

Original Articles

Smoking intensity and lipoprotein abnormalities in active smokers

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KEYWORDS:

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BACKGROUND: Smoking is associated with decreased high-density lipoprotein cholesterol (HDL-C) and increased levels of triglycerides.

OBJECTIVE: We sought to evaluate the effects of five markers of smoking intensity on lipoprotein concentrations and particle sizes in a large, modern cohort of current smokers.

METHODS: Fasting nuclear magnetic resonance spectroscopy lipoprotein profiles were obtained in a large cohort of current smokers enrolled in a smoking-cessation trial. Multivariate linear regression models were constructed to determine predictors of lipoprotein fractions. Models included age, sex, race, waist circumference, level of physical activity, and alcohol consumption. Smoking intensity parameters included current cigarettes smoked/day, pack-years, the Fagerström Test of Nicotine Dependence score, and carbon monoxide (CO) levels.

RESULTS: The 1504 subjects (58% women, 84% white) had a mean (standard deviation) age of 45 (11.0) years. They smoked 21.4 (8.9) cigarettes/day (29.4 [20.4] pack-years). HDL-C (42.0 [13.5] mg/dL) and total HDL particles (30.3 [5.9] $\mu\text{mol/L}$) were low. Cigarettes smoked/day independently predicted greater total cholesterol ($P = .009$), low-density lipoprotein cholesterol ($P = .023$), and triglycerides ($P = .002$). CO levels predicted lower HDL-C ($P = .027$) and total HDL particles ($P = .009$). However, the incremental R^2 for each marker of smoking intensity on each lipoprotein was small. Relationships between the Fagerström Test of Nicotine Dependence score and lipoproteins were weak and inconsistent. Participants in the lowest quintiles of current smoking, pack-years, and CO had more favorable lipoproteins (all $P < .04$).

CONCLUSIONS: Among current smokers, increased smoking burden is associated with small increases in total cholesterol, low-density lipoprotein cholesterol, and triglycerides. Increased recent smoke exposure is associated with small decreases in HDL-C and HDL particles.

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Cigarette smoking is a major modifiable risk factor for cardiovascular disease (CVD). More than 30% of the population-attributable risk for myocardial infarction is directly attributable to smoking.¹ The adverse effects of

smoking on CVD risk are mediated through multiple inter-related mechanisms, including increased oxidative stress, endothelial injury and dysfunction, altered blood coagulation, and derangements of lipid composition and metabolism.^{2,3}

There is a clear dose response between the magnitude of smoking and CVD risk; the risk of a nonfatal MI increases by 5.6% per additional cigarette smoked compared with not smoking.⁴

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Cigarette smoking is associated with reductions in high-density lipoprotein cholesterol (HDL-C) and small increases in serum triglycerides.^{2,5} Quitting or reducing smoking is recommended to reduce CVD risk and to improve lipid levels among smokers.⁶⁻¹² However, previous studies in which the authors evaluated the effects of smoking and smoking cessation on lipids tended to be small, frequently did not adjust for confounders that affect HDL-C levels (such as age, sex, race, adiposity, alcohol use, and physical activity), and may not be representative of contemporary smokers. The authors of previous studies also did not use advanced lipoprotein testing to evaluate lipoprotein particle concentrations or sizes, which may be better predictors of CVD risk than lipids, especially in patients with metabolic syndrome or triglycerides disorders.^{12,13} Finally, reports that investigated the dose-response between smoking and lipids only evaluated cigarettes smoked per day, one marker of smoking burden, rather than other markers of smoking burden including lifetime smoking exposure, nicotine dependence, and recent smoke exposure. The purpose of this study was to evaluate the effects of smoking intensity on lipoprotein concentrations and particle sizes in a large, modern cohort of current smokers.

