

Supplementary Material

Menopausal hormone therapy and risk of dementia: Health Insurance Database in South Korea-based retrospective cohort study

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Supplementary table 1. A detailed list of menopausal hormones (generic and brand name)

MHT (generic name)	Brand name
TIB	
Tibolone 2.5mg	Livial, Rabilone, Libolone, Libron, Live on, Liviem, Tiborisi, Tibolan, Tibiol, Pharmbio Korea Tibolone, Hyundai Tibolone
CEPM	
Estradiol Hemihydrate 1.03mg, Drospirenone 2mg	Angelic
Estradiol Valerate 2mg, Medroxyprogesterone Acetate 10mg	Divina
Estradiol Valerate 1mg, Medroxyprogesterone Acetate 2.5mg	Indivina Tab 1mg/2.5mg
Estradiol Valerate 1mg, Medroxyprogesterone Acetate 5mg	Indivina Tab 1mg/5mg
Estradiol Valerate 2mg, Medroxyprogesterone Acetate 2.5mg	Indivina Tab 2mg/2.5mg
Estradiol Hemihydrate 2mg, Norethisterone Acetate 1mg	Cliane
Estradiol Hemihydrate 2.06mg, Dydrogesterone 10mg	Femoston 2/10
Estradiol Hemihydrate 1.03mg, Dydrogesterone 10mg	Femoston 1/10
Estradiol Hemihydrate 1.03mg, Dydrogesterone 5mg	Femoston Conti
Cyproterone Acetate 1mg, Estradiol Valerate 2mg	Climen
Estradiol Hemihydrate 1.03mg, Norethisterone Acetate 0.5mg	Esdiol-half
Estradiol Valerate 1.31mg, Norethisterone Acetate 0.5mg	Cliovelle
Estrogen	
Conjugated Estrogens 0.3mg	Premina 0.3mg
Conjugated Estrogens 0.625mg	Premina 0.625mg
Estradiol Valerate 1mg	Progynova 1mg
Estradiol Valerate 2mg	Progynova 2mg
Estradiol Hemihydrate 1mg	Preda 1mg
CEPP^a	
Progesterone Micronized 100mg	Utrogestan 100mg
Medroxyprogesterone Acetate 5mg	Provera 5mg
Medroxyprogesterone Acetate 10mg	Provera 10mg
Dydrogesterone 10mg	Duphaston
Transdermal estrogen	
Estradiol Hemihydrate, Estradiol	Estreva Gel, Climara patch, Divigel Gel

MHT, menopausal hormone therapy; TIB, Tibolone; CEPMP, Combined estrogen plus progestin by manufacturer; CEPP, Combined estrogen plus progestin by physician.

^aThis group used the progestin below and the estrogen group above simultaneously.

Supplementary table 2. Association of reproductive factors and dementia risk in women of MHT

