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Race/Ethnicity-Specific Associations between Smoking, Serum Leptin, and Abdominal Fat: The Multi-Ethnic Study of Atherosclerosis

Sina Kianoush, MD, MPH[1]; Andrew P. DeFilippis, MD, MSc[2]; Carlos J. Rodriguez, MD, MPH[3]; Mahmoud Al Rifai, MD, MPH[4]; Emelia J. Benjamin, MD, ScM[5]; Michael E. Hall, MD, MS[6]; Pamela Ouyang, MBBS[7]; Matthew A. Allison, MD, MPH[8]; Michael J. Blaha, MD, MPH[9]

Objective: Smoking is a well-known cardiovascular risk factor associated with weight loss. We aimed to evaluate the association between smoking, serum leptin levels, and abdominal fat.

Design: Cross-sectional

Setting: Data from examinations 2 or 3 (2002-2005) of the Multi-Ethnic Study of Atherosclerosis (MESA)

Participants: 1,875 asymptomatic, community-dwelling adults

Main Outcomes Measures: We used multivariable linear regression models to assess the race/ethnicity-specific associations between smoking, serum $\log_e$-leptin levels, and computed tomography ascertained abdominal fat. Results were adjusted for demographic and relevant clinical covariates.

Results: Participants (mean age 64.5±9.6 years; 50.6% women; 42.2% former, 11.4% current smokers) were White (40.1%), Hispanic (25.8%), African American (21.1%), and Chinese (13.0%). Overall, median (25th – 75th percentile) leptin levels were significantly lower among current (11.14 ng/mL; 4.13 – 26.18) and former smokers (11.68 ng/mL; 4.72 – 27.57), as compared with never smokers (15.61 ng/mL; 3.05 – 30.12) (P<.001). The difference in median leptin levels between current and never smokers were significantly higher for Hispanics (Δ9.64 ng/mL) and African Americans (Δ8.81 ng/mL) than Whites (Δ2.10 ng/mL) and Chinese (Δ4.70 ng/mL) (P<.001). After adjustment for total abdominal fat, $\log_e$-leptin levels remained lower for former (-.14 [-.22 – -.07]) and current (-.17 [-.28 – -.05]) smokers, compared with never smokers. Results differed by race/ethnicity, with significantly lower $\log_e$-leptin levels observed only among current and former African Americans and Hispanic smokers, compared with their never smoker counterparts. (Ps for interaction <.05)

Conclusions: Among smokers, leptin levels significantly vary by race/ethnicity. Former and current smoking are associated with lower leptin levels, although this may be restricted to Hispanics and African Americans. *Ethn Dis.* 2018;28(4):531-538; doi:10.18865/ed.28.4.531.

Keywords: Smoking; Adipokines; Leptin; Body Weight; Abdominal Fat

[1] Yale University, Department of Internal Medicine, New Haven, CT
[2] University of Louisville, Department of Medicine, Louisville, KY
[3] Wake Forest School of Medicine, Department of Public Health Sciences, Winston Salem, NC
[4] University of Kansas School of Medicine, Department of Internal Medicine, Wichita, KS
[5] Boston University, Department of Medicine, Boston, MA
[6] University of Mississippi Medical Center, Department of Cardiology, Jackson, MS
[7] Johns Hopkins University School of Medicine, Department of Medicine, Baltimore, MD
[8] University of California-San Diego, Department of Family Medicine / Public Health, La Jolla, CA
[9] Johns Hopkins Ciccarone Center for the Prevention of Heart Disease, Baltimore, MD

Address correspondence to Sina Kianoush, Yale University School of Medicine, New Haven, CT, USA; sina.kianoush@yale.edu.

Introduction

Smoking, a major preventable cause of cardiovascular disease (CVD) and death, is associated with multiple derangements in cardiometabolic pathways.[1-5] For example, tobacco smoking is associated with lower body weight,[5] but higher waist circumference, suggesting a potential increase in the visceral fat.[2,4]

Prior studies have suggested that the metabolic changes in smoking may be mediated by adipokines, such as leptin, which is secreted from adipose tissue.[6] Although prior studies have demonstrated that higher leptin levels are associated with insulin resistance, atherosclerosis, and coronary artery disease,[7,8] results are conflicting on the association between smoking and serum leptin, as a marker of cardiometabolic health and injury.[9-15] These discrepant results may

be explained by differences in adipokine levels, particularly leptin, across racial/ethnic groups.[10,11] Furthermore, the joint roles of abdominal fat, as the source of adipokines, in modifying or mediating the relationship between smoking and leptin levels are yet to be determined.