Methods

Study participants and design

This study was approved by the institutional review board at the University of Wisconsin School of Medicine and Public Health. All subjects provided written informed consent. Subjects were participants in a longitudinal, randomized, double-blind, placebo-controlled smoking-cessation trial to evaluate the efficacy of several smoking-cessation pharmacotherapies and examine the natural history of continued smoking and smoking cessation.¹⁴ Each subject's consent for the randomized clinical trial included permission to evaluate his or her baseline physiological data, which were used for this report. Inclusion and exclusion criteria were based on the requirements for the clinical trial. Major inclusion criteria were: age ≥ 18 years of age, current smoking of at least 10 cigarettes/day for the previous 6 months, an expired carbon monoxide (CO) level >9 ppm, and stated motivation to try to quit smoking. Major exclusion criteria were uncontrolled hypertension (blood pressure $>160/100$ mmHg), history of bipolar disorder, psychosis, myocardial infarction within the previous 4 weeks, history of diagnosed anorexia and/or bulimia, diagnosis of alcohol dependence in the previous 6 months or drinking 6 or more drinks on 6 or more days a week, history of seizure and/or serious head injury involving loss of consciousness, use of contraindicated medications (monoamine oxidase inhibitors, bupropion, lithium, anticonvulsants, antipsychotics), current pregnancy or breast-feeding, and unwillingness to use effective contraception during the treatment phase.

Study procedures

All subjects were recruited from communities in or around Madison and Milwaukee, Wisconsin, via television, radio and newspaper advertisements, flyers, and earned media, including press conferences and television and radio news interviews from January 2005 to June 2007. The baseline clinical trial visits included measurement of anthropometric data, fasting laboratory tests, and completion of validated questionnaires and interviews. Moderate and vigorous physical activity were measured by the use of the long form of the International Physical Activity Questionnaire.¹⁵ Five parameters related to smoking intensity were evaluated. Smoking burden was evaluated by three parameters (current cigarette smoking [cigarettes/day], current pack-years [current cigarettes/day * number of years smoked], and peak pack-years [most cigarettes/day * number of years smoked]); nicotine dependence was evaluated by the Fagerström Test for Nicotine Dependence (FTND),¹⁶ and recent smoke exposure was evaluated by exhaled CO levels, which reflect smoking efficiency, recent smoking, and recent smoke exposure.

Measurement of lipoproteins

Fasting blood samples were obtained by venipuncture and refrigerated. Plasma aliquots were isolated by centrifugation and frozen at -70°C . Samples were sent monthly to LipoScience, Inc. (Raleigh, NC) for nuclear magnetic resonance spectroscopic lipoprotein analysis (Lipoprofile-2, LipoScience, Inc.) by the use of previously published methods.¹⁷ Concentrations of very low-density lipoprotein (VLDL) and low-density lipoprotein (LDL, including intermediate-density lipoprotein) subclasses in nmol/L units and HDL subclasses in $\mu\text{mol/L}$ units were obtained from the measured amplitudes of distinct lipid methyl group nuclear magnetic resonance signals. The nine measured subclasses were defined as follows: large VLDL (>60 nm), medium VLDL (35–60 nm), small VLDL (28–35 nm), intermediate-density lipoprotein (IDL, 23–27 nm), large LDL (21.2–23.0 nm), small LDL (18.0–21.2 nm), large HDL (8.8–13.0 nm), medium HDL (8.2–8.8 nm), and small HDL (7.3–8.2 nm). Total LDL particle concentrations are the sum of the intermediate-density lipoprotein, large LDL, and small LDL subclass concentrations. Total HDL particle concentrations are the sum of large, medium, and small HDL subclass concentrations. Weighted-average VLDL, LDL, and HDL particle sizes were determined by summing the diameter of each subclass multiplied by its relative mass percentage as estimated by the amplitude of its methyl NMR signal.¹⁷ Nuclear magnetic resonance-derived cholesterol (-C) and triglycerides (TG) were determined by conversion of lipoprotein particle data to lipid concentration units (mg/dL) based on the expected amount of cholesterol and triglycerides in each particle.¹⁷

