

Determinants of Population Changes in Fibrinogen and Factor VII Over 6 Years

The Atherosclerosis Risk in Communities (ARIC) Study

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Abstract—Although numerous cross-sectional studies have identified possible determinants of plasma fibrinogen and factor VII levels, few prospective studies exist. We assessed the longitudinal relation of changes in fibrinogen and factor VII over 6 years with changes to other cardiovascular risk factors in a sample of 440 men and 549 women from the Atherosclerosis Risk in Communities (ARIC) study. Fibrinogen increased more in older participants, those with or who developed diabetes, those who at any time smoked, and those whose plasma HDL cholesterol or triglycerides decreased and increased less in female participants who started hormonal replacement therapy. Factor VII coagulant activity increased more in younger participants, women, those who gained greater weight or developed diabetes, those who quit smoking, those in whom plasma triglycerides decreased, and female participants who received hormonal replacement therapy. Thus, our longitudinal data suggest with some exceptions that adverse changes in cardiovascular risk factors are accompanied by increases in plasma levels of fibrinogen and factor VII. (*Arterioscler Thromb Vasc Biol.* 2000;20:601-606.)

Key Words: fibrinogen ■ factor VII ■ diabetes mellitus ■ studies, prospective

Considerable epidemiological evidence implicates plasma fibrinogen¹⁻⁷ and possibly factor VII_c^{2,5} as risk factors for coronary heart disease (CHD). Cross-sectional epidemiological studies and short-term experiments have identified several determinants of fibrinogen and factor VII_c levels.^{8,9} However, we know of only 1 longitudinal population-based study of long-term changes in hemostatic factors.¹⁰ That study showed that changes in fibrinogen were positively associated with changes in cigarette smoking and negatively associated with changes in alcohol consumption but were not associated with weight change. In addition, factor VII_c increased with weight gain but was not independently related to changes in smoking and alcohol intake.¹⁰

To further examine potential determinants of long-term changes in fibrinogen and factor VII_c, we repeated these measurements 6 years after baseline in a population-based study, the Atherosclerosis Risk in Communities (ARIC) study.

Methods

Study Population

The ARIC study¹¹ selected population samples from Forsyth County, NC; Jackson, Miss (blacks only); the northwest suburbs of Minne-

apolis, Minn; and Washington County, Md, and examined a cohort that totaled 15 792 persons between 45 and 64 years of age at recruitment from 1987 through 1989. The study reexamined participants from 1990 through 1992 (93% return rate) and from 1993 through 1995 (86% return rate). We measured hemostatic factors in the entire cohort during the 1987 through 1989 examination and in a stratified sample in the 1993 through 1995 examination. The 1993 through 1995 sample included a random sample of the 12 885 returning participants, with nonmissing values for smoking and diabetes status and oversampling for new diabetics and people who quit smoking. The sample (n=1030) included 122 (20%) of the new diabetics but not cigarette quitters, 17 (26%) of the new diabetics who quit cigarettes, 134 (17%) of the other cigarette quitters, and 757 (7%) of the remaining 1993 through 1995 group.

Measurements

After participants underwent an 8-hour fasting period, technicians drew blood from an antecubital vein in each participant, with minimal trauma. We have published detailed methods for hemostatic factors.^{12,13} In brief, the laboratory measured fibrinogen by the thrombin-time titration method¹⁴ with reagents and calibration materials (Fibriquik) obtained from General Diagnostics (Organon-Technika Co). Factor VII coagulant activity (factor VII_c) was measured by determination of the ability of the testing sample to correct the clotting time of human factor VII-deficient plasma obtained from George King Biomedical Inc. The reference material for assays was the universal coagulation reference plasma (Thrombocreen; Pacific Hemostasis; Curtin Matheson Scientific, Inc). During the 1987 through 1989 period, the reliability coefficients

Received March 15, 1999; revision accepted August 13, 1999.