Prior studies included homogenous populations, were underpowered, or lacked accurate information regarding abdominal fat composition to show the role of race/ethnicity in the association between smoking and leptin levels.[9,10,13-16] In our present study, using a large subset of individuals enrolled in Multi-Ethnic Study of Atherosclerosis (MESA), we aimed to assess the race/ethnicity-specific associations between smoking status (current, former, and never), leptin levels, and CT measures of total abdominal fat. Results from this study may shed light on the complicated relationship between race/ethnicity, smoking, and smoking cessation on body composition, cardiometabolic health, and cardiovascular disease. These results may inform clinical guidelines and tobacco regulatory agencies in understanding whether there are higher-risk races/ethnicities, in whom the association between smoking and leptin – as a marker of cardiometabolic health – is more pronounced.

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Methods

Participants

Design and methods of MESA have been described previously.[17] Briefly, MESA comprises 6,814 men and women of different races/ethnicities (White, Hispanic, African American, and Chinese American) enrolled from six different sites, all of whom were free of clinical CVD. A random subset of 1,875 participants, with available data related to smoking status, who underwent measurement of adipokine levels and abdominal CT scanning at examinations 2 or 3 (2002-2005) were included in our present study. All protocols were approved by the institutional review board at participating institutions and written informed consents were obtained from all participants.

Measurement of Covariates

Participants self-reported smoking exposure. The primary smoking variable was smoking status categorized as never, former, and current smoking. Never smoking was defined as lifetime use of less than 100 cigarettes. Former smokers had a previous history of smoking but had not consumed cigarettes within the last 30 days.

Stored fasting blood samples were used to measure leptin, adiponectin, and resistin levels by Bio-Rad Luminex flow cytometry at the MESA central laboratory. Mean coefficients of variation across control samples were between 6.0–13.0%.[18]

Anthropometric components were measured twice using standard protocols and the average was recorded. BMI was derived from weight (measured to the nearest .5 lb using a balance beam scale) and height (measured to the nearest .5 cm using a vertical ruler). Waist circumference was measured at the minimum abdominal circumference to the nearest .1 cm.

Electron-beam and multidetector CT scanners at Northwestern University, University of California, Columbia University, Wake Forest University, and University of Minnesota field centers were used to measure total abdominal, visceral, and internal abdominal fat and lean areas. Fat tissue was identified as being between -190 and -30 Hounsfield units (HU). Lean tissue was identified as being between 0 and 100 HU. Densities outside of these two ranges were labeled as undefined tissue type. Six transverse cross-sectional slices of data were assessed (2 at L2–3, 2 at L3–4, and 2 at L4–5). Fat and lean measured were reported in cm^2. To calculate visceral fat and lean areas, we calculated the sum of visceral areas over all six available slices. Fat and lean areas were indexed to height (in meters). Inter-rater and intra-rater reliabilities were .99 for

Table 1. Characteristics of 1,875 participants in MESA who underwent abdominal CT scanning and were assessed for biomarkers of inflammation in Exams 2 or 3, part 1

Variable	Study population, N=1,875	Smoking status			P
		Never, n=871	Former, n=791	Current, n=213	
Age	64.5 ± 9.6	64.3 ± 9.8	66.0 ± 9.2	59.7 ± 8.6	<.001
Male	927 (49.4)	332 (38.1)	475 (60.1)	120 (56.3)	<.001
Race					
White	752 (40.1)	301 (34.6)	361 (45.6)	90 (42.3)	
Hispanics	484 (25.8)	236 (27.1)	191 (24.2)	57 (26.8)	<.001
African American	395 (21.1)	164 (18.8)	175 (22.1)	56 (26.3)	
Chinese American	244 (13.0)	170 (19.5)	64 (8.1)	10 (4.7)	
Completed high school	1536 (82.0)	690 (79.2)	667 (84.5)	179 (84.0)	.014
Income level ≥ $40K	909 (50.6)	409 (48.8)	392 (51.7)	108 (53.7)	.314
Having insurance	110 (5.9)	60 (6.9)	30 (3.8)	20 (9.4)	.002
Sedentary and light activity[a]	2160. (1260, 3390)	2100 (1192.5, 3210)	2160 (1320, 3360)	2940 (1470, 3960)	<.001
Moderate-to-vigorous physical activity[a]	3570 (1837, 6390)	3352 (1800, 6285)	3780 (1845, 6700)	4050 (1860, 6892)	.109
Pack-years of smoking[b]	22.5 ± 32.0	0	20.0 ± 24.7	31.7 ± 49.8	<.001
Alcohol use	967 (51.6)	351 (40.3)	475 (60.0)	141 (66.2)	<.001
Systolic blood pressure, mm Hg	124.1 ± 20.8	124.4 ± 21.3	124.7 ± 20.1	120.3 ± 21.1	.019

