Effects of smoking and smoking cessation on lipids and lipoproteins: Outcomes from a randomized clinical trial

Adam D. Gepner, MD, Megan E. Piper, PhD, Heather M. Johnson, MD, Michael C. Fiore, MD, MPH, Timothy B. Baker, PhD, and James H. Stein, MD ***Madison, WI***

Background The effects of smoking and smoking cessation on lipoproteins have not been studied in a large contemporary group of smokers. This study was designed to determine the effects of smoking cessation on lipoproteins.

Methods This was a 1-year, prospective, double-blind, randomized, placebo-controlled clinical trial of the effects of 5 smoking cessation pharmacotherapies. Fasting nuclear magnetic resonance spectroscopy lipoprotein profiles were obtained before and 1 year after the target smoking cessation date. The effects of smoking cessation and predictors of changes in lipoproteins after 1 year were identified by multivariable regression.

Results The 1,504 current smokers were (mean [SD]) 45.4 (11.3) years old and smoked 21.4 (8.9) cigarettes per day at baseline. Of the 923 adult smokers who returned at 1 year, 334 (36.2%) had quit smoking. Despite gaining more weight (4.6 kg [5.7] vs 0.7 kg [5.1], $P < .001$), abstainers had increases in high-density lipoprotein cholesterol (HDL-C) (2.4 [8.3] vs 0.1 [8.8] mg/dL, $P < .001$), total HDL (1.0 [4.6] vs –0.3 μmol/L [5.0], $P < .001$), and large HDL (0.6 [2.2] vs 0.1 [2.1] μmol/L, $P = .003$) particles compared with continuing smokers. Significant changes in low-density lipoprotein (LDL) cholesterol and particles were not observed. After adjustment, abstinence from smoking ($P < .001$) was independently associated with increases in HDL-C and total HDL particles. These effects were stronger in women.

Conclusions Despite weight gain, smoking cessation improved HDL-C, total HDL, and large HDL particles, especially in women. Smoking cessation did not affect LDL or LDL size. Increases in HDL may mediate part of the reduced cardiovascular disease risk observed after smoking cessation. (Am Heart J 2011;161:145-51.)

Background

Each year, smoking contributes to >443,000 smoking-related deaths in the United States[1]; and nearly 20% of all coronary heart disease deaths can be attributed to smoking.[1,2] Although the strong relationship between smoking and cardiovascular disease (CVD) has been well-documented,[3,4] the mechanisms by which smoking increases CVD risk appear to be multifactorial and incompletely understood, in part because these associations have been derived from observational studies.[5-8] These studies, and smaller clinical trials, suggest that cigarette smoking is associated with a more atherogenic lipid profile[6,8,9] characterized by higher total cholesterol and triglycerides (TG) with lower levels of high-density lipoprotein cholesterol (HDL-C).

Smoking intensity also has been associated with small, statistically significant increases in low-density lipoprotein cholesterol (LDL-C) and decreases in HDL-C.[6,8,10] Some have described small dense LDL particles among current smokers and improvements in lipids after smoking cessation; however, these findings have been less consistent.[11,12] No studies, to date, have prospectively evaluated the effects of continued smoking and smoking cessation on lipoproteins in a large, contemporary cohort of current smokers. This is a matter of considerable importance because smokers in the 21st century are significantly more overweight than those studied previously.[6,8,13] Because smoking cessation is associated with weight gain[14-16] and weight gain affects lipoproteins,[8,17,18] the effects of smoking cessation on lipoproteins remain unclear.

We evaluated the effects of current smoking and smoking cessation on lipids and lipoproteins in a prospective, randomized clinical trial of smoking cessation pharmacotherapy.[19]

Methods

Study participants and design

The institutional review board at the University of Wisconsin School of Medicine and Public Health approved this study.

From the University of Wisconsin School of Medicine and Public Health, Madison, WI.
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Submitted July 27, 2010; accepted September 26, 2010.
Reprint requests: James H. Stein, MD, University of Wisconsin School of Medicine and Public Health, 600 Highland Avenue, G7/341 CSC (MC 3248), Madison, WI 53792.
E-mail: jhs@medicine.wisc.edu
0002-8703/$ - see front matter

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All subjects provided informed consent. Subjects were participants in a randomized, double-blind, placebo-controlled trial to evaluate the efficacy of smoking cessation pharmacotherapies and to examine the natural history of continued smoking and smoking cessation on CVD risk (clinicaltrials.gov registration no. NCT00332644).[19] Specific recruitment strategies have been described previously.[19] This article describes the effects of smoking cessation and continued smoking on lipids and lipoprotein subfractions 1 year after the target quit date, a prespecified analysis in this study. The authors are solely responsible for the design and conduct of this study; all study analyses, the drafting and editing of the paper, and its final contents.

