

CLINICAL STUDIES

Coronary Atherosclerosis

Anemia as a Risk Factor for Cardiovascular Disease in the Atherosclerosis Risk in Communities (ARIC) Study

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OBJECTIVES	We investigated whether the presence of anemia is a risk factor for cardiovascular disease (CVD) outcomes in the general population.
BACKGROUND	Chronic anemia is a risk factor for CVD outcomes in patients with kidney disease and in patients with heart failure, but has not been evaluated as a risk factor in the general population.
METHODS	The Atherosclerosis Risk in Communities (ARIC) study was used to evaluate the relationship of anemia, defined by hemoglobin <13 g/dl in men and <12 g/dl in women, to CVD. Cox proportional hazards regression was used to adjust the relationship between anemia and CVD outcomes for other covariates in the entire study cohort, as well as in subgroups of men, women, African Americans and whites.
RESULTS	A total of 14,410 subjects (6,267 men and 8,143 women) without CVD at baseline had hemoglobin levels measured. Three hundred men (4.8%) and 1,058 women (13.0%) were anemic. During an average follow-up of 6.1 years there was a total of 549 (3.8%) CVD events. The presence of anemia was independently associated with an increased risk of CVD (hazard ratio [95% confidence interval] of 1.41 [1.01, 1.95]) in the entire study cohort. In subgroup analyses the hazard ratios were in the same direction, although not statistically significant in all cases.
CONCLUSIONS	Anemia is an independent risk factor for CVD outcomes in the ARIC cohort, a community cohort of subjects between the ages of 45 and 64 years. (J Am Coll Cardiol 2002;40:27-33) © 2002 by the American College of Cardiology Foundation

Anemia has been shown to be a risk factor for left ventricular hypertrophy (LVH) as well as de novo and recurrent congestive heart failure in patients with end-stage renal disease (1). A lower hematocrit is also a risk factor for all-cause mortality in patients with left ventricular dysfunction (2). Anemia has not, however, been evaluated as a risk factor for cardiovascular disease (CVD) in low-risk patients in the general population.

There are physiologic reasons, however, to suspect that the presence of chronic anemia may result in adverse long-term cardiovascular consequences. Chronic anemia may result in an increased cardiac output secondary to decreased afterload, increased preload and increased chronotropic and inotropic effects. Over time this may lead to ventricular dilation and LVH (3-5). The chronic increase in cardiac output may also lead to arterial remodeling of central elastic arteries such as the aorta or the carotids. This remodeling in turn results in arterial enlargement and compensatory arterial intima-media thickening, or arterio-

sclerosis (5,6). The presence of either LVH or arteriosclerosis may be more directly associated with future CVD risk.

The Atherosclerosis Risk in Communities (ARIC) study is a prospective cohort study in the general population designed to investigate the risk factors for atherosclerosis in subjects whose age was between 45 and 64 years at baseline (7). It is a suitable population to evaluate the hypothesis that the presence of anemia is a risk factor for CVD outcomes in a low-risk population who are not preselected for having CVD.

METHODS

The ARIC study is a prospective cohort study of atherosclerosis and its risk factors in four U.S. communities (7): Forsyth County, North Carolina; Jackson, Mississippi; the northwest suburbs of Minneapolis, Minnesota; and Washington County, Maryland. A total of 15,792 subjects age 45 to 64 years at recruitment were enrolled from 1986 to 1989. The data for our analyses were obtained from the public use database. The public use database includes extensive data on baseline demographics, CVD risk factors and subsequent CVD outcomes. To ensure confidentiality of the subjects in the public use databases, center location was not made available.