Statistical analysis

Analyses were performed with SPSS software (Version 17.0, SPSS, Inc., Chicago, IL). Means, standard deviations, and interquartile ranges were used for descriptive statistics. Pearson correlations were calculated to describe the unadjusted relationships between the smoking intensity, exercise, and lipoprotein parameters. Multivariate linear regression models were created for prediction of each lipoprotein fraction and their lipid content. A basic model was created for each lipoprotein parameter that included age, sex, race, waist circumference, alcohol use, moderate and vigorous physical activity, and use of lipid-lowering medications. Separate models for each lipoprotein parameter were created by individually adding each of the five smoking intensity parameters to the basic model. Models are described by the change in R^2 after adding the smoking intensity marker to the variables in the basic model, with beta coefficients and P values. To evaluate for the presence of a linear relationship and for the presence of a threshold effect, we also created linear regression models for each lipoprotein parameter by quintiles of each smoking intensity parameter, adjusting for the variables described above.

Results

Subject characteristics

Subject characteristics are provided in Table 1. This study included 1504 current smokers (58% women, 84% white, 14% African American, 2% American Indian/Alaskan/Asian/Pacific). Their age was 45 (11.1) years. Subjects smoked approximately one pack of cigarettes daily and had a total smoking burden of 29 (20.4) current pack-years. On average, subjects consumed 16 (23.9) alcohol-containing beverages a month. Total cholesterol and LDL-C levels were normal; however, HDL-C levels were low and TG were high-normal. Men had lower HDL-C (36 [11.6] mg/dL) than women (46 [13.4] mg/dL) ($t = -13.9$, $P < .001$). Lipoprotein particle concentrations and sizes were as expected for the lipid values. Only 11% of the participants were taking lipid-lowering medications.

Correlations between smoking intensity parameters, alcohol use, and physical activity

The smoking intensity parameters were highly intercorrelated (all $r > 0.24$, $P < .001$). The strongest correlations were between current and peak pack-years ($r = 0.85$, $P < .001$), cigarettes/day and current pack-years ($r = 0.79$, $P < .001$), and cigarettes/day and the FTND score ($r = 0.59$, $P < .001$). Weak correlations were observed between moderate exercise and cigarettes/day, FTND, and CO ($r = -0.05$ to -0.07 , $P < .04$) and between alcohol

Table 1 Subject characteristics (N = 1504)

	Mean (SD)	Range
Age, years	45 (11.1)	18–79
Sex, % male	42	–
Race, % white	84	–
Body mass index, kg/m ²	29.0 (6.5)	15.5–69.2
Waist circumference, cm	96 (16.2)	34–197
Markers of smoking intensity*		
Current smoking, cigs/day	21 (8.9)	1–80
Smoking burden, current pack-yrs	29 (20.4)	0–156
Smoking burden, peak pack-yrs	38 (26.4)	0–221
Fagerström Test of Nicotine Dependence Score	5 (2.1)	0–10
Carbon monoxide, ppm	26 (12.5)	1–110
Alcohol consumption, drinks/month	16 (23.9)	0–168
IPAQ moderate-vigorous activity, met-hours/day	122.0 (150.1)	0–1022
IPAQ leisure activity, met-hours/day	11.1 (21.4)	0–199
Use of lipid-lowering medications, %	11%	–
Lipids and lipoproteins		
Total cholesterol, mg/dL	184 (35.4)	77–342
LDL cholesterol, mg/dL	119 (30.6)	26–250.0
Total LDL particles, nmol/L	1318 (392.8)	271–2961
Small LDL particles, nmol/L	775 (455.2)	0–2565
Mean LDL particle diameter, nm	21.1 (0.8)	18.8–23.0
HDL cholesterol, mg/dL	42 (13.5)	14–104
Total HDL particles, μ mol/L	30 (5.9)	12–52
Small HDL particles, μ mol/L	23 (4.9)	4–41
Mean HDL particle diameter, nm	8.7 (0.5)	8.0–11.2
Triglycerides, mg/dL	143 (101.7)	27–1460

CO, carbon monoxide; HDL, high-density lipoprotein; IPAQ, International Physical Activity Questionnaire; LDL, low-density lipoprotein.

*106 participants (7%) had missing CO values or CO <10 ppm; 13 participants (0.8%) had missing data on cigarettes/day or reported smoking <10 cigarettes/day.

consumption and CO and leisure activity ($r = -0.06$ to -0.20 , $P < .04$; data not shown).

