Online Supplement

Does transition through menopause affect cardiovascular disease risk factors? Results from a population-based cohort in Lausanne (CoLaus Study)

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Short title

Cardiovascular risk across reproductive stage

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Conflicts of Interests

The authors declare no conflicts of interest.

Keywords

Female, Cardiovascular Diseases, Risk Factors, Reproduction, Cardiovascular System, Menopause

Table S1.a. Demographic and baseline characteristics of included and excluded women

	Women INCLUDED analysis 2558	Women EXCLUDED analysis[1] 986	p value[2]
Demographic and lifestyle factors			
Age, mean (SD)	52.7 (10.5)	53.9 (11.1)	0.001
Educational attainment (%) • High • Middle • Low	 455 (17.8) 683 (26.7) 1420 (55.5)	 117 (11.9) 212 (21.7) 605 (66.4)	<0.001
Physical activity (PAFQ, min/day) • None • 1 per week • 2 per week • 3 per week	 835 (33.2) 214 (8.5) 1438 (57.1) 31 (1.2)	 399 (41.2) 75 (7.9) 464 (48.5) 18 (1.9)	<0.001
Drinker (%)	1658 (64.8)	527 (53.4)	<0.001
• Alcohol consumption (units/week)	3.9 (5.4)	3.6 (5.9)	0.107
Hypertension (%)	705 (27.6)	362 (36.7)	<0.001
• Use of antihypertensive	361 (14.1)	193 (19.6)	<0.001
Smoking • Current smoker (%) • Former smoker (%) • Never (%)	 620 (24.2) 741 (28.9) 1197 (46.8)	 260 (26.4) 231 (23.5) 493 (50.1)	0.005
Diabetes	79 (3.1)	63 (6.4)	<0.001
• Use of antidiabetic meds (%)	50 (1.9)	42 (4.3)	<0.001
Use of Statins (Lipid lowering drugs) (%)	181 (7.1)	77 (8.8)	0.078
Use of Hormone replacement therapy (%)	848 (33.2)	346 (35.1)	0.273
Intermediate cardiovascular risk			
Body mass index (kg/m2) mean (SD)	24.9 (4.7)	25.6 (5.1)	0.0003
Blood pressure mean (SD)			
• Systolic blood pressure (mmHg)	123.6 (17.6)	126.6 (19.4)	0.001
• Diastolic blood pressure (mmHg)	77.1 (10.5)	78.5 (10.9)	0.001
Lipid profile, mean (SD)			
• Total cholesterol	5.57 (0.99)	5.67 (1.10)	0.0076
• High-density lipoprotein	1.81 (0.42)	1.78 (0.43)	0.0654
• Triglycerides*	1.0 (0.6)	1.0 (0.7)	<0.001
Glucose metabolism, mean (SD)			
• Fasting glucose	5.29 (0.92)	5.44 (1.2)	<0.001
• Insulin*	6.17 (1.7)	6.61 (5.09)	0.0075
Inflammatory markers, mean (SD)			
• High sensitivity C reactive protein*	1.3 (2.2)	1.4 (2.8)	0.0016
• Leptin (score)*	1.17 (1.25)	1.23 (1.3)	0.0725
• Adiponectin (score)*	1.14 (0.91)	1.08 (0.95)	0.1566
• Tumor necrosis alpha*	2.68 (2.65)	2.93 (2.78)	0.0713
• Interleukin 6*	1.18 (2.36)	1.21 (2.42)	0.9828
• Interleukin 1B*	0.46 (1.95)	0.43 (1.86)	0.8248

[1]Women excluded from the analysis were those with invalid/incorrect menstruation responses, and those without follow-up data
[2]Students t-test for continuous variables and chi-squared test for categorical variables
*Values were log-transformed before performing statistical test (summary expressed as median and interquartile range)

Table S1.b. Number of participants for paired testing (longitudinal analyses)

	PRE	TRANS	EPOST	LPOST
Body mass index (kg/m2)	704	504	277	1045
Systolic blood pressure (mmHg)	704	505	279	1057
Diastolic blood pressure (mmHg)	704	505	279	1057
Total cholesterol (mmol/L)	704	505	279	1059
High density lipoprotein (mmol/L)	704	505	279	1059
Triglycerides (mmol/L)[3]	704	505	279	1059
Fasting glucose (mmol/L)	704	505	279	1059
Insulin (microIU/mL)[3]	527	387	226	901
High sensitivity c-reactive protein[3]	690	495	278	1050
Leptin (ng/mL)[3, 4]	552	379	228	888
Adiponectin (ng/mL)[3,4]	573	396	243	935
Tumor necrosis factor alpha (pg/mL)[3]	612	419	251	947
Interleukin 6 (pg/mL)[3]	521	364	220	858
Interleukin 1b (pg/mL) [3]	353	238	137	464

Abbreviations: PRE, premenopausal; TRANS, menopause transition; EPOST, early postmenopausal; LPOST, late menopausal

Table S1.c. Participant characteristics on follow-up

	Premenopause (n=717)	Transition (n=507)	Early Postmenopause (0-5y) n=280	Late Postmenopause (>/=5 y) N=1,064	p value[1]
Demographic and Lifestyle factors					
Drinker (%)	568 (80.34)	401 (79.09)	224 (80.00)	799 (75.09)	0.038
Smoking					<0.001
• Current smoker (%)	152 (21.87)	146 (29.14)	57 (20.50)	157 (15.00)	
• Former smoker (%)	222 (31.94)	153 (30.54)	85 (30.58)	373 (35.63)	
• Never (%)	321 (46.19)	202 (40.32)	136 (48.92)	157 (15.00)	
Hypertension (%)	63 (8.91)	78 (15.38)	64 (22.86)	420 (39.47)	<0.001
• Use of antihypertensive	30 (4.26)	31 (6.13)	40 (14.34)	311 (29.37)	<0.001
Diabetes	10 (1.42)	19 (3.75)	22 (7.89)	106 (10.00)	<0.001
• Use of antidiabetic meds (%)	3 (0.42)	7 (1.38)	13 (4.64)	56 (5.26)	<0.001
Cardiovascular disease (%)	15 (2.09)	13 (2.56)	18 (6.4)	123 (11.56)	<0.001
Use of Statins (Lipid lowering drugs) (%)	15 (2.12)	33 (6.51)	52 (18.57)	284 (26.69)	<0.001
Cardiovascular risk factors					
Body mass index (kg/m2) mean (SD)	24.75 (4.73)	24.97 (4.71)	25.73 (5.01)	26.34 (5.09)	<0.001
Systolic blood pressure (mmHg)	112.9 (13.6)	117.0 (14.9)	122.1 (18.1)	130.7 (18.8)	<0.001
Diastolic blood pressure (mmHg)	74.2 (10.4)	76.1 (10.2)	76.9 (11.0)	77.7 (10.8)	<0.001
Total cholesterol (mmol/L)	5.39 (0.89)	5.85 (0.98)	6.00 (1.01)	5.97 (1.04)	<0.001
High density lipoprotein (mmol/L)	1.77 (0.41)	1.84 (0.48)	1.81 (0.45)	1.82 (0.46)	0.028
Triglycerides (mmol/L)[3]	0.9 (0.5)	1.0 (0.6)	1.0 (0.7)	1.1 (0.6)	<0.001
Fasting glucose (mmol/L)	5.37 (0.77)	5.55 (0.67)	5.73 (1.01)	5.86 (0.98)	<0.001
Insulin (microIU/mL)[3]	5.5 (4.0)	5.4 (4.3)	6.2 (4.8)	7.1 (5.7)	<0.001
High sensitivity c-reactive protein (pg/mL)[3]	1.1 (2.2)	1.1 (1.7)	1.35 (1.9)	1.7 (2.7)	<0.001
Leptin (ng/mL)[3, 4]	0.56 (0.95)	0.60 (0.91)	0.68 (0.88)	0.81 (1.12)	<0.001
Adiponectin (ng/mL) [3,4]	0.89 (0.69)	0.91 (0.80)	1.06 (0.99)	1.13 (0.94)	<0.001
Tumor necrosis factor alpha (pg/mL)[3]	4.02 (4.68)	4.39 (5.62)	4.28 (5.09)	5.05 (5.69)	<0.001
Interleukin 6 (pg/mL) [3]	2.20 (6.65)	2.21 (6.14)	2.05 (6.13)	2.47 (5.81)	0.677
Interleukin 1b (pg/mL) [3]	0.62 (2.29)	0.48 (1.80)	0.42 (2.17)	0.39 (1.72)	0.902
Framingham risk score[5]	3.17 (2.63)	5.37 (3.76)	8.35 (7.18)	14.23 (9.41)	<0.001

