

ATVB Online Supplement

**The Relationship of Cigarette Smoking with Inflammation and Subclinical Vascular Disease: The Multi-Ethnic Study of Atherosclerosis.**

*McEvoy. Smoking, inflammation, and atherosclerosis*

**Supplementary E-Table I: Reclassification of smoking status based on Urinary Cotinine**

		Smoking Status by Self Report			
	Number (% reclassified)	Never Smoker	Former Smoker	Current Smoker	<b><i>Total</i></b>
Smoking Status Corrected by Urine Cotinine Levels	Never Smoker	3218	0	0	<b><i>3218</i></b>
	Former Smoker	175 (2.6%)	2432	0	<b><i>2607</i></b>
	Current Smoker	28 (0.4%)	56 (0.8%)	887	<b><i>971</i></b>
	<i>Total</i>	3421	2488	887	<b><i>6796</i></b>

Never smokers at the baseline visit who reported being former smokers at MESA visit 2 were reclassified as baseline former smokers. In subjects with urinary cotinine values (n=3,965), former-smokers and never-smokers with cotinine levels >500ng/mL were reclassified as current-smokers.

**Supplementary E-Table II: Association of Smoking Status with Domains of CVD, with and without adjustment for Alcohol, Fever and Anti-inflammatory medications\***

	Model Covariates	SMOKING STATUS		
		Never Smokers	Former Smokers	Current Smokers
<b>Inflammation</b>				
hsCRP, β-Coefficient ‡	Base Model *	0 (ref)	<b>0.08 (0.02 to 0.14)</b>	<b>0.31 (0.23 to 0.38)   </b>
	Base Model +Alcohol status and calories +Recent Fever + Anti-inflammatory medications†	0 (ref)	<b>0.08 (0.02 to 0.14)</b>	<b>0.31 (0.23 to 0.39)   </b>
IL-6, β-Coefficient ‡	Base Model *	0 (ref)	<b>0.06 (0.02 to 0.09)</b>	<b>0.18 (0.14 to 0.23)   </b>
	Base Model +Alcohol status and calories +Recent Fever + Anti-inflammatory medications†	0 (ref)	<b>0.05 (0.02 to 0.08)</b>	<b>0.19 (0.14 to 0.23)   </b>
<b>Vascular Function</b>				
Carotid Distensibility, β-Coefficient §	Base Model *	0 (ref)	0.03 (-0.01 to 0.07)	<b>0.18 (0.12 to 0.23)   </b>
	Base Model +Alcohol status and calories +Recent Fever + Anti-inflammatory medications†	0 (ref)	0.02 (-0.02 to 0.06)	<b>0.17 (0.11 to 0.23)   </b>
Aortic Distensibility, β-Coefficient ‡, §	Base Model *	0 (ref)	-0.01 (-0.04 to 0.03)	<b>-0.05 (-0.10 to -0.01)</b>
	Base Model +Alcohol status and calories +Recent Fever + Anti-inflammatory medications†	0 (ref)	-0.01 (-0.05 to 0.03)	<b>-0.06 (-0.11 to -0.01)</b>
Flow-Mediated Dilation, β-Coefficient §	Base Model *	0 (ref)	0.13 (-0.08 to 0.35)	0.02 (-0.27 to 0.32)
	Base Model +Alcohol status and calories +Recent Fever + Anti-inflammatory medications†	0 (ref)	0.09 (-0.14 to 0.31)	-0.03 (-0.33 to 0.27)

<b>Subclinical Atherosclerosis</b>				
CIMT, $\beta$ -Coefficient	Base Model *	0 (ref)	<b>0.05 (0.03 to 0.07)</b>	<b>0.09 (0.06 to 0.12)</b>
	Base Model +Alcohol status and calories +Recent Fever + Anti-inflammatory medications†	0 (ref)	<b>0.04 (0.02 to 0.07)</b>	<b>0.07 (0.03 to 0.13)</b>
CAC>0, Odds Ratio,	Base Model *	1 (ref)	<b>1.38 (1.21 to 1.57)   </b>	<b>1.79 (1.49 to 2.14)   </b>
	Base Model +Alcohol status and calories +Recent Fever + Anti-inflammatory medications†	1 (ref)	<b>1.40 (1.22 to 1.60)   </b>	<b>1.81 (1.50 to 2.17)   </b>
ABI <1, Odds Ratio	Base Model *	1 (ref)	<b>1.24 (1.02 to 1.50)</b>	<b>2.22 (1.74 to 2.83)   </b>
	Base Model +Alcohol status and calories +Recent Fever + Anti-inflammatory medications†	1 (ref)	<b>1.19 (0.97 to 1.45)</b>	<b>2.19 (1.70 to 2.81)   </b>

