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## **Anemia in old age**

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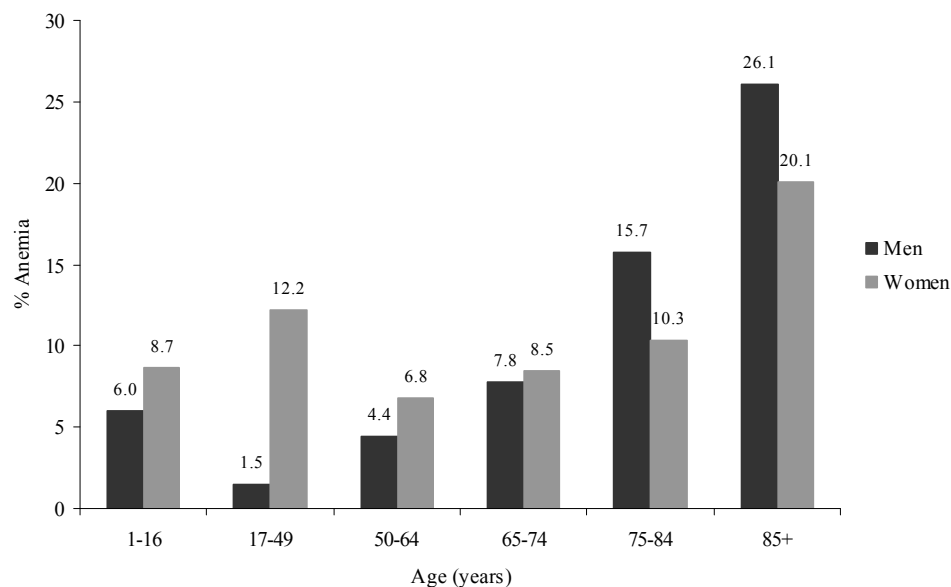
General introduction



For many years, researchers and clinicians have had a long-lasting and continuous interest in the clinical implications and pathophysiology of anemia in older individuals. Yet, to date, the consequences and underlying pathophysiological mechanisms of anemia in the oldest old in the general population at large are still under debate. Therefore, the aim of this thesis is to study the impact and etiology of anemia in older individuals in the general population.

## THE IMPACT OF ANEMIA

Anemia can be defined as a reduction in the quantity of hemoglobin. Anemia is very common in older individuals. The reported prevalence ranges from <3% in healthy persons aged 65 years and over to 61% in older patients newly admitted to geriatric wards.<sup>1,2</sup> These numbers not only diverge because of various definitions of anemia, but also because of large differences in study populations with respect to gender, age, race, living situation, and health status.<sup>1,2</sup> In the Third National Health and Nutrition Examination Survey (NHANES III), a nationally representative study of non-institutionalized civilian adults in the United States, the overall prevalence of anemia among adults aged 65 years and older was 11.0% in men and 10.2% in women.<sup>3</sup> For this study anemia was defined according to World Health Organization criteria (hemoglobin concentration less than 12 g/dL (7.5 mmol/L) in women and less than 13 g/dL (8.1 mmol/L) in men<sup>4</sup>). Interestingly, the prevalence of anemia increased significantly with age, up to 26.1% in men and 20.1% in women aged 85 years and over (Figure 1).<sup>3</sup>



**Figure 1.** Prevalence of anemia according to age and gender in NHANES III (adapted from Guralnik et al. Blood 2004;104(8):2263-2268)<sup>3</sup>

In older persons, anemia is associated with impaired survival,<sup>5-9</sup> and also with decreased physical performance, disability in daily living, cognitive impairment, depression, diminished quality of life, and an increased number of hospital admissions.<sup>1;10-20</sup>

In the Netherlands, the proportion of persons aged 80 years and over is expected to increase from 1 in 27 in the year 2009 up to 1 in 10 in the year 2050. In 2050, 1.75 million persons will be aged 80 years and over.<sup>21</sup> This exponential rise in the number of very old individuals with time, in combination with the steep increase in the prevalence of anemia in old age, indicates that anemia in the oldest old will have a significant effect on healthcare needs and costs in the decades to come.<sup>22</sup>

## THE ETIOLOGY OF ANEMIA

Anemia may be caused by a number of different conditions, among which iron deficiency, (undetected) blood loss, vitamin B12 deficiency, folate deficiency, renal failure, chronic disease and inflammation are commonly identified in older persons with anemia.<sup>3</sup>