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TABLE 1. Risk Factor Levels for 1987 through 1989 and 1993 through 1995 for the ARIC Study

Risk Factor	Sample*		Entire Cohort*	
	1987–1989	1993–1995	1987–1989	1993–1995
Age, y	54 (6)	60 (8)	54 (6)	60 (6)
Current smoker, %	21.2†	16.6†	26.2	17.7
Alcohol intake, g/w	39 (86)	32 (87)	43 (97)	35 (89)
BMI, kg/m ²	27.6 (5.2)	28.6 (5.7)	27.7 (5.4)	28.5 (5.6)
Sport index, range 0–5	2.4 (0.8)	2.5 (0.8)	2.4 (0.8)	2.5 (0.8)
Diabetes mellitus, %	6.5†	11.5†	10.0	12.9
Women treated with hormonal replacement therapy, %	21.9	41.6	18.6	39.6
LDL-cholesterol, mg/dL	139 (39)	128 (36)	138 (39)	127 (35)
HDL-cholesterol, mg/dL	52 (17)	52 (18)	52 (17)	52 (18)
Triglycerides, mg/dL	131 (84)	144 (106)	132 (91)	142 (91)
Fibrinogen, mg/dL	298 (62)	324 (85)	304 (66)	NA
Factor VII _c , %	118 (27)	106 (31)	119 (30)	NA

Risk factors are mean (SD) or percentage, as indicated.

*Based on 549 women and 440 men. Entire cohort based on 8710 women and 7082 men.

†Participants who quit smoking or with new diabetes were oversampled.

NA indicates not available.

(method variance plus intraindividual variance), obtained from repeated testing of individuals during several weeks, were $r=0.72$ for fibrinogen, and $r=0.78$ for factor VII.¹⁵ The Pearson correlation on 815 split, blind, duplicate specimens was $r=0.88$ for fibrinogen and $r=0.86$ for factor VII_c for the 1987 through 1989 examination, and on 33 duplicates was $r=0.61$ for fibrinogen and $r=0.56$ for factor VII_c for the 1993 through 1995 examination. During the entire 6-year interval, laboratory controls were continuously in the established range.

At each examination, we asked participants whether they smoked cigarettes and, if so, the number of cigarettes smoked per day. We classified participants as continued nonsmokers, continued smokers, new smokers, or quitters. We assessed usual alcohol intake and classified it as an increase, no change, or decrease during the 6 years. We defined diabetes mellitus as a fasting glucose level ≥ 140 mg/dL, nonfasting glucose level ≥ 200 mg/dL, or a history of or treatment for diabetes. We classified participants as having become diabetic, staying diabetic, or never having had diabetes. Technicians measured height and weight with participants in scrub suits, and we computed the body mass index (in kg/m²). We assessed physical activity by a sport index with the use of a questionnaire by Baecke et al.¹⁶ For analysis, we categorized changes in BMI and the sport index in tertiles.

The laboratory staff measured plasma total cholesterol and triglycerides by enzymatic methods^{17,18} and calculated LDL cholesterol.¹⁹ HDL cholesterol level was measured after dextran-magnesium precipitation of non-HDL lipoproteins.²⁰ We categorized changes in plasma lipids in tertiles.

Statistical Methods

A total of 549 women and 440 men had fibrinogen and factor VII measurements taken at baseline and 6 years. To account for the stratified random sampling design, we conducted analyses using SUDAAN software²¹ and weighted each observation for the inverse of the sampling fraction. We first computed the mean values or prevalences (in percentage) of risk factors in the 1987 through 1989 and 1993 through 1995 examinations. We then used ANCOVA to relate changes to adjusted mean fibrinogen (or factor VII) over the 6 years to changes in other risk factors, with adjustments for age, race, sex, and initial value of fibrinogen (or factor VII_c). We adjusted for initial values of fibrinogen (or factor VII_c) because it is a likely confounder of the association between risk factor change and change in fibrinogen (factor VII_c). We computed the adjusted mean change in both fibrinogen and factor VII_c by category of risk factor change and by net change (by subtraction)

relative to a specified reference category of risk factor. We present overall probability value for differences between groups.

We also fit multiple linear regression to calculate the adjusted mean change of fibrinogen (or factor VII_c) in relation to multiple other risk factor changes simultaneously. We included the baseline values of fibrinogen (or factor VII_c) as covariates. The reported regression coefficient ($\hat{\beta}$) represents the change in the hemostatic factor per level of change in the determinant, with adjustments for the other variables in the model.

We also considered the impact that measurement error of baseline fibrinogen (or factor VII_c) would have on our results. In theory, measurement error due to laboratory or within-person variability could bias the $\hat{\beta}$ estimates if baseline fibrinogen (or factor VII_c) were related to risk factor changes. We corrected for the bias from measurement error by adapting published methods.²² Results after correction were similar to the uncorrected results; thus, only the latter are presented.