\*All values are expressed as Odds Ratios or  $\beta$ -Coefficients; with 95% confidence Intervals. The base model is adjusted for age, gender, race, MESA site, BMI, hypertension status, diabetes status, heart rate, LDL-C, HDL-C, triglycerides, treatment for dyslipidemia, family history of MI, and level of education.

† Anti-inflammatory medications (yes/no for reported current use of either aspirin, NSAIDs, or steroids)

‡ Log-transformed § See Table 1 for sample sizes

**Significant values (P<0.05) are presented in bold.**

**|| P-value <0.001**

**Supplementary E-Table III: Smoking and Domains of subclinical CVD; stratified by Gender\***

	MALE			FEMALE†			Interaction p-value
	Never Smokers	Former Smokers	Current Smokers	Never Smokers	Former Smokers	Current Smokers	
<b>Inflammation</b>							
hsCRP ≥2mg/L, Odds Ratio	1 (ref)	1.16 (0.96 to 1.39)	<b>2.10 (1.63 to 2.70)   </b>	1 (ref)	1.21 (0.99 to 1.46)	<b>1.34 (1.02 to 1.75)</b>	0.12
hsCRP, β-Coefficient ‡	0 (ref)	0.05 (-0.02 to 0.13)	<b>0.39 (0.28 to 0.50)   </b>	0 (ref)	0.06 (-0.02 to 0.14)	<b>0.16 (0.04 to 0.28)</b>	0.17
IL-6, β-Coefficient ‡	0 (ref)	<b>0.07 (0.02 to 0.11)</b>	<b>0.22 (0.15 to 0.29)   </b>	0 (ref)	0.04 (-0.01 to 0.88)	<b>0.13 (0.07 to 0.20)   </b>	0.21
Fibrinogen, β-Coefficient	0 (ref)	-2.87 (-7.78 to 2.05)	<b>16.25 (9.48 to 23.02)   </b>	0 (ref)	-4.79 (-10.24 to 0.66)	2.89 (-4.58 to 10.37)	<b>0.01</b>
<b>Vascular Function</b>							
Carotid Distensibility, β-Coefficient §	0 (ref)	0.01 (-0.05 to 0.07)	<b>0.13 (0.04 to 0.21)</b>	0 (ref)	0.02 (-0.03 to 0.08)	<b>0.22 (0.14 to 0.30)   </b>	0.17
Aortic Distensibility, β-Coefficient ‡, §	0 (ref)	0.01 (-0.04 to 0.06)	<b>-0.07 (-0.01 to -0.14)</b>	0 (ref)	-0.05 (-0.10 to 0.01)	-0.02 (-0.10 to 0.06)	0.95
Flow-Mediated Dilation, β-Coefficient §	0 (ref)	0.02 (-0.26 to 0.31)	0.15 (-0.24 to 0.54)	0 (ref)	0.24 (-0.11 to 0.60)	-0.07 (-0.54 to 0.39)	0.50
<b>Subclinical Atherosclerosis</b>							
CAC>0, Odds Ratio,	1 (ref)	<b>1.30 (1.08 to 1.53)</b>	<b>1.61 (1.24 to 2.09)   </b>	1 (ref)	<b>1.62 (1.33 to 1.98)   </b>	<b>2.21 (1.69 to 2.89)   </b>	0.19
CAC >75 <sup>th</sup> centile, Odds Ratio §	1 (ref)	1.04 (0.82 to 1.31)	1.29 (0.93 to 1.78)	1 (ref)	1.33 (0.98 to 1.79)	<b>1.54 (1.00 to 2.37)</b>	<b>0.04</b>
ABI<1, Odds Ratio	1 (ref)	1.30 (0.91 to 1.86)	<b>2.73 (1.76 to 4.23)   </b>	1 (ref)	1.14 (0.89 to 1.46)	<b>2.12 (1.54 to 2.92)   </b>	0.41

\*All values are expressed as Odds Ratios or β-Coefficients; with 95% confidence Intervals. Each robust linear and logistic model is adjusted for age, gender, race, MESA site, BMI, hypertension status, diabetes status, heart rate, LDL-C, HDL-C, triglycerides, treatment for dyslipidemia, family history of MI, and level of education.

