ANEMIA IN GEORGIA CENTENARIANS AND OCTOGENARIANS

by

Alyson Haslam

(Under the Direction of Dorothy B. Hausman)

ABSTRACT

This secondary data analysis examined the prevalence and proportion of several classifications of anemia in Georgia centenarians and octogenarians: anemia of chronic disease, nutritional anemia, combination (nutritional and chronic disease), and unexplained anemia. Data were collected as part of the Georgia Centenarian Study and included 69 octogenarians and 185 centenarians and near centenarians (98+ years). Centenarians had a higher prevalence of anemia of chronic disease (25.4% vs. 8.7%) and combination anemia (15.7% vs. 2.9%) than octogenarians. Being centenarian, being African American and having abnormal serum values for albumin (<3.6 g/dL), creatinine (>1.4 mg/dL), or ferritin (<12 ng/mL) were all found to be predictors of anemia. In summary, there is a high prevalence of anemia of chronic disease and combination anemia in centenarians. Disease management is important in the very old in order to reduce the burden of anemia and the resulting negative health consequences.

INDEX WORDS: Anemia, Centenarians, Octogenarians, Chronic disease, Nutrition

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ALYSON HASLAM

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ALYSON HASLAM

Major Professor: Dorothy B. Hausman

Committee: Mary Ann Johnson
Alex Kojo Anderson

Electronic Version Approved:

Maureen Grasso
Dean of the Graduate School
The University of Georgia
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DEDICATION

This work is dedicated to my husband and son, Brett and Will, who have been such a source of strength throughout the entire process. Without you two, this never would have happened.

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Lastly, I would like to thank my family for all of their support. Brett, I couldn't have done it without your faith in me and for helping me with responsibilities outside of school. Will, thank you for your understanding during long hours of study and writing, even when a game would have been so much more fun. You are both inspirations to me.

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CHAPTER 1

INTRODUCTION

Older Americans constitute a rapidly growing segment of the population. Census data show that the number of individuals 85 years and older has increased over 350% in just 50 years, increasing from 38 per 10,000 individuals in 1950 to 172 per 10,000 in 2000 (National Center for Health Statistics, 2007). While the trend of more Americans living to advanced age is encouraging – and a positive indicator of the overall quality of health in the United States – there are resulting negative consequences of an aging population, including multiple chronic health conditions (American Geriatrics Society, 2005).

Of the conditions that affect older individuals, anemia has an increasing prevalence as people age. Guralnik et al. (2004) estimated that the prevalence of anemia in persons 65 years and older is 10.6%. The study, which was based on data from phases 1 and 2 of the NHANES III survey, further estimated that for individuals over the age of 85 the prevalence of anemia rose to 26.1% for males and 20.1% for females. While the NHANES study evaluated the general prevalence of anemia in those 85 and older, no further details describing anemia were given in this age category, and studies focusing primarily on anemia and the oldest of old are very difficult to find.

Strictly speaking, anemia is defined by the World Health Organization as having a blood hemoglobin of <12.0 g/dL for females and <13.0 g/dL for males (WHO, 1968). In mild to moderate anemia, it is not uncommon to be asymptomatic (National Institute of Health, 2009). When signs and symptoms are present, anemia often presents itself in the individual as fatigue

and pallor, which can be misinterpreted as common occurrences as people age, perhaps masking the actual seriousness of this disease in older individuals.

Anemia is an insidious disease that has been associated with a wide range of negative health conditions in the elderly. The continuum of conditions range from the simple, for example a decrease in physical performance and muscle strength (Penninx et al., 2004), to the more severe, as a predictor of hospitalization and mortality (Denny et al., 2006; Penninx et al., 2003 and 2006; Zakai et al., 2005). Furthermore, studies have shown higher mortality rates among those with anemia even when anemia was not the primary health condition (Dunkelgrun et al., 2008). In addition to the physical costs, anemia can have tremendous financial costs. It has been estimated that patients with a chronic health condition and anemia may incur $7,000-$30,000 more in health care costs as compared to those with only the chronic health condition without anemia (Ershler et al., 2005).

To gain a better understanding of anemia, researchers often classify anemia in three ways – nutritional anemia, anemia of chronic disease, and unexplained anemia (Artz et al., 2004; Guralnik et al., 2004; Semba et al., 2007). This classification system helps healthcare workers in identifying potential etiologies of anemia in older individuals, and can help to guide them in prevention and treatment programs. NHANES data (Guralnik et al., 2004) showed the proportion of the three classifications to be fairly evenly distributed among non-institutionalized individuals over 65 years. In that study, the classifications of anemia were examined across the entire group of older adults age 65 and older, although it was also noted that the prevalence of anemia increased with age from 64-75 yr to 85+ yr. Thus the question remains: "Do the proportions of the different classifications of anemia also change as people age?"

In the past, little research on anemia has been done in the oldest old, particularly centenarians. One reason may be due to the historically low number of centenarians in the US population, however, the numbers are expected to grow significantly by the year 2050 (Krach and Velkoff, 1999). Another reason may be due to the seemingly benign nature of anemia in older individuals, but studies have shown that even mild cases of anemia can have negative health consequences (Chavez et al., 2006).

The Georgia Centenarian Study (GCS: Poon et al., 2007), a multidisciplinary population based study of octogenarians (age 80-89) and centenarians and near centenarians, (98 years and above) in northern Georgia, provides an excellent population for studying differences in anemia between age groups. The present study was a secondary analysis of GCS data and was designed to 1) determine the difference in anemia prevalence between octogenarians and centenarians, 2) determine the proportion and prevalence of the different classifications of anemia for both age groups, and 3) determine potential predictors, including demographic and health factors, of anemia in the two groups.

As the population ages, understanding a disease such as anemia with many negative outcomes in older individuals becomes increasingly important, not only for keeping health care costs down, but also for maintaining the quality of life for aging individuals. This study was designed to help broaden the understanding of anemia and to characterize its presence in older populations.

Chapter 2 is a review of the literature and covers topics such as prevalence of older individuals, including those who are centenarians, prevalence and definition of anemia, physical and financial costs associated with anemia, classifications of anemia, and variables that could be predictors of anemia.

Chapter 3 is a manuscript that will be submitted to the *Journal of Nutrition, Health, and Aging*. Methods for the research study, results, data tables, and discussion of anemia prevalence and predictors are included.

Chapter 4 is a summary of the findings from this study and includes general conclusions and suggestions for future research.

CHAPTER 2

LITERATURE REVIEW

Prevalence of Older Individuals

Older Americans constitute a rapidly growing segment of the population. Census data show that the number of individuals 85 years and older has increased over 350% in just 50 years, increasing from 38 per 10,000 individuals in 1950 to 172 per 10,000 individuals in 2000 (National Center for Health Statistics, 2007). Recently, the Administration on Aging reported that the number of individuals in the 85+ years group was estimated to be 45 times larger in 2007 (5.5 million individuals) than what it was in 1900 (approximately 122,000 individuals) (AOA, 2009), and is expected to grow to 21 million by 2050 (AOA, 2009). While the trend of more Americans living to advanced age is encouraging – and a positive indicator of the overall quality of health in the United States – there are resulting negative consequences of an aging population, including that of multiple chronic health conditions (American Geriatrics Society, 2005).

Prevalence and Definition of Anemia

Of the conditions that affect older individuals, anemia has increasing prevalence as people age. Guralnik et al. (2004) estimated that the prevalence of anemia in persons 65 years and older is 10.6%. The study, which was based on data from phases 1 and 2 of the NHANES III survey, further estimated that the prevalence rose to 26.1% and 20.1% for males and females respectively for those who were over the age of 85. While the NHANES study evaluated the general prevalence of anemia in those 85 and older, studies focusing primarily on the oldest of old or the predictors of anemia in the very old are very difficult to find.

Strictly speaking, anemia is defined by the World Health Organization as having a blood hemoglobin of <12.0 g/dL for females and <13.0 g/dL for males (WHO, 1968). In mild to moderate anemia, it is not uncommon to be asymptomatic (National Institute of Health, 2009). Although when signs and symptoms are present, anemia often presents itself in the individual as fatigue and pallor, which can be misinterpreted as common occurrences as people age, perhaps masking the actual seriousness of this disease in older individuals.

Physical and Financial Costs of Anemia

Anemia is an insidious disease that has been associated with a wide range of negative health conditions in the elderly. The continuum of conditions range from the simple, for example a decrease in physical performance and muscle strength (Penninx et al., 2004), to the more severe, as a predictor of hospitalization and mortality (Denny et al., 2006; Penninx et al., 2003 and 2006; Zakai et al., 2005). Furthermore, studies have shown higher mortality rates among those with anemia even when anemia was not the primary health condition (Dunkelgrun et al., 2008). Studies have also shown that even mild cases of anemia have associations with negative health consequences (Chavez et al., 2006). In addition to the physical costs, anemia can have tremendous financial costs. One study compared patients with a chronic health condition and anemia to those with the health condition, but with no anemia, and calculated that those with anemia incurred $7,000-$30,000 more in health care costs than those without anemia (Ershler et al., 2005). Gaining a clear picture of this condition, its characterization, and its scope in the very elderly population is important due to the negative outcomes associated with anemia.

Classifications of Anemia

The causes of anemia can be characterized into three broad categories: anemia of nutritional deficiencies, anemia of chronic inflammation (ACI), including renal insufficiency, and unexplained anemia (UA) (Guralnik et al., 2004; Semba et al., 2007). The prevalence of the different classifications of anemia has been shown to vary, depending on the age of the participants and the ways used to define each type of anemia. In one study (Guralnik et al., 2004), the prevalence of anemia in people 65 years and older was nearly equivalent to 33% in each of these categories. Another study (Artz et al., 2001) found that among the elderly living in a nursing home, 23% of the individuals had iron-deficient anemia, 33% had ACI, and 45% had UA. Yet another study (Semba et al., 2007) found that among women over 65 years the prevalence of nutritional anemia (15.0%) was less than that of unexplained anemia (34.7%), but the prevalence of anemia of chronic disease (50.2%) was greatest. These studies have focused on generally younger populations than the population of the Georgia Centenarian Study, and have grouped participants into one group, combining those in their sixties with those in their eighties and nineties.

Nutritional anemia can include deficiencies of iron, vitamin B12, and/or folate. Of the nutrition-related anemias, iron-deficiency is the most common, and maybe the most familiar, making up nearly half of the nutritional anemias in persons over 65 (Guralnik et al., 2004). Iron is a major constituent of hemoglobin in red blood cells, helping to carry oxygen from the lungs to the tissues of the body, and when iron is low, smaller and fewer red blood cells are manufactured, leading to less oxygenation of the tissues (National Anemia Action Council, 2010). Although not as common, vitamin B12 and folate deficiencies contribute to anemia by impairing DNA synthesis, which leads to ineffective red cell production and hemolysis (Beutler

et al., 1995). Fortunately, most people with this type of anemia can benefit from vitamin supplementation (Andres et al., 2005) as long as there is an awareness of their condition.

Anemias relating to chronic inflammation often refer to anemic individuals with a high burden of chronic disease and who often have high blood levels of inflammatory markers, such as C-reactive protein (CRP), which are stimulated by an increase in inflammatory cytokines (Gabay and Kushner, 1999). People with a high burden of chronic disease often have a slightly shortened life-span of the red blood cell, disrupted iron metabolism, and are unable to adequately compensate for deficiencies of red blood cells, thus leading to their anemic state (Beutler et al., 2005). Anemia of chronic disease results from a complex interaction of cytokines on inflammatory proteins, iron homeostasis, and erythropoiesis. Inflammatory cytokines, such as interferon-γ, lipopolysaccharide, TNF-α, interleukin-1, and interleukin-6 all play a role in iron balance (Weiss and Goodnough, review, 2005). Primarily, these inflammatory cytokines stimulate the production of the iron regulatory protein, hepcidin (Flemming and Bacon, review, 2005). Higher levels of these inflammatory proteins can lead to increased ferritin uptake by macrophages, decreased release of ferritin by the macrophages, increased degradation of RBCs, decreased iron uptake in the duodenum, and inhibition of erythropoiesis in the bone marrow (Weiss and Goodnough, review, 2005). In addition, inflammatory proteins appear to inhibit erythropoietin production in the kidney (Weiss and Goodnough, review, 2005), a major promoter of immature RBC (erythroid burst-forming units) production. Individuals with anemia in the NHANES study were more likely to have chronic conditions such as, diabetes and arthritis, as well as elevated CRP levels (Guralnik et al., 2004).

Anemia associated with renal dysfunction could also be included in this classification because it is a chronic health condition and shares some of the inflammatory mechanisms as

chronic disease. However, the primary mechanism for renal-associated anemia is slightly different than that of anemia of chronic disease. Anemia from chronic kidney disease results mainly from decreased production of the hormone erythropoietin, which normally would stimulate the production of red blood cells (NKUDIC, 2008). One concern with this classification is that kidney dysfunction appears to be exacerbated by the presence of anemia. In a recent cohort study, people with lower hemoglobin levels experienced a greater decline in kidney function than those with higher hemoglobin levels (Lee et al., 2008), thus suggesting reverse causality.

Unexplained anemias (UA) are those that seem to have no clear etiology and do not fit into the classifications of nutritional anemias or of anemia of chronic disease. This category may be more significant to the population group in the proposed study because of their advanced age. Guralnik et al. (2004) found that those categorized as having UA tended to be older than those without anemia and older than those who had anemia due to ACI. Similarly, another study (Artz et al., 2001) demonstrated that residents of a nursing home had a higher proportion of UA than other anemias.

