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Hemoglobin Decline, Function and Mortality in the Elderly: The Cardiovascular Health Study

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Abstract

Background—While anemia is associated with poor functional and mortality outcomes in the elderly, the impact of hemoglobin decline is less studied.

Methods—We evaluated the determinants and consequences of hemoglobin decline in 3.758 non-anemic participants from the Cardiovascular Health Study, a prospective cohort of community-dwelling elderly ≥65 years old at baseline and followed for up to 16 years. Hemoglobin was measured at baseline and 3 years later and anemia defined by World Health Organization (WHO) criteria. We modeled hemoglobin decline in two ways: 1) per each 1g/dL decrease in hemoglobin and 2) development of anemia by the WHO criteria.

Results—Among participants without baseline anemia, hemoglobin decreased by 0.4g/dL and 9% developed anemia over 3 years. Baseline increasing age, female sex, diabetes, and kidney disease predicted hemoglobin decline over 3 years. Baseline increasing age, being African-American, and kidney disease predicted anemia development over 3 years. Hemoglobin decline was associated with subsequent worse cognitive function in men and anemia development with subsequent worse cognitive function in women. Both anemia development (HR 1.39, 95% CI 1.15, 1.69) and hemoglobin decline (HR 1.11, 95% CI 1.04, 1.18 per 1g/dL decrease) predicted subsequent mortality in men and women.

Conclusions—Hemoglobin decreases identified a large group of elderly individuals at risk for subsequent adverse outcomes who would not be identified using the WHO anemia criteria. These data may allow clinicians to identify at-risk elderly individuals for early intervention to improve the quality and quantity of life.

Keywords

Anemia; Hemoglobin; Elderly; Mortality; Function; Epidemiology

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Introduction

Anemia is associated with increased morbidity and mortality in the elderly, though what constitutes a normal hemoglobin level is less clear[1-5]. Increasing evidence suggests that the World Health Organization (WHO) anemia criteria are insensitive to important clinical endpoints such as functional decline, cognitive impairment, and mortality especially in the elderly[1, 6]. Although hemoglobin levels decrease with age[6], there is little information on the association this decline with development of medical conditions, cognitive or physical impairment, and mortality[1, 7-9].

An individual's hemoglobin concentration is determined by a complex interplay of environmental and genetic factors[10-12]. Falling hemoglobin levels may serve as a surrogate marker of declining health or could be a cause of adverse outcomes[13]. While baseline hemoglobin levels are associated with functional, cognitive, and mortality endpoints in population studies, these data fail to account for the individual variation of hemoglobin concentrations[1, 5, 14, 15]. Further, the data for hemoglobin decline on similar outcomes is sparse. Hemoglobin decline over time may identify a group of elderly at risk for poor survival and accelerated functional decline, allowing timely interventions to improve both quantity and quality of life.

The Cardiovascular Health Study (CHS) offers a unique opportunity to study the correlates and consequences of hemoglobin decline in the elderly given the repeated hemoglobin measures in the cohort, the careful and repeated longitudinal ascertainment of many health outcomes (including mortality and measures of functional and cognitive decline), and the long follow-up. We hypothesized that changes in hemoglobin levels, to which conventional anemia criteria are insensitive, would identify a group of elderly at risk for subsequent physical and cognitive decline and increased mortality independent of absolute hemoglobin concentration.

Methods

Cohort

The CHS is a prospective, observational cohort study conducted in four US communities of risk factors for and consequences of cardiovascular disease in adults ≥65 years-old[16]. Baseline exclusion criteria were being wheelchair-bound, receiving active treatment for cancer, being institutionalized, or participant inability/refusal to give informed consent. Among those approached 9.6% were ineligible and 57% participated[17]. The cohort enrolled 5201 men and women in 1989-90 with a supplemental minority cohort of 687 African-Americans enrolled in 1992-3. The supplemental minority cohort did not have a repeat hemoglobin determination and could not be included in this analysis.