Correlations between smoking intensity parameters and lipoproteins

In general, the smoking intensity parameters had weak, positive ($r = 0.06$ – 0.15 , $P < .05$) correlations with total cholesterol, LDL-C, total and small LDL particles. The only statistically significant correlation with LDL size was cigarettes/day ($r = -0.08$, $P = .003$). Correlations between HDL measurements and the smoking intensity parameters were of a similar magnitude ($r = -0.05$ to -0.12 , $P < .05$). Triglycerides were weakly correlated with

cigarettes/day ($r = 0.14, P < .001$) and current pack-years ($r = .11, P < .001$).

Multivariate regression models: variation explained by smoking intensity parameters

For prediction of each lipoprotein parameter, a basic model was created that included variables that are known to affect lipoproteins including age, sex, race, waist circumference, alcohol use, physical activity, and use of lipid-lowering medications (Table 2). The basic model explained a significant component of the variability in each lipoprotein parameter ($P < .001$), with the greatest adjusted R^2 values for HDL-C, large HDL particles, and HDL particle size (adjusted $R^2 > 0.23, P < .001$). More modest adjusted R^2 values (adjusted $R^2 = 0.10-0.15, P < .001$) were observed in the basic models for LDL particles, small LDL, LDL size, and total HDL.

We then added a smoking intensity parameter to the basic model for each lipoprotein parameter to see if the addition of the smoking intensity parameter changed the adjusted R^2 (ΔR^2 ; Table 2). The addition of markers of smoking burden (cigarettes/day, current pack-years, peak pack-years) provided small ($\Delta R^2 = 0.003-0.007$) but statistically significant ($P < .04$) increases in the adjusted R^2 for total cholesterol, LDL-C, and triglycerides. Results for current pack-years and peak pack-years were nearly identical and therefore the data for peak pack-years data are not shown. In contrast, the addition of the FTND score, a marker of nicotine dependence, provided small ($\Delta R^2 = 0.002-0.003$) but statistically significant ($P < .05$) increases in the adjusted R^2 for HDL-C and HDL particles. The addition of CO levels, which reflect recent smoke exposure, also provided small ($\Delta R^2 = 0.003-0.005$) but statistically significant ($P < .03$) increases in the adjusted R^2 for HDL-C and HDL particles, as well as for small HDL particles.

To address the possibility that the effects of smoking intensity on lipoproteins were mediated by smoking's effects on waist circumference or by differences in responses between the sexes,¹⁸⁻²⁰ we re-ran all of the analyses in Table 2 not controlling for waist circumference or sex and did not observe major differences in the directionality or degree of statistical significance of the relationships between smoking parameters and lipoprotein levels (data not shown).

Multivariate regression models: quintiles analyses

Multivariate linear regression models for each lipoprotein parameter by quintiles of each smoking intensity parameter are shown in Table 3. Only the lipoprotein variables with significant linear trends ($P_{\text{trend}} < .05$) are presented. Significant positive linear relationships between current smoking (cigarettes/day) and total cholesterol,

Table 2 Adjusted associations between lipoproteins and smoking intensity parameters

	Basic model*		Basic model + current smoking (cigarettes/day)		Basic model + smoking burden (current pack-years)		Basic model + FTND score		Basic model + carbon monoxide					
	R ²	P	β	ΔR^2	P	β	ΔR^2	P	β	ΔR^2	P			
Total cholesterol	0.061	<.001	0.075	0.005	.009	0.083	0.004	.019	0.041	0.002	.142	0.009	<0.001	.734
LDL cholesterol	0.053	<.001	0.065	0.004	.023	0.073	0.003	.040	0.047	0.002	.091	0.027	0.001	.340
Total LDL particles	0.100	<.001	0.050	0.002	.073	0.045	0.001	.195	0.044	0.002	.105	0.044	0.002	.106
Small LDL particles	0.135	<.001	0.019	<0.001	.494	0.006	<0.001	.857	0.024	0.001	.358	0.043	0.002	.105
LDL size	0.147	<.001	0.010	<0.001	.721	0.023	<0.001	.503	-0.007	0.000	.799	-0.038	0.001	.152
HDL cholesterol	0.239	<.001	-0.021	<0.001	.413	-0.009	<0.001	.789	-0.049	0.002	.048	-0.055	0.003	.027
Total HDL particles	0.111	<.001	-0.016	<0.001	.559	-0.008	<0.001	.821	-0.058	0.003	.032	-0.071	0.005	.009
Small HDL particles	0.018	<.001	-0.016	<0.001	.594	-0.014	<0.001	.691	-0.042	0.002	.136	-0.06	0.004	.016
HDL size	0.277	<.001	-0.016	<0.001	.512	0.004	<0.001	.905	-0.022	<0.001	.365	-0.026	0.001	.288
Triglycerides	0.089	<.001	0.089	0.007	.002	0.089	0.005	.011	0.040	0.002	.147	0.007	<0.001	.792