Participants were randomized to 1 of 6 treatment conditions: nicotine lozenge, nicotine patch, sustained-release bupropion, nicotine patch plus nicotine lozenge, sustained-release bupropion plus nicotine lozenge, or placebo.[19] All participants received individual cessation counseling.[19] Major inclusion criteria were age ≥18 years, smoking ≥10 cigarettes per day, expired carbon monoxide (CO) level >9 ppm, and stated motivation to quit smoking. Exclusion criteria have been reported previously[19]; the major ones were blood pressure (BP) >160/100 mm Hg, recent myocardial infarction, heavy alcohol use, use of contraindicated medications, and current pregnancy or breast-feeding.

Study procedures

Subjects were recruited from communities in and around Madison and Milwaukee, WI, from January 2005 to June 2007.[19] The baseline clinical trial visits included measurement of anthropometric data, fasting laboratory tests, and completion of questionnaires and interviews. Baseline physical activity was assessed by the International Physical Activity Questionnaire.[20] Baseline alcohol use was measured as alcoholic drinks consumed per month.[21] Smoking burden was evaluated by current cigarette smoking (cigarettes per day) and pack-years (current cigarettes per day ∗ years smoked). Recent smoke exposure was measured by an exhaled CO level, which reflects smoking efficiency and recent smoke exposure. Smoking status was assessed by self-reported 7-day point-prevalence abstinence using a smoking calendar and the timeline follow-back method, confirmed by an exhaled CO level of <10 ppm (Micro-3 Smokerlyzer; Bedfont Scientific, Williamsburg, VA).[21,22]

Measurement of lipids and lipoproteins

Fasting blood samples were obtained by venipuncture and refrigerated. Plasma aliquots were isolated by centrifugation and frozen at −70°C. Samples underwent nuclear magnetic resonance spectroscopic lipoprotein analysis (Lipoprofile-2; LipoScience, Inc, Raleigh, NC) using previously published methods.[23] Concentrations of very low-density lipoprotein (VLDL) and LDL (including intermediate-density lipoprotein [IDL]) subclasses (in nanomoles per liter) and HDL subclasses (in micromoles per liter) were determined. The 9 measured subclasses were defined as follows: large VLDL (>60 nm), medium VLDL (35-60 nm), small VLDL (27-35 nm), 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 IDL, large LDL, and small LDL subclass concentrations. Total HDL particle concentrations are the sum of large, medium, and small HDL subclass concentrations. Weighted-average 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 nuclear magnetic resonance signal.[23,24] Nuclear magnetic resonance–derived cholesterol and TG were determined by conversion of lipoprotein particle data to lipid concentration units (in milligrams per deciliter) based on the expected amount of cholesterol and TG in each particle.[23]

Statistical analysis

All analyses were conducted using PASW Statistics 18 software (SPSS Inc, Chicago, IL). Means (SDs) were determined for the subject characteristics and smoking intensity parameters in Table I. Variable disributions were evaluated for normality. Skewed variables (TG, alcohol consumption, and International Physical Activity Questionnaire activity scores) were log-transformed. Pearson correlations were used to identify univariate associations between age, sex, body mass index (BMI), waist circumference, weight, glucose, baseline cigarettes per day, baseline physical activity, and baseline alcohol use with lipids and lipoproteins at baseline and after 1 year. Changes were computed by subtracting year 1 from baseline values. *t* Tests were used to compare change scores for BMI, weight, waist circumference, glucose, CO levels, and the lipid and lipoprotein measures between participants who were abstinent at 1 year and those who were smoking.