Baseline and follow-up interviews and physical exams were conducted using standardized methods. Baseline cognitive function was measured using the Mini-Mental State Exam (MMSE), scored from 0 to 30 with a score less than 23 indicating cognitive impairment[17]. During follow-up, the Modified Mini-Mental State Exam (3MSE) was done annually and scored from 0 to 100 with lower scores indicating greater cognitive impairment. Grip strength was assessed annually by averaging three measures in each hand using a hand-held Jamar dynamometer (Asinow Engineering Co., Los Angeles, California). Gait speed was assessed annually by timing the participant walking 15 feet at their normal pace (measured in seconds). All participants gave written informed consent and institutional review boards approved the protocol at each study site.

Definitions

Anemia was defined by the World Health Organization (WHO) criteria as a hemoglobin concentration <13 g/dL in men and <12 g/dL in women[18]. Ethnicity was defined by participant self-report from the following list: White, Black, American Indian/Alaskan Native, Asian/Pacific Islander, or Other and was dichotomized as black versus other for analyses. Hypertension was defined as blood pressure >140/90 mmHg or use of antihypertensive medications with a physician's diagnosis of hypertension. Diabetes was defined as a fasting glucose level >126 mg/dL, a non-fasting glucose >200 mg/dL, a self-report of a physician diagnosis of diabetes, or current treatment for diabetes. Cardiovascular disease (CVD) was confirmed by medical record review and defined as myocardial infarction or coronary artery revascularization, stroke, or symptomatic peripheral arterial disease. Chronic kidney disease (CKD) was defined as estimated glomerular filtration rate (eGFR) less than 60ml/min/1.73m^2 defined by the 4-variable Modification of Diet in Renal Disease equation[19]. Body mass index (BMI) was calculated as weight in kilograms divided by the height in meters squared. Inflammation was defined as C-reactive protein (CRP) ≥10mg/L and/or white cell count (WBC) ≥15 × 10^9/L. Other cytopenia was defined as WBC <3.0 × 10^9/L and/or platelet count <150 × 10^9/L.

Laboratory Analyses

Phlebotomy was performed the morning of enrollment after an 8-12 hour fast[20, 21]. Repeat phlebotomy for creatinine, inflammatory markers, and complete blood counts were done three years after enrollment using identical methods.

Outcomes and Follow-up

Participants were contacted semiannually, alternating between telephone interviews and clinic examinations through 1999, with telephone interviews ongoing. Deaths were reported by next of kin or recorded through searches of the national death index[17, 22]. Incident CVD was obtained by medical record review, in-person examinations/lab data, telephone interviews (when in person exam not possible), reports from proxies of participants, and periodic searches of Medicare utilization files[16, 22]. Incident hypertension and diabetes were obtained during in-person examinations/lab data, telephone interviews, or reports from proxies of participants. Outcomes were complete through June 30, 2005 for this analysis.

Statistical Analyses

Hemoglobin change was modeled as 1) anemia development (WHO criteria) and 2) hemoglobin decline (follow-up minus baseline hemoglobin). Baseline characteristics were compared across groups using *t*-tests, χ^2 tests, or Wilcoxon rank-sum tests as appropriate. Covariates were chosen for multivariable models based on previous data from the CHS and the association of the covariates with measures of hemoglobin change[1]. Age-, sex-, race-, and baseline hemoglobin-adjusted linear or logistic regression models were used to evaluate the association of baseline CVD, hypertension, diabetes, CKD, inflammation, and other cytopenias and subsequent measures of hemoglobin decline. Age-, sex-, race-, and baseline hemoglobin-adjusted regression models were used to evaluate the association of measures of hemoglobin decline with concurrent development of CVD, hypertension, diabetes, CKD, inflammation, and other cytopenias over 3 years.

