

University of Groningen

Association of anemia with health-related quality of life and survival

Wouters, Hanneke J C M; van der Klauw, Melanie M; de Witte, Theo; Stauder, Reinhard; Swinkels, Dorine W; Wolffenbuttel, Bruce H R; Huls, Gerwin

Published in:
Haematologica

DOI:
[10.3324/haematol.2018.195552](https://doi.org/10.3324/haematol.2018.195552)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2019

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Wouters, H. J. C. M., van der Klauw, M. M., de Witte, T., Stauder, R., Swinkels, D. W., Wolffenbuttel, B. H. R., & Huls, G. (2019). Association of anemia with health-related quality of life and survival: A large population-based cohort study. *Haematologica*, 104(3), 468-476. <https://doi.org/10.3324/haematol.2018.195552>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.



Ferrata Storti Foundation

Association of anemia with health-related quality of life and survival: a large population-based cohort study

Hanneke J.C.M. Wouters,^{1,2} Melanie M. van der Klauw,² Theo de Witte,³ Reinhard Stauder,⁴ Dorine W. Swinkels,^{5,6} Bruce H.R. Wolffenbuttel² and Gerwin Huls¹

¹Department of Hematology, University Medical Center Groningen, the Netherlands;

²Department of Endocrinology, University Medical Center Groningen, the Netherlands;

³Department of Hematology, Radboud University Medical Center, Nijmegen, the

Netherlands; ⁴Department of Internal Medicine V (Hematology and Oncology), Medical

University, Innsbruck, Austria; ⁵Department of Laboratory Medicine, Radboud University

Medical Center, Nijmegen, the Netherlands and ⁶Hepcidinanalysis.com, Nijmegen, the Netherlands

HJCMW and MMvdK contributed equally to this work.

BHRW and GH contributed equally to this work.

Haematologica 2019

Volume 104(3):468-476

Correspondence:

HANNEKE J.C.M. WOUTERS
h.j.c.m.wouters@umcg.nl

Received: April 11, 2018.

Accepted: October 2, 2018.

Pre-published: October 11, 2018.

doi:10.3324/haematol.2018.195552

Check the online version for the most updated information on this article, online supplements, and information on authorship & disclosures: www.haematologica.org/content/104/3/468

©2019 Ferrata Storti Foundation

Material published in *Haematologica* is covered by copyright. All rights are reserved to the Ferrata Storti Foundation. Use of published material is allowed under the following terms and conditions:

<https://creativecommons.org/licenses/by-nc/4.0/legalcode>.

Copies of published material are allowed for personal or internal use. Sharing published material for non-commercial purposes is subject to the following conditions:

<https://creativecommons.org/licenses/by-nc/4.0/legalcode>,

sect. 3. Reproducing and sharing published material for commercial purposes is not allowed without permission in writing from the publisher.



ABSTRACT

Anemia is highly prevalent, especially in older individuals. In selected populations, anemia has been reported to be associated with impaired survival and health-related quality of life. However, data on this impact in the general population are rare. Furthermore, discussions on the optimal definition of anemia have not been conclusive. We investigated these issues using survival data, scores from a health-related quality of life questionnaire (RAND-36), and hemoglobin concentration from 138670 subjects, aged 18-93 years, participating in the Lifelines cohort. Anemia was defined according to World Health Organization criteria and was further subclassified in participants over 60 years old. Anemia was present in 5510 (4.0%) of all 138670 subjects and 516 (2.8%) in the 18667 individuals older than 60 years. Anemia had no impact on overall survival and limited impact on health-related quality of life in individuals less than 60 years old. In contrast, in individuals over 60 years old anemia significantly impaired overall survival and health-related quality of life. The lower health-related quality of life was mainly observed in subscales representing physical functioning. Although consensus on the subclassification of anemia is lacking, our data suggest that particularly anemia of chronic inflammation was associated with worse overall survival and decreased health-related quality of life. Multivariate models confirmed that anemia was an independent risk factor for decreased health-related quality of life in older individuals. Finally, women with a hemoglobin concentration between 12.0-13.0 g/dL (considered anemia in men, but not in women) experienced a significantly lower health-related quality of life. This large, prospective, population-based study indicates that anemia is associated with worse overall survival and health-related quality of life in older individuals, but not in younger individuals. The findings of this study challenge the definition of anemia in women over 60 years old, and suggest that the optimal definition of anemia, in the perspective of health-related quality of life, in women over 60 years old should be altered to a hemoglobin concentration below 13.0 g/dL (8.0 mmol/L), which is comparable to that in men.