Predictors of Anemia

There are several potential factors which may predict anemia, in general, in the very old including diet quality, BMI, race/ethnicity, gender, type of residence, and number of medications. Overall nutrition, based on dietary habits, and BMI, appears to have a significant association with anemia in persons over 65 (Choi et al., 2004; Ramel et al., 2008). Similarly, type of residence could be a predictor for anemia. In one study, it was shown that centenarians in Georgia who resided in a skilled nursing facility had higher diet quality scores than those who resided in the community (Johnson et al., 2006). Because of the associations of overall nutrition

and supplementation with anemia, and the understanding that individuals residing in skilled nursing facilities receive a more nutritious diet, there could also be an association between type of residence and anemia. Conversely, people in nursing homes may have more health conditions, are more advanced in age and, therefore, may be more at risk for developing anemia.

There is typically little surprise when looking at gender as a predictor of anemia. In almost every age category, females have a higher prevalence of anemia than males. The oldest age groups seem to be the exception to this pattern, as shown by several studies that found a higher prevalence of anemia in men than women, among older individuals (Artz et al., 2001; den Elzen et al., 2009; and Guralnik et al., 2004).

Ethnic origins and race have also been shown to be predictors of anemia. In one study (Guralnik et al., 2004), the percentage of anemia in persons over 65 who were non-Hispanic black was found to be close to 30%. This was much greater than the percentage of anemic individuals who were non-Hispanic white or Mexican American. Conversely, while there is a much higher percentage of non-Hispanic blacks with anemia, the risk of mortality associated with anemia has been shown to be higher in whites than in blacks (Patel et al., 2007).

Many specific medications have been shown to cause anemia (Beutler et al., 1995) including drugs classified as anti-inflammatories, anti-cancer, anti-convulsant, and anti-bacterial. The mechanism for drug-induced anemia can include either a single, or multiple actions, of the following: increased bleeding, hemolysis, or poor nutrient absorption or utilization, which leads to poorly functioning RBCs (Buetler et al., 1995; Edwards and Coghill, 1966). As people age, they develop more conditions (American Geriatrics Society, 2005), increasing the likelihood of taking one of these drugs, thus increasing their risk of developing anemia due to medication usage.

Serum pepsinogen may be a predictor for nutritional deficiency anemia in older adults. Atrophic gastritis can lead to decreased pepsinogen levels (Wolters et al., 2004), and consequently decreased absorption of vitamin B12 (Andres et al., 2005 and 2000). Lack of vitamin B12, can lead to improperly made red blood cells and decreased red blood cell count (NHLBI, 2009). Atrophic gastritis has been found in up to 37% of those 80 years and above, making it the main reason that many older adults experience vitamin B12 deficiency (Wolters et al., 2004).

Myelodysplastic syndrome is one possible explanation for UA. It has been estimated that this condition could account for approximately 17% of the UAs, or 5% of the total anemias (Guralnik et al., 2004). In this condition, a person's bone marrow begins to dysfunction and the production of peripheral blood cells, including red blood cells, is decreased. Myelodysplasia has been found to occur at a higher prevalence with increasing age (Steensma et al., 2006), and at higher rates in men than in women (Sandhu et al., 2008). Interestingly, the NHANES data revealed that in the most advanced age group, men had a higher prevalence of anemia than women (Guralnik et al., 2004), which is the same population demographic that appears to have a higher prevalence of myelodysplastic syndrome.

Centenarians

Anemia in the very elderly is understudied because, historically, those individuals have represented such a small number within the population. According to the US Census Bureau (Krach and Velkoff, 1999), the number of centenarians in the US increased from 37,000 to 70,000 between 1990 and 2000. This number is expected to double each decade thereafter, and is estimated to reach 834,000 by 2050 (Krach and Velkoff, 1999). Hence, understanding the specific needs of centenarians and managing their health concerns becomes increasingly

important. One study that has tried to understand the health of the very elderly, as well as how certain individuals achieve extraordinary longevity is the Georgia Centenarian Study. The Georgia Centenarian study is a population-based, multi-disciplinary study that targets octogenarians (80-89 years) and centenarians and near centenarians (98 years and older). As part of this larger study, the proposed study will focus on anemia in very old individuals.

Rationale, Specific Aims, and Hypothesis

The over-85 segment of the population is projected to be the fastest growing segment in the United States this next century (US Census Bureau, 2008). With the growing segment of older individuals comes additional chronic health conditions (American Geriatrics, 2005), one of which is anemia. Anemia is an insidious disease that causes mild symptoms, such as weakness and tiredness, but can lead to more serious health conditions. Anemia has been associated with decreased physical performance and muscle strength and increased hospitalization and mortality (Denny et al., 2006; Penninx et al., 2003, 2004, and 2006; Zakai et al., 2005). To get a better understanding of anemia, researchers often classify anemia in several categories: nutritional anemia, anemia of chronic disease, and unexplained anemia. This gives researchers a better understanding of possible etiologies of anemia (Artz et al., 2004; Guranik et al., 2004; Semba et al., 2007). Often these studies examine the classifications across the entire group of older adults age 65 and older. Very few studies have looked at anemia in the very old, and to our knowledge, none have classified anemia in this group and determined the prevalence for the different classifications.

The Georgia Centenarian Study includes an excellent population to study because of the advanced age of the participants. The two distinct older age groups allow for comparisons to be

made between octogenarians and centenarians (and near centenarians). The study is also population-based, and covers a broader spectrum of the population than a convenience sample.

It is hypothesized that the prevalence of anemia is higher in the centenarians than in the octogenarians. It is further hypothesized that there is a higher proportion of anemia that is "unexplained" in the Georgia centenarians than in the octogenarians. It is also hypothesized that being African American, being centenarian, being male, high serum creatinine, and low serum albumin concentrations are possible predictors of anemia in this study population.

The first specific aim of this study is to determine the prevalence of anemia in the centenarians and octogenarians, and test for differences in the prevalence of anemia between the two groups. The second specific aim is to determine the prevalence of the different classifications of anemia in the two age-groups, and also to determine the proportion of the different classifications among those who are anemic. The third specific aim is to determine the possible predictors of anemia, such as race/ethnicity, gender, BMI, creatinine, and albumin, among the centenarians and octogenarians.

CHAPTER 3

PREVALENCE AND PREDICTORS OF ANEMIA IN GEORGIA CENTENARIANS AND OCTOGENARIANS[1]

[1] Haslam A, Johnson MA, Poon LW, Hausman DB. To be submitted to *The Journal of Nutrition, Health and Aging*.

Abstract

Objectives: The primary objectives of this study are to examine the prevalence of anemia in octogenarians and centenarians in Georgia, to classify the different types of anemia, to examine how the classifications differ between the two age-groups, and to explore possible predictors of anemia. **Design:** Cross-sectional study, secondary data analysis. **Setting:** 44 counties in northern Georgia, USA. **Participants:** Centenarians and near-centenarians (98+, n = 185) and octogenarians (n = 69) were recruited as part of the population-based, multi-disciplinary Georgia Centenarian Study. **Measurements:** Hemoglobin was used to identify those with anemia. Other blood markers, such as ferritin, vitamin B12, RBC folate, creatinine, and C-reactive protein (CRP) were used to classify anemia as either nutritional anemia, anemia of chronic disease, both nutritional anemia and anemia of chronic disease, and unexplained anemia. **Results:** Among octogenarians, the prevalence of anemia was 27.5%, while the centenarians had a significantly higher ($p<0.05$) prevalence of anemia (50.3%). In the centenarians the prevalence of the different classifications of anemia was found to be 3.2% with nutritional anemia, 25.4% with anemia of chronic disease, 15.7% with both nutritional anemia and anemia of chronic disease, and 6.0% with unexplained anemia, For the octogenarians, the prevalence of the different classifications was found to be 5.8% with nutritional anemia, 8.7% with anemia of chronic disease, 2.9% with both nutritional anemia and anemia of chronic disease, and 10.1% with unexplained anemia. Being centenarian, being African American, having low serum albumin (<3.6 g/dL), having high serum creatinine (>1.4 mg/dL), and having low serum ferritin (<12 ng/mL) were all found to be predictors of anemia in the total analytical sample. **Conclusion:** Anemia is a major health issue, particularly as people age. Because of the high prevalence of anemia in older individuals, awareness of the different classifications becomes

increasingly important so as to reduce the negative consequences associated with it and allow us to identify the steps that can be taken to correct anemia, including managing chronic disease.

Introduction

The over-85 segment of the population is projected to be the fastest growing segment in the United States this next century (US Census Bureau, 2008). With the growing segment of older individuals comes additional chronic health conditions (American Geriatrics, 2005), one of which is anemia. Anemia is an insidious disease that causes mild symptoms, such as weakness and tiredness, but can lead to more serious health conditions. Anemia has been associated with decreased physical performance and muscle strength and increased hospitalization and mortality (Denny et al., 2006; Penninx et al., 2003, 2004, and 2006; Zakai et al., 2005). In addition to the physical costs, anemia can have tremendous financial costs. It has been estimated that those with anemia, in addition to a chronic health condition incur between $7,000 and $30,000 more in health care costs than those with similar health conditions, but no anemia (Ershler et al., 2005).

To get a better understanding of anemia, researchers often classify anemia in several categories: nutritional anemia, anemia of chronic disease, and unexplained anemia. This provides a better understanding of possible etiologies of anemia (Artz et al., 2004; Guranik et al., 2004; Semba et al., 2007). Using the NHANES data, it was estimated that, among those over 65-years, roughly one-third of anemia comes from nutritional deficiencies, one-third from chronic disease, and one-third are unexplained (Guralnik et al., 2004). A higher prevalence of anemia of chronic disease than nutritional anemias has been found in older women (Semba et al., 2007), whereas a higher prevalence of unexplained anemia than nutritional anemia or anemia of chronic disease has been reported among those in nursing homes (Artz et al., 2004).

Often these studies examine the classifications across the entire group of older adults age 65 and older. Considering that the fastest growing segment of the population is those over 85-years and the relatively rapid growth of individuals reaching their 100s (Krach and Velkoff, 1999), there could potentially be differences in anemia status between those in their sixties and those in their eighties or one-hundreds. Consequently, there is a need for better understanding of anemia in the older population. Hence, the question, "Are there differences in the prevalence of the different classifications of anemia between octogenarians and centenarians?" Very few studies have looked at anemia in the very old, and to our knowledge, none have classified anemia in the very old and determined the prevalence for the different classifications in the different age groups.

Therefore, the purpose of this study was to determine whether or not centenarians have a higher prevalence of anemia than octogenarians, to determine whether or not there are differences in the prevalence of the different classifications of anemia between the two age groups, and to determine possible predictors of anemia in octogenarians and centenarians. Based on previous studies (Artz et al., 2004; Choi et al., 2004; Guralnik et al., 2004), it is hypothesized that the prevalence of anemia is higher in centenarians than in octogenarians. It is further hypothesized that there is a higher proportion of anemia that is "unexplained" in Georgia centenarians than in octogenarians. It is also hypothesized that being African American, being centenarian, being male, high serum creatinine, and low serum albumin concentrations are possible predictors of anemia in this study population. The findings of this study will help identify potential etiologies of anemia in the very old, which can then help in prevention and treatment programs for anemia.

Experimental Design

The data used in this secondary data analysis were collected as part of the National Institute on Aging Program Project 1P01-AG17553 (Leonard W. Poon, PI, Dorothy B. Hausman, Co-Investigator, and Mary Ann Johnson, Co-Investigator; these scientists require that collaborators using these data acknowledge the source of funding for these previously collected data).

Study Participants

Data for the secondary analysis came from the multidisciplinary Georgia Centenarian Study (2002-2005), which has been previously described (Poon et al., 2007). This study is comprised of 244 centenarians and near centenarians (98 years and older) and 80 octogenarians (80 – 89 years) residing in the community, personal care homes, and skilled nursing facilities in 44 counties of northern Georgia. The original study population was selected to parallel the 2000 US Census data with regard to gender (males: 37 centenarians, 27 octogenarians; females: 207 centenarians, 53 octogenarians), and race/ethnicity (centenarians: 46 African American women; 6 African American men; octogenarians: 11 African American females; 3 African American males) and requested census tabulations for residence (community-dwelling and "institutionalized" individuals) (W. Rodgers, unpublished data). This study has been approved by the University of Georgia Institutional Review Board, as is required when studying human subjects.

Blood Values

To obtain values for each variable several techniques were used, as identified in previous studies (Johnson et al., in press). Vitamin B12 (B12) and red blood cell folate concentrations

were determined by radioimmunoassay (Quantaphase II Vitamin B12/Folate Radioassay; Bio-Rad, Richmond, CA). Serum pepsinogen values were obtained through enzyme immunoassay (Pepsinogen I ELISA; ALPCO Diagnostics, Windham, NH). Serum methylmalonic acid and 2-methylcitrate values were obtained through capillary gas chromatography-mass spectrometry (Stabler et al., 1998). The remaining lab values, such as the complete blood count, including red cell indices, ferritin, c-reactive protein (CRP), creatinine, blood urea nitrogen (BUN), and albumin, were obtained through the independent clinical laboratory LabCorp (LabCorp, Inc., Burlington, NC). The estimated glomerular filtration rate (eGFR) was determined using the Cockcroft-Gault equation (Cockcroft and Gault, 1976):

For Men: $\frac{(140\text{-age}) \times (\text{wt in kg})}{72 \times (\text{serum creat in mg/dL})}$	For Women: use men's formula result and multiply by 0.85

Participants were not fasting at time of blood draw because of the frail state of some of the participants and because of the varying times that the samples and information was collected. All blood was processed within four hours of collection.

