

## 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 <sup>1</sup> 986	p value <sup>2</sup>
Demographic and lifestyle factors			
Age, mean (SD)	52.7 (10.5)	53.9 (11.1)	0.001
Educational attainment (%)			<0.001
• High	455 (17.8)	117 (11.9)	
• Middle	683 (26.7)	212 (21.7)	
• Low	1420 (55.5)	605 (66.4)	
Physical activity (PAFQ, min/day)			<0.001
• None	835 (33.2)	399 (41.2)	
• 1 per week	214 (8.5)	75 (7.9)	
• 2 per week	1438 (57.1)	464 (48.5)	
• 3 per week	31 (1.2)	18 (1.9)	
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			0.005
• Current smoker (%)	620 (24.2)	260 (26.4)	
• Former smoker (%)	741 (28.9)	231 (23.5)	
• Never (%)	1197 (46.8)	493 (50.1)	
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/m <sup>2</sup> ) 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

<sup>1</sup>Women excluded from the analysis were those with invalid/incorrect menstruation responses, and those without follow-up data

<sup>2</sup>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/m <sup>2</sup> )	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) <sup>3</sup>	704	505	279	1059
Fasting glucose (mmol/L)	704	505	279	1059
Insulin (microIU/mL) <sup>3</sup>	527	387	226	901
High sensitivity c-reactive protein <sup>3</sup>	690	495	278	1050
Leptin (ng/mL) <sup>3,4</sup>	552	379	228	888
Adiponectin (ng/mL) <sup>3,4</sup>	573	396	243	935
Tumor necrosis factor alpha (pg/mL) <sup>3</sup>	612	419	251	947
Interleukin 6 (pg/mL) <sup>3</sup>	521	364	220	858
Interleukin 1b (pg/mL) <sup>3</sup>	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 <sup>1</sup>
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/m <sup>2</sup> ) 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) <sup>3</sup>	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 (microlU/mL) <sup>3</sup>	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) <sup>3</sup>	1.1 (2.2)	1.1 (1.7)	1.35 (1.9)	1.7 (2.7)	<0.001
Leptin (ng/mL) <sup>3,4</sup>	0.56 (0.95)	0.60 (0.91)	0.68 (0.88)	0.81 (1.12)	<0.001
Adiponectin (ng/mL) <sup>3,4</sup>	0.89 (0.69)	0.91 (0.80)	1.06 (0.99)	1.13 (0.94)	<0.001
Tumor necrosis factor alpha (pg/mL) <sup>3</sup>	4.02 (4.68)	4.39 (5.62)	4.28 (5.09)	5.05 (5.69)	<0.001
Interleukin 6 (pg/mL) <sup>3</sup>	2.20 (6.65)	2.21 (6.14)	2.05 (6.13)	2.47 (5.81)	0.677
Interleukin 1b (pg/mL) <sup>3</sup>	0.62 (2.29)	0.48 (1.80)	0.42 (2.17)	0.39 (1.72)	0.902
Framingham risk score <sup>5</sup>	3.17 (2.63)	5.37 (3.76)	8.35 (7.18)	14.23 (9.41)	<0.001

<sup>1</sup>ANOVA for continuous variables and chi-square test for categorical variables