Multivariable linear regression models were constructed to determine associations of changes in lipids and lipoproteins from baseline to 1 year after the target quit date. Separate models were created for predicting changes in each lipid fraction hypothesized to be influenced by smoking status (HDL-C, LDL-C, and TG) and selected lipoprotein measures chosen because of established relationships with smoking and/or CVD risk (total LDL particles, small LDL particles, LDL size, total HDL particles, large HDL particles, HDL size). Because there were 9 lipid and lipoprotein variables of interest, a Bonferroni-corrected $\alpha < .0056$ was used to control for type I error. For other variables, a standard $\alpha < .05$ was used. Each model was adjusted for baseline values of each lipid or lipoprotein parameter. All models included covariates that could affect the dependent variables independently of smoking cessation, such as age, sex, race, weight change, treatment arm, baseline cigarettes per day, baseline physical activity, baseline alcohol consumption, smoking status at year 1 (abstinent or continued smoker), and change in glucose level. Change in weight was used rather than change in BMI or waist circumference because it had the strongest univariate associations with changes in the lipoprotein parameters. Multivariable models are described using R^2 values and β coefficients. Partial regression plots of change in HDL-C by quartile of baseline cigarettes per day and quintile of baseline CO (adjusted for change in weight and baseline HDL-C) also were examined to determine if changes in HDL-C among abstainers were related to baseline smoking intensity.

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Results

Subject characteristics

Subject characteristics at baseline and year 1 are provided in Table I. There were 1,504 smoking subjects randomized. As often observed in smoking cessation clinical trials,[25-27] 581 (39%) subjects did not return for their 1-year follow-up visit. Individuals who returned for this visit were slightly older (mean 1.2 years, $P < .001$) and had slightly higher HDL-C (mean 1.4 mg/dL, $P = .041$) than those who did not return, but otherwise had similar CO levels, waist circumference, serum glucose, total cholesterol, TG, LDL-C, and high-sensitivity C-reactive protein (all Ps > .20).[15,28]

Of the 923 subjects who attended the year 1 visit, 58% were women, 84% were white, and 13% were African American. Abstinence from smoking was confirmed in 334 (36.2%) participants. Only 5% were using lipid-lowering medications. Excluding these subjects did not change the results significantly (data not shown). Only 2.8% of subjects had hemoglobin A_1C >7%; 14.4% had hemoglobin A_1C >6%, percentages similar to the proportions of smokers with values above these thresholds in the 2005-2006 National Health and Nutrition Examination Survey (Jon Keevil and Matt Tattersall, personal communication, September 1, 2010). In addition, 11 subjects self-reported a diagnosis of diabetes mellitus. Baseline alcohol use and physical activity level were similar for abstainers and continued smokers. At baseline, the subjects performed 122.0 (150.1) metabolic equivalent–h/d of moderate-vigorous activity and 11.1 (21.4) metabolic equivalent–h/d of leisure activity.[15] Compared with those who relapsed, abstainers had slightly lower baseline CO levels (23.4 [11.1] vs 26.4 [12.3] ppm, $P < .001$), smoked fewer cigarettes per day (20.0 [8.7] vs 21.8 [9.2], $P = .003$), and had fewer pack-years (27.3 [19.9] vs 30.7 [21.1], $P = .014$). Baseline levels of all lipid and lipoprotein parameters were similar for abstainers and continued smokers, except for small HDL particles that were slightly higher at baseline in those who abstained (24.1 [4.5] vs 23.4 [5.1] μmol/L, $P = .035$) (Table I).

Effects of smoking cessation

Comparisons between abstainers and continuing smokers are summarized in Table I. After 1 year, CO levels decreased in both abstainers and continued smokers; however, subjects who abstained had significantly greater CO reductions (−21.3 [11.2] vs −7.2 [13.0] ppm, $P < .001$). Compared with continued smokers, abstainers had more weight gain (4.6 [5.7] vs 0.7 [5.1] kg, $P < .001$) and greater increases in waist circumference (2.8 [10.6] vs 1.0 [6.3] cm, $P < .001$) and BMI (1.6 [2.0] vs 0.2 [1.7] kg/m^2, $P < .0010$). Abstainers had significant increases in HDL-C (2.4 [8.3] vs 0.1 [8.8] mg/dL, $P < .001$), total HDL particles (1.0 [4.6] vs −0.3 [5.0] μmol/L, $P < .001$), and large HDL particles (0.6 [2.2] vs 0.1 [2.1] μmol, $P = .003$) compared with those who continued to smoke (Figure 1). Statistically significant differences in other lipid and lipoprotein fractions were not observed.