Additional Measurements

Height and weight were usually measured using a stadiometer and scale but in some instances data was obtained from the patient's chart or from self-report. BMI was calculated using the standard formula of weight in kg divided by height in meters, squared (kg/m^2). Several of the variables were obtained through an interview process. This included a trained interviewer reading the questions followed by a response from the study participant, and then the interviewer recording the answer given. This revealed information about the subject's food intake (daily or weekly servings of meat, green leafy vegetables, orange vegetables, eggs and dairy),

race/ethnicity, gender, place of residence, and all medications and supplements. In some instances, such as those living in a skilled nursing facility, this information was recorded from the participants' chart or from a proxy.

Nutritional status was assessed with nutritional scores based upon food groups consumed over the course of a week, or daily in the case of dairy, and has been previously described (Johnson et al., 2006). The total number of medications consumed by each individual was evaluated as a potential predictor for anemia. Supplement use was a dichotomous variable ("Was the participant taking any of the included supplements?" yes or no) used as a potential predictor for anemia and included the following supplements: B-vitamin, B-vitamins + omega-3 fatty acids, herbals + vitamins, iron, minerals, multi-vitamin, multi-vitamin + calcium, multi-vitamin + iron, multi-vitamin + minerals, multi-vitamin + zinc, vitamin, vitamins + minerals, vitamins + zinc, vitamins; b complex + c. Disease sum was based on a formula described previously by Jang et al. (2004). Each participant was asked about their disease history, and certain diseases considered significant were used in the disease calculation. Significant diseases for this study included osteoporosis, chronic kidney disease, diabetes, chronic airway obstruction, cancers (present), hypertension, Parkinson's, and peripheral vascular disease. For each disease listed the participant received one point. The points were then summed and used as a predictor for anemia.

Definition and Characterization of Anemia

Participants were categorized as anemic or non-anemic according to the definition set by the World Health Organization (< 12 g Hb/dL for females and < 13 g Hb/dL for males [WHO, 1968]). The participants were then further categorized as having mild anemia (Hb concentration greater than or equal to 10 g/dL but less than 12 or 13 g/dL for females and males, respectively), moderate anemia (Hb concentration greater than or equal to 8 g/dL but less than 10 g/dL), or

severe anemia (Hb concentration less than 8 g/dL) based on classifications set by the National Cancer Institute (Mock and Olsen, 2003). The characterization of anemia was then made among those who were anemic. Anemia was classified as a "nutritional anemia" or "anemia of chronic disease", depending on various laboratory findings. If the anemic participant appeared to have both classifications of anemia they were classified as having "combination anemia", and those who appeared to have neither type of anemia were classified as having "unexplained anemia".

Nutrient deficiency anemia included cases associated with deficiencies of iron, vitamin B12 or folate. To stay consistent with other studies (Guralnik et al., 2004), serum ferritin of less than 12 ng/mL was the criteria for characterizing iron-deficiency, but data was also analyzed using a higher cut-off for ferritin (Joosten et al., 1999) of less than 50 ng/mL. Vitamin B12 deficiency was defined as having serum B12 levels <258 pmol/L, serum methylmalonic acid (MMA) >271 nmol/L (Stabler et al., 1999), and serum 2- methylcitric acid level less than MMA (Johnson et al., 2003). Folate deficiency was defined as RBC folate levels < 317 nmol/L based on the criteria used by the National Health and Nutrition Examination Survey (NHANES; Pfeiffer et al., 2007).

Anemia relating to chronic inflammation was identified with the circulating inflammatory protein CRP (>5.0 mg/L) (Rothkrantz-Kos et al., 2003). Those individuals with anemia of chronic kidney disease were identified by an estimated glomerular filtration rate (eGFR) <30 mL/min (Guralnik et al., 2004). Those who had anemia but could not be classified as having either nutrient-deficiency anemia or anemia of chronic disease were classified as having unexplained anemia.

Exclusions from Data Analysis

Ultimately, data from 69 octogenarians and 185 centenarians were included in the study, as some participants had missing blood values and were excluded (excluded participants: n=11 octogenarians; n=59 centenarians). Participants were excluded because of one or more missing values, including: hemoglobin (n=10), albumin (n=18), CRP (n=37), BUN (n=18), ferritin (n=22), RBC folate (n=15), vitamin B12 (n=11), pepsinogen (n=2), MMA (n=21), cystathionine (n=19), 2-methylcytric acid (n=20), and BMI (n=9).

Characteristic differences between those included in the analysis and those excluded indicated that mean hemoglobin levels for excluded octogenarians (13.7 g/dL) was not statistically different ($p>0.05$) than for octogenarians (13.2 g/dL) included in the study. Mean age for excluded octogenarians (83.0 years) was also not statistically different than octogenarians (84.5 years) included in the study. Among the octogenarians there were no statistical differences ($p>0.05$) in regards to being female (66.7% vs. 63.6%), being African American (17.4% vs. 12.5%), living in a nursing home (17.4% vs. 0%), having low ferritin (4.4% vs. 9.1%), having vitamin B12 deficiency (24.6% vs. 9.1%), or having high creatinine concentrations (7.2% vs. 0.0%) between those included and those excluded in the analysis. Mean hemoglobin concentrations were not statistically different between excluded centenarians (12.0 g/dL) and included centenarians (12.0 g/dL), but the excluded centenarians (101.2 years) were significantly older ($p=0.03$) than the included centenarians (100.4 years) and more likely to have low ferritin ($p<0.001$) than included centenarians (35.6% vs. 4.3%). Among the centenarians there were no statistical differences ($p>0.05$) between those included and excluded in the study in regards to being female (84.9% vs. 84.8%), being African American (19.5% vs.

25.5%), living in a nursing home (42.2% vs. 49.0%), having vitamin B12 deficiency (32.4% vs. 28.8%), and having high creatinine concentrations (17.3% vs. 10.2%).

Statistics

Since the sample size of the study was already set, minimum effect size that would yield significant results needed to be determined. To achieve a power of 0.8, there needed to be prevalence of anemia in at least 37% of the centenarians ($p<0.05$). This is assuming a prevalence of 22% in the octogenarians, which is based on the prevalence rate determined in the NHANES study (Guralnik et al., 2004). Thirty-seven percent prevalence seemed reasonable based on several studies that show the prevalence rates in the very old to be well above that (Artz et al., 2004; Beght et al., 2004). To detect a significant difference in the proportions of anemia type in the centenarians ($p<0.05$) there needed to be about a 19% difference in the proportion of unexplained anemia and nutrient deficient anemia or anemia of chronic inflammation, assuming a power of at least 0.8 and a 42% prevalence of anemia. To detect a difference in unexplained anemia between the centenarians and octogenarians ($p<0.05$), there needed to be about a 13% difference in those classified as "unexplained," also assuming a power of 0.8.

Descriptive statistics were performed, and included mean, median, standard deviation, and range, or percentage. Chi square tests and Wilcoxon Rank Sum tests were used to determine differences between the octogenarians and centenarians, those with anemia and those without anemia, as well as those who were included in the analysis and those who were excluded from the analysis. Chi squared tests were used to determine the statistical difference in anemia prevalence between the 69 octogenarians and 185 centenarians, and in the proportion of anemia classified as nutritional, inflammatory or "unexplained' between the two age groups. Multivariate logistic regression analysis was used to identify predictors of anemia in the two

groups. The predictors included nutritional supplements, BMI, race/ethnicity, gender, type of residence, disease score, medications, and other blood tests such as albumin, creatinine, B12 status, ferritin, and CRP. Several models were used to determine the predictors. Model one included demographics, such as age, race, gender, and place of residence. Model two included demographics and biological variables, such as albumin, CRP, creatinine, ferritin, and B12 deficiency. Model three included demographics, biological variables, and other variables, such as low BMI, disease score, medications, and nutritional supplements. Spearman correlation was also performed to find correlations between hemoglobin and different variables, as well as stepwise regression to determine possible predictors of anemia for centenarians, octogenarians, and the combined analytical sample. Statistical analysis was performed using SAS software (version 9.1, SAS Institute, Carey, NC). $P < 0.05$ was considered statistically significant.

Results

Among octogenarians the prevalence of anemia was 27.5% and among centenarians the prevalence of anemia was 50.3%. The overall prevalence of anemia for this study population was 44.1%. Additional participant characteristics are presented in Table 3.1. Overall, centenarians were more likely than octogenarians to be female and have anemia, lower BMI scores, lower eGFR, lower albumin and folate concentrations, higher BUN, CRP, and MMA concentrations, higher nutrition scores, and live in a nursing home. In contrast, there were no differences between centenarians and octogenarians with regard to race.

In the total analytical sample of centenarians and octogenarians, those with anemia were more likely to have significantly lower albumin concentrations, BMI, and eGFR, and higher BUN, CRP, MMA, and 2-methlycytric acid concentrations, higher nutrition scores, abnormal MCV, and to be African American as compared to those without anemia (Table 3.2). In contrast,

there were no differences between those with and without anemia with regard to gender, or place of residence.

When comparing those with anemia to those without anemia within the two age categories, octogenarians with anemia were more likely to be African American and have lower albumin concentrations as compared to those without anemia. Centenarians with anemia were more likely to have lower albumin concentrations, and have higher creatinine and BUN concentrations (Table 3.3), but did not differ by race/ethnicity.

Anemia was classified as nutritional anemia, anemia of chronic disease, combination anemia, and unexplained anemia. There were two ways that iron-deficiency was defined (ferritin <12 ng/mL and ferritin <50 ng/mL), based on previous suggested cut-off points (Choi et al, 2005; Guralnik et al., 2004; Holyoake et al., 1993; Joosten et al., 1999). Analysis of the data showed that when a ferritin cut-off of 12 ng/mL was used to define those with iron deficiency (Table 3.4) the overall prevalence of anemia was higher for the centenarians as compared to the octogenarians, and this was accounted for by a higher prevalence of anemia of chronic disease and combination anemia. Prevalence of nutritional anemia and unexplained anemia were similar for the two age groups. Centenarians were found to have a significantly lower percentage of unexplained anemia, but there were trends that nutritional anemia was lower in centenarians and combination anemia was greater in the centenarians. There were no differences in the percentage of anemia of chronic disease between the centenarians and octogenarians.

As previously suggested (Joosten et al., 1999), analysis of the data using a ferritin cut-off of 50 ng/mL to identify those with iron deficiency anemia was also performed (Table 3.5). When the higher cut-off for ferritin was used, there were significantly more centenarians than octogenarians with anemia of chronic disease and combination anemia. The higher cut-off value

for ferritin also supports the concept of higher prevalence of anemia in centenarians stemming from a higher prevalence of anemia of chronic disease and combination anemia. Proportionally, there was a greater percentage of centenarians than octogenarians with anemia of chronic disease, but a lower percentage with nutritional anemia and unexplained anemia.

There were several variables significantly correlated (Spearman) with having anemia in the total analytical sample, centenarians, and octogenarians ($p<0.05$). In the total analytic sample age, race, having low albumin, low eGFR, low BMI, and high creatinine were all correlated with having anemia (Table 3.6). In octogenarians having low albumin and high creatinine were correlated with having anemia (Table 3.7), and in centenarians race and low eGFR were correlated with having anemia (Table 3.8).

Multivariate regression analysis was subsequently performed to determine possible predictors of anemia for centenarians and octogenarians. Models were first set up using a lower ferritin cut-off (<12 ng/mL) for determining those with iron deficiency. In model one (including demographics, such as age, gender, race, and residence) centenarians were 2.7 times more likely and African Americans were 2.6 times more likely to develop anemia than those who were octogenarian or white (Table 3.9). When biological and nutritional variables (albumin, CRP, creatinine, ferritin, B12 deficiency) were included with demographic variables, centenarians (>2.2 fold) and African American (>2.6 fold) remained significant, while those with low albumin (<3.6 g/dL), high creatinine (>1.4 mg/dL), or low ferritin (<12 ng/mL), were respectively 2.5, 2.4 and 5.5 times more likely to have anemia than those with normal values. When looking only at the centenarians (Table 3.10), no variables were significant in model one (demographics - age, gender, race, and residence). Low albumin (<3.6 g/dL) and high creatinine (>1.4 mg/dL) predicted at least a 2.4-fold increase in having anemia as compared with those with normal

albumin and creatinine levels in both model 2 (demographics and biological – low albumin, high CRP, high creatinine, low ferritin, and B12 deficiency) and 3 (demographics, biological and other – low BMI, disease score, medications, and supplements). Among the octogenarians (Table 3.11), race was the only variable found to be significant in all three models. The odds of having anemia as an African American was 8.5 times, 10.1 times, and 5.0 times more likely than for those who were white in models 1 (demographics), 2 (demographics and biological), and 3 (demographics, biological, and other).

Stepwise logistic regression analysis was also performed to determine the potential predictors of anemia, using the variables that were significantly correlated with having anemia. Being centenarian, being African American, having low albumin, having low ferritin, or having high creatinine were associated with having anemia at the 0.05 significance level (Table 3.12). Respectively, individuals were 2.2 times, 2.6 times, 2.3 times, 2.2 times, and 5.3 times more likely to have anemia than those with normal values or who were white. No other variables were associated with having anemia when the significance level was expanded to 0.1.

Among the centenarians, stepwise logistic regression analysis revealed that low albumin and high creatinine were the two variables associated with having anemia at the 0.05 significance level (Table 3.12). Centenarians with these abnormalities were, respectively, 2.2-times and 2.4-times more likely to have anemia than those with normal creatinine and albumin levels. No other variables were associated with having anemia when the significance level was expanded to 0.1. Among the octogenarians, being African American or having low eGFR were both found to be associated with having anemia at the 0.05 significance level. Octogenarians who were African American or had low ferritin were, respectively 9.0-times and 10.8-times more likely to have anemia than those who were white or had a normal ferritin level.

