

# Supplementary Material

## Association Between Menopausal Hormone Therapy and Risk for Parkinson's Disease

**Supplementary Table 1.** Comparison of characteristics of women in MHT and non-MHT groups in the study before propensity score matching.

	Non-MHT	MHT	Total	<i>p</i>	Standardized mean difference	Missing, %
Number of participants	197,741	158,368	356,109			
Median age (y)	52 [49–57]	50 [48–53]	51 [48–55]	<0.001	0.445	
Follow-up period (y)	8 [6.9–9]	8 [6.9–8.9]	8 [6.9–9]	0.001	0.032	
Calendar year at inclusion				<0.001	0.042	0
2011	56,284 (28.5)	42,166 (26.6)	98,450 (27.6)			
2012	52,218 (26.4)	42,371 (26.8)	94,589 (26.6)			
2013	46,546 (30)	38,433 (31.3)	84,979 (30.6)			
2014	42,693 (21.6)	35,398 (22.4)	78,091 (21.9)			
Age at inclusion (y)				<0.001	0.442	0
40~49	62,298 (31.5)	66,259 (41.8)	128,557 (36.1)			
50~59	99,637 (50.4)	84,460 (53.3)	184,097 (51.7)			
60~69	33,651 (17.2)	7,508 (4.7)	41,159 (11.6)			
70~	2,155 (1.1)	141 (0.1)	2,296 (0.6)			
SES				<0.001	0.022	0
Mid~high SES	192,831 (97.5)	153,870 (97.2)	346,701 (97.4)			
Low SES	4,910 (2.5)	4,498 (2.8)	9,408 (2.6)			
Region				<0.001	0.024	0
Urban area	99,333 (50.2)	77,684 (49.1)	177,017 (49.7)			
Rural area	98,408 (49.8)	80,684 (50.9)	179,092 (50.3)			
CCI				<0.001	0.022	0
0	140,077 (70.8)	111,142 (70.2)	251,219 (70.5)			
1	35,268 (17.8)	29,573 (18.7)	64,841 (18.2)			
≥2	22,396 (11.3)	17,653 (11.1)	40,049 (11.2)			
Hypertension				<0.001	0.105	0

No	144,203 (72.9)	122,655 (77.4)	266,858 (74.9)			
Yes	53,538 (27.1)	35,713 (22.6)	89,251 (25.1)			
DM				<0.001	0.073	0
No	170,319 (86.1)	140,270 (88.6)	310,589 (87.2)			
Yes	27,422 (13.9)	18,098 (11.4)	45,520 (12.8)			
Dyslipidemia				<0.001	0.057	0
No	136,165 (68.9)	113,179 (71.5)	249,344 (70)			
Yes	61,576 (31.1)	45,189 (28.5)	106,765 (30)			
Uterine fibroids				<0.001	0.11	0
No	170,275 (86.1)	130,013 (82.1)	300,288 (84.3)			
Yes	27,466 (13.9)	28,355 (17.9)	55,821 (15.7)			
Endometriosis				<0.001	0.102	0
No	190,977 (96.6)	149,615 (94.5)	340,592 (95.6)			
Yes	6,764 (3.4)	8,753 (5.5)	15,517 (4.4)			
Previous hysterectomy				<0.001	0.179	0
No	191,636 (96.9)	147,316 (93)	338,952 (95.2)			
Yes	6,105 (3.1)	11,052 (7)	17,157 (4.8)			
Previous adnexal surgery				<0.001	0.121	0
No	194,654 (98.4)	152,909 (96.6)	347,563 (97.6)			
Yes	3,087 (1.6)	5,459 (3.4)	8,546 (2.4)			

CCI, Charlson comorbidity index; DM, diabetes mellitus; MHT, menopausal hormone therapy; SES, socioeconomic status  
The data are presented as either percentages (in parentheses) or as medians with interquartile ranges [25th percentile, 75th percentile].

**Supplementary Table 2.** Comparison of characteristics of women in MHT (detailed MHT) and non-MHT groups in the study after propensity score matching.

