## **Supplementary Figures**

# A systematic review and meta-analysis of effects of menopausal hormone therapy on cardiovascular diseases

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Supplementary Figure S1.1. Pooled results of MHT and all-cause death in the RCTs: (a) forest plot and (b) funnel plot.

(a)

Study	Summary	Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
DOPS , Schierbeck et al. 2012	-+-	-	0.66	[0.40; 1.08]	0.7%	0.7%
ELITE , Hodis et al. 2016			0.99	[0.06; 15.77]	0.0%	0.0%
EMS, Tierney et al. 2009		<u>+</u>	1.03	[0.15; 7.10]	0.0%	0.0%
EPHT, Veerus et al. 2006	+	<u>+</u>	0.78	[0.21; 2.91]	0.1%	0.1%
ERA, Herrington et al. 2000		+	0.94	[0.36; 2.48]	0.2%	0.2%
ESPRIT, Cherry et al. 2014		+	1.07	[0.89; 1.29]	5.0%	5.0%
Greenspan, Greenspan et al. 2005		<u> </u>	0.50	[0.05; 5.44]	0.0%	0.0%
HERSI,II, Hulley et al. 2002		+	1.10	[0.92; 1.31]	5.7%	5.7%
PHASE , Clarke et al. 2002	-		2.41	[0.65; 8.87]	0.1%	0.1%
STOP-IT, Gallagher et al. 2001			1.02	[0.06; 16.07]	0.0%	0.0%
WAVE , Waters et al. 2002	-	+ +	1.78	[0.76; 4.14]	0.2%	0.2%
WELL-HART , Hodis et al. 2003	+	+	0.63	[0.18; 2.29]	0.1%	0.1%
WEST, Viscoli et al. 2001	-	<u>+</u>	1.20	[0.80; 1.80]	1.1%	1.1%
WHII, Manson et al. 2017		+	1.02	[0.96; 1.08]	53.0%	53.0%
WHIII, Manson et al. 2017		÷.	0.94	[0.87; 1.01]	33.6%	33.6%
WHISP , Collins et al. 2006	•		0.52	[0.05; 5.56]	0.0%	0.0%
WISDOM , Vickers et al. 2007	_		1.59	[0.52; 4.87]	0.1%	0.1%
Fixed effect model Random effects model			1.00 1.00	[0.96; 1.04] [0.96; 1.04]	100.0% 	 100.0%
Heterogeneity: $T = 0\%$ , $\tau = 0$ , $p = 0.61$	0.1 0.5	1 2 10				
(b)						



Summary estimates (95% CI) were measured by fixed-effect models if  $I^2$  was <30% and P for heterogeneity was >0.05; otherwise, the summary estimates (95% CI) were measured by random-effect models. Forest and funnel plots were generated by "meta" package in R version 3.4.1. MHT, menopausal hormone therapy; RCTs, randomized controlled trials; SE, summary estimates.

Supplementary Figure S1.2. Pooled results of MHT and cardiovascular death in the RCTs: (a) forest plot and (b) funnel plot.

(a)





Summary estimates (95% CI) were measured by fixed-effect models if  $I^2$  was <30% and P for heterogeneity was >0.05; otherwise, the summary estimates (95% CI) were measured by random-effect models. Forest and funnel plots were generated by "meta" package in R version 3.4.1. MHT, menopausal hormone therapy; RCTs, randomized controlled trials; SE, summary estimates.

Supplementary Figure S1.3. Pooled results of MHT and stroke in the RCTs: (a) forest plot and (b) funnel plot.

(a)

Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
DOPS , Schierbeck et al. 2012		0.89	[0.48; 1.65]	2.3%	2.3%
EMS, Tierney et al. 2009	<u>i+</u>	1.29	[0.36; 4.59]	0.5%	0.5%
EPHT, Veerus et al. 2006	<u>  </u> +	1.61	[0.38; 6.77]	0.4%	0.4%
ERA, Herrington et al. 2000		0.94	[0.36; 2.48]	1.0%	1.0%
ESPRIT, The ESPIRIT team. 2002	- <u>  </u> +	1.64	[0.60; 4.46]	0.9%	0.9%
HERSI,II, Grady et al. 2002	÷	1.09	[0.88; 1.35]	19.5%	19.5%
KEEPS, Gleason et al. 2015		- 3.72	[0.15; 90.93]	0.1%	0.1%
STOP-IT , Gallagher et al. 2001	<u> </u> +	1.36	[0.31; 5.93]	0.4%	0.4%
WAVE, Waters et al. 2002	- <del>   •</del>	2.28	[0.71; 7.30]	0.7%	0.7%
WEST, Viscoli et al. 2001	- <del>1</del> -	1.10	[0.76; 1.60]	6.3%	6.3%
WHII, Manson et al. 2013	÷	1.16	[1.00; 1.35]	38.7%	38.7%
WHIII, Manson et al. 2013		1.15	[0.97; 1.37]	29.1%	29.1%
WHISP , Collins et al. 2006		0.35	[0.01; 8.31]	0.1%	0.1%
Fixed effect model		1.14	[1.04: 1.25]	100.0%	
Random effects model	•	1.14	[1.04; 1.25]		100.0%
Heterogeneity: $l^2 = 0\%$ , $\tau^2 = 0$ , $p = 0.98$					
J , , ,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	0.1 0.51 2 10				



Summary estimates (95% CI) were measured by fixed-effect models if  $I^2$  was <30% and P for heterogeneity was >0.05; otherwise, the summary estimates (95% CI) were measured by random-effect models. Forest and funnel plots were generated by "meta" package in R version 3.4.1. MHT, menopausal hormone therapy; RCTs, randomized controlled trials; SE, summary estimates.

Supplementary Figure S1.4. Pooled results of MHT and VTE in the RCTs: (a) forest plot and (b) funnel plot.

(a)

Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
DOPS , Schierbeck et al. 2012		0.63	[0.21; 1.90]	4.7%	4.9%
ELITE , Hodis et al. 2016		1.49	[0.25; 8.83]	1.8%	1.9%
EMS, Tierney et al. 2009		- 3.09	[0.13; 74.46]	0.6%	0.6%
ERA, Herrington et al. 2000		3.60	[0.45; 28.90]	1.3%	1.4%
ESPRIT, The ESPIRIT team. 2002		1.23	[0.33; 4.55]	3.4%	3.6%
Greenspan, Greenspan et al. 2005		1.99	[0.18; 21.75]	1.0%	1.1%
HERSI,II, Hulley et al. 2002		2.08	[1.27; 3.40]	24.1%	23.7%
KEEPS, Gleason et al. 2015	<u> +</u> ]	1.24	[0.08; 19.73]	0.8%	0.8%
STOP-IT, Gallagher et al. 2001	<u> </u>	2.03	[0.19; 22.13]	1.0%	1.1%
WAVE, Waters et al. 2002		1.01	[0.26; 4.00]	3.1%	3.2%
WEST, Viscoli et al. 2001		0.80	[0.19; 3.40]	2.8%	2.9%
WHII, Rossouw et al. 2002		2.11	[1.25; 3.55]	21.5%	21.4%
WHIII, Anderson et al. 2004		1.33	[0.85; 2.08]	29.1%	28.2%
WHISP . Collins et al. 2006	<del>_</del>	1.04	10.07: 16.18	0.8%	0.8%
WISDOM , Vickers et al. 2007		7.64	[2.30; 25.41]	4.0%	4.2%
Fixed effect model		1.70	[1.33: 2.16]	100.0%	
Random effects model		1.70	[1.32: 2.17]		100.0%
Heterogeneity: $l^2 = 2\%$ , $\tau^2 = 0.0049$ , $p = 0.43$			. ,		
	0.1 0.51 2 10				



Summary estimates (95% CI) were measured by fixed-effect models if  $I^2$  was <30% and P for heterogeneity was >0.05; otherwise, the summary estimates (95% CI) were measured by random-effect models. Forest and funnel plots were generated by "meta" package in R version 3.4.1. MHT, menopausal hormone therapy; RCTs, randomized controlled trials; SE, summary estimates; VTE, venous thromboembolism.

Supplementary Figure S1.5. Pooled results of MHT and PE in the RCTs: (a) forest plot and (b) funnel plot.

(a)

Study		Summary	Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
DOPS , Schierbeck et al. 2012		+	<u><u></u></u>	0.33	[0.03; 3.21]	0.6%	1.3%
ELITE, Hodis et al. 2016				4.95	[0.24; 102.77]	0.3%	0.7%
ESPRIT, The ESPIRIT team. 2002			1	0.98	[0.20; 4.84]	1.1%	2.5%
HERSI,II, Hulley et al. 2002			<del>{</del>	2.86	[1.13; 7.26]	3.3%	6.9%
WEST , Viscoli et al. 2001			1	1.00	[0.14; 7.10]	0.8%	1.7%
WHII, Manson et al. 2013			<b>—</b>	1.26	[1.00; 1.59]	53.6%	44.7%
WHIII, Manson et al. 2013			÷.	1.15	[0.88; 1.51]	39.1%	39.4%
WISDOM , Vickers et al. 2007				- 4.98	[1.09; 22.72]	1.3%	2.8%
Fixed effect model			÷.	1.26	[1.06; 1.50]	100.0%	
Random effects model			•	1.31	[1.01; 1.70]		100.0%
Heterogeneity: $I^2 = 21\%$ , $\tau^2 = 0.0247$ , $p = 0.27$	I		I I	I			
	0.01	0.1	1 10	100			



Summary estimates (95% CI) were measured by fixed-effect models if  $I^2$  was <30% and P for heterogeneity was >0.05; otherwise, the summary estimates (95% CI) were measured by random-effect models. Forest and funnel plots were generated by "meta" package in R version 3.4.1. MHT, menopausal hormone therapy; PE, pulmonary embolism; RCTs, randomized controlled trials; SE, summary estimates.

Supplementary Figure S1.6. Pooled results of MHT and MI in the RCTs: (a) forest plot and (b) funnel plot.

(a)



Summary estimates (95% CI) were measured by fixed-effect models if  $I^2$  was <30% and P for heterogeneity was >0.05; otherwise, the summary estimates (95% CI) were measured by random-effect models. Forest and funnel plots were generated by "meta" package in R version 3.4.1. MHT, menopausal hormone therapy; MI, myocardial infarction; RCTs, randomized controlled trials; SE, summary estimates.

Supplementary Figure S1.7. Pooled results of MHT and CHD in the RCTs: (a) forest plot and (b) funnel plot.

(a)

Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
EPHT, Veerus et al. 2006 ERA, Herrington et al. 2000 HERSI,II, Grady et al. 2002 WHII, Manson et al. 2013 WHIII, Manson et al. 2013		1.12 0.86 0.99 1.09 0.94	[0.90; 1.40] [0.61; 1.23] [0.84; 1.17] [0.96; 1.24] [0.81; 1.09]	11.8% 4.7% 21.1% 35.4% 26.9%	11.8% 4.7% 21.1% 35.4% 26.9%
Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0$ , $p = 0.43$	0.75 1 1.5	1.02 1.02	[0.94; 1.10] [0.94; 1.10]	100.0% 	 100.0%



Summary estimates (95% CI) were measured by fixed-effect models if  $I^2$  was <30% and P for heterogeneity was >0.05; otherwise, the summary estimates (95% CI) were measured by random-effect models. Forest and funnel plots were generated by "meta" package in R version 3.4.1. CHD, coronary heart disease; MHT, menopausal hormone therapy; RCTs, randomized controlled trials; SE, summary estimates.

Supplementary Figure S1.8. Pooled results of MHT and angina in the RCTs: (a) forest plot and (b) funnel plot.

(a)

Study	Summary	Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
EAGAR, Ouyang et al. 2006	-	<b>1</b>	1.29	[0.63; 2.65]	3.1%	4.0%
ELITE , Hodis et al. 2016		<u> </u>	- 4.95	[0.24; 102.77]	0.2%	0.2%
ERA, Herrington et al. 2000	-*	ŧ	0.77	[0.48; 1.25]	6.7%	8.4%
HERSI,II, Grady et al. 2002		2	0.87	[0.69; 1.09]	31.2%	28.8%
PHASE , Clarke et al. 2002		-	1.30	[0.89; 1.89]	11.1%	13.0%
WHII, Manson et al. 2003		ŧ	0.82	[0.57; 1.17]	12.6%	14.4%
WHIII, Hsia et al. 2006		÷	0.97	[0.78; 1.20]	35.0%	31.0%
WISDOM, Vickers et al. 2007		¦	6.98	[0.36; 135.00]	0.2%	0.2%
Fixed effect model	•	4	0.95	[0.84; 1.08]	100.0%	
Random effects model		÷	0.95	[0.82; 1.11]		100.0%
Heterogeneity: $I^2 = 14\%$ , $\tau^2 = 0.0065$ , $p = 0.32$	I	1 1				
0.01	0.1	1 10	100			



Summary estimates (95% CI) were measured by fixed-effect models if  $I^2$  was <30% and P for heterogeneity was >0.05; otherwise, the summary estimates (95% CI) were measured by random-effect models. Forest and funnel plots were generated by "meta" package in R version 3.4.1. MHT, menopausal hormone therapy; RCTs, randomized controlled trials; SE, summary estimates.

Supplementary Figure S1.9. Pooled results of MHT and revascularization in the RCTs: (a) forest plot and (b) funnel plot.

(a)

Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
EAGAR, Ouyang et al. 2006		- 8.60	[1.13; 65.73]	0.3%	0.3%
EPAT , Hodis et al. 2001		0.50	[0.05; 5.43]	0.2%	0.3%
ERA, Herrington et al. 2000		0.82	[0.52; 1.28]	5.1%	6.6%
HERSI,II, Grady et al. 2002	<u>i</u>	1.02	[0.86; 1.21]	35.7%	33.1%
WAVE, Waters et al. 2002		0.78	[0.52; 1.17]	6.4%	8.1%
WHII, Manson et al. 2003	÷	1.01	[0.78; 1.31]	15.4%	17.6%
WHIII, Hsia et al. 2006	Ē.	0.93	[0.79; 1.10]	37.0%	33.9%
Fixed effect model	4	0.96	[0.87; 1.06]	100.0%	
<b>Random effects model</b> Heterogeneity: $l^2 = 14\%$ , $\tau^2 = 0.0038$ , $p = 0.32$	r	0.96	[0.85; 1.08]		100.0%
neterogeneity. 7 1176, t = 0.0000, p = 0.02	01 051 2 10				



Summary estimates (95% CI) were measured by fixed-effect models if  $l^2$  was <30% and P for heterogeneity was >0.05; otherwise, the summary estimates (95% CI) were measured by random-effect models. Forest and funnel plots were generated by "meta" package in R version 3.4.1. MHT, menopausal hormone therapy; RCTs, randomized controlled trials; SE, summary estimates.

Supplementary Figure S2.1. Pooled results of MHT and all-cause death in the observational studies: (a) forest plot and (b) funnel plot.

(a)



Summary estimates (95% CI) were measured by fixed-effect models if  $I^2$  was <30% and P for heterogeneity was >0.05; otherwise, the summary estimates (95% CI) were measured by random-effect models. Forest and funnel plots were generated by "meta" package in R version 3.4.1. MHT, menopausal hormone therapy; SE, summary estimates.

2.0 Summary Estimates

1.0

0.5

0

5.0

Supplementary Figure S2.2. Pooled results of MHT and cardiovascular death in the observational studies: (a) forest plot and (b) funnel plot.

(a)





Summary estimates (95% CI) were measured by fixed-effect models if  $I^2$  was <30% and P for heterogeneity was >0.05; otherwise, the summary estimates (95% CI) were measured by random-effect models. Forest and funnel plots were generated by "meta" package in R version 3.4.1. MHT, menopausal hormone therapy; SE, summary estimates.

Supplementary Figure S2.3. Pooled results of MHT and stroke in the observational studies: (a) forest plot and (b) funnel plot.

(a)

Study		Sumi	mary Estir	nates	SE	9	5%-CI	Weight (fixed)	Weight (random)
Apostolakis et al. 2014 / AFFIRM			-+		0.78	[0.42;	1.43]	0.8%	4.0%
Lokkegaard et al. 2017 / DaHoRS					1.10	[0.97;	1.24]	19.4%	14.9%
Lokkegaard et al. 2003 (a) / DNS			+		1.16	[0.82;	1.65]	2.4%	8.1%
Canonico et al. 2016 / French NHI			+		1.13	[0.60;	2.13]	0.8%	3.8%
Lemaitre et al. 2006 / GHC			+		0.85	[0.75;	0.95]	21.4%	15.0%
Renoux et al. 2008 / GPRD			+		1.22	[1.11;	1.35]	32.2%	15.6%
Chen et al. 2015 / NHI					0.34	[0.12;	0.97]	0.3%	1.6%
Su et al. 2012 / NHI			-+		0.77	[0.49;	1.19]	1.6%	6.4%
Bhupathiraiu et al. 2018 / NHS			+		0.85	[0.56;	1.29]	1.7%	6.7%
Grodstein et al. 2000 / NHS			Ē.		1.08	[0.95;	1.23]	17.5%	14.7%
Shlipak et al. 2001 / NRMI-3					<u> </u>	[2.06; 1	03.64]	0.1%	0.5%
de Lecinana et al. 2007 / PIVE					0.62	[0.28;	1.35]	0.5%	2.7%
Crandall et al. 2018 / WHI-OS					0.78	[0.49;	1.24]	1.4%	5.9%
Fixed effect model					1.05	[0.99;	1.11]	100.0%	
Random effects model	-	~	+		0.98	[0.85;	1.13]	1.1	100.0%
Heterogeneity: $I^2 = 71\%$ , $\tau^2 = 0.0301$ , $p < 0.01$	100000-1000-0		1	1000000	1				
	0.01	0.1	1	10	100				



Summary estimates (95% CI) were measured by fixed-effect models if  $l^2$  was <30% and P for heterogeneity was >0.05; otherwise, the summary estimates (95% CI) were measured by random-effect models. Forest and funnel plots were generated by "meta" package in R version 3.4.1. MHT, menopausal hormone therapy; SE, summary estimates.

Supplementary Figure S2.4. Pooled results of MHT and VTE in the observational studies: (a) forest plot and (b) funnel plot.

(a)





Summary estimates (95% CI) were measured by fixed-effect models if  $l^2$  was <30% and P for heterogeneity was >0.05; otherwise, the summary estimates (95% CI) were measured by random-effect models. Forest and funnel plots were generated by "meta" package in R version 3.4.1. MHT, menopausal hormone therapy; SE, summary estimates; VTE, venous thromboembolism.

Supplementary Figure S2.5. Pooled results of MHT and PE in the observational studies: (a) forest plot and (b) funnel plot.