The models for predicting anemia were then repeated, using a higher ferritin cut-off (<50 ng/mL) for determining those with iron deficiency. In model one (including demographics, such as age, gender, race, and residence) centenarians were 2.7 times more likely and African Americans were 2.6 times more likely to develop anemia than those who were octogenarian or white. When biological and nutritional variables (albumin, CRP, creatinine, ferritin, B12 deficiency) were included with demographic variables (Table 3.13), centenarians were 2.2 times more likely and African Americans were 2.5 times more likely to have anemia than octogenarians or white, while those having low albumin (<3.6 g/dL), or high creatinine (>1.4 mg/dL), were respectively 2.5 and 2.2 times more likely to have anemia than those with normal values. When looking only at the centenarians (Table 3.14), no variables were associated with having anemia in model one (demographics - age, gender, race, and residence). Low albumin (<3.6 g/dL) was associated with a 2.5-fold increase and 2.4-fold increase in anemia prevalence as compared to those with normal albumin levels in model 2 (demographics and biological – low albumin, high CRP, high creatinine, low ferritin, and B12 deficiency) and model 3 (demographics, biological and other – low BMI, disease score, medications, and supplements). High creatinine was only associated with having anemia (2.5-fold) in model 3. Among the octogenarians, race was the only variable found to be significant in all three models. As shown in Table l3.15, the odds of having anemia as an African American was 8.5 times, 10.0 times, and 13.8 times more likely than for those who were white in models 1 (demographics), 2 (demographics and biological), and 3 (demographics, biological, and other).

Discussion

The objectives of this study were to examine the differences between centenarians and octogenarians in the overall prevalence of anemia, as well as differences in the classifications of

anemia, and also to examine the predictors for anemia in the two age groups. The results of this study support the hypothesis that centenarians have a much higher prevalence of anemia (50.3%) than octogenarians (27.5%). There was also a greater prevalence of anemia of chronic disease and combined anemia in the centenarians than in the octogenarians. The hypothesis that there would be differences in the proportions of anemia was partially supported. There was, indeed, a difference in the proportions, but not in the direction that was expected. It was hypothesized that there would be a higher proportion of unexplained anemia in the centenarians than in the octogenarians, based on results from nursing home figures (Artz et al., 2004). Conversely, there was a lower proportion of unexplained anemia in the centenarians than in the octogenarians in the present study. However, there were trends of a greater proportion of combination anemia and lower proportion of nutritional anemia in the centenarians than the octogenarians. In multivariate regression analysis having low albumin, being African American, being centenarian, having low ferritin, and having high creatinine were predictive of having anemia. Among octogenarians, being African American was predictive of having anemia, and among centenarians, having low albumin and high creatinine were predictive of having anemia. To our knowledge, this is the first study analyzing the prevalence, proportion, and predictors of anemia in the very old.

Previous studies of anemia classification yielded inconsistent results, partly because of different ways to define the classifications, but also because of the different populations being studied. NHANES data (Guralnik et al., 2004) showed that among those individuals over 65 years, anemia was fairly evenly distributed among the three classifications of nutritional, chronic disease and unexplained. Another study showed a greater proportion of individuals with anemia of chronic disease and a lower proportion of nutritional anemia (Semba et al., 2007). In the

present study, 21.1% of the octogenarians with anemia were classified as having nutritional anemia, 31.6% were classified as having anemia of chronic disease, 36.8% were classified as having unexplained anemia, and 10.5% were classified as having combined anemia, which is somewhat similar to figures from the NHANES study (Guralnik et al., 2004). Centenarians, however, had very different proportions of the various classifications of anemia than the octogenarians.

In this study the most significant difference in the classifications of anemia between the centenarians and octogenarians was in the "unexplained" classification. In the centenarian group there was a significantly lower proportion of individuals with unexplained anemia than for the octogenarians. And, while not significant, in centenarians with anemia there was a trend toward a decrease ($p=0.06$) in the proportion of nutritional anemias and concomitant increase in the proportion of combination anemias ($p=0.05$). Based on the results of this study, it appears that as a population ages, there are changes in the proportion of anemias in the different classifications. It appears that there is a greater proportion of anemia that can be explained, or is at least associated, with another condition – nutritional, disease, or both, in the centenarian population. Perhaps in the octogenarian population there were underlying nutritional deficiencies or disease that had not been fully manifested according to the definitions set in the study, as suggested in a previous study (Izaks et al., 1999), leading to more unexplained cases of anemia.

One particularly noteworthy finding from this study is the overall prevalence of anemia, particularly anemia of chronic disease. Over 40% of the Georgian centenarian population was found to have anemia of chronic disease, alone, or in combination with nutritional deficiencies. The high prevalence of anemia overall and the high percentage of the anemia associated with chronic disease in the centenarians reflects the close interaction between aging, anemia and

inflammation. As people age, there is a greater risk of developing disease in general, and a greater risk of developing multiple diseases (American Geriatrics Society, 2005). The disease process activates a host of inflammatory responses that can affect the production of red blood cells. Inflammatory proteins, such as interferon-γ, lipopolysaccharide, TNF-α, interleukin-1, and interleukin-6 all play a role in iron balance (Weiss and Goodnough, review, 2005). Primarily, these inflammatory proteins stimulate the production of the iron regulatory protein, hepcidin (Flemming and Bacon, review, 2005). Higher levels of these inflammatory proteins can lead to increased ferritin uptake by macrophages, decreased release of ferritin by the macrophages, increased degredation of RBCs, decreased iron uptake in the duodenum, and inhibition of erythropoiesis in the bone marrow (Weiss and Goodnough, review, 2005). In addition, inflammatory proteins appear to inhibit erythropoietin production in the kidney (Weiss and Goodnough, review, 2005), a major promoter of immature RBC (erythroid burst-forming units) production. Understanding this interaction, especially in light of the high prevalence of anemia of chronic disease, emphasizes the importance of managing chronic disease in the older population and finding ways to attenuate the interaction of inflammation and anemia.

In these analyses several definitions for classifying those with iron deficiencies were used (ferritin<12 ng/mL and ferritin<50ng/mL) based on previously suggested cut-off points for ferritin in the older population (Choi et al., 2005; Guralnik et al., 2004; Holyoake et al., 1993). The two definitions of iron-deficiency led to different proportions and prevalences of anemia in the different classifications. Interestingly, by increasing the ferritin cut-off point (<50 ng/mL), as suggested by Joosten et al. (1999), associations between age and the proportion of the different classifications seemed to be strengthened, especially in regard to nutritional anemia and combination anemia. This may have been due to a shift in the numbers in each of the

classifications, particularly from the unexplained classification to the nutritional and combined classifications, resulting in a stronger association. Another difference is that in regression analysis, the lower cut-off point for ferritin (<12 ng/mL) was found to be a predictor of anemia in the total analytic sample, but the higher cut-off point (<50 ng/mL) was not. The cut-off point for ferritin in identifying those with iron deficiency anemia can be controversial because ferritin can also be an acute phase inflammatory marker in addition to being a marker for iron status (Rogers et al., 1990). It appears that a lower cut-off, as opposed to the higher cut-off, for ferritin is more specific in identifying iron-deficiency anemia even in centenarians.

One hypothesis of this study was that there would be a higher prevalence of anemia in the centenarians than in the octogenarians. It was determined that the centenarians in this study, do indeed, have a higher prevalence of anemia (50.3%), than the octogenarians (27.5%). This is consistent with other studies (Beghe et al., 2004; Guralnik et al., 2003) that have shown that the prevalence of anemia generally increases with age and sharply increases after the age of 85 years.

Another reason for the higher prevalence of anemia in this study may be due to institutionalized individuals being included in this study. The percentage of octogenarians residing in nursing homes was 17.4%, and the percentage was even greater among centenarians (42.2%). Omission of institutionalized individuals in many studies may be excluding individuals who have more chronic disease and who are more likely to be anemic. Studies focusing on individuals in nursing homes and hospitals (Artz et al., 2004; Ramel et al., 2008) have found a higher prevalence of anemia than studies that have excluded these individuals (Guralnik et al., 2004; Semba et al., 2007).

Surprisingly, there were no significant differences in the prevalence of anemia in males compared with females. Results from other studies, looking at gender differences in the prevalence of anemia in individuals over 85 years old, have shown a higher prevalence of anemia in men than in women (Beghe et al., review, 2004; den Elzen et al., 2009; Guralnik et al., 2004). However, results of the present study showed that, among octogenarian participants, the prevalence of anemia was slightly less for males than females. Interestingly, although the prevalence of anemia in octogenarian males was lower than octogenarian females, there was a trend towards a higher prevalence ($p=0.08$) of anemia in centenarian males than centenarian females. The GCS was a population-based study and was very imbalanced in the number of males and females included in the study, particularly among the centenarians. Almost 85% of centenarians were female. Perhaps, had there been more males involved with the study, particularly in the centenarian group, the prevalence of anemia in males would have been significantly higher than in the centenarian females, and perhaps increased the proportion of males with anemia in the overall analysis of anemia prevalence.

When looking at the association of race and anemia, there was a very strong association between anemia and being African American in the octogenarian analysis and in the combined octogenarian and centenarian analysis, but not in the centenarian analysis. The higher prevalence of anemia in African Americans, as compared to whites, is consistent with other studies (Denny et al., 2006; Patel et al., 2007), which focused on "younger" older adult populations. No studies were found that compared the prevalence of anemia in different races in the very old or in those close to one-hundred years of age. From this study it appears that racial differences were not present in the centenarians and may be partially due to the low representation of African Americans in the study.

One of the strengths of this study is the advanced ages of the participants. Most studies on anemia focus on a much younger population, but there can still be many years to be lived, even after age 65. Individuals who are 65 years of age can anticipate living an additional 19 years, on average (AOA, 2009). Focusing on octogenarians and centenarians provides insight on disease trends that occur in a very old and less-studied population. Another strength of this study is the attempt that was made to obtain a representative sample of the Georgia population, covering a broader spectrum of the population than a convenience sample.

There are several limitations to this study, including the small sample size. The numbers become small when stratifying by age, but become even smaller when stratifying by age and anemia classification. This made it difficult to see significant results, even when there were seemingly large differences in the classification percentages. Even with the small numbers in the different groups, trends were detected, which may have been significant if the sample size was larger. Another limitation was in the way that iron deficiency anemia was defined. A definitive diagnosis of this type of anemia is particularly difficult in older individuals and would include a bone marrow examination, but other iron-status parameters, such as iron, TIBC (total iron binding capacity), or serum transferrin receptor would have helped to strengthen the definition of iron-deficiency. Using the ferritin values to define iron deficiency could potentially lead to an over- or under-estimation of iron deficiency in this study. However, several studies (Choi et al, 2005; Joosten et al., 2002) have concluded that ferritin is the most specific lab value for identifying iron deficiency anemia.

In conclusion, anemia is a very insidious disease, particularly in the elderly. The significantly greater prevalence of anemia among the centenarians than the octogenarians is certainly a major concern, especially considering the large number of individuals expected to

enter into these age categories. What may be more of a concern is the high prevalence of anemia in the centenarians – over 50%. The high prevalence of anemia, combined with the increasing number of individuals reaching "centenarian" status, and the negative health conditions associated with anemia, make for an increasing need to understand anemia in the very old. Understanding the trends in the classifications of anemia in the very old could help in better treatment, and potentially fewer negative consequences associated with anemia in the very old, thus leading to a higher quality of life and lower health care costs.