Variables	AD dementia ^a		Non-AD dementia ^a		Total dementia ^a	
	HR (95% CI) ^a	P-value	HR (95% CI) ^a	P-value	HR (95% CI) ^a	P-value
MHT						
TIB	1.041 (1.01-1.072)	0.009	1.335 (1.303-1.368)	<0.001	1.212 (1.188-1.236)	<0.001
CEPM	0.975 (0.933-1.019)	0.266	1.25 (1.209-1.292)	<0.001	1.137 (1.106-1.169)	<0.001
Oral Estrogen	1.081 (1.03-1.134)	0.002	1.128 (1.079-1.179)	<0.001	1.092 (1.054-1.13)	<0.001
CEPP	1.131 (0.997-1.283)	0.055	1.046 (0.925-1.183)	0.469	1.087 (0.991-1.193)	0.077
Transdermal estrogen	0.989 (0.757-1.292)	0.937	0.919 (0.722-1.17)	1.493	0.892 (0.736-1.083)	0.249
Age at inclusion (years)						
50~59	3.471 (3.159-3.814)	<0.001	1.961 (1.869-2.058)	<0.001	2.23 (2.136-2.329)	<0.001
60~69	13.181 (11.929-14.565)	<0.001	3.565 (3.362-3.78)	<0.001	5.353 (5.092-5.627)	<0.001
70~	46.048 (41.603-50.967)	<0.001	6.767 (6.357-7.204)	<0.001	14.992 (14.23-15.794)	<0.001
BMI (kg/m2)						
<18.5	1.295 (1.234-1.358)	<0.001	1.026 (0.965-1.09)	0.414	1.184 (1.136-1.233)	<0.001
23-24.9	0.936 (0.917-0.956)	<0.001	1.023 (1.001-1.045)	0.038	0.983 (0.968-0.999)	0.033
25-29.9	0.91 (0.893-0.928)	<0.001	1.009 (0.989-1.03)	0.38	0.965 (0.951-0.98)	<0.001
≥30	0.908 (0.873-0.944)	<0.001	0.97 (0.929-1.012)	0.159	0.941 (0.912-0.97)	<0.001
SES						
Low SES	1.741 (1.681-1.803)	<0.001	1.96 (1.888-2.034)	<0.001	1.843 (1.793-1.895)	<0.001
Region						
Rural area	1.221 (1.198-1.244)	<0.001	1.131 (1.11-1.153)	<0.001	1.168 (1.152-1.185)	<0.001
CCI						
1	1.214 (1.191-1.236)	<0.001	1.141 (1.119-1.164)	<0.001	1.184 (1.167-1.202)	<0.001
≥2	1.288 (1.261-1.316)	<0.001	1.172 (1.145-1.199)	<0.001	1.238 (1.218-1.259)	<0.001
Parity (years)						
0	1.201 (1.142-1.263)	<0.001	0.993 (0.949-1.039)	0.758	1.07 (1.033-1.109)	<0.001
2	1.113 (1.063-1.165)	<0.001	1.028 (0.988-1.069)	0.176	1.066 (1.033-1.1)	<0.001
≥3	1.257 (1.197-1.32)	<0.001	1.043 (0.998-1.09)	0.06	1.116 (1.078-1.155)	<0.001
Age at menarche (years)						
≥13	0.953 (0.926-0.98)	<0.001	0.905 (0.879-0.932)	<0.001	0.915 (0.896-0.936)	<0.001
Age at menopause (years)						
45-49	1.03 (1.001-1.06)	0.043	1.13 (1.096-1.165)	<0.001	1.084 (1.06-1.108)	<0.001
50-54	1.099 (1.069-1.13)	<0.001	1.218 (1.18-1.257)	<0.001	1.161 (1.136-1.188)	<0.001
55-	1.187 (1.143-1.233)	<0.001	1.415 (1.356-1.476)	<0.001	1.288 (1.25-1.328)	<0.001
Smoking						
Past	1.249 (1.16-1.344)	<0.001	1.165 (1.081-1.255)	<0.001	1.212 (1.146-1.281)	<0.001
Current	1.292 (1.234-1.353)	<0.001	1.172 (1.118-1.229)	<0.001	1.239 (1.197-1.284)	<0.001
Alcohol (g/week)						
~2/week	0.878 (0.852-0.905)	<0.001	1.004 (0.978-1.032)	0.751	0.951 (0.931-0.971)	<0.001
3~6/week	0.923 (0.847-1.007)	0.071	1.11 (1.034-1.191)	0.004	1.044 (0.986-1.106)	0.139
Daily	1.021 (0.92-1.134)	0.694	1.152 (1.041-1.274)	0.006	1.084 (1.003-1.171)	0.043
Physical exercise (per week)						
1~2	0.844 (0.824-0.865)	<0.001	0.899 (0.878-0.921)	<0.001	0.867 (0.851-0.883)	<0.001
3~4	0.781 (0.756-0.807)	<0.001	0.868 (0.841-0.895)	<0.001	0.825 (0.806-0.845)	<0.001
5~6	0.791 (0.749-0.835)	<0.001	0.92 (0.875-0.967)	0.001	0.862 (0.829-0.896)	<0.001
Daily	0.955 (0.927-0.983)	0.002	0.974 (0.944-1.005)	0.101	0.957 (0.935-0.979)	<0.001
Period from menopause to inclusion (years)						
5~9	1.581 (1.516-1.648)	<0.001	1.391 (1.352-1.432)	<0.001	1.413 (1.379-1.448)	<0.001
10~	2.783 (2.66-2.911)	<0.001	1.926 (1.857-1.997)	<0.001	2.165 (2.103-2.228)	<0.001

MHT, menopausal hormone therapy; AD, Alzheimer's disease; HR, hazard ratio; CI, confidence interval; TIB, Tibolone; CEPM, Combined estrogen plus progestin by manufacturer; CEPP, Combined estrogen plus progestin by physician; BMI, Body mass index; CCI, Charlson comorbidity index; SES, socioeconomic status.