(a)

Study	Summary	Estimates	SE	95%-Cl	Weight (fixed)	Weight (random)
Tannen et al. 2007 / GPRD		<u> </u>	1.73	[1.12; 2.67]	22.7%	22.7%
Weiner et al. 2008 / GPRD			1.40	[1.06; 1.86]	52.9%	52.9%
Sweetland et al. 2012 / MWS		<b></b>	1.29	[0.82; 2.03]	20.7%	20.7%
Su et al. 2012 / NHI	15	•	— 1. <mark>1</mark> 3	[0.38; 3.35]	3.6%	3.6%
Fixed effect model		-	1.44	[1.17; 1.76]	100.0%	
Random effects model	0.		1.44	[1.17; 1.76]		100.0%
Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0$ , $p = 0.77$	1	1 1				
na sensena 📕 yang yang kuna kuna kuna kuna kuna kuna kuna kuna	0.5	1 2				



Summary estimates (95% CI) were measured by fixed-effect models if  $l^2$  was <30% and P for heterogeneity was >0.05; otherwise, the summary estimates (95% CI) were measured by random-effect models. Forest and funnel plots were generated by "meta" package in R version 3.4.1. MHT, menopausal hormone therapy; PE, pulmonary embolism; SE, summary estimates.

Supplementary Figure S2.6. Pooled results of MHT and MI in the observational studies: (a) forest plot and (b) funnel plot.

(a)



Summary Estimates

Summary estimates (95% CI) were measured by fixed-effect models if  $I^2$  was <30% and P for heterogeneity was >0.05; otherwise, the summary estimates (95% CI) were measured by random-effect models. Forest and funnel plots were generated by "meta" package in R version 3.4.1. MHT, menopausal hormone therapy; MI, myocardial infarction; SE, summary estimates.

Supplementary Figure S2.7. Pooled results of MHT and CHD in the observational studies: (a) forest plot and (b) funnel plot.

(a)







Summary estimates (95% CI) were measured by fixed-effect models if  $I^2$  was <30% and P for heterogeneity was >0.05; otherwise, the summary estimates (95% CI) were measured by random-effect models. Forest and funnel plots were generated by "meta" package in R version 3.4.1. CHD, coronary heart disease; MHT, menopausal hormone therapy; SE, summary estimates.

Supplementary Figure S2.8. Pooled results of MHT and angina in the observational studies: (a) forest plot.

(a)

Study	Summary Estimates	SE 95%-CI
Alexander et al. 2001 / CARS	0.8 1 1.25	— 1.11 [0.86; 1.43]

Summary estimates (95% CI) were measured by fixed-effect models if  $I^2$  was <30% and P for heterogeneity was >0.05; otherwise, the summary estimates (95% CI) were measured by random-effect models. Forest and funnel plots were generated by "meta" package in R version 3.4.1. CHD, coronary heart disease; MHT, menopausal hormone therapy; SE, summary estimates.

Supplementary Figure S3.1.1. MHT and all-cause death in RCTs: subgroup results by regimen type.

(a) estrogen only

Study	Summ	ary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
ERA , Herrington et al. 2000 ESPRIT , Cherry et al. 2014 WELL-HART . Hodis et al. 2003			1.40 1.07 0.50	[0.50; 3.89] [0.89; 1.29] [0.09: 2.65]	0.4% 12.4% 0.2%	0.4% 12.4% 0.2%
WEST , Viscoli et al. 2001 WHI II , Manson et al. 2017			1.20 0.94	[0.80; 1.80] [0.87; 1.01]	2.6% 84.3%	2.6% 84.3%
Fixed effect model Random effects model Heterogeneity: $l^2 = 0\%$ , $\tau^2 = 0$ , $p = 0.42$			0.96	[0.90; 1.03] [0.90; 1.03]	100.0% 	 100.0%
	0.1 0.3	512	10			

(b) combine EP

Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
EMS, Tierney et al. 2009		1.03	[0.15; 7.10]	0.1%	0.1%
EPHT, Veerus et al. 2006		0.78	[0.21; 2.91]	0.2%	0.2%
ERA, Herrington et al. 2000		0.50	[0.13; 1.97]	0.2%	0.2%
HERSI,II, Hulley et al. 2002		1.10	[0.92; 1.31]	9.6%	9.6%
WELL-HART, Hodis et al. 2003		0.77	[0.18; 3.32]	0.1%	0.1%
WHIT, Manson et al. 2017		1.02	[0.96; 1.08]	89.6%	89.6%
WHISP, Collins et al. 2006		0.52	[0.05; 5.56]	0.1%	0.1%
WISDOM, Vickers et al. 2007		1.59	[0.52; 4.87]	0.2%	0.2%
Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0$ , $p = 0.89$	0.1 0.5 1 2 10	1.03 1.03	[0.97; 1.08] [0.97; 1.08]	100.0% 	 100.0%

Summary estimates (95% CI) were measured by fixed-effect models if  $I^2$  was <30% and P for heterogeneity was >0.05; otherwise, the summary estimates (95% CI) were measured by random-effect models. Forest and funnel plots were generated by "meta" package in R version 3.4.1. MHT, menopausal hormone therapy; RCTs, randomized controlled trials; SE, summary estimates.

Supplementary Figure S3.1.2. MHT and all-cause death in RCTs: subgroup results by duration of use.

## (a) duration < 5 years

Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
EMS , Tierney et al. 2009		1.03	[0.15; 7.10]	0.7%	0.7%
EPHT . Veerus et al. 2006		0.78	[0.21: 2.91]	1.4%	1.4%
ERA, Herrington et al. 2000		0.94	[0.36; 2.48]	2.6%	2.6%
ESPRIT, Cherry et al. 2014		1.07	[0.89; 1.29]	70.7%	70.7%
Greenspan , Greenspan et al. 2005		0.50	[0.05; 5.44]	0.4%	0.4%
PHASE , Clarke et al. 2002		2.41	[0.65; 8.87]	1.5%	1.5%
STOP-IT , Gallagher et al. 2001		- 1.02	[0.06; 16.07]	0.3%	0.3%
WAVE , Waters et al. 2002		1.78	[0.76; 4.14]	3.4%	3.4%
WELL-HART, Hodis et al. 2003		0.63	[0.18; 2.29]	1.5%	1.5%
WEST, Viscoli et al. 2001		1.20	[0.80; 1.80]	15.0%	15.0%
WHISP , Collins et al. 2006		0.52	[0.05; 5.56]	0.4%	0.4%
WISDOM , Vickers et al. 2007		1.59	[0.52; 4.87]	2.0%	2.0%
Fixed effect model	L L	1.10	[0.94; 1.29]	100.0%	
Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0$ , $p = 0.92$	0.1 0.5 1 2 10	1.10	[0.94, 1.29]		100.0 %

(b) duration  $\geq$  5 years

Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
DOPS , Schierbeck et al. 2012 ELITE , Hodis et al. 2016 HERSI,II , Hulley et al. 2002 WHI I , Manson et al. 2017 WHI II , Manson et al. 2017		0.66 	[0.40; 1.08] [0.06; 15.77] [0.92; 1.31] [0.96; 1.08] [0.87; 1.01]	0.8% 0.0% 6.1% 57.0% 36.1%	2.4% 0.1% 14.8% 44.0% 38.7%
Fixed effect model Random effects model Heterogeneity: $I^2 = 43\%$ , $\tau^2 = 0.0027$ , $p = 0.13$	0.1 0.5 1 2 10	0.99 0.99	[0.95; 1.04] [0.91; 1.07]	100.0% 	 100.0%

Summary estimates (95% CI) were measured by fixed-effect models if  $I^2$  was <30% and P for heterogeneity was >0.05; otherwise, the summary estimates (95% CI) were measured by random-effect models. Forest and funnel plots were generated by "meta" package in R version 3.4.1. MHT, menopausal hormone therapy; RCTs, randomized controlled trials; SE, summary estimates.

Supplementary Figure S3.1.3. MHT and all-cause death in RCTs: subgroup results by timing of initiation.

(a) early users

Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
DOPS , Schierbeck et al. 2012 ELITE , Hodis et al. 2016 EPHT , Veerus et al. 2006		0.66 0.33 0.78	[0.40; 1.08] [0.01; 7.93] [0.21; 2.91]	40.1% 1.0% 5.7%	40.1% 1.0% 5.7%
ESPRIT, Cherry et al. 2014	Ť	0.90	[0.59; 1.38]	53.3%	53.3%
Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0$ , $p = 0.76$		0.78 0.78	[0.57; 1.07] [0.57; 1.07]	100.0% 	 100.0%

## (b) late users

Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
ELITE , Hodis et al. 2016		- 3.00	[0.12; 73.17]	0.0%	0.0%
EMS, Tierney et al. 2009		1.03	[0.15; 7.10]	0.0%	0.0%
ERA, Herrington et al. 2000		0.94	[0.36; 2.48]	0.2%	0.2%
ESPRIT, Cherry et al. 2014	+	1.11	[0.89; 1.38]	3.7%	3.7%
Greenspan, Greenspan et al. 2005		0.50	[0.05; 5.44]	0.0%	0.0%
HERSI,II, Hulley et al. 2002	+	1.10	[0.92; 1.31]	5.8%	5.8%
PHASE, Clarke et al. 2002		2.41	[0.65; 8.87]	0.1%	0.1%
STOP-IT, Gallagher et al. 2001		1.02	[0.06; 16.07]	0.0%	0.0%
WAVE, Waters et al. 2002		1.78	[0.76; 4.14]	0.2%	0.2%
WELL-HART, Hodis et al. 2003		0.63	[0.18; 2.29]	0.1%	0.1%
WEST, Viscoli et al. 2001	- <del> -</del> -	1.20	[0.80; 1.80]	1.1%	1.1%
WHII, Manson et al. 2017	•	1.02	[0.96; 1.08]	54.2%	54.2%
WHIII, Manson et al. 2017		0.94	0.87; 1.01]	34.3%	34.3%
WHISP . Collins et al. 2006		0.52	10.05: 5.561	0.0%	0.0%
WISDOM, Vickers et al. 2007		1.59	[0.52; 4.87]	0.1%	0.1%
Fixed effect model Random effects model		1.00 1.00	[0.96; 1.05] [0.96; 1.05]	100.0% 	 100.0%
Heterogeneity: $I^{-} = 0\%$ , $\tau^{-} = 0$ , $p = 0.62$					
	0.1 0.51 2 10				

Summary estimates (95% CI) were measured by fixed-effect models if  $l^2$  was <30% and P for heterogeneity was >0.05; otherwise, the summary estimates (95% CI) were measured by random-effect models. Forest and funnel plots were generated by "meta" package in R version 3.4.1. MHT, menopausal hormone therapy; RCTs, randomized controlled trials; SE, summary estimates.

Supplementary Figure S3.1.4. MHT and all-cause death in RCTs: subgroup results by underlying disease.

#### (a) women with diseases

Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
EMS , Tierney et al. 2009		1.03	[0.15; 7.10]	0.0%	0.0%
ERA, Herrington et al. 2000		0.94	[0.36; 2.48]	0.2%	0.2%
ESPRIT, Cherry et al. 2014	+	1.07	[0.89; 1.29]	5.0%	5.1%
HERSI,II, Hulley et al. 2002	-	1.10	[0.92; 1.31]	5.7%	5.8%
PHASE, Clarke et al. 2002		2.41	[0.65; 8.87]	0.1%	0.1%
WAVE, Waters et al. 2002		1.78	[0.76; 4.14]	0.2%	0.2%
WELL-HART , Hodis et al. 2003		0.63	[0.18; 2.29]	0.1%	0.1%
WEST, Viscoli et al. 2001	-+	1.20	[0.80; 1.80]	1.1%	1.1%
WHII, Manson et al. 2017	+	1.02	[0.96; 1.08]	53.6%	53.3%
WHIII, Manson et al. 2017		0.94	[0.87; 1.01]	33.9%	34.0%
WHISP , Collins et al. 2006		0.52	[0.05; 5.56]	0.0%	0.0%
Fixed effect model	ł	1.00	[0.96; 1.04]	100.0%	
Random effects model		1.00	[0.96; 1.05]		100.0%
Heterogeneity: $I^2 = 0\%$ , $\tau^2 < 0.0001$ , $p = 0.44$					
	0.1 0.5 1 2 10	)			

(b) women without diseases (relatively healthy)

Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
DOPS , Schierbeck et al. 2012 ELITE , Hodis et al. 2016 EPHT , Veerus et al. 2006 Greenspan , Greenspan et al. 2005 STOP-IT , Gallagher et al. 2001 WISDOM , Vickers et al. 2007		0.66 0.99 0.78 0.50 - 1.02 1.59	[0.40; 1.08] [0.06; 15.77] [0.21; 2.91] [0.05; 5.44] [0.06; 16.07] [0.52; 4.87]	69.4% 2.2% 9.8% 2.9% 2.2% 13.5%	69.4% 2.2% 9.8% 2.9% 2.2% 13.5%
Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0$ , $p = 0.82$	0.1 0.5 1 2 10	0.76 0.76	[0.51; 1.15] [0.51; 1.15]	100.0% 	 100.0%

Summary estimates (95% CI) were measured by fixed-effect models if  $I^2$  was <30% and P for heterogeneity was >0.05; otherwise, the summary estimates (95% CI) were measured by random-effect models. Forest and funnel plots were generated by "meta" package in R version 3.4.1. MHT, menopausal hormone therapy; RCTs, randomized controlled trials; SE, summary estimates.

Supplementary Figure S3.2.1. MHT and cardiovascular death in RCTs: subgroup results by regimen type.

(a) estrogen only

Study	Summary Estimates	SE	95%-C	Weight (fixed)	Weight (random)
ERA, Herrington et al. 2000	<u> </u>	1.40	[0.32; 6.10]	0.6%	0.6%
ESPRIT, The ESPIRIT team. 2002		0.68	[0.39; 1.19]	4.1%	4.1%
WEST, Viscoli et al. 2001		0.80	[0.34; 1.90]	1.7%	1.7%
WHI II , Manson et al. 2017	1	0.97	[0.86; 1.09]	93.6%	93.6%
Fixed effect model Random effects model Heterogeneity: $l^2 = 0.96$ , $r^2 = 0.9$ , $p = 0.59$		0.96 0.96	[0.85; 1.07] [0.85; 1.07]	100.0%   	 100.0%
Hereiogenerity. $r = 0.0, t = 0, p = 0.00$	0.2 0.5 1 2	5			
(b) combined EP					
Study	Summary Estimates	SE	W 95%-CI (	/eight fixed) (ra	Weight andom)
ERA . Herrington et al. 2000	<b>i</b>	0.67 [0	.11: 3.951	0.3%	0.3%
HERSI,II, Hulley et al. 2002	+	1.11 [0	.89; 1.39]	19.3%	19.3%
WHII, Manson et al. 2017		1.03 [0	.92; 1.15] 8	30.3%	80.3%
WHISP , Collins et al. 2006		0.21 [0	.01; 4.23]	0.1%	0.1%
Fixed effect model	•	1.04 [0.	94; 1.15] 10	0.0%	
<b>Random effects model</b> Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0$ , $p = 0.64$		1.04 [0.	94; 1.15]	'	100.0%
	0.1 0.51 2 10				

Summary estimates (95% CI) were measured by fixed-effect models if  $l^2$  was <30% and P for heterogeneity was >0.05; otherwise, the summary estimates (95% CI) were measured by random-effect models. Forest and funnel plots were generated by "meta" package in R version 3.4.1. MHT, menopausal hormone therapy; RCTs, randomized controlled trials; SE, summary estimates.

Supplementary Figure S3.2.2. MHT and cardiovascular death in RCTs: subgroup results by duration of use.

(a) duration < 5 years

Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
EAGAR , Ouyang et al. 2006 ERA , Herrington et al. 2000 ESPRIT , The ESPIRIT team. 2002 PHASE , Clarke et al. 2002 WAVE , Waters et al. 2002 WEST , Viscoli et al. 2001 WHISP , Collins et al. 2006 —		0.54 1.03 0.68 5.42 1.35 0.80 0.21	[0.10; 2.78] [0.26; 4.03] [0.39; 1.19] [0.66; 44.36] [0.48; 3.83] [0.34; 1.90] [0.01; 4.23]	5.5% 8.0% 47.7% 3.4% 13.8% 20.0% 1.6%	5.5% 8.0% 47.7% 3.4% 13.8% 20.0% 1.6%
Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0$ , $p = 0.47$	0.1 0.51 2 10	0.83 0.83	[0.56; 1.22] [0.56; 1.22]	100.0% 	 100.0%

(b) duration  $\geq$  5 years

Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
DOPS , Schierbeck et al. 2012 HERSI,II , Hulley et al. 2002 WHI I , Manson et al. 2017 WHI II , Manson et al. 2017		0.26 1.11 1.03 0.97	[0.11; 0.64] [0.89; 1.39] [0.92; 1.15] [0.86; 1.09]	0.7% 11.2% 46.6% 41.6%	3.3% 24.5% 36.4% 35.8%
Fixed effect model Random effects model Heterogeneity: $I^2$ = 70%, $\tau^2$ = 0.0174, $p$ = 0.02	0.2 0.5 1 2 5	1.00 0.98	[0.93; 1.08] [0.83; 1.16]	100.0% 	 100.0%

Summary estimates (95% CI) were measured by fixed-effect models if  $l^2$  was <30% and P for heterogeneity was >0.05; otherwise, the summary estimates (95% CI) were measured by random-effect models. Forest and funnel plots were generated by "meta" package in R version 3.4.1. MHT, menopausal hormone therapy; RCTs, randomized controlled trials; SE, summary estimates.

Supplementary Figure S3.2.3. MHT and cardiovascular death in RCTs: subgroup results by timing of initiation.

(a) early users

Study	Summary Estimates	SE 95%-CI
DOPS , Schierbeck et al. 2012		0.26 [0.11; 0.64]

(b) late users

Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
EAGAR, Ouyang et al. 2006	<b>,</b>	0.54	[0.10; 2.78]	0.2%	0.2%
ERA, Herrington et al. 2000		1.03	[0.26; 4.03]	0.3%	0.3%
ESPRIT, The ESPIRIT team. 2002	-+-	0.68	[0.39; 1.19]	1.8%	1.8%
HERSI,II, Hulley et al. 2002	+	1.11	[0.89; 1.39]	10.8%	10.8%
PHASE , Clarke et al. 2002		5.42	[0.66; 44.36]	0.1%	0.1%
WAVE , Waters et al. 2002	<del></del>	1.35	[0.48; 3.83]	0.5%	0.5%
WEST, Viscoli et al. 2001	<b>+</b>	0.80	[0.34; 1.90]	0.7%	0.7%
WHII, Manson et al. 2017	+	1.03	[0.92; 1.15]	45.2%	45.2%
WHIII, Manson et al. 2017	÷	0.97	[0.86; 1.09]	40.3%	40.3%
WHISP , Collins et al. 2006		0.21	[0.01; 4.23]	0.1%	0.1%
Fixed effect model	+	1.01	[0.93; 1.08]	100.0%	
Random effects model		1.01	[0.93; 1.08]		100.0%
Heterogeneity: $I^{-} = 0\%$ , $\tau^{-} = 0$ , $p = 0.55$	04 054 0 40				
	0.1 0.51 2 10				

Summary estimates (95% CI) were measured by fixed-effect models if  $I^2$  was <30% and P for heterogeneity was >0.05; otherwise, the summary estimates (95% CI) were measured by random-effect models. Forest and funnel plots were generated by "meta" package in R version 3.4.1. MHT, menopausal hormone therapy; RCTs, randomized controlled trials; SE, summary estimates.

Supplementary Figure S3.2.4. MHT and cardiovascular death in RCTs: subgroup results by underlying disease.