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

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

<sup>4</sup>Converted to standardized scores

<sup>5</sup> 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)<sup>1</sup>

	Pre	Transition	p	Early	p	Late	p	P value <sup>1</sup>
Body mass index								
• Model 1 (Beta, 95%CI)	Ref	0.364 (-0.163, 0.890)	0.176	<b>1.425 (0.787, 2.064)*</b>	0.000	<b>2.009 (1.571, 2.448)*</b>	0.000	<b>0.696 (0.555, 0.837)*</b>
• Model 2 (Beta, 95%CI)	Ref	0.278 (-0.300, 0.856)	0.346	<b>1.260 (0.474, 2.047)*</b>	0.002	<b>1.736 (0.857, 2.615)*</b>	0.000	<b>0.606 (0.316, 0.895)*</b>
• Model 3 (Beta, 95%CI)	Ref	0.457 (-0.081, 0.996)	0.096	<b>1.467 (0.722, 2.213)*</b>	0.000	<b>1.993 (1.142, 2.844)*</b>	0.000	<b>0.672 (0.389, 0.954)*</b>
• Model 4 (Beta, 95%CI)	Ref	-		-		-		
Systolic blood pressure								
• Model 1 (Beta, 95%CI)	Ref	<b>4.074 (2.312, 5.836)*</b>	0.000	<b>7.522 (5.379 - 9.666)*</b>	0.000	<b>14.64 (13.13, 16.15)*</b>	0.000	<b>4.889 (4.403, 5.376)*</b>
• 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	<b>1.762 (0.599, 2.925)*</b>	0.003	<b>3.196 (1.781, 4.611)*</b>	0.000	<b>2.733 (1.738, 3.728)*</b>	0.000	<b>0.876 (0.555, 1.198)*</b>
• Model 2 (Beta, 95%CI)	Ref	<b>1.999 (0.721, 3.277)*</b>	0.002	<b>3.648 (1.911, 5.384)*</b>	0.000	<b>3.481 (1.539, 5.424)*</b>	0.000	<b>1.177 (0.537, 1.818)*</b>
• Model 3 (Beta, 95%CI)	Ref	<b>2.191 (0.909, 3.473)*</b>	0.001	<b>4.144 (2.371, 5.916)*</b>	0.000	<b>4.231 (2.205, 6.257)*</b>	0.000	<b>1.448 (0.777, 2.119)*</b>
• Model 4 (Beta, 95%CI)	Ref	<b>1.950 (0.700, 3.200)*</b>	0.002	<b>3.366 (1.634, 5.098)*</b>	0.000	<b>3.195 (1.213, 5.177)*</b>	0.002	<b>1.098 (0.442, 1.754)*</b>
Total cholesterol								
• Model 1 (Beta, 95%CI)	Ref	<b>0.276 (0.171, 0.381)*</b>	0.000	<b>0.784 (0.656, 0.911)*</b>	0.000	<b>0.936 (0.847, 1.026)*</b>	0.000	<b>0.318 (0.289, 0.347)*</b>
• Model 2 (Beta, 95%CI)	Ref	0.106 (-0.007, 0.220)	0.066	<b>0.458 (0.303, 0.614)*</b>	0.000	<b>0.399 (0.226, 0.573)*</b>	0.000	<b>0.146 (0.088, 0.203)*</b>
• Model 3 (Beta, 95%CI)	Ref	0.098 (-0.017, 0.213)	0.097	<b>0.472 (0.312, 0.632)*</b>	0.000	<b>0.424 (0.241, 0.606)*</b>	0.000	<b>0.154 (0.093, 0.214)*</b>
• Model 4 (Beta, 95%CI)	Ref	0.087 (-0.027, 0.202)	0.136	<b>0.440 (0.280, 0.599)*</b>	0.000	<b>0.380 (0.197, 0.562)*</b>	0.000	<b>0.139 (0.079, 0.200)*</b>
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	<b>0.028 (0.014 - 0.041)*</b>
• 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	<b>0.049 (0.001, 0.098)*</b>	0.045	<b>0.071 (0.004, 0.139)*</b>	0.037	0.066 (-0.010, 0.143)	0.092	0.021 (-0.004, 0.046)
Triglycerides (log)								
• Model 1 (Beta, 95%CI)	Ref	<b>0.077 (0.027, 0.128)*</b>	0.002	<b>0.138 (0.077, 0.199)*</b>	0.000	<b>0.243 (0.200, 0.286)*</b>	0.000	<b>0.081 (0.067, 0.094)*</b>
• Model 2 (Beta, 95%CI)	Ref	0.035 (-0.019, 0.090)	0.200	0.058 (-0.016, 0.133)	0.124	<b>0.110 (0.027, 0.194)*</b>	0.009	<b>0.036 (0.008, 0.063)*</b>