Bold items indicate statistical significance.
 FTND, Fagerström Test of Nicotine Dependence Score; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
 *Basic model = age, sex, race, waist circumference, alcohol use, International Physical Activity Questionnaire scores (leisure and vigorous), and use of lipid-lowering medications. All models adjusted for components of basic model.

Table 3 Mean (standard deviation) and ranges of lipoprotein values by quintiles of smoking intensity parameters*

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	<i>P</i> _{trend}
Current smoking, cigarettes/day [†]	10.9 (1.8) [0-15]	15.7 (1.10) [16-19]	—	20.2 (0.6) [20-24]	32.3 (7.3) [≥25]	
Total cholesterol, mg/dL	178.3 (3.5)	183.4 (3.5)	—	183.3 (3.4)	188.5 (3.8)	.005
LDL cholesterol, mg/dL	113.0 (30.7)	119.8 (30.3)	—	119.7 (30.1)	121.2 (31.4)	.014
Total LDL particles, nmol/L	1213.4 (374.1)	1329.5 (396.8)	—	1320.1 (384.0)	1369.4 (403.7)	.040
Triglycerides, mg/dL	127.9 (86.7)	124.6 (66.7)	—	148.1(101.3)	162.8 (129.1)	.004
Smoking burden, current pack-years	7.8 (3.2) [0-12]	16.8 (2.3) [13-20]	24.7 (2.5) [21-29]	35.3 (3.9) [30-42]	60.9 (18.3) [≥43]	
Total cholesterol, mg/dL	169.2 (3.5)	183.0 (3.3)	187.9 (3.3)	190.6 (3.4)	189.1 (3.9)	<.001
LDL cholesterol, mg/dL	106.6 (30.4)	118.9 (28.2)	123.1 (29.1)	124.1 (29.4)	122.0 (32.6)	<.001
Total LDL particles, nmol/L	1192.3 (394.6)	1303.8 (392.9)	1355.1 (370.2)	1390.3 (398.7)	1346.1 (380.5)	.004
Triglycerides, mg/dL	124.8 (79.6)	137.2 (90.0)	138.7 (78.1)	152.2 (105.8)	163.1 (137.7)	<.001
Carbon monoxide, ppm	11.3 (3.3) [0-15]	18.4 (1.7) [16-21]	24.0 (1.4) [22-26]	29.9 (1.9) [27-33]	43.8 (10.5) [≥34]	
HDL cholesterol, mg/dL	43.2 (14.2)	42.0 (13.2)	41.7 (12.9)	41.2 (12.4)	41.8 (14.6)	.012
Total HDL particles, μmol/L	31.1 (6.1)	30.1 (5.8)	30.4 (6.2)	30.1 (5.6)	29.9 (6.3)	.004
Small HDL particles, mol/L	24.1 (5.2)	23.2 (5.0)	23.7 (4.8)	23.4 (4.6)	22.8 (4.6)	.016

HDL, high-density lipoprotein; LDL, low-density lipoprotein.

*Adjusted for age, sex, race, waist circumference, alcohol use, International Physical Activity Questionnaire scores (leisure and vigorous), and use of lipid-lowering medications. Only lipoproteins with *P*_{trend} < 0.05 are shown.