	Non-MHT	Tibolone	E+P	E alone	Total	<i>p</i>	Missing, %
Number of participants	151,630	71,499	64,555	15,576	303,260		
Median age (y)	51 [48-54]	51 [48-54]	50 [47-52]	51 [48-53]	50 [48-54]	<0.001	
Calendar year at inclusion						<0.001	0
2011	40,849 (26.9)	18,543 (25.9)	17,567 (27.2)	4,498 (28.9)	81,457 (26.9)		
2012	40,217 (26.5)	18,957 (26.5)	17,426 (27.0)	4,191 (26.9)	80,791 (26.6)		
2013	36,653 (31.1)	17,550 (24.5)	15,588 (24.1)	3,668 (29.7)	73,459 (31.2)		
2014	33,911 (22.4)	16,449 (23.0)	13,974 (21.6)	3,219 (20.7)	67,553 (22.3)		
Age at inclusion (y)						<0.001	0
40~49	62,012 (40.9)	24,536 (34.3)	31,306 (48.5)	5,834 (37.5)	123,688 (40.8)		
50~59	81,867 (54)	42,092 (58.9)	31,425 (48.7)	8,790 (56.4)	164,174 (54.1)		
60~69	7,611 (5)	4,794 (6.7)	1,787 (2.8)	925 (5.9)	15,117 (5.0)		
70~	140 (0.1)	77 (0.1)	37 (0.1)	27 (0.2)	281 (0.1)		
SES						<0.001	0
Mid~high SES	147,677 (97.4)	69,354 (97.0)	63,022 (97.6)	15,207 (97.6)	295,260 (97.4)		
Low SES	3,953 (2.6)	2,145 (3.0)	1,533 (2.4)	369 (2.4)	8,000 (2.6)		
Region						<0.001	0
Urban area	74,750 (49.3)	35,272 (49.3)	31,092 (48.2)	7,819 (50.2)	148,933 (49.1)		
Rural area	76,880 (50.7)	36,227 (50.7)	33,463 (51.8)	7,757 (49.8)	154,327 (50.9)		
CCI						<0.001	0
0	108,130 (71.3)	49,379 (69.1)	46,903 (72.7)	10,854 (69.7)	215,266 (71.0)		
1	27,030 (17.8)	13,736 (19.2)	11,441 (17.7)	2,805 (18.0)	55,012 (18.1)		
≥2	16,470 (10.9)	8,384 (11.7)	6,211 (9.6)	1,917 (12.3)	32,982 (10.9)		
Hypertension						<0.001	0
No	117,981 (77.8)	53,159 (74.3)	52,543 (81.4)	11,595 (74.4)	235,278 (77.6)		
Yes	33,649 (22.2)	18,340 (25.7)	12,012 (18.6)	3,981 (25.6)	67,982 (22.4)		
DM						<0.001	0
No	134,591 (88.8)	62,003 (86.7)	58,628 (90.8)	13,633 (87.5)	268,855 (88.7)		
Yes	17,039 (11.2)	9,496 (13.3)	5,927 (9.2)	1,943 (12.5)	34,405 (11.3)		
Dyslipidemia						<0.001	0
No	110,177 (72.7)	49,478 (69.2)	48,580 (75.3)	10,806 (69.4)	219,041 (72.2)		

Yes	41,453 (27.3)	22,021 (30.8)	15,975 (24.7)	4,770 (30.6)	84,219 (27.8)		
Uterine fibroids						<0.001	0
No	127,636 (84.2)	61,417 (85.9)	55,975 (86.7)	10,735 (68.9)	255,763 (84.3)		
Yes	23,994 (15.8)	10,082 (14.1)	8,580 (13.3)	4,841 (31.1)	47,497 (15.7)		
Endometriosis						<0.001	0
No	145,435 (95.9)	69,009 (96.5)	62,590 (97.0)	13,714 (88.0)	290,748 (95.9)		
Yes	6,195 (4.1)	2,490 (3.5)	1,965 (3.0)	1,862 (12.0)	12,512 (4.1)		
Previous hysterectomy						<0.001	0
No	145,642 (96.1)	69,923 (97.8)	63,855 (98.9)	11,737 (75.4)	291,157 (96.0)		
Yes	5,988 (3.9)	1,576 (2.2)	700 (1.1)	3,839 (24.6)	12,103 (4.0)		
Previous adnexal surgery						<0.001	0
No	148,692 (98.1)	70,432 (98.5)	63,536 (98.4)	14,664 (94.1)	297,324 (98.0)		
Yes	2,938 (1.9)	1,067 (1.5)	1,019 (1.6)	912 (5.9)	5,936 (2.0)		

CCI, Charlson comorbidity index; DM, diabetes mellitus; E, estrogen; MHT, menopausal hormone therapy; P, progestogen; SES, socioeconomic status

The data are presented as either percentages (in parentheses) or as medians with interquartile ranges [25th percentile, 75th percentile].