Generalized estimating equations with an exchangeable correlation structure were used to investigate the association between measures of hemoglobin change and longitudinal measures of cognitive and physical function[23, 24]. The outcomes assessed were 3MSE, gait speed, and grip strength. Missing data on grip strength or gait speed straddled by non-missing values were filled in with the mean of the two straddling values. Participants unable

to complete the timed walk were assigned a gait speed of 0.05 m/s, and participants unable to do grip strength were assigned a grip strength of 0. The Telephone Interview for Cognitive Status and the Informant Questionnaire on Cognitive Decline in the Elderly, were used when available to estimate missing 3MSE scores[25]. Analyses were stratified by gender after statistically significant interactions with gender were found.

We used age-, sex-, race-, hypertension-, CVD-, diabetes, CKD-, and baseline hemoglobin-adjusted Cox proportional hazard models to quantify the association between hemoglobin change and all-cause mortality. All analyses were completed using R (R Foundation for Statistical Computing, Vienna, Austria) or STATA version 10 (StataCorp, College Station, Texas, USA).

Results

Of 5,201 participants in the original cohort, 45 had a missing baseline hemoglobin, 353 died prior to having a repeat hemoglobin assessed and 797 were missing a hemoglobin measure at follow-up, and 248 were anemic at baseline leaving 3,758 participants for this analysis (Figure 1). Surviving participants without follow-up hemoglobin measures were older and more likely to have poorer health and worse functional status at baseline than participants who had both measures (data not shown). The mean age at baseline was 72.1 years, 42% were male and 4% black (Table I). The mean (standard deviation) baseline hemoglobin was 14.2 (1.2) g/dL; 15.0 (1.0) for men and 13.8 (0.9) for women (Table I). The median 3-year change (inter-quartile range) in hemoglobin was −0.4 (−0.9, 0.1) g/dL; −0.3 (−0.9, 0.2) g/dL for men and −0.5 (−1.1, 0.1) g/dL for women (Figure 2). Individuals with higher baseline hemoglobin tended to have a larger decrease in hemoglobin than those with lower baseline hemoglobin levels and 27% of individuals had a hemoglobin decrease of at least 1g/dL (Supplementary Figure 1). Anemia developed in 161 of 1,596 men (10.1%) and 180 of 2,162 women (8.3%) and 65% of individuals who developed anemia had a >1g/dL decline in hemoglobin, but only 27% of individuals with hemoglobin decline >1g/dL also developed anemia.

Increased age, black race, lower BMI, CKD, higher creatinine and lower hemoglobin were more common among those with incident anemia (Table I). In a multivariable linear regression models including age, gender, race, and baseline hemoglobin; increasing age, being male, higher baseline hemoglobin, baseline CVD, diabetes, and CKD were associated with a hemoglobin decline over 3 years (Table II). Older age, male sex, black race, lower baseline hemoglobin and CKD were associated with anemia development (Table II).

Supplementary Table I presents the age-, sex-, race-, and baseline hemoglobin-adjusted logistic regression models for the association of change in hemoglobin with the concurrent development of co-morbid conditions. For hemoglobin decline (≥ 1g/dL drop), there was an increased odds of concurrent development of CVD, hypertension, inflammation, and other cytopenias (Supplementary Table I). Anemia development was associated with concurrent development of CKD, inflammation, and other cytopenias (Supplementary Table I).

Supplementary Table II presents the association of hemoglobin measures with future gait speed, grip strength, and 3MSE. Lower baseline hemoglobin was associated with future lower gait speeds and 3MSE scores among women and lower grip strength in men and women. For instance, women who had incident anemia scored on average 1.63 (95% CI 0.36, 2.90) points lower on future 3MSE exams.

