

# **SUPPLEMENTAL MATERIAL**

**Table S1. Baseline variables and CAC progression for women included and excluded from the analytical sample.**

<b>Variables*</b>	<b>Included N=474</b>	<b>Excluded N=253</b>	<b>P value †</b>
<b>Age at baseline, mean (SD), Yr</b>	52.7 (2.6)	52.7 (2.5)	0.70
<b>Age at menopause, mean (SD), Yr</b>	50.9 (2.6)	50.8 (2.6)	0.79
<b>Time since menopause, mean (SD), Yr</b>	1.8 (0.8)	1.9 (0.8)	0.03
<b>White Race, N (%)</b>	370 (78.1)	187 (73.9)	0.21
<b>Education, N (%)</b>			0.01
Declined to Answer	5 (1.1)	5 (2.0)	
High School graduate or less	29 (6.1)	29 (11.5)	
Some college	80 (16.9)	52 (20.6)	
College graduate	360 (75.9)	167 (66.0)	
<b>Employed, N (%)</b>	391 (82.5)	201 (79.4)	0.31
<b>Income, N (%)</b>			0.47
<\$60K	84 (17.7)	55 (21.7)	
\$60K-<\$100K	65 (13.7)	36 (14.2)	
>\$100K	85 (17.9)	37 (14.6)	

Unknown	240 (50.6)	125 (49.4)	
<b>Physical activity level, median(Q1, Q3), MET-hr/wk</b>	16.7 (7.0, 28.6)	17.5 (7.5, 28.3)	0.84
<b>Alcohol consumption, N (%)</b>	361 (76.2)	176 (69.6)	0.05
<b>Smoking Status, N (%)</b>			0.03
Never	380 (80.2)	191 (75.5)	
Past	70 (14.8)	36 (14.2)	
Current	24 (5.1)	26 (10.3)	
<b>Ever use hormone therapy, N (%)</b>	100 (21.1)	52 (20.6)	0.86
<b>Anti-Hypertensive medication use, N (%)</b>			0.29
Never	392 (82.7)	220 (87.0)	
Past	26 (5.5)	12 (4.7)	
Current	56 (11.8)	21 (8.3)	
<b>BMI, mean (SD), Kg/m<sup>2</sup></b>	26.0 (4.3)	26.5 (4.4)	0.20
<b>Waist circumference, mean (SD), cm</b>	84.4 (11.70)	84.3 (11.7)	0.92
<b>Systolic blood pressure, mean (SD), mmHg</b>	118.4 (15.1)	119.6 (14.5)	0.29
<b>HDL cholesterol, mean (SD), mg/dL</b>	72.2 (15.0)	71.7 (13.8)	0.68
<b>LDL cholesterol, mean (SD), mg/dL</b>	111.4 (27.5)	110.1 (28.4)	0.56

<b>Fasting glucose, median (Q1, Q3), mg/dL</b>	78.5 (74.0, 85.5)	78.0 (73.0, 84.0)	0.32
<b>Insulin, median (Q1, Q3), <math>\mu</math>U/mL</b>	4.2 (2.0, 7.4)	4.4 (2.10, 7.2)	0.75
<b>HOMA, median (Q1, Q3)</b>	0.8 (0.3, 1.5)	0.8 (0.4 1.4)	0.88
<b>EAT volume, median (Q1, Q3), cm<sup>3</sup></b>	36.8 (25.6, 54.5)	38.9 (27.7, 53.0)	0.50
<b>PAT volume, median (Q1, Q3), cm<sup>3</sup></b>	14.5 (10.2, 21.3)	6.5 (3.2, 11.8)	<0.001
<b>CAC Agatston score, median (Q1, Q2)</b>	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.24
<b>Any CAC (CAC&gt;0), N (%)</b>	55 (11.6)	37 (14.6)	0.24
<b>CAC progression, N (%)</b>	66 (13.9)	13 (13.5)	0.92
<b>Treatment groups, N (%)</b>			0.44
o-CEE	143 (30.2)	87 (34.4)	
t-E2	145 (30.6)	77 (30.4)	
Placebo	186 (39.2)	89 (35.2)	

