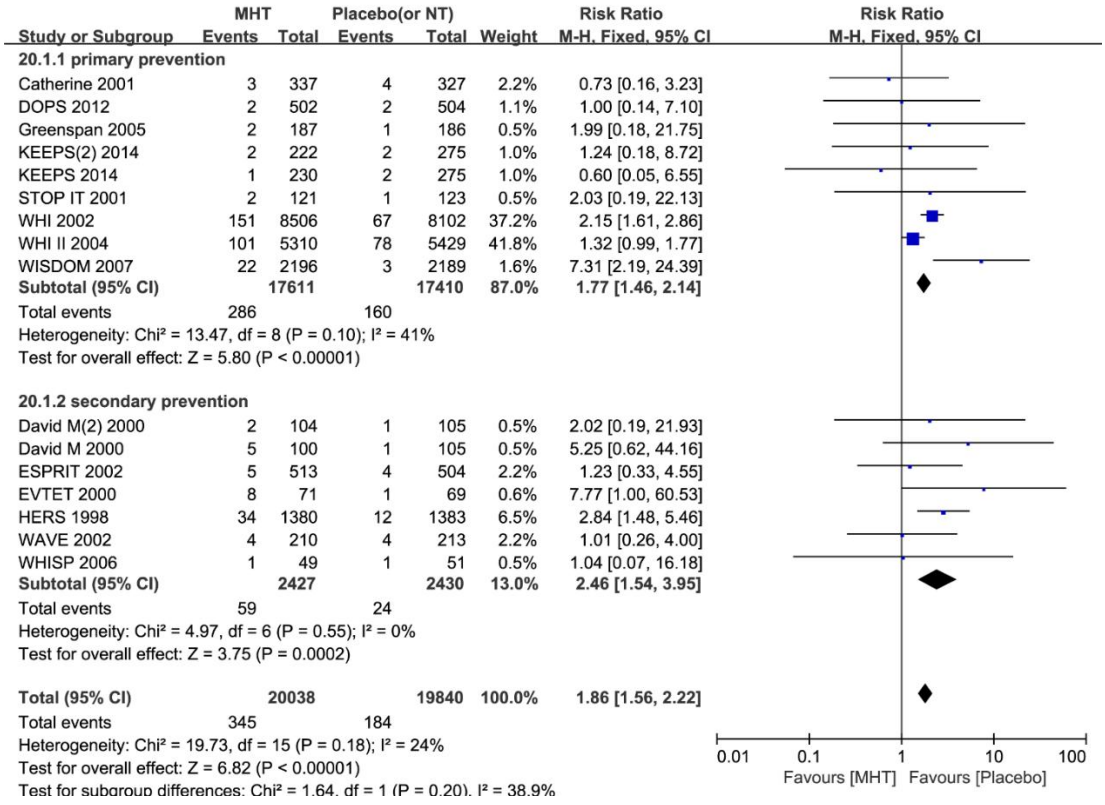
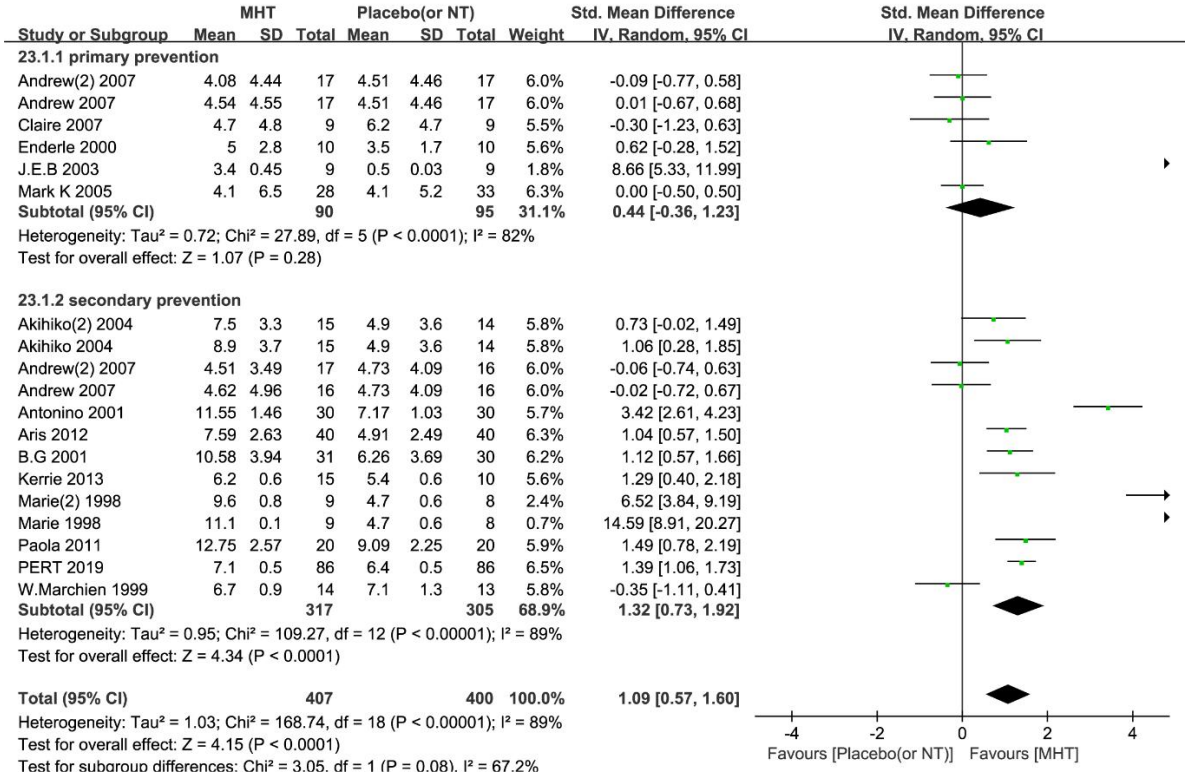