**Supplementary Table 3.** Hazard ratios of Parkinson's disease risk associated with MHT.

MHT	No PD cases (%)	PD cases (%)	PD cases / 100,000 person-years	Crude HR (95% CI)
Non-MHT	151,319 (99.8)	311 (0.2)	311/1,288,393 (24)	1
Total-MHT	151,267 (99.8)	363 (0.2)	363/1,089,406 (33)	1.377 (1.184–1.602)
Category 1				
Tibolone	71,309 (99.7)	190 (0.3)	190/507,479 (37)	1.554 (1.297–1.861)
E + P	64,422 (99.8)	133 (0.2)	133/469,573 (28)	1.167 (0.952–1.429)
E alone	15,536 (99.7)	40 (0.3)	40/112,353 (36)	1.465 (1.054–2.036)
Category 2				
Tibolone	71,309 (99.7)	190 (0.3)	190/507,479 (37)	1.554 (1.297–1.861)
EH/DRSP	35,547 (99.8)	82 (0.2)	82/257,009 (32)	1.318 (1.033–1.681)
EH/NETA	4,460 (99.8)	9 (0.2)	9/33,382 (27)	1.099 (0.566–2.132)
EH/DYD	6,479 (99.9)	9 (0.1)	9/45,795 (20)	0.818 (0.421–1.586)
EV/CPA	15,285 (99.8)	24 (0.2)	24/114,057 (21)	0.861 (0.569–1.304)
EV/MPA	943 (99.7)	3 (0.3)	3/7,209 (42)	1.69 (0.542–5.268)
EV/NETA	135 (99.3)	1 (0.7)	1/1,068 (94)	3.765 (0.529–26.814)
CEE	2,022 (99.5)	10 (0.5)	10/13,044 (77)	3.272 (1.743–6.142)
EV	13,105 (99.8)	26 (0.2)	26/95,791 (27)	1.113 (0.746–1.66)
EH	200 (99)	2 (1)	2/1,610 (124)	4.854 (1.208–19.496)
CEE/MP	417 (99.8)	1 (0.2)	1/2,863 (35)	1.473 (0.207–10.494)
CEE/MPA	112 (100)	0 (0)	0/663 (0)	–
CEE/DYD	33 (100)	0 (0)	0/218 (0)	–
EV/MP	447 (99.6)	2 (0.4)	2/3,205 (62)	2.577 (0.642–10.35)
EV/MPA	308 (99.4)	2 (0.6)	2/2,179 (92)	3.83 (0.954–15.381)
EV/DYD	29 (100)	0 (0)	0/231 (0)	–
EH/MP	224 (100)	0 (0)	0/1,633 (0)	–
EH/MPA	7 (100)	0 (0)	0/53 (0)	–
EH/DYD	1 (100)	0 (0)	0/8 (0)	–
TE	249 (99.2)	2 (0.8)	2/1,909 (105)	4.211 (1.049–16.914)

CEE, conjugated equine estrogen; CI, confidence interval; CPA, cyproterone acetate; DRSP, drospirenone; DYD, dydrogesterone; E, estrogen; EH, estradiol hemihydrate; EV, estradiol valerate; HR, hazard ratio; MHT, menopausal hormone therapy; MP, micronized progesterone; MPA, medroxyprogesterone acetate; NETA, norethisterone acetate; P, progesterone; PD, Parkinson's disease; TE, Transdermal estrogen