[1]ANOVA for continuous variables and chi-square test for categorical variables

[2]Physical activity was obtained by self-report of doing physical activity for more than 20 mins/day per week

[3]Crude values. Transformation of values done in logarithmic scale prior to testing for statistical significance. Summary values expressed as median (interquartile range)

[4]Converted to standardized scores

[5] Framingham Risk score computed only for women without a history of cardiovascular disease (PRE 706, TRANS 498, EPOST 266, LPOST 975)

Table S2a. Multivariate regression analysis of cardiovascular risk of women at baseline (cross-sectional analysis)[1]

	Pre	Transition	p	Early	p	Late	p	P value[1]
Body mass index								
• Model 1 (Beta, 95%CI)	Ref	0.364 (-0.163, 0.890)	0.176	**1.425 (0.787, 2.064)***	0.000	**2.009 (1.571, 2.448)***	0.000	**0.696 (0.555, 0.837)***
• Model 2 (Beta, 95%CI)	Ref	0.278 (-0.300, 0.856)	0.346	**1.260 (0.474, 2.047)***	0.002	**1.736 (0.857, 2.615)***	0.000	**0.606 (0.316, 0.895)***
• Model 3 (Beta, 95%CI)	Ref	0.457 (-0.081, 0.996)	0.096	**1.467 (0.722, 2.213)***	0.000	**1.993 (1.142, 2.844)***	0.000	**0.672 (0.389, 0.954)***
• Model 4 (Beta, 95%CI)	Ref	-		-		-		
Systolic blood pressure								
• Model 1 (Beta, 95%CI)	Ref	**4.074 (2.312, 5.836)***	0.000	**7.522 (5.379 - 9.666)***	0.000	**14.64 (13.13, 16.15)***	0.000	**4.889 (4.403, 5.376)***
• Model 2 (Beta, 95%CI)	Ref	-1.138 (-3.083, 0.807)	0.251	-1.683 (-4.329, 0.963)	0.212	-0.419 (-3.379, 2.541)	0.781	-0.102 (-1.047, 0.841)
• Model 3 (Beta, 95%CI)	Ref	-0.429 (-2.314, 1.455)	0.655	-1.061 (-3.667, 1.545)	0.425	0.385 (-2.594, 3.364)	0.800	0.074 (-0.910, 1.060)
• Model 4 (Beta, 95%CI)	Ref	-0.615 (-2.489, 1.257)	0.519	-1.663 (-4.259, 0.932)	0.209	-0.416 (-3.387, 2.554)	0.783	-0.198 (-1.181, 0.783)
Diastolic blood pressure								
• Model 1 (Beta, 95%CI)	Ref	**1.762 (0.599, 2.925)***	0.003	**3.196 (1.781, 4.611)***	0.000	**2.733 (1.738 , 3.728)***	0.000	**0.876 (0.555, 1.198)***
• Model 2 (Beta, 95%CI)	Ref	**1.999 (0.721, 3.277)***	0.002	**3.648 (1.911, 5.384)***	0.000	**3.481 (1.539, 5.424)***	0.000	**1.177 (0.537, 1.818)***
• Model 3 (Beta, 95%CI)	Ref	**2.191 (0.909, 3.473)***	0.001	**4.144 (2.371, 5.916)***	0.000	**4.231 (2.205, 6.257)***	0.000	**1.448 (0.777, 2.119)***
• Model 4 (Beta, 95%CI)	Ref	**1.950 (0.700, 3.200)***	0.002	**3.366 (1.634, 5.098)***	0.000	**3.195 (1.213, 5.177)***	0.002	**1.098 (0.442, 1.754)***
Total cholesterol								
• Model 1 (Beta, 95%CI)	Ref	**0.276 (0.171, 0.381)***	0.000	**0.784 (0.656, 0.911)***	0.000	**0.936 (0.847, 1.026)***	0.000	**0.318 (0.289, 0.347)***
• Model 2 (Beta, 95%CI)	Ref	0.106 (-0.007, 0.220)	0.066	**0.458 (0.303, 0.614)***	0.000	**0.399 (0.226, 0.573)***	0.000	**0.146 (0.088, 0.203)***
• Model 3 (Beta, 95%CI)	Ref	0.098 (-0.017, 0.213)	0.097	**0.472 (0.312, 0.632)***	0.000	**0.424 (0.241, 0.606)***	0.000	**0.154 (0.093, 0.214)***
• Model 4 (Beta, 95%CI)	Ref	0.087 (-0.027, 0.202)	0.136	**0.440 (0.280, 0.599)***	0.000	**0.380 (0.197, 0.562)***	0.000	**0.139 (0.079, 0.200)***
High-density lipoprotein								
• Model 1 (Beta, 95%CI)	Ref	0.056 (0.008, 0.104)	0.022	0.074 (0.015, 0.132)	0.014	0.089 (0.048, 0.130)	0.000	**0.028 (0.014 - 0.041)***
• Model 2 (Beta, 95%CI)	Ref	0.027 (-0.024, 0.080)	0.298	0.019 (-0.052, 0.091)	0.594	-0.0004 (-0.080, 0.079)	0.991	-0.0009 (-0.027, 0.025)
• Model 3 (Beta, 95%CI)	Ref	0.035 (-0.015, 0.087)	0.172	0.027 (-0.043, 0.098)	0.440	0.006 (-0.074, 0.087)	0.868	0.001 (-0.024, 0.028)
• Model 4 (Beta, 95%CI)	Ref	**0.049 (0.001, 0.098)***	0.045	**0.071 (0.004, 0.139)***	0.037	0.066 (-0.010, 0.143)	0.092	0.021 (-0.004, 0.046)
Triglycerides (log)								
• Model 1 (Beta, 95%CI)	Ref	**0.077 (0.027, 0.128)***	0.002	**0.138 (0.077, 0.199)***	0.000	**0.243 (0.200, 0.286)***	0.000	**0.081 (0.067, 0.094)***
• Model 2 (Beta, 95%CI)	Ref	0.035 (-0.019, 0.090)	0.200	0.058 (-0.016, 0.133)	0.124	**0.110 (0.027, 0.194)***	0.009	**0.036 (0.008, 0.063)***
• Model 3 (Beta, 95%CI)	Ref	0.029 (-0.024, 0.083)	0.285	0.055 (-0.019, 0.130)	0.150	**0.120 (0.035, 0.206)***	0.006	**0.038 (0.010, 0.067)***
• Model 4 (Beta, 95%CI)	Ref	0.014 (-0.036, .0066)	0.580	0.008 (-0.063, 0.079)	0.822	0.057 (-0.024, 0.138)	0.170	0.017 (-0.009, 0.044)