Independent associations with change in HDL parameters

Models to identify independent predictors of changes in HDL-C and particles are described in Table II. All analyses were adjusted for baseline values of each lipid or lipoprotein parameter, as well as the parameters described in the "Methods." As expected, the most powerful predictors of changes in the HDL-related parameters were baseline values, with larger changes among those with the lowest baseline levels of HDL-C, total HDL particles, and large HDL particles and the smallest HDL diameters. For HDL-C, total HDL particles, and large HDL particles, the next most powerful predictors were abstinence from smoking and female sex, except for HDL particle size, for which change in weight was nearly as powerful a predictor as baseline HDL diameter. In abstainers, neither baseline number of cigarettes smoked per day ($P = .834$) nor baseline CO levels ($P = .107$) predicted changes in *any* HDL-related parameter after adjustment for changes in weight and baseline HDL-C.

Discussion

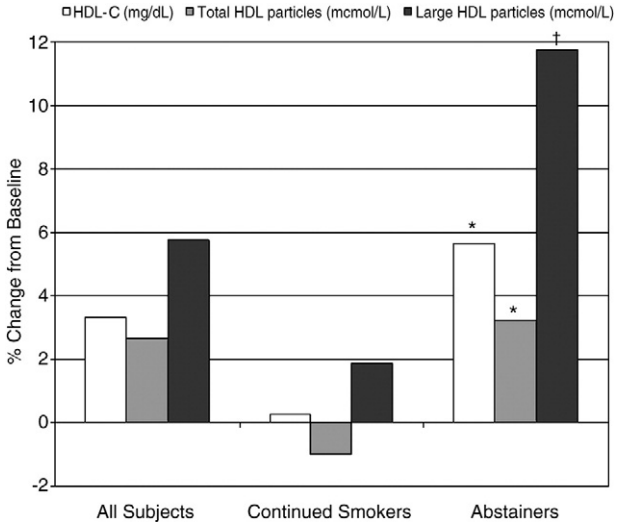
To our knowledge, this is the largest prospective, randomized clinical trial that has evaluated the effects of smoking cessation on lipid and lipoprotein levels. Although smoking is associated with low HDL-C, previous studies suggesting that smoking cessation increases HDL-C levels were from older, observational studies with less contemporary cohorts or from smaller clinical trials. Smokers in our study had higher BMIs than in previous reports and are more representative of the current United States population.[6,8,9,13,29] Despite our subjects being more overweight and gaining weight after smoking cessation, we showed that smoking cessation was related to higher HDL-C and higher total and large HDL particles. Patients with the lowest HDL-related parameters had the largest increases in HDL. After baseline levels of HDL-C and HDL particles, abstinence from cigarette smoking was the next most powerful predictor of changes in these parameters, followed by female sex and weight change. The observation that women had larger increases in HDL-C and HDL particles after smoking cessation is consistent

Table I. Subject characteristics at baseline and 1 year after the target quit date

	All subjects		CS		
	Baseline n = 1504	**Year 1 n = 923**	**Baseline n = 589**	**Year 1 n = 589**	**Δ n = 589**
Age (y)	45.4 (11.3)	–	45.2 (11.0)	–	–
BMI (kg/m^2)	29.0 (6.5)	29.6 (6.5)	28.8 (6.2)	29.0 (6.4)	0.24 (1.7)
Waist circumference (cm)	95.9 (16.2)	97.5 (16.0)	95.0 (15.2)	96.0 (15.8)	1.0 (6.3)
Weight (kg)	83.6 (20.5)	85.3 (21.0)	82.5 (20.0)	83.3 (20.5)	0.7 (5.1)
Cigarettes smoked/d	21.4 (8.9)	–	21.8 (9.2)	–	–
Pack-y	29 (20.4)	–	30.7 (21.1)	–	–
CO (ppm)	25.7 (12.4)	13. (12.6)	26.4 (12.3)	19.1 (12.1)	–7.2 (13.0)
Systolic BP (mm Hg)	124.9 (14.7)	116.6 (14.6)	119.2 (14.5)	116.6 (14.5)	–2.6 (13.5)
Diastolic BP (mm Hg)	74.0 (9.4)	72.8 (10.3)	73.8 (10.3)	72.3 (10.1)	–1.5 (9.9)
Glucose (mg/dL)	94.9 (17.7)	97.6 (25.0)	96.2 (20.4)	97.1 (23.0)	0.8 (15.8)
LDL-C (mg/dL)	118.9 (30.6)	119.3 (31.9)	118.6 (30.6)	119.2 (32.7)	0.5 (22.2)
Total LDL particles (nmol/L)	1318.0 (392.8)	1317.1 (408.9)	1310.2 (396.1)	1306.3 (410.1)	–2.7 (294.9)
Small LDL particles (nmol/L)	775.0 (455.2)	768.5 (472.9)	765.5 (462.0)	750.2 (462.0)	–11.8 (354.9)
Mean LDL particle diameter (nm)	21.1 (0.8)	21.1 (0.9)	21.1 (0.8)	21.1 (0.8)	0.02 (0.62)
HDL-C (mg/dL)	42.0 (13.5)	43.4 (14.0)	42.4 (13.9)	42.6 (14.2)	0.1 (8.8)
Total HDL particles (μmol/L)	30.0 (5.9)	30.8 (6.2)	30.4 (6.2)	30.2 (6.2)	–0.3 (5.0)
Small HDL particles (μmol/L)	23.0 (4.9)	23.7 (4.9)	23.4 (5.1)	22.8 (5.3)	–0.6 (4.7)
Large HDL particles (μmol/L)	5.2 (3.3)	5.5 (3.5)	5.3 (3.4)	5.4 (3.4)	0.1 (2.1)
Mean HDL particle diameter (nm)	8.7 (0.5)	8.7 (0.5)	8.7 (0.5)	8.7 (0.5)	0.02 (0.28)
TG (mg/dL)	143.3 (101.7)	134.6 (89.3)	146.0 (105.6)	132.7 (91.1)	–11.9 (78.5)