**Supplementary Table 4.** The incidence of Parkinson's disease per 100,000 person-years subsequent to MHT in this study

	Non-MHT	MHT
Total	311/1,288,393 (24)	363/1,089,406 (33)
Calendar year at inclusion		
2011	111/409,853 (27)	137/341,910 (40)
2012	95/359,976 (26)	89/306,558 (29)
2013	54/288,579 (19)	80/246,330 (32)
2014	51/229,985 (22)	57/194,608 (29)
Age at inclusion (y)		
40~49	66/542,844 (12)	79/424,819 (19)
50~59	184/682,138 (27)	215/606,072 (35)
60~69	60/62,217 (96)	67/57,467 (117)
70~	1/1,194 (84)	2/1,048 (191)
SES		
Mid~high SES	291/1,255,126 (23)	330/1,060,081 (31)
Low SES	20/33,267 (60)	33/29,324 (113)
Region		
Urban area	160/634,280 (25)	148/538,227 (27)
Rural area	151/654,113 (23)	215/551,178 (39)
CCI		
0	186/917,889 (20)	218/766,616 (28)
1	60/230,798 (26)	85/202,534 (42)
≥2	65/139,706 (47)	60/120,255 (50)
Hypertension		
No	205/1,004,594 (20)	228/835,016 (27)
Yes	106/283,799 (37)	135/254,389 (53)
DM		
No	242/1,146,526 (21)	293/962,209 (30)
Yes	69/141,867 (49)	70/127,196 (55)
Dyslipidemia		
No	213/942,799 (23)	220/778,462 (28)
Yes	98/345,594 (28)	143/310,943 (46)
Uterine fibroids		

No	271/1,086,775 (25)	323/924,552 (35)
Yes	40/201,618 (20)	40/164,854 (24)
Endometriosis		
No	297/1,236,401 (24)	353/1,045,503 (34)
Yes	14/51,992 (27)	10/43,903 (23)
Previous hysterectomy		
No	296/1,239,161 (24)	352/1,045,113 (34)
Yes	15/49,232 (30)	11/44,292 (25)
Previous adnexal surgery		
No	306/1,264,483 (24)	361/1,067,973 (34)
Yes	5/23,910 (21)	2/21,433 (9)

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DM, diabetes mellitus; CCI, Charlson comorbidity index; MHT, menopausal hormone therapy; SES, socioeconomic status  
The data is displayed as the incidence of cases per person-years (cases per 100,000 person-years).

**Supplementary Table 5.** Analysis of each variable and its interaction with MHT (subdivided by hormonal agent)

	Tibolone HR (95% CI)	p for interaction	E+P HR (95% CI) <sup>a</sup>	p for interaction	E alone HR (95% CI) <sup>a</sup>	p for interaction
Age at inclusion (y)						
40~49	1.581 (1.032–2.423)		1.446 (0.973–2.149)		1.796 (0.895–3.604)	
50~59	1.291 (1.017–1.638)	0.411	1.315 (1.016–1.702)	0.691	1.374 (0.898–2.102)	0.52
60~69	1.411 (0.970–2.054)	0.692	0.741 (0.379–1.447)	0.092	1.053 (0.481–2.303)	0.32
70~	4.151 (0.376–45.86)	0.422	–		–	
SES		0.363		0.356		0.705
Mid~high SES	1.501 (1.243–1.813)		1.141 (0.923–1.409)		1.445 (1.026–2.034)	
Low SES	2.053 (1.095–3.847)		1.643 (0.787–3.43)		1.845 (0.548–6.208)	
Region		0.023		0.052		0.063
Urban area	1.236 (0.944–1.619)		0.933 (0.685–1.27)		1.028 (0.605–1.744)	
Rural area	1.898 (1.485–2.425)		1.41 (1.074–1.851)		1.959 (1.283–2.991)	
CCI						
0	1.58 (1.249–1.999)		1.181 (0.911–1.531)		1.567 (1.032–2.378)	
1	1.8 (1.226–2.643)	0.573	1.417 (0.918–2.185)	0.477	1.506 (0.72–3.149)	0.926
≥2	1.157 (0.761–1.759)	0.208	0.946 (0.573–1.562)	0.45	1.077 (0.494–2.348)	0.408
Hypertension		0.646		0.878		0.586
No	1.456 (1.155–1.836)		1.179 (0.922–1.508)		1.528 (1.016–2.299)	
Yes	1.58 (1.182–2.112)		1.218 (0.849–1.746)		1.263 (0.723–2.205)	
DM		0.575		0.226		0.296
No	1.584 (1.29–1.945)		1.261 (1.009–1.575)		1.583 (1.1–2.278)	
Yes	1.3 (0.891–1.898)		0.893 (0.537–1.484)		1.001 (0.46–2.179)	
Dyslipidemia		0.117		0.219		0.682
No	1.365 (1.082–1.722)		1.074 (0.836–1.379)		1.525 (1.022–2.276)	
Yes	1.838 (1.372–2.462)		1.407 (0.994–1.993)		1.319 (0.739–2.352)	
Uterine fibroids		0.418		0.36		0.074
No	1.587 (1.312–1.921)		1.122 (0.902–1.396)		1.787 (1.257–2.541)	
Yes	1.232 (0.699–2.173)		1.483 (0.85–2.586)		0.723 (0.285–1.831)	
Endometriosis		0.306		0.552		0.349
No	1.582 (1.317–1.9)		1.181 (0.961–1.451)		1.541 (1.095–2.169)	
Yes	0.886 (0.292–2.691)		0.81 (0.233–2.818)		0.836 (0.24–2.91)	