Introduction

Anemia, according to the World Health Organization (WHO) criteria, is defined as a hemoglobin concentration <13.0 g/dL (8.0 mmol/L) in adult men and <12.0 g/dL (7.5 mmol/L) in adult, non-pregnant women. Anemia affects nearly 25% of the world population.^{1,2} In developed countries, anemia is one of the most frequent conditions in older individuals, with a presumed prevalence of over 10% individuals who are 65 years or older in selected populations.^{3,4} More than half of anemic older individuals can be diagnosed with nutritional deficiencies or have anemia of chronic inflammation (ACI). The etiology of anemia remains unknown in about one-third of the older population.⁴ In older individuals the presence of anemia, even mild anemia, is associated with an increased risk of falls,⁵ decreased physical performance,⁶ longer and more frequent stays in hospital,^{7,9} and increased mortality.^{7,9,10} Suggestions to raise the hemoglobin thresholds for the definition of anemia in older individuals have been made in several studies.^{11,12}

The impact of anemia on health-related quality of life (HRQoL) has been studied in different populations of patients, including patients with chronic kidney disease,¹³ chronic obstructive pulmonary disease,¹⁴ cancer¹⁵ and heart failure.¹⁶ In these studies, anemia was reported to be associated with a reduced HRQoL. However, little research has been done on this potential association in community-dwelling populations. Better understanding of the impact of anemia on HRQoL in a community-dwelling general population is therefore essential and could provide critical entry points for interventions that affect anemia, especially in older individuals.

In this study, we investigated the association between anemia and survival, and between anemia and HRQoL. In addition, we used this association to evaluate the definition of anemia, considering the impact of age and gender on this association in the large community-dwelling population from the Lifelines cohort.¹⁷

Methods

Subjects

In this study we used data from 138670 subjects participating in the Lifelines cohort study. Data from quality of life questionnaires and on hemoglobin concentration were available for these subjects. Lifelines is a multidisciplinary, prospective, population-based cohort study examining, in a unique three-generation design, the health and health-related behaviors of persons living in the north of the Netherlands. It has been shown that the Lifelines cohort is representative of the population of the northern part of the Netherlands.¹⁸ The local ethics committee approved the research protocol and informed consent was signed by every participant.

Health-related quality of life

HRQoL was measured using the RAND 36-Item Health Survey.¹⁹ Since HRQoL scores are not normally distributed, for each subscale we defined a sex-specific and age-specific cut-off point at the 25th percentile of the non-anemic Lifelines population. Participants with a score lower than 25th percentile were considered to have an abnormally low score for that specific subscale.

Survival

All participants were followed from the moment of their inclusion in the Lifelines cohort until death or up to May 2018

(maximum follow-up 138 months, median 79 months). Information on participants' deaths was obtained from the municipal personal records database.

Definition of anemia and classification into subtypes of anemia

In accordance with the WHO criteria, anemia was defined as a hemoglobin concentration <13.0 g/dL (8.0 mmol/L) in adult men and <12.0 g/dL (7.5 mmol/L) in adult, non-pregnant women.²⁰ In anemic subjects older than 60 years of age additional biochemical tests were performed, using stored plasma, to determine the type of anemia: anemia due to nutritional deficiency, ACI or unexplained anemia. There is no worldwide accepted classification into subtypes of anemia. Reference values were taken from the University Medical Center Groningen or from published literature, as indicated. Iron deficiency was considered present if the participant had two or three of the following criteria: serum ferritin concentration <30 µg/L, transferrin saturation rate <16% or hepcidin concentration <0.5 nmol/L.²¹⁻²³ Transferrin saturation was calculated by dividing serum iron by total iron-binding capacity [transferrin (g/L)×25]. Folate deficiency was defined as a serum folate level <9.8 nmol/L. Vitamin B12 deficiency was defined as a serum methylmalonic acid concentration >340 nmol/L, if the estimated glomerular filtration was >30 mL/min (because methylmalonic acid levels may be elevated in people with severely impaired renal function²⁴). If there was no evidence of nutrient deficiency, subjects with anemia were evaluated for other causes. Subjects were classified as having anemia related to chronic renal disease if the estimated glomerular filtration rate was <30 mL/min. The Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) formula was used to calculate the estimated glomerular filtration rate. ACI was defined as present if the participant had (i) a C-reactive protein concentration >5.0 mg/L or an absolute number of leukocytes >10×10⁹/L and (ii) two or more of the following criteria: transferrin saturation rate <16%, serum ferritin concentration >100 µg/L, serum iron <10 µmol/L and hepcidin >14.7 nmol/L in men or hepcidin >15.6 nmol/L in women.^{25,26} If subjects with anemia could not be classified into any of these categories, they were considered, by exclusion, to have unexplained anemia.