Figure S6C: Effect of different MHT prevention modes on stroke; Figure S6D: Effect of different MHT prevention modes on venous thromboembolism

(E)



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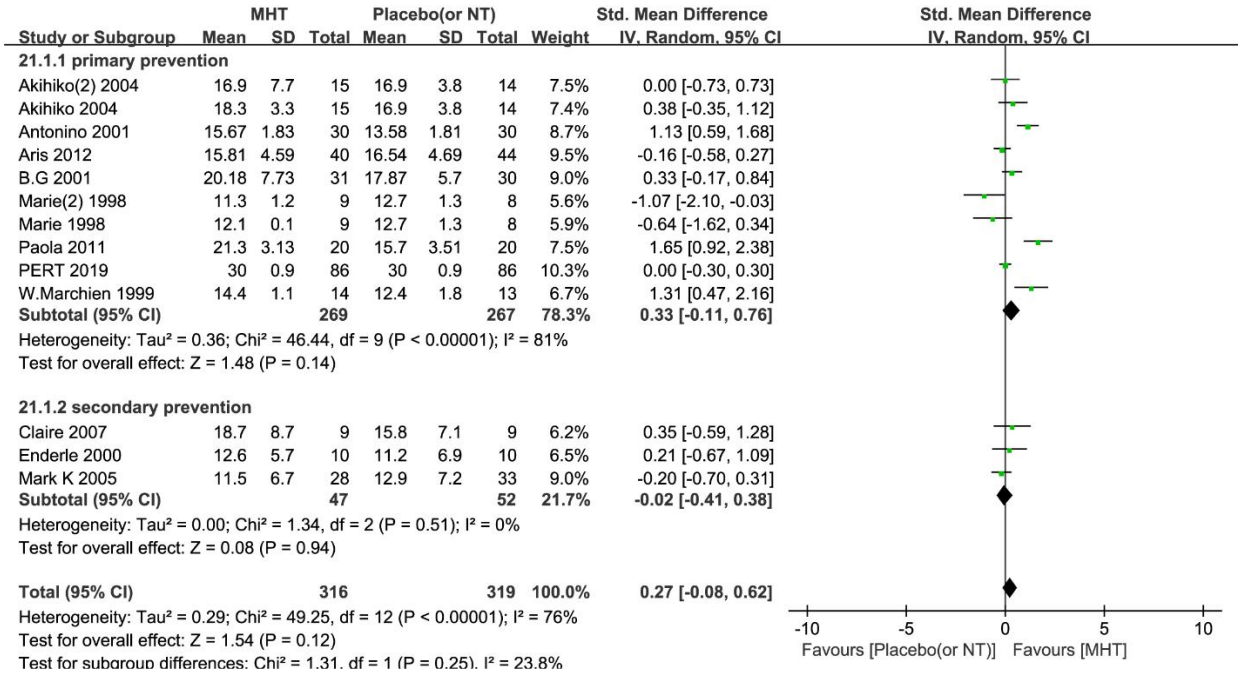
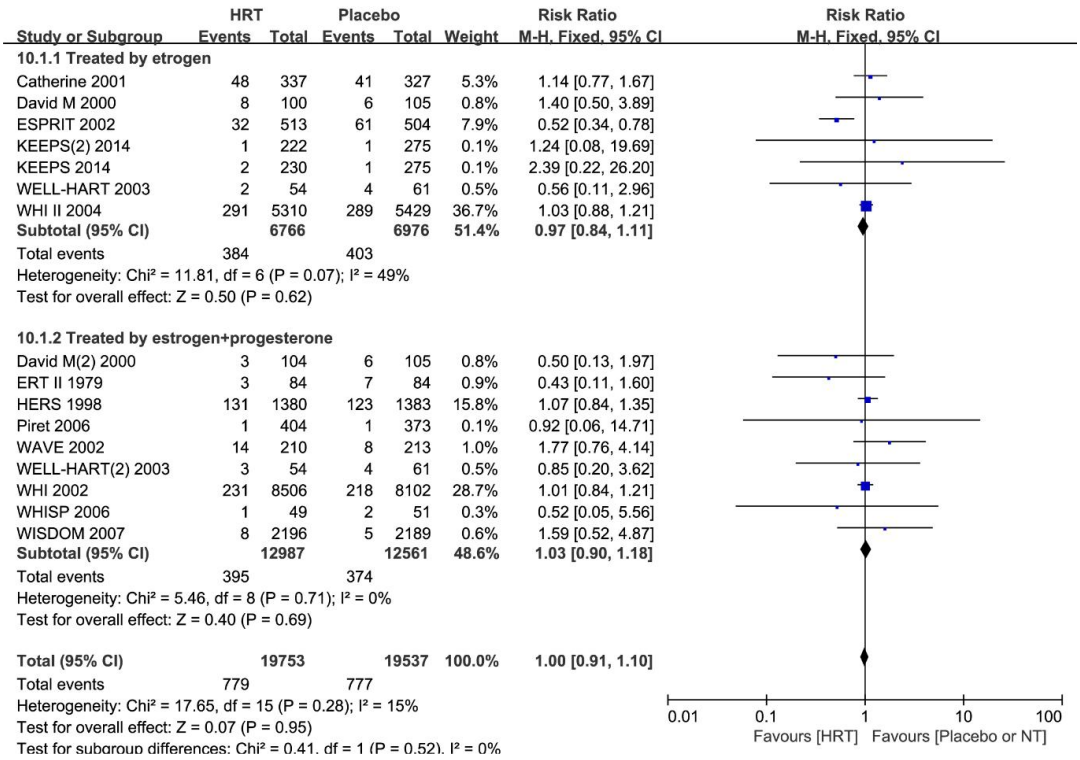