During 12 years of follow-up 2,263 of 3,758 (60%) participants died. After adjustment for baseline age, sex, race, hypertension, CVD, diabetes, CKD and follow-up hemoglobin, both incident anemia [HR: 1.39, 95% CI: (1.15, 1.69)] and hemoglobin decline ([HR: 1.11, 95%

CI: (1.04, 1.18)] were associated with increased mortality. Associations were similar in sensitivity analyses adjusting for baseline hemoglobin or not including baseline or follow-up hemoglobin. There was a significant interaction between hemoglobin change and follow-up hemoglobin, and subsequent mortality ($p = 0.03$). Supplementary Figure 2 graphically presents the interaction; hemoglobin decreases at lower baseline hemoglobin levels were associated with a greater risk of mortality than hemoglobin decreases at higher baseline hemoglobin levels. There was no interaction between anemia development, follow-up hemoglobin and subsequent mortality ($p = 0.26$).

Discussion

In this study of 3.758 elderly individuals, the median hemoglobin level declined 0.4mg/dL over 3 years and 9% of participants without anemia at baseline developed anemia. Increasing age, higher baseline hemoglobin, diabetes, CKD, and female sex were risk factors for subsequent hemoglobin decline. Age, being African-American, and CKD were associated with the development of anemia. Each 1g/dL decrease in hemoglobin was associated with an increased odds of concurrently developing CVD, hypertension, inflammation, and other cytopenias while the development of anemia was associated with an increased odds of concurrently developing CKD, inflammation, and other cytopenias. Lower hemoglobin levels were associated with future lower gait speed and 3MSE scores among women and grip strength among men and women, hemoglobin decline was associated with reduced 3MSE scores in men and anemia development with reduced 3MSE scores in women. Both hemoglobin decline and incident anemia were independent risk factors for mortality even after adjusting for hemoglobin levels. The impact of hemoglobin decrease on mortality was worse with a greater decrease and with lower baseline hemoglobin levels.

Anemia is common among the elderly[1], though the determinants and consequences of hemoglobin decline are not well studied. Anemia is associated with concurrent co-morbid conditions (such as diabetes, hypertension, CVD, kidney disease)[11], cognitive impairment[3, 5], and poor physical function[4, 5, 26]. Further, anemia is associated with all-cause mortality in a variety of populations[1, 2, 5]. Whether anemia is causal or is an “innocent bystander” is hotly debated, though increasing evidence suggests hemoglobin levels may play a role in health[13]. The adverse impact of hemoglobin decline over time is of particular concern in the elderly due to the known decline in hemoglobin associated with aging[6, 11, 27].

There are few data on risk factors for hemoglobin decline over time in the general elderly population. The different findings on risk factors for hemoglobin decline and anemia development are likely due to a threshold effect caused by defining a specific hemoglobin level as normal or abnormal. Our data linking hemoglobin decline with concurrent development of inflammation are consistent with the Valsartan Heart Failure Trial, where increases in hemoglobin over one year were associated with concurrent decreases in CRP[9].

In terms of the consequences of hemoglobin decline, our data are novel. Anemia measured at one timepoint is associated with future physical and cognitive decline in the elderly[4, 5, 26]. We originally hypothesized that hemoglobin decline would be associated with steeper functional declines, however apart from more rapid cognitive decline among women who developed anemia or hemoglobin, this was not confirmed by our data. While we were somewhat limited in numbers due to the need to stratify by sex, these data suggest either that the absolute hemoglobin concentration reflects future functional decline or that functional decline occurs in close temporal association with hemoglobin decline.

While a onetime determination of hemoglobin concentration is associated with mortality, we are not aware of other studies in a general elderly population reporting on the association of hemoglobin decline and mortality[1, 2, 5]. In heart failure patients, a 1.6 g/dL decrease in hemoglobin over 1 year was associated with a 1.6-fold increased mortality over subsequent follow-up[7]. While we demonstrated that the impact of hemoglobin decline on mortality was greatest at lower hemoglobin concentrations, hemoglobin decline did impact survival at higher hemoglobin concentrations as well. Thus, these data argue strongly that both the absolute level of hemoglobin and the change of hemoglobin over time are important when evaluating the association of hemoglobin concentrations with mortality. It is not clear whether active interventions to increase hemoglobin levels or stop hemoglobin decline are appropriate in the elderly to improve quality and quantity of life. While trials of erythropoiesis stimulating agents in CKD patients usually show improved quality of life, they often show increased incidence of vascular complications and even mortality[28-30]. Whether interventions to increase hemoglobin other than treating nutritional deficiencies, addressing blood loss, and managing chronic diseases have any role in ameliorating the adverse functional, cognitive, and mortality outcomes requires further study.