• Model 3 (Beta, 95%CI)	Ref	0.029 (-0.024, 0.083)	0.285	0.055 (-0.019, 0.130)	0.150	<b>0.120 (0.035, 0.206)*</b>	0.006	<b>0.038 (0.010, 0.067)*</b>
• 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	<b>0.184 (0.070, 0.299)*</b>	0.002	<b>0.301 (0.223, 0.380)*</b>	0.000	<b>0.101 (0.076 - 0.127)*</b>	
• Model 2 (Beta, 95%CI)	Ref	0.073 (-0.030, 0.176)	0.166	<b>0.166 (0.025, 0.306)*</b>	0.021	<b>0.270 (0.113, 0.428)*</b>	0.001	<b>0.090 (0.038, 0.142)*</b>	
• Model 3 (Beta, 95%CI)	Ref	<b>0.105 (0.016, 0.195)*</b>	0.020	<b>0.194 (0.070, 0.317)*</b>	0.002	<b>0.282 (0.141, 0.423)*</b>	0.000	<b>0.093 (0.046, 0.139)*</b>	
• Model 4 (Beta, 95%CI)	Ref	<b>0.089 (0.002, 0.176)*</b>	0.045	<b>0.143 (0.022, 0.264)*</b>	0.020	<b>0.213 (0.075, 0.351)*</b>	0.003	<b>0.070 (0.024, 0.115)*</b>	
Serum insulin (log)									
• Model 1 (Beta, 95%CI)	Ref	-0.024 (-0.092, 0.044)	0.494	<b>0.020 (-0.061, 0.102)*</b>	0.624	<b>0.119 (0.063, 0.176)*</b>	0.000	<b>0.044 (0.026, 0.062)*</b>	
• Model 2 (Beta, 95%CI)	Ref	-0.013 (-0.088, 0.062)	0.728	0.040 (-0.059, 0.140)	0.427	<b>0.153 (0.041, 0.266)*</b>	0.007	<b>0.052 (0.014, 0.089)*</b>	
• Model 3 (Beta, 95%CI)	Ref	-0.001 (-0.075, 0.073)	0.977	0.045 (-0.055, 0.146)	0.377	<b>0.169 (0.054, 0.285)*</b>	0.004	<b>0.093 (0.046, 0.139)*</b>	
• 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	<b>0.070 (0.024, 0.116)*</b>	
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	<b>0.440 (0.335, 0.545)*</b>	0.000	<b>0.154 (0.120 - 0.188)*</b>	
• Model 2 (Beta, 95%CI)	Ref	-0.027 (-0.166, 0.111)	0.698	0.069 (-0.119, 0.257)	0.469	<b>0.311 (0.101, 0.521)*</b>	0.004	<b>0.104 (0.035, 0.174)*</b>	
• Model 3 (Beta, 95%CI)	Ref	-0.006 (-0.143, 0.130)	0.927	0.025 (-0.163, 0.214)	0.791	<b>0.234 (0.018, 0.450)*</b>	0.033	<b>0.073 (0.002, 0.145)*</b>	
• 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	<b>0.158 (0.049, 0.267)*</b>	0.005	<b>0.242 (0.167, 0.317)*</b>	0.000	<b>0.087 (0.063, 0.111)*</b>	
• Model 2 (Beta, 95%CI)	Ref	-0.010 (-0.111, 0.090)	0.840	<b>0.153 (0.018, 0.288)*</b>	0.026	<b>0.233 (0.082, 0.385)*</b>	0.003	<b>0.084 (0.034, 0.134)*</b>	
• Model 3 (Beta, 95%CI)	Ref	0.020 (-0.078, 0.118)	0.685	<b>0.181 (0.046, 0.315)*</b>	0.008	<b>0.261 (0.107, 0.415)*</b>	0.001	<b>0.073 (0.002, 0.145)*</b>	
• 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 (-0.009, 0.071)	
Adiponectin (log-score)									
• Model 1 (Beta, 95%CI)	Ref	0.0001 (-0.075, 0.075)	0.997	<b>0.126 (0.038, 0.215)*</b>	0.005	<b>0.167 (0.106, 0.229)*</b>	0.000	<b>0.060 (0.041, 0.080)*</b>	
• 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	<b>0.137 (0.028, 0.246)*</b>	0.013	<b>0.173 (0.047, 0.298)*</b>	0.007	<b>0.061 (0.020, 0.103)*</b>	
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	<b>0.178 (0.091, 0.266)*</b>	0.000	<b>0.062 (0.034, 0.090)*</b>	
• 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	<b>0.033 (-0.011, 0.078)*</b>	