Figure S6E: Effect of different MHT prevention modes on FMD; Figure S6F: Effect of different MHT prevention modes on NMD

Figure S7 Subgroup analysis of MHT protocols

(A)



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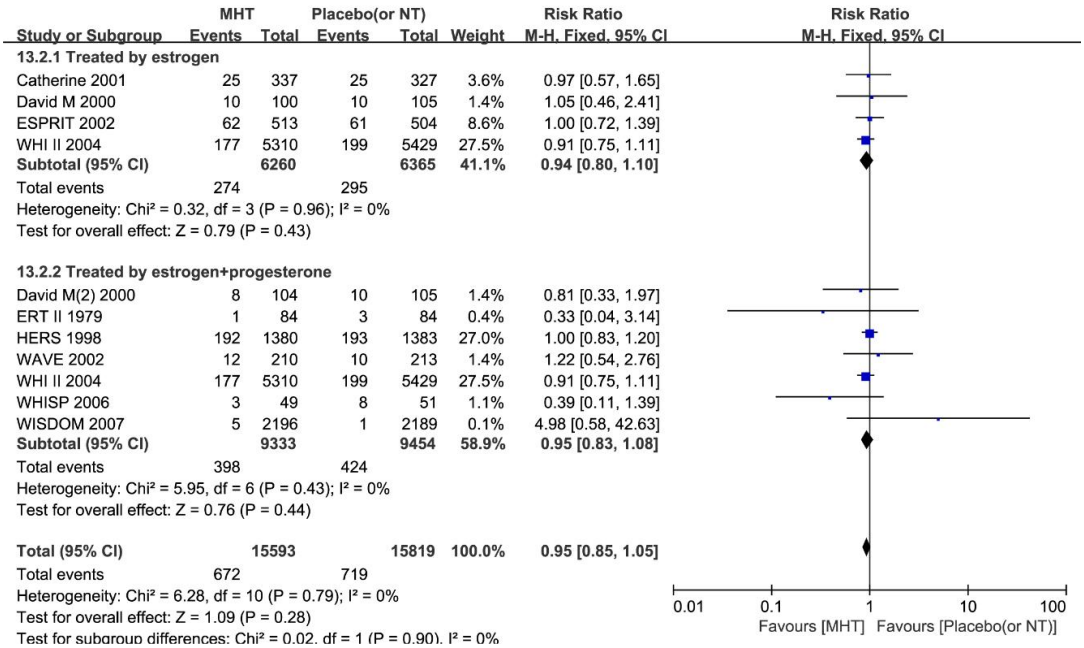
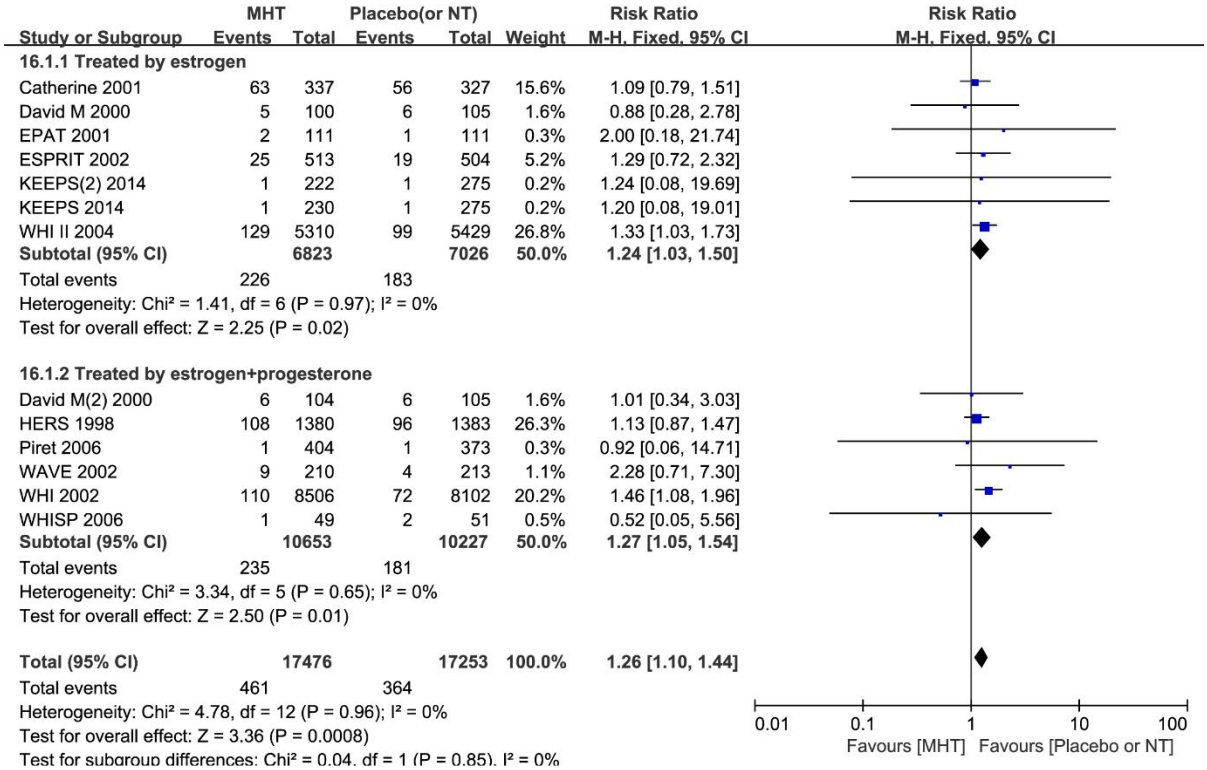


Figure S7A: Effect of different MHT protocols on all-cause death; Figure S7B: Effect of different MHT protocols on cardiovascular events

(C)