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Tables

Table 3.1: Selected participant characteristics: The Georgia Centenarian Study

	Octogenarians Median, Range, Mean (SD), or %(n)	**Centenarians Median, Range, Mean (SD), or %(n)**
Age (years)	84.0, 80.5-90.1, 84.5 (2.8)	100.1, 97.0-108.6 100.4 (1.9)***
Gender Male Female	 33.3 (23) 66.7 (46)	 15.1 (28)** 84.9 (157)
Race White African American	 82.6 (57) 17.4 (12)	 80.5 (149) 19.5 (36)
Living Arrangement Nursing home Community/Personal care	 17.4 (12) 82.6 (57)	 42.2 (78)*** 57.8 (107)
Anemia Yes No	 27.5 (19) 72.5 (50)	 50.3 (93)*** 49.7 (92)
Anemia Severity Mild (Hgb≥10 and <12 [F] or <13 [M]) Moderate (Hgb≥8 and <10) Severe (Hgb <8)	 26.1 (18) 1.4 (1) 0.0 (0)	 41.1 (76)* 8.6 (16)* 0.5 (1)
Hemoglobin (g/dL)	13.2, 9.7-16.5 13.2 (1.6)	12.0, 7.5-16.7 12.0 (1.5)***
Hematocrit (%)	39.4, 28.1-48.0 39.0 (4.7)	35.3, 22.7-51.5 35.7 (4.5)***
Albumin (g/dL)	4.0, 2.3-4.8 4.0 (0.4)	3.7, 2.6-4.7 3.7 (0.4)***
BUN (mg/dL)	19.0, 9.0-48.0 19.9 (7.0)	23.0, 8.0-63.0 25.1 (9.8)***
CRP (mg/L)	3.0, 0.4-33.4 4.4 (5.5)	3.3, 0.3-150 9.3 (18.5)*
Creatinine (mg/dL)	0.9, 0.4-33.4 1.0 (0.3)	1.0, 0.3-5.5 1.1 (0.5)

High creatinine (>1.4 mg/dL)	7.2 (5)	17.3 (32)*
eGFR (mL/min)[1]	51.2, 17.3-107 52.3 (16.5)	26.8, 7.9-59.3 27.0 (8.6)***
eGFR categories low (<30 ml/min)	5.8 (4)	63.8 (118)***
Ferritin (ng/mL)	67.0, 8.0-1257 108 (160)	78.0, 1.6-1955 120 (175)
Low ferritin (<12 ng/mL)	4.4 (3)	4.3 (8)
Low ferritin (<50 ng/mL)	39.1 (27)	37.3 (69)
MMA (nmol/L)	303, 144-1130 350 (198)	380, 163-8078 493 (633)***
High MMA (>271 nmol/L)	60.9 (42)	76.2 (141)*
RBC folate (nmol/L)	823, 268-2092 909 (410)	748, 146-2563 835 (446)
Low RBC folate (<317 nmol/L)	1.4 (1)	7.0 (13)
2-methylcitric acid (nmol/L)	204, 112-416 224 (74.5)	241, 97.0-703 267 (103)**
Vitamin B12 (pmol/L)	290, 73.7-847 313 (134)	330, 73.7-4830 402 (429)
Low vitamin B12 (<258 pmol/L)	37.7 (26)	36.2 (67)
Vitamin B12 deficiency [ii]	24.6 (17)	32.4 (60)
Pepsinogen (ng/mL)	78.3, -9.0-296 97.8 (74.2)	79.5, -9.0-300 91.4 (68.4)
Pepsinogen categories Severe atrophic gastritis (< 10 ng/mL) Moderate gastritis (10-59 ng/mL) No atrophic gastritis (≥ 60 ng/mL)	 8.8 (6) 19.1 (13) 72.1(49)	 6.0 (11) 27.5 (50) 66.5 (121)
MCV (fL)	91.0, 74.0-103 91.0 (5.2)	92.0, 71.0-135 91.5 (6.8)
BMI (kg/m^2)	26.2, 17.4-39.7 26.0 (4.3)	22.6, 15.1-35.2 22.6 (4.4)***

BMI classification Underweight (<18.5 kg/m^2) Normal (18.5-24.9 kg/m^2) Overweight (25.0-29.9 kg/m^2) Obesity (≥30 kg/m^2)	 2.9 (2) 39.1 (27) 46.4 (32) 11.6 (8)	 18.4 (34)*** 56.2 (104) 20.0 (37) 5.4 (10)
Nutrition score[iii]	2.0, 0.0-5.0 2.4 (1.1)	3.0, 0.0-5.0 3.1 (1.6)**
Servings of meat, poultry, fish/week	7.0, 0.0-14.0 7.8 (3.6)	7.0, 0.0-14.0 9.9 (4.7)
Servings of green vegetables/week	7.0, 1.0-14.0 7.6 (3.4)	7.0, 0.0-14.0 9.3 (4.3)
Medications - total number	6, 0-13 6 (3)	7, 0-15 7 (4)
Supplements [iv] Yes No	 42.0 (29) 58.0 (40)	 48.1 (89) 51.9 (96)
Disease score [v]	1.0, 0.0-5.0 1.3 (1.2)	1.0, 0.0-5.0 1.3 (1.0)

i. Estimated glomerular filtration rate formula:

For men: $\frac{(140\text{-age}) \times (\text{wt in kg})}{72\ (\text{serum creat in mg/dL})}$

For women: use men's formula result and multiply by 0.85

ii. Vitamin B12 deficiency: Serum B12 <258 pmol/L, methylmalonic acid >271 nmol/L, and 2, methylcitric acid level less than MMA.

iii. Nutrition score: one point for 2+ serving of meat, poultry/day; one point for 2+ serving of dairy/day; one point for 3+ servings fruit/day; one point for 3+ serving yellow/orange vegetables/week; one point for 4+ green vegetables/week. Points then summed for a nutrition score.

iv. Supplements: B-vitamin, B-vitamins + omega-3 fatty acids, herbals + vitamins, iron, minerals, multi-vitamin, multi-vitamin + calcium, multi-vitamin + iron, multi-vitamin + minerals, multi-vitamin + zinc, vitamin, vitamins + minerals, vitamins + zinc, vitamins; b complex + c.

v. Disease score: one point for a self-report of osteoporosis, chronic kidney disease, diabetes chronic airway obstruction, present cancer, hypertension, Parkinson's, and peripheral vascular disease. Points were then summed for a score.

* $p<0.05$

** $p<0.01$

***$p<0.001$

Table 3.2: Selected characteristics of Georgia Centenarian Study participants with and without anemia

	Anemia Median, Range, Mean (SD), or %(n)	**No Anemia Median, Range, Mean (SD), or %(n)**
Age (years)	99.3, 80.5-105.0 97.5 (6.4)	99.0, 80.5-108.6 95.0 (7.9)
Gender Male Female	 8.3 (21) 35.8 (91)	 11.8 (30) 44.1 (112)
Race White African American	 32.3 (82) 11.8 (30)	 48.8 (124)** 7.1 (18)
Living Arrangement Community/personal care Skilled nursing facility	 26.8 (68) 17.3 (44)	 31.8 (96) 18.1 (46)
Hemoglobin (g/dL)	11.1, 7.5-12.8 11.0 (0.9)	13.3, 12.0-16.7 13.4 (1.1)***
Hematocrit (%)	33.0, 22.7-38.8 32.5 (2.7)	39.6, 33.8-51.5 39.8 (3.3)***
Albumin (g/dL)	3.7, 2.6-4.4 3.6 (0.4)	3.9, 2.3-4.8 3.8 (0.4)***
Bun (mg/dL)	24.5, 8.0-63.0 26.3 (10.6)	20.0, 9.0-43.0 21.6 (7.7)***
CRP (mg/dL)	3.4, 0.4-106 9.9 (18.7)	3.2, 0.3-150 6.5 (13.7)*
Creatinine (mg/dL)	1.1, 0.5-2.5 1.1 (0.4)	1.0, 0.4-5.5 1.0 (0.5)
High creatinine (>1.4 mg/dL)	21.4 (24)	9.2 (13) **
EGFR (mL/min)[i]	27.3, 11.1-72.1 29.0 (12.7)	34.0, 7.9-107 37.8 (17.2)***
Low eGFR (<30 mL/min)	58.0 (65)	40.1 (57) **
Ferritin (ng/mL)	76.5, 1.6-1955 144 (238)	74.0, 10.0-480 96.0 (82.8)
Low ferritin (<12 ng/mL)	7.1 (8)	2.1 (3)

Low ferritin (<50 ng/mL)	41.1 (46)	35.2 (50)
MMA (nmol/L)	391, 144-8078 507 (772)	328, 174-1975 412 (276)*
MMA >271 (nmol/L)	68.3 (86)	76.8 (97)
RBC folate (nmol/L)	810, 146-2531 872 (442)	758, 192-2563 842 (434)
Low RBC folate (<140 nmol/L)	5.4 (6)	5.6 (8)
2-methylcitric acid (nmol/L)	256, 97.0-703 276 (102)	214, 122-618 238 (91.2)***
Vitamin B12 (pmol/L)	318, 73.7-2286 393 (313)	300, 73.7-4830 365 (417)
Low vitamin B12 (<258 pmol/L)	34.8 (39)	38.0 (54)
Vitamin B12 deficiency[ii]	31.0 (33)	29.5 (44)
Pepsin (ng/mL)	81.7, -9.0-262 99.2 (70.7)	75.6, -9.0-300 88.4 (69.3)
Pepsiongen Severe atrophic gastritis (< 10 ng/mL) Moderate gastritis (10-59 ng/mL) No atrophic gastritis (≥ 60 ng/mL)	 2.8 (7) 11.2 (28) 30.4 (76)	 4.0 (10) 14.0 (35) 37.6 (94)
MCV (fL)	91.0, 71.0-135 91.0 (7.9)	92.0, 80.0- 103 91.7 (4.8)
Abnormal MCV (<80 or >100 fL)	9.8 (11)	2.8 (4)*
Macrocytosis (>100 fL)	3.6 (4)	2.8 (4)
Microcytosis (<80 fL)	6.2 (7)	0.0 (0)***
BMI (kg/m^2)	22.7, 13.1-36.8 22.8 (4.6)	23.6, 14.0-39.7 24.1 (4.5)*
BMI classification Underweight (<18.5 kg/m^2) Normal (18.5-24.9 kg/m^2) Overweight (25.0-29.9 kg/m^2) Obesity (≥30 kg/m^2)	 8.7 (22) 22.0 (56) 11.0 (28) 2.4 (6)	 5.5 (14) 29.5 (75) 16.1 (41) 4.7 (12)
Nutrition score[iii]	3.0, 0.0-5.0 3.2 (1.5)	2.0, 0.0-5.0 2.7 (1.5)*

Servings of meat, poultry, fish/week	7.0,0.0-14.0, 9.6 (4.2)	7.0, 0.0-14.0, 9.0 (3.9)
Servings of green vegetables	7.0, 0.0-14.0, 9.1 (4.3)	7.0, 1.0-14.0, 8.6 (4.0)
Total number or medications	7, 0-15 7 (4)	7, 0-15 7 (4)
Supplement use (yes)[iv]	45.5 (51)	47.2 (67)
Disease score[v]	1.0, 0.0-5.0 1.4 (1.1)	1.0, 0.0-5.0 1.2 (1.1)

i. Estimated glomerular filtration rate formula:

For mMen: $\frac{(140\text{-age}) \times (\text{wt in kg})}{72 \times (\text{serum creat in mg/dL})}$

For women: use men's formula result and multiply by 0.85

iiVitamin B12 deficiency: Serum B12 <258 pmol/L, methylmalonic acid >271 nmol/L, and 2, methylcitric acid level less than MMA.

iii. Nutrition score: one point for 2+ serving of meat, poultry/day; one point for 2+ serving of dairy/day; one point for 3+ servings fruit/day; one point for 3+ serving yellow/orange vegetables/week; one point for 4+ green vegetables/week. Points then summed for a nutrition score.

iv. SupplementsB-vitamin, B-vitamins + omega-3 fatty acids, herbals + vitamins, iron, minerals, multi-vitamin, multi-vitamin + calcium, multi-vitamin + iron, multi-vitamin + minerals, multi-vitamin + zinc, vitamin, vitamins + minerals, vitamins + zinc, vitamins; b complex + c.

v. Disease score: one point for a self-report of osteoporosis, chronic kidney disease, diabetes chronic airway obstruction, present cancer, hypertension, Parkinson's, and peripheral vascular disease. Points were then summed for a score.

* $p<0.05$

** $p<0.01$

***$p<0.001$

Table 3.3: Selected characteristics of Georgia Centenarian Study participants with and without anemia, stratified by age group

	Octogenarian		**Centenarian**	
	With Anemia Median, Range, Mean (SD), or %(n)	**Without anemia Median, Range, Mean (SD), or %(n)**	**With anemia Median, Range, Mean (SD), or %(n)**	**Without anemia Median, Range, Mean (SD), or %(n)**
Age (years)	83.2, 80.5-90.1, 84.2 (3.1)	85.4, 80.5-90.0, 84.7 (2.8)	99.6, 98.1-105.0, 100.2 (1.7)	100.2, 98.1-108.6, 100.6 (1.9)
Gender				
Male	13.0 (3)	87.0 (20)*	64.3 (18)	35.7 (10)
Female	34.8 (16)	65.2 (30)	47.8 (75)	52.2 (82)
Race				
White	19.3 (11)	80.7 (46)**	47.6 (71)	52.4 (78)
African American	66.7 (8)	33.3 (4)	61.1 (22)	38.9 (14)
Living arrangement				
Skilled nursing facility	33.3 (4)	66.7 (8)	51.3 (40)	48.7 (38)
Community/personal care	26.3 (15)	73.7 (42)	49.5 (53)	50.5 (54)
Hemoglobin (g/dL)	11.2, 9.7-12.8, 11.2 (0.8)	13.8, 12.0-16.5, 13.9 (1.1)***	11.1, 7.5-12.6, 10.9 (1.0)	12.9, 12.0-16.7, 13.1 (0.9)***
Hematocrit (%)	33.3, 28.1-37.7, 33.2 (2.6)	41.0, 35.1-48.0, 41.2 (3.2)***	33.0, 22.7-38.8, 32.4 (2.8)	38.6, 33.8-51.5, 39.0 (3.2)
Albumin (g/dL)	3.9, 3.0-4.3, 3.8 (0.3)	4.1, 2.3-4.8, 4.0 (0.4)**	3.6, 2.6-4.4, 3.6 (0.4)	3.8, 2.9-4.7, 3.7 (0.3)**
BUN (mg/dL)	23.0, 10.0-48.0, 23.5 (8.8)	18.0, 9.0-43.0, 18.6 (5.7)*	25.0, 8.0-63.0, 26.8 (10.9)	21.5, 10.0-43.0, 23.3 (8.1)*
CRP (mg/dL)	4.4, 0.4-20.5, 5.4 (4.8)	2.0, 0.4-33.4, 4.1 (5.8)	3.2, 0.4-106.0, 10.0 (20.4)	3.6, 0.3-149.9, 7.8 (16.4)