CAC: coronary artery calcification; MET: metabolic equivalents; BMI: body mass index; HDL: high density lipoprotein; LDL: low density lipoprotein; HOMA: Homeostasis Model Assessment insulin resistance index EAT: epicardial adipose tissue; PAT: paracardial adipose tissue; o-CEE: oral conjugated equine estrogen; t-E2: transdermal 17 $\beta$ -estradiol;

\* Baseline levels presented unless otherwise specified

† Chi-square test for categorical variables; ANOVA or Wilcoxon Mann Whitney tests for continuous variables as appropriate

**Table S2. Baseline Study variables by 48-month CAC progression.**

Variables *	48-month CAC progression		P value †
	Yes N=66 (13.9%)	No N=408 (86.1%)	
<b>Age at baseline, mean (SD), Yr</b>	52.76 (2.73)	52.63 (2.55)	0.70
<b>Age at menopause, mean (SD), Yr</b>	50.80 (2.70)	50.89 (2.55)	0.79
<b>Time since menopause, mean (SD), Yr</b>	1.95 (0.82)	1.73 (0.77)	0.03
<b>White Race, N (%)</b>	54 (81.8)	316 (77.5)	0.43
<b>Education, N (%)</b>			0.01
Declined to Answer	0 (0.0)	5 (1.2)	
High School graduate or less	10 (15.2)	19 (4.7)	
Some college	14 (21.2)	66 (16.2)	
College graduate	42 (63.6)	318 (77.9)	
<b>Employed, N (%)</b>	51 (77.3)	340 (83.3)	0.23
<b>Income, N (%)</b>			0.78
<\$60K	13 (19.7)	71 (17.4)	
\$60K-<\$100K	10 (15.2)	55 (13.5)	
>\$100K	9 (13.6)	76 (18.6)	

Unknown	34 (51.5)	206 (50.5)	
<b>Physical activity level, median(Q1, Q3), MET-hr/wk</b>	16.2 (7.3, 29.8)	16.7 (7.0, 28.5)	0.62
<b>Alcohol consumption, N (%)</b>	48 (72.7)	313 (76.7)	0.48
<b>Smoking Status, N (%)</b>			0.24
Never	52 (78.8)	328 (80.4)	
Past	8 (12.1)	62 (15.2)	
Current	6 (9.1)	18 (4.4)	
<b>Ever use hormone therapy, N (%)</b>	18 (27.3)	82 (20.1)	0.19
<b>Anti-Hypertensive medication use, N (%)</b>	N=66	N=408	0.62
Never	52 (78.8)	340 (83.3)	
Past	5 (7.6)	21 (5.1)	
Current	9 (13.6)	47 (11.5)	
<b>BMI, mean (SD), Kg/m<sup>2</sup></b>	26.3 (4.3)	26.0 (4.3)	0.55
<b>Waist circumference, mean (SD), cm</b>	85.4 (11.1)	84.2 (11.8)	0.43
<b>Systolic blood pressure, mean (SD), mmHg</b>	118.9 (14.2)	118.3 (15.3)	0.77
<b>HDL cholesterol, mean (SD), mg/dL</b>	70.7 (17.0)	72.4 (14.7)	0.39

<b>LDL cholesterol, mean (SD), mg/dL</b>	113.5 (26.4)	111.1 (27.6)	0.51
<b>Triglycerides, median (Q1, Q3), mg/dL</b>	80.0 (64.0, 131.0)	68.0 (49.0, 103.0)	0.01
<b>Fasting glucose, median (Q1, Q3), mg/dL</b>	83.0 (73.0, 89.0)	78.0 (74.0, 85.0)	0.11
<b>Insulin, median (Q1, Q3), <math>\mu</math>U/mL</b>	5.1 (3.0, 9.7)	3.9 (1.0, 7.0)	0.01
<b>HOMA, median (Q1, Q3)</b>	1.1 (0.6, 1.9)	0.8 (0.2, 1.4)	0.01
<b>EAT volume, median (Q1, Q3), cm<sup>3</sup></b>	41.6 (29.5, 60.3)	36.5 (25.4, 51.7)	0.20
<b>PAT volume, median (Q1, Q3), cm<sup>3</sup></b>	16.7 (10.6, 21.3)	14.3 (10.2, 21.5)	0.23
<b>Treatment groups, N (%)</b>			0.93
o-CEE	20 (30.3)	123 (30.1)	
t-E2	19 (28.8)	126 (30.9)	
Placebo	27 (40.9)	159 (39.0)	