a. Met-min/wk m-su.
b. Excludes never smokers. Only former and current smokers were compared.
Column percentages were used. Continuous variables are described as mean ± standard deviation or median (interquartile range). Categorical variables are described as number (percentage). Number may not sum up to total due to missing observations. Percentages may not sum up to 100% due to rounding.
MESA, Multi-Ethnic Study of Atherosclerosis; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol

all measures. Information regarding settings, devices, and protocols were explained in detail previously.[19]

Data Analysis

We report mean ± standard deviation for normally distributed and median (interquartile range) for non-normally distributed baseline data, stratified by smoking status. We then compared absolute leptin levels by smoking status across categories of race/ethnicity. Using multivariable linear regression, we assessed the association between smoking status and $\log_e$-transformed fat and lean abdominal areas. Models were adjusted for sex, age, race/ethnicity, education, sedentary lifestyle, current alcohol use, triglyceride, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, diabetes mellitus, and lipid-lowering medications.

We used two multivariable linear regression models to evaluate the potential independent association between smoking status and log-transformed leptin ($\log_e$-leptin) levels. These included a baseline multivariable model (Model 1) and another model that was further adjusted for CT measures of total abdominal fat (Model 2).

Interaction terms between smoking status and sex, age, race/ethnicity in their associations with CT measures and adipokine levels were tested. In sensitivity analyses, we further adjusted for other measures of adiposity including BMI, waist circumference, and dietary patterns as well as inflammatory biomarkers such as high-sensitivity C-reactive protein (hsCRP) and tumor necrosis factor alpha (TNF-alpha). We used Stata 13 for all analyses. A two-sided P <.05 was considered significant.

Results

Baseline characteristics of the 1,875 MESA participants (mean age 64.5 ± 9.6 years, 49.4% men, 42.2% former, 11.4% current smokers) are shown in Tables 1 and 2, stratified according to smoking status. A total of 1,875 participants were included in our study, and 40.1% of participants were White, 25.8% Hispanic, 21.1% African American, and 13.0% Chinese American. Current smokers were younger (59.7 ± 8.6) than former (66.0 ± 9.2) and never smokers (64.3 ± 9.8). The prevalence of current smoking within groups was highest among African Americans (14.2%) and lowest among

Table 2. Characteristics of 1,875 participants in MESA who underwent abdominal CT scanning and were assessed for biomarkers of inflammation in Exams 2 or 3, part 2