We are limited in that CHS is an observational cohort mostly of European-Americans and that not all eligible individuals agreed to participate. As anemia and hemoglobin decline are associated with poor outcomes, our results are likely biased towards the null (as these individuals may not have survived to the second hemoglobin determination)[1]. Differences between African-Americans and European-Americans are vitally important to evaluate in future studies given the large differences in hemoglobin distribution and conflicting outcomes data on anemia in African-Americans and European-Americans[1, 5, 11, 31, 32]. Given that African-Americans have lower baseline hemoglobin levels and the current study's finding that hemoglobin decline increases mortality more at lower hemoglobin levels, the increased mortality seen with hemoglobin decline could disproportionately affect African-Americans[11]. Another weakness is that the clinical impact of the observed functional changes on an individual is difficult to assess, however small changes in grip strength, gait speed, and cognition on a population level may be much more significant. Finally, we have hemoglobin levels at only 2 time points separated by 3 years, further study is needed on whether rate of hemoglobin decline with more frequent measures is associated with functional and mortality outcomes.

While the quest for what constitutes a normal hemoglobin level continues[1, 10, 13], measurement of serial hemoglobin levels may help answer this question on an individual level. While a single hemoglobin determination is an invaluable measure of health, we show that within-individual changes to which current anemia criteria are insensitive are associated with significant adverse health consequences in the elderly. Future studies are needed to address the impact of hemoglobin change in younger and ethnically diverse populations, and whether interventions directed towards preventing hemoglobin decline improve health outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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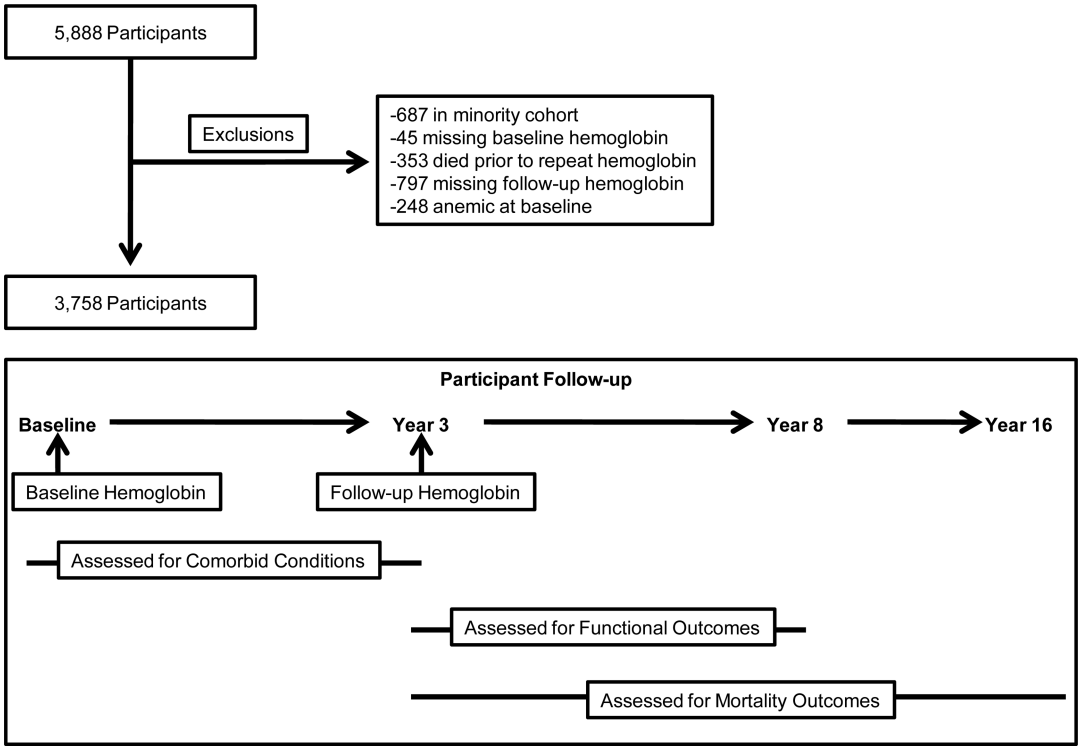