Red blood cell production requires an adequate supply of iron, vitamin B12, and folate. Iron is an important component of hemoglobin, the oxygen carrying molecule within red blood cells. Evidence of deficiencies in iron, vitamin B12 and folate can be found in about one third of older persons with anemia.<sup>3;23;24</sup> In older adults, iron deficiency is sometimes related to impaired dietary intake of iron, but usually results from occult gastrointestinal blood loss.<sup>25;26</sup> Pernicious anemia or malabsorption of food-bound vitamin B12 are the prime causes of vitamin B12 deficiency in older adults.<sup>25;26</sup> Folate deficiency is most often caused by poor dietary intake and alcohol abuse.<sup>25;26</sup>

Erythropoietin is primarily produced by the kidney and is the principal regulator of red blood cell production.<sup>27-30</sup> Erythropoietin is required for the maintenance of committed erythroid progenitor cells that, in the absence of erythropoietin, undergo programmed cell death (apoptosis).<sup>29</sup> Erythropoietin production is impaired in patients with chronic kidney disease or renal failure.<sup>24;31</sup> Renal failure (creatinine clearance <30 mL/min) is found in 12% of older individuals with anemia.<sup>3</sup>

Patients with chronic inflammatory diseases, such as infectious diseases, autoimmune diseases and cancer, often develop anemia. The exact pathophysiological mechanism is not clear, but the 'anemia of chronic disease' or the 'anemia of inflammation' is likely to be mediated by immune-driven processes.<sup>32-35</sup> Inflammation may hamper erythropoiesis by inhibiting erythropoietin production, by inhibiting proliferation and differentiation of erythroid progenitor cells or by down-regulating the response to erythropoietin (erythropoietin resistance).<sup>36;37</sup> Another plausible, but yet hypothetical, mechanism for the development of anemia of inflammation is the upregulation of hepcidin -

the main regulator of iron homeostasis - by pro-inflammatory cytokines.<sup>38</sup> Hepcidin induces the degradation of ferroportin, the iron efflux channel on the surface of absorptive enterocytes, macrophages and hepatocytes, thereby blocking the export of iron from cells<sup>39</sup> and reducing the intestinal absorption and recycling of iron.<sup>37</sup>

Approximately one third of older adults with anemia do not meet the criteria of nutritional anemia, anemia of chronic kidney disease or anemia of inflammation.<sup>3;24;40</sup> These anemias are classified as ‘unexplained anemia’. Although the underlying pathophysiological mechanisms of unexplained anemia have yet to be established, (a combination of) several age-related physiological changes may contribute to the development of unexplained anemia, such as renal insufficiency, stem cell aging, androgen insufficiency, chronic inflammation, and myelodysplasia or other types of bone marrow failure.<sup>3;24;40</sup>

## CLINICAL PRACTICE

In primary care, older patients with anemia are carefully examined to detect and treat the underlying cause of the anemia. Thus, treating physicians will inquire about recent blood loss, signs and symptoms from the digestive tract, nutritional habits, weight loss, and drugs and alcohol intake.<sup>41</sup>

In most diagnostic laboratory algorithms for anemia, the mean corpuscular volume (MCV) plays a central role.<sup>41-43</sup> In patients with microcytic anemia (MCV<80 fL), ferritin levels are measured to determine the presence of iron deficiency anemia. Vitamin B12 and folate are measured in patients with macrocytic anemia (MCV>100 fL) to determine or rule out the presence of vitamin B12 or folate deficiency. Normocytic anemias (MCV 80-100 fL) are often caused by chronic diseases, malignancies or bone marrow conditions.<sup>41-43</sup> However, a major drawback of the MCV is that its diagnostic accuracy is poor,<sup>44;45</sup> because of medication use or the presence of multiple coexisting conditions or deficiencies that affect the MCV.<sup>43;46</sup> As older persons often have multiple diseases,<sup>3;47-49</sup> the MCV seems an insufficient criterion for the selection of additional tests in the evaluation of anemia, especially in older persons.<sup>44</sup>

## WHY THIS THESIS?

Most studies on anemia have been performed in older persons aged 65 years and over and in selected patient groups, like patients in hospital wards and residents in institutions for older persons, and not in very old persons from the general population. Increasingly, data become available that question the extrapolation of ‘common’ medical knowledge into the highest age groups. For instance, the effects of some classical determinants of disease and mortality in middle age, like hypothyroidism, hypertension and hypercholesterolemia, have been shown to disappear or even reverse in the oldest old,<sup>50-53</sup> indicating that physiological processes in the oldest old may be distinct from those in younger individuals.