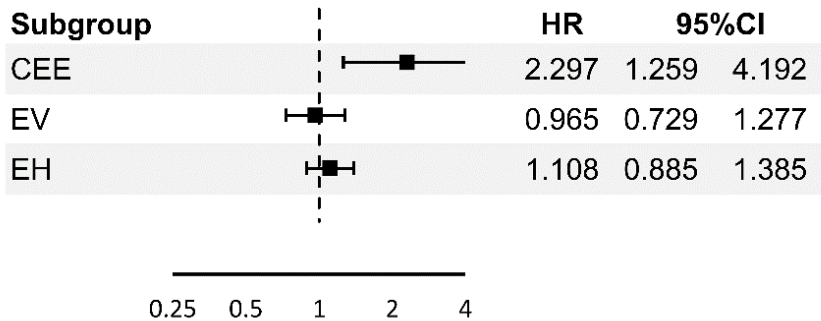
Previous hysterectomy						
No	1.564 (1.302–1.88)		1.192 (0.972–1.463)		1.67 (1.171–2.381)	
Yes	1.456 (0.529–4.007)		–		0.704 (0.273–1.814)	
Previous adnexal surgery		0.985		0.877		0.986
No	1.573 (1.312–1.885)		1.164 (0.949–1.428)		1.555 (1.119–2.163)	
Yes	–		1.338 (0.26–6.9)		–	

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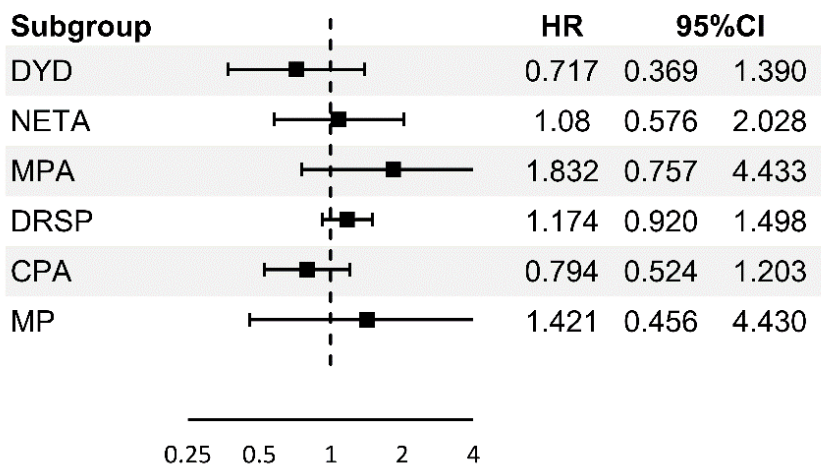
CCI, Charlson comorbidity index; DM, diabetes mellitus; E, estrogen, MHT, menopausal hormone therapy; P, progestogen; SES, socioeconomic status