Variable	Study population, N=1,875	Smoking status			P
		Never , n=871	Former , n=791	Current, n=213	
Triglycerides, mg/dL	114, (78, 163)	116, (80, 164)	112, (75, 160)	116, (83.0-181)	.089
Total cholesterol, mg/dL	190.3 ± 35.1	193.3 ± 34.6	187.7 ± 34.6	187.7 ± 37.9	.003
LDL-C, mg/dL	112.5 ± 31.1	114.6 ± 31.2	110.3 ± 30.4	111.5 ± 32.7	.017
HDL-C, mg/dL	51.6 ± 15.2	52.4 ± 14.6	51.6 ± 15.7	48.2 ± 15.6	.002
Body mass index, kg/m^2	28.2 ± 5.2	27.6 ± 4.9	28.8 ± 5.4	28.2 ± 5.3	<.001
Waist circumference, cm	98.2 ± 14.1	96.4 ± 13.4	100.2 ± 14.4	98.64± 14.8	<.001
Height-indexed total abdominal fat, cm^2/m	1290, (980, 1636)	1277, (994, 1603)	1351, (955, 1724)	1227, (950, 1612)	.144
Height-indexed visceral fat, cm^2/m	541, (358, 768)	495, (345.5, 709)	601, (394, 820)	523, (332, 754)	<.001
Height-indexed total abdominal internal fat area, cm^2/m	588, (413, 828)	555, (406, 767)	656, (439, 882)	538, (372, 777)	<.001
Diabetes	259 (13.8)	115 (13.2)	116 (14.7)	28 (13.1)	.657
Hypertension	872 (46.9)	415 (48.1)	386 (49.2)	71 (33.5)	<.001
Blood pressure medications	783 (42.9)	365 (43.2)	352 (45.7)	66 (31.43)	.001
Statin use	1096 (16.1)	208 (24.6)	201 (26.1)	36 (17.4)	.027
Leptin, ng/mL	13.5, (5.7, 28.3)	15.6, (7.0, 30.1)	11.7, (4.7, 27.6)	11.1, (41.3, 26.2)	<.001
Adiponectin, micg/mL	17.4, (11.8, 26.3)	18.0, (12.1, 26.4)	17.3, (11.4, 26.4)	15.4, (11.5, 23.1)	.030
Resistin, ng/mL	15.0, (11.9, 19.0)	14.7, (11.4, 18.6)	15.2, (12.2, 19.4)	15.3, (12.6, 18.5)	.068

Column percentages were used. Continuous variables are described as mean ± standard deviation or median (interquartile range). Categorical variables are described as number (percentage). Number may not sum up to total due to missing observations. Percentages may not sum up to 100% due to rounding.
MESA, Multi-Ethnic Study of Atherosclerosis; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Chinese Americans (4.1%), with that in Whites and Hispanics being 12.0% and 11.8%, respectively.

Median (Interquartile range) leptin levels were significantly lower among former (11.68 [4.72, 27.57] ng/mL) and current smokers (11.14 [4.13, 26.18] ng/mL) compared with never smokers (15.61 [7.04, 30.12] ng/mL) (P<.001). Figure 1 illustrates leptin levels by smoking status across racial/ethnic categories. Leptin levels were not different by smoking status among Whites (P=.73). Among African Americans, Hispanics, and Chinese Americans, former and current smokers had significantly lower leptin levels than never smokers (P<.001). The difference in median leptin levels between current and never smokers were

Table 3. The association between smoking and abdominal fat and lean areas, measured by abdominal CT scan among 1,875 participants in MESA. Beta-coefficients indicate absolute differences in fat and lean areas.

Measures of abdominal CT scan[a]		Smoking status				
		Never, n=871	Former, n=791	P	Current, n=213	P
Fat area						
	Total abdominal	Ref	-.02, (-.05 – .00)	.066	-.05, (-.09 – -.01)	.009
	Visceral	Ref	-.03, (-.06 – .01)	.138	-.09, (-.15 – -.04)	.001
Lean area						
	Total abdominal	Ref	.04, (.02 – .05)	<.001	.08, (.05 – .10)	<.001
	Visceral	Ref	.07, (.04 – .10)	<.001	.17, (.12 – .21)	<.001

a. Height-indexed values (fat/lean area divided by participant's height) were used in both models. All measures were log-transformed due to their non-normal destitutions. Linear regression models were adjusted for sex, age, race/ethnicity, education, sedentary lifestyle, current alcohol use, triglyceride, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, diabetes mellitus, and lipid-lowering medications.
MESA, Multi-Ethnic Study of Atherosclerosis.