†For the stratified analysis in females we also controlled for Hormone-Replacement Therapy status in the fully adjusted model

‡ Log-transformed § See Table 1 for sample sizes

**Significant values (P<0.05) are presented in bold.**

**|| P-value <0.001**

**Supplementary E-Table IV: Smoking, inflammation and atherosclerosis; stratified by Ethnicity**

	Former Smokers*†	Current Smokers*†
<b>hsCRP, <math>\beta</math>-Coefficient, ‡</b>		
White	0.04 (-0.05, 0.13)	<b>0.33 (0.19, 0.46) §</b>
Chinese American	0.03 (-0.16, 0.21)	0.17 (-0.11, 0.44)
African American	<b>0.14 (0.03, 0.26)</b>	<b>0.37 (0.22, 0.51) §</b>
Hispanic	0.02 (-0.10, 0.14)	0.15 (-0.01, 0.31)
<i>Smoking-ethnicity interaction, p=0.89</i>		
<b>hsCRP <math>\geq</math>2mg/L, Odds Ratio</b>		
White	1.14 (0.94, 1.38)	<b>1.91 (1.41, 2.59) §</b>
Chinese American	1.09 (0.61, 1.94)	0.94 (0.39-2.26)
African American	<b>1.40 (1.10, 1.77)</b>	<b>2.04 (1.48, 2.82) §</b>
Hispanic	1.07 (0.82, 1.39)	1.30 (0.90, 1.87)
<i>Smoking-ethnicity interaction, p=0.96</i>		
<b>CAC&gt;0, Odds Ratio,</b>		
White	<b>1.37 (1.11, 1.68)</b>	<b>2.00 (1.45, 2.76) §</b>
Chinese American	0.98 (0.60, 1.57)	1.03 (0.50-2.09)
African American	<b>1.43 (1.12, 1.82)</b>	<b>1.91 (1.41, 2.60) §</b>
Hispanic	<b>1.74 (1.29, 2.33) §</b>	<b>1.77 (1.18, 2.65)</b>
<i>Smoking-ethnicity interaction, p=0.92</i>		
<b>CAC &gt;75<sup>th</sup> Percentile, Odds Ratio</b>		
White	1.28 (0.99, 1.66)	<b>1.56 (1.07, 2.30)</b>
Chinese American	1.18 (0.62, 2.27)	0.41 (0.15, 1.10)
African American	1.41 (0.97, 2.06)	1.45 (0.89, 2.36)
Hispanic	0.87 (0.58, 1.30)	<b>1.93 (1.06, 3.52)</b>
<i>Smoking-ethnicity interaction, p=0.80</i>		
<b>ABI &lt;1.0, Odds Ratio</b>		
White	<b>1.62 (1.17, 2.23)</b>	<b>2.73 (1.78, 4.18) §</b>
Chinese American	1.59 (0.56, 4.55)	0.53 (0.06, 4.58)
African American	1.24 (0.91, 1.68)	<b>2.15 (1.48, 3.10) §</b>
Hispanic	0.57 (0.33, 1.00)	<b>1.90 (1.00, 3.61)</b>
<i>Smoking-ethnicity interaction, p=0.11</i>		

\*All values are compared to Never Smokers and expressed as Odds Ratios or  $\beta$ -Coefficients; with 95% Confidence Intervals and p-values. The  $\beta$ -Coefficient should be interpreted as the absolute adjusted difference in a variable compared to never smokers.

† Adjusted for age, gender, MESA site, BMI, hypertension status, diabetes status, heart rate, LDL-C, HDL-C, triglycerides, treatment for dyslipidemia, family history of MI, and level of education. Race removed from model.