#### (a) women with diseases

Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
EAGAR, Ouyang et al. 2006		0.54	[0.10; 2.78]	0.2%	0.2%
ERA, Herrington et al. 2000		1.03	[0.26; 4.03]	0.3%	0.3%
ESPRIT, The ESPIRIT team. 2002	-+-	0.68	[0.39; 1.19]	1.8%	1.8%
HERSI,II, Hulley et al. 2002	+	1.11	[0.89; 1.39]	10.8%	10.8%
PHASE, Clarke et al. 2002		5.42	[0.66; 44.36]	0.1%	0.1%
WAVE , Waters et al. 2002	<del></del>	1.35	[0.48; 3.83]	0.5%	0.5%
WEST, Viscoli et al. 2001	<b>+</b>	0.80	[0.34; 1.90]	0.7%	0.7%
WHII, Manson et al. 2017		1.03	[0.92; 1.15]	45.2%	45.2%
WHIII, Manson et al. 2017		0.97	[0.86; 1.09]	40.3%	40.3%
WHISP, Collins et al. 2006		0.21	[0.01; 4.23]	0.1%	0.1%
Fixed effect model	•	1.01	[0.93; 1.08]	100.0%	
Random effects model	<b>•</b>	1.01	[0.93; 1.08]		100.0%
Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0$ , $p = 0.55$					
	0.1 0.51 2 10				

(b) women without diseases (relatively healthy)

Study	Summary	SE	95%-Cl	
DOPS , Schierbeck et al. 2012			0.26	[0.11; 0.64]
	0.2 0.5 1	125		

Summary estimates (95% CI) were measured by fixed-effect models if  $I^2$  was <30% and P for heterogeneity was >0.05; otherwise, the summary estimates (95% CI) were measured by random-effect models. Forest and funnel plots were generated by "meta" package in R version 3.4.1. MHT, menopausal hormone therapy; RCTs, randomized controlled trials; SE, summary estimates.

Supplementary Figure S3.3.1. MHT and stroke in RCTs: subgroup results by regimen type.

(a) estrogen only

Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
ERA , Herrington et al. 2000 ESPRIT_The ESPIRIT team_2002		0.88	[0.28; 2.78] [0.60: 4.46]	1.8% 2.4%	1.8% 2.4%
WEST, Viscoli et al. 2001 WHI II, Manson et al. 2013		1.10 1.15	[0.76; 1.60] [0.97; 1.37]	17.2% 78.6%	17.2% 78.6%
Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0$ , $\rho = 0.86$	0.5 1 2	1.15 1.15	[0.98; 1.34] [0.98; 1.34]	100.0% 	 100.0%
	0.5 1 2				

## (b) combined EP

Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
EMS, Tierney et al. 2009	<u> </u>	1.29	[0.36; 4.59]	0.9%	0.9%
EPH1, Veerus et al. 2006 ERA, Herrington et al. 2000		1.61 1.01	[0.38; 6.77] [0.34; 3.03]	0.7% 1.2%	0.7% 1.2%
HERSI,II, Grady et al. 2002	÷	1.09	[0.88; 1.35]	32.4%	32.4%
KEEPS , Gleason et al. 2015		- 3.72	[0.15; 90.93]	0.1%	0.1%
WHII, Manson et al. 2013	+	1.16	[1.00; 1.35]	64.4%	64.4%
WHISP , Collins et al. 2006		0.35	[0.01; 8.31]	0.1%	0.1%
Fixed effect model	•	1.14	[1.01; 1.29]	100.0%	
<b>Random effects model</b> Heterogeneity: $l^2 = 0\%$ , $\tau^2 = 0$ , $p = 0.95$		1.14	[1.01; 1.29]		100.0%
J , , , , , , , , , , , , , , , , , , ,	0.1 0.51 2 10				

Summary estimates (95% CI) were measured by fixed-effect models if  $l^2$  was <30% and P for heterogeneity was >0.05; otherwise, the summary estimates (95% CI) were measured by random-effect models. Forest and funnel plots were generated by "meta" package in R version 3.4.1. MHT, menopausal hormone therapy; RCTs, randomized controlled trials; SE, summary estimates.

Supplementary Figure S3.3.2. MHT and stroke in RCTs: subgroup results by duration of use.

## (a) duration < 5 years

Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
EMS , Tierney et al. 2009		1.29	[0.36; 4.59]	5.3%	5.3%
EPHT, Veerus et al. 2006		1.61	[0.38; 6.77]	4.1%	4.1%
ERA , Herrington et al. 2000		0.94	[0.36; 2.48]	9.2%	9.2%
ESPRIT, The ESPIRIT team. 2002		1.64	[0.60; 4.46]	8.5%	8.5%
KEEPS, Gleason et al. 2015		- 3.72	[0.15; 90.93]	0.8%	0.8%
STOP-IT, Gallagher et al. 2001		1.36	[0.31; 5.93]	3.9%	3.9%
WAVE , Waters et al. 2002		2.28	[0.71; 7.30]	6.3%	6.3%
WEST, Viscoli et al. 2001	÷	1.10	[0.76; 1.60]	60.9%	60.9%
WHISP, Collins et al. 2006		0.35	[0.01; 8.31]	0.8%	0.8%
Fixed effect model	<b>\</b>	1.21	[0.91; 1.63]	100.0%	
Random effects model Heterogeneity: $l^2 = 0\%$ $\tau^2 = 0$ , $p = 0.92$		1.21	[0.91; 1.63]		100.0%
	0.1 0.51 2 10				

(b) duration  $\geq$  5 years

Study	Sun	nmary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
DOPS , Schierbeck et al. 2012 HERSI,II , Grady et al. 2002 WHI I , Manson et al. 2013 WHI II , Manson et al. 2013			0.89 1.09 1.16 1.15	0 [0.48; 1.65] 0 [0.88; 1.35] 0 [1.00; 1.35] 0 [0.97; 1.37]	2.6% 21.7% 43.2% 32.4%	2.6% 21.7% 43.2% 32.4%
Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0$ , $p = 0.84$	0.5	1	1.13 1.13 2	[1.03; 1.25] [1.03; 1.25]	100.0% 	 100.0%

Summary estimates (95% CI) were measured by fixed-effect models if  $l^2$  was <30% and P for heterogeneity was >0.05; otherwise, the summary estimates (95% CI) were measured by random-effect models. Forest and funnel plots were generated by "meta" package in R version 3.4.1. MHT, menopausal hormone therapy; RCTs, randomized controlled trials; SE, summary estimates.

Supplementary Figure S3.3.3. MHT and stroke in RCTs: subgroup results by timing of initiation.

(a) early users

Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
DOPS , Schierbeck et al. 2012 EPHT , Veerus et al. 2006 KEEPS , Gleason et al. 2015 WHI I , Manson et al. 2013 WHI II , Manson et al. 2013		0.89 1.61 - 3.72 1.53 1.86	[0.48; 1.65] [0.38; 6.77] [0.15; 90.93] [0.80; 2.93] [0.83; 4.17]	36.9% 6.8% 1.4% 33.3% 21.6%	36.9% 6.8% 1.4% 33.3% 21.6%
Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0$ , $p = 0.57$	0.1 0.51 2 10	1.33 1.33	[0.91; 1.93] [0.91; 1.93]	100.0% 	 100.0%

(b) late users

Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
EMS, Tierney et al. 2009	<b> </b>	1.29	[0.36; 4.59]	1.4%	1.4%
ERA, Herrington et al. 2000	<u> </u>	0.94	[0.36; 2.48]	2.4%	2.4%
ESPRIT, The ESPIRIT team. 2002		1.64	[0.60; 4.46]	2.3%	2.3%
HERSI,II, Grady et al. 2002		1.09	[0.88; 1.35]	49.6%	49.6%
STOP-IT, Gallagher et al. 2001	<u> </u> }	1.36	[0.31; 5.93]	1.0%	1.0%
WAVE, Waters et al. 2002		2.28	[0.71; 7.30]	1.7%	1.7%
WEST, Viscoli et al. 2001	<del>\</del>	1.10	[0.76; 1.60]	16.2%	16.2%
WHII, Manson et al. 2013	- <del> </del> #-	1.23	[0.83; 1.82]	14.8%	14.8%
WHIII, Manson et al. 2013	+ <del>  =</del> -	1.53	[0.96; 2.44]	10.4%	10.4%
WHISP, Collins et al. 2006		0.35	[0.01; 8.31]	0.2%	0.2%
Fixed effect model	÷.	1.17	[1.01; 1.37]	100.0%	
Random effects model Heterogeneity: $l^2 = 0.6$ , $z^2 = 0.6$ , $p = 0.89$	<b>→</b>	1.17	[1.01; 1.37]		100.0%
Here over the second s	0.1 0.51 2 10				

Summary estimates (95% CI) were measured by fixed-effect models if  $I^2$  was <30% and P for heterogeneity was >0.05; otherwise, the summary estimates (95% CI) were measured by random-effect models. Forest and funnel plots were generated by "meta" package in R version 3.4.1. MHT, menopausal hormone therapy; RCTs, randomized controlled trials; SE, summary estimates.

Supplementary Figure S3.3.4. MHT and stroke in RCTs: subgroup results by underlying disease.

#### (a) women with diseases

Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
EMS, Tierney et al. 2009	<u> </u> ,	1.29	[0.36; 4.59]	0.6%	0.6%
ERA, Herrington et al. 2000		0.94	[0.36; 2.48]	1.0%	1.0%
ESPRIT, The ESPIRIT team. 2002	- <u>  </u>	1.64	[0.60; 4.46]	0.9%	0.9%
HERSI,II, Grady et al. 2002	÷	1.09	[0.88; 1.35]	20.1%	20.1%
WAVE, Waters et al. 2002	- <u>  </u> •	2.28	[0.71; 7.30]	0.7%	0.7%
WEST, Viscoli et al. 2001	- <del>  </del> -	1.10	[0.76; 1.60]	6.6%	6.6%
WHII, Manson et al. 2013		1.16	[1.00; 1.35]	40.0%	40.0%
WHIII, Manson et al. 2013	÷	1.15	[0.97; 1.37]	30.1%	30.1%
WHISP , Collins et al. 2006		0.35	[0.01; 8.31]	0.1%	0.1%
Fixed effect model	•	1.14	[1.04: 1.26]	100.0%	
<b>Random effects model</b> Heterogeneity: $J^2 = 0\%$ , $\tau^2 = 0$ , $p = 0.94$	r - 1 <del>    1</del> - 1	1.14	[1.04; 1.26]		100.0%
	0.1 0.51 2 10				

## (b) women without diseases (relatively healthy)

Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
DOPS , Schierbeck et al. 2012 EPHT , Veerus et al. 2006 KEEPS , Gleason et al. 2015 STOP-IT , Gallagher et al. 2001		0.89 1.61 — 3.72 1.36	[0.48; 1.65] [0.38; 6.77] [0.15; 90.93] [0.31; 5.93]	71.6% 13.2% 2.7% 12.5%	71.6% 13.2% 2.7% 12.5%
Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0$ , $p = 0.72$	0.1 0.51 2 10	1.05 1.05	[0.63; 1.78] [0.63; 1.78]	100.0% 	 100.0%

Summary estimates (95% CI) were measured by fixed-effect models if  $l^2$  was <30% and P for heterogeneity was >0.05; otherwise, the summary estimates (95% CI) were measured by random-effect models. Forest and funnel plots were generated by "meta" package in R version 3.4.1. MHT, menopausal hormone therapy; RCTs, randomized controlled trials; SE, summary estimates.

Supplementary Figure S3.4.1. MHT and VTE in RCTs: subgroup results by regimen type.

(a) estrogen only

Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
ERA , Herrington et al. 2000 ESPRIT , The ESPIRIT team. 2002		- 5.25 1.23	[0.62; 44.15] [0.33; 4.55]	3.5% 9.3%	3.5% 9.3%
WEST , Viscoli et al. 2001 WHI II , Anderson et al. 2004	*	0.80 1.33	[0.19; 3.40] [0.85; 2.08]	7.6% 79.6%	7.6% 79.6%
Fixed effect model Random effects model Heterogeneity: $l^2 = 0\%$ , $\tau^2 = 0$ , $p = 0.55$		1.33 1.33	[0.89; 1.99] [0.89; 1.99]	100.0% 	 100.0%
	0.1 0.5 1 2 10				

## (b) combined EP

Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
EMS, Tierney et al. 2009 ERA, Herrington et al. 2000 HERSI,II, Hulley et al. 2002 KEEPS, Gleason et al. 2015 WHI, Rossouw et al. 2002 WHISP, Collins et al. 2006 WISDOM, Vickers et al. 2007		- 3.09 2.02 2.08 1.24 2.11 1.04 7.64	[0.13; 74.46] [0.19; 21.93] [1.27; 3.40] [0.08; 19.73] [1.25; 3.55] [0.07; 16.18] [2.30; 25.41]	1.1% 1.9% 45.7% 1.4% 40.8% 1.5% 7.6%	1.1% 1.9% 45.7% 1.4% 40.8% 1.5% 7.6%
Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0$ , $p = 0.59$	0.1 0.51 2 10	2.28 2.28	[1.63; 3.18] [1.63; 3.18]	100.0% 	 100.0%

Summary estimates (95% CI) were measured by fixed-effect models if  $I^2$  was <30% and P for heterogeneity was >0.05; otherwise, the summary estimates (95% CI) were measured by random-effect models. Forest and funnel plots were generated by "meta" package in R version 3.4.1. MHT, menopausal hormone therapy; RCTs, randomized controlled trials; SE, summary estimates; VTE, venous thromboembolism.

Supplementary Figure S3.4.2. MHT and VTE in RCTs: subgroup results by duration of use.

## (a) duration < 5 years

Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
EMS, Tierney et al. 2009 ERA, Herrington et al. 2000 ESPRIT, The ESPIRIT team. 2002 Greenspan, Greenspan et al. 2005 KEEPS, Gleason et al. 2015 STOP-IT, Gallagher et al. 2001 WAVE, Waters et al. 2001 WHISP, Collins et al. 2006 WISDOM, Vickers et al. 2007			0.13; 74.46] 0.45; 28.90] 0.33; 4.55] 0.18; 21.75] 0.08; 19.73] 0.19; 22.13] 0.26; 4.00] 0.19; 3.40] 0.07; 16.18] 0.07; 16.18]	3.1% 7.1% 18.1% 5.4% 4.1% 5.4% 16.4% 14.8% 4.1% 21.5%	3.1% 7.1% 18.1% 5.4% 5.4% 16.4% 14.8% 4.1% 215%
Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0$ , $p = 0.49$	0.1 0.51 2 10	1.93 [ 1.93 [	1.10; 3.36] 1.10; 3.36]	100.0% 	 100.0%

(b) duration  $\geq$  5 years

Study	Summary Estimates	SE 95%	Weigh %-CI (fixed	t Weight ) (random)
DOPS , Schierbeck et al. 2012 ELITE , Hodis et al. 2016 HERSI,II , Hulley et al. 2002 WHI I, Rossouw et al. 2002 WHI II , Anderson et al. 2004		0.63 [0.21; 7 - 1.49 [0.25; 8 2.08 [1.27; 3 2.11 [1.25; 3 1.33 [0.85; 2	1.90]         5.8%           3.83]         2.3%           3.40]         29.7%           3.55]         26.5%           2.08]         35.8%	8.3% 3.4% 29.0% 27.0% 32.4%
Fixed effect model Random effects model Heterogeneity: $I^2$ = 28%, $\tau^2$ = 0.0402, $p$ = 0.24	0.2 0.5 1 2 5	1.65 [1.26; 2 1.62 [1.15; 2	2.15] 100.0% 2.27] -	- 100.0%

Summary estimates (95% CI) were measured by fixed-effect models if  $I^2$  was <30% and P for heterogeneity was >0.05; otherwise, the summary estimates (95% CI) were measured by random-effect models. Forest and funnel plots were generated by "meta" package in R version 3.4.1. MHT, menopausal hormone therapy; RCTs, randomized controlled trials; SE, summary estimates; VTE, venous thromboembolism.

Supplementary Figure S3.4.3. MHT and VTE in RCTs: subgroup results by timing of initiation.

(a) early users

WAVE , Waters et al. 2002 WEST , Viscoli et al. 2001

WHII, Rossouw et al. 2002

WHI II, Anderson et al. 2004 WHISP, Collins et al. 2006

Fixed effect model Random effects model

WISDOM, Vickers et al. 2007

Heterogeneity:  $I^2 = 0\%$ ,  $\tau^2 = 0$ , p = 0.53

Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
DOPS , Schierbeck et al. 2012 KEEPS , Gleason et al. 2015		0.63 - 1.24	[0.21; 1.90] [0.08; 19.73]	86.1% 13.9%	86.1% 13.9%
Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0$ , $p = 0.65$	0.1 0.5 1 2 10	0.69 0.69	[0.25; 1.93] [0.25; 1.93]	100.0% 	 100.0%
(b) late users					
Study	Summary Estimates	S	E 95%-0	Weigh Cl (fixed	nt Weight 1) (random)
ELITE , Hodis et al. 2016 EMS , Tierney et al. 2009 ERA , Herrington et al. 2000 ESPRIT , The ESPIRIT team. 2002 Greenspan , Greenspan et al. 2005		1.4 3.0 3.6 1.2	9 [0.25; 8.8 9 [0.13; 74.4 0 [0.45; 28.9 3 [0.33; 4.5 9 [0.18: 21.7	3] 1.99 6] 0.69 0] 1.49 5] 3.69	%         1.9%           %         0.6%           %         1.4%           %         3.6%           %         1.1%
HERSI,II, Hulley et al. 2002 STOP-IT, Gallagher et al. 2001		2.0	)8 [1.27; 3.4( )3 [0.19; 22.1;	0] 25.59 3] 1.19	% 25.5% % 1.1%

1.33 [0.85; 2.08]

1.04 [0.07; 16.18]

7.64 [2.30; 25.41]

[0.26; 4.00]

[0.19; 3.40]

[1.25: 3.55]

1.79 [1.39; 2.29] 100.0% 1.79 [1.39; 2.29] --

1.01

0.80

2.11

3.3% 2.9%

22.7%

30.8%

0.8%

4.3%

3.3% 2.9%

22.7%

30.8%

0.8%

4.3%

100.0%

Summary estimates (95% CI) were measured by fixed-effect models if  $I^2$  was <30% and P for heterogeneity was >0.05; otherwise, the summary estimates (95% CI) were measured by random-effect models. Forest and funnel plots were generated by "meta" package in R version 3.4.1. MHT, menopausal hormone therapy; RCTs, randomized controlled trials; SE, summary estimates; VTE, venous thromboembolism.

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Supplementary Figure S3.4.4. MHT and VTE in RCTs: subgroup results by underlying disease.