Details of the Lifelines cohort, clinical examination, biochemical measurements, RAND 36-Item Health Survey and data description and statistical analysis are provided in the *Online Supplementary Data*.

Results

Relevant baseline characteristics are shown in Table 1 for anemic and non-anemic participants from the population-based Lifelines cohort. In total 551 men and 4959 women met the WHO criteria for anemia. The overall prevalence of anemia was 4.0% (Figure 1A). The prevalence of anemia in women was highest (about 8%) in the age cohort 40-49 years and showed a second peak of about 4% at an older age (older than 70 years). In contrast, the prevalence of anemia in men gradually increased with age, with a peak of about 5% in older age (older than 70 years). In the population of individuals 60 years of age and older the overall prevalence of anemia was 2.8%, with a prevalence of 2.7% in men and 3.0% in women. The distribution of the hemoglobin concentration according to age is shown in *Online Supplementary Figure S2A,C*. In men, unlike in women, the mean hemo-

globin concentration decreased with age (*Online Supplementary Figure S2B,D*). Over 90% of the anemic individuals had mild anemia [>10 g/dL, (> 6.2 mmol/L)]. In individuals younger than 60 years the presence of anemia did not have any impact on overall survival (Figure

1B). In contrast, the overall survival of anemic individuals older than 60 years was significantly lower than that of non-anemic individuals older than 60 years (Figures 1C).

The mean of the total HRQoL score was significantly lower in anemic individuals in all age groups than in non-

Table 1. Baseline characteristics of the study cohort.

	Anemic individuals (N=5510)	Non-anemic individuals (N=133160)	P-value
Men/women	551 (10.0)/4959 (90.0)	57283 (43.0)/75877 (57.0)	<0.001
Age (years)	43.4 ± 11.9	44.3 ± 12.7	<0.001
Body mass index (kg/m ²)	24.2 (22.1 - 27.2)	25.4 (23.1 - 28.2)	<0.001
Creatinine (μmol/L)	69 ± 18	74 ± 13	<0.001
Estimated glomerular filtration rate (mL/min)	98 ± 17	97 ± 15	0.003
HbA1c (%)	5.6 ± 0.5	5.5 ± 0.4	<0.001
Glucose (mmol/L)	4.9 ± 0.8	5.0 ± 0.8	<0.001
Leukocytes (10 ⁹ /L)	5.6 ± 1.7	6.1 ± 1.8	<0.001
Platelets (10 ⁹ /L)	278 ± 70	249 ± 56	<0.001
Number of medications	2 (1 - 3)	2 (1 - 3)	<0.001
Multiple drug use	712 (12.9)	12360 (9.3)	<0.001
Non-smokers/former smokers/current smokers	3048 (55.3)/1754 (31.8)/708 (12.8)	62228 (46.7)/42411 (31.8)/28521 (21.4)	<0.001

Data are given as mean ± standard deviation, median (interquartile range) when not normally distributed, or n (%). HbA1c: glycated hemoglobin.