The current study is an analysis of the relationship of the presence of anemia, as well as its interaction with traditional coronary disease risk factors on CVD outcomes. We fo-

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Abbreviations and Acronyms

ARIC	= Atherosclerosis Risk in Communities study
CHD	= coronary heart disease
CI	= confidence interval
CVD	= cardiovascular disease
HR	= hazard ratio
LVH	= left ventricular hypertrophy
MI	= myocardial infarction

cused our analysis on subjects without CVD at baseline. Therefore, we excluded 1,382 subjects (8.8%) who had either prevalent coronary heart disease (CHD) (defined by history of physician-diagnosed myocardial infarction (MI), prior MI by electrocardiogram, prior coronary artery bypass surgery or coronary angioplasty) ($n = 765$), missing data on prevalent CHD ($n = 403$) or missing hemoglobin levels at baseline ($n = 307$). This left 14,410 subjects in the study cohort.

Anemia was defined by the World Health Organization criteria; that is, hemoglobin <12 g/dl in women and <13 g/dl in men (8). We chose this criterion because it is a well-accepted definition, which has been used in multiple studies including international comparisons (9-11). Therefore, it is generalizable. We acknowledge, however, that different cutoff levels to define anemia have been described (12,13).

The measured baseline characteristics included patient demographics (age, ethnicity, gender, education level [less than high school, high school, above high school]), past medical history (diabetes, hypertension, history of cerebrovascular disease, current smoking, current alcohol consumption), other traditional coronary risk factors as defined in the Framingham population (systolic blood pressure, diastolic blood pressure, total cholesterol, low density lipoprotein and high density lipoprotein cholesterol, body mass index, waist-hip ratio, LVH defined by voltage in electrocardiogram lead AVL being >11 mm), nontraditional CVD risk factors (sports activity index [defined on a continuous scale from 1 to 5]), albumin level, fibrinogen level, white blood cell count, uric acid, factor VIII activity, von Willebrand factor, predicted glomerular filtration rate using a recently validated formula from the Modification of Diet in Renal Disease Study and a calibration factor adjusting for differences in serum creatinine measurements between the Modification of Diet in Renal Disease and the National Health and Nutrition Examination Survey laboratories (14,15) and medication use (aspirin, diuretics, vasodilator agents, cardiac agents).

Hemoglobin was determined in hospital-based independent laboratories within 24 h after venipuncture, after storage at 4°C , using automated particle counters (Coulter Diagnostics, Hialeah, Florida): in Jackson, Coulter S+IV, calibration S-Cal; in Washington County, at two laboratories, both using Coulter S+IV, calibration S-Cal; in Minneapolis, at one laboratory using two different counters, Coulter S+III and Coulter S+IV, calibration S-Cal; in

Forsyth County, Technicon H-6000 (Technicon Corporation, Tarrytown, New York), calibration Fisher ("Compu-trol") (16). Blood tests for lipids, chemistries and hemostatic factors were measured in the ARIC central laboratories as previously described (7,17). Serum iron, transferrin saturation, ferritin, folate, B12 and measures of hemolysis were not measured in the full cohort.

The primary outcome was CVD defined by definite or probable MI, coronary angioplasty, coronary artery bypass surgery or definite CHD death. We also report the adjusted hazard ratios (HRs) for all-cause mortality, primarily to evaluate whether the results are consistent with the CVD data. We do not, however, focus on mortality and do not present the detailed partially and fully adjusted regression models. An ARIC Morbidity and Mortality Classification Committee used published criteria to adjudicate all potential clinical events (18).

Statistical analysis. Means, standard deviations and percentages were used to describe the baseline characteristics. Data were stratified by gender and the presence or absence of anemia. Chi-square tests for categorical variables and the Student *t* test for continuous variables were used to compare baseline data for each of these groupings.

Kaplan-Meier survival analyses for CVD outcomes stratified by the presence of versus the absence of anemia were performed separately in men and women. Log-rank statistics were used to test survival time differences between those with and without anemia.

Cox proportional-hazards regression was used to adjust the relationship between anemia and CVD for other covariates. All baseline characteristics were evaluated as risk factors for CVD in univariate analysis. Those variables significant in univariate analysis ($p < 0.05$) were then evaluated in a stepwise multivariable model in the entire study sample. The same variables significant ($p < 0.05$) in multivariable analysis in the entire sample were then adjusted for in subgroups of men, women, African Americans and whites.