#### (a) women with diseases

Study	Summary Est	timates SE	95%-CI	Weight (fixed)	Weight (random)
EMS, Tierney et al. 2009		3.09	[0.13; 74.46]	0.7%	0.7%
ERA, Herrington et al. 2000	-++	-+ 3.60	[0.45; 28.90]	1.5%	1.5%
ESPRIT, The ESPIRIT team. 2002		<u> </u>	[0.33; 4.55]	3.9%	3.9%
HERSI,II, Hulley et al. 2002	+	+- 2.08	[1.27; 3.40]	27.8%	27.8%
WAVE, Waters et al. 2002	+-	— 1.01	[0.26; 4.00]	3.6%	3.6%
WEST, Viscoli et al. 2001		- 0.80	[0.19; 3.40]	3.2%	3.2%
WHII, Rossouw et al. 2002		+- 2.11	[1.25; 3.55]	24.8%	24.8%
WHIII, Anderson et al. 2004		- 1.33	[0.85; 2.08]	33.6%	33.6%
WHISP , Collins et al. 2006		1.04	[0.07; 16.18]	0.9%	0.9%
Fixed effect model		1.67	[1.29; 2.17]	100.0%	
<b>Random effects model</b> Heterogeneity: $J^2 = 0\% \tau^2 = 0, p = 0.75$	♦	1.67	[1.29; 2.17]		100.0%
Hotorogenery, 1 = 0, p = 0.10	0.1 0.51 2	2 10			

# (b) women without diseases (relatively healthy)

Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
DOPS , Schierbeck et al. 2012 ELITE , Hodis et al. 2016 Greenspan , Greenspan et al. 2005 KEEPS , Gleason et al. 2015 STOP-IT , Gallagher et al. 2001 WISDOM , Vickers et al. 2007		0.63 1.49 1.99 1.24 2.03 - 7.64	[0.21; 1.90] [0.25; 8.83] [0.18; 21.75] [0.08; 19.73] [0.19; 22.13] [2.30; 25.41]	35.3% 13.7% 7.6% 5.7% 7.6% 30.1%	26.0% 16.9% 11.6% 9.4% 11.6% 24.5%
Fixed effect model Random effects model Heterogeneity: $I^2$ = 45%, $\tau^2$ = 0.6241, $p$ = 0.10	0.1 0.5 1 2 10	1.86 1.87	[0.96; 3.60] [0.71; 4.94]	100.0% 	 100.0%

Supplementary Figure S3.5.1. MHT and PE in RCTs: subgroup results by regimen type.

(a) estrogen only

Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
ESPRIT , The ESPIRIT team. 2002		0.98	[0.20; 4.84]	2.8%	2.8%
WEST, Viscoli et al. 2001		— 1.00	[0.14; 7.10]	1.8%	1.8%
WHIII, Manson et al. 2013		1.15	[0.88; 1.51]	95.4%	95.4%
Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0$ , $p = 0.97$	0.2 0.5 1 2 5	1.14 1.14	[0.88; 1.49] [0.88; 1.49]	100.0% 	 100.0%
(b) combined EP					
Study	Summary Estimates	SE	V 95%-CI	Veight (fixed) (I	Weight random)
HERSUL Hullev et al. 2002	+ + + +	2.86 [1	13 <sup>.</sup> 7 261	57%	31.0%
WHIL Manson et al. 2013		1 26 [1	00: 1.59]	92.1%	50.6%
WISDOM , Vickers et al. 2007		4.98 [1.	09; 22.72]	2.2%	18.4%
Fixed effect model		1.36 [1	09: 1.701 1	00.0%	
Random effects model		2.09 0	93: 4.701		100.0%
Heterogeneity: $l^2 = 65\%$ , $\tau^2 = 0.3219$ , $p = 0.06$					

Summary estimates (95% CI) were measured by fixed-effect models if  $I^2$  was <30% and P for heterogeneity was >0.05; otherwise, the summary estimates (95% CI) were measured by random-effect models. Forest and funnel plots were generated by "meta" package in R version 3.4.1. MHT, menopausal hormone therapy; PE, pulmonary embolism; RCTs, randomized controlled trials; SE, summary estimates.

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Supplementary Figure S3.5.2. MHT and PE in RCTs: subgroup results by duration of use.

(a) duration < 5 years

Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
ESPRIT , The ESPIRIT team. 2002 WEST , Viscoli et al. 2001 WISDOM , Vickers et al. 2007		0.98 1.00 — 4.98	[0.20; 4.84] [0.14; 7.10] [1.09; 22.72]	36.1% 23.9% 40.0%	35.7% 25.9% 38.4%
Fixed effect model Random effects model Heterogeneity: $l^2 = 24\%$ , $\tau^2 = 0.2291$ , $p = 0.27$		1.89 1.84	[0.72; 4.92] [0.61; 5.56]	100.0% 	 100.0%

# (b) duration $\geq$ 5 years

Study		Summary	Estima	ates	SE	9	5%-CI	Weight (fixed)	Weight (random)
DOPS , Schierbeck et al. 2012	-	•			0.33	[0.03;	3.21]	0.6%	1.3%
ELITE , Hodis et al. 2016					- 4.95	[0.24; 1	02.77]	0.3%	0.7%
HERSI,II, Hulley et al. 2002				-	2.86	[1.13;	7.26]	3.4%	7.1%
WHII, Manson et al. 2013					1.26	[1.00;	1.59]	55.3%	48.5%
WHIII, Manson et al. 2013			¥ 		1.15	[0.88;	1.51]	40.3%	42.4%
Fixed effect model			\$		1.25	[1.05;	1.48]	100.0%	
Random effects model			$\diamond$		1.28	[0.98;	1.65		100.0%
Heterogeneity: $I^2 = 27\%$ , $\tau^2 = 0.0221$ , $p = 0.24$						- /	-		
0	.01	0.1	1	10	100				

Supplementary Figure S3.5.3. MHT and PE in RCTs: subgroup results by timing of initiation.

(a) early users

Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
DOPS , Schierbeck et al. 2012 WHI I , Manson et al. 2013 WHI II , Manson et al. 2013		0.33 1.94 2.51	[0.03; 3.21] [0.88; 4.30] [0.49; 12.97]	9.0% 73.7% 17.3%	11.9% 66.6% 21.5%
Fixed effect model Random effects model Heterogeneity: $l^2 = 14\%$ , $\tau^2 = 0.0911$ , $p = 0.31$	0.1 0.5 1 2 10	1.73 1.66	[0.87; 3.42] [0.74; 3.73]	100.0% 	 100.0%

(b) late users

Study		Summar	y Esti	imates	SE	9	5%-CI	Weight (fixed)	Weight (random)
ELITE , Hodis et al. 2016				+		[0.24; 1	02.77]	1.6%	1.6%
ESPRIT, The ESPIRIT team. 2002			++		0.98	[0.20;	4.84]	5.9%	5.9%
HERSI,II, Hulley et al. 2002			-   +	•	2.86	[1.13;	7.26]	17.5%	17.5%
WEST, Viscoli et al. 2001			++		1.00	[0.14;	7.10]	3.9%	3.9%
WHII, Manson et al. 2013				-	2.02	[1.11;	3.68]	42.1%	42.1%
WHIII, Manson et al. 2013			- <b>•</b> +		1.11	[0.49;	2.53]	22.3%	22.3%
WISDOM, Vickers et al. 2007				-	4.98	[1.09;	22.72]	6.6%	6.6%
Fixed effect model			-	•	1.88	[1.28;	2.78]	100.0%	
Random effects model				•	1.88	[1.28;	2.78]		100.0%
Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0$ , $p = 0.49$	I	I	I	I	I				
(	0.01	0.1	1	10	100				

Supplementary Figure S3.5.4. MHT and PE in RCTs: subgroup results by underlying disease.

### (a) women with diseases

Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
ESPRIT , The ESPIRIT team. 2002		0.98	[0.20; 4.84]	1.2%	1.2%
HERSI,II, Hulley et al. 2002	<del>  • • •</del>	- 2.86	[1.13; 7.26]	3.4%	3.4%
WEST, Viscoli et al. 2001		- 1.00	[0.14; 7.10]	0.8%	0.8%
WHII, Manson et al. 2013		1.26	[1.00; 1.59]	54.7%	54.7%
WHII, Manson et al. 2013		1.15	[0.88; 1.51]	39.9%	39.9%
Fixed effect model	↓	1.24	[1.05; 1.48]	100.0%	
Random effects model		1.24	[1.05; 1.48]		100.0%
Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0$ , $p = 0.47$					
<b>3 1 1 1</b>	02 05 1 2 5				

# (b) women without diseases (relatively healthy)

Study		Summ	ary E	stimates	SE	95%-CI	Weight (fixed)	Weight (random)
DOPS , Schierbeck et al. 2012					0.33	[0.03; 3.21]	26.2%	32.1%
ELITE, Hodis et al. 2016		-		-	4.95	[0.24; 102.77]	14.8%	23.0%
WISDOM , Vickers et al. 2007			-		4.98	[1.09; 22.72]	59.0%	44.9%
Fixed effect model			- +		2.44	[0.76: 7.83]	100.0%	
Random effects model					2.08	[0.34; 12.59]		100.0%
Heterogeneity: $I^2 = 50\%$ , $\tau^2 = 1.2797$ , $p = 0.13$		I				- / -		
0	.01	0.1	1	10	100			

Supplementary Figure S3.6.1. MHT and MI in RCTs: subgroup results by regimen type.

(a) estrogen only

Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
EPAT , Hodis et al. 2001 ERA , Herrington et al. 2000 WEST , Viscoli et al. 2001 WHI II , Manson et al. 2013		- 1.00 0.90 1.20 1.01	[0.06; 15.79] [0.31; 2.59] [0.58; 2.50] [0.86; 1.19]	0.3% 2.2% 4.6% 92.8%	0.3% 2.2% 4.6% 92.8%
Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0$ , $p = 0.97$	0.1 0.5 1 2 10	1.02 1.02	[0.87; 1.19] [0.87; 1.19]	100.0% 	 100.0%

# (b) combined EP

Study	5	Summa	ary Estin	nates		SE	9	5%-CI	Weight (fixed)	Weight (random)
EMS, Tierney et al. 2009			•	_		0.34	[0.01;	8.27]	0.1%	0.2%
EPHT, Veerus et al. 2006 ERA, Herrington et al. 2000						1.62 0.87	[0.27; [0.30;	9.69] 2.49]	0.5% 1.3%	0.6% 1.8%
HERSI,II, Grady et al. 2002 WHII, Manson et al. 2013			+			0.94	[0.77; [0.99;	1.15]	35.5% 61.7%	38.8% 57.1%
WHISP, Collins et al. 2006 WISDOM, Vickers et al. 2007			- <u>-</u>			0.52	[0.14;	1.97]	0.8%	1.2%
						0.57	10.40, 1	00.02	0.2 /0	0.270
<b>Random effects model</b> Heterogeneity: $l^2 = 7\%$ , $\tau^2 = 0.0034$ , $p = 0.38$	<b></b>		-			1.06	[0.94; [0.91;	1.20] 1.22]	100.0%	 100.0%
/ //	0.01	0.1	1	10	100					

Supplementary Figure S3.6.2. MHT and MI in RCTs: subgroup results by duration of use.

(a) duration < 5 years

Study	Summary Estimates	SE	95%-C	Weigh I (fixed	t Weight ) (random)
EAGAR, Ouyang et al. 2006		1.08	[0.16; 7.27	7] 4.5%	4.5%
EMS, Tierney et al. 2009		0.34	[0.01; 8.27	7] 1.6%	5 1.6%
EPAT , Hodis et al. 2001		1.00	[0.06; 15.79	9] 2.1%	5 <u>2.1%</u>
EPHT, Veerus et al. 2006		1.62	[0.27; 9.69	9] 5.1%	5.1%
ERA, Herrington et al. 2000		0.88	[0.36; 2.17	7] 20.1%	b 20.1%
Greenspan, Greenspan et al. 2005		0.33	[0.03; 3.16	3.2%	3.2%
PHASE, Clarke et al. 2002		0.23	[0.03; 1.99	9] 3.4%	3.4%
STOP-IT, Gallagher et al. 2001	<u> </u>	2.71	[0.74; 9.98	3] 9.6%	9.6%
WAVE, Waters et al. 2002		1.01	[0.26; 4.00	J 8.7%	0 8.1%
WEST, VISCOIL et al. 2001 WHISD, Collins at al. 2006		1.20	[0.58; 2.50	/] 30.4% /] 0.2%	b 30.4%
WHISP, COUNTS EL al. 2000 WISDOM, Vickors et al. 2007		0.52	10.14, 1.97	1 9.3% 01 1.00/	9.3% 1.0%
WISDOW, VICKEIS EL al. 2007		0.97	[0.40, 100.52		0 1.970
Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0$ , $p = 0.62$	0.01 0.1 1 10	<b>1.03</b> <b>1.03</b> 100	[0.69; 1.55 [0.69; 1.55	5] 100.0% 5] -	- 100.0%
(b) duration $\geq$ 5 years					
			1	Weight	Weight
Study	Summary Estimates	SE	95%-CI	(fixed) (r	andom)
DOPS, Schierbeck et al. 2012		0.45	[0.15; 1.31]	0.8%	1.7%
ELITE , Hodis et al. 2016		0.33	[0.03; 3.16]	0.2%	0.4%
HERSI,II, Grady et al. 2002	÷	0.94	[0.77; 1.15]	23.3%	27.5%
WHII, Manson et al. 2013	+	1.15	[0.99; 1.34]	40.5%	36.4%
WHI II , Manson et al. 2013	÷	1.01	[0.86; 1.19]	35.2%	34.1%
Fixed effect model	Î	1.04	[0.94; 1.14] 1	00.0%	
Random effects model Heterogeneity: $I^2 = 34\%$ , $\tau^2 = 0.0079$ , $p = 0.19$		1.02	[0.89; 1.17]		100.0%

Summary estimates (95% CI) were measured by fixed-effect models if  $I^2$  was <30% and P for heterogeneity was >0.05; otherwise, the summary estimates (95% CI) were measured by random-effect models. Forest and funnel plots were generated by "meta" package in R version 3.4.1. MHT, menopausal hormone therapy; MI, myocardial infarction; RCTs, randomized controlled trials; SE, summary estimates.

0.5 1 2

10

0.1

Supplementary Figure S3.6.3. MHT and MI in RCTs: subgroup results by timing of initiation.

(a) early users

Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
DOPS , Schierbeck et al. 2012 ELITE , Hodis et al. 2016 EPHT , Veerus et al. 2006 WHI I , Manson et al. 2013 WHI II , Manson et al. 2013		0.45 0.33 1.62 0.91 0.46	[0.15; 1.31] [0.01; 7.93] [0.27; 9.69] [0.54; 1.52] [0.17; 1.22]	14.3% 1.6% 5.1% 61.9% 17.1%	14.3% 1.6% 5.1% 61.9% 17.1%
Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0$ , $p = 0.50$	0.1 0.51 2 10	0.74 0.74	[0.50; 1.11] [0.50; 1.11]	100.0% 	 100.0%

(b) late users

Study	s	Summa	ry Esti	mates		SE	9	5%-CI	Weight (fixed)	Weight (random)
EAGAR, Ouyang et al. 2006			_			1.08	[0.16;	7.27]	0.6%	0.6%
ELITE, Hodis et al. 2016			+	_		0.50	[0.05;	5.47]	0.4%	0.4%
EMS, Tierney et al. 2009						0.34	[0.01;	8.27]	0.2%	0.2%
ERA, Herrington et al. 2000						0.88	[0.36;	2.17]	2.8%	2.8%
Greenspan, Greenspan et al. 2005						0.33	[0.03;	3.16]	0.5%	0.5%
HERSI,II, Grady et al. 2002			+-			0.94	[0.77;	1.15]	56.9%	56.9%
PHASE, Clarke et al. 2002	-					0.23	[0.03;	1.99]	0.5%	0.5%
STOP-IT, Gallagher et al. 2001			+-•			2.71	[0.74;	9.98]	1.4%	1.4%
WAVE, Waters et al. 2002		-		-		1.01	[0.26;	4.00]	1.2%	1.2%
WEST, Viscoli et al. 2001			-+			1.20	[0.58;	2.50]	4.3%	4.3%
WHII, Manson et al. 2013			-			1.16	[0.80;	1.69]	16.3%	16.3%
WHIII, Manson et al. 2013			+			1.12	[0.74;	1.70]	13.3%	13.3%
WHISP, Collins et al. 2006			• <del> </del> -			0.52	[0.14;	1.97]	1.3%	1.3%
WISDOM , Vickers et al. 2007			-			8.97	[0.48; 1	66.52]	0.3%	0.3%
Fixed effect model			+			1.00	[0.86;	1.17]	100.0%	
<b>Random effects model</b> Heterogeneity: $l^2 = 0\% \tau^2 = 0.0 = 0.66$	Γ		+	1		1.00	0.86;	1.17]		100.0%
······································	0.01	0.1	1	10	100					

Supplementary Figure S3.6.4. MHT and MI in RCTs: subgroup results by underlying disease.

### (a) women with diseases

Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
EAGAR, Ouyang et al. 2006		1.08	[0.16; 7.27]	0.3%	0.3%
EMS, Tierney et al. 2009		0.34	[0.01; 8.27]	0.1%	0.1%
ERA, Herrington et al. 2000	<b></b>	0.88	[0.36; 2.17]	1.1%	1.1%
HERSI,II, Grady et al. 2002		0.94	[0.77; 1.15]	22.5%	22.5%
PHASE, Clarke et al. 2002		0.23	[0.03; 1.99]	0.2%	0.2%
WAVE, Waters et al. 2002		1.01	[0.26; 4.00]	0.5%	0.5%
WEST , Viscoli et al. 2001	_ <del>+</del>	1.20	[0.58; 2.50]	1.7%	1.7%
WHII, Manson et al. 2013	+	1.15	[0.99; 1.34]	39.1%	39.1%
WHI II , Manson et al. 2013		1.01	[0.86; 1.19]	34.0%	34.0%
WHISP , Collins et al. 2006		0.52	[0.14; 1.97]	0.5%	0.5%
Fixed effect model	+	1.04	[0.94; 1.14]	100.0%	
Random effects model	<b>▶</b>	1.04	[0.94; 1.14]		100.0%
Herefogeneity. $7 = 0\%$ , $\tau = 0$ , $p = 0.70$	0.1 0.51 2 10				

(b) women without diseases (relatively healthy)

Study	Summary	Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
DOPS , Schierbeck et al. 2012			0.45	[0.15; 1.31]	36.2%	27.0%
ELITE, Hodis et al. 2016		1	0.33	[0.03; 3.16]	8.1%	10.6%
EPAT , Hodis et al. 2001		<u> </u>	1.00	[0.06; 15.79]	5.4%	7.7%
EPHT, Veerus et al. 2006			1.62	[0.27; 9.69]	12.9%	15.0%
Greenspan, Greenspan et al. 2005			0.33	[0.03; 3.16]	8.1%	10.6%
STOP-IT, Gallagher et al. 2001	-	• •	2.71	[0.74; 9.98]	24.4%	22.2%
WISDOM , Vickers et al. 2007	—		8.97	[0.48; 166.52]	4.8%	6.9%
Fixed effect model	-	-	0.94	[0.50; 1.80]	100.0%	
Random effects model		<b>-</b>	1.00	[0.43; 2.29]		100.0%
Heterogeneity: $I^2 = 31\%$ , $\tau^2 = 0.3694$ , $p = 0.19$		1	I			
	0.01 0.1	1 10	100			

Supplementary Figure S3.7.1. MHT and CHD in RCTs: subgroup results by regimen type.