• Model 2 (Beta, 95%CI)	Ref	0.175 (-0.012 -0.362)	0.067	<b>0.361 (0.111, 0.611)*</b>	0.005	<b>0.493 (0.210, 0.775)*</b>	0.001	<b>0.165 (0.072, 0.258)*</b>
• Model 3 (Beta, 95%CI)	Ref	0.175 (-0.013, 0.365)	0.069	<b>0.374 (0.116, 0.631)*</b>	0.004	<b>0.479 (0.182, 0.775)*</b>	0.002	<b>0.165 (0.066, 0.263)*</b>
• Model 4 (Beta, 95%CI)	Ref	0.163 (-0.025, 0.352)	0.090	<b>0.342 (0.084, 0.600)*</b>	0.009	<b>0.436 (0.138, 0.734)*</b>	0.004	<b>0.151 (0.052, 0.249)*</b>
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

<sup>1</sup>Beta-coefficients with 95% confidence interval

<sup>2</sup>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)<sup>1</sup>

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	<b>1.467 (0.722, 2.213)</b>	<b>0.000*</b>	<b>1.993 (1.142, 2.844)</b>	<b>0.000*</b>
• Natural menopause	Ref	0.267 (-0.280, 0.815)	0.339	<b>0.893 (0.127, 1.659)</b>	<b>0.022*</b>	0.799 (-0.078, 1.679)	0.075
• Non-HRT users	Ref	0.542 (-0.042, 1.128)	0.069	<b>1.451 (0.537, 2.365)</b>	<b>0.002*</b>	<b>2.361 (1.277, 3.444)</b>	<b>0.000*</b>
• 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	<b>1.950 (0.700, 3.200)</b>	<b>0.002*</b>	<b>3.366 (1.634, 5.098)</b>	<b>0.000*</b>	<b>3.195 (1.213, 5.177)</b>	<b>0.002*</b>
• Natural menopause	Ref	<b>1.891 (0.610, 3.173)</b>	<b>0.004*</b>	<b>2.681 (0.887, 4.476)</b>	<b>0.003*</b>	<b>2.302 (0.241, 4.363)</b>	<b>0.029*</b>
• Non-HRT users	Ref	<b>1.542 (0.205, 2.881)</b>	<b>0.024*</b>	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	<b>0.440 (0.280, 0.599)</b>	<b>0.000*</b>	<b>0.380 (0.197, 0.562)</b>	<b>0.000*</b>
• Natural menopause	Ref	0.073 (-0.044, 0.191)	0.221	<b>0.365 (0.201, 0.5298)</b>	<b>0.000*</b>	<b>0.287 (0.099, 0.476)</b>	<b>0.003*</b>
• Non-HRT users	Ref	0.054 (-0.066, 0.174)	0.373	<b>0.388 (0.201, 0.576)</b>	<b>0.000*</b>	<b>0.248 (0.024, 0.471)</b>	<b>0.029*</b>
• No comorbidities	Ref	-0.011 (-0.145, 0.122)	0.868	<b>0.250 (0.019, 0.481)</b>	<b>0.034*</b>	0.228 (-0.049, 0.506)	0.107
High density lipoprotein							
• Fully corrected model	Ref	<b>0.049 (0.001, 0.098)</b>	<b>0.045*</b>	<b>0.071 (0.004, 0.139)</b>	<b>0.037*</b>	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	<b>0.087 (0.010, 0.165)</b>	<b>0.027*</b>	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	<b>0.125 (0.021, 0.230)</b>	<b>0.018*</b>
• 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	<b>0.089 (0.002, 0.176)</b>	<b>0.045*</b>	<b>0.143 (0.022, 0.264)*</b>	<b>0.020*</b>	<b>0.213 (0.075, 0.351)</b>	<b>0.003*</b>