Figure 1.
Study Schema: Participant Exclusions and Follow-up

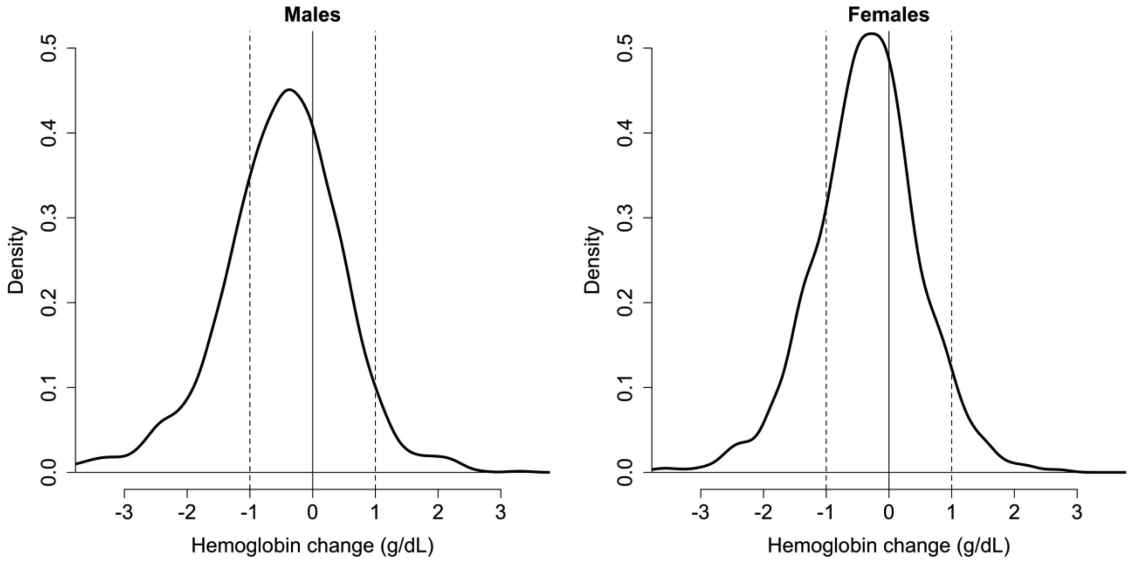

Figure 2.
Distribution of Change in Hemoglobin Concentration between Baseline and 3 Years Later Among Males and Females

Table I

Summary statistics of the cohort at baseline by incident anemia (WHO criteria) three years later, presented as *n* (%) with χ^2-test *p*-values or mean (standard deviation) with two-sample *t*-test *p*-values unless otherwise indicated