We present the data initially after partial adjustment for age and race in subgroups of men and women, and age and gender in subgroups of African Americans and whites. We then present fully adjusted models in all subgroups. We chose to partially adjust for age, gender and race (19,20) in all models, because of their well-recognized effects on the prevalence of anemia. In women we performed one model using all women and a separate model using only postmenopausal women. We did not perform a separate model on premenopausal women because $<25\%$ of women for whom the variable "menopausal status" was ascertained were considered premenopausal (21). We did, however, adjust for menopausal status in all women. Models were formally tested for assumptions of proportional hazards by using a time-varying coefficient model and evaluating the *p* values for global and individual covariates.

We repeated the above analyses excluding coronary procedures in our composite CVD outcome. We also repeated

Table 1. Baseline Characteristics of the Study Population Stratified by Gender and Presence or Absence of Anemia

	Men					Women			
	All (n = 14,410)	All (n = 6,267)	Anemic (n = 300)	Nonanemic (n = 5,697)	p Values*	All (n = 8,143)	Anemic (n = 1,058)	Nonanemic (n = 7,085)	p Values†
Demographics									
Age (yrs)	54.0	54.4	55.5	54.3	<0.001	53.8	52.8	53.9	<0.001
African American (%)	26.6	23.2	63.7	21.2	<0.001	29.1	60.3	24.5	<0.001
Education (% less than high school)	55.5	49.7	64.3	49.0	<0.001	59.9	61.4	59.7	0.310
Past medical history									
Current smoker (%)	26.0	27.5	25.7	27.6	0.454	24.8	14.0	26.4	<0.001
Current consumer of alcohol (%)	56.4	65.5	53.7	66.1	<0.001	49.5	35.0	51.6	<0.001
Diabetes (%)	11.1	10.9	15	10.7	0.021	11.2	12.9	11.2	0.067
Cerebrovascular disease (%)	4.5	3.4	4.0	3.3	0.513	5.3	6.4	5.3	0.105
Hypertension (%)	33.8	32.9	46.0	32.9	<0.001	34.4	37.3	34.0	0.037
Pre menopausal (%)						22	33.8	20.2	<0.001
LVH (%)‡	4.8	5.3	8.7	5.1	0.008	4.4	7.6	3.9	<0.001
% Sports activity index above level III	20	25.7	19.1	26	0.007	15.6	12.6	16.0	0.005
Physical exam									
Mean SBP (mm Hg)	121.1	122.4	129.7	122.1	<0.001	120.2	122.6	119.8	<0.001
Mean DBP (mm Hg)	73.7	75.7	77.4	75.6	0.009	72.2	72.7	72.1	0.138
Mean body mass index (kg/m ²)	27.6	27.4	26.5	27.5	<0.001	27.8	28.4	27.7	<0.001
Laboratory values									
Mean hemoglobin (g/dl)	13.9	14.8	12.1	15	<0.001	13.1	11.2	13.4	<0.001
Mean hematocrit (%)	41.6	44.3	37.3	44.7	<0.001	39.5	34.5	40.2	<0.001
Mean albumin (g/dl)	3.9	3.9	3.8	3.9	<0.001	3.8	3.7	3.8	<0.001
Mean GFR (ml/min/1.73 m ²)	93.2	92.2	96	92	0.001	93.9	97.2	93.4	<0.001
Mean LDL cholesterol (mg/dl)	137.1	138.7	132.8	139	0.004	135.9	128.2	137.1	<0.001
Mean HDL cholesterol (mg/dl)	52.1	44.9	49.2	44.6	<0.001	57.7	59.5	57.4	<0.001
Mean fibrinogen (mg/dl)	302.5	296.1	310.8	295.3	<0.001	307.5	315.1	306.3	<0.001
Mean white blood count (1,000/ μ l)	6.1	6.2	5.6	6.2	<0.001	6.0	5.5	6.1	<0.001
Mean Von Willebrand Factor (%)	117.7	116.9	131	116.2	<0.001	118.2	127.8	116.8	<0.001
Mean Factor VIII (%)	131.1	126.9	146.4	126	<0.001	134.3	148.3	132.2	<0.001
Medications used									
Aspirin (%)	39.7	35.7	34	35.8	0.522	42.7	41.4	42.9	0.359
Vasodilators (%)	1.7	1.8	4	1.7	0.003	1.7	1.5	1.7	0.622
Diuretics (%)	16.8	11.8	16.3	11.6	0.012	20.7	19.5	20.8	0.302
Cardiac agents (%)§	10.2	10.4	11.7	10.3	0.463	10.1	10.1	10.1	0.983