CAC: coronary artery calcification; MET: metabolic equivalents; BMI: body mass index; HDL: high density lipoprotein; LDL: low density lipoprotein; HOMA: Homeostasis Model Assessment insulin resistance index EAT: epicardial adipose tissue; PAT: paracardial adipose tissue; o-CEE: oral conjugated equine estrogen; t-E2: transdermal 17 $\beta$ -estradiol;

\* Baseline levels presented unless otherwise specified

†Chi-square test: for categorical variables, ANOVA or Wilcoxon Mann Whitney tests for continuous variables as appropriate

**Table S3. Multivariable logistic regression results of the association between the change in heart fat depots and CAC progression.**

Change in heart fat depots	Model 1 *		Model 2 †	
	OR (95% CIs) ‡	P value	OR (95% CIs) ‡	P value
<b>EAT change</b>	1.08(0.83,1.42)	0.57	1.04(0.75,1.45)	0.80
<b>PAT change</b>	1.11(0.85,1.45)	0.44	1.04(0.77,1.42)	0.79

CAC: coronary artery calcification; MET: metabolic equivalents; BMI: body mass index; LDL-C: low density lipoprotein cholesterol;

EAT: epicardial adipose tissue; PAT: paracardial adipose tissue

\* Model 1: Adjusted for age, race (white vs. non-white) and study site (east, west and middle)

† Model 2: Model 1 + smoke, METs, education, triglycerides, LDL-C, anti-hypertensive medication, alcohol consumption, SBP, WC, treatment and baseline heart fat (EAT in model for EAT change and Pat in model for PAT change).

‡ OR represents the relative increase in the odds of CAC per 1 SD increase in the change of heart fat volume

**Table S4. Multivariable logistic regression results of the association between the change in heart fat depots and the CAC progression, by treatment.**

Change in heart fat depots	Treatment	Model 1 *			Model 2 †		
		OR (95% CIs) ‡	P value		OR (95% CIs) ‡	P value	
EAT change	<b>o-CEE</b>	1.05(0.68,1.63)	0.69	ref	1.04(0.63,1.70)	0.56	ref
	<b>t-E2</b>	1.54(0.81,2.91)	0.20	0.34	1.52(0.79,2.91)	0.14	0.34
	<b>Placebo</b>	0.94(0.63,1.39)	ref	0.69	0.86(0.55,1.35)	ref	0.56
<b>EAT change*treatment P values</b>		0.43			0.34		
PAT change	<b>o-CEE</b>	0.96(0.62,1.48)	0.79	ref	0.82(0.50,1.36)	0.99	ref
	<b>t-E2</b>	2.89(1.4,5.98)	0.005	0.01	2.73(1.29,5.75)	0.007	0.008
	<b>Placebo</b>	0.88(0.6,1.3)	ref	0.79	0.82(0.52,1.27)	ref	0.99
<b>PAT change*treatment P values</b>		0.01			0.02		

CAC: coronary artery calcification; MET: metabolic equivalents; BMI: body mass index; LDL-C: low density lipoprotein cholesterol;

EAT: epicardial adipose tissue; PAT: paracardial adipose tissue

\* Model 1: Adjusted for age, race (white vs. non-white) and study site (east, west and middle)

† Model 2: Model 1 + smoke, METs, education, triglycerides, LDL-C, anti-hypertensive medication, alcohol consumption, SBP, WC, treatment and baseline heart fat (EAT in model for EAT change and Pat in model for PAT change).