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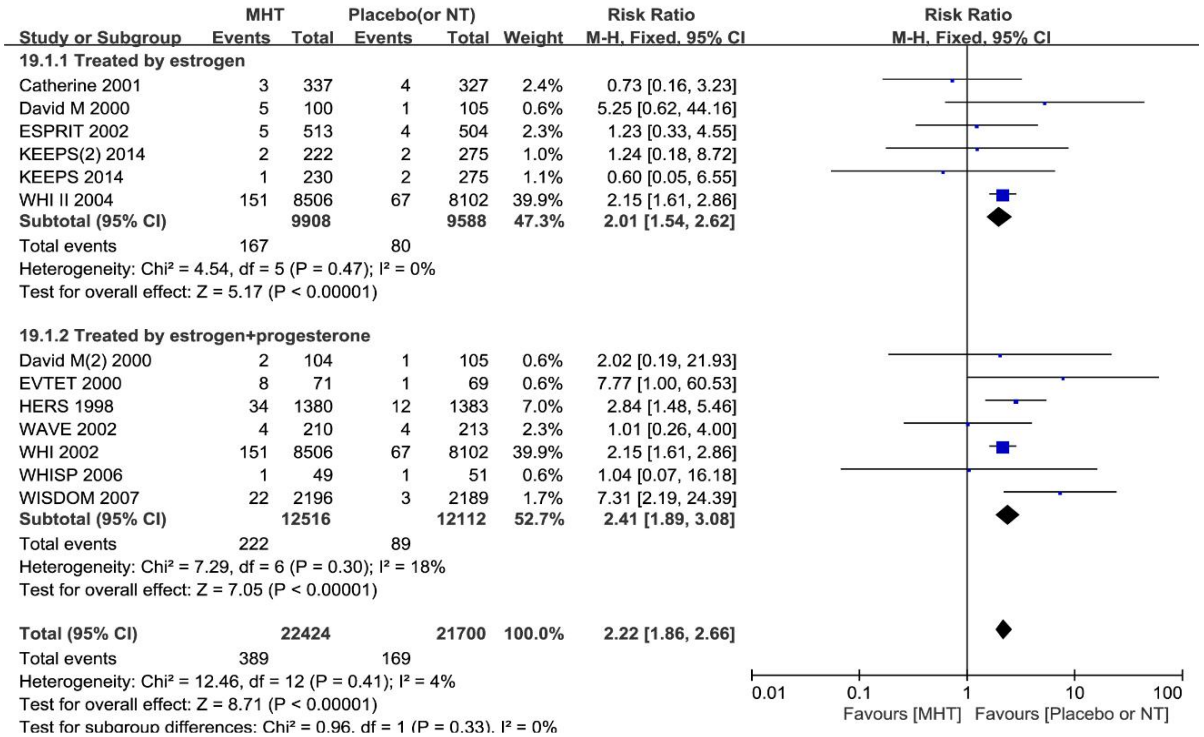
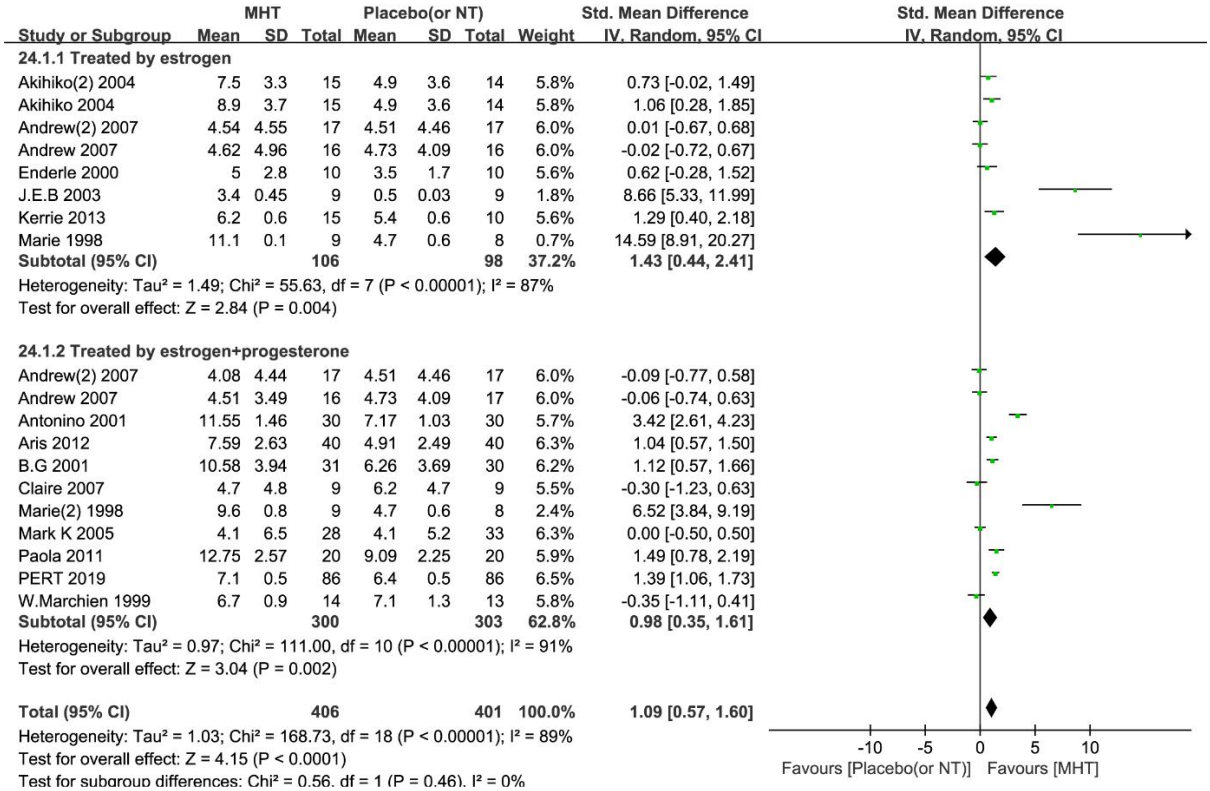