• Natural menopause	Ref	<b>0.094 (0.016, 0.172)</b>	<b>0.018*</b>	<b>0.160 (0.051, 0.269)</b>	<b>0.004*</b>	<b>0.184 (0.059, 0.310)</b>	<b>0.004*</b>
• Non-HRT users	Ref	0.075 (-0.016, 0.166)	0.106	0.081 (-0.061, 0.224)	0.264	<b>0.202 (0.032, 0.371)</b>	<b>0.020*</b>
• 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	<b>0.181 (0.034, 0.329)</b>	<b>0.016*</b>
• 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	<b>0.184 (0.030, 0.338)</b>	<b>0.019*</b>
• 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	<b>0.137 (0.028, 0.246)</b>	<b>0.013*</b>	<b>0.173 (0.047, 0.298)</b>	<b>0.007*</b>
• Natural menopause	Ref	-0.001 (-0.083, 0.081)	0.979	<b>0.131 (0.019, 0.244)</b>	<b>0.022*</b>	<b>0.173 (0.042, 0.304)</b>	<b>0.010*</b>
• Non-HRT users	Ref	0.015 (-0.070, 0.099)	0.735	<b>0.223 (0.094, 0.353)</b>	<b>0.001*</b>	<b>0.213 (0.057, 0.369)</b>	<b>0.007*</b>
• No comorbidities	Ref	0.015 (-0.081, 0.111)	0.762	<b>0.230 (0.068, 0.392)</b>	<b>0.006*</b>	<b>0.234 (0.034, 0.434)</b>	<b>0.022*</b>
Interleukin 6							
• Fully corrected model	Ref	0.163 (-0.025, 0.352)	0.090	<b>0.342 (0.084, 0.600)</b>	<b>0.009*</b>	<b>0.436 (0.138, 0.734)</b>	<b>0.004*</b>
• Natural menopause	Ref	0.153 (-0.046, 0.351)	0.132	<b>0.355 (0.080, 0.629)</b>	<b>0.011*</b>	<b>0.499 (0.181, 0.818)</b>	<b>0.002*</b>
• Non-HRT users	Ref	<b>0.216 (0.008, 0.424)</b>	<b>0.042*</b>	<b>0.410 (0.093, 0.729)</b>	<b>0.011*</b>	<b>0.532 (0.146, 0.919)</b>	<b>0.007*</b>
• No comorbidities	Ref	0.151 (-0.098, 0.400)	0.235	<b>0.469 (0.045, 0.892)</b>	<b>0.030*</b>	<b>0.568 (0.0412, 1.095)</b>	<b>0.035*</b>
Tumor necrosis factor alpha							

• Fully corrected model	<i>Ref</i>	-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	<i>Ref</i>	-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	<i>Ref</i>	-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	<i>Ref</i>	-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	<i>Ref</i>	-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	<i>Ref</i>	-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	<i>Ref</i>	-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	<i>Ref</i>	-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)

<sup>1</sup>Beta-coefficients with 95% confidence interval

**Table S3a.** Mean difference and 95% confidence interval of intermediate cardiovascular risk across different reproductive stages over time<sup>1</sup>