CS, Continued smokers; *A*, abstainers; *Δ*, change in variable.

Figure 1



Percentage change in HDL parameters at 1 year compared with baseline values. *P* values compare continued smokers to abstainers. *$P < .001$; † $P = .002$.

with our previous observation that, among current smokers, the association between pack-years of smoking and the presence of carotid plaque was stronger in women[30] and a previous observation that smoking has a stronger association with coronary heart disease incidence in women compared with men.[31]

The mechanisms by which smoking decreases HDL-C are incompletely understood. Smoking increases catecholamine release, causing a surge in circulating free fatty acids, which may increase VLDL and LDL concentrations and reduce HDL-C concentrations.[8] Smoking reduces lecithin-cholesterol acyltransferase, the enzyme responsible for esterifying free cholesterol and increasing HDL size,[32] and may reduce levels of cholesterol ester transfer protein; however, studies of the effects of smoking on these enzymes have had mixed results.[33-35] In population-based studies, a 1-mg/dL increase in HDL-C has been associated with a 2% to 3% decrease in CVD events.[36,37] This implies that, in our subjects, smoking abstinence could reduce CVD events by 4% to 6% over a decade. Our study also suggests that abstinence from smoking is associated with increases in HDL-C, regardless of baseline smoking intensity. This important finding may encourage clinicians to emphasize abstinence even in light smokers.

Weight gain after smoking cessation can be a significant barrier to quitting.[14-16] In our study, those who abstained gained approximately 4 kg more than those who resumed smoking. Increased weight has been associated with lower HDL-C, such that every kilogram of additional weight can reduce HDL-C by 0.5% to 1%[17,18]; however, HDL-C increased by 5.2% among abstainers in our study. Weight gain was independently associated with increased HDL-C as well as total and large HDL particles.

A			*P* values	
Baseline n = 334	**Year 1 n = 334**	**Δ n = 334**	**Baseline, CS versus A**	**Δ, CS versus A**
45.6 (11.7)	–	–	.604	–
29.0 (6.7)	30.5 (6.7)	1.6 (2.0)	.567	<.001
97.2 (17.2)	100.0 (16.0)	2.8 (10.6)	.050	.002
84.6 (21.7)	88.9 (21.5)	4.6 (5.7)	.150	<.001
20.0 (8.7)	–	–	.003	–
27.3 (19.9)	–	–	.014	–
23.4 (11.1)	2.1 (1.9)	−21.3 (11.2)	<.001	<.001
120.8 (14.5)	116.5 (15.0)	−4.3 (14.6)	.102	.102
75.1 (9.7)	73.7 (10.7)	−1.4 (10.4)	.055	.744
94.3 (13.8)	98.4 (28.3)	4.0 (23.9)	.126	.018
120.2 (28.4)	119.5 (30.5)	−0.3 (24.0)	.431	.616
1353.8 (395.5)	1335.8 (481.2)	−15.8 (329.3)	.115	.558
821.1 (481.2)	800.0 (490.3)	−22.9 (391.5)	.086	.678
21.0 (0.9)	21.0 (0.9)	0.02 (0.68)	.185	.882
42.5 (13.7)	44.7 (13.6)	2.4 (8.3)	.872	<.001
30.9 (5.9)	31.9 (6.0)	1.0 (4.6)	.304	<.001
24.1 (4.5)	24.0 (5.3)	−0.1 (4.4)	.035	.106
5.1 (3.4)	5.7 (3.6)	0.6 (2.2)	.412	.003
8.7 (0.5)	8.7 (0.5)	0.06 (0.27)	.184	.043
139.8 (80.5)	137.8 (86.3)	−0.4 (75.3)	.957	.041