Fasting blood glucose								
• Model 1 (Beta, 95%CI)	Ref	0.082 (-0.011, 0.177)	0.085	**0.184 (0.070, 0.299)***	0.002	**0.301 (0.223, 0.380)***	0.000	**0.101 (0.076 - 0.127)***
• Model 2 (Beta, 95%CI)	Ref	0.073 (-0.030, 0.176)	0.166	**0.166 (0.025, 0.306)***	0.021	**0.270 (0.113, 0.428)***	0.001	**0.090 (0.038, 0.142)***
• Model 3 (Beta, 95%CI)	Ref	**0.105 (0.016, 0.195)***	0.020	**0.194 (0.070, 0.317)***	0.002	**0.282 (0.141, 0.423)***	0.000	**0.093 (0.046, 0.139)***
• Model 4 (Beta, 95%CI)	Ref	**0.089 (0.002, 0.176)***	0.045	**0.143 (0.022, 0.264)***	0.020	**0.213 (0.075, 0.351)***	0.003	**0.070 (0.024, 0.115)***
Serum insulin (log)								
• Model 1 (Beta, 95%CI)	Ref	-0.024 (-0.092, 0.044)	0.494	**0.020 (-0.061, 0.102)***	0.624	**0.119 (0.063, 0.176)***	0.000	**0.044 (0.026, 0.062)***
• Model 2 (Beta, 95%CI)	Ref	-0.013 (-0.088, 0.062)	0.728	0.040 (-0.059, 0.140)	0.427	**0.153 (0.041, 0.266)***	0.007	**0.052 (0.014, 0.089)***
• Model 3 (Beta, 95%CI)	Ref	-0.001 (-0.075, 0.073)	0.977	0.045 (-0.055, 0.146)	0.377	**0.169 (0.054, 0.285)***	0.004	**0.093 (0.046, 0.139)***
• Model 4 (Beta, 95%CI)	Ref	-0.030 (-0.099, 0.038)	0.386	-0.026 (-0.119, 0.067)	0.586	0.067 (-0.039, 0.174)	0.217	**0.070 (0.024, 0.116)***
High sensitivity C reactive protein (log)								
• Model 1 (Beta, 95%CI)	Ref	0.013 (-0.113, 0.139)	0.839	0.147 (-0.005, 0.300)	0.059	**0.440 (0.335, 0.545)***	0.000	**0.154 (0.120 - 0.188)***
• Model 2 (Beta, 95%CI)	Ref	-0.027 (-0.166, 0.111)	0.698	0.069 (--0.119, 0.257)	0.469	**0.311 (0.101, 0.521)***	0.004	**0.104 (0.035, 0.174)***
• Model 3 (Beta, 95%CI)	Ref	-0.006 (-0.143, 0.130)	0.927	0.025 (-0.163, 0.214)	0.791	**0.234 (0.018, 0.450)***	0.033	**0.073 (0.002, 0.145)***
• Model 4 (Beta, 95%CI)	Ref	-0.057 (-0.182, 0.067)	0.371	-0.125 (-0.298, 0.047)	0.154	0.030 (-0.167, 0.228)	0.761	0.005 (-0.059, 0.071)
Leptin (log-score)								
• Model 1 (Beta, 95%CI)	Ref	-0.007 (-0.099, 0.084)	0.870	**0.158 (0.049, 0.267)***	0.005	**0.242 (0.167, 0.317)***	0.000	**0.087 (0.063, 0.111)***
• Model 2 (Beta, 95%CI)	Ref	-0.010 (-0.111, 0.090)	0.840	**0.153 (0.018 , 0.288)***	0.026	**0.233 (0.082, 0.385)***	0.003	**0.084 (0.034, 0.134)***
• Model 3 (Beta, 95%CI)	Ref	0.020 (-0.078, 0.118)	0.685	**0.181 (0.046, 0.315)***	0.008	**0.261 (0.107, 0.415)***	0.001	**0.073 (0.002, 0.145)***
• Model 4 (Beta, 95%CI)	Ref	-0.019 (-0.097, 0.058)	0.628	0.064 (-0.042, 0.170)	0.240	0.085 (-0.037, 0.208)	0.171	0.030 (-.009, 0.071)
Adiponectin (log-score)								
• Model 1 (Beta, 95%CI)	Ref	0.0001 (-0.075, 0.075)	0.997	**0.126 (0.038, 0.215)***	0.005	**0.167 (0.106, 0.229)***	0.000	**0.060 (0.041, 0.080)***
• Model 2 (Beta, 95%CI)	Ref	-0.028 (-0.111, 0.053)	0.491	0.071 (-0.037, 0.181)	0.199	0.075 (-0.047, 0.198)	0.229	0.030 (-0.009, 0.071)
• Model 3 (Beta, 95%CI)	Ref	-0.023 (-0.105, 0.058)	0.576	0.090 (0.020, 0.201)	0.111	0.107 (-0.020, 0.235)	0.099	0.040 (-0.001, 0.082)
• Model 4 (Beta, 95%CI)	Ref	-0.004 (-0.085, 0.075)	0.910	**0.137 (0.028, 0.246)***	0.013	**0.173 (0.047, 0.298)***	0.007	**0.061 (0.020, 0.103)***
TNF alpha (log)								
• Model 1 (Beta, 95%CI)	Ref	0.023 (-0.083, 0.129)	0.668	0.135 (0.008, 0.261)	0.037	**0.178 (0.091, 0.266)***	0.000	**0.062 (0.034, 0.090)***
• Model 2 (Beta, 95%CI)	Ref	0.003 (-0.113, 0.119)	0.958	0.096 (-0.059, 0.252)	0.228	0.114 (-0.061, 0.289)	0.204	0.041 (-0.016, 0.099)
• Model 3 (Beta, 95%CI)	Ref	0.0009 (-0.116, 0.118)	0.988	0.066 (-0.094, 0.226)	0.419	0.082 (-0.102, 0.267)	0.382	0.030 (-0.030, 0.091)
• Model 4 (Beta, 95%CI)	Ref	-0.007 (-0.124, 0.109)	0.897	0.042 (-0.118, 0.203)	0.605	0.050 (-0.134, 0.235)	0.594	0.019 (-0.041, 0.080)
Interleukin 6 (log)								
• Model 1 (Beta, 95%CI)	Ref	0.0531 (-0.118, 0.224)	0.542	0.128 (-0.076, 0.331)	0.218	0.101 (-0.039, 0.242)	0.158	**0.033 (-0.011, 0.078)***

• Model 2 (Beta, 95%CI)	Ref	0.175 (-0.012 -0.362)	0.067	**0.361 (0.111, 0.611)***	0.005	**0.493 (0.210, 0.775)***	0.001	**0.165 (0.072, 0.258)***
• Model 3 (Beta, 95%CI)	Ref	0.175 (-0.013, 0.365)	0.069	**0.374 (0.116, 0.631)***	0.004	**0.479 (0.182, 0.775)***	0.002	**0.165 (0.066, 0.263)***
• Model 4 (Beta, 95%CI)	Ref	0.163 (-0.025, 0.352)	0.090	**0.342 (0.084, 0.600)***	0.009	**0.436 (0.138, 0.734)***	0.004	**0.151 (0.052, 0.249)***
Interleukin 1b (log)								
• Model 1 (Beta, 95%CI)	Ref	-0.187 (-0.396, 0.020)	0.077	-0.139 (-0.389. 0.111)	0.276	-0.167 (-0.342, 0.007)	0.060	-0.046 (-0.102, 0.010)
• Model 2 (Beta, 95%CI)	Ref	-0.158 (-0.386, 0.070)	0.175	-0.081 (-0.391, 0.227)	0.604	-.071 (-0.423, 0.280)	0.692	-0.017 (-0.133, 0.098)
• Model 3 (Beta, 95%CI)	Ref	-0.181 (-0.413, 0.049)	0.124	-0.122 (-0.443, 0.197)	0.451	-0.124 (0.494, 0.245)	0.509	-0.035 (-0.158, 0.086)
• Model 4 (Beta, 95%CI)	Ref	-0.169 (-0.401, 0.062)	0.152	-0.097 (-0.418, 0.222)	0.550	-0.087 (-0.459, 0.283)	0.644	-0.023 (-0.146, 0.098)

Model 1: corrected for medication

Model 2: corrected for model 1+ age

Model 3: corrected for model 2 + smoking history, alcohol-use, baseline physical activity, baseline cardiovascular disease, use of hormone replacement therapy

Model 4: corrected for model 3+ body mass index

[1]Beta-coefficients with 95% confidence interval

[2]p value for trend using simple linear regression showing trend **(*p value >0.05)**

Table S2b. Sensitivity analysis 1 (Linear regression model using different inclusion criteria for women)[1]