	Premenopause (PRE)	Transition (TRANS)	Early Menopause (EPOST)	Late Menopause (LPOST)	p-value <sup>2</sup>
Body mass index (kg/m <sup>2</sup> )	0.9 (0.7, 1.0)	0.8 (0.6, 0.9)	0.4 (0.2, 0.7)	0.5 (0.4, 0.6)	<b>&lt;0.0001</b>
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)	<b>&lt;0.0001</b>
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) <sup>3</sup>	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) <sup>3</sup>	-0.6 (-1.1, -0.2)	0.01 (-0.5, 0.5)	1.38 (0.5, 2.3)	0.6 (0.2, 1.0)	<b>&lt;0.0001</b>
High sensitivity c-reactive protein <sup>3</sup>	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) <sup>3,4</sup>	-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) <sup>3,4</sup>	-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) <sup>3</sup>	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) <sup>3</sup>	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) <sup>3</sup>	-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 <sup>5</sup>	-0.9 (-1.0, -0.7)	-1.6 (-1.8, -1.3)	-2.1 (-2.7, -1.4)	-2.2 (-2.6, -1.8)	<b>&lt;0.0001</b>

<sup>1</sup> 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.

<sup>2</sup>Statistical significance computed using ANOVA to compare the mean difference across groups

<sup>3</sup>Crude mean change. Transformation of values done in logarithmic scale prior to testing for statistical significance.

<sup>4</sup>Converted to standardized scores

<sup>5</sup>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<sup>1</sup>

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	<b>19.34 (2.634,36.06)*</b>	<b>0.023</b>
• 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	<b>1.418 (0.0250, 2.810)*</b>	<b>0.046</b>	<b>1.245 (0.261, 2.229)*</b>	<b>0.013</b>
• 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	<b>0.667 (0.131, 1.202)*</b>	0.015	0.244 (-0.423, 0.911)	0.474	0.169 (-0.301, 0.641)	0.480

• Model 2 (Beta, 95%CI)	Ref	<b>0.617 (0.082, 1.153)*</b>	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)	<i>Ref</i>	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)	<i>Ref</i>	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)	<i>Ref</i>	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)	<i>Ref</i>	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)	<i>Ref</i>	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)	<i>Ref</i>	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)	<i>Ref</i>	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)	<i>Ref</i>	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)	<i>Ref</i>	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

<sup>1</sup>Beta-coefficients with 95% confidence interval

**Table S3c.** Sensitivity analysis (Linear mixed models analysis using different inclusion criteria for women)<sup>1</sup>

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	<b>1.489 (0.419, 2.558)</b>	<b>0.006</b>
• 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	<b>1.990 (0.089, 3.890)</b>	<b>0.040</b>	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	<i>Ref</i>	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	<i>Ref</i>	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	<i>Ref</i>	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	<i>Ref</i>	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	<i>Ref</i>	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	<i>Ref</i>	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	<i>Ref</i>	-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	<i>Ref</i>	-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	<i>Ref</i>	-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	<i>Ref</i>	-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	<i>Ref</i>	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	<i>Ref</i>	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	<i>Ref</i>	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	<i>Ref</i>	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	<i>Ref</i>	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	<i>Ref</i>	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	<i>Ref</i>	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	<i>Ref</i>	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	<i>Ref</i>	-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	<i>Ref</i>	-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	<i>Ref</i>	-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	<i>Ref</i>	-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	<i>Ref</i>	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	<i>Ref</i>	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	<i>Ref</i>	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	<i>Ref</i>	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	<i>Ref</i>	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	<i>Ref</i>	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	<i>Ref</i>	-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	<i>Ref</i>	-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	<i>Ref</i>	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	<i>Ref</i>	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	<i>Ref</i>	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	<i>Ref</i>	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

<sup>1</sup>Beta-coefficients with 95% confidence interval