(a) estrogen only

	Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
	ERA , Herrington et al. 2000		0.90 0.94	[0.59; 1.35] [0.81; 1.09]	11.4% 88.6%	11.4% 88.6%
	Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0$ , $p = 0.83$	0.75 1 1.5	0.93 0.93	[0.81; 1.07] [0.81; 1.07]	100.0% 	 100.0%
(b) co	mbined EP					
	Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
	EPHT , Veerus et al. 2006 ERA , Herrington et al. 2000 HERSI,II , Grady et al. 2002 WHI I , Manson et al. 2013		1.12 0.83 0.99 1.09	[0.90; 1.40] [0.55; 1.27] [0.84; 1.17] [0.96; 1.24]	16.5% 4.6% 29.4% 49.4%	16.5% 4.6% 29.4% 49.4%
	Fixed effect model		1.05	[0.96; 1.15]	100.0%	

Supplementary Figure S3.7.2. MHT and CHD in RCTs: subgroup results by duration of use.

(a) duration < 5 years

Study	Summ	ary Estimates	5	SE	95%-CI	Weight (fixed)	Weight (random)
EPHT , Veerus et al. 2006 ERA , Herrington et al. 2000 —			_	1.12 0.86	[0.90; 1.40] [0.61; 1.23]	71.5% 28.5%	64.4% 35.6%
Fixed effect model Random effects model Heterogeneity: $l^2 = 33\%$ , $\tau^2 = 0.0113$ , $p = 0.22$	-==			1.04 1.02	[0.86; 1.26] [0.80; 1.30]	100.0% 	 100.0%
	0.75	1	1.5				

(b) duration  $\geq 5$  years

Study	Summary Es	timates SE	95%-CI	Weight (fixed)	Weight (random)
HERSI,II, Grady et al. 2002 WHI I, Manson et al. 2013 WHI II, Manson et al. 2013 —		0.99 	9 [0.84; 1.17] 9 [0.96; 1.24] 4 [0.81; 1.09]	25.3% 42.5% 32.2%	26.3% 41.2% 32.5%
Fixed effect model Random effects model Heterogeneity: $I^2$ = 13%, $\tau^2$ = 0.0008, $p$ = 0.32	0.9 1	1.0°	I [0.93; 1.10] I [0.93; 1.11]	100.0% 	 100.0%

Supplementary Figure S3.7.3. MHT and CHD in RCTs: subgroup results by timing of initiation.

(a) early users

Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
EPHT , Veerus et al. 2006 WHI I , Manson et al. 2013 WHI II , Manson et al. 2013		1.12 0.90 0.50	[0.90; 1.40] [0.56; 1.45] [0.21; 1.18]	77.7% 17.0% 5.2%	55.9% 30.7% 13.4%
Fixed effect model Random effects model Heterogeneity: $l^2$ = 44%, $\tau^2$ = 0.0434, $p$ = 0.17	0.5 1 2	1.03 0.94	[0.85; 1.26] [0.66; 1.33]	100.0% 	 100.0%
(b) late users					
Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
ERA , Herrington et al. 2000		0.86 0.99	[0.61; 1.23] [0.84; 1.17]	13.8% 61.8%	13.8% 61.8%

WHI I , Manson et al. 2013 WHI I , Manson et al. 2013		*		1.19 1.00	[0.83; 1.70] [0.67; 1.49]	13.6% 10.8%	13.6% 10.8%
Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0$ , $p = 0.66$	0.75	1	1.5	1.00 1.00	[0.87; 1.14] [0.87; 1.14]	100.0% 	 100.0%

Supplementary Figure S3.7.4. MHT and CHD in RCTs: subgroup results by underlying disease.

#### (a) women with diseases

Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
ERA , Herrington et al. 2000 HERSI,II , Grady et al. 2002 WHI I, Manson et al. 2013 WHI II , Manson et al. 2013		0.86 0.99 1.09 0.94	[0.61; 1.23] [0.84; 1.17] [0.96; 1.24] [0.81; 1.09]	5.3% 24.0% 40.2% 30.5%	5.5% 24.1% 39.9% 30.5%
Fixed effect model Random effects model Heterogeneity: $I^2 = 2\%$ , $\tau^2 = 0.0001$ , $p = 0.38$	0.75 1 1.	1.01 1.01 5	[0.93; 1.09] [0.93; 1.09]	100.0% 	 100.0%

(b) women without diseases (relatively healthy)

Study	Summa	ary Estima	tes	SE	95%-CI
EPHT , Veerus et al. 2006				- 1.12	[0.9; 1.4]
	0.8	1	1.25		

Supplementary Figure S3.8.1. MHT and angina in RCTs: subgroup results by regimen type.

(a) estrogen only

(b)

Study		Summary Estimates	SE	95%-CI	Weight (fixed) (	Weight (random)
ERA , Herrington et al. 2000 WHI II , Hsia et al. 2006			0.86 0.97	[0.49; 1.50] [0.78; 1.20]	12.6% 87.4%	12.6% 87.4%
Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0$ , $p = 0.69$	Γ		0.96 0.96	[0.78; 1.17] [0.78; 1.17]	100.0% 	 100.0%
	0.5	1	2			
combined EP						
Study		Summary Estimates	SE	95%-0	Weight Cl (fixed)	t Weight ) (random)
Study ERA , Herrington et al. 2000 HERSI,II , Grady et al. 2002 WHIL Manson et al. 2003		Summary Estimates	SE 0.69 0.87 0.82	<b>95%-C</b> [0.38; 1.29 [0.69; 1.09 [0.57; 1.10]	Weight Cl (fixed) 5] 9.2% 9] 64.5% 71 25.9%	t Weight (random) 9.2% 64.5% 25.9%
Study ERA , Herrington et al. 2000 HERSI,II , Grady et al. 2002 WHI I , Manson et al. 2003 WISDOM , Vickers et al. 2007		Summary Estimates	SE 0.69 0.87 0.82 	<b>95%-C</b> [0.38; 1.24 [0.69; 1.09 [0.57; 1.17 [0.36; 135.00	Weight (fixed) 5] 9.2% 9] 64.5% 7] 25.9% 0] 0.4%	t Weight (random) 9.2% 64.5% 9.25.9% 9.0.4%
Study ERA, Herrington et al. 2000 HERSI,II, Grady et al. 2002 WHI I, Manson et al. 2003 WISDOM, Vickers et al. 2007 Fixed effect model Random effects model Heterogeneity: $J^2 = 0\%$ $\tau^2 = 0.p = 0.48$		Summary Estimates	SE 0.69 0.87 0.82 6.98 0.85 0.85	95%-C [0.38; 1.29 [0.69; 1.09 [0.57; 1.17 [0.36; 135.00 [0.71; 1.01 [0.71; 1.01	Weight   [] 9.2%   [] 64.5%   [] 25.9%   [] 0.4%   [] 100.0%	t Weight (random) 9.2% 64.5% 25.9% 0.4% - 100.0%

Supplementary Figure S3.8.2. MHT and angina in RCTs: subgroup results by duration of use.

(a) duration < 5 years

(b)

Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
EAGAR , Ouyang et al. 2006 ERA , Herrington et al. 2000 PHASE , Clarke et al. 2002 WISDOM , Vickors et al. 2007	÷.	1.29 0.77 1.30	[0.63; 2.65] [0.48; 1.25] [0.89; 1.89] [0.36: 135.00]	14.5% 32.0% 52.6%	20.4% 34.2% 43.9%
Fixed effect model Random effects model Heterogeneity: $l^2 = 33\%$ , $\tau^2 = 0.0475$ , $p = 0.22$		1.11 1.12	[0.85; 1.47] [0.76; 1.63]	0.9% 100.0% 	 100.0%
0.01 duration $\geq 5$ years	0.1 1 10	100			
Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
ELITE , Hodis et al. 2016 HERSI,II , Grady et al. 2002 WHI I , Manson et al. 2003	- <u> </u>	4.95 0.87 0.82	[0.24; 102.77] [0.69; 1.09] [0.57; 1.17]	0.2% 39.5% 15.9%	0.2% 39.5% 15.9%

WHIII, Hsia et al. 2006			+		0.97	[0.78;	1.20]	44.4%	44.4%
Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0$ , $p = 0.57$	0.01	0.1	1	10	0.91 0.91 100	[0.79; [0.79;	1.05] 1.05]	100.0% 	 100.0%

Supplementary Figure S3.8.3. MHT and angina in RCTs: subgroup results by timing of initiation.

(a) early users

Study	Summary Estimates	SE	95%-CI
WHII, Manson et al. 2003		0.87	[0.54; 1.41]
	0.75 1 1.5		

(b) late users

Study	S	umma	nry Estin	nates	SE	9	5%-CI	Weight (fixed)	Weight (random)
EAGAR . Ouvang et al. 2006					1.29	[0.63:	2.651	4.8%	7.8%
ELITE, Hodis et al. 2016		-		•	4.95	[0.24; 1	02.77	0.3%	0.5%
ERA, Herrington et al. 2000			-		0.77	[0.48;	1.25]	10.5%	14.6%
HERSI,II, Grady et al. 2002					0.87	[0.69;	1.09]	48.5%	34.5%
PHASE, Clarke et al. 2002			-		1.30	[0.89;	1.89]	17.2%	20.6%
WHII, Manson et al. 2003			÷.		1.18	[0.82;	1.70]	18.5%	21.5%
WISDOM, Vickers et al. 2007			_		6.98	[0.36; 1	35.00]	0.3%	0.5%
Fixed effect model Random effects model Heterogeneity: $J^2 = 28\%$ , $\tau^2 = 0.0221$ , $p = 0.21$			•	10	1.00 1.04	[0.86; [0.84;	1.17] 1.29]	100.0% 	 100.0%
0.	01	0.1	1	10	100				

Supplementary Figure S3.8.4. MHT and angina in RCTs: subgroup results by underlying disease.

#### (a) women with diseases

Study	Summary Estimates	; SE	95%-CI	Weight (fixed)	Weight (random)
EAGAR, Ouyang et al. 2006		1.29	[0.63; 2.65]	3.1%	3.3%
ERA , Herrington et al. 2000		0.77	[0.48; 1.25]	6.8%	7.2%
HERSI,II, Grady et al. 2002	— • <del>   </del>	0.87	[0.69; 1.09]	31.3%	30.7%
PHASE, Clarke et al. 2002	<u>+ </u> <u>≖</u>	- 1.30	[0.89; 1.89]	11.1%	11.7%
WHII, Manson et al. 2003		0.82	[0.57; 1.17]	12.6%	13.1%
WHIII, Hsia et al. 2006		0.97	[0.78; 1.20]	35.2%	34.0%
Fixed effect model	+	0.94	[0.83; 1.07]	100.0%	
<b>Random effects model</b> Heterogeneity: $I^2 = 5\%$ , $\tau^2 = 0.0015$ , $p = 0.38$		0.94	[0.83; 1.08]		100.0%
	0.5 1	2			

# (b) women without diseases (relatively healthy)

Study		Summa	ry Est	imates	SE	95%-CI	Weight (fixed)	Weight (random)
ELITE , Hodis et al. 2016 WISDOM , Vickers et al. 2007		-		-	4.98 6.98	5 [0.24; 102.77] 3 [0.36; 135.00]	48.8% 51.2%	48.8% 51.2%
Fixed effect model Random effects model Heterogeneity: $J^2 = 0\%$ , $\tau^2 = 0$ , $p = 0.87$	0.01	0.1		10	- 5.90 - 5.90	0 [0.71; 49.13] 0 [0.71; 49.13]	100.0% 	 100.0%

Supplementary Figure S3.9.1. MHT and revascularization in RCTs: subgroup results by regimen type.

(a) estrogen only

Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
EPAT , Hodis et al. 2001 ERA , Herrington et al. 2000 WHI II , Hsia et al. 2006		0.50 0.79 0.93	[0.05; 5.43] [0.46; 1.36] [0.79; 1.10]	0.5% 8.6% 91.0%	0.5% 8.6% 91.0%
Fixed effect model Random effects model Heterogeneity: $J^2 = 0\%$ , $\tau^2 = 0$ , $p = 0.75$	0.1 0.5 1 2 10	0.91 0.91	[0.78; 1.07] [0.78; 1.07]	100.0% 	 100.0%
(b) combined EP					
Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
ERA , Herrington et al. 2000 HERSI,II , Grady et al. 2002 WHI I , Manson et al. 2003		0.84 1.02 1.01	[0.50; 1.43] [0.86; 1.21] [0.78; 1.31]	6.8% 65.1% 28.1%	6.8% 65.1% 28.1%
Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0$ , $p = 0.79$	0.5 1	1.00 1.00	[0.87; 1.15] [0.87; 1.15]	100.0% 	 100.0%

Supplementary Figure S3.9.2. MHT and revascularization in RCTs: subgroup results by duration of use.

(a) duration < 5 years

Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
EAGAR , Ouyang et al. 2006 EPAT , Hodis et al. 2001 ERA , Herrington et al. 2000 WAVE , Waters et al. 2002		- 8.60 0.50 0.82 0.78	[1.13; 65.73] [0.05; 5.43] [0.52; 1.28] [0.52; 1.17]	2.1% 1.5% 42.7% 53.6%	5.7% 4.2% 43.4% 46.7%
Fixed effect model Random effects model Heterogeneity: $I^2$ = 44%, $\tau^2$ = 0.1008, $p$ = 0.15	0.1 0.51 2 10	0.83 0.90	[0.62; 1.12] [0.54; 1.49]	100.0% 	 100.0%
(b) duration $\geq$ 5 years					
Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
HERSI,II , Grady et al. 2002 WHI I, Manson et al. 2003 WHI II , Hsia et al. 2006		1.02 - 1.01 0.93	[0.86; 1.21] [0.78; 1.31] [0.79; 1.10]	40.5% 17.5% 42.0%	40.5% 17.5% 42.0%
Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0$ , $p = 0.73$		0.98 0.98	[0.88; 1.09] [0.88; 1.09]	100.0% 	 100.0%

Summary estimates (95% CI) were measured by fixed-effect models if  $I^2$  was <30% and P for heterogeneity was >0.05; otherwise, the summary estimates (95% CI) were measured by random-effect models. Forest and funnel plots were generated by "meta" package in R version 3.4.1. MHT, menopausal hormone therapy; RCTs, randomized controlled trials; SE, summary estimates.

1

1.25

0.8

Supplementary Figure S3.9.3. MHT and revascularization in RCTs: subgroup results by timing of initiation.

(a) early users

Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
WHII, Manson et al. 2013 WHII, Manson et al. 2013		0.74 0.88	[0.47; 1.16] [0.45; 1.72]	69.0% 31.0%	69.0% 31.0%
Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0$ , $p = 0.67$	0.5 1 2	0.78 0.78	[0.54; 1.13] [0.54; 1.13]	100.0% 	 100.0%
(b) late users					
Study	Summary Estimates	SE	95%-C	Weight (fixed)	Weight (random)
EAGAR, Ouyang et al. 2006 ERA, Herrington et al. 2000 HERSI,II, Grady et al. 2002		- 8.60 0.82 1.02	[1.13; 65.73] [0.52; 1.28] [0.86; 1.21]	0.4% 7.7% 54.4%	0.6% 10.8% 40.8%
WHII, Manson et al. 2013 WHII, Manson et al. 2013	*	0.78 0.97 0.99	[0.52; 1.17] [0.70; 1.34] [0.70; 1.41]	9.7% 15.2% 12.7%	13.0% 18.6% 16.2%

Supplementary Figure S3.9.4. MHT and revascularization in RCTs: subgroup results by underlying disease.

### (a) women with diseases

Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
EAGAR, Ouyang et al. 2006	+	- 8.60	[1.13; 65.73]	0.3%	0.4%
ERA, Herrington et al. 2000		0.82	[0.52; 1.28]	5.1%	7.5%
HERSI,II, Grady et al. 2002	÷-	1.02	[0.86; 1.21]	35.8%	31.8%
WAVE , Waters et al. 2002	-*-	0.78	[0.52; 1.17]	6.4%	9.2%
WHII, Manson et al. 2003	<u>÷</u>	1.01	[0.78; 1.31]	15.4%	18.6%
WHIII, Hsia et al. 2006	+	0.93	[0.79; 1.10]	37.1%	32.4%
Fixed effect model	•	0.96	[0.87; 1.07]	100.0%	
<b>Random effects model</b> Heterogeneity: $l^2 = 25\%$ , $\tau^2 = 0.0065$ , $p = 0.24$	r	0.96	[0.84; 1.09]		100.0%
	0.1 0.51 2 10				

(b) women without diseases (relatively healthy)

Study	Summary	Estima	tes	SE	95%-CI
EPAT , Hodis et al. 2001		1		0.50	0.05; 5.43]
	0.1 0.5	12	10		

Supplementary Figure S4.1.1. MHT and all-cause death in observational studies: subgroup results by regimen type.

(a) estrogen only

Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
Stram et al. 2011 / CTS Holm et al. 2019 / DCH Lokkegaard et al. 2003 (b) / DNS Tannen et al. 2007 / GPRD Su et al. 2012 / NHI Ryan et al. 2012 / TCS Crandall et al. 2018 / WHI-OS		0.84 0.99 0.95 0.68 0.89 0.94 0.78	[0.80; 0.87] [0.88; 1.11] [0.75; 1.21] [0.57; 0.81] [0.67; 1.19] [0.38; 2.30] [0.59; 1.04]	77.4% 11.4% 2.6% 4.9% 1.8% 0.2% 1.8%	29.7% 22.7% 11.6% 16.6% 9.1% 1.3% 9.2%
Fixed effect model Random effects model Heterogeneity: $I^2 = 59\%$ , $\tau^2 = 0.0089$ , $p = 0.02$	0.5 1 2	0.85 0.85	[0.82; 0.88] [0.77; 0.95]	100.0% 	 100.0%

*(b) combined EP* 

Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
Stram et al. 2011 / CTS	+	0.24	[0.22: 0.26]	40.9%	15.0%
Holm et al. 2019 / DCH		1.01	[0.94; 1.10]	32.5%	15.0%
Lokkegaard et al. 2003 (b) / DNS	1	0.89	[0.68; 1.17]	2.7%	14.6%
Weiner et al. 2008 / GPRD	-	0.75	[0.68; 0.84]	16.8%	15.0%
Su et al. 2012 / NHI	- <del>1=-</del> -	0.56	[0.47: 0.67]	6.2%	14.8%
Graff-Iversen et al. 2004 / NR		0.57	[0.31; 1.06]	0.5%	12.9%
Ryan et al. 2012 / TCS		0.57	[0.30; 1.09]	0.5%	12.8%
Fixed effect model		0.51	[0.49: 0.53]	100.0%	
Random effects model		0.61	[0.34; 1.09]		100.0%
Heterogeneity: $I^2 = 99\%$ , $\tau^2 = 0.6040$ , $p < 0.01$					
5, 7, 7, 7,	0.5 1 2				

Supplementary Figure S4.1.2. MHT and all-cause death in observational studies: subgroup results by duration of use.

(a) duration < 5 years



Supplementary Figure S4.1.3. MHT and all-cause death in observational studies: subgroup results by timing of initiation.