^aHRs were adjusted for age group, BMI, SES region, CCI, parity, age at menarche, age at menopause, smoking, alcohol, physical exercise, and period from menopause to inclusion.

Supplementary table 3. Case/person-years of dementia in Korea National Health Insurance Data, 2002-2019

	Non-MHT	TIB	CEPM	Oral Estrogen	CEPP	Transdermal estrogen
Total	96,853/11,494,291 (843)	13,372/2,457,317 (544)	6,183/1,577,476 (392)	3,696/705,854 (524)	494/86,555 (571)	115/28,317 (406)
Age at inclusion (years)						
40~49	960/1,126,771 (85)	757/447,153 (169)	538/369,975 (145)	265/193,333 (137)	28/15,817 (177)	4/6,297 (64)
50~59	15,742/5,748,549 (274)	6,489/1,611,114 (403)	3,496/1,042,616 (335)	1,374/394,763 (348)	168/51,625 (325)	53/17,347 (306)
60~69	40,843/3,452,219 (1183)	4,818/362,572 (1329)	1,795/154,264 (1164)	1,457/100,597 (1448)	231/17,108 (1350)	46/4,292 (1072)
70~	39,308/1,166,752 (3369)	1,308/36,478 (3586)	354/10,621 (3333)	600/17,161 (3496)	67/2,005 (3342)	12/381 (3147)
BMI (kg/m2)						
<18.5	2,256/201,226 (1121)	211/40,784 (517)	106/30,490 (348)	63/10,012 (629)	10/1,754 (570)	7/549 (1275)
18.5-22.9	28,254/3,870,257 (730)	4,382/976,520 (449)	2,222/701,457 (317)	1,178/257,286 (458)	159/35,587 (447)	33/10,469 (315)
23-24.9	23,649/3,023,316 (782)	3,698/680,970 (543)	1,719/424,716 (405)	960/197,175 (487)	140/24,262 (577)	34/7,569 (449)
25-29.9	32,654/3,755,281 (870)	4,237/677,852 (625)	1,810/380,023 (476)	1,273/212,846 (598)	159/22,548 (705)	37/8,755 (423)
≥30	4,183/481,581 (869)	420/61,365 (684)	177/31,048 (570)	129/23,916 (539)	12/1,862 (644)	1/791 (126)
SES						
Mid-high SES	86,602/11,096,322 (780)	12,267/2,380,190 (515)	5,790/1,541,666 (376)	3,467/689,153 (503)	466/84,743 (550)	109/27,603 (395)
Low SES	10,251/397,968 (2576)	1,105/77,127 (1433)	393/35,810 (1097)	229/16,701 (1371)	28/1,812 (1545)	6/714 (840)
Region						
Urban area	22,426/3,419,846 (656)	4,080/772,984 (528)	2,085/538,692 (387)	1,011/224,957 (449)	221/44,248 (499)	51/12,860 (397)
Rural area	74,427/8,074,444 (922)	9,292/1,684,333 (552)	4,098/1,038,784 (394)	2,685/480,897 (558)	273/42,306 (645)	64/15,457 (414)
CCI						
0	55,403/7,643,636 (725)	8,059/1,677,987 (480)	3,978/1,120,359 (355)	2,270/494,421 (459)	289/60,214 (480)	68/18,666 (364)
1	24,278/2,225,501 (1091)	3,096/477,204 (649)	1,341/285,020 (470)	854/127,772 (668)	126/16,074 (784)	30/5,199 (577)
≥2	17,172/1,625,154 (1057)	2,217/302,127 (734)	864/172,097 (502)	572/83,661 (684)	79/10,267 (769)	17/4,452 (382)
Parity (years)						