	Cohort	**Incident Anemia (WHO criteria)**		**p**
	***n* = 3758**	**Yes 341 (9%)**	**No 3417 (91%)**	
Age (years)	72.1 (5.1)	73.3 (5.5)	72.0 (5.0)	< 0.01
Male gender	1596 (42%)	161 (47%)	1435 (42%)	0.07
African-American race	146 (4%)	29 (8%)	117 (3%)	< 0.01
Body mass index (kg/m^2)	26.5 (4.4)	25.9 (4.6)	26.6 (4.4)	0.02
Smoker (current or former)	2033 (54%)	182 (53%)	1851 (54%)	0.81
High school graduate	2854 (76%)	247 (72%)	2607 (76%)	0.11
Income				0.37
< $12,000	706 (20%)	72 (23%)	634 (20%)	
$12,000 - $35,000	1858 (53%)	157 (50%)	1701 (53%)	
> $35,000	952 (27%)	88 (28%)	864 (27%)	
MMSE ≤ 23	81 (2%)	12 (4%)	69 (2%)	0.10
Gait speed (m/s)	0.89 (0.20)	0.87 (0.21)	0.89 (0.20)	0.19
Grip strength (kg)	28.9 (11)	29.6 (11)	28.9 (11)	0.25
Hemoglobin (g/dL)	14.2 (1.2)	13.4 (1.0)	14.4 (1.1)	< 0.01
White cell count	6.29 (2.1)	6.30 (3.9)	6.29 (1.8)	0.93
Platelet count (× 10^3/L)	251 (74)	249 (71)	251 (74)	0.54
C-reactive protein (mg/L)[†]	2.31 (1.0)	2.42 (3.1)	2.30 (2.8)	0.34
Serum creatinine (mg/dL)	1.03 (0.27)	1.10 (0.33)	1.02 (0.27)	< 0.01
Cardiovascular disease[*]	824 (22%)	83 (24%)	741 (22%)	0.29
Hypertension	1601 (43%)	148 (44%)	1453 (43%)	0.77
Diabetes Mellitus	504 (13%)	50 (15%)	454 (13%)	0.53
Kidney disease (eGFR < 60)	1479 (39%)	167 (49%)	1312 (38%)	< 0.01
Inflammation (CRP ≥ 10 or WBC ≥ 15)	315 (8%)	36 (11%)	279 (8%)	0.15
Hypoproliferation (WBC < 3.0 or PLT < 150)	177 (5%)	18 (5%)	159 (5%)	0.72

Abbreviations: WHO, World Health Organization; MMSE, Mini-Mental Status Exam; eGFR, estimated glomerular filtration rate; CRP, C-reactive protein; WBC, white cell count; PLT, platelet count

[*] Includes myocardial infarction, angina, congestive heart failure, claudication, stroke, and trans-ischemic attack

[†] Median (inter-quartile range) with Wilcoxon rank-sum test *p*-values

Table II

Association of baseline characteristics with hemoglobin change

	Change in Hemoglobin Over 3 Years (g/dL) (95% CI)	Incident Anemia OR (95% CI)
Demographic characteristics *		
Age (quartiles)		
65 - 67 years	Reference	Reference
68 - 71 years	−0.06 (−0.13, 0.02)	1.48 (1.10, 1.98)
72 - 75 years	−0.07 (−0.16, 0.02)	1.53 (1.11, 2.11)
76 - 95 years	−0.15 (−0.24, −0.06)	1.96 (1.45, 2.64)
Male gender	0.21 (0.14, 0.28)	1.18 (0.97, 1.45)
African-American	−0.02 (−0.17, 0.14)	2.34 (1.66, 3.29)
Baseline hemoglobin (g/dL)	−0.31 (−0.34, −0.28)	--
Disease conditions †		
Cardiovascular disease	−0.05 (−0.13, 0.02)	1.06 (0.84, 1.34)
Hypertension	−0.01 (−0.07, 0.05)	1.01 (0.82, 1.24)
Diabetes Mellitus	−0.09 (−0.18, −0.002)	1.04 (0.78, 1.38)
Kidney disease	−0.09 (−0.16, −0.03)	1.39 (1.13, 1.71)
Inflammation	−0.07 (−0.18, 0.04)	1.31 (0.95, 1.80)
Hypoproliferation	−0.06 (−0.21, 0.08)	0.98 (0.63, 1.54)

Abbreviations: OR, odds ratio; CI, confidence interval

*Each adjusted for all other demographic characteristics

†Hemoglobin change adjusted for age, gender, race, and baseline hemoglobin; incident anemia adjusted for age, gender, and race