Multivariate linear regression on fully corrected models (model 4) using different "inclusion criteria" (1) fully corrected model (n=2588), (2) natural menopause (n=2241), (3) non-HRT users (n=1715), (4) women with no comorbidities (n=1213)

	Pre	Transition	p	Early	p	Late	p
Body mass index							
• Fully corrected model	Ref	0.457 (-0.081, 0.996)	0.096	**1.467 (0.722, 2.213)**	**0.000***	**1.993 (1.142, 2.844)**	**0.000***
• Natural menopause	Ref	0.267 (-0.280, 0.815)	0.339	**0.893 (0.127, 1.659)**	**0.022***	0.799 (-0.078, 1.679)	0.075
• Non-HRT users	Ref	0.542 (-0.042, 1.128)	0.069	**1.451 (0.537, 2.365)**	**0.002***	**2.361 (1.277, 3.444)**	**0.000 ***
• No comorbidities	Ref	0.228 (-0.369, 0.826)	0.454	0.084 (-0.953, 1.121)	0.874	0.593 (-0.653, 1.839)	0.351
Systolic blood pressure							
• Fully corrected model	Ref	-0.615 (-2.489, 1.257)	0.519	-1.663 (-4.259, 0.932)	0.209	-0.416 (-3.387, 2.554)	0.783
• Natural menopause	Ref	-0.603 (-2.492, 1.285)	0.531	-1.983 (-4.629, 0.662)	0.142	-1.204 (-4.243, 1.834)	0.437
• Non-HRT users	Ref	-0.463 (-2.358, 1.432)	0.632	-2.597 (-5.563, 0.368)	0.086	-0.267 (-3.797, 3.262)	0.882
• No comorbidities	Ref	0.129 (-1.415, 1.673)	0.870	-1.629 (-4.307, 1.049)	0.233	0.850 (-2.369, 4.069)	0.604
Diastolic blood pressure							
• Fully corrected model	Ref	**1.950 (0.700, 3.200)**	**0.002***	**3.366 (1.634, 5.098)**	**0.000***	**3.195 (1.213, 5.177)**	**0.002***
• Natural menopause	Ref	**1.891 (0.610, 3.173)**	**0.004***	**2.681 (0.887, 4.476)**	**0.003***	**2.302 (0.241, 4.363)**	**0.029***
• Non-HRT users	Ref	**1.542 (0.205, 2.881)**	**0.024***	1.322 (-0.771, 3.416)	0.216	1.793 (-0.699, 4.285)	0.158
• No comorbidities	Ref	0.361 (-0.833, 1.556)	0.553	-0.692 (-2.764, 1.379)	0.512	-0.148 (-2.639, 2.342)	0.907
Total cholesterol							
• Fully corrected model	Ref	0.087 (-0.027, 0.202)	0.136	**0.440 (0.280, 0.599)**	**0.000***	**0.380 (0.197, 0.562)**	**0.000***
• Natural menopause	Ref	0.073 (-0.044, 0.191)	0.221	**0.365 (0.201, 0.5298)**	**0.000***	**0.287 (0.099, 0.476)**	**0.003***
• Non-HRT users	Ref	0.054 (-0.066, 0.174)	0.373	**0.388 (0.201, 0.576)**	**0.000***	**0.248 (0.024, 0.471)**	**0.029***
• No comorbidities	Ref	-0.011 (-0.145, 0.122)	0.868	**0.250 (0.019, 0.481)**	**0.034***	0.228 (-0.049, 0.506)	0.107
High density lipoprotein							
• Fully corrected model	*Ref*	**0.049 (0.001, 0.098)**	**0.045***	**0.071 (0.004, 0.139)**	**0.037***	0.066 (-0.010, 0.143)	0.092
• Natural menopause	*Ref*	0.044 (-0.006, 0.094)	0.082	0.058 (-0.012, 0.128)	0.103	0.047 (-0.033, 0.127)	0.251
• Non-HRT users	*Ref*	0.044 (-0.005, 0.094)	0.081	**0.087 (0.010, 0.165)**	**0.027***	0.015 (-0.077, 0.108)	0.744
• No comorbidities	*Ref*	0.027 (-0.030, 0.0835)	0.360	0.044 (-0.055, 0.143)	0.380	0.048 (-0.166, 0.071)	0.431
Triglycerides (log)							
• Fully corrected model	*Ref*	0.014 (-0.036, .0066)	0.580	0.008 (-0.063, 0.079)	0.822	0.057 (-0.024, 0.138)	0.170
• Natural menopause	*Ref*	0.015 (-0.038, 0.068)	0.569	-0.008 (-0.082, 0.066)	0.825	0.007 (-0.078, 0.092)	0.865

• Non-HRT users	*Ref*	0.019 (-0.037, 0.075)	0.507	0.029 (-0.058, 0.117)	0.506	**0.125 (0.021, 0.230)**	**0.018***
• No comorbidities	*Ref*	0.031 (-0.044, 0.106)	0.418	-0.032 (-0.162, 0.098)	0.632	0.109 (-0.047, 0.2659)	0.172
Fasting blood glucose							
• Fully corrected model	*Ref*	**0.089 (0.002, 0.176)**	**0.045***	**0.143 (0.022, 0.264)***	**0.020***	**0.213 (0.075, 0.351)**	**0.003***
• Natural menopause	*Ref*	**0.094 (0.016, 0.172)**	**0.018***	**0.160 (0.051, 0.269)**	**0.004***	**0.184 (0.059, 0.310)**	**0.004***
• Non-HRT users	*Ref*	0.075 (-0.016, 0.166)	0.106	0.081 (-0.061, 0.224)	0.264	**0.202 (0.032, 0.371)**	**0.020***
• No comorbidities	*Ref*	0.058 (-0.012, 0.129)	0.105	-0.017 (-0.139, 0.105)	0.785	0.064 (-0.083, 0.211)	0.392
Serum insulin (log)							
• Fully corrected model	*Ref*	-0.030 (-0.099, 0.038)	0.386	-0.026 (-0.119, 0.067)	0.586	0.067 (-0.039, 0.174)	0.217
• Natural menopause	*Ref*	-0.032 (-0.104, 0.039)	0.372	-0.042 (-0.140, 0.055)	0.394	0.006 (-0.059, 0.169)	0.342
• Non-HRT users	*Ref*	-0.041 (-0.116, 0.033)	0.277	-0.052 (-0.168, 0.064)	0.379	0.104 (-0.033, 0.241)	0.137
• No comorbidities	*Ref*	-0.244 (-1.030, 0.543)	0.543	-0.237 (-1.616, 1.142)	0.736	1.162 (-0.498, 2.823)	0.170
High sensitive C reactive protein							
• Fully corrected model	*Ref*	-0.057 (-0.182, 0.067)	0.371	-0.125 (-0.298, 0.047)	0.154	0.030 (-0.167, 0.228)	0.761
• Natural menopause	*Ref*	-0.031 (-0.161, 0.099)	0.636	-0.023 (-0.205, 0.159)	0.806	0.182 (-0.027, 0.391)	0.088
• Non-HRT users	*Ref*	-0.031 (-0.123, 0.060)	0.503	-0.023 (-0.151, 0.106)	0.728	**0.181 (0.034, 0.329)**	**0.016***
• No comorbidities	*Ref*	0.038 (-0.123, 0.120)	0.642	-0.059 (-0.339, 0.220)	0.675	0.295 (-0.042, 0.631)	0.086
Leptin (log-score)							
• Fully corrected model	*Ref*	-0.019 (-0.097, 0.058)	0.628	0.064 (-0.042, 0.170)	0.240	0.085 (-0.037, 0.208)	0.171
• Natural menopause	*Ref*	0.0005 (-0.078, 0.079)	0.989	0.090 (0.019, 0.199)	0.106	0.104 (-0.022, 0.232)	0.105
• Non-HRT users	*Ref*	0.007 (-0.076, 0.091)	0.860	0.102 (-0.027, 0.230)	0.121	**0.184 (0.030, 0.338)**	**0.019***
• No comorbidities	*Ref*	0.015 (-0.081, 0.112)	0.755	0.131 (-0.035, 0.296)	0.121	0.169 (-0.033, 0.371)	0.100
Adiponectin (log-score)							
• Fully corrected model	*Ref*	-0.004 (-0.085, 0.075	0.910	**0.137 (0.028, 0.246)**	**0.013***	**0.173 (0.047, 0.298)**	**0.007***
• Natural menopause	*Ref*	-0.001 (-0.083, 0.081)	0.979	**0.131 (0.019, 0.244)**	**0.022***	**0.173 (0.042, 0.304)**	**0.010***
• Non-HRT users	*Ref*	0.015 (-0.070, 0.099)	0.735	**0.223 (0.094, 0.353)**	**0.001***	**0.213 (0.057, 0.369)**	**0.007***
• No comorbidities	*Ref*	0.015 (-0.081, 0.111)	0.762	**0.230 (0.068, 0.392)**	**0.006***	**0.234 (0.034, 0.434)**	**0.022***
Interleukin 6							
• Fully corrected model	*Ref*	0.163 (-0.025, 0.352)	0.090	**0.342 (0.084, 0.600)**	**0.009***	**0.436 (0.138, 0.734)**	**0.004***
• Natural menopause	*Ref*	0.153 (-0.046, 0.351)	0.132	**0.355 (0.080, 0.629)**	**0.011***	**0.499 (0.181, 0.818)**	**0.002***
• Non-HRT users	*Ref*	**0.216 (0.008, 0.424)**	**0.042***	**0.410 (0.093, 0.729)**	**0.011***	**0.532 (0.146, 0.919)**	**0.007***
• No comorbidities	*Ref*	0.151 (-0.098, 0.400)	0.235	**0.469 (0.045, 0.892)**	**0.030***	**0.568 (0.0412, 1.095)**	**0.035***
Tumor necrosis factor alpha							