Creatinine (mg/dL)	1.0, 0.7-2.1, 1.1 (0.3)	0.9, 0.6-1.9, 0.9 (0.2)	1.1, 0.5-2.5, 1.1 (0.4)	1.0, 0.5-5.5, 1.0 (0.6)*
High creatinine (>1.4 mg/dL)	10.5 (2)	6.0 (3)	23.7 (22)	10.9 (10)*
eGFR (mL/min)[i]	42.6, 17.3-72.1, 45.4 (16.5)	54.2, 28.8-107.4, 54.9 (16.0)*	23.9. 11.1-51.1, 25.6 (8.6)	27.6, 7.9-59.3, 28.5 (8.5)*
eGFR categories low (<30 mL/min)	15.8 (3)	2.0 (1)	66.7 (62)	60.9 (56)
Ferritin (ng/mL)	59.0, 8.0-1257, 166 (284)	70.5, 11.0-280, 86.0 (65.3)	80.0, 1.6-1955, 139 (231)	76.5, 10.0-409, 101 (90.7)
Low ferritin (<12 ng/mL)	10.5 (2)	2.0 (1)	39.8 (37)	34.8 (32)
Low ferritin (<50 ng/mL)	47.3 (9)	36.0 (18)	6.4 (6)	2.2 (2)
MMA (nmol/L)	303, 144-600, 326 (116)	304, 175-1130, 359 (221)	406, 163-8078, 544 (845)	352, 174-1975, 441 (299)
MMA >271 nmol/L	63.2 (12)	60.0 (30)	79.6 (74)	72.8 (67)
RBC folate (nmol/L)	808, 351-2052 882 (450)	849 268-2092 919 (399)	812, 146-2531 870 (443)	740, 192-2563 800 (448)
Low RBC folate (<140 nmol/L)	0.0 (0)	2.0 (1)	6.4 (6)	7.6 (7)
2-methyl citric acid (nmol/L)	234, 112-377, 250 (83.0)	192, 122-416, 214 (69.4)	256, 97.0-703, 282 (105)	224, 134-618, 251 (99.0)*
Vitamin B12 (pmol/L)	309, 191-576, 334 (113)	283, 73.7-847, 304 (142)	320, 73.7-2286, 405 (341)	345 73.7-4830, 398 (506)

Low vitamin B12 (<258 pmol/L)	31.6 (6)	40.0 (20)	35.5 (33)	37.0 (34)
Vitamin B12 deficiency[ii]	21.0 (4)	26.0 (13)	31.23 (29)	33.7 (31)
Pepsinogen (ng/mL)	86.0, 22.4-258, 110 (72.0)	76.2, -9.0-296, 92.9 (75.2)	81.2, -9-262, 96.9 (69.9)	75.1, -9.0-300, 85.9 (66.2)
Pepsinogen Severe atrophic gastritis (< 10 ng/mL) Moderate gastritis (10-59 ng/mL) No atrophic gastritis (≥ 60 ng/mL)	 0.0 (0) 26.3 (5) 73.7 (14)	 12.2 (6) 16.3 (8) 71.4 (35)	 7.6 (7) 25.0 (23) 67.4 (62)	 4.4 (4) 30.0 (27) 65.6 (59)
MCV (fL)	89.0, 74.0-100, 89.9 (6.0)	91.0, 80.0-103, 91.4 (4.9)	92.0, 71.0-135, 91.2 (8.3)	92.0, 80.0-102, 91.9 (4.8)
Platelets x 10^{-9}/L	241, 137-369, 250 (73.3)	215, 109-421, 225 (69.2)	212, 39.0-760, 228 (99.5)	224, 132-363, 236 (58.0)
Neutrophils x 10^{-3}/µL	3.6, 1.9-9.9, 4.2 (1.9)	4.0, 1.4-9.6, 4.3 (1.5)	3.8, 1.3-10.7, 4.3 (1.8)	4.10, 1.5-9.3, 4.5 (1.6)
Monocytes x 10^{-3}/µL	0.5, 0.1-1.1, 0.5 (0.2)	0.5, 0.2-1.0, 0.5 (0.2)	0.5, 0.0-1.8, 0.5 (0.3)	0.5, 0.0-1.9, 0.5 (0.3)
BMI (kg/m^2)	27.2, 17.4-36.8, 26.4 (4.6)	25.6, 18.3-39.7, 25.9 (4.3)	21.4, 13.1-31.7, 22.0 (4.2)	22.8, 14.0-35.2, 23.1 (4.4)
BMI categories Underweight (<18.5 kg/m^2) Normal (18.5-24.9 kg/m^2) Overweight (25.0-29.9 kg/m^2) Obesity (≥30 kg/m^2)	 5.3 (1) 31.7 (6) 47.4 (9) 15.8 (3)	 2.0 (1) 42.0 (21) 46.0 (23) 10.0 (5)	 22.6 (21) 53.8 (50) 20.4 (19) 3.2 (3)	 14.1 (13) 58.7 (54) 19.6 (18) 7.6 (7)
Nutrition score[iii]	2.0, 1.0-5.0, 2.6 (1.2)	2.0, 0.0-5.0, 2.4 (1.1)	3.0, 0.0-5.0, 3.3 (1.5)	2.5, 0.0-5.0, 2.9 (1.6)

Servings of meat, poultry, fish/ week	7.0, 0.0-14.0, 8.0 (3.6)	7.0, 0.0-14.0, 7.7 (3.6)	8.0, 0.0-14.0, 10.0 (1.7)	7.0, 2.0-8.0, 7.1 (1.2)
Servings of green vegetables/ week	7.0, 2.0-14.0, 7.5 (3.8)	7.0, 1.0-14.0 , 7.6 (3.3)	7.0, 0.0-14.0, 9.4 (4.4)	7.0, 1.0-14.0, 9.1 (4.4)
Total number of medications	8, 2-12 7 (3)	6, 0-13 6 (3)	7, 0-15 7 (4)	7, 0-15 7 (4)
Supplement use[iv] Yes No	 27.6 (8) 27.5 (11)	 72.4 (21) 72.5 (29)	 48.3 (43) 52.1 (50)	 51.7 (46) 47.9 (46)
Disease score[v]	1.0, 0.0-5.0 1.8 (1.4)	1.0, 0.0-5.0 1.2 (1.1)	1.0, 0.0-5.0 1.3 (1.0)	1.0, 0.0-4.0 1.3 (1.1)

i. Estimated glomerular filtration rate formula:

For men: $\frac{(140\text{-age}) \times (\text{wt in kg})}{72\ (\text{serum creat in mg/dL})}$

For women: use men's formula result and multiply by 0.85

ii. Vitamin B12 deficiency: Serum B12 <258 pmol/L, methylmalonic acid >271 nmol/L, and 2, methylcitric acid level less than MMA.

iii. Nutrition score: one point for 2+ serving of meat, poultry/day; one point for 2+ serving of dairy/day; one point for 3+ servings fruit/day; one point for 3+ serving yellow/orange vegetables/week; one point for 4+ green vegetables/week. Points then summed for a nutrition score.

iv. Supplements: B-vitamin, B-vitamins + omega-3 fatty acids, herbals + vitamins, iron, minerals, multi-vitamin, multi-vitamin + calcium, multi-vitamin + iron, multi-vitamin + minerals, multi-vitamin + zinc, vitamin, vitamins + minerals, vitamins + zinc, vitamins; b complex + c.

v. Disease score: one point for a self-report of osteoporosis, chronic kidney disease, diabetes chronic airway obstruction, present cancer, hypertension, Parkinson's, and peripheral vascular disease. Points were then summed for a score.

* $p<0.05$

** $p<0.01$

***$p<0.001$

Table 3.4: Distribution of classifications of anemia using a ferritin cut-off of <12 ng/mL in identifying those with iron deficiency anemia.

	Combined			Octogenarians			Centenarians		
Classification of Anemia	**Number**	**Percent of total analytical sample**	**Percent of Participants with anemia**	**Number**	**Percent of octogenarian participants**	**Percent of Octogenarians with anemia**	**Number**	**Percent of centenarian participants**	**Percent of Centenarians with anemia**
Nutritional Anemia	10	3.9	8.9	4	5.8	21.1	6	3.2	6.4 §
Anemia of chronic disease	53	20.1	47.3	6	8.7	31.6	47	25.4**	50.5
Unexplained anemia	18	7.1	16.1	7	10.1	36.8	11	6.0	11.8*
Combination anemia	31	12.2	27.7	2	2.9	10.5	29	15.7**	31.2 §
Total of all anemias	112	44.1	100	19	27.5	100	93	50.3	100

Percent of octogenarian participants was compared to percentage of centenarian participants with the use of Fisher's test. Similarly, the percent of octogenarians with anemia was compared to the percent of centenarians with anemia.

* $p<0.05$

**$p<0.01$

***$p<0.001$

§ trend ($p<0.09$)

Table 3.5: Distribution of classifications of anemia using a ferritin cut-off of <50 ng/mL in identifying those with iron deficiency anemia.

	Combined			Octogenarians			Centenarians		
Classification of Anemia	**Number**	**Percent of total analytical sample**	**Percent of Participants with anemia**	**Number**	**Percent of octogenarian participants**	**Percent of Octogenarians with anemia**	**Number**	**Percent of centenarian participants**	**Percent of Centenarians with anemia**
Nutritional anemia	19	7.5	17.0	7	10.1	36.8	12	6.5	12.9**
Anemia of chronic disease	35	13.8	31.2	4	5.8	21.0	31	16.8*	33.3
Unexplained anemia	9	3.5	8.0	4	5.8	21.0	5	2.7	5.4*
Combination anemia	49	19.3	43.8	4	5.8	21.0	45	24.3***	48.4*
Total of all anemias	112	44.1	100	19	27.5	99.8	93	50.3	100

Percent of octogenarian participants was compared to percentage of centenarian participants with the use of Fisher's test. Similarly, the percent of octogenarians with anemia was compared to the percent of centenarians with anemia.

* $p<0.05$

** $p<0.01$

***$P<0.001$

Table 3.6: Spearman correlation between variables of interest in total analytical sample

	Anemia	Age	African American	Nursing home	Female	Low albumin	Low ferritin	Low vitamin B12	High MMA	Low RBC folate	High CRP	High creatinine	Los eGFR	Low BMI	Disease score	Total medications
Anemia	1.00															
Age	0.20**	1.00														
African American	0.18**	0.02	1.00													
Nursing home	0.07	0.23***	0.10	1.00												
Female	0.03	0.20**	0.04	0.10	1.00											
Low albumin	0.22***	0.23***	0.04	0.21***	-0.02	1.00										
Low ferritin	0.12	-0.0005	-0.10	-0.08	0.01	0.01	1.00									
Low vitamin B12	-0.03	-0.01	-0.10	-0.10	-0.07	-0.05	-0.001	1.00								
High MMA	0.09	0.15*	-0.15	0.06	0.04	0.04	0.05	0.22***	1.00							
Low RBC folate	-0.01	0.11	0.06	0.04	-0.09	0.17**	-0.05	0.14*	0.07	1.00						
High CRP	-0.12	0.11	0.03	0.09	-0.03	0.27***	0.04	-0.11	0.03	0.10	1.00					
High creatinine	0.17**	0.13*	0.11	0.04	-0.10	0.12	-0.09	0.08	0.18**	-0.05	0.11	1.00				
Low eGFR	0.18**	0.52***	0.02	0.14*	0.19**	0.16*	-0.01	0.02	0.28***	0.01	0.05	0.36***	1.00			
Low BMI	0.14*	0.20**	-0.02	0.17**	0.15*	0.23***	-0.03	-0.10	0.05	0.001	0.09	-0.07	0.24***	1.00		
Disease score	0.08	-0.002	0.05	0.23***	0.14*	-0.03	0.01	-0.15*	0.05	-0.11	0.08	0.14	0.12	-0.02	1.00	
Total medications	0.09	0.08	-0.03	0.40***	0.08	0.04	-0.09	-0.16	0.04	-0.10	0.14*	0.09	0.08	0.03	0.42***	1.00

*p<0.05
**p<0.01
***p<0.001

Variables coded as follows: age (1 = ≥ 98) gender (1 = female), race (1 = black), nursing home (1 = nursing home), low albumin (1 = <3.6 g/dL), low ferritin (1 = <12 ng/mL), low vitamin B12 (1 = <258 pmol/L), high MMA (1 = >271 nmol/L), low RBC folate (1 = <140 nmol/L), high CRP (1 = >5.0 mg/L), high creatinine (1 = >1.4 mg/dL), low eGFR (1 = <30 mL/min), low BMI (1 = <18.5 kg/m^2), disease score (One point for a self-report of osteoporosis, chronic kidney disease, diabetes chronic airway obstruction, present cancer, hypertension, Parkinson's, and peripheral vascular disease. Points were then summed for a score.), total number medications.