Table II. Significant predictors of changes in lipoprotein parameters from baseline to 1 year

Dependent variable	Adjusted R^2	Significant independent predictors	Standardized β	*P* value
Δ HDL-C	0.101	Baseline HDL-C	−0.299	<.001
		Abstinence status	0.195	<.001
		Female sex	0.140	<.001
		Δ Weight (kg)	0.130	.001
Δ Total HDL particles	0.141	Baseline total HDL particles	−0.376	<.001
		Abstinence status	0.161	<.001
		Female sex	0.108	.003
Δ Large HDL particles	0.110	Baseline large HDL particles	−0.322	<.001
		Abstinence status	0.170	<.001
		Female sex	0.151	<.001
		Δ Weight (kg)	0.133	<.001
Δ HDL particle diameter	0.125	Baseline HDL particle diameter	−0.281	<.001
		Δ Weight (kg)	0.256	<.001
		Abstinence status	0.162	<.001
		Female sex	0.106	.006

Models included age, sex, race, study treatment arm, baseline cigarettes per day, baseline physical activity level, baseline alcohol consumption, smoking status at year 1 (abstinent or continued smoker), change in weight, and change in glucose, as well as the baseline value of the lipid or lipoprotein dependent variable.

This suggests that the impact of weight gain on HDL may be counteracted by the impact of smoking cessation. This important finding has not been reported previously in a cohort of this size. Smoking has been associated with increased TG.[6] In our study, abstinence from smoking was associated with only mild TG reductions that were not statistically significant after correcting for multiple comparisons, likely because of the counterbalancing effect of weight gain. Significant changes in LDL-C, LDL particle concentrations, and LDL size were not observed.

Limitations

Because this was a randomized clinical trial of smoking cessation interventions, there were no nonsmoking controls; so we cannot determine the extent to which lipoprotein values normalized after smoking cessation. In smoking cessation studies, it is common for subjects who

relapse to drop out or miss follow-up visits.[25-27] In our study, 38.6% of subjects did not return for their 1-year follow-up visit, which is consistent with the 30% to 43% 1-year dropout rates reported in other recent clinical trials of smoking cessation pharmacotherapy.[26,27] Subjects who did not attend the follow-up visit had similar age, sex, and race distributions to those who did return; and they smoked a similar number of cigarettes per day at baseline.[15] Although significant efforts were made to recruit racially diverse participants, only16% of the study cohort was nonwhite. In addition, changes in alcohol use and physical activity levels were not included in the analysis because 1-year follow-up data were not yet coded for analysis. Alcohol use and exercise can increase HDL-C levels. Smoking cessation is not associated with increased exercise levels; however, we cannot exclude the possibility that the increases in HDL we observed among abstainers were related to increased alcohol intake. Most smoking cessation trials have not systematically evaluated alcohol use.[38] Smoking cessation studies that did evaluate alcohol use have had conflicting results[39,40]; however, our statistical models did not show that baseline exercise levels or alcohol use independently predicted changes in HDL parameters. Although LDL particles and LDL-C did not change significantly with smoking cessation, we did not measure oxidized LDL levels.

Conclusion

In this large, prospective, contemporary study of current smokers, smoking cessation improved HDL-C, total HDL, and large HDL particle concentrations, despite weight gain. These findings were especially strong in women. Smoking cessation, not baseline smoking intensity, predicted increased HDL parameters. These findings suggest that an increase in HDL may mediate some of the reduced CVD risk observed after smoking cessation.

Potential conflicts of interest

A. D. Gepner, M. E. Piper, H. M. Johnson, J. H. Stein: no conflicts to disclose.

M. C. Fiore: Over the last 3 years, Dr Fiore has served as an investigator in research studies at the University of Wisconsin that were funded by Pfizer, GlaxoSmithKline, and Nabi Biopharmaceuticals. In 1998, the University of Wisconsin appointed Dr Fiore to a named Chair funded by an unrestricted gift to UW from Glaxo Wellcome.

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