‡ Log transformed

**Significant values (P<0.05) are presented in bold.** Abbreviations and sample numbers per Table 1.

**§ P-value <0.001**

**Supplementary E-Table V- Association of Smoking Cessation Interval with Domains of CVD, after further correction for pack-years\***

	<b>Former Smokers- 1-yr quit interval</b>	<b>Former Smokers- 1-yr quit interval further corrected for pack-years</b>	<b>Former Smokers- 5-yr quit interval</b>	<b>Former Smokers- 5-yr quit interval further corrected for pack-years</b>
<b>Inflammation</b>				
hsCRP ≥2mg/L, Odds Ratio	<b>0.98 ‡ (0.97, 0.99)</b>	<b>0.98 ‡ (0.97, 0.99)</b>	<b>0.91 ‡ (0.88 to 0.95)</b>	<b>0.92 ‡ (0.87 to 0.96)</b>
IL-6 , β-Coefficient †	<b>-0.003 (-0.005, -0.001)</b>	<b>-0.003 (-0.005, -0.001)</b>	<b>-0.02 (-0.03 to -0.01)</b>	<b>-0.01 (-0.02 to -0.01)</b>
<b>Subclinical Atherosclerosis</b>				
cIMT, β-Coefficient	<b>-0.002 (-0.004, -0.001)</b>	-0.001 (-0.002, 0.001)	<b>-0.01 (-0.02 to -0.004)</b>	-0.003 (-0.01, 0.006)
CAC>0, Odds Ratio,	<b>0.98 ‡ (0.97, 0.99)</b>	0.99 (0.98, 1.00)	<b>0.94 ‡ (0.90 to 0.97)</b>	0.97 (0.92 to 1.01)
ABI<1, Odds Ratio	<b>0.98 (0.97, 0.99)</b>	0.99 (0.98, 1.00)	<b>0.91 (0.86 to 0.96)</b>	0.95 (0.89 to 1.01)

\*All values are expressed as Odds Ratios or β-Coefficients; with 95% confidence Intervals. Each robust linear and logistic model is adjusted for age, gender, race, MESA site, BMI, hypertension status, diabetes status , heart rate, LDL-C, HDL-C, triglycerides, treatment for dyslipidemia, family history of MI, and level of education. The pack-year adjustment then adds pack-years, as a continuous variable, to this model.

† Log-transformed

**Significant values (P<0.05) are presented in bold.**

**‡ P-value <0.001**

**Supplementary E-Table VI: Smoking status in subsamples of Cardiac MRI (N=3530) and Flow-Mediated Dilation (N=3027)**

	Smoking Status			Total
	Never	Former	Current	
<b>ENTIRE SAMPLE, n (%)</b>	3218 (47)	2607 (38)	971 (14)	6796
<b>IMAGING SUB-SAMPLES</b>				
<b>FMD, n (%)</b>	1450 (48)	1115 (38)	422 (14)	3027
<b>Aortic MRI, n (%)</b>	1702 (49)	1296 (37)	497 (14)	3495

*FMD-Flow-Mediated Dilation, MRI=Magnetic Resonance Imaging*



**Supplementary E-Table VII: Effect Modification of Inflammation on the association between smoking and CAC; with and without adjustment for cumulative exposure**

	Never Smokers	Former Smokers	Current Smokers
<b>Odds Ratio of CAC&gt;0</b>			
If hsCRP <2 mg/L	1 (ref)	<b>1.32</b> ( <b>1.11, 1.59</b> ) <i>1.16 *</i> ( <i>0.96, 1.41</i> )	<b>1.58 §</b> ( <b>1.21, 2.07</b> ) <i>1.28 *</i> ( <i>0.96, 1.71</i> )
If hsCRP >2 mg/L	0.92 (0.77, 1.09) <i>0.92 *</i> ( <i>0.77, 1.09</i> )	<b>1.30</b> ( <b>1.08, 1.57</b> ) <i>1.11 *</i> ( <i>0.90, 1.36</i> )	<b>1.85 † §</b> ( <b>1.45, 2.36</b> ) <i>1.45 *, †</i> ( <i>1.10, 1.90</i> )
<b>Odds Ratio of CAC&gt;75<sup>th</sup> centile</b>			
If hsCRP <2 mg/L	1 (ref)	1.09 (0.86, 1.39) <i>1.01 *</i> ( <i>0.79, 1.31</i> )	0.95 (0.67, 1.36) <i>0.84 *</i> ( <i>0.58, 1.22</i> )
If hsCRP >2 mg/L	0.86 (0.67-1.12) <i>0.86 *</i> ( <i>0.67-1.12</i> )	1.13 (0.88, 1.45) <i>1.02 *</i> ( <i>0.78, 1.33</i> )	<b>1.64 ‡</b> ( <b>1.17, 2.29</b> ) <i>1.39 *, †</i> ( <i>0.96, 2.02</i> )