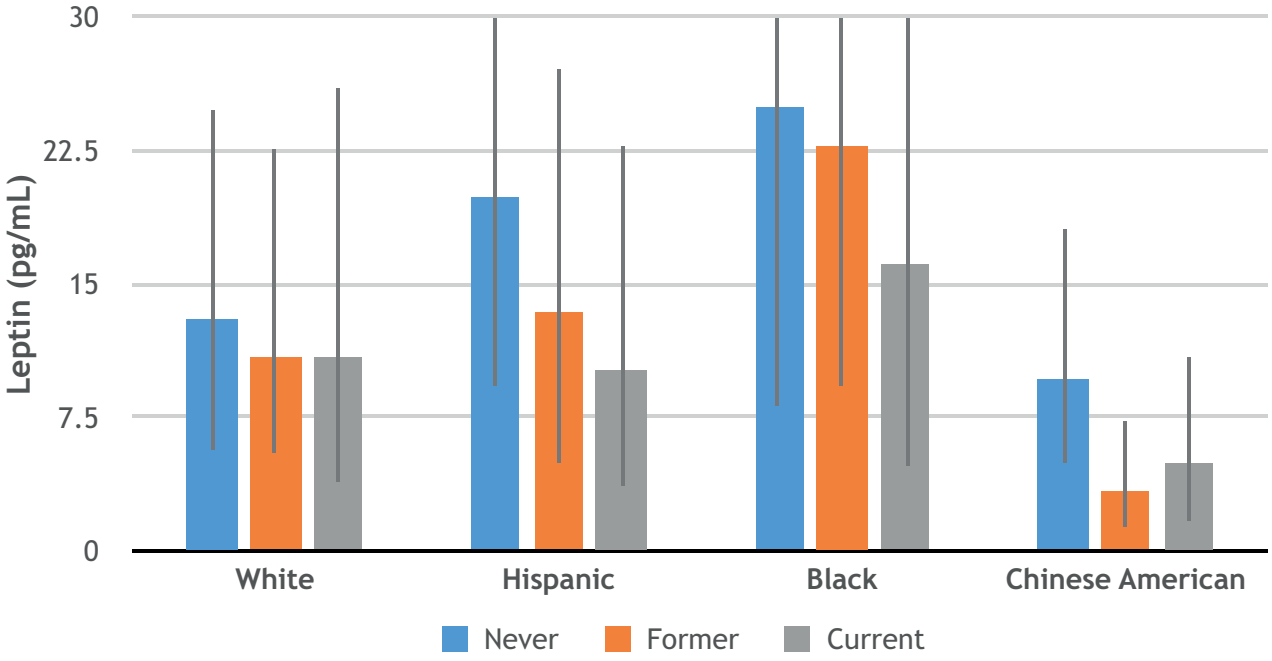

Figure 1. Leptin levels by smoking status across racial/ethnic categories of 1,875 participants in MESA
MESA, Multi-ethnic Study on Atherosclerosis

significantly higher for Hispanics (Δ9.64 ng/mL) and African Americans (Δ8.81 ng/mL) compared with Whites (Δ2.10 ng/mL) and Chinese (Δ4.70 ng/mL) (P<.001).

Multivariable linear regression models showed that, compared with never smokers, current smokers had significantly lower fat, but higher lean areas in total abdominal and visceral compartments (P<.05). Former smokers also had significantly higher lean areas in total abdominal and visceral compartments (P<.001). (Table 3)

Table 4 shows results for the association between smoking status and log-leptin, stratified by race/ethnicity. Multivariable linear regression models demonstrated that compared with never smokers, former and current smokers had lower $\log_e$-leptin without (Model 1) and with adjusting for CT measures of abdominal fat (Model 2). Log_e-leptin was not significantly different by smoking status among White and Chinese participants. Among Hispanics, $\log_e$-leptin was consistently lower among former smokers than never smokers in both models while among African Americans results were consistently significant for current smokers (P<.05). There were statistically significant interactions between smoking status and race with significantly lower $\log_e$-leptin levels observed among African American current smokers (P=.048) as well as Hispanic former smokers (P=.025), compared with their never smoker counterparts.

There were no changes in the overall conclusions after adjusting for other measures of abdominal fat (BMI, and waist circumference, and CT measures of visceral fat) and dietary patterns in Model 1, and after adjusting for inflammatory markers (hsCRP and TNF-alpha) in Model 2. Also race/ethnicity-specific results were not significant for the association between other measures of smoking behavior, such as pack-years of smoking, number of cigarettes smoke per day, and time since smoking cessation, and leptin levels.

Discussion

We demonstrated that smokers have significantly lower leptin levels, with absolute values varying substantively by race/ethnicity. Whereas smokers have lower abdominal

Table 4. The association between smoking status and log_e-transformed leptin levels (per standard deviation) among 1,875 participants in MESA. Beta-coefficients (absolute differences in leptin levels) are reported by race/ethnicity.