(a) early users

#### Study

Alexander et al. 2001 / CARS Stram et al. 2011 / CTS Weiner et al. 2008 / GPRD Su et al. 2012 / NHI Graff-Iversen et al. 2004 / NR Pentti et al. 2006 / OSTPRE Alexandersen et al. 2006 / PERF Ryan et al. 2012 / TCS

# Fixed effect model

Random effects model Heterogeneity:  $l^2 = 95\%$ ,  $\tau^2 = 0.1438$ , p < 0.01



(b) late users

Study	Su	mmar	y Es	timat	tes	SE	98	5%-CI	Weight (fixed)	Weight (random)
Apostolakis et al. 2014 / AFFIRM		-	i i			0.95	[0.66;	1.36]	3.7%	16.2%
Stram et al. 2011 / CTS						0.93	[0.85;	1.01]	71.0%	23.6%
Tannen et al. 2007 / GPRD		-9	+ii			0.68	[0.57;	0.81]	16.0%	21.7%
Shlipak et al. 2001 / NRMI-3				<u>(3)</u>		6.39	[2.63;	15.52]	0.6%	6.1%
Ryan et al. 2012 / TCS			-			0.87	[0.57;	1.35]	2.6%	14.1%
Crandall et al. 2018 / WHI-OS		4 <u>001</u> 0	+			0.78	[0.59;	1.04]	5.9%	18.4%
Fixed effect model			*			0.88	[0.82;	0.95]	100.0%	
Random effects model			+			0.94	[0.73;	1.21]		100.0%
Heterogeneity: $I^2 = 83\%$ , $\tau^2 = 0.0687$ , $p < 0.01$	L	1		1						
	0.1	0.5	1	2	10					

Supplementary Figure S4.1.4. MHT and all-cause death in observational studies: subgroup results by route of administration.

(a) oral

Study	Summary Estimates	SE 95%-CI	Weight Weight (fixed) (random)
Holm et al. 2019 / DCH Ryan et al. 2012 / TCS		1.01 [0.94; 1.08] 0.84 [0.27; 2.65]	99.7% 99.7% 0.3% 0.3%
Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0$ , $p = 0.75$	0.5 1 2	1.01 [0.94; 1.08] 1.01 [0.94; 1.08]	100.0% 100.0%
(a) non-oral			
Study	Summary Estimates	SE 95%-C	Weight Weight I (fixed) (random)
Holm et al. 2019 / DCH Ryan et al. 2012 / TCS Crandall et al. 2018 / WHI-OS		0.95 [0.81; 1.11 0.48 [0.22; 1.04 0.78 [0.59; 1.04	] 75.0% 54.7% -] 3.0% 9.1% -] 22.0% 36.2%
Fixed effect model Random effects model Heterogeneity: $l^2$ = 49%, $\tau^2$ = 0.0235, $p$ = 0.14	0.5 1 2	0.89 [0.78; 1.02 0.83 [0.65; 1.07	] 100.0% ] 100.0%

Supplementary Figure S4.1.5. MHT and all-cause death in observational studies: subgroup results by underlying disease.

#### (a) women with diseases

Study	Summa	ry E	timat	tes	SE	95%-CI	Weight (fixed)	Weight (random)
Apostolakis et al. 2014 / AFFIRM		-			0.95	[0.66; 1.36]	71.8%	35.8%
Alexander et al. 2001 / CARS		-			0.36	[0.17; 0.77]	16.3%	32.7%
Shlipak et al. 2001 / NRMI-3			<u></u>		- 6.39	[2.63; 15.52]	11.9%	31.5%
Fixed effect model		+			1.02	[0.75; 1.38]	100.0%	
Random effects model			1	-	1.26	[0.34; 4.64]		100.0%
Heterogeneity: $I^2 = 92\%$ , $\tau^2 = 1.2008$ , $p < 0.01$	l d	Į.	1	10				
	0.1 0.5	i 1	2	10				

# (b) women without diseases (relatively healthy)

Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
Wilson et al. 2019 / ALSWH	<del></del>	1.30	[1.13; 1.48]	6.2%	10.2%
Stram et al. 2011 / CTS		0.85	[0.81; 0.90]	34.2%	11.3%
Holm et al. 2019 / DCH		1.10	[1.04; 1.17]	34.7%	11.3%
Lokkegaard et al. 2003 (b) / DNS		0.95	[0.81; 1.11]	4.6%	9.8%
Tannen et al. 2007 / GPRD		0.68	[0.57; 0.81]	3.7%	9.4%
Weiner et al. 2008 / GPRD		0.75	[0.68; 0.84]	9.4%	10.6%
Su et al. 2012 / NHI	· · · · · · · · · · · · · · · · · · ·	0.70	[0.44; 1.09]	0.5%	4.5%
Graff-Iversen et al. 2004 / NR		0.88	[0.61; 1.26]	0.9%	5.9%
Pentti et al. 2006 / OSTPRE	÷++**	1.05	[0.86; 1.29]	2.8%	8.8%
Alexandersen et al. 2006 / PERF	s <del></del>	0.70	[0.51; 0.97]	1.1%	6.4%
Ryan et al. 2012 / TCS	8 <b></b> 13	0.87	[0.57; 1.35]	0.6%	4.8%
Crandall et al. 2018 / WHI-OS		0.78	[0.59; 1.04]	1.4%	7.1%
Fixed effect model	•	0.94	[0.91; 0.98]	100.0%	
Random effects model	-	0.89	[0.78: 1.01]		100.0%
Heterogeneity: $I^2 = 89\%$ , $\tau^2 = 0.0348$ , $p < 0.01$		1			
States in the st	0.5 1 2	2			

Supplementary Figure S4.1.6. MHT and all-cause death in observational studies: subgroup results by recency of MHT.

(a) past

Study	Summary	Estimates	SE	95%-CI	(fixed)	Weight (random)
Stram et al. 2011 / CTS			0.88	[0.83; 0.93]	65.6%	42.3%
Holm et al. 2019 / DCH	H		1.00	[0.92; 1.09]	27.0%	34.7%
Lokkegaard et al. 2003 (b) / DNS			0.98	[0.81; 1.19]	5.3%	15.4%
Ryan et al. 2012 / TCS		•	- 1.04	[0.77; 1.41]	2.2%	7.6%
Fixed effect model	-		0.92	[0.88; 0.96]	100.0%	
Random effects model			0.95	[0.86; 1.04]	<del></del>	100.0%
Heterogeneity: $I^2 = 58\%$ , $\tau^2 = 0.0043$ , $p = 0.07$						
	0.8	1 1.25				
(b) current						

Weight Weight Study Summary Estimates SE 95%-CI (fixed) (random) Stram et al. 2011 / CTS 64.3% 36.3% 0.83 [0.79; 0.87] Holm et al. 2019 / DCH 1.00 [0.93; 1.07] 31.1% 34.8% Lokkegaard et al. 2003 (b) / DNS 0.93 [0.77; 1.12] 4.1% 22.9% Ryan et al. 2012 / TCS 0.66 [0.39; 1.12] 0.5% 6.0% Fixed effect model 0.88 [0.85; 0.92] 100.0% Random effects model Heterogeneity:  $I^2$  = 86%,  $\tau^2$  = 0.0137, p < 0.01 0.90 [0.78; 1.03] 100.0% ---0.5 2 1

Supplementary Figure S4.1.7. MHT and all-cause death in observational studies: subgroup results by study design.

(a) cohort

					Weight	Weight
Study	Summary	Estimates	SE	95%-CI	(fixed)	(random)
Apostolakis et al. 2014 / AFFIRM			0.95	[0.66; 1.36]	0.8%	5.5%
Wilson et al. 2019 / ALSWH		*	1.30	[1.13; 1.48]	6.1%	9.0%
Alexander et al. 2001 / CARS			0.36	[0.17; 0.77]	0.2%	2.2%
Stram et al. 2011 / CTS	+		0.85	[0.81; 0.90]	33.8%	9.8%
Holm et al. 2019 / DCH		+	1.10	[1.04; 1.17]	34.3%	9.8%
Lokkegaard et al. 2003 (b) / DNS		-	0.95	[0.81; 1.11]	4.6%	8.7%
Tannen et al. 2007 / GPRD			0.68	[0.57; 0.81]	3.6%	8.4%
Weiner et al. 2008 / GPRD	<b>±</b>		0.75	[0.68; 0.84]	9.3%	9.3%
Su et al. 2012 / NHI			0.70	[0.44; 1.09]	0.5%	4.4%
Graff-Iversen et al. 2004 / NR		1	0.88	[0.61; 1.26]	0.9%	5.6%
Shlipak et al. 2001 / NRMI-3			6.39	[2.63; 15.52]	0.1%	1.7%
Pentti et al. 2006 / OSTPRE	<u>51</u> 51	-	1.05	[0.86; 1.29]	2.7%	8.0%
Alexandersen et al. 2006 / PERF	-+		0.70	[0.51; 0.97]	1.0%	6.1%
Ryan et al. 2012 / TCS			0.87	[0.57; 1.35]	0.6%	4.6%
Crandall et al. 2018 / WHI-OS			0.78	[0.59; 1.04]	1.3%	6.6%
Fixed effect model			0.95	[0.91; 0.98]	100.0%	
Random effects model	÷		0.90	[0.79; 1.02]		100.0%
Heterogeneity: $I^2 = 89\%$ , $\tau^2 = 0.0422$ , $p < 0.01$				and the second sec		
5 C S	0.1 0.5 1	2 10				

Supplementary Figure S4.1.8. MHT and all-cause death in observational studies: subgroup results by study quality.

(a) good and fair

Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
Wilson et al. 2019 / ALSWH		1.30	[1.13; 1.48]	6.2%	10.2%
Stram et al. 2011 / CTS		0.85	[0.81; 0.90]	34.2%	11.3%
Holm et al. 2019 / DCH		1.10	[1.04; 1.17]	34.7%	11.3%
Lokkegaard et al. 2003 (b) / DNS		0.95	[0.81; 1.11]	4.6%	9.8%
Tannen et al. 2007 / GPRD		0.68	[0.57; 0.81]	3.7%	9.4%
Weiner et al. 2008 / GPRD		0.75	[0.68; 0.84]	9.4%	10.6%
Su et al. 2012 / NHI	· · · · · · · · · · · · · · · · · · ·	0.70	[0.44; 1.09]	0.5%	4.5%
Graff-Iversen et al. 2004 / NR		0.88	[0.61; 1.26]	0.9%	5.9%
Pentti et al. 2006 / OSTPRE		1.05	[0.86; 1.29]	2.8%	8.8%
Alexandersen et al. 2006 / PERF	· · · · · · · · · · · · · · · · · · ·	0.70	[0.51; 0.97]	1.1%	6.4%
Ryan et al. 2012 / TCS		0.87	[0.57; 1.35]	0.6%	4.8%
Crandall et al. 2018 / WHI-OS		0.78	[0.59; 1.04]	1.4%	7.1%
Fixed effect model	•	0.94	[0.91; 0.98]	100.0%	
<b>Random effects model</b> Heterogeneity: $l^2 = 89\%$ , $\tau^2 = 0.0348$ , $p < 0.01$	-	0.89	[0.78; 1.01]		100.0%
	0.5 1	2			

(b) poor

Study	S	ummai	y I	stim	ates	SE	95%	∕₀-CI	Weight (fixed)	Weight (random)
Apostolakis et al. 2014 / AFFIRM		2	1			0.95	[0.66; 1	.36]	71.8%	35.8%
Alexander et al. 2001 / CARS	_		-			0.36	[0.17; 0	).77]	16.3%	32.7%
Shlipak et al. 2001 / NRMI-3				-		6.39	[2.63; 15	5.52]	11.9%	<mark>31.5</mark> %
Fixed effect model			+	-		1.02	[0.75; 1	.38]	100.0%	
Random effects model			-			1.26	[0.34; 4	.64]	044	100.0%
Heterogeneity: $l^2 = 92\%$ , $\tau^2 = 1.2008$ , $p < 0.01$			12				-	0.000		
	0.1	0.5	1	2	10					

Supplementary Figure S4.2.1. MHT and stroke in observational studies: subgroup results by regimen type.

(a) estrogen only

Study	Summary I	stimates	SE	95%-CI	Weight (fixed)	Weight (random)
Lokkegaard et al. 2017 / DaHoRS		1	1.12	[1.05; 1.19]	64.7%	22.4%
Lokkegaard et al. 2003 (a) / DNS			0.84	[0.42; 1.69]	0.5%	2.8%
Lemaitre et al. 2006 / GHC	-		0.88	[0.76; 1.01]	11.7%	18.1%
Renoux et al. 2008 / GPRD		<del>.</del>	1.26	[1.09; 1.45]	12.1%	18.2%
Chen et al. 2015 / NHI			0.34	[0.12; 0.97]	0.2%	1.4%
Su et al. 2012 / NHI	-4	-	0.97	[0.74; 1.28]	3.1%	11.0%
Bhupathiraiu et al. 2018 / NHS	-+	<u>11</u>	0.85	[0.56; 1.29]	1.4%	6.5%
Grodstein et al. 2000 / NHS		<b>-</b>	1.18	[0.95; 1.46]	5.2%	14.1%
Crandall et al. 2018 / WHI-OS			0.78	[0.49; 1.24]	1.1%	5.6%
Fixed effect model	•		1.09	[1.04; 1.14]	100.0%	
<b>Random effects model</b> Heterogeneity: $I^2 = 66\%$ , $\tau^2 = 0.0174$ , $p < 0.01$	<u>г</u> т 🛉		1.02	[0.90; 1.16]	See	100.0%
	0.2 0.5 1	2 5				

#### (b) combined EP

Study	Summary	/ Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
Lokkegaard et al. 2017 / DaHoRS		3	1.17	[1.03; 1.34]	23.4%	18.5%
Lokkegaard et al. 2003 (a) / DNS		++ +	1.55	[0.94; 2.56]	1.6%	11.1%
Lemaitre et al. 2006 / GHC		-	0.79	[0.66; 0.95]	12.8%	17.8%
Renoux et al. 2008 / GPRD			1.22	[1.11; 1.35]	43.8%	19.0%
Su et al. 2012 / NHI			0.62	[0.52; 0.74]	13.1%	17.8%
Grodstein et al. 2000 / NHS			1.45	[1.10; 1.92]	5.2%	15.8%
Fixed effect model		+	1.06	[1.00; 1.13]	100.0%	
<b>Random effects model</b> Heterogeneity: $l^2 = 92\%$ , $\tau^2 = 0.0863$ , $p < 0.01$			1.05	[0.81; 1.35]		100.0%
5, , , , , , , , , , , , , , , , , , ,	0.5	1 2	2			

Supplementary Figure S4.2.2. MHT and stroke in observational studies: subgroup results by duration of use.

(a) duration < 5 years

Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
Lokkegaard et al. 2017 / DaHoRS Bhupathiraiu et al. 2018 / NHS		1.11 0.85	[1.04; 1.19] [0.56; 1.29]	91.0% 2.2%	91.0% 2.2%
Grodstein et al. 2000 / NHS		1.16	[0.91; 1.47]	6.8%	6.8%
Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0$ , $p = 0.43$	0.75 1 1	1.11 1.11 .5	[1.04; 1.18] [1.04; 1.18]	100.0% 	 100.0%
(b) duration $\geq$ 5 years					
Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
Lokkegaard et al. 2017 / DaHoRS	-	· 1.23	[1.17; 1.30]	91.3%	89.2%
Grodstein et al. 2000 / NHS		1.12	[0.93; 1.34]	8.7%	10.8%
	5 I I I I I I I I I I I I I I I I I I I				
Fixed effect model		1.22	[1.16; 1.29]	100.0%	

Supplementary Figure S4.2.3. MHT and stroke in observational studies: subgroup results by timing of initiation.

(a) early users

Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
Canonico et al. 2016 / French NHI		1.13	[0.60; 2.13]	17.5%	20.0%
Sulet al 2012 / NHI		0.34	[0.12, 0.97]	0.3% 36.3%	8.2% 34.7%
Bhupathiraiu et al. 2018 / NHS	-	0.85	[0.56; 1.29]	39.9%	37.1%
Fixed effect model		0.81	[0.62; 1.06]	100.0%	
<b>Random effects model</b> Heterogeneity $l^2 = 22\%$ $\tau^2 = 0.0227$ $p = 0.28$		0.81	[0.59; 1.10]	876	100.0%
	0.2 0.5 1 2 5				

# (b) late users

Study		Sum	mary <mark>Es</mark> t	imates	SE	9	5%-CI	Weight (fixed)	Weight (random)
Apostolakis et al. 2014 / AFFIRM			+		0.78	[0.42;	1.43]	2.9%	12.7%
Lemaitre et al. 2006 / GHC			+		0.85	[0.75;	0.95]	77.0%	33.6%
Renoux et al. 2010 (a) / GPRD			21 <u>-</u>		1.12	[0.84;	1.50]	13.0%	25.4%
Shlipak et al. 2001 / NRMI-3			- i		- 14.60	[2.06; 1	03.64]	0.3%	1.8%
de Lecinana et al. 2007 / PIVE					0.62	[0.28;	1.35]	1.8%	9.0%
Crandall et al. 2018 / WHI-OS					0.78	[0.49;	1.24]	5.1%	17.5%
Fixed effect model					0.87	[0.79;	0.97]	100.0%	
Random effects model	27	25	•	25	0.91	[0.69;	1.19]		100.0%
Heterogeneity: $I^2 = 59\%$ , $\tau^2 = 0.0530$ , $p = 0.03$	L			1					
	0.01	0.1	1	10	100				

Supplementary Figure S4.2.4. MHT and stroke in observational studies: subgroup results by route of administration.

(a) oral

Study	Summary Est	imates	SE	95%-CI	Weight (fixed)	Weight (random)
Lokkegaard et al. 2017 / DaHoRS			1.19	[1.10; 1.30]	50.7%	37.5%
Canonico et al. 2016 / French NHI			1.58	[1.00; 2.49]	1.8%	5.2%
Renoux et al. 2010 (a) / GPRD	(		1.28	[1.15; 1.42]	34.3%	33.8%
Chen et al. 2015 / NHI			0.34	[0.12; 0.97]	0.3%	1.1%
Grodstein et al. 2000 / NHS	+		1.27	[1.07; 1.51]	12.8%	22.5%
Fixed effect model			1.23	[1.16; 1.31]	100.0%	
Random effects model	•		1.24	[1.11; 1.39]		100.0%
Heterogeneity: $I^2 = 51\%$ , $\tau^2 = 0.0065$ , $p = 0.09$		1 1				
	0.2 0.5 1	2 5				

(b) non-oral

Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
Lokkegaard et al. 2017 / DaHoRS Canonico et al. 2016 / French NHI Renoux et al. 2010 (a) / GPRD Bhupathiraiu et al. 2018 / NHS Crandall et al. 2018 / WHI-OS		0.84 0.83 0.95 0.85 0.78	[0.73; 0.96] [0.56; 1.24] [0.75; 1.20] [0.56; 1.29] [0.49; 1.24]	60.5% 7.0% 20.7% 6.5% 5.3%	60.5% 7.0% 20.7% 6.5% 5.3%
Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0$ , $p = 0.91$	0.5 1	0.86 0.86 2	[0.77; 0.96] [0.77; 0.96]	100.0% 	 100.0%

Supplementary Figure S4.2.5. MHT and stroke in observational studies: subgroup results by underlying disease.