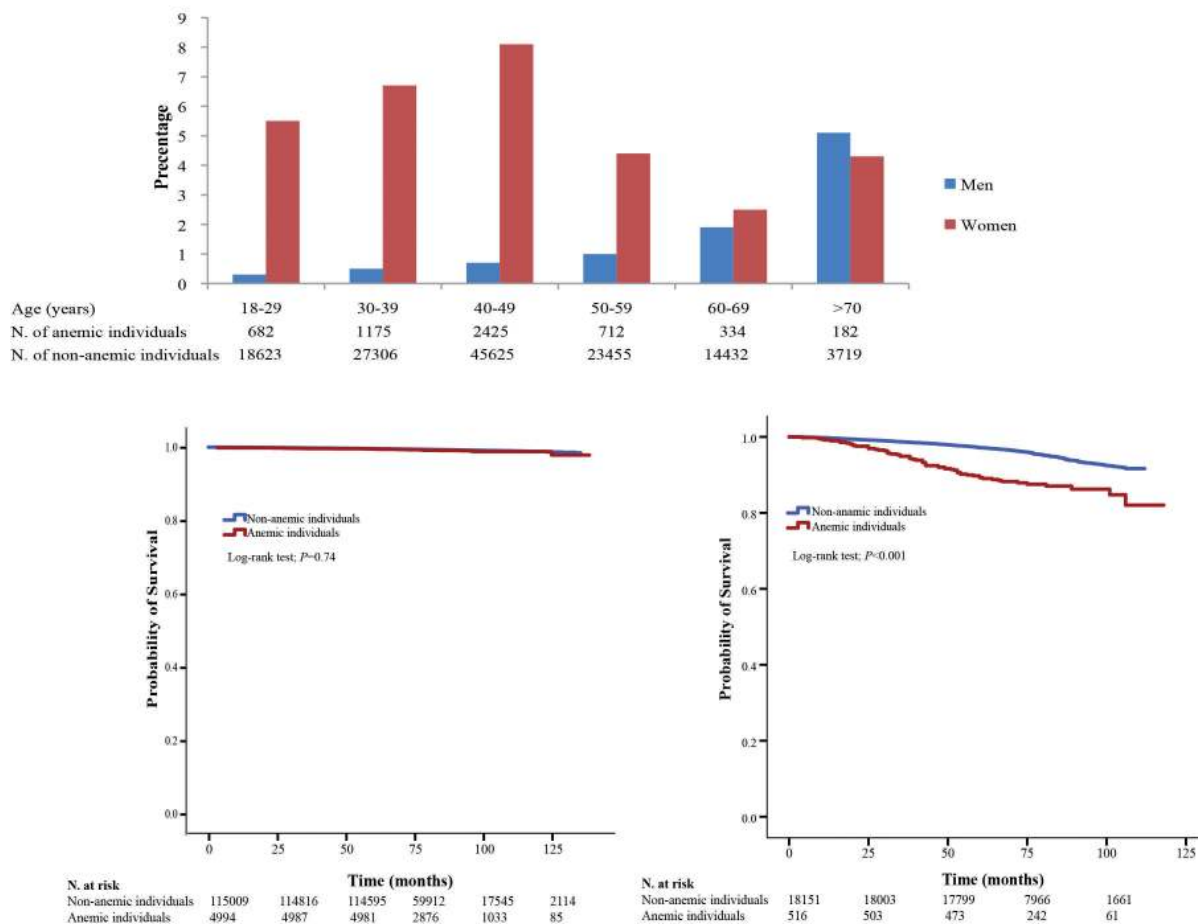


Figure 1. Prevalence of anemia and overall survival in individuals younger and older than 60 years. (A) The prevalence of anemia as a function of sex and age. (B) Overall survival of non-anemic and anemic individuals younger than 60 years. (C) Overall survival of non-anemic and anemic individuals older than 60 years.

anemic individuals (*Online Supplementary Figure S3A*). At a younger age the mean difference was relatively small, but after the age of 60 years this difference in mean HRQoL increased substantially. Because HRQoL scores are not normally distributed, we also studied the percentage of individuals with a HRQoL score below a cut-off value. This analysis revealed that the percentage of individuals with a total score below the 25th percentile was significantly higher among the group of individuals over 60 years old (*Online Supplementary Figure S3B*). Older individuals had a significantly lower mean HRQoL in the subscales physical functioning, social functioning, physical role functioning, emotional role health, vitality, bodily pain and general health (*Online*

Supplementary Figure S4). Moreover, a significantly larger proportion of anemic subjects older than 70 years had a score below the cut-off value, indicating a poor score, in six of the eight subscales: physical functioning (40% versus 25%), social functioning (42% versus 33%), physical role functioning (35% versus 23%), vitality (36% versus 27%), bodily pain (45% versus 32%) and general health (42% versus 32%). In subjects between 60-70 years old there was a difference in the subscales physical functioning (36% versus 27%) and physical role functioning (29% versus 21%) (Figure 2). Between 18-60 years no significant differences were observed when comparing percentages of individuals with a HRQoL score below the cut-off value. Finally, we used multivariate logistic