[†]Quintiles 3 and 4 collapsed into quintile 4, due to large number of subjects reporting that they smoked 20 cigarettes per day.

LDL-C, LDL particles, and TG were observed, confirming the relationships identified in the previous analysis. For total cholesterol, LDL-C, and total LDL particles, there was a distinct step function from the lowest (mean 11 cigarettes/day, quintile 1) to the next higher quintile of current smoking (mean 16 cigarettes/day, quintile 2), with little change in quintiles 3–5. For TG, however, there was a monotonic linear relation with levels rising steadily with each category. For smoking burden (current pack-years), significant linear relationships again were observed with total cholesterol, LDL-C, total LDL particles, and TG. For total cholesterol, LDL-C, and total LDL particles, a distinct step function again was observed from the lowest (mean 7.8 pack-years, quintile 1) to the next greater quintile (16.8 pack-years, quintile 2), but little change in quintiles 3–5. However, TG increased fairly steadily across quintiles. For CO, significant inverse, linear relationships with HDL-C, total HDL particles, and small HDL particles were observed. These relationships showed a distinct step function with the greatest decreases occurring in the step from the lowest CO quintile (mean 11.3 ppm) to the next highest quintile (mean 18.4 ppm, quintile 2), with little change in quintiles 3–5. However differences between the quintiles were small, with an overall decrease in HDL-C of approximately 1 mg/dL.

Discussion

This large cohort study confirmed that current smokers have an atherogenic lipoprotein profile characterized by low HDL-C and mildly increased triglycerides.^{2,5} Given that low HDL-C is associated with increased CVD risk,

the adverse effect of smoking on HDL metabolism likely contributes to increased CVD risk seen among smokers. Complete smoking cessation is recommended to increase HDL-C and to reduce CVD risk^{6,10,11}; however, reducing smoking as a “harm-reduction” strategy also has been advocated, although it is an unproven strategy for CVD risk reduction.^{21–25} Uncertainty about the potential benefits of harm reduction for cardiovascular and other diseases has led to calls from the Institute of Medicine and other groups for more research on the relationships between tobacco exposure and biomarkers of health risk.^{25,26} Smoking reduction is an appealing strategy for improving lipoproteins, but we observed only a modest dose effect of several markers of smoking intensity on lipoproteins in this contemporary cohort of current smokers.

Correlations between the 5 markers of smoking intensity and each lipoprotein were weak. In multivariate models that considered the effects of other factors that affect lipoproteins (such as age, sex, race, waist circumference, alcohol use, and physical activity), the additional effects of the markers of smoking intensity on some of the adjusted *R*² values were statistically significant, but small. Markers of smoking burden, such as cigarettes/day and pack-years were associated with higher total cholesterol, LDL-C, and TG, whereas markers of nicotine dependence and recent smoking exposure, such as the FTND score and CO levels, were associated with lower HDL-C.

With the exception of the weak relationships between FTND and HDL, these lipoprotein relationships were confirmed in analyses by quintiles of smoking intensity parameters. Participants in the lowest quintile of smoking burden had more favorable total cholesterol, LDL-C, and

LDL particles than those with a greater smoking burden. We observed stronger linear trends between these parameters and TG values; however, smoking burden was not related to parameters that are thought to mediate the increased CVD risk associated with high TG, such as HDL-C, HDL particles, or LDL size, so the importance of this observation is unclear. Given the wide standard deviations of TG values within the quintiles, this relationship may reflect some residual confounding. Lower HDL-C and HDL particles only were related to increased CO levels; the effect was small and predominantly was seen above the CO levels of 13 ppm. The overriding observation is that the effects of smoking intensity on lipoprotein metabolism are modest in this sample of moderately heavy smokers and are more related to LDL and TG metabolism than HDL metabolism. In the absence of strong linear relations between smoking measures and risk factors (except in the case of TG, see Table 3), there was little evidence to suggest that smoking reductions would reliably decrease lipoprotein values. However, this conclusion must be tempered by the modest evidence that smokers in the lowest quintiles of exposure did have somewhat more favorable lipoprotein profiles than heavier smokers. Thus, it is possible that smoking reduction to less than 10 cigarettes/day may produce greater CVD risk reduction. Overall, this study shows little evidence that smoking reduction, as opposed to smoking cessation, would improve lipoproteins significantly among smokers, although it may reduce CVD risk by other mechanisms.⁴