### (a) women with diseases

Study		Sumn	nary Est	timates	SE	9	5%-CI	Weight (fixed)	Weight (random)
Apostolakis et al. 2014 / AFFIRM Chen et al. 2015 / NHI		_			0.78 0.34	[0.42; [0.12;	1.43] 0.97]	69.8% 23.5%	40.1% 35.4%
Shlipak et al. 2001 / NRMI-3			-			[2.06; 1	03.64]	6.7%	24.6%
Fixed effect model Random effects model Hatersconstby $l^2 = 92\%$ $c^2 = 1.2241$ , $p < 0.01$	<b></b>			<b>-</b> -	0.78 1.19	[0.47; [0.27;	1.30] 5.26]	100.0% 	 100.0%
Herefore $p = 02\%$ , $t = 1.3341$ , $p < 0.01$	0.01	0.1	1	10	100				

# (b) women without diseases (relatively healthy)

					Weight	Weight
Study	Summary	Estimates	SE	95%-CI	(fixed)	(random)
Lokkegaard et al. 2017 / DaHoRS	c.	<u>im</u> -	1.10	[0.97; 1.24]	19.6%	16.8%
Lokkegaard et al. 2003 (a) / DNS	1 <u></u>	<u>i</u>	1.16	[0.82; 1.65]	2.5%	7.9%
Canonico et al. 2016 / French NHI	<del></del>	<u>+</u> +	1.13	[0.60; 2.13]	0.8%	3.4%
Lemaitre et al. 2006 / GHC	-		0.85	[0.75; 0.95]	21.6%	17.1%
Renoux et al. 2008 / GPRD			1.22	[1.11; 1.35]	32.6%	18.0%
Su et al. 2012 / NHI			0.77	[0.49; 1.19]	1.6%	6.0%
Bhupathiraiu et al. 2018 / NHS	<del>- •</del>		0.85	[0.56; 1.29]	1.8%	6.4%
Grodstein et al. 2000 / NHS	-	-	1.08	[0.95; 1.23]	17.7%	16.5%
de Lecinana et al. 2007 / PIVE	· · · · ·		0.62	[0.28; 1.35]	0.5%	2.4%
Crandall et al. 2018 / WHI-OS			0.78	[0.49; 1.24]	1.4%	5.5%
Fixed effect model		•	1.05	[1.00; 1.11]	100.0%	
Random effects model			1.00	[0.88; 1.14]	:	100.0%
Heterogeneity: $I^{-} = 70\%$ , $\tau^{-} = 0.0211$ , $p < 0.01$						
	0.5	1 2				

Supplementary Figure S4.2.6. MHT and stroke in observational studies: subgroup results by recency of MHT.

(a) past

	Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
	Lokkegaard et al. 2017 / DaHoRS Lokkegaard et al. 2003 (a) / DNS		1.03	[0.99; 1.07] [0.65; 1.69]	95.7% 0.6%	95.7% 0.6%
	Grodstein et al. 2000 / NHS		1.02	[0.84; 1.24]	3.6%	3.6%
	Fixed effect model Random effects model Heterogeneity: $J^2 = 0\%$ , $\tau^2 = 0$ , $p = 0.99$	0.75 1 1.5	1.03 1.03	[0.99; 1.07] [0.99; 1.07]	100.0% 	 100.0%
(b) d	current					
	Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
	Lokkegaard et al. 2017 / DaHoRS		1.17	[1.12; 1.22]	93.9%	93.9%
	Grodstein et al. 2000 / NHS		1.13	[0.83; 1.92] [0.95; 1.35]	0.9% 5.2%	0.9% 5.2%
	Fixed effect model	•	1.17	[1.12; 1.22]	100.0%	
	Random effects model Heterogeneity: $l^2 = 0\%$ , $\tau^2 = 0$ , $p = 0.88$	<b>┌</b> ─┤ <b>◆</b>	1.17	[1.12; 1.22]	1.77	100.0%
		0.75 1 1.5				

Supplementary Figure S4.2.7. MHT and stroke in observational studies: subgroup results by study design.

(a) cohort

Study		Sumn	mary Estim	ates	SE	9	5%-CI	Weight (fixed)	Weight (random)
Apostolakis et al. 2014 / AFFIRM					0.78	[0.42;	1.43]	1.8%	6.0%
Lokkegaard et al. 2017 / DaHoRS			+		1.10	[0.97;	1.24]	42.9%	24.7%
Lokkegaard et al. 2003 (a) / DNS			-		1.16	[0.82;	1.65]	5.4%	12.7%
Chen et al. 2015 / NHI			+		0.34	[0.12;	0.97]	0.6%	2.4%
Su et al. 2012 / NHI			-++		0.77	[0.49;	1.19]	3.5%	9.8%
Bhupathiraiu et al. 2018 / NHS					0.85	[0.56;	1.29]	3.8%	10.4%
Grodstein et al. 2000 / NHS			+		1.08	[0.95;	1.23]	38.7%	24.3%
Shlipak et al. 2001 / NRMI-3				,	- 14.60	[2.06; 1	03.64]	0.2%	0.7%
Crandall et al. 2018 / WHI-OS			-+		0.78	[0.49;	1.24]	3.1%	9.0%
Fixed effect model			ļ.		1.05	[0.97;	1.14]	100.0%	
Random effects model Heterogeneity: $l^2 = 55\%$ , $\tau^2 = 0.0259$ , $p = 0.02$	r	1	<b>†</b>	Ţ	0.97	[0.82;	1.15]		100.0%
10000 gollowy. 1 0000, 1 00000, p = 0.02	0.01	0.1	1	10	100				

(b) case-control study

Study	Summary Estimate	s SE	95%-CI	Weight (fixed)	Weight (random)
Lemaitre et al. 2006 / GHC de Lecinana et al. 2007 / PIVE		0.85 0.62	[0.75; 0.95] [0.28; 1.35]	97.7% 2.3%	97.7% 2.3%
Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0$ , $p = 0.44$	0.5 1 2	0.84 0.84	[0.75; 0.94] [0.75; 0.94]	100.0% 	 100.0%

(c) nested case-control study

Study	Summar	y Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
Canonico et al. 2016 / French NHI Renoux et al. 2008 / GPRD		++		[0.60; 2.13] [1.11; 1.35]	2.3% 97.7%	2.3% 97.7%
Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0$ , $p = 0.82$	0.5	<b>*</b>	1.22	[1.11; 1.34] [1.11; 1.34]	100.0% 	 100.0%
	0.5	1	2			
Supplementary Figure S4.2.8. MHT and stroke in observational studies: subgroup results by study quality.

## (a) good and fair

Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
Lokkegaard et al. 2017 / DaHoRS	-	1.10	[0.97: 1.24]	19.6%	16.7%
Lokkegaard et al. 2003 (a) / DNS		1.16	[0.82; 1.65]	2.5%	8.3%
Canonico et al. 2016 / French NHI	: <u>i</u> ₊	1.13	[0.60; 2.13]	0.8%	3.7%
Lemaitre et al. 2006 / GHC		0.85	[0.75; 0.95]	21.7%	16.9%
Renoux et al. 2008 / GPRD	+	1.22	[1.11; 1.35]	32.7%	17.7%
Chen et al. 2015 / NHI	·	0.34	[0.12; 0.97]	0.3%	1.5%
Su et al. 2012 / NHI		0.77	[0.49; 1.19]	1.6%	6.3%
Bhupathiraiu et al. 2018 / NHS		0.85	[0.56; 1.29]	1.8%	6.7%
Grodstein et al. 2000 / NHS	÷	1.08	[0.95; 1.23]	17.7%	16.4%
Crandall et al. 2018 / WHI-OS		0.78	[0.49; 1.24]	1.4%	5.8%
Fixed effect model	•	1.05	[1.00; 1.11]	100.0%	
Random effects model	+	0.99	[0.87; 1.14]		100.0%
Heterogeneity: $I^2 = 72\%$ , $\tau^2 = 0.0240$ , $p < 0.01$					
	0.2 0.5 1 2 5				
(b) poor					
				Weight	Weight
Study	Summary Estimates	SE	95%-C	(fixed)	(random)
Apostolakis et al. 2014 / AFFIRM		0.78	[0.42; 1.43]	58.5%	41.5%
Shlipak et al. 2001 / NRMI-3		14.60	[2.06; 103.64]	5.6%	19.8%
de Lecinana et al. 2007 / PIVE		0.62	[0.28; 1.35]	35.8%	38.7%
Fixed effect model	+	0.85	[0.53; 1.35]	100.0%	

Fixed effect model Random effects model Heterogeneity:  $l^2 = 77\%$ ,  $\tau^2 = 0.7301$ , p = 0.010.01 0.1 1 10

Summary estimates (95% CI) were measured by fixed-effect models if  $l^2$  was <30% and P for heterogeneity was >0.05; otherwise, the summary estimates (95% CI) were measured by random-effect models. Forest and funnel plots were generated by "meta" package in R version 3.4.1. MHT, menopausal hormone therapy; SE, summary estimates.

100.0%

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1.27 [0.40; 4.02]

100

Supplementary Figure S4.3.1. MHT and VTE in observational studies: subgroup results by regimen type.

(a) estrogen only

Study	Summary	Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
Scarabin et al. 2003 / ESTHER	3 <del>1</del>	,	- 1.07	[0.36; 3.19]	1.9%	1.9%
Smith et al. 2004 / GHC		22	0.86	[0.71; 1.06]	56.4%	56.4%
Roach et al. 2013 / MEGA			0.60	[0.30; 1.20]	4.8%	4.8%
Sweetland et al. 2012 / MWS	8	<b>a</b>	1.09	[0.64; 1.87]	8.0%	8.0%
Lee et al. 2015 / NHI	17 <u>-</u>		1.29	[0.84; 1.98]	12.6%	12.6%
Bhupathiraiu et al. 2018 / NHS	3	a	1.06	[0.58; 1.93]	6.5%	6.5%
Douketis et al. 2005 / NR		•	1.22	[0.57; 2.61]	4.0%	4.0%
Crandall et al. 2018 / WHI-OS			0.68	[0.36; 1.28]	5.8%	5.8%
Fixed effect model	-	-	0.93	[0.79; 1.08]	100.0%	
Random effects model		-	0.93	[0.79; 1.08]		100.0%
Heterogeneity: $l^2 = 0\%$ , $\tau^2 = 0$ , $p = 0.51$						
	0.5	1 2				

*(b) combined EP* 

Study	Su	ımmar	y Es	timates	s SE	95%-C	Weight I (fixed)	Weight (random)
Scarabin et al. 2003 / ESTHER		1	-	-+	1.7	8 [0.46; 6.93	0.4%	5.9%
Smith et al. 2004 / GHC			-		1.1	5 [0.95; 1.38	] 22.3%	22.3%
Roach et al. 2013 / MEGA				H	+ 4.0	0 [1.95; 8.20	] 1.5%	12.8%
Sweetland et al. 2012 / MWS					2.0	7 [1.85; 2.32	59.3%	23.1%
Lee et al. 2015 / NHI					- 3.0	1 [2.39; 3.79	] 14.5%	21.7%
Douketis et al. 2005 / NR				++	- 2.7	0 [1.44; 5.07	] 1.9%	14.3%
Fixed effect model				•	1.9	5 [1.78; 2.12	] 100.0%	
Random effects model	_			-	2.2	1 [1.51; 3.22	]	100.0%
Heterogeneity: $I^2 = 90\%$ , $\tau^2 = 0.1586$ , $p < 0.01$					-			
	0.2	0.5	1	2	5			

Supplementary Figure S4.3.2. MHT and VTE in observational studies: subgroup results by duration of use.

(a) duration < 5 years

	Study	Summary	Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
	Scarabin et al. 2003 / ESTHER Roach et al. 2013 / MEGA Sweetland et al. 2012 / MWS	3 <u></u>		0.99	[0.48; 2.04] [1.02; 1.56] [0.74; 2.25]	6.2% 73.9% 10.7%	6.2% 73.9% 10.7%
	Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0$ , $p = 0.88$	0.5		1.06 1.23 1.23	[0.58; 1.93] [1.02; 1.47] [1.02; 1.47]	9.2% 100.0% 	9.2%  100.0%
(b) c	$luration \ge 5$ years						

Study	Sun	nmary Estimat	es	SE	95%-CI	(fixed)	(random)
Roach et al. 2013 / MEGA Sweetland et al. 2012 / MWS				1.12 1.40	[0.85; 1.48] [0.91; 2.15]	70.4% 29.6%	70.4% 29.6%
Fixed effect model Random effects model Heterogeneity: $l^2 = 0\%$ , $\tau^2 = 0$ , $p = 0.39$	0.5	1	2	1.19 1.19	[0.95; 1.51] [0.95; 1.51]	100.0% 	 100.0%

Supplementary Figure S4.3.3. MHT and VTE in observational studies: subgroup results by timing of initiation.

(a) early users

Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
Canonico et al. 2010 / E3N		1.36	[0.89; 2.09]	16.3%	16.8%
Roach et al. 2013 / MEGA		1.41	[0.92; 2.15]	16.5%	17.0%
Sweetland et al. 2012 / MWS		1.23	[0.74; 2.04]	11.6%	13.2%
Lee et al. 2015 / NHI		1.80	[1.27; 2.54]	24.8%	22.0%
Bhupathiraiu et al. 2018 / NHS		1.06	[0.58; 1.93]	8.2%	10.1%
Bergendal et al. 2012 / THES		- 2.22	[1.54; 3.19]	22.5%	20.8%
Fixed effect model	-	1.59	[1.33; 1.88]	100.0%	
Random effects model		1.55	[1.26; 1.92]		100.0%
Heterogeneity: $I^2 = 31\%$ , $\tau^2 = 0.0217$ , $p = 0.20$	1 1				
	0.5 1 2				

(b) late users

Study	Summary	/ Estimates	s SE	95%-CI	Weight (fixed)	Weight (random)
Canonico et al. 2007 / ESTHER			1.2	4 [1.01; 1.53]	20.9%	21.5%
Smith et al. 2004 / GHC			1.0	0 [0.86; 1.16]	38.3%	22.1%
Renoux et al. 2010 (b) / GPRD			1.3	4 [1.03; 1.73]	13.4%	20.7%
Lee et al. 2015 / NHI			2.3	9 [1.98; 2.88]	25.3%	21.7%
Crandall et al. 2018 / WHI-OS			0.6	3 [0.36; 1.28]	2.2%	14.0%
Fixed effect model		-	1.3	4 [1.22; 1.47]	100.0%	
Random effects model			1.2	7 [0.87; 1.86]		100.0%
Heterogeneity: $I^2 = 93\%$ , $\tau^2 = 0.1652$ , $p < 0.01$						
	0.5	1	2			

Supplementary Figure S4.3.4. MHT and VTE in observational studies: subgroup results by route of administration.

(a) oral

Study	Summ	ary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
Canonico et al. 2010 / E3N		<u> </u>	1.7	0 [1.03; 2.80]	0.6%	7.5%
Canonico et al. 2007 / ESTHER			4.2	0 [1.52; 11.60]	0.2%	2.5%
Smith et al. 2004 / GHC		+	1.0	0 [0.86; 1.16]	7.0%	18.0%
Renoux et al. 2010 (b) / GPRD		+	1.3	5 [1.31; 1.42]	86.6%	20.7%
Ohira et al. 2010 / LITE		-	1.3	2 [0.89; 1.95]	1.0%	9.9%
Roach et al. 2013 / MEGA		- <u></u>	1.7	0 [1.16; 2.50]	1.1%	10.1%
Sweetland et al. 2012 / MWS		- <del></del>	1.7	2 [1.19; 2.49]	1.2%	10.6%
Lee et al. 2015 / NHI		<del>         </del>	1.8	0 [1.27; 2.54]	1.3%	11.2%
Douketis et al. 2005 / NR			0.9	9 [0.66; 1.48]	<mark>1.0%</mark>	9.6%
Fixed effect model			1.3	4 [1.29; 1.40]	100.0%	
Random effects model		•	1.4	1 [1.19; 1.67]		100.0%
Heterogeneity: $I^2 = 72\%$ , $\tau^2 = 0.0360$ , $p < 0.01$	1 1	1 1	2			
	0.1 0.	5 <mark>1 2</mark>	10			

(b) non-oral

Study	Sum	imary Estima	ates	SE	95%-CI	Weight (fixed)	Weight (random)
Canonico et al. 2007 / ESTHER				0.90	[0.39; 2.10]	1.4%	8.3%
Renoux et al. 2010 (b) / GPRD				1.00	[0.89; 1.12]	73.0%	25.1%
Roach et al. 2013 / MEGA				1.10	[0.67; 1.80]	4.2%	15.1%
Sweetland et al. 2012 / MWS		-		0.82	[0.63; 1.06]	15.3%	21.8%
Bhupathiraiu et al. 2018 / NHS				1.06	[0.58; 1.93]	2.8%	12.6%
Douketis et al. 2005 / NR	· · ·	-		0.08	[0.03; 0.26]	0.8%	5.2%
Crandall et al. 2018 / WHI-OS				0.68	[0.36; 1.28]	2.5%	11.9%
Fixed effect model		+		0.94	[0.85; 1.04]	100.0%	-
<b>Random effects model</b> Heterogeneity: $l^2 = 71\%$ , $\tau^2 = 0.0871$ , $p < 0.01$	Ē			0.81	[0.60; 1.09]		100.0%
	0.1	0.5 1 2	10				

Supplementary Figure S4.3.5. MHT and VTE in observational studies: subgroup results by underlying disease.

(a) women without diseases (relatively healthy)

Study	Summary	Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
Canonico et al. 2010 / E3N		<u>+</u>	1.21	[0.96; 1.52]	13.0%	11.4%
Canonico et al. 2007 / ESTHER			1.24	[1.01; 1.53]	16.7%	12.1%
Smith et al. 2004 / GHC	-		1.00	[0.86; 1.16]	30.6%	13.3%
Renoux et al. 2010 (b) / GPRD			1.34	[1.03; 1.73]	10.7%	10.8%
Ohira et al. 2010 / LITE	3 <del>.</del>	+ 10	1.32	[0.89; 1.95]	4.5%	7.7%
Roach et al. 2013 / MEGA	82 <u>-</u>		1.41	[0.92; 2.15]	3.9%	7.2%
Sweetland et al. 2012 / MWS	10	+	1.23	[0.74; 2.04]	2.8%	5.8%
Lee et al. 2015 / NHI			1.80	[1.27; 2.54]	5.9%	8.7%
Bhupathiraiu et al. 2018 / NHS	5		1.06	[0.58; 1.93]	2.0%	4.7%
Douketis et al. 2005 / NR			- 1.93	[1.16; 3.22]	2.7%	5.7%
Bergendal et al. 2012 / THES			- 2.22	[1.54; 3.19]	5.4%	8.3%
Crandall et al. 2018 / WHI-OS			0.68	[0.36; 1.28]	1.8%	4.3%
Fixed effect model		•	1.24	[1.14; 1.34]	100.0%	
Random effects model		-	1.32	[1.13; 1.54]		100.0%
Heterogeneity: $l^2 = 63\%$ , $\tau^2 = 0.0409$ , $p < 0.01$	I					
	0.5	1 2				

Supplementary Figure S4.3.6. MHT and VTE in observational studies: subgroup results by recency of MHT.