*p value for difference between anemic and nonanemic men. †p value for difference between anemic and nonanemic women. ‡LVH defined by voltage in electrocardiogram lead AVL > 11 mm. §Cardiac agents not including vasodilator agents, diuretics or aspirin.

DBP = diastolic blood pressure; GFR = glomerular filtration rate; HDL = high density lipoprotein; LDL = low density lipoprotein; LVH = left ventricular hypertrophy; SBP = systolic blood pressure.

the above analyses including patients with prevalent CVD at baseline. We performed the latter two analyses primarily to evaluate the consistency of our results.

Interactions between anemia status and both gender and race, as well as between anemia and other traditional coronary risk factors (as defined in the Framingham population) were tested by including a cross-product factor in the multivariable model and retaining it when significant ($p < 0.05$).

Data were analyzed using the Statistical Analysis System Version 8.1 (SAS Institute, Cary, North Carolina). Microsoft Excel 97 and S-Plus (MathSoft, Seattle, Washington) were used for graphs and tables. Testing was two-sided and p values < 0.05 were considered significant.

RESULTS

Baseline characteristics. The mean age of the cohort was 54 years; 26.6% of subjects were African Americans and 56.5% were women (Table 1). Among participants, 4.5%,

11.1% and 33.8% had a history of cerebrovascular disease, diabetes and hypertension, respectively. Mean hemoglobin was 14.8, 13.1, 14.1 and 13.2 g/dl in men, women, whites and African Americans, respectively. Anemia was present among 4.8%, 13.0%, 21.6% and 5% of men, women, African Americans and whites, respectively. Mean hemoglobin was 12.1 g/dl in anemic men and 11.2 g/dl in anemic women (Table 1).

Several differences were noted when one compared baseline characteristics between anemic and nonanemic participants stratified by gender (Table 1). For example, anemic men tended to be slightly older, less educated, exercised less, were more likely African American and had a higher percentage of history of diabetes, LVH or hypertension as well as an increased use of cardiac medications. Anemic women tended to be slightly younger, exercised less, were more likely to be premenopausal, were more likely to be African American, were less likely to be smokers and had a