Results

The ARIC sample with measurements of fibrinogen and factor VII_c levels in both the 1987 through 1989 and 1993 through 1995 periods included 549 women and 440 men; 25% were blacks and 75% were whites. During the 6 years between examinations, mean alcohol intake in these participants decreased 7 g/wk; BMI increased 1.0 kg/m²; the sports index increased 0.1 unit; LDL cholesterol declined 11 mg/dL; HDL cholesterol increased 0.76 mg/dL; triglycerides increased 13 mg/dL; and among women, hormone replacement therapy increased nearly 20% (Table 1). As expected from oversampling and cohort aging, the prevalence of smoking decreased and of diabetes increased.

Baseline mean fibrinogen (298 mg/dL) and factor VII_c (118%) levels in this sample assessed twice were similar to the baseline mean fibrinogen (304 mg/dL) and factor VII_c (119%) levels in the entire ARIC cohort (n=15 792). During the 6 years between examinations, mean fibrinogen in the sample increased 26 mg/dL and mean factor VII_c decreased 12%. Spearman correlations for 1987 through 1989 and 1993 through 1995 values were 0.51 for fibrinogen and 0.52 for factor VII_c.

TABLE 2. Adjusted* Mean Changes in Fibrinogen and Factor VII_c During 6 Years in Relation to Changes in Other Risk Factors for the ARIC Study

Change in Risk Factor	n	Fibrinogen (mg/dL)			VII _c		
		Absolute Δ	Net Δ	P†	Absolute Δ	Net Δ	P†
Smoking							
Continued nonsmoker	689	+23	Ref	0.14	-12	Ref	0.004
Became smoker	20	+49	+26		-18	-6	
Stayed smoker	133	+33	+10		-13	-1	
Quit smoking	143	+36	+13		-2	+10	
Alcohol (g/w)							
Decreased	246	+33	+8		-12	-1	
No change	606	+25	Ref	0.16	-11	Ref	0.53
Increased	126	+17	-8		-14	-3	
BMI (kg/m²)‡							
≤+0.24	327	+29	Ref	0.67	-15	Ref	0.0009
+0.25 to 1.67	326	+25	-4		-13	+3	
≥+1.67	336	+24	-5		-7	+8	
Sport index‡							
≤-0.25	371	+24	Ref	0.88	-11	Ref	0.69
0.00 to +0.25	269	+26	+2		-13	-2	
≥+0.50	338	+27	+3		-12	-1	
Diabetes							
Continued nondiabetic	792	+24	Ref	0.0005	-12	Ref	0.12
Became diabetic	133	+53	+29		-7	+6	
Stayed diabetic	59	+38	+15		-12	+1	
Hormone replacement therapy (women)							
Continued nonuser	245	+28	Ref	0.11	-11	Ref	0.03
Became user	88	+10	-18		-4	+7	
Stayed user	80	+13	-15		-1	+9	
Quit using	6	+44	+16		-4	+7	
LDL-cholesterol‡ (mg/dL)							
≤-23	293	+20	Ref	0.33	-12	Ref	0.69
-22 to -0.2	346	+29	+9		-12	-0	
≥-0.1	325	+29	+8		-11	-1	
HDL-cholesterol‡ (mg/dL)							
≤-3.7	334	+28	Ref	0.09	-11	Ref	0.74
-3.7 to +4.1	339	+32	+4		-13	-2	
≥4.2	314	+19	-9		-12	-1	
Triglycerides‡ (mg/dL)							
<-6.0	342	+37	Ref	0.005	-15	Ref	<0.0001
-5.0 to 30	320	+24	-13		-14	+2	
≥31	326	+17	-20		-6	+9	

*Adjusted for age, race, sex, and initial value of fibrinogen or VII_c.

†Test of differences in net changes.

‡Tertiles of change for BMI, sport index, and plasma lipids.

Mean changes in fibrinogen and factor VII_c in relation to changes in other risk factors are shown in Tables 2 (adjusted for age, race, sex, and baseline level) and 3 (multivariately). In multivariate models without biochemical factors (Table 3, model 1), fibrinogen appeared to increase slightly more in older versus younger participants, 14 to 29 mg/dL more in those with or who developed diabetes versus nondiabetics, and 10 to 13 mg/dL more in those who at any time had smoked versus never-smokers. Conversely, in comparison

with continued smokers, those who quit had a 2 to 3 mg/dL rise in fibrinogen. In model 1, for women only (not shown in Table 3), starting hormonal therapy was associated with a 20-mg/dL-greater decline ($P=0.02$), continuation of hormonal therapy with a 16-mg/dL-greater decline ($P=0.11$), and cessation of hormonal therapy with a 10-mg/dL-greater rise ($P=0.66$) compared with women who were not treated with hormonal replacement. Addition of lipid variables (model 2) did not greatly change the patterns observed in model 1,