**Supplementary Figure 1.** Hazard risk of Parkinson's disease according to menopausal hormone classification.

**A. Classification based on the use of oral estrogen**

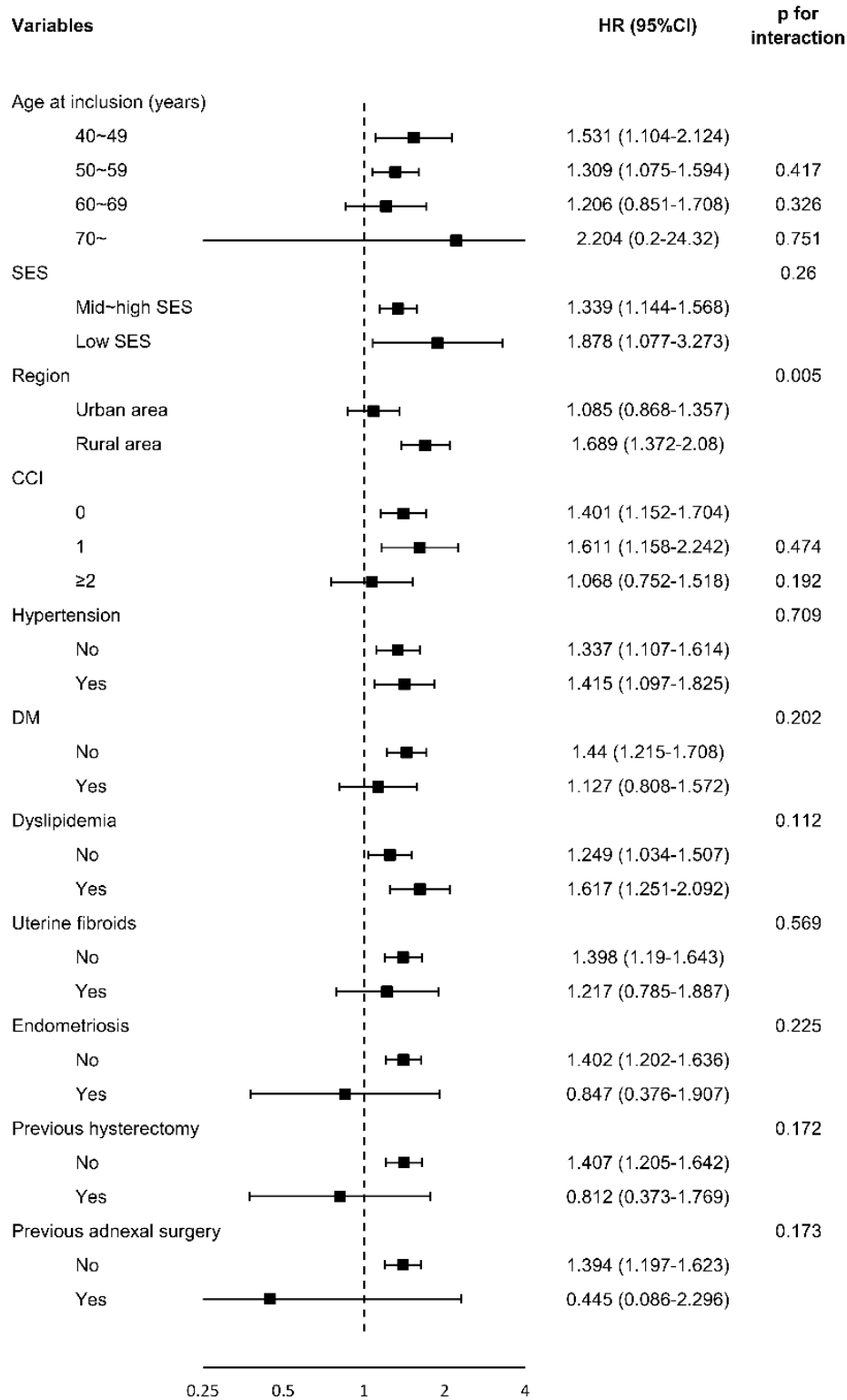


**B. Classification based on the use of oral progestogen**



CEE, conjugated equine estrogen; CI, confidence interval; CPA, cyproterone acetate; DRSP, drospirenone; DYD, dydrogesterone; EH, estradiol hemihydrate; EV, estradiol valerate; HR, hazard ratio; MP, micronized progesterone; NETA, norethisterone acetate

**Supplementary Figure 2.** Analysis of each variable and its interaction with MHT



CCI, Charlson comorbidity index; DM, diabetes mellitus; E, estrogen, MHT, menopausal hormone therapy; P, progesterone; SES, socioeconomic status