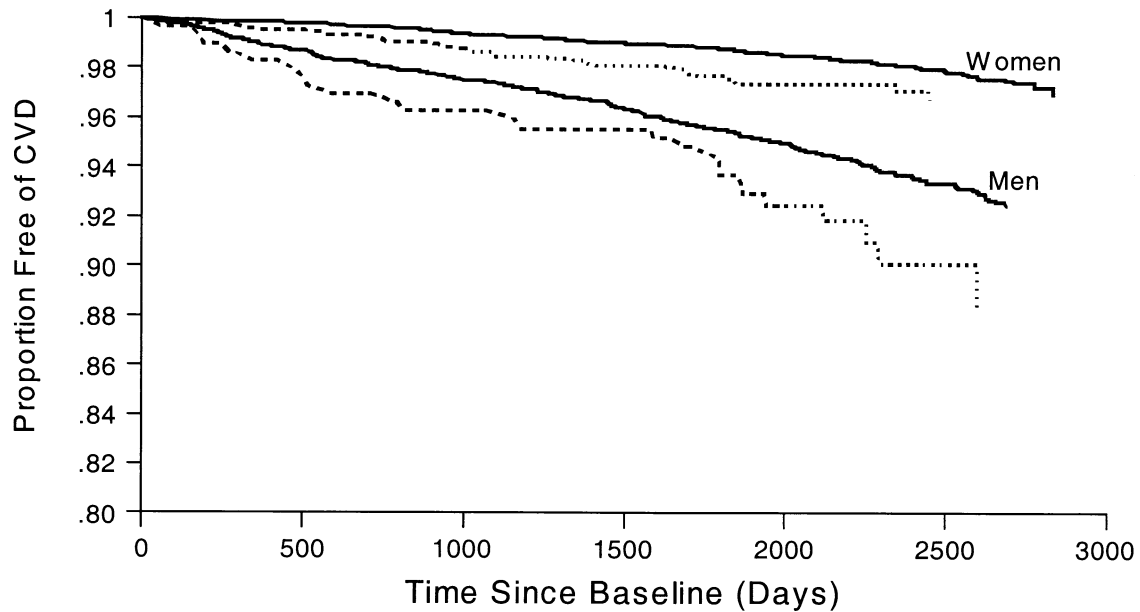


Figure 1. Kaplan-Meier survival analysis for cardiovascular disease (CVD) in men and women stratified by presence versus absence of anemia. Log-rank statistics were significant ($p = 0.03$ for men and $p = 0.04$ for women) for differences between anemic and nonanemic subjects. **Dotted line** = anemia; **solid line** = nonanemia.

higher percentage of LVH or hypertension. Of note, the higher prevalence of anemia in African American men and women is consistent with the prior literature (19,20).

Outcomes. Mean and median follow-up times were 2,243 and 2,266 days, respectively. There were 549 (3.8%) CVD events with 385 (6.1%) occurring in men, 164 (2.0%) in women, 129 (3.4%) in African Americans and 420 (4%) in whites. There were 640 (4.4%) deaths with 357 (5.7%) occurring in men, 283 (3.5%) in women, 262 (6.8%) in African Americans and 378 (3.6%) in whites.

Relationship between presence of anemia and outcomes. Kaplan-Meier survival analysis (Fig. 1) demonstrates that the presence of anemia is a risk factor for CVD survival in both men and women (log-rank $p = 0.03$ for men and $p = 0.04$ for women).

The presence of anemia is associated with an adjusted HR (95% confidence interval [CI]) of 1.41 (1.01, 1.95) for CVD in the entire cohort (Table 2). In subgroup analysis, the presence of anemia is also a risk factor for CVD outcomes in women (HR 1.71 [95% CI 1.01, 2.89]) and

Table 2. The Effect of the Presence Versus Absence of Anemia on De Novo Cardiovascular Disease

	N	Events (%)	Partially Adjusted*			N	Events (%)	Fully Adjusted†		
			HR	CI	p Value			HR	CI	p Value
Total										
Anemia	1,358	54 (4.0)	1.57	1.17, 2.11	0.003	1,313	51 (3.9)	1.41	1.01, 1.95	0.040
Nonanemia	13,052	495 (3.8)	1.00			12,570	464 (3.7)	1.00		
Men										
Anemia	300	25 (8.3)	1.57	1.03, 2.39	0.035	294	24 (8.2)	1.33	0.85, 2.08	0.212
Nonanemia	5,967	360 (6.0)	1.00			5,707	338 (5.9)	1.00		
Women										
Anemia	1,058	29 (2.7)	1.56	1.03, 2.39	0.038	891	24 (2.7)	1.71	1.01, 2.89	0.045
Nonanemia	7,085	135 (1.9)	1.00			6,008	110 (1.8)	1.00		
African American										
Anemia	829	33 (4.0)	1.53	1.03, 2.29	0.037	797	31 (3.9)	1.18	0.74, 1.88	0.494
Nonanemia	3,000	96 (3.2)	1.00			2,830	90 (3.2)	1.00		
White										
Anemia	529	21 (4.0)	1.52	0.98, 2.36	0.064	516	20 (3.9)	1.63	1.03, 2.59	0.037
Nonanemia	10,052	399 (4.0)	1.00			9,740	374 (3.8)	1.00		