TABLE 3. Adjusted Mean Change in Fibrinogen and Factor VII_c During 6 Years in Relation to Specified Differences in Other Variables for the ARIC Study

Variable (Difference)	Fibrinogen Change (mg/dL)*				Factor VII _c Change (%)*			
	Model 1		Model 2		Model 1		Model 2	
	$\hat{\beta}$	SE	$\hat{\beta}$	SE	$\hat{\beta}$	SE	$\hat{\beta}$	SE
Age (5 y)	0.8†	0.4	0.9†	0.4	-0.4†	0.2	-0.4†	0.2
Women (vs men)	0.4	5.0	4.0	4.7	10.6†	1.7	9.4†	1.8
White (vs black)	3.8	6.2	2.2	6.1	-2.7	2.2	-2.5	2.1
Alcohol change (30 g/w)	-1.3	1.2	-0.4	1.1	0.3	0.3	0.1	0.3
BMI change (5 kg/m ²)	2.2	6.4	5.9	7.0	7.9†	1.8	4.6†	1.9
Sports score change (1 units)	0.1	3.0	-0.0	2.9	0.7	1.1	0.7	1.1
Started smoking (vs stayed nonsmoker)	13.2	12.7	19.7	13.1	-3.8	3.4	-6.2†	3.1
Stayed smoker (vs stayed nonsmoker)	10.4	7.8	13.5‡	7.7	0.4	2.1	0.2	2.1
Quit smoking (vs stayed nonsmoker)	12.2‡	7.3	10.1	7.3	7.8†	3.1	8.4†	3.1
Became diabetic (vs never diabetic)	29.2†	7.8	31.0†	8.0	5.9†	2.7	5.3‡	2.8
Stayed diabetic (vs never diabetic)	14.0	9.6	12.8	10.5	2.6	5.1	4.4	5.4
LDL-C change (40 mg/dL)			3.8	3.3			0.8	1.1
HDL-C change (15 mg/dL)			-11.3†	3.8			1.2	1.3
Triglyceride change (70 mg/dL)			-14.8†	3.9			5.2†	1.1

$\hat{\beta}$ indicates regression coefficient (see text).

*Adjusted for baseline values of fibrinogen or factor VII_c.

† $P < 0.05$.

‡ $P < 0.10$.

except that the association for starting hormone replacement weakened by approximately one half. Fibrinogen increased more in those whose HDL cholesterol or triglycerides decreased.

With model 1 (Table 3), factor VII_c increased more in younger versus older participants, 11% more in women versus men, 8% per 5 kg/m² increase in BMI, 8% more in those who quit smoking, and 6% more in those who developed diabetes. In model 1, for women only (not shown in Table 3), starting hormonal therapy was associated with a 7%-greater increase in factor VII_c ($P=0.10$), continuation of hormonal therapy with a 9%-greater increase ($P=0.01$), and cessation of hormonal therapy with a 3%-greater increase ($P=0.68$) compared with women who were not treated with hormonal replacement. Addition of lipid variables (model 2) attenuated the relation between factor VII_c change and BMI change (and hormonal therapy initiation) by $\approx 40\%$. Increases in triglyceride concentrations appeared to increase factor VII_c.

The relation of fibrinogen to smoking or quitting is shown further in the Figure. Compared with nonsmokers at both visits, those who started smoking or recently quit had the most dramatic rises in fibrinogen concentration. Yet the continued smokers and longer-term quitters still had slightly greater rises in fibrinogen than the never-smokers. However, owing to limited sample sizes, none of these apparent differences were statistically significant.

Discussion

Over the last decade, researchers have discovered that virtually every cardiovascular risk factor is correlated cross-sectionally with plasma fibrinogen concentrations,⁹ and several are correlated with factor VII_c.⁸ Clearly, not all of these

correlations reflect causal relations. Two types of studies that can help to clarify the true determinants of fibrinogen and factor VII_c include controlled clinical trials and population studies of changes in hemostatic factors. Clinical trials (which should be randomized and controlled because of potential bias, laboratory drift, and regression to the mean) generally focus on short-term changes. Epidemiological studies, such as ours, can examine long-term changes in representative population samples, but without randomization, such studies may exhibit selection bias. For example, people who chose to quit smoking may have uncontrollable differences from other subjects that affect physiological changes.