Smoking status	Overall, N=1,875	P	White, n=752	P	Hispanic, n=484	P	African American, n=395	P	Chinese American, n=244	P
Never, n=871	Ref		Ref		Ref		Ref		Ref	
Former, n=791										
Model 1[a]	-.013, (-.20 – -.05)	.001	-.05, (-.16 – .05)	.354	-.24, (-.38 – -.10)	.001	-.07, (-.24 – .08)	.374	-.24, (-.50 – .02)	.065
Model 2[b]	-.08, (-.16 – -.01)	.033	.00, (-.11– .12)	.927	-.21, (-.38 – -.05)	.013	-.10, (-.27 – .06)	.259	-.15, (-.38 – .08)	.220
Current, n=213										
Model 1[a]	-.22, (-.33 – -.11)	<.001	-.10, (-.28 – .07)	.232	-.31, (-.53 – .09)	.005	-.39, (-.57 – -.12)	.003	.10, (-.37 – .57)	.668
Model 2[b]	-.13, (-.25 – -.01)	.028	-.04, (-.22 – .14)	.639	-.20, (-.47 – .08)	.167	-.34, (-.58 – -.11)	.004	.21, (-.21 – .63)	.326

a. Model 1 is adjusted for sex, age, race/ethnicity, education, sedentary lifestyle, current alcohol use, triglyceride, body mass index, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, diabetes mellitus, and lipid-lowering medications.
b. Model 2 is adjusted for Model 1 covariates plus CT measures of total abdominal fat.
MESA, Multi-Ethnic Study of Atherosclerosis.

fat compared with never smokers, multivariable-adjusted leptin levels are lower in smokers vs never smokers accounting for various measures of body fat, including CT-measured abdominal fat, BMI, and waist circumference. However, we found marked race/ethnicity dimorphism in our results, with smoking associated with lower adjusted leptin levels in African Americans and Hispanics.

Prior studies in different populations have reported that smoking is associated with lower,[20-23] unchanged,[24, 25] or higher [26] leptin levels. For example, one small study comprising 236 Middle Eastern healthy participants, showed that smoking was associated with lower leptin levels.[10] Another study among 708 Japanese men reported that leptin levels were not affected by cigarette smoking.[25] Yet, another study including African and Australian participants suggested that smoking was associated with higher leptin levels.[26] Our results support the hypothesis that there are race-specific metabolic changes linked to smoking.

Our findings have clinical and research implications for smokers and those who have recently quit smoking with regard to body composition, metabolism, and adipocyte mediated inflammation. Leptin, as a marker of cardiometabolic health and disease, may be useful to identify higher-risk smokers, who may benefit from preventive measures. As higher leptin is suggested to be associated with CVD,[7,8] lower leptin levels in smokers vs non-smokers among African Americans and Hispanic suggest that other mechanisms play the predominant role for smoking-related cardiometabolic injury in these groups. On the contrary, White smokers had similar serum leptin levels compared with non-smokers (despite having lower total and visceral body fat) that may signify higher cardiometabolic risk from relative increase in leptin among former and current smokers in this group. White ever-smokers in particular may retain disordered metabolism and may benefit from strategies to reduce inflammation. However, additional larger studies are needed to evaluate and confirm the leptin-driven CVD risk across racial/ethnic groups by smoking status.

We found marked race/ethnicity dimorphism in our results, with smoking associated with lower adjusted leptin levels in African Americans and Hispanics.

The strengths of our study are the multi-ethnic/racial cohort and adjustment for various measures of body fat in our comprehensive anal-

yses. Limitations of this study were the cross-sectional and observational design, possible residual confounding, and lack of enough power for Chinese Americans to detect statistically significant results. Additionally, in this study, measure of smoking status was based on self-report data rather than urinary cotinine levels. However, previous reports have shown that discordance between self-report data and urinary cotinine measures is only 1.2% in MESA.[27]

Conclusion

Our results have clinical and regulatory implications and help with understanding the complex metabolic changes among smokers. Future prospective studies should closely consider the race/ethnicity-specific interplay of other demographic, lifestyle, and clinical characteristics in the association of smoking and adipokines in order to better understand metabolic health effects of smoking.

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Compliance with Ethical Standards and Disclosure

All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (both national and institutional review boards at participating institutions of MESA) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all participants included in the study.

Author Contributions

Design and concept of study: Kianoush, DeFilippis, Rodriguez, Al Rifai, Benjamin, Hall, Ouyang, Allison, Blaha; Data analysis and interpretation: Kianoush, Blaha; Manuscript draft: Kianoush, DeFilippis, Rodriguez, Al Rifai, Benjamin, Hall, Ouyang, Allison, Blaha; Supervision: Blaha.

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