(a) past

Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
Canonico et al. 2010 / E3N	· · · · · ·	1.10	[0.81; 1.50]	4.4%	9.2%
Canonico et al. 2007 / ESTHER	· · · · · · · · · · · · · · · · · · ·	1.07	[0.79; 1.46]	4.4%	9.3%
Renoux et al. 2010 (b) / GPRD		1.17	[1.08; 1.27]	62.3%	42.9%
Ohira et al. 2010 / LITE		1.07	[0.71; 1.62]	2.4%	5.5%
Sweetland et al. 2012 / MWS		0.95	[0.84; 1.08]	25.5%	30.7%
Douketis et al. 2005 / NR		— 1.02	[0.54; 1.93]	1.0%	2.5%
Fixed effect model	+	1.10	[1.03; 1.17]	100.0%	
Random effects model		1.07	[0.97; 1.19]		100.0%
Heterogeneity: $I^2 = 31\%$ , $\tau^2 = 0.0046$ , $p = 0.20$					
	0.75 1 1.5				
(b) current					

Weight Weight 95%-CI (fixed) (random) Study Summary Estimates SE Canonico et al. 2010 / E3N 1.36 [0.89; 2.09] 1.2% 1.2% Canonico et al. 2007 / ESTHER 1.31 [1.06; 1.63] 4.8% 4.8% 1.52 [1.44; 1.61] 1.60 [1.08; 2.36] Renoux et al. 2010 (b) / GPRD 67.0% 67.0% 1.5% Ohira et al. 2010 / LITE 1.5% Sweetland et al. 2012 / MWS 1.59 [1.44; 1.75] 24.1% 24.1% 1.36 [0.91; 2.02] Douketis et al. 2005 / NR 1.4% 1.4% Fixed effect model 1.52 [1.45; 1.60] 100.0% ÷ Random effects model 1.52 [1.45; 1.60] 100.0% ---Г Heterogeneity:  $I^2 = 0\%$ ,  $\tau^2 = 0$ , p = 0.660.5 1 2

Supplementary Figure S4.3.7. MHT and VTE in observational studies: subgroup results by study design.

(a) cohort

Study		Summary	/ Estimat	es	SE	95%-CI	Weight (fixed)	Weight (random)
Canonico et al. 2010 / E3N	e:				1.21	[0.96; 1.52]	43.5%	29.4%
Ohira et al. 2010 / LITE			<u> </u>		1.32	[0.89; 1.95]	15.1%	17.8%
Sweetland et al. 2012 / MWS	92		- 10	<u> </u>	1.23	[0.74; 2.04]	9.2%	12.9%
Lee et al. 2015 / NHI				-	1.80	[1.27; 2.54]	19.7%	20.7%
Bhupathiraiu et al. 2018 / NHS		26			1.06	[0.58; 1.93]	6.5%	10.0%
Crandall et al. 2018 / WHI-OS	61	*			0.68	[0.36; 1.28]	5.9%	9.1%
Fixed effect model			-		1.27	[1.09; 1.48]	100.0%	
Random effects model		a <u></u>	-	_	1.25	[1.01; 1.55]	442	100.0%
Heterogeneity: $I^2 = 39\%$ , $\tau^2 = 0.0266$ , $p = 0.15$		0.5		0				
		0.5	1	2				

(b) case-control study

Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
Canonico et al. 2007 / ESTHER		24	[1.01; 1.53]	28.2%	23.9%
Smith et al. 2004 / GHC		00	[0.86; 1.16]	51.6%	25.2%
Roach et al. 2013 / MEGA		41	[0.92, 2.15]	0.0%	17.2%
Douketis et al. 2005 / NR	1	93	[1.16; 3.22]	4.5%	14.1%
Bergendal et al. 2012 / THES	2	22	[1.54; 3.19]	9.0%	19.0%
Fixed effect model	+ 1	20	[1.08; 1.34]	100.0%	
<b>Random effects model</b> Heterogeneity: $I^2 = 81\%$ , $\tau^2 = 0.0810$ , $p < 0.01$		43	[1.07; 1.91]		100.0%

(b) nested case-control study

Study	Summary Estimates	SE	95%-CI
Renoux et al. 2010 (b) / GPRD		1.34	[1.03; 1.73]
	0.75 1 1	.5	

Supplementary Figure S4.3.8. MHT and VTE in observational studies: subgroup results by study quality.

## (a) good and fair

Study	Summary	Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
Canonico et al. 2010 / E3N			1.21	[0.96; 1.52]	14.0%	13.1%
Canonico et al. 2007 / ESTHER			1.24	[1.01; 1.53]	17.9%	13.8%
Smith et al. 2004 / GHC	-		1.00	[0.86; 1.16]	32.8%	15.3%
Renoux et al. 2010 (b) / GPRD			1.34	[1.03; 1.73]	11.5%	12.4%
Ohira et al. 2010 / LITE	8 <del></del>		1.32	[0.89; 1.95]	4.9%	8.8%
Sweetland et al. 2012 / MWS	·		1.23	[0.74; 2.04]	3.0%	6.7%
Lee et al. 2015 / NHI		-	1.80	[1.27; 2.54]	6.3%	10.0%
Bhupathiraiu et al. 2018 / NHS		*	1.06	[0.58; 1.93]	2.1%	5.4%
Bergendal et al. 2012 / THES			- 2.22	[1.54; 3.19]	5.7%	9.6%
Crandall et al. 2018 / WHI-OS	. <b>.</b>		0.68	[0.36; 1.28]	1.9%	5.0%
Fixed effect model		•	1.21	[1.11; 1.32]	100.0%	
Random effects model Heterogeneity: $I^2 = 66\%$ , $\tau^2 = 0.0415$ , $p < 0.01$	[	-	1.28	[1.08; 1.51]		100.0%
	0.5	1 2				

(b) poor

Study	Summ	ary Esti	mates	SE	95%-CI	Weight (fixed)	Weight (random)
Roach et al. 2013 / MEGA Douketis et al. 2005 / NR		-		1.41 — 1.93	[0.92; 2.15] [1.16; 3.22]	59.4% 40.6%	59.4% 40.6%
Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0$ , $p = 0.35$	0.5	 	2	1.60 1.60	[1.15; 2.22] [1.15; 2.22]	100.0%	 100.0%

Supplementary Figure S4.4.1. MHT and MI in observational studies: subgroup results by regimen type.

(a) estrogen only

Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
Lokkegaard et al. 2008 / DaHoRS		0.94	[0.83; 1.06]	33.2%	33.2%
Lokkegaard et al. 2003 (b) / DNS		0.97	[0.49; 1.93]	1.0%	1.0%
Lemaitre et al. 2006 / GHC		0.79	[0.70; 0.89]	32.1%	32.1%
Kim et al. 2006 / GPRD		0.79	[0.65; 0.96]	12.6%	12.6%
Ferrara et al. 2003 / KPMCP		0.88	[0.72; 1.07]	12.5%	12.5%
Su et al. 2012 / NHI		0.69	[0.31; 1.52]	0.8%	0.8%
Bhupathiraiu et al. 2018 / NHS		0.73	[0.47; 1.13]	2.5%	2.5%
Chilvers et al. 2003 / NR		0.82	[0.53; 1.28]	2.4%	2.4%
Petitti et al. 2000 / NR		0.80	[0.53; 1.20]	2.9%	2.9%
Fixed effect model	+	0.85	[0.79; 0.91]	100.0%	
Random effects model	÷	0.85	[0.79; 0.91]		100.0%
Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0$ , $p = 0.67$			•		
terrene and the second s	0.5 1 2				

## *(b) combined EP*

Study	Summary	Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
Lokkegaard et al. 2008 / DaHoRS	ţ —	-	1.10	[0.83; 1.47]	9.3%	11.3%
Lokkegaard et al. 2003 (b) / DNS			- 1.09	[0.54; 2.21]	1.6%	2.2%
Lemaitre et al. 2006 / GHC			0.76	[0.65; 0.88]	34.2%	28.2%
Kim et al. 2006 / GPRD			0.73	[0.62; 0.86]	29.0%	25.6%
Ferrara et al. 2003 / KPMCP		5	0.76	[0.58; 0.99]	11.1%	13.1%
Su et al. 2012 / NHI			0.76	[0.50; 1.16]	4.4%	5.8%
Chilvers et al. 2003 / NR	—	<u>2 - 0</u> 2	0.76	[0.53; 1.10]	5.7%	7.4%
Petitti et al. 2000 / NR			0.60	[0.40; 0.90]	4.7%	6.3%
Fixed effect model	+		0.77	[0.71; 0.84]	100.0%	
Random effects model Haterageneity $l^2 = 20\%$ $r^2 = 0.0047$ $p = 0.27$	· · ·		0.78	[0.70; 0.87]		100.0%
neterogeneity. $I = 20\%, \tau = 0.004I, p = 0.2I$	0.5	1 2				

Supplementary Figure S4.4.2. MHT and MI in observational studies: subgroup results by duration of use.

(a) duration < 5 years

Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
Bhupathiraiu et al. 2018 / NHS		0.73	[0.47; 1.13]	24.5%	24.5%
Chilvers et al. 2003 / NR		0.97	[0.71; 1.32]	49.3%	49.3%
Carrasquilla et al. 2015 / SHEEP		0.97	[0.64; 1.48]	26.2%	26.2%
Fixed effect model		0.91	[0.73; 1.12]	100.0%	
Random effects model		0.91	[0.73; 1.12]		100.0%
Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0$ , $p = 0.54$	k k	20			
	0.5 1	2			
(b) duration $\geq$ 5 years					
				Weight	Weight
Study	Summary Estimates	SE	95%-CI	(fixed)	(random)
Chilvers et al. 2003 / NR		0.42	[0.24; 0.73]	55.1%	55.0%
Carrasquilla et al. 2015 / SHEEP		0.64	[0.35; 1.18]	44.9%	45.0%
Fixed effect model	-	0.51	[0.34; 0.76]	100.0%	
Random effects model		0.51	[0.34; 0.77]		100.0%
Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0.0002$ . $p = 0.32$			150 C		
	0.5 1 2				

Supplementary Figure S4.4.3. MHT and MI in observational studies: subgroup results by timing of initiation.

(a) early users

Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
Su et al. 2012 / NHI Bhupathiraiu et al. 2018 / NHS Carrasquilla et al. 2015 / SHEEP		0.74 0.73 0.87	[0.51; 1.08] [0.47; 1.13] [0.58; 1.30]	38.6% 28.1% 33.3%	38.6% 28.1% 33.3%
Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0$ , $p = 0.80$	0.5 1	0.78 0.78	[0.62; 0.98] [0.62; 0.98]	100.0% 	 100.0%
(b) late users					
Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
Lemaitre et al. 2006 / GHC Kim et al. 2006 / GPRD Ferrara et al. 2003 / KPMCP Carrasquilla et al. 2015 / SHEEP		0.78 0.76 0.84 - 0.97	[0.70; 0.86] [0.67; 0.86] [0.72; 0.98] [0.53; 1.76]	47.6% 31.1% 20.0% 1.3%	47.6% 31.1% 20.0% 1.3%
Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0$ , $p = 0.68$	0.75 1 1.5	0.79 0.79	[0.73; 0.84] [0.73; 0.84]	100.0% 	 100.0%

Supplementary Figure S4.4.4. MHT and MI in observational studies: subgroup results by route of administration.

(a) oral

Study	5	Summary Estimates	S	E 95%-CI	Weight (fixed)	Weight (random)
Lokkegaard et al. 2008 / DaHoRS Chilvers et al. 2003 / NR	÷	•	1.0 0.6	4 [0.97; 1.13] 8 [0.49; 0.95]	94.8% 5.2%	57.5% 42.5%
Fixed effect model Random effects model Heterogeneity: $I^2 = 83\%$ , $\tau^2 = 0.0767$ , $p = 0.01$	0.5		1.0 0.8 2	2 [0.95; 1.10] 7 [0.57; 1.32]	100.0% 	 100.0%
(b) non-oral						
Study	S	Summary Estimates	s	E 95%-CI	Weight (fixed)	Weight (random)
Lokkegaard et al. 2008 / DaHoRS Bhupathiraiu et al. 2018 / NHS Chilvers et al. 2003 / NR	3	*	0.6 0.7 0.9	7 [0.49; 0.91] 3 [0.47; 1.13] 5 [0.61; 1.46]	49.9% 25.0% 25.1%	49.9% 25.0% 25.1%
Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0$ , $p = 0.45$	0.5	÷	0.7	5 [0.60; 0.93] 5 [0.60; 0.93]	100.0% 	 100.0%

Supplementary Figure S4.4.5. MHT and MI in observational studies: subgroup results by underlying disease.

(a) women with diseases

Study	Summary Estimate	s	SE	95%-CI
Ferrara et al. 2003 / KPMCP		_	0.84 [	0.72; 0.98]
	0.8 1	1.25		

## (b) women without diseases (relatively healthy)

Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
Lokkegaard et al. 2008 / DaHoRS	+	0.92	[0.73; 1.16]	7.8%	7.8%
Lokkegaard et al. 2003 (b) / DNS		0.95	[0.63; 1.44]	2.5%	2.5%
Lemaitre et al. 2006 / GHC		0.78	[0.70; 0.86]	43.0%	43.0%
Kim et al. 2006 / GPRD		0.76	[0.67; 0.86]	28.1%	28.1%
Su et al. 2012 / NHI		0.74	[0.51; 1.08]	3.1%	3.1%
Bhupathiraiu et al. 2018 / NHS		0.73	[0.47; 1.13]	2.2%	2.2%
Chilvers et al. 2003 / NR		0.74	[0.55; 0.99]	5.1%	5.1%
Petitti et al. 2000 / NR		0.80	[0.59; 1.07]	4.9%	4.9%
Carrasquilla et al. 2015 / SHEEP		0.89	[0.62; 1.27]	3.4%	3.4%
Fixed effect model	. ↓	0.79	[0.74; 0.84]	100.0%	
Random effects model Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0$ , $p = 0.88$	· •	0.79	[0.74; 0.84]	-	<mark>100.0%</mark>
3	0.5 1	2			

Supplementary Figure S4.4.6. MHT and MI in observational studies: subgroup results by recency of MHT.

(a) past

Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
Lokkegaard et al. 2008 / DaHoRS		0.81	[0.71; 0.93]	75.9%	75.9%
Lokkegaard et al. 2003 (b) / DNS		- 0.93	[0.54; 1.60]	4.9%	4.9%
Chilvers et al. 2003 / NR		0.89	[0.55; 1.44]	6.3%	6.3%
Petitti et al. 2000 / NR		1.00	[0.71; 1.40]	12.8%	12.8%
Fixed effect model		0.84	[0.75; 0.95]	100.0%	
Random effects model		0.84	[0.75; 0.95]		100.0%
Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0$ , $p = 0.68$	li di li				
	0.75 1 1.5	i.			
(b) current					
				Weight	Weight
Study	Summary Estimates	SE	95%-CI	(fixed)	(random)
Lokkegaard et al. 2008 / DaHoRS		1.03	[0.96; 1.11]	90.1%	35.6%
Lokkegaard et al. 2003 (b) / DNS	· · · · · · · · · · · · · · · · · · ·	0.97	[0.57: 1.65]	1.8%	17.8%
Chilvers et al. 2003 / NR	· • •	0.53	[0.32: 0.88]	2.0%	18.7%
Petitti et al. 2000 / NR		0.69	[0.52; 0.92]	6.1%	27.9%
Fixed effect model	4	0.99	[0.92; 1.06]	100.0%	
Random effects model		0.81	[0.59; 1.10]	1000	100.0%
Heterogeneity: $l^2 = 77\%$ , $\tau^2 = 0.0706$ , $p < 0.01$					

Summary estimates (95% CI) were measured by fixed-effect models if  $l^2$  was <30% and P for heterogeneity was >0.05; otherwise, the summary estimates (95% CI) were measured by random-effect models. Forest and funnel plots were generated by "meta" package in R version 3.4.1. MHT, menopausal hormone therapy; MI, myocardial infarction; SE, summary estimates.

1 2

0.5

Supplementary Figure S4.4.7. MHT and MI in observational studies: subgroup results by study design.

(a) cohort

Study	Summary E	Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
Lokkegaard et al. 2008 / DaHoRS			0.92	[0.73; 1.16]	23.1%	23.1%
Lokkegaard et al. 2003 (b) / DNS			0.95	[0.63; 1.44]	7.4%	7.4%
Ferrara et al. 2003 / KPMCP			0.84	[0.72; 0.98]	53.7%	53.7%
Su et al. 2012 / NHI		-	0.74	[0.51; 1.08]	9.2%	9.2%
Bhupathiraiu et al. 2018 / NHS			0.73	[0.47; 1.13]	6.7%	6.7%
Fixed effect model	+		0.85	[0.76; 0.95]	100.0%	122
Random effects model Heterogeneity: $l^2 = 0\%$ , $\tau^2 = 0$ , $p = 0.79$	· · · ·		0.85	[0.76; 0.95]	8.57	100.0%
1000000000000000000000000000000000000	0.5 1	2				
(b) case-control study						
Study	Summary E	stimates	SE	95%-CI	Weight (fixed)	Weight (random)
<b>-</b>	-		925 254		1	

Study	Summary Estimates	SE	95%-CI	(fixed)	(random)
Lemaitre et al. 2006 / GHC		0.78	[0.70; 0.86]	50.9%	50.9%
Kim et al. 2006 / GPRD		0.76	[0.67; 0.86]	33.3%	33.3%
Chilvers et al. 2003 / NR		0.74	[0.55; 0.99]	6.0%	6.0%
Petitti et al. 2000 / NR		0.80	[0.59; 1.07]	5.8%	5.8%
Carrasquilla et al. 2015 / SHEEP		0.89	[0.62; 1.27]	4.0%	4.0%
Fixed effect model	+	0.77	[0.72; 0.83]	100.0%	1122
Random effects model	÷	0.77	[0.72; 0.83]		100.0%
Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0$ , $p = 0.94$					
	0.75 1 1.5				

Supplementary Figure S4.4.8. MHT and MI in observational studies: subgroup results by study quality.

(a) good and fair

Study	Summary Estimates	SE	95%-CI	Weight (fixed)	Weight (random)
Lokkegaard et al. 2008 / DaHoRS		0.92	2 [0.73; 1.16]	8.5%	8.5%
Lokkegaard et al. 2003 (b) / DNS		0.95	5 [0.63; 1.44]	2.7%	2.7%
Lemaitre et al. 2006 / GHC	-	0.78	8 [0.70; 0.86]	46.9%	46.9%
Kim et al. 2006 / GPRD		0.76	6 [0.67; 0.86]	30.6%	30.6%
Su et al. 2012 / NHI		0.74	[0.51; 1.08]	3.4%	3.4%
Bhupathiraiu et al. 2018 / NHS		0.73	3 [0.47; 1.13]	2.5%	2.5%
Chilvers et al. 2003 / NR		0.74	[0.55; 0.99]	5.5%	5.5%
Fixed effect model	. ↓	0.78	8 [0.73; 0.84]	100.0%	
<b>Random effects model</b> Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0$ , $p = 0.78$	. ◆	0.78	8 [0.73; 0.84]		100.0%
	0.5 1	2			

(b) poor

Study	Summary Estim	nates SE	95%-CI	Weight (fixed)	Weight (random)
Ferrara et al. 2003 / KPMCP Petitti et al. 2000 / NR		0.84 0.80	[0.72; 0.98]	68.5% 18.6%	68.5% 18.6%
Carrasquilla et al. 2015 / SHEEP		- 0.89	[0.62; 1.27]	12.9%	12.9%
Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0$ , $p = 0.89$		0.84 0.84	[0.74; 0.95] [0.74; 0.95]	100.0% 	 100.0%
	0.75 1	1.5			