Over 6 years, we found an overall increase in mean fibrinogen of 26 mg/dL and a decrease in mean factor VII_c of 12%. These changes undoubtedly are partly due to aging and true secular changes. It is nevertheless virtually impossible to rule out some laboratory drift, although blood collection, laboratory methods, and assay control materials were identical for the 1987 through 1989 and 1993 through 1995 periods. As a result, we were uncertain of the absolute level of fibrinogen and factor VII_c change for each individual, but no reason exists to suspect that laboratory drift would have been differential with respect to the correlates we studied. Thus, our measure of net change should have properly ranked individuals and permitted us to assess whether changes in (rank of) fibrinogen and factor VII_c were related to changes in other risk factors.

Our main finding for fibrinogen was that a greater 6-year increase occurred for participants who developed diabetes. Previous studies have established a strong cross-sectional association between diabetes and fibrinogen,⁹ but no study has explored whether change in fibrinogen level over time also differs according to diabetes status. Diabetes is a pro-

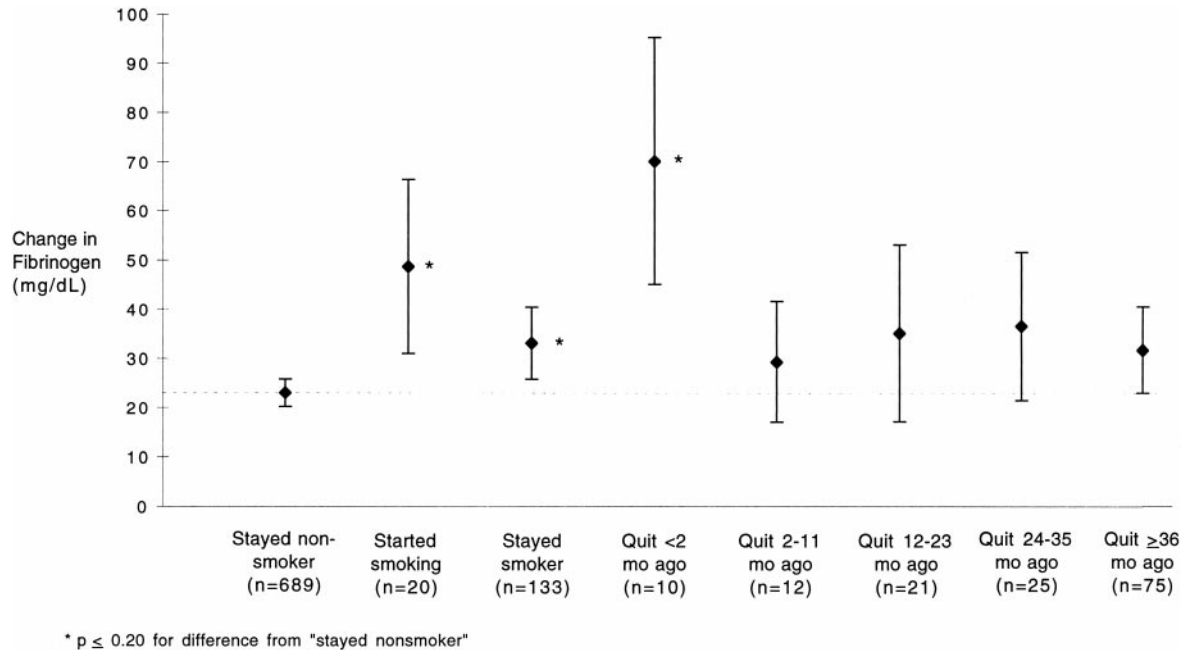


Figure 1. Age-, race-, sex-, and baseline fibrinogen—adjusted mean \pm SE change in fibrinogen over 6 years related to changes in smoking in the ARIC study.

thrombotic condition, and elevated fibrinogen appears to contribute to increased risk of cardiovascular disease in diabetics.²³ Fibrinogen appears to be elevated particularly in diabetics with poor metabolic control.²⁴

Fibrinogen increased more in those who reported starting, continuing, or recently quitting smoking than in consistent nonsmokers, but these findings were statistically nonsignificant due, in part, to the small sample sizes. Other than chance occurrence, we are unclear as to why quitting smoking did not reduce fibrinogen in the present study as it did in short-term clinical trials of smoking cessation^{9,25} and the longitudinal study by Meade et al.¹⁰ Lifestyle factors not related to fibrinogen change were alcohol change, BMI change, and sports score change. These findings are consistent with those of most clinical trials⁹; however, Meade et al found longitudinal changes in fibrinogen negatively associated with changes in alcohol consumption.¹⁰

We also found that participants who had larger increases in HDL cholesterol and triglycerides seemed to have a greater decline in fibrinogen concentrations. Cross-sectional data also have consistently found HDL cholesterol inversely associated with fibrinogen.⁹ In the ARIC study, positive cross-sectional univariate association existed between triglycerides and fibrinogen that reversed to a negative association with adjustment for multiple covariates.⁸ This suggests that no real association may exist between triglycerides and fibrinogen, and that our finding of one may be an artifact of statistical overadjustment for triglyceride correlates such as race, obesity, diabetes, and HDL cholesterol.