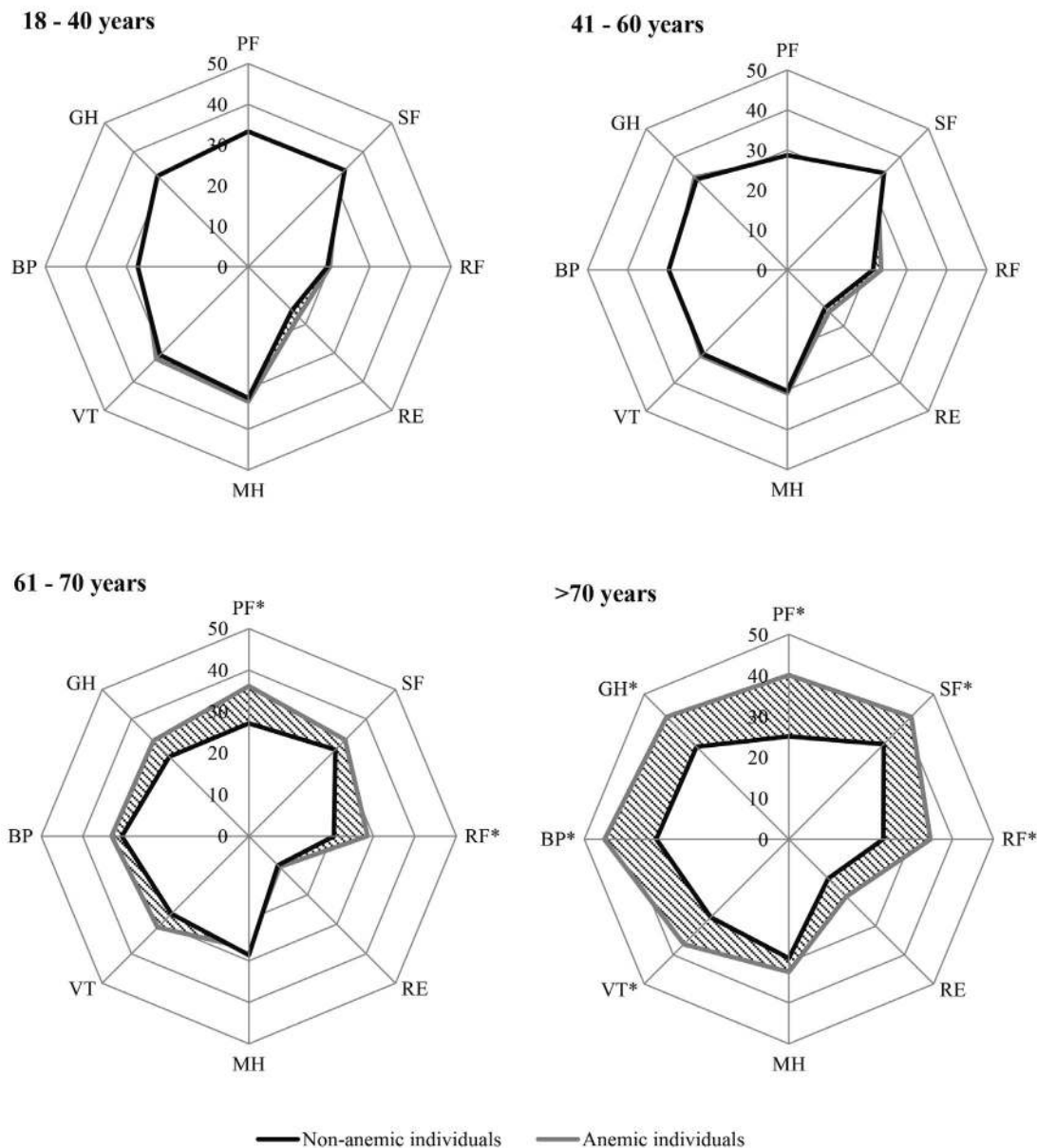


Figure 2. Percentages of individuals, divided according to age group, with scores below the sex- and age-specific cut-off values for the different subscales of the RAND-36 health survey. An asterisk indicates a significantly (P -value <0.01) larger percentage below the sex- and age-specific cut-off value in anemic individuals compared with non-anemic individuals. PF: physical functioning; SF: social functioning; RF: physical role functioning; RE: emotional role functioning; MH: mental health; VT: vitality; BP: bodily pain; GH: general health.

regression analysis to investigate whether anemia was an independent risk factor for HRQoL. This analysis showed that anemia, adjusted for body mass index, being a current smoker, multiple drug use, educational level and living situation independently increased the risk of having a lower total HRQoL (OR 1.28; 95% CI: 1.00 – 1.64; $P=0.046$).