*Adjusting for age, and either gender (for African Americans and whites) or race (for subgroups of men and women). †All of the following models adjust for age, gender, race, left ventricular hypertrophy, diabetes, smoking status, current consumption of alcohol, systolic blood pressure, hypertension, low density lipoprotein cholesterol, high density lipoprotein cholesterol, body mass index, waist hip ratio, vasodilator use, fibrinogen, predicted glomerular filtration rate, albumin, sport activity index and menopausal status for women only.

HR = hazard ratio; CI = 95% confidence interval.

whites (HR 1.63 [1.03, 2.59]). In exclusively postmenopausal women the HR is 1.65 (95% CI 0.94, 2.89).

The presence of anemia is associated with an adjusted HR (95% CI) of 1.65 (1.30, 2.10) for all-cause mortality in the entire cohort. In subgroup analysis, the presence of anemia is also an independent risk factor for death in men (HR 2.01 [95% CI 1.44, 2.82]), African Americans (HR 1.43 [95% CI 1.06, 1.94]) and whites (HR 2.01 [95% CI 1.35, 2.99]), and the HR is in the same direction in all women (HR 1.38 [95% CI 0.98, 1.93]). In exclusively postmenopausal women the adjusted HR is 1.50 (95% CI 1.03, 2.19).

Results were not substantially different if the primary outcome excluded coronary procedures or if subjects with prevalent CVD were included in the analyses (data not shown).

Interactions. There were no significant interactions between gender and race, or other traditional coronary risk factors as defined in the Framingham population, with the presence/absence of anemia on CVD outcomes.

DISCUSSION

Prior studies have suggested that a lower hematocrit or hemoglobin may be a risk factor for CVD outcomes in high-risk patients who already have CVD or have many risk factors for CVD. For example, in end-stage renal disease patients each 1 g/dl decrease in hemoglobin is associated with a 14% increased risk of death and a 28% increased risk for de novo heart failure (1). Similarly, in patients with a decreased ejection fraction a lower hematocrit is associated with an increased risk for death, which is primarily due to CVD (2).

Prior studies have also suggested that the relationship between level of hematocrit (hemoglobin) and CVD in the general population is not linear (22,23) and may better be described as a U-shaped relationship (24). That is, patients with both low and high hematocrit have an increased risk of developing CVD. In the current analysis we evaluate whether subjects in the general population with low hemoglobin, that is, patients who meet the definition of having anemia, are at increased risk for developing CVD.

We chose a well-accepted cut-point for definition of anemia for our analyses (8), namely a hemoglobin <13 g/dl in men and <12 g/dl in women. Our results demonstrated that the presence of anemia is an independent risk factor for CVD outcomes in the full cohort. Subgroup analysis suggested that the HR for CVD is similar in men, women, African Americans and whites, although the results are not statistically significant in all subgroups. Our retrospective analysis is unable to evaluate whether there are true differences in subgroups versus inadequate power to detect significant relationships in some of the subgroups; the similarity between the HRs in subgroups would tend to support the latter.

Our study is the first we know of that demonstrates that

anemia is an independent risk factor for CVD outcomes in the general population. The mean hemoglobin levels in the anemic group were 12.1 g/dl and 11.2 g/dl in men and women, respectively. These values of hemoglobin are significantly higher than the traditional, but not rigorously proven, transfusion threshold of 10 g/dl in patients with pre-existing symptomatic CVD (25). Levels of hematocrit above 10 g/dl have not previously been considered to be risk factors for CVD outcomes, even in patients with preexisting CVD.