Factor VII_c decreased overall, but net increases (or smaller decreases) were apparent in several groups. In particular, factor VII_c increased more in participants with greater weight and triglyceride increases; in those who became diabetic; and in women, particularly those who were treated with hormonal replacement therapy. Clinical trials and longitudinal studies

support weight and triglyceride associations with factor VII_c.^{9,10} Cross-sectional studies support higher factor VII_c levels in women and diabetics,⁹ but we believe that no previous study has documented greater longitudinal factor VII_c increase in people who develop diabetes or in women. A high proportion of ARIC women were perimenopausal; thus, endogenous hormonal changes could be important. On the other hand, hormonal replacement therapy increases triglyceride concentrations, which probably explains why hormonal replacement also raises factor VII_c.

We observed no change in factor VII_c with changes in alcohol intake or physical activity, consistent with most clinical trials and longitudinal studies,⁹ and we observed no factor VII_c change with changes in HDL or LDL cholesterol levels. People who started smoking had a net decrease in factor VII_c, and those who quit had an increase. Factor VII_c change has not consistently been associated with smoking changes previously,¹⁰ although we have reported an inverse cross-sectional association in men.⁸ It nevertheless seems paradoxical that smoking, a prothrombotic stimulant, would be associated with lower factor VII_c than is nonsmoking. Because smoking affects body weight and triglyceride levels, our smoking findings may reflect residual effects of these determinants on factor VII_c.

The public health importance of elevated fibrinogen and factor VII_c remains uncertain. Fibrinogen is clearly a marker of increased risk for CHD.¹⁻⁷ Factor VII_c is a less-consistent CHD risk marker.^{2,5,6} Whether lowering fibrinogen or factor VII_c could reduce CHD risk is uncertain, but it nevertheless seems prudent to avoid high levels of these clotting factors. Our finding that smoking, obesity, diabetes, and hypertriglyceridemia may affect these hemostatic factors suggests that unhealthy lifestyles may increase CHD risk, in part, by thrombotic mechanisms. Our findings also provide additional support for control of lifestyle risk factors for cardiovascular health.

Acknowledgments

The ARIC study was funded by contracts N01-HC-55015, N01-HC-55016, N01-HC-55018, N01-HC-55019, N01-HC-55020, N01-HC-55021, N01-HC-55022 from the US National Heart, Lung, and Blood Institute. The authors thank Mark Triputti for programming assistance; Laura Kemmis for manuscript preparation; and the following ARIC staff members for their contributions: Phyllis Johnson, Catherine Paton, James Pankow, and Sharon Pope from the University of North Carolina, Chapel Hill; Melinda Cochran, Shirley Cothorn, Amy Haire, Delilah Posey, and Carol Smith from the University of North Carolina, Forsyth County; Bobbie Alliston, Agnes Hayes, Penny Lowery, Stephanie Parker, and Betty Warren from the University of Mississippi Medical Center, Jackson; Collette Cosgriff, Maxine Dammen, Caryl DeYoung, and Jaci Dion from the University of Minnesota, Minneapolis; Patricia Crowley, Tammy Crunkleton, Lily Downs, and Chris Fornwalt from the Johns Hopkins University, Baltimore, Md; Chul Ahn, Ashley Ewing, Harinder Juneja, and Susan Mitterling from the University of Texas Medical School, Houston; Wanda Alexander, Christine Ballantyne, Charles Rhodes, and Andre Surguchov from the Methodist Hospital, Atherosclerosis Clinical Laboratory, Houston, Tex; Carolyn Bell, Delilah Cook, Bob Ellison, and Kathy Joyce from the Bowman-Gray School of Medicine, Ultrasound Reading Center, Winston-Salem, NC; and Margaret Misch, Eunsik Park, Debbie Rubin-Williams, and June Stevens from the ARIC Coordinating Center, University of North Carolina, Chapel Hill.

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