Table 3.7: Spearman correlation between variables of interest in octogenarians

	Anemia	African American	Nursing home	Female	Low albumin	Low ferritin	Low vitamin B12	High MMA	Low RBC folate	High CRP	High creatinine	Low eGFR	Low BMI	Disease score	Total medications
Anemia	1.00														
African American	0.40***	1.00													
Nursing home	0.06	0.09	1.00												
Female	0.22	0.08	0.08	1.00											
Low albumin	0.16	0.13	0.27*	0.00	1.00										
Low ferritin	0.19	-0.10	0.09	0.15	-0.06	1.00									
Low vitamin B12	-0.08	-0.12	-0.12	-0.02	-0.03	0.13	1.00								
High MMA	0.03	-0.02	0.13	0.06	0.04	0.02	0.07	1.00							
Low RBC folate	-0.07	-0.06	0.26*	-0.17	-0.04	-0.02	0.16	0.10	1.00						
High CRP	0.13	0.14	0.06	0.02	0.39**	0.03	-0.08	0.03	-0.07	1.00					
High creatinine	0.08	0.02	0.02	-0.04	0.11	-0.06	0.13	0.11	-0.03	0.08	1.00				
Low eGFR	0.26*	0.05	0.05	0.18	0.14	-0.05	-0.06	0.07	-0.03	0.12	0.41***	1.00			
Low BMI	0.09	-0.08	-0.08	0.12	0.25*	-0.04	-0.13	0.14	-0.02	0.09	0.28*	0.33**	1.00		
Disease score	0.22	0.14	0.03	0.26*	-0.09	0.08	-0.20	0.01	-0.02	0.06	0.14	0.22	-0.04	1.00	
Total medications	0.21	0.10	0.44***	0.15	0.20	0.01	-0.16	-0.08	0.09	0.08	0.10	0.14	0.16	0.24*	1.00

*p<0.05
**p<0.01
***p<0.001

Variables coded as follows: age (1 = ≥ 98) gender (1 = female), race (1 = black), nursing home (1 = nursing home), low albumin (1 = <3.6 g/dL), low ferritin (1 = <12 ng/mL), low vitamin B12 (1 = <258 pmol/L), high MMA (1 = >271 nmol/L), low RBC folate (1 = <140 nmol/L), high CRP (1 = >5.0 mg/L), high creatinine (1 = >1.4 mg/dL), low eGFR (1 = <30 mL/min), low BMI (1 = <18.5 kg/m^2), disease score (One point for a self-report of osteoporosis, chronic kidney disease, diabetes chronic airway obstruction, present cancer, hypertension, Parkinson's, and peripheral vascular disease. Points were then summed for a score.), total number medications.

Table 3.8: Spearman correlation between variables of interest in centenarians

	Anemia	African American	Nursing home	Female	Low albumin	Low ferritin	Low vitamin B12	High MMA	Low RBC folate	High CRP	High creatinine	Low eGFR	Low BMI	Disease score	Total medications
Anemia	1.00														
African American	0.11	1.00													
Nursing home	0.02	0.11	1.00												
Female	0.12	0.02	0.06	1.00											
Low albumin	0.19**	0.02	0.14	-0.10	1.00										
Low ferritin	0.11	-0.10	-0.13	-0.06	0.02	1.00									
Low vitamin B12	-0.02	-0.09	-0.10	-0.09	-0.06	-0.05	1.00								
High MMA	0.08	-0.21	-0.01	-0.02	0.0001	0.06	0.29***	1.00							
Low RBC folate	-0.02	0.08	-0.02	-0.12	0.17*	-0.06	0.14*	0.05	1.00						
High CRP	-0.04	-0.006	0.07	-0.09	0.23**	0.04	-0.12	0.009	0.12	1.00					
High creatinine	0.17*	0.14	0.01	-0.16*	0.08	-0.10	0.07	0.19*	-0.07	0.10	1.00				
Low eGFR	0.06	0.001	0.03	0.09	0.03	-0.006	0.05	0.29***	-0.06	-0.04	0.34***	1.00			
Low BMI	0.11	-0.02	0.16*	0.12	0.18*	-0.03	-0.10	0.003	-0.02	0.07	-0.14	0.15*	1.00		
Disease score	0.04	0.02	0.30***	0.08	-0.02	-0.01	-0.13	0.07	-0.11	0.09	0.14	0.14	-0.02	1.00	
Total medications	0.04	-0.08	0.38***	0.04	-0.01	-0.12	-0.15*	0.07	-0.15	0.15*	0.08	0.02	-0.01	0.49***	1.00

*p<0.05
**p<0.01
***p<0.001

Variables coded as follows: age (1 = ≥ 98) gender (1 = female), race (1 = black), nursing home (1 = nursing home), low albumin (1 = <3.6 g/dL), low ferritin (1 = <12 ng/mL), low vitamin B12 (1 = <258 pmol/L), high MMA (1 = >271 nmol/L), low RBC folate (1 = <140 nmol/L), high CRP (1 = >5.0 mg/L), high creatinine (1 = >1.4 mg/dL), low eGFR (1 = <30 mL/min), low BMI (1 = <18.5 kg/m^2), disease score (One point for a self-report of osteoporosis, chronic kidney disease, diabetes chronic airway obstruction, present cancer, hypertension, Parkinson's, and peripheral vascular disease. Points were then summed for a score.), total number medications.

Table 3.9: Multivariate regression analysis exploring predictors of anemia: octogenarians and centenarians combined (ferritin<12 ng/mL was used to identify those with iron deficiency)

	Model 1			**Model 2**			**Model 3**		
Variable	b	Odds Ratio (95% CI)	p	b	Odds Ratio (95% CI)	P	b	Odds Ratio (95% CI)	p
Centenarian	1.00	2.72 (1.44-5.5)	0.002	0.79	2.21 (1.13-4.31)	0.021	0.79	2.20 (1.10-4.42)	0.026
Female	-0.11	0.90 (0.46-1.75)	0.755	0.04	1.04 (0.51-2.10)	0.917	-0.12	0.88 (0.42-1.83)	0.736
African American	0.94	2.56 (1.31-4.99)	0.006	0.97	2.64 (1.31-5.20)	0.006	1.08	2.96 (1.45-6.04)	0.003
Skilled nursing facility	0.04	1.04 (0.60-1.80)	0.890	-0.04	0.96 (0.54-1.71)	0.882	-0.32	0.72 (0.38-1.39)	0.328
Low albumin (<3.6 g/dL)				0.94	2.55 (1.32-4.90)	0.005	0.93	2.54 (1.29-4.98)	0.007
High CRP (>5.0mg/L)				-0.33	0.72 (0.40-1.29)	0.269	-0.46	0.63 (0.34-1.16)	0.141
High creatinine (>1.4 mg/dL)				0.86	2.37 (1.08-5.19)	0.031	0.83	2.30 (1.03-5.13)	0.043
Low ferritin (<12 ng/mL)				1.70	5.47 (1.33-22.5)	0.019	1.86	6.45 (1.54-27.0)	0.011
B12 deficiency[i]				-0.10	0.90 (0.50-1.62)	0.726	-0.03	0.97 (0.53-1.78)	0.922
Disease score[ii]							0.09	1.10 (0.82-1.46)	0.526
# medications							0.08	1.08 (0.99-1.18)	0.092
# supplements[iii]							-0.28	0.76 (0.42-1.38)	0.364
Low BMI (<18.5 kg/m^2)							0.73	2.08 (0.93-4.68)	0.075
Intercept	-1.09		0.02	-1.31			-1.73		0.0004

Model 1: demographics (age, gender, race, residence)
Model 2: demographics and biological (albumin, crp, creatinine, ferritin, B12 deficiency)
Model 3: demographics, biological, and other (low BMI, disease score, medications, supplements)
i. Vitamin B12 deficiency: Serum B12 <258 pmol/L, methylmalonic acid >271 nmol/L, and 2, methylcitric acid level less than MMA.
ii. One point given for current conditions and summed. Diseases include: osteoporosis, chronic kidney disease, congestive heart failure, diabetes, chronic airway obstruction, cancer, hypertension, Parkinson's, and peripheral vascular disease.
iii. Supplements: B-vitamin, B-vitamins + omega-3 fatty acids, herbals + vitamins, iron, minerals, multi-vitamin, multi-vitamin + calcium, multi-vitamin + iron, multi-vitamin + minerals, multi-vitamin + zinc, vitamin, vitamins + minerals, vitamins + zinc, vitamins; b complex + c.

Table 3.10: Multivariate regression analysis exploring predictors of anemia: centenarians (ferritin<12 ng/mL was used to identify those with iron deficiency)

	Model 1			**Model 2**			**Model 3**		
Variable	b	Odds Ratio (95% CI)	p	b	Odds Ratio (95% CI)	p	b	Odds Ratio (95% CI)	p
Female	-0.70	0.50 (0.21-1.15)	0.103	-0.52	0.60 (0.24-1.46)	0.258	-0.62	0.54 (0.22-1.34)	0.182
African American	0.56	1.75 (0.82-3.70)	0.146	0.51	1.67 (0.76-3.69)	0.205	0.64	1.89 (0.83-4.32)	0.129
Skilled nursing facility	0.05	1.06 (0.58-1.91)	0.860	0.02	1.02 (0.54-1.91)	0.962	-0.19	0.83 (0.40-1.70)	0.608
Low albumin (<3.6 g/dL)				0.88	2.42 (1.22-4.82)	0.012	0.85	2.35 (1.16-4.76)	0.018
High CRP (>5.0mg/L)				-0.50	0.60 (0.31-1.16)	0.132	-0.64	0.53 (0.26-1.04)	0.066
High creatinine (>1.4 mg/dL)				0.89	2.42 (1.03-5.74)	0.046	0.997	2.71 (1.11-6.61)	0.028
Low ferritin (<12 ng/mL)				1.38	3.97 (0.74-21.2)	0.107	1.57	4.79 (0.87-26.4)	0.072
B12 deficiency[i]				-0.10	0.90 (0.46-1.76)	0.764	-0.05	0.95 (0.48-1.99)	0.892
Disease score[ii]							-0.02	0.98 (0.69-1.28)	0.900
# medications							0.07	1.08 (0.97-1.91)	0.156
# supplements[iii]							-0.39	0.68 (0.34-1.32)	0.251
Low BMI (<18.5 kg/m^2)							0.80	2.22 (0.96-5.14)	0.061
Intercept	0.48		0.248	0.093		0.853	-0.20		0.73

Model 1: demographics (age, gender, race, residence)
Model 2: demographics and biological (albumin, crp, creatinine, ferritin, B12 deficiency)
Model 3: demographics, biological, and other (low BMI, disease score, medications, supplements)

i. Vitamin B12 deficiency: Serum B12 <258 pmol/L, methylmalonic acid >271 nmol/L, and 2, methylcitric acid level less than MMA.
ii. One point given for current conditions and summed. Diseases include: osteoporosis, chronic kidney disease, congestive heart failure, diabetes, chronic airway obstruction, cancer, hypertension, Parkinson's, and peripheral vascular disease.
iii. Supplements: B-vitamin, B-vitamins + omega-3 fatty acids, herbals + vitamins, iron, minerals, multi-vitamin, multi-vitamin + calcium, multi-vitamin + iron, multi-vitamin + minerals, multi-vitamin + zinc, vitamin, vitamins + minerals, vitamins + zinc, vitamins; b complex + c.

Table 3.11: Multivariate regression analysis exploring predictors of anemia: octogenarians (ferritin<12 ng/mL was used to identify those with iron deficiency)

	Model 1			**Model 2**			**Model 3**		
Variable	b	Odds Ratio (95% CI)	p	b	Odds Ratio (95% CI)	p	b	Odds Ratio (95% CI)	p
Female	1.30	3.66 (0.84-16.0)	0.084	1.13	3.09 (0.70-13.7)	0.138	0.73	2.07 (0.41-10.4)	0.377
African American	2.14	8.50 (2.03-35.6)	0.003	2.31	10.08 (2.23-45.7)	0.003	2.70	4.96 (2.52-38.7)	0.003
Skilled nursing facility	0.08	1.09 (0.24-4.86)	0.911	-0.30	0.74 (0.14-3.96)	0.722	-0.67	0.51 (0.08-3.45)	0.492
Low albumin (<3.6 g/dL)				1.14	3.314 (0.25-39.1)	0.375	1.05	2.85 (0.22-37.3)	0.424
High CRP (>5.0mg/L)				-0.01	0.99 (0.21-4.60)	0.993	0.20	1.22 (0.25-5.96)	0.806
High creatinine (>1.4 mg/dL)				0.77	2.12 (0.22-21.4)	0.512	0.40	1.49 (0.11-19.6)	0.763
Low ferritin (<12 ng/mL)				2.26	9.61 (0.70-131.9)	0.090	2.52	12.42 (0.80-192)	0.072
B12 deficiency[i]				-0.50	0.60 (0.13-2.78)	0.517	0.22	1.24 (0.21-7.51)	0.811
Disease score[i]							0.55	1.73 (0.86-3.46)	0.123
# medications							0.06	1.07 (0.83-3.46)	0.608
# supplements[ii]							1.13	3.09 (0.52-18.5)	0.217
Low BMI (<18.5 kg/m^2)							1.43	4.18 (0.09-196)	0.467
Intercept	-2.40		0.0008	-0.24		0.001	-4.14		0.002

Model 1: demographics (age, gender, race, residence)
Model 2: demographics and biological (albumin, crp, creatinine, ferritin, B12 deficiency)
Model 3: demographics, biological, and other (low BMI, disease score, medications, supplements)
i. Vitamin B12 deficiency: Serum B12 <258 pmol/L, methylmalonic acid >271 nmol/L, and 2, methylcitric acid level less than MMA.
ii. One point given for current conditions and summed. Diseases include: osteoporosis, chronic kidney disease, congestive heart failure, diabetes, chronic airway obstruction, cancer, hypertension, Parkinson's, and peripheral vascular disease.
iii. Supplements: B-vitamin, B-vitamins + omega-3 fatty acids, herbals + vitamins, iron, minerals, multi-vitamin, multi-vitamin + calcium, multi-vitamin + iron, multi-vitamin + minerals, multi-vitamin + zinc, vitamin, vitamins + minerals, vitamins + zinc, vitamins; b complex + c.