Several studies,^{2,5,27,28} predominantly conducted in the 1970s and 1980s, demonstrated dose-related increases in total cholesterol, LDL-C, and TG as well as decreases in HDL-C among light, moderate, and heavy smokers. We also observed dose-dependent relationships with lipoproteins in our study; however, the effects of smoking intensity were more modest than previously described, especially for HDL-C. There are several possible explanations for the apparent differences in our findings. First, many of the studies that found stronger associations between smoking burden (ie, cigarettes/day) and lipoproteins did not adjust for other factors that are associated with smoking and lipids, such as age, obesity, alcohol consumption, and level of physical activity. It is possible that some of the associations previously described between smoking burden and dyslipidemia among smokers were confounded by these relationships. In the Framingham Study, however, the relationship between the number of cigarettes smoked/day and HDL-C remained relatively strong even after adjustment for body-mass index and alcohol intake,²⁷ and a significant inverse relationship between HDL-C with cigarettes smoked per day also was observed in the National Heart, Lung, and Blood Institute Family Heart Study.²⁹ Although the latter observation was independent of age, body-mass index, educational level, estrogen use, alcohol consumption, and leisure time physical activity, the proportion of variance in HDL-C accounted for by smoking was modest -6.7% in men and 3.3% in women—observations

that generally are consistent with our findings.²⁹ Another possibility is that smoking intensity has a weaker effect on lipoproteins in modern smokers, who tend to be overweight. Indeed, the mean body mass indexes in both our male and female participants were 29.0 kg/m^2 , whereas in the Framingham Study, the mean body mass index was only 24.8 kg/m^2 in women and 26.8 kg/m^2 in men.²⁷ Our participants also have a significantly greater BMI than current smokers from the 2005–2006 National Health and Nutrition Examination Survey.³⁰ It is possible that the effects of adiposity and insulin resistance outweigh the incremental effects of increased smoking intensity on lipoproteins. Also, our study included a significant number of nonwhite participants (16%). African-Americans tend to have higher HDL-C, lower TG, and larger LDL particles than non-Hispanic white individuals,³¹ an observation that may have partially obscured the adverse lipoprotein effects of smoking intensity. Finally, some of the earlier studies included a wider range of smoking burden with subjects who had levels of smoking exposure that would have been too low to participate in our study. It is possible that restriction of the lower end of the range in our study attenuated some of the observed relations.

Strengths of this study included its large size and the wide range of data collected on each subject, which permitted extensive modeling and adjustment for confounders that might affect lipoprotein metabolism in this contemporary cohort of current smokers. Five parameters related to smoking intensity were evaluated rather than simply the current number of cigarettes smoked per day. Although these parameters were highly intercorrelated, different relationships between markers of smoking burden and markers of nicotine dependence and smoking efficiency with various lipoproteins were observed. Lipoproteins were quantified by nuclear magnetic resonance spectroscopy, a precise technique for evaluating lipoprotein concentrations, sizes, and for determining lipid concentrations.¹⁷ Because the incremental effect of smoking intensity on lipoproteins was small, it is not surprising that evaluation of lipoprotein subfractions and particle sizes did not yield additional insights. Longitudinal follow-up of this cohort after implementation of smoking cessation strategies is planned, and will better characterize the response of lipoproteins to smoking cessation and continued smoking.

Conclusions

Increased smoking burden is associated with small increases in total cholesterol, LDL-C, and triglycerides. Recent smoke exposure is associated with small decreases in HDL-C and HDL particles. Given the modest dose-effect of smoking intensity on lipoproteins, smoking reduction is unlikely to be an effective strategy for improving dyslipoproteinemia among smokers. Complete smoking cessation, as recommended in current guidelines, is a more promising strategy for improving lipoproteins and reducing CVD risk among smokers.

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