0 or not respond	18,092/2,322,929 (779)	2,632/430,151 (612)	1,099/230,173 (477)	784/159,797 (491)	123/18,702 (658)	29/6,427 (451)
1	3,596/640,030 (562)	818/203,712 (402)	472/155,569 (303)	177/52,433 (338)	33/6,059 (545)	6/2,170 (276)
2	58,322/6,931,124 (841)	8,131/1,585,265 (513)	3,894/1,067,781 (365)	2,170/420,807 (516)	264/52,513 (503)	69/16,727 (413)
≥3	16,843/1,600,208 (1053)	1,791/238,188 (752)	718/123,953 (579)	565/72,817 (776)	74/9,280 (797)	11/2,993 (368)
Age at menarche (years)						
<13	11,942/2,147,233 (556)	1,893/376,306 (503)	885/235,760 (375)	601/134,231 (448)	83/16,726 (496)	25/5,331 (469)
≥13	84,033/9,278,588 (906)	11,311/2,059,612 (549)	5,241/1,331,232 (394)	3,045/562,041 (542)	399/69,071 (578)	89/22,625 (393)
Age at menopause (years)						
40-44	10,198/1,592,617 (640)	1,418/314,531 (451)	631/191,354 (330)	526/157,459 (334)	48/11,726 (409)	19/5,781 (329)
45-49	28,159/3,357,951 (839)	4,082/812,168 (503)	1,912/533,609 (358)	1,231/252,216 (488)	152/28,349 (536)	40/10,310 (388)
50-54	48,937/5,590,750 (875)	6,352/1,147,837 (553)	3,002/747,809 (401)	1,661/262,482 (633)	238/39,765 (599)	44/10,484 (420)
55-	9,559/952,973 (1003)	1,520/182,782 (832)	638/104,704 (609)	278/33,697 (825)	56/6,715 (834)	12/1,741 (689)
Smoking						
Never	82,953/10,554,898 (786)	11,676/2,221,262 (526)	5,453/1,428,125 (382)	3,294/645,767 (510)	438/80,008 (547)	101/25,967 (389)
Past	946/106,246 (890)	192/39,560 (485)	109/27,215 (401)	51/9,210 (554)	7/1,037 (675)	3/416 (721)
Current	2,442/270,156 (904)	528/104,887 (503)	264/70,295 (376)	116/24,395 (476)	18/2,381 (756)	1/627 (159)
Alcohol (g/week)						
None	78,421/9,344,469 (839)	10,328/1,852,354 (558)	4,679/1,169,205 (400)	3,015/546,510 (552)	405/69,695 (581)	94/22,525 (417)
~2/week	6,845/1,413,974 (484)	1,794/454,008 (395)	997/315,235 (316)	387/121,162 (319)	57/12,786 (446)	12/4,337 (277)
3-6/week	787/161,030 (489)	247/58,429 (423)	149/40,625 (367)	52/12,511 (416)	2/1,139 (176)	1/409 (245)
Daily	497/62,593 (794)	101/19,171 (527)	41/11,184 (367)	20/5,110 (391)	/546 (0)	1/129 (774)
Physical exercise (per week)						
None	61,712/7,020,391 (879)	7,690/1,391,927 (552)	3,550/904,542 (392)	2,292/402,707 (569)	271/47,271 (573)	59/14,198 (416)
1-2	10,875/1,882,383 (578)	2,089/462,046 (452)	1,003/303,777 (330)	520/133,582 (389)	76/16,642 (457)	22/5,969 (369)
3-4	5,642/1,052,865 (536)	1,263/279,816 (451)	627/183,212 (342)	292/77,528 (377)	57/11,049 (516)	16/4,025 (397)
5-6	2,035/343,656 (592)	423/90,813 (466)	230/59,543 (386)	94/24,170 (389)	22/3,291 (668)	4/1,177 (340)

Daily	6,465/699,292 (925)	1,004/157,073 (639)	457/84,806 (539)	287/46,722 (614)	37/5,831 (635)	6/1,914 (314)
Period from menopause to inclusion (years)						
<5	9,247/4,597,657 (201)	4,278/1,421,016 (301)	2,549/1,060,103 (240)	882/375,879 (235)	113/44,622 (253)	27/14,679 (184)
5~9	11,956/2,571,664 (465)	3,110/581,051 (535)	1,447/324,295 (446)	715/177,693 (402)	96/21,355 (450)	27/7,437 (363)
10~	75,650/4,324,970 (1749)	5,984/455,250 (1314)	2,187/193,078 (1133)	2,099/152,283 (1378)	285/20,578 (1385)	61/6,201 (984)

TIB, Tibolone; CEPM, Combined estrogen plus progestin by manufacturer; CEPP, Combined estrogen plus progestin by physician; BMI, Body mass index; CCI, Charlson comorbidity index; MHT, menopausal hormone therapy; SES, socioeconomic status.

Data are expressed as the case/person-years (case/ 100,000 person-years).