Table 3.12: Stepwise regression analysis exploring predictors of anemia in octogenarians and centenarians combined

	Centenarians and Octogenarians, combined			**Centenarians**			**Octogenarians**		
Step entered	Variable	Odds Ratio (95% CI)	p	Variable	Odds Ratio (95% CI)	p	Variable	Odds Ratio (95% CI)	p
1	Centenarian	2.16 (1.13-4.11)	0.019	Low albumin (<3.6 g/dL)	2.25 (1.18-4.30)	0.014	African American	8.98 (2.19-36.8)	0.002
2	African American	2.62 (1.32-5.21)	0.006	High creatinine (>1.4 mg/dL)	2.41 (1.06-5.50)	0.037	Low eGFR (<30 mL/min)	9.48 (0.94-125)	0.056
3	Low albumin (<3.6 g/dL)	2.31 (1.24-4.30)	0.008						
4	High creatinine (>1.4 mg/dL)	2.24 (1.04-4.84)	0.040						
5	Low ferritin (<12 ng/mL)	5.34 (1.30-21.9)	0.020						

Table 3.13: Multivariate regression analysis exploring predictors of anemia: octogenarians and centenarians combined (ferritin<50 ng/mL was used to identify those with iron deficiency)

	Model 1			**Model 2**			**Model 3**		
Variable	b	Odds Ratio (95% CI)	p	b	Odds Ratio (95% CI)	p	b	Odds Ratio (95% CI)	p
Centenarian	1.00	2.72 (1.44-5.5)	0.002	0.80	2.22 (1.14-4.31)	0.019	0.80	2.22 (1.12-4.42)	0.023
Female	-0.11	0.90 (0.46-1.75)	0.755	-0.008	0.99 (0.49-2.00)	0.982	-0.16	0.85 (0.41-1.75)	0.654
African American	0.94	2.56 (1.31-4.99)	0.006	0.91	2.48 (1.24-4.98)	0.01	1.00	2.73 (1.34-5.55)	0.006
Skilled nursing facility	0.04	1.04 (0.60-1.80)	0.890	-0.08	0.92 (0.53-1.65)	0.782	-0.34	0.71 (0.37-1.35)	0.299
Low albumin (<3.6 g/dL)				0.92	2.51 (1.31-4.80)	0.005	0.92	2.50 (1.28-4.87)	0.007
High CRP (>5.0mg/L)				-0.26	0.77 (0.43-1.38)	0.383	-0.37	0.69 (0.38-1.26)	0.229
High creatinine (>1.4 mg/dL)				0.78	2.18 (1.00-4.75)	0.049	0.73	2.08 (0.94-4.63)	0.071
Low ferritin (<50 ng/mL)				0.35	1.41 (0.81-2.46)	0.220	0.36	1.43 (0.82-2.52)	0.211
B12 deficiency[i]				-0.12	0.89 (0.50-1.59)	0.690	-0.05	0.95 (0.52-1.73)	0.864
Disease score[i]							0.11	1.11 (0.84-1.48)	0.457
# medications							0.06	1.07 (0.98-1.17)	0.142
# supplements[ii]							-0.25	0.78 (0.43-1.40)	0.397
Low BMI (<18.5 kg/m^2)							0.67	1.95 (0.88-4.33)	0.100
Intercept	-1.09		0.02	-1.32		0.0012	-1.69		0.0006

Model 1: demographics (age, gender, race, residence)
Model 2: demographics and biological (albumin, crp, creatinine, ferritin, B12 deficiency)
Model 3: demographics, biological, and other (low BMI, disease score, medications, supplements)
i. Vitamin B12 deficiency: Serum B12 <258 pmol/L, methylmalonic acid >271 nmol/L, and 2, methylcitric acid level less than MMA.
ii. One point given for current conditions and summed. Diseases include: osteoporosis, chronic kidney disease, congestive heart failure, diabetes, chronic airway obstruction, cancer, hypertension, Parkinson's, and peripheral vascular disease.
iii. Supplements: B-vitamin, B-vitamins + omega-3 fatty acids, herbals + vitamins, iron, minerals, multi-vitamin, multi-vitamin + calcium, multi-vitamin + iron, multi-vitamin + minerals, multi-vitamin + zinc, vitamin, vitamins + minerals, vitamins + zinc, vitamins; b complex + c.

Table 3.14: Multivariate regression analysis exploring predictors of anemia: centenarians (ferritin<50 ng/mL was used to identify those with iron deficiency)

	Model 1			**Model 2**			**Model 3**		
Variable	b	Odds Ratio (95% CI)	p	b	Odds Ratio (95% CI)	p	b	Odds Ratio (95% CI)	p
Female	-0.70	0.50 (0.21-1.15)	0.103	-0.57	0.56 (0.23-1.37)	0.204	-0.68	0.50 (0.20-1.24)	0.137
African American	0.56	1.75 (0.82-3.70)	0.146	0.49	1.60 (0.72-3.52)	0.245	0.57	1.77 (0.78-4.02)	0.170
Skilled nursing facility	0.05	1.06 (0.58-1.91)	0.860	-0.04	0.97 (0.52-1.81)	0.909	-0.24	0.79 (0.39-1.61)	0.515
Low albumin (<3.6 g/dL)				0.90	2.45 (1.24-4.86)	0.01	0.86	2.37 (1.18-4.80)	0.016
High CRP (>5.0mg/L)				-0.44	0.64 (0.33-1.24)	0.191	-0.56	0.57 (0.29-1.13)	0.110
High creatinine (>1.4 mg/dL)				0.83	2.29 (0.97-5.41)	0.058	0.92	2.51 (1.03-6.08)	0.042
Low ferritin (<50 ng/mL)				0.28	1.33 (0.71-2.50)	0.378	0.30	1.35 (0.71-2.57)	0.367
B12 deficiency[i]				-011	0.90 (0.46-1.74)	0.748	-0.06	1.94 (0.48-1.85)	0.845
Disease score[i]							-0.003	1.00 (0.71-1.40)	0.986
# medications							0.06	1.06 (0.96-1.18)	0.217
# supplements[ii]							-0.36	0.70 (0.36-1.36)	0.294
Low BMI (<18.5 kg/m^2)							0.76	2.14 (0.93-4.90)	0.073
Intercept	0.48		0.248	0.10		0.838	-0.14		0.809

Model 1: demographics (age, gender, race, residence)
Model 2: demographics and biological (albumin, crp, creatinine, ferritin, B12 deficiency)
Model 3: demographics, biological, and other (low BMI, disease score, medications, supplements)
i. Vitamin B12 deficiency: Serum B12 <258 pmol/L, methylmalonic acid >271 nmol/L, and 2, methylcitric acid level less than MMA.
ii. One point given for current conditions and summed. Diseases include: osteoporosis, chronic kidney disease, congestive heart failure, diabetes, chronic airway obstruction, cancer, hypertension, Parkinson's, and peripheral vascular disease.
iii. Supplements: B-vitamin, B-vitamins + omega-3 fatty acids, herbals + vitamins, iron, minerals, multi-vitamin, multi-vitamin + calcium, multi-vitamin + iron, multi-vitamin + minerals, multi-vitamin + zinc, vitamin, vitamins + minerals, vitamins + zinc, vitamins; b complex + c.

Table 3.15: Multivariate regression analysis exploring predictors of anemia: octogenarians (ferritin<50 ng/mL was used to identify those with iron deficiency)

	Model 1			**Model 2**			**Model 3**		
Variable	b	Odds Ratio (95% CI)	p	b	Odds Ratio (95% CI)	p	b	Odds Ratio (95% CI)	p
Female	1.30	3.66 (0.84-16.0)	0.084	1.08	2.96 (0.65-13.5)	0.162	0.70	2.02 (0.39-10.5)	0.406
African American	2.14	8.50 (2.03-35.6)	0.003	2.30	9.98 (2.10-47.5)	0.004	2.63	13.83 (2.30-83.0)	0.004
Skilled nursing facility	0.08	1.09 (0.24-4.86)	0.911	-0.08	0.92 (0.19-4.43)	0.920	-0.37	0.69 (0.12-4.16)	0.687
Low albumin (<3.6 g/dL)				0.86	2.36 (0.20-27.2)	0.492	0.71	2.04 (0.15-22.1)	0.588
High CRP (>5.0mg/L)				0.10	1.10 (0.26-4.66)	0.895	0.23	1.26 (0.28-5.60)	0.761
High creatinine (>1.4 mg/dL)				0.42	1.53 (0.16-14.3)	0.710	-0.01	0.99 (0.08-5.60)	0.991
Low ferritin (<50 ng/mL)				0.71	2.03 (0.52-7.95)	0.309	0.70	2.00 (0.46-8.80)	0.358
B12 deficiency[i]				-0.54	0.58 (0.13-2.58)	0.476	0.06	1.06 (0.19-6.04)	0.947
Disease score[i]							0.52	1.68 (0.86-3.28)	0.126
# medications							0.05	1.05 (0.82-1.35)	0.681
# supplements[ii]							0.98	2.68 (0.49-14.5)	0.256
Low BMI (<18.5 kg/m^2)							1.51	4.51 (0.10-211)	0.443
Intercept	-2.40		0.0008	-2.55		0.001	-4.03		0.001

Model 1: demographics (age, gender, race, residence)
Model 2: demographics and biological (albumin, crp, creatinine, ferritin, B12 deficiency)
Model 3: demographics, biological, and other (low BMI, disease score, medications, supplements)
i. Vitamin B12 deficiency: Serum B12 <258 pmol/L, methylmalonic acid >271 nmol/L, and 2, methylcitric acid level less than MMA.
ii. One point given for current conditions and summed. Diseases include: osteoporosis, chronic kidney disease, congestive heart failure, diabetes, chronic airway obstruction, cancer, hypertension, Parkinson's, and peripheral vascular disease.
iii. Supplements: B-vitamin, B-vitamins + omega-3 fatty acids, herbals + vitamins, iron, minerals, multi-vitamin, multi-vitamin + calcium, multi-vitamin + iron, multi-vitamin + minerals, multi-vitamin + zinc, vitamin, vitamins + minerals, vitamins + zinc, vitamins; b complex + c

CHAPTER 4

CONCLUSION

The aims of this study were to 1) determine the overall prevalence of anemia for octogenarian and centenarian participants of the Georgia Centenarian Study, 2) determine the proportion and prevalence of anemia attributable to nutritional anemia, anemia of chronic disease, combination anemia, and unexplained anemia within each age group and determine if there are significant differences between the centenarians and octogenarians, and 3) determine potential predictors, including demographic and health factors, of anemia in centenarians and octogenarians. It was hypothesized that 1) there would be a higher prevalence of anemia in the centenarians than in the octogenarians, 2) there would be a higher proportion and prevalence of "unexplained" anemia in the Georgia centenarians than in the octogenarians, and 3) being male, being older, being African American, having a higher creatinine level, having a lower BMI, and having a lower albumin level would be independent predictors of anemia in multivariate regression analysis.

Results of this study confirm the hypothesis that centenarians have a higher prevalence of anemia than octogenarians. Over fifty percent of the centenarians (50.3%) were found to have anemia, while 27.5% of the octogenarians had anemia. However, results from this study were contrary to the hypothesis of a higher prevalence and proportion of unexplained anemia in centenarians and, in this regard, contrary to other studies (Artz et al., 2004, Makipour et al., review, 2008). In this study, a lower proportion of unexplained anemia and a higher prevalence of anemia of chronic disease and combination anemia (anemia of chronic disease and nutritional

anemia) were found in the centenarians than in the octogenarians. The difference in the proportions of anemia between the centenarians and octogenarians is important to note because it indicates that generalizing anemia in everyone over sixty-five or eighty-five may be misleading and fails to adequately characterize anemia in those who are very old.

The prevalence of anemia of chronic disease in the centenarians was 25.4%, and was even higher (41.1%) when those with combination anemia were included. The prevalence of anemia of chronic disease in the octogenarians was only 11.6% when both anemia of chronic disease and combination anemia were included. Chronic disease is very common among older individuals, and becomes even more common as people age (American Geriatrics Society, 2009), a trend that mirrors the higher prevalence of anemia in the centenarians than in the octogenarians. The much higher prevalence of anemia in the centenarians emphasizes the importance of preventing and managing chronic disease in older individuals, especially considering the increasing number of centenarians, as well as the decreased quality of life and increased financial costs associated with anemia.

Nutritional anemia is also a consideration in older individuals, particularly in centenarians. The prevalence of nutritional anemia was 5.8% in octogenarians, and was only 3.2% in centenarians. When including those with combination anemia octogenarians had an 8.7% prevalence of nutritional anemia, and centenarians had a prevalence of 18.9%. These results indicate that there is a need to monitor nutritional status as people age, especially for those with chronic disease.

The high prevalence of anemia is particularly concerning, especially considering that many of the participants may have been unaware of their anemic status. In a previous study reporting chronic disease in Georgia Centenarian Study participants (Poon et al., in press), the

prevalence of anemia, based on self-report, was reported as 3% in the octogenarians and 10% in the centenarians. These figures are much lower than the prevalence of anemia, based on blood hemoglobin levels, reported in this study. As evident from these figures, anemia in older individuals is a condition that needs to be both screened for and monitored. Furthermore, older adults or their caretakers need to be made aware of the individual's anemia, so preventative or therapeutic measures can be implemented.

Predictors of anemia were analyzed with multivariate regression analysis. In the centenarians, having low albumin and high creatinine were both found to be predictors of anemia, and in the octogenarians, being African American was predictive of having anemia. In combined analysis of octogenarians and centenarians, having low albumin, being African American, being a centenarian, having low ferritin, and high creatinine were predictive of having anemia. These findings, particularly with creatinine and albumin as predictors, again suggest the importance of disease management and prevention as a means to control anemia in older populations.

Anemia is a major health issue, particularly as people age. Because of the high prevalence of anemia in the very old, awareness of the classifications and predictors of anemia is important. Better awareness could help to better manage and reduce the negative consequences of this condition, to reduce associated health care costs and to improve health-related quality of life in these older adults.

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