Since anemia had a particular impact on overall survival and HRQoL in subjects older than 60 years within the Lifelines cohort, the type of anemia in these individuals was further characterized (see the Methods section). In total 174 (35.0%) subjects were classified as having nutrient deficiency anemia, 81 (16.3%) as having ACI, and 242 (48.7%) as having unexplained anemia (*Online Supplementary Table S1*). Compared with individuals from the general population, a significantly larger proportion of individuals with ACI had a HRQoL score lower than the cut-off value in seven of the eight subscales (all except mental health) (Table 2). Nutrient deficiency anemia was associated with a significantly lower score in only one subscale (physical functioning). Individuals with unexplained anemia had a significantly lower score in the subscale bodily pain. These results were more explicit in men than in women (*Online Supplementary Tables S2 and S3*). In order to determine which type of anemia was an independent risk factor for HRQoL in individuals older than 60 years, we performed logistic regression analysis in individuals older than 60 years (Table 3 and *Online Supplementary Table S4*). After adjusting for body mass index, being a current smoker, multiple drug use, educational level and living situation, ACI was associated with a higher risk of having a score below the cut-off in all seven subscales which were affected by anemia (i.e. all subscales except mental health) (Table 3). Overall survival was significantly lower in individuals with ACI than in those with nutrient deficiency anemia or unexplained anemia (Figure 3).

Although the difference between the median values of the hemoglobin concentration decreased during aging, (*Online Supplementary Figure S5*), the definition of anemia is based on hemoglobin concentrations obtained in younger adults. Consequently, there are persistent discussions regarding whether the definition of anemia in older individuals is appropriate or should be corrected using a higher hemoglobin threshold. Because of the clear correlation between anemia in individuals older than 60 years and survival and HRQoL, we used these associations to reassess the definition of anemia in individuals older than 60 years. We assumed that anemia should be considered in the case that a certain hemoglobin level was associated with a significant (negative) impact on HRQoL. Logistic regression was used to model the relationship between hemoglobin concentration and total HRQoL in both men and women. These analyses revealed that men older than 60 years with a hemoglobin concentration between 13.0-13.7 g/dL (8.0-8.5 mmol/L) (just above the current WHO defined threshold) did not have a lower HRQoL compared with men with a hemoglobin concentration >13.7 g/dL (8.5 mmol/L), suggesting that the current threshold which defines anemia in men is appropriate. However, when specifically comparing women older than 60 years with a hemoglobin concentration between 12.0-13.0 g/dL (7.5-8.0 mmol/L) (considered anemic for men but not anemic for women according to the current WHO definition), this group had a lower HRQoL than that of women with a hemoglobin concentration >13.0 g/dL (8.0 mmol/L). These data strongly suggest that the optimal definition of anemia for women older than 60 years should be a hemoglobin concentration <13.0 g/dL (8.0 mmol/L) (Figure 4). So, in the case that HRQoL is used to define anemia, there would be no difference in the definition between older men and women. Due to the limited number of deaths among groups of individuals divid-

Table 2. Percentage of individuals older than 60 years with anemia with HRQoL below the sex- and age-specific cut-off value for the different HRQoL subscales as a function of their type of anemia.

	General population older than 60 years (N=18152)	Nutrient deficiency anemia (N=174)	Anemia of chronic inflammation (N=81)	Unexplained anemia (N=242)
Physical functioning	4869 (26.8)	67 (38.5)* $P<0.001$	40 (49.4)* $P<0.001$	78 (32.2)
Social functioning	5482 (30.2)	53 (30.5)	41 (50.6)* $P<0.001$	85 (26.0)
Physical role functioning	3820 (21.0)	49 (28.2)	41 (50.6)* $P<0.001$	63 (26.0)
Emotional role functioning	1936 (10.7)	20 (11.5)	17 (21.0)* $P=0.003$	30 (12.4)
Mental health	5216 (28.7)	42 (24.1)	26 (32.1)	72 (29.8)
Vitality	4820 (26.5)	49 (28.2)	39 (47.0)* $P<0.001$	75 (31.0)
Bodily pain	5618 (30.9)	60 (34.5)	40 (49.4)* $P<0.001$	95 (39.3)* $P=0.006$
General health	5104 (28.1)	60 (34.5)	40 (49.4)* $P<0.001$	79 (32.6)

Data are given as n (%) below the sex- and age-specific cut-off value for the different HRQoL subscales. * P -value <0.01 between individuals from the non-anemic group of the general population and individuals with the given type of anemia.

ed according to the various intervals of hemoglobin concentration, survival could not be used to model the optimal definition of anemia.

Discussion

In this study we observed that anemia is associated with worse overall survival and is an independent risk factor for HRQoL in individuals older than 60 years, in contrast to younger individuals. Although consensus on the subclassification of anemia is lacking, our data suggest that particularly ACI was an independent risk factor for HRQoL in subscales representing physical functioning. Furthermore, we observed that women (but not men) older than 60 years with a hemoglobin concentration in the lower normal WHO range experienced decreased HRQoL. This suggests that the definition of anemia in women older than 60 years should be altered to a hemoglobin concentration <13.0 g/dL (8.0 mmol/L), which is comparable to the definition of anemia in men.