‡ OR represents the relative increase in the odds of CAC progression per 1 SD increase in the change of heart fat

**Table S5. IPW sensitivity analysis for odds ratio (95% CI) of any increase in heart fat depots over 48 months by treatment group.**

Treatment	Any increase after 48 month			
	EAT *		PAT †	
	OR(95% CI)	P value	OR(95% CI)	P value
			0.06	
<b>o-CEE</b>	0.62(0.40, 0.97)	0.03	1.26(0.81, 1.97)	0.30
<b>t-E2</b>	0.99(0.64, 1.55)	0.99	1.20(0.77, 1.86)	0.42
<b>Placebo</b>	----	---	----	---

EAT: epicardial adipose tissue; PAT: paracardial adipose tissue; o-CEE: oral conjugated

equine estrogen; t-E2: transdermal 17 $\beta$ -estradiol

\* EAT: o-CEE vs. t-E2; OR(95% CI): 0.62(0.39, 0.99), P=0.02

† PAT: o-CEE vs. t-E2; OR(95% CI): 1.05(0.66, 1.68), P=0.49

**Table S6. IPW sensitivity analysis of the association between the change in heart fat depots and CAC progression from multivariable logistic regression.**

Change in heart fat depots	Model 1 *		Model 2 †	
	OR (95% CIs) ‡	P value	OR (95% CIs) ‡	P value
<b>EAT change</b>	1.11 (0.83,1.49)	0.48	1.06 (0.75,1.50)	0.73
<b>PAT change</b>	1.09 (0.82,1.44)	0.55	1.01 (0.73,1.40)	0.95

CAC: coronary artery calcification; MET: metabolic equivalents; BMI: body mass index; LDL-C: low density lipoprotein cholesterol;

EAT: epicardial adipose tissue; PAT: paracardial adipose tissue

\* Model 1: Adjusted for age, race (white vs. non-white) and study site (east, west and middle)

† Model 2: Model 1 + smoke, METs, education, triglycerides, LDL-C, anti-hypertensive medication, alcohol consumption, SBP, WC, treatment and baseline heart fat (EAT in model for EAT change and Pat in model for PAT change).

‡ OR represents the relative increase in the odds of CAC progression per 1 SD increase in the change of heart fat volume

**Table S7. IPW sensitivity analysis of the association between the change in heart fat depots and the CAC progression from multivariable logistic regression, by treatment.**

Change in heart fat depots	Treatment	Model 1 *			Model 2 †		
		OR (95% CIs) ‡	P value		OR (95% CIs) ‡	P value	
EAT change	<b>o-CEE</b>	1.01 (0.63,1.64)	0.99	ref	0.98 (0.58,1.68)	0.86	ref
	<b>t-E2</b>	1.48 (0.78,2.83)	0.33	0.35	1.49 (0.77,2.87)	0.23	0.32
	<b>Placebo</b>	1.01 (0.66, 1.55)	ref	0.99	0.92 (0.57,1.49)	ref	0.86
<b>EAT change*treatment P values</b>		0.58			0.47		
PAT change	<b>o-CEE</b>	0.91 (0.56,1.48)	0.81	ref	0.74 (0.44,1.27)	0.89	Ref
	<b>t-E2</b>	2.91 (1.39,6.10)	0.004	0.009	2.68 (1.26,5.74)	0.007	0.006
	<b>Placebo</b>	0.85 (0.57,1.26)	ref	0.81	0.78 (0.48,1.26)	ref	0.89
<b>PAT change*treatment P values</b>		0.01			0.01		

CAC: coronary artery calcification; MET: metabolic equivalents; BMI: body mass index; LDL-C: low density lipoprotein cholesterol;

EAT: epicardial adipose tissue; PAT: paracardial adipose tissue

\* Model 1: Adjusted for age, race (white vs. non-white) and study site (east, west and middle)

† Model 2: Model 1 + smoke, METs, education, triglycerides, LDL-C, anti-hypertensive medication, alcohol consumption, SBP, WC, treatment and baseline heart fat (EAT in model for EAT change and Pat in model for PAT change).

‡ OR represents the relative increase in the odds of CAC progression per 1 SD increase in the change of heart fat