Never smokers with hsCRP<2mg/L are the referent group. Models adjusted for age, gender, race, MESA site, BMI, hypertension status, diabetes status, heart rate, LDL-C, HDL-C, triglycerides, treatment for dyslipidemia, family history of MI, and level of education.

\*Hierarchical model with additional adjustment for pack-years.

†Interaction of hsCRP on smoking and CAC>0, p=0.20 (Interaction p=0.30 when adjusted for pack-years). ‡Interaction of hsCRP on smoking and CAC>75<sup>th</sup> centile, p=0.01 (Interaction p=0.02 when adjusted for pack-years).

**Significant values (P<0.05) presented in bold.**

**§ P-value <0.001**

CAC>75<sup>th</sup> %= Coronary artery calcium greater than the 75<sup>th</sup> percentile for age and sex, CAC>0 AU= Coronary Artery Calcium greater than zero Agatston Units, FS=Former Smokers, CS=Current Smokers, hsCRP=high-sensitivity C-Reactive Protein

**Supplementary E-Table VIII: Effect Modification of Inflammation on the association between smoking and either CIMT or ABI <1.0**

	Never Smokers	Former Smokers	Current Smokers
<b>Beta-coefficient CIMT</b>			
If hsCRP <2 mg/L	1 (ref)	0.015 (-0.001, 0.023)	<b>0.026 §</b> <b>(0.015, 0.039)</b>
If hsCRP >2 mg/L	<b>0.011</b> <b>(0.001, 0.023)</b>	0.008 (-0.003, 0.194)	<b>0.029 † §</b> <b>(0.013, 0.044)</b>
<b>Odds Ratio of ABI &lt;1.0</b>			
If hsCRP <2 mg/L	1 (ref)	<b>1.52</b> <b>(1.01, 2.30)</b>	<b>1.59 §</b> <b>(1.22, 2.07)</b>
If hsCRP >2 mg/L	1.20 (0.91, 1.59)	1.27 (0.97, 1.65)	<b>3.32 ‡ §</b> <b>(2.36, 4.40)</b>

Never smokers with hsCRP<2mg/L are the referent group. Models adjusted for age, gender, race, MESA site, BMI, hypertension status, diabetes status, heart rate, LDL-C, HDL-C, triglycerides, treatment for dyslipidemia, family history of MI, and level of education.

†Interaction of hsCRP on smoking and CIMT, p=0.02

‡Interaction of hsCRP on smoking and ABI<1.0, p=0.004

**Significant values (P<0.05) presented in bold.**

**§ P-value <0.001**

*CIMT=Carotid intima-media thickness, ABI=Ankle-Brachial Index., FS=Former Smokers, CS=Current Smokers, hsCRP=high-sensitivity C-Reactive Protein*

**Supplementary E-Table IX: Sensitivity Analysis evaluating the association between smoking status and hs-CRP outcomes, excluding persons with hs-CRP  $\geq 10$ mg/L (Compare to Table 2)**

	Smoking Status*		
	Never Smokers	Former Smokers	Current Smokers
<b>Inflammation</b>			
hsCRP $\geq 2$ mg/L, Odds Ratio	1 (ref)	<b>1.19</b> (1.04 to 1.36)	<b>1.74 ‡</b> (1.44 to 2.09)
hsCRP, $\beta$ -Coefficient †	0 (ref)	<b>0.06</b> (0.003 to 0.11)	<b>0.27 ‡</b> (0.20 to 0.34)

\*All values are expressed as Odds Ratios or  $\beta$ -Coefficients; with 95% confidence Intervals. Each robust linear and logistic model is adjusted for age, gender, race, MESA site, BMI, hypertension status, diabetes status, heart rate, LDL-C, HDL-C, triglycerides, treatment for dyslipidemia, family history of MI, and level of education.

† Log-transformed

**Significant values (P<0.05) are presented in bold.**

**‡ P-value <0.001**