• Fully corrected model	*Ref*	-0.007 (-0.124, 0.109)	0.897	0.042 (-0.118, 0.203)	0.605	0.050 (-0.134, 0.235)	0.594
• Natural menopause	*Ref*	-0.032 (-0.155, 0.091)	0.609	0.081 (-0.090, 0.251)	0.353	0.054 (-0.143, 0.253)	0.586
• Non-HRT users	*Ref*	-0.004 (-0.130, 0.123)	0.954	0.146 (-0.050, 0.343)	0.145	0.067 (-0.169, 0.303)	0.578
• No comorbidities	*Ref*	-0.032 (-0.184, 0.120)	0.678	0.158 (-0.104, 0.419)	0.237	0.102 (-0.219, 0.423)	0.534
Interleukin 1b (log)							
• Fully corrected model	*Ref*	-0.169 (-0.401, 0.062)	0.152	-0.097 (-0.418, 0.222)	0.550	-0.087 (-0.459, 0.283)	0.644
• Natural menopause	Ref	-0.170 (-0.411, 0.071)	0.167	-0.042 (-0.378, 0.292)	0.802	0.042 (-0.351, 0.435)	0.833
• Non-HRT users	Ref	-0.110 (-0.363, 0.142)	0.390	0.155 (-0.242, 0.553)	0.443	-0.143 (-0.619, 0.333)	0.556
• No comorbidities	Ref	-0.105 (-0.395, 0.185)	0.477	0.144 (-0.364, 0.651)	0.578	-0.021 (-0.632, 0.590)	0.947

Model 1: corrected for medication
Model 2: corrected for model 1+ age
Model 3: corrected for model 2 + smoking history, alcohol-use, baseline physical activity, baseline cardiovascular disease, use of hormone replacement therapy
Model 4: corrected for model 3+ body mass index (except for BMI as an outcome)
[1]Beta-coefficients with 95% confidence interval

Table S3a. Mean difference and 95% confidence interval of intermediate cardiovascular risk across different reproductive stages over time[1]

	Premenopause (PRE)	Transition (TRANS)	Early Menopause (EPOST)	Late Menopause (LPOST)	p-value[2]
Body mass index (kg/m2)	0.9 (0.7, 1.0)	0.8 (0.6, 0.9)	0.4 (0.2, 0.7)	0.5 (0.4, 0.6)	**<0.0001**
Systolic blood pressure (mmHg)	-1.7 (-2.5, -0.8)	-1.9 (-3.1, -0.7)	-1.3 (-3.1, 0.5)	-1.0 (-2.1, 0.03)	0.6850
Diastolic blood pressure (mmHg)	-0.4 (-1.1, 0.2)	-0.5 (-1.3, 0.4,)	-1.6 (-0.4, -2.7)	-1.0 (-1.6, -0.4)	0.2819
Total cholesterol (mmol/L)	0.3 (0.3, 0.4)	0.5 (0.4, 0.6)	0.2 (0.05, 0.3)	0.03 (0.04, 0.1)	**<0.0001**
High density lipoprotein (mmol/L)	-0.003 (-0.02, 0.02)	0.002 (-0.02, 0.02)	-0.01 (-0.05, 0.02)	-0.01 (-0.03, 0.01)	0.2282
Triglycerides (mmol/L)[3]	0.5 (0.02, 0.09)	0.08 (0.03, 0.1)	0.10 (0.03, 0.16)	0.02 (-0.02, 0.05)	0.0475
Fasting glucose (mmol/L)	0.3 (0.2, 0.3)	0.4 (0.3, 0.4)	0.4 (0.3, 0.5)	0.4 (0.3, 0.4)	0.0296
Insulin (microIU/mL)[3]	-0.6 (-1.1, -0.2)	0.01 (-0.5, 0.5)	1.38 (0.5, 2.3)	0.6 (0.2, 1.0)	**<0.0001**
High sensitivity c-reactive protein[3]	0.1 (-0.2, 0.4)	-0.1 (-0.4, 0.1)	0.3 (-0.1, 0.6)	0.1 (-0.2, 0.3)	0.5578
Leptin (ng/mL)[3,4]	-0.4 (-0.5, -0.4)	-0.4 (-0.5, -0.4)	-0.6 (-0.6, -0.5)	-0.6 (-0.6, -0.5)	0.0242
Adiponectin (ng/mL)[3,4]	-0.05, (-0.1, 0.01)	-0.01 (-0.08, 0.06)	-0.08 (-0.2, 0.04)	-0.01 (-0.07, 0.04)	0.8100
Tumor necrosis factor alpha (pg/mL)[3]	3.8 (-11.9, 19.5)	4.1 (2.2, 6.0)	-1.9 (-11.5, 7.8)	3.1, (1.2, 5.0)	0.9024
Interleukin 6 (pg/mL)[3]	9.1 (3.7, 14.5)	10.7 (3.1, 18.6)	11.6 (3.1, 20.1)	9.5 (4.2, 14.7)	0.9639
Interleukin 1b (pg/mL) [3]	-1.0 (-5.5, 3.4)	-0.4 (-1.9, 1.1)	2.6 (-1.6, 6.8)	0.5 (-0.3, 1.3)	0.4981
Framingham Risk score[5]	-0.9 (-1.0, -0.7)	-1.6 (-1.8, -1.3)	-2.1 (-2.7, -1.4)	-2.2 (-2.6, -1.8)	**<0.0001**

[1] Mean difference of baseline and follow-up and confidence interval (baseline levels minus follow-up levels). Positive values denote decreasing levels, while negative values mean increasing levels.

[2]Statistical significance computed using ANOVA to compare the mean difference across groups

[3]Crude mean change. Transformation of values done in logarithmic scale prior to testing for statistical significance.