There are several potential reasons anemia may be a risk factor for CVD outcomes. First, the presence of anemia, if extended for a long period, may result in ventricular remodeling and cardiac dysfunction. Chronic anemia with hemoglobin <10 g/dl is known to result in increased cardiac output that may lead to LVH (3,4). The latter is well appreciated in patients who are anemic secondary to their kidney disease (26-28), as well as in patients with sickle cell disease (29). It remains unknown, however, whether chronic anemia in the range of anemic patients in the ARIC cohort could result in similar cardiovascular abnormalities. Second, the presence of anemia may in theory be a risk factor for myocardial ischemia. Although it is generally believed that lower levels of hemoglobin, compared with the mean level in anemic subjects in the ARIC cohort, are required to induce myocardial ischemia, this has not been rigorously studied. Third, reduced hemoglobin may be associated with other risk factors for CVD that were not ascertained in this study, such as decreased nutritional status, additional measures of lower socioeconomic status, or increased inflammatory status. (The observational nature of ARIC does not allow us to account for these factors.) For example, an increased inflammatory status may indeed be the causal risk factor associated with CVD outcomes, with the presence of anemia simply being a marker of an underlying inflammatory process. Against the latter hypothesis is the fact that other putative markers of inflammation, such as fibrinogen, white blood cell count, factor VIII and von Willebrand factor, do not change the strength of the association between anemia and CVD outcomes (data not shown).

Study limitations. There are a few potential limitations of our analyses. We have alluded to the fact that because of the observational nature of our study we are unable to adjust for potential unmeasured confounding factors. In addition, it is theoretically possible that subclinical CVD may have caused anemia, rather than anemia having predisposed to CVD.

There are, however, two more specific limitations. The first is that we were unable to control for center effect. The public use database does not provide center information because of concern for confidentiality. We are unable to completely overcome this limitation, but have endeavored to control for all variables that may track with center location, such as education level, ethnicity and numerous comorbid conditions. Because we are unable to control for center effect, we also are unable to control for any differences in hemoglobin measurement among the four centers. Mea-

surement of hemoglobin has been standardized for many years in the U.S., and all labs involved in ARIC measured hemoglobin using the cyanmethemoglobin method, the procedure recommended by the International Congress of Hematology (30). Therefore, we believe it is unlikely that there would be a significant variation in hemoglobin measurements among centers.

The second limitation relates to the fact that our analysis only takes into account measurement of hemoglobin at one point in time. This results in two potential concerns. First, there may be misclassification of anemic subjects because of laboratory error, and second, duration of anemia is unknown. With regard to the latter, some subjects, particularly those with iron deficiency anemia who are treated with iron, may have a shorter duration of anemia than other subjects. We believe this potential bias would tend to weaken the association between anemia and CVD; therefore, our results showing an association between anemia and CVD appear robust.

Unanswered questions. There are also two unanswered questions that should be investigated in future studies. First, the ARIC study did not assess laboratory factors or conditions that would help us ascertain the cause of the anemia, for example, subclinical liver disease or hemoglobinopathy, and indices of iron, folate or B12 deficiency. In theory, knowledge of these data may be instructive in suggesting potential mechanisms relating anemia to CVD. Second, we do not have sufficient statistical power to assess the relationship between anemia and CVD in exclusively premenopausal women because only 21% of women with sufficient data on menopausal status were premenopausal. Investigation of an exclusively premenopausal group would be important, because this subgroup in particular has a higher prevalence of iron deficiency anemia, which has traditionally been thought to be a benign condition. In fact, demonstration that iron deficiency anemia is a risk for CVD events would be counter to current thinking that suggests higher levels of iron may actually be a risk factor for atherosclerosis (31,32).

Conclusions. The presence of anemia appears to be an independent risk factor for CVD outcomes in the ARIC population, a community cohort of patients between the ages of 45 and 64 years. Further studies are required to determine whether this is indeed a cause-and-effect relationship.

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