The prevalence of anemia according to the WHO criteria was 4.0% in the whole cohort and 2.8% among subjects older than 60 years, which is consistent with the findings of population-based studies from Sweden (3.8% in patients 44 - 73 years old)²⁷ and Germany (3.2% in

subjects 45-75 years old²⁸ and 6.9% in subjects over 65 years old²⁹). However, the prevalence of anemia in older individuals in our community-dwelling population was remarkably lower than that found in previous studies.^{3,4,30} A possible explanation for this discrepancy could be a participation bias in the Lifelines cohort, although earlier observations showed that the Lifelines study population is representative of the general population, with a low risk of selection.¹⁸ The relatively low prevalence of anemia in older individuals could also be related to the high quality and accessibility of the general health system nowadays, especially for older individuals. Furthermore, the prevalence of anemia and the types of anemia might differ according to race and geographical area.^{2,4}

Anemia did not have an impact on survival in individuals younger than 60 years. In contrast, among individuals older than 60 years, anemic subjects had a significantly decreased survival. The decreased survival in older anemic individuals is in accordance with that in multiple previous studies.^{7,9,10} In our study there was increased mortality in older individuals with ACI: this finding is partly in line with the findings of a study by Willems *et al.* who reported increased mortality in subjects with nutrient deficiency anemia and ACI, but not in those with unexplained anemia.³¹

Since an aging population results in an increased prevalence of anemia, an understanding of the association between anemia and HRQoL is important. Remarkably, only a few, relatively small studies of community-dwelling populations have described this association. In a study of 717 subjects, Lucca *et al.* showed, after adjustment for a large number of demographic and clinical confounders, that anemia in elderly Italians (65 - 84 years old) was significantly associated with lower disease-specific QoL, measured with the Functional Assessment of Cancer Therapy-Anemia.³² Thein *et al.* studied an American cohort of 328 individuals and showed that anemia in subjects older than 65 years was independently associated with impairments in multiple subscales of HRQoL (measured with the Short Form-36), especially in measures of functional limitation.³³ Bang *et al.* also found that anemia was associated with physical impairment in 695 Korean individuals older than 65 years.³⁴ Our data, in an unprecedented large cohort, confirms the relationship between anemia and HRQoL in older individuals (but not in younger individuals).

There is no worldwide accepted classification into subtypes of anemia. To be able to study the subtypes, we based our criteria on literature or reference values from the local laboratory. In addition to those criteria, we also analyzed the data with different classification criteria (see *Online Supplementary Data* for definitions). Although misclassification within the various subtypes of anemia cannot be excluded, our data suggest that the impact of anemia on HRQoL is mainly present in individuals with ACI (*Online Supplementary Tables S5 and S6*). The pathophysiology of ACI is multifactorial, including increased levels of inflammatory cytokines that lead to altered iron metabolism, with a key role for the iron regulatory peptide hormone hepcidin.^{35,36} Indeed, elevated levels of inflammatory markers, which are found in older anemic individuals, have been shown to be associated with physical disability.^{37,38} Our observation that anemia mainly affects HRQoL of subjects with ACI is supported by studies showing that erythropoiesis-stimulating agents

Table 3. Risk of having a lower score than the (age- and sex- specific) 25th percentile cut-off due to anemia per HRQoL subscale among individuals older than 60 years.

HRQoL subscale	Type of anemia	Odds ratio (95% CI)
Physical functioning	Nutritional deficiency anemia	1.16 (0.75 - 1.79)
	Anemia of chronic inflammation	3.30 (1.76 - 6.21) ** <i>P</i> <0.001
	Unexplained anemia	1.04 (0.74 - 1.48)
Social functioning	Nutritional deficiency anemia	0.89 (0.58 - 1.35)
	Anemia of chronic inflammation	2.39 (1.32 - 4.31) ** <i>P</i> =0.004
	Unexplained anemia	1.04 (0.75 - 1.44)
Physical role functioning	Nutritional deficiency anemia	1.15 (0.74 - 1.78)
	Anemia of chronic inflammation	3.75 (2.05 - 6.83) ** <i>P</i> <0.001
	Unexplained anemia	1.03 (0.72 - 1.48)
Emotional role functioning	Nutritional deficiency anemia	0.89 (0.49 - 1.59)
	Anemia of chronic inflammation	2.53 (1.31 - 4.90) ** <i>P</i> =0.006
	Unexplained anemia	1.04 (0.66 - 1.65)
Vitality	Nutritional deficiency anemia	0.92 (0.60 - 1.42)
	Anemia of chronic inflammation	2.89 (1.59 - 5.24) ** <i>P</i> <0.001
	Unexplained anemia	1.13 (0.81 - 1.57)
Bodily pain	Nutritional deficiency anemia	0.96 (0.63 - 1.45)
	Anemia of chronic inflammation	1.84 (1.02 - 3.33) * <i>P</i> =0.04
	Unexplained anemia	1.16 (0.84 - 1.60)
General health	Nutritional deficiency anemia	0.87 (0.57 - 1.34)
	Anemia of chronic inflammation	2.44 (1.33 - 4.45) ** <i>P</i> =0.004
	Unexplained anemia	0.99 (0.71 - 1.38)