[4]Converted to standardized scores

[5]Framingham Risk score computed only for women without cardiovascular disease (Number of women included in analyses: PRE 668, TRANS 477, EPOST 255, LPOST 900)

Table S3b. Linear mixed models analysis[1]

Repeated measures linear mixed models analyzed with restricted maximum likelihood analysis of square root corrected for (1) medication, (2) age, (3) other factors, (4) other factors+BMI comparing cardiovascular risk factors from baseline and 5 years follow-up (follow-up1), reporting beta coefficient, confidence interval, and p-values for random effects

	Pre	Transition	p	Early	p	Late	p
Body mass index							
• Model 1 (Beta, 95%CI)	*Ref*	4.031 (-2.186, 10.25)	0.204	1.031 (-6.722, 8.784)	0.794	-0.733 (-6.204, 4.739)	0.793
• Model 2 (Beta, 95%CI)	*Ref*	3.941 (-2.289, 10.17)	0.215	0.900 (-6.873, 8.673)	0.820	-0.862 (-6.361, 4.636)	0.759
• Model 3 (Beta, 95%CI)	*Ref*	2.926 (-2.764, 8.615)	0.314	1.494 (-5.604, 8.591)	0.680	0.324 (-4.795, 5.443)	0.901
• Model 4 (Beta, 95%CI)	*Ref*	-		-		-	
Systolic blood pressure							
• Model 1 (Beta, 95%CI)	*Ref*	9.579 (-9.368,28.53)	0.322	1.077 (-22.53,24.68)	0.929	**19.34 (2.634,36.06)***	**0.023**
• Model 2 (Beta, 95%CI)	*Ref*	2.122 (-16.13,20.38)	0.820	-10.25 (-33.01,12.51)	0.377	8.262 (-7.885,24.41)	0.316
• Model 3 (Beta, 95%CI)	*Ref*	-0.292 (-18.44,17.85)	0.975	-11.46 (-34.08,11.16)	0.321	7.707 (-8.647,24.06)	0.356
• Model 4 (Beta, 95%CI)	*Ref*	-1.279 (-19.33,16.78)	0.890	-12.04 (-34.54,10.47)	0.294	7.611 (-8.659,23.88)	0.359
Diastolic blood pressure							
• Model 1 (Beta, 95%CI)	*Ref*	5.442 (-6.887, 17.77)	0.387	-1.151 (-16.51, 14.21)	0.883	5.262 (-5.611, 16.135)	0.343
• Model 2 (Beta, 95%CI)	*Ref*	5.725 (-6.624, 18.07)	0.364	-0.723 (-16.12, 14.68)	0.927	5.680 (-5.243, 16.60)	0.308
• Model 3 (Beta, 95%CI)	*Ref*	3.681 (-8.582, 15.95)	0.557	-1.926 (-17.23, 13.38)	0.805	5.100 (-5.963, 16.16)	0.366
• Model 4 (Beta, 95%CI)	*Ref*	2.173 (-9.796, 14.14)	0.722	-2.734 (-17.66, 12.19)	0.719	4.892 (-5.895, 15.68)	0.374
Total cholesterol							
• Model 1 (Beta, 95%CI)	*Ref*	0.761 (-0.356, 1.878)	0.182	**1.418 (0.0250, 2.810)***	**0.046**	**1.245 (0.261, 2.229)***	**0.013**
• Model 2 (Beta, 95%CI)	*Ref*	0.534 (-0.574, 1.643)	0.345	1.074 (-0.310, 2.457)	0.128	0.903 (-0.0767, 1.883)	0.071
• Model 3 (Beta, 95%CI)	*Ref*	0.568 (-0.550, 1.686)	0.319	1.125 (-0.270, 2.520)	0.114	0.990 (-0.0162, 1.996)	0.054
• Model 4 (Beta, 95%CI)	*Ref*	0.537 (-0.579, 1.654)	0.346	1.107 (-0.286, 2.500)	0.119	0.992 (-0.013,1.996)	0.053
High-density lipoprotein							
• Model 1 (Beta, 95%CI)	*Ref*	-0.312 (-0.861, 0.238)	0.267	-0.277 (-0.962, 0.409)	0.429	0.0951 (-0.389, 0.579)	0.700
• Model 2 (Beta, 95%CI)	*Ref*	-0.356 (-0.906, 0.194)	0.205	-0.343 (-1.030, 0.343)	0.327	0.0282 (-0.458, 0.514)	0.910
• Model 3 (Beta, 95%CI)	*Ref*	-0.271 (-0.800, 0.259)	0.316	-0.396 (-1.057, 0.265)	0.240	0.0388 (-0.438, 0.515)	0.873
• Model 4 (Beta, 95%CI)	*Ref*	-0.187 (-0.690, 0.315)	0.465	-0.348 (-0.975, 0.279)	0.277	0.0449 (-0.407, 0.497)	0.846
Triglycerides							
• Model 1 (Beta, 95%CI)	*Ref*	**0.667 (0.131, 1.202)***	0.015	0.244 (-0.423, 0.911)	0.474	0.169 (-0.301, 0.641)	0.480

• Model 2 (Beta, 95%CI)	*Ref*	**0.617 (0.082, 1.153)***	0.024	0.170 (-0.497, 0.839)	0.616	0.095 (-0.377, 0.568)	0.692
• Model 3 (Beta, 95%CI)	*Ref*	0.520 (-0.00356,1.043)	0.052	0.237 (-0.416,0.890)	0.477	0.0457 (-0.425,0.517)	0.849
• Model 4 (Beta, 95%CI)	*Ref*	0.441 (-0.0581,0.941)	0.083	0.198 (-0.425,0.821)	0.534	0.0412 (-0.408,0.491)	0.857
Fasting blood glucose							
• Model 1 (Beta, 95%CI)	*Ref*	0.584 (-0.387, 1.554)	0.239	0.0908 (-1.119, 1.301)	0.883	0.289 (-0.566, 1.144)	0.508
• Model 2 (Beta, 95%CI)	*Ref*	0.550 (-0.422, 1.522)	0.268	0.0403 (-1.173, 1.253)	0.948	0.239 (-0.619, 1.098)	0.585
• Model 3 (Beta, 95%CI)	*Ref*	0.355 (-0.397, 1.108)	0.355	0.0607 (-0.878, 0.999)	0.899	0.152 (-0.525, 0.829)	0.659
• Model 4 (Beta, 95%CI)	*Ref*	0.274 (-0.461, 1.009)	0.465	0.0149 (-0.902, 0.932)	0.975	0.146 (-0.515, 0.807)	0.665
Serum insulin (log)							
• Model 1 (Beta, 95%CI)	*Ref*	-0.105 (-0.807, 0.597)	0.769	-0.264 (-1.131, 0.604)	0.552	-0.234 (-0.836, 0.368)	0.446
• Model 2 (Beta, 95%CI)	*Ref*	-0.118 (-0.820, 0.585)	0.743	-0.284 (-1.154, 0.585)	0.522	-0.254 (-0.859, 0.351)	0.411
• Model 3 (Beta, 95%CI)	*Ref*	-0.240 (-0.902, 0.421)	0.476	-0.201 (-1.020, 0.617)	0.630	-0.118 (-0.698, 0.463)	0.691
• Model 4 (Beta, 95%CI)	*Ref*	-0.338 (-0.928, 0.253)	0.262	-0.206 (-0.935, 0.523)	0.580	-0.0686 (-0.585,0.448)	0.794
High sensitive C reactive protein (log)							
• Model 1 (Beta, 95%CI)	*Ref*	0.580 (-0.740, 1.900)	0.389	-0.443 (-2.079, 1.193)	0.596	0.184 (-0.976, 1.345)	0.756
• Model 2 (Beta, 95%CI)	*Ref*	0.533 (-0.789, 1.855)	0.429	-0.512 (-2.151, 1.128)	0.541	0.116 (-1.049, 1.282)	0.845
• Model 3 (Beta, 95%CI)	*Ref*	0.327 (-0.969, 1.623)	0.621	-0.634 (-2.242, 0.973)	0.439	-0.0589 (-1.222, 1.104)	0.921
• Model 4 (Beta, 95%CI)	*Ref*	0.0541 (-1.126, 1.234)	0.928	-0.775 (-2.237, 0.686)	0.298	-0.0709 (-1.129, 0.987)	0.895
Leptin (log-score)							
• Model 1 (Beta, 95%CI)	*Ref*	0.458 (-0.734, 1.649)	0.452	0.815 (-0.623, 2.254)	0.266	0.155 (-0.878, 1.187)	0.769
• Model 2 (Beta, 95%CI)	*Ref*	0.445 (-0.748, 1.638)	0.465	0.793 (-0.648, 2.234)	0.281	0.132 (-0.905, 1.169)	0.802
• Model 3 (Beta, 95%CI)	*Ref*	0.334 (-0.848,1.516)	0.580	0.698 (-0.731,2.121)	0.338	0.255 (-0.792,1.302)	0.646
• Model 4 (Beta, 95%CI)	*Ref*	0.173 (-0.835,1.181)	0.736	0.716 (-0.493,1.925)	0.246	0.250 (-0.640,1.139)	0.582
Adiponectin (log-score)							
• Model 1 (Beta, 95%CI)	*Ref*	-0.135 (-0.912, 0.641)	0.732	0.303 (-0.645, 1.251)	0.531	0.444 (-0.221, 1.111)	0.191
• Model 2 (Beta, 95%CI)	*Ref*	-0.192 (-0.969, 0.583)	0.626	0.208 (-0.739, 1.157)	0.666	0.347 (-0.321, 1.016)	0.308
• Model 3 (Beta, 95%CI)	*Ref*	-0.153 (-0.923, 0.616)	0.696	-0.0001 (-0.941, 0.940)	1.000	0.315 (-0.361, 0.991)	0.361
• Model 4 (Beta, 95%CI)	*Ref*	-0.103 (-0.858, 0.651)	0.788	-0.003 (-0.925, 0.919)	0.994	0.313 (-0.349, 0.975)	0.355
Interleukin 6 (log)							
• Model 1 (Beta, 95%CI)	*Ref*	0.298 (-1.523, 2.120)	0.748	-0.0802 (-2.281, 2.121)	0.943	-0.580 (-2.163, 1.004)	0.473
• Model 2 (Beta, 95%CI)	*Ref*	0.481 (-1.340, 2.301)	0.605	0.174 (-2.027, 2.375)	0.877	-0.314 (-1.902, 1.275)	0.699
• Model 3 (Beta, 95%CI)	*Ref*	0.0474 (-1.794, 1.889)	0.960	-0.158 (-2.388, 2.071)	0.889	-0.544 (-2.184, 1.096)	0.516