Consequently, the impact and etiology of anemia in very old individuals in the general population is largely unknown. To develop evidence-based diagnostic and treatment strategies for anemia in the very old, research into the causes and consequences of anemia in the oldest old is warranted.

## **AIM AND OUTLINE OF THIS THESIS**

### ***Aim***

The aim of this thesis is to study the impact and etiology of anemia in the oldest old, in order to support the development of evidence-based diagnostic and treatment recommendations for anemia in the oldest old.

### ***Study populations***

The studies presented in this thesis were performed within the Leiden 85-plus Study and the Newcastle 85-plus Study.

The Leiden 85-plus Study is an observational population-based prospective follow-up study of inhabitants of Leiden, the Netherlands, aged 85 years and over. The first cohort was enrolled between December 1986 and March 1988. December 1, 1986, the community of Leiden in the Netherlands had 105 000 inhabitants, of whom 1258 (1%) were 85 years and over. During the enrolment period from December 1, 1986, to March 1, 1988, 221 participants died before they could be visited. Of the remaining 1037 people that were eligible for the study, 977 (94%) agreed to participate. During two home visits, participants were interviewed and blood samples were taken according to predefined protocols under non-fasting conditions. The medical history was obtained from the participants and in memory-impaired subjects from partners and carers.

For the second cohort of the Leiden 85-plus Study, all individuals turning 85 years old between September 1997 and September 1999 and living in Leiden, the Netherlands, were invited for study participation. No exclusion criteria were applied for the study. Of the 599 subjects that participated in the study, 397 (66%) subjects were women, 108 (18%) subjects were institutionalized in a nursing home or care home for older persons, and 217 (36%) subjects had a low socio-economic status. Due to the population-based nature of the study and the high response rate (87%), the study truly reflects the oldest old in the population at large in the Netherlands.<sup>54</sup> At baseline and annually thereafter for 5 years, study participants were visited and interviewed at home. Mortality data were obtained from the municipal registry. Causes of death were assigned by Statistics Netherlands, according to the ICD, 10th revision,<sup>55</sup> and based on completed death certificates.

The Newcastle 85-plus Study is a population-based study of 85-year-old inhabitants of Newcastle and North Tyneside, United Kingdom. All individuals who turned 85 during the year 2006 (i.e. born in 1921) and who were registered

with any Newcastle or North Tyneside Primary Care Trust general practice were eligible for study participation (n=1453). 1042 persons agreed to participate (response 71.7%); 778 participants agreed to blood sampling.

At baseline, all information was obtained during three home visits at the participant's place of residence. During these visits, several questionnaires on socio-economic status (income, level of education) and lifestyle were completed, and a number of measurements and function tests were performed (e.g. Mini Mental State Examination). One additional visit was made to collect fasting blood samples. The participants' GP records were reviewed to obtain information about medical history.

### ***Outline of this thesis***

Chapter 2 describes the impact of anemia on functional status and mortality in old age, and demonstrates the possible role of comorbidity in these associations. The etiology of anemia is studied in the subsequent chapters. In Chapter 3, the effect of low vitamin B12 and low folate levels at the age of 85 years on the incidence of anemia in the years thereafter is investigated. In Chapter 4, the association between low vitamin B12 levels and anemia in older individuals is further evaluated in a systematic review of published studies on this association. Chapter 5 describes the prognostic value of low ferritin levels at age 85 on anemia, and the effect of inflammation on this association. In Chapter 6, an attempt was made to unravel the association between erythropoietin, hemoglobin and renal function in older individuals. The association between erythropoietin levels and mortality is further investigated in Chapter 7. Because earlier studies have shown an association between shorter telomeres and myelodysplastic syndromes and other bone marrow failure syndromes,<sup>56-60</sup> we investigate in Chapter 8 if telomere length is associated with (unexplained) anemia in old age. In Chapter 9 the results are summarized and discussed. Chapter 9 includes a description of the possible clinical implications of this thesis and recommendations for further studies. Chapters 10 and 11 are summaries of this thesis in English and in Dutch, respectively.

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