Figure S7C: Effect of different MHT protocols on stroke; Figure S7D: Effect of different MHT protocols on venous thromboembolism

(E)



(F)

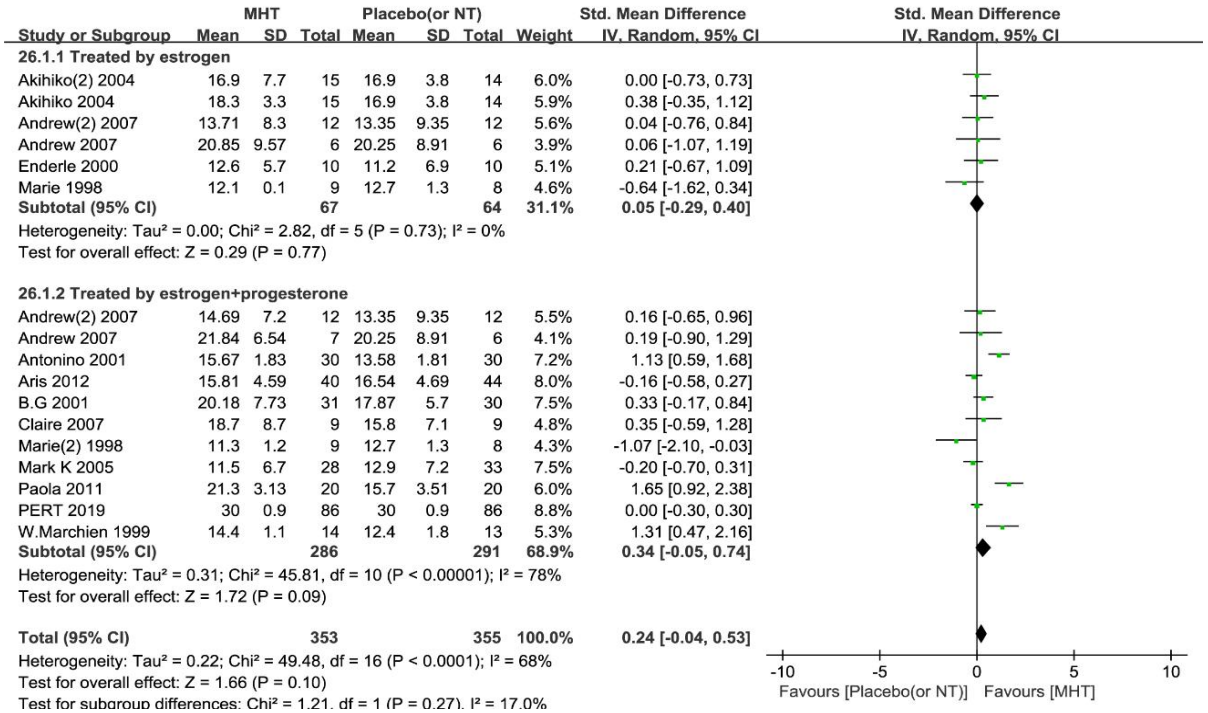


Figure S7E: Effect of different MHT protocols on FMD; Figure S7F: Effect of different MHT protocols on NMD