• Model 4 (Beta, 95%CI)	*Ref*	0.0174 (-1.824, 1.858)	0.985	-0.173 (-2.401, 2.056)	0.879	-0.554 (-2.193, 1.085)	0.508
Tumor necrosis factor alpha (log)							
• Model 1 (Beta, 95%CI)	*Ref*	0.256 (-0.845, 1.358)	0.648	0.392 (-0.940, 1.724)	0.564	0.318 (-0.637, 1.273)	0.515
• Model 2 (Beta, 95%CI)	*Ref*	0.205 (-0.898, 1.309)	0.715	0.316 (-1.018, 1.651)	0.642	0.239 (-0.720, 1.199)	0.624
• Model 3 (Beta, 95%CI)	*Ref*	0.135 (-0.980,1.250)	0.813	0.169 (-1.182,1.519)	0.807	0.241 (-0.750,1.231)	0.634
• Model 4 (Beta, 95%CI)	*Ref*	0.106 (-1.008,1.219)	0.852	0.157 (-1.191,1.506)	0.819	0.234 (-0.754,1.223)	0.642
Interleukin 1b (log)							
• Model 1 (Beta, 95%CI)	*Ref*	0.344 (-1.503, 2.190)	0.715	-0.837 (-3.113, 1.439)	0.471	0.0813 (-1.537, 1.699)	0.922
• Model 2 (Beta, 95%CI)	*Ref*	0.455 (-1.394, 2.303)	0.630	-0.661 (-2.943, 1.620)	0.570	0.239 (-1.386, 1.864)	0.773
• Model 3 (Beta, 95%CI)	*Ref*	0.0963 (-1.781, 1.974)	0.920	-1.073 (-3.392, 1.245)	0.364	-0.208 (-1.897, 1.481)	0.809
• Model 4 (Beta, 95%CI)	*Ref*	0.135 (-1.740, 2.010)	0.888	-1.043 (-3.358, 1.272)	0.377	-0.197 (-1.884,1.490)	0.819

Model 1: corrected for medication
Model 2: corrected for model 1+ age
Model 3: corrected for model 2 + smoking history, alcohol-use, baseline physical activity, baseline cardiovascular disease, use of hormone replacement therapy at baseline and follow-up
Model 4: corrected for model 3+ body mass index at baseline and follow-up
[1]Beta-coefficients with 95% confidence interval

Table S3c. Sensitivity analysis (Linear mixed models analysis using different inclusion criteria for women)[1]

Repeated measures linear mixed models analyzed with restricted maximum likelihood analysis of square on fully corrected models (model 4) using different "inclusion criteria" (1) fully corrected model (n=2588), (2) natural menopause (n=2241), (3) non-HRT users (n=1715), (4) healthy women without comorbidities (n=1213)

	Pre	Transition	p	Early	p	Late	p
Body mass index							
• Fully corrected model	*Ref*	2.926 (-2.764, 8.615)	0.314	1.494 (-5.604,8.591)	0.680	0.324 (-4.795,5.443)	0.901
• Natural menopause	Ref	3.153 (-2.547,8.854)	0.278	1.305 (-5.821, 8.432)	0.720	0.014 (-5.422, 5.451)	0.996
• Non-HRT users	Ref	3.882 (-2.050,9.815)	0.200	0.853 (-6.946,8.653)	0.830	1.332 (-5.577,8.241)	0.706
• Healthy women	Ref	3.186 (-2.512, 8.884)	0.273	-0.255 (-9.204, 8.692)	0.955	-10.46 (-25.99, 5.07)	0.187
Systolic blood pressure							
• Fully corrected model	*Ref*	-1.279 (-19.33, 16.78)	0.890	-12.04 (-34.54, 10.47)	0.294	7.611 (-8.659, 23.88)	0.359
• Natural menopause	Ref	-1.441 (-19.64, 16.76)	0.877	-11.44 (-34.18, 11.28)	0.324	4.31 (-13.09, 21.73)	0.627
• Non-HRT users	Ref	-2.472 (-20.09, 15.14)	0.783	-7.451 (-30.57, 15.67)	0.528	-6.039 (-26.74, 14.66)	0.568
• Healthy women	Ref	-5.865 (-20.41, 8.678)	0.429	1.367 (-21.45, 24.19)	0.907	-29.28 (-68.94, 10.37)	0.148
Diastolic blood pressure							
• Fully corrected model	*Ref*	2.173 (-9.796, 14.14)	0.722	-2.734 (-17.66, 12.19)	0.719	4.892 (-5.895, 15.68)	0.374
• Natural menopause	Ref	1.614 (-10.58, 13.81)	0.795	-4.27 (-19.51, 10.96)	0.582	0.032 (-11.63, 11.70)	0.996
• Non-HRT users	Ref	1.139 (-11.07, 13.358)	0.855	-1.107 (-17.14, 14.93)	0.892	-2.413 (-16.76, 11.93)	0.742
• Healthy women	Ref	-2.410 (-13.32, 8.500)	0.665	8.500 (-8.624, 25.62)	0.331	-19.28 (-49.03, 10.46)	0.204
Total cholesterol							
• Fully corrected model	*Ref*	0.537 (-0.579, 1.654)	0.346	1.107 (-0.286, 2.500)	0.119	0.992 (-0.013,1.996)	0.053
• Natural menopause	*Ref*	0.413 (-0.708, 1.535)	0.470	1.103 (-0.299, 2.505)	0.123	**1.489 (0.419, 2.558)**	**0.006**
• Non-HRT users	*Ref*	0.445 (-0.683, 1.594)	0.433	1.442 (-0.054, 2.939)	0.059	0.853 (-0.471, 2.179)	0.207
• Healthy women	*Ref*	0.630 (-0.581, 1.841)	0.308	**1.990 (0.089, 3.890)**	**0.040**	0.297 (-3.004, 3.598)	0.860
High density lipoprotein							
• Fully corrected model	*Ref*	-0.187 (-0.690, 0.315)	0.465	-0.348 (-0.975, 0.279)	0.277	0.0449 (-0.407, 0.497)	0.846
• Natural menopause	*Ref*	-0.177 (-0.686, 0.331)	0.494	-0.332 (-0.968, 0.302)	0.305	0.098 (-0.386, 0.584)	0.690
• Non-HRT users	*Ref*	-0.231 (-0.728, 0.266)	0.362	0.009 (-0.644, 0.664)	0.977	0.0164 (-0.562, 0.595)	0.956
• Healthy women	*Ref*	-0.083 (-0.612, 0.447)	0.759	-0.039 (-0.870, 0.792)	0.927	-0.134 (-1.579, 1.309)	0.855
Triglycerides (log)							
• Fully corrected model	*Ref*	0.441 (-0.0581,0.941)	0.083	0.198 (-0.425,0.821)	0.534	0.0412 (-0.408,0.491)	0.857
• Natural menopause	*Ref*	0.477 (-0.027, 0.982)	0.063	0.111 (-0.519, 0.742)	0.730	0.016 (-0.465, 0.496)	0.949

• Non-HRT users	*Ref*	0.513 (-0.004, 1.031)	0.052	0.279 (-0.401, 0.959)	0.421	0.325 (-0.276, 0.928)	0.289
• Healthy women	*Ref*	0.347 (-0.216, 0.912)	0.227	-0.094 (-0.980, 0.791)	0.834	0.062 (-1.476, 1.601)	0.937
Fasting blood glucose							
• Fully corrected model	*Ref*	0.274 (-0.461, 1.009)	0.465	0.0149 (-0.902, 0.932)	0.975	0.146 (-0.515, 0.807)	0.665
• Natural menopause	*Ref*	0.237 (-0.423, 0.897)	0.482	0.130 (-.6951098 .9560296)	0.757	0.393 (-0.235, 1.022)	0.220
• Non-HRT users	*Ref*	0.308 (-0.455, 1.072)	0.429	-0.251 (-1.255, 0.753)	0.624	-0.194 (-1.082, 0.695)	0.670
• Healthy women	*Ref*	0.415 (-0.166, 0.997)	0.162	-0.206 (-1.120, 0.707)	0.658	1.027 (-0.560, 2.614)	0.205
Serum insulin (log)							
• Fully corrected model	*Ref*	-0.338 (-0.928, 0.253)	0.262	-0.206 (-0.935, 0.523)	0.580	-0.0686 (-0.585,0.448)	0.794
• Natural menopause	*Ref*	-0.285 (-0.890, 0.318)	0.354	-0.268 (-1.015, 0.478)	0.481	-0.173 (-0.731, 0.385)	0.544
• Non-HRT users	*Ref*	-0.174 (-0.784, 0.437)	0.577	-0.379 (-1.176, 0.418)	0.351	-0.305 (-0.988, 0.378)	0.381
• Healthy women	*Ref*	-0.091 (-0.733, 0.551)	0.781	-0.220 (-1.201, 0.761)	0.660	-0.422 (-2.094, 1.248)	0.620
High sensitive C reactive protein							
• Fully corrected model	*Ref*	0.0541 (-1.126, 1.234)	0.928	-0.775 (-2.237, 0.686)	0.298	-0.0709 (-1.129, 0.987)	0.895
• Natural menopause	*Ref*	0.134 (-1.077, 1.347)	0.827	-0.699 (-2.203, 0.804)	0.362	-0.167 (-1.320, 0.984)	0.776
• Non-HRT users	*Ref*	0.199 (-1.035, 1.435)	0.751	-1.083 (-2.693, 0.526)	0.187	-0.227 (-1.662,1.206)	0.769
• Healthy women	*Ref*	0.529 (-0.825, 1.884)	0.444	-0.254 (-2.366, 1.858)	0.813	1.736 (-1.906, 5.379)	0.350
Leptin (log-score)							
• Fully corrected model	*Ref*	0.173 (-0.835,1.181)	0.736	0.716 (-0.493,1.925)	0.246	0.250 (-0.640,1.139)	0.582
• Natural menopause	*Ref*	0.189 (-0.837, 1.216)	0.718	0.862 (-0.366, 2.091)	0.169	0.196 (-0.761, 1.153)	0.688
• Non-HRT users	*Ref*	0.241 (-0.791, 1.273)	0.647	0.778 (-0.519, 2.075)	0.240	0.273 (-0.873, 1.419)	0.640
• Healthy women	*Ref*	0.076 (-1.062, 1.216)	0.895	.276 (-1.494, 2.046)	0.760	-0.614 (-3.542, 2.313)	0.681
Adiponectin (log-score)							
• Fully corrected model	*Ref*	-0.103 (-0.858, 0.651)	0.788	-0.003 (-0.925, 0.919)	0.994	0.313 (-0.349, 0.975)	0.355
• Natural menopause	*Ref*	-0.204 (-0.966, 0.558)	0.600	-0.065 (-0.996, 0.864)	0.890	0.432 (-0.274, 1.140)	0.230
• Non-HRT users	*Ref*	-0.330 (-1.007, 0.440)	0.401	0.403 (-0.588, 1.392)	0.425	0.110 (-0.745, 0.965)	0.801
• Healthy women	*Ref*	-0.301 (-1.106, 0.505)	0.465	0.989 (-0.251, 2.229)	0.118	-0.041 (-2.108, 2.026)	0.969
Interleukin 6							
• Fully corrected model	*Ref*	0.0174 (-1.824, 1.858)	0.985	-0.173 (-2.401, 2.056)	0.879	-0.554 (-2.193, 1.085)	0.508
• Natural menopause	*Ref*	0.234 (-1.666, 2.134)	0.810	-0.045 (-2.345, 2.255)	0.969	-0.695 (-2.485, 1.094)	0.446
• Non-HRT users	*Ref*	0.206 (-1.726, 2.138)	0.834	-0.511 (-2.958, 1.937)	0.683	-1.296 (-3.494, 0.901)	0.248
• Healthy women	*Ref*	0.905 (-1.241, 3.052)	0.408	0.034 (-3.207, 3.275)	0.984	-1.448 (-7.147, 4.250)	0.618
Tumor necrosis factor alpha							

• Fully corrected model	*Ref*	0.106 (-1.008,1.219)	0.852	0.157 (-1.191,1.506)	0.819	0.234 (-0.754,1.223)	0.642
• Natural menopause	*Ref*	0.141 (-1.009, 1.291)	0.810	0.344 (-1.046, 1.735)	0.628	-0.049 (-1.131, 1.031)	0.928
• Non-HRT users	*Ref*	-0.025 (-1.188, 1.137)	0.966	-0.00154 (-1.477, 1.474)	0.998	0.461 (-0.863, 1.785)	0.495
• Healthy women	*Ref*	-0.283 (-1.575, 1.008)	0.667	0.085 (-1.878, 2.047)	0.933	0.621 (-2.788, 4.031)	0.721
Interleukin 1b (log)							
• Fully corrected model	*Ref*	0.135 (-1.740, 2.010)	0.888	-1.043 (-3.358, 1.272)	0.377	-0.197 (-1.884,1.490)	0.819
• Natural menopause	*Ref*	0.354 (-1.575, 2.284)	0.719	-0.963 (-3.341, 1.415)	0.427	-0.709 (-2.557, 1.140)	0.453
• Non-HRT users	*Ref*	0.529 (-1.412, 2.471)	0.593	-0.502 (-3.008,2.004)	0.695	0.481 (-1.759,2.722)	0.674
• Healthy women	*Ref*	1.158 (-0.938, 3.254)	0.279	0.531 (-2.663, 3.727)	0.744	0.949 (-4.905, 6.804)	0.751

Model 1: corrected for medication
Model 2: corrected for model 1+ age
Model 3: corrected for model 2 + smoking history, alcohol-use, baseline physical activity, baseline cardiovascular disease, use of hormone replacement therapy at baseline and follow up
Model 4: corrected for model 3+ body mass index at baseline and follow-up
[1]Beta-coefficients with 95% confidence interval