Adjusted for body mass index, smoking status, multiple drug use, educational level and living situation. Data are shown as odds ratio and 95% confidence interval (95% CI). ***P*value <0.01; **P*value <0.05.

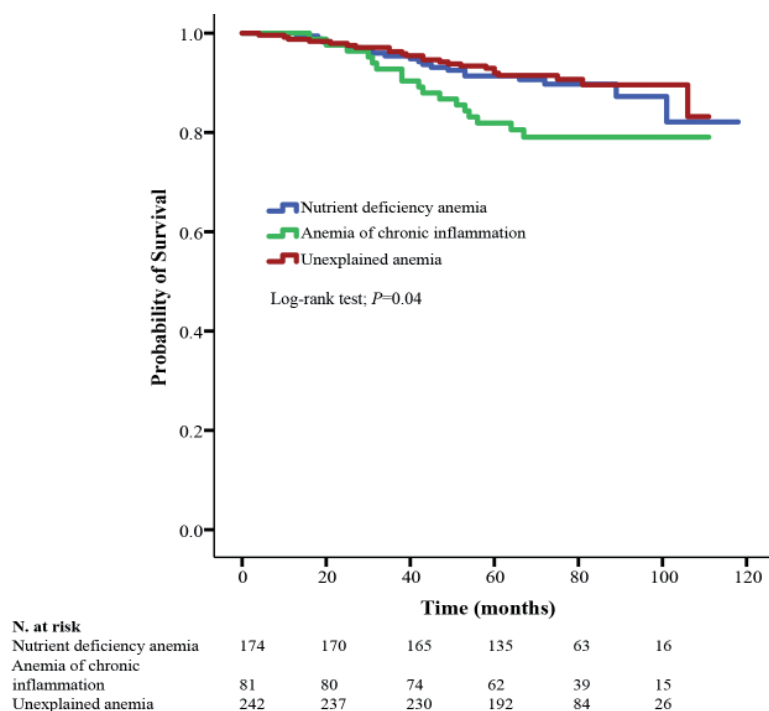


Figure 3. Kaplan-Meier curves of survival of individuals with different types of anemia.

have an impact on the HRQoL of patients with cancer, HIV/AIDS and chronic kidney disease.³⁹ In older individuals a positive effect of erythropoiesis-stimulating agents on QoL has been shown in patients with chronic kidney disease,⁴⁰ and chemotherapy-induced anemia.⁴¹ In one randomized, blinded, placebo-controlled trial in predominantly African-American elderly women with ACI or unexplained anemia an increase of the hemoglobin concentration by 2 g/dL led to improvements in QoL as measured by the Functional Assessment of Chronic Illness Therapy instrument.⁴²

The most pronounced association between HRQoL and anemia was observed in older individuals and in subscales related to physical health. This suggests that younger individuals can compensate better for the physical consequences of anemia, limiting the impact of anemia on their HRQoL. For older individuals these compensatory mechanisms might be limited compared to those in younger persons. The ability to engage in physical activities is known to be important for maintaining QoL in older persons.^{43,44}

In this study we defined anemia according to the WHO criteria, which define anemia as a hemoglobin concentration <13.0 g/dL (8.0 mmol/L) in adult men and <12.0 g/dL (7.5 mmol/L) in adult, non-pregnant women. This is the most commonly used definition of anemia, but the use of this definition in older/elderly populations has been criticized.^{11,12} The WHO criteria were derived from a small study population of healthy, young participants nearly 50 years ago.²⁰ Based on data from two large American databases, Beutler *et al.* proposed new, slightly higher cut-offs for white women older than 50 years and white men older than 60 years.¹²

Although the different distributions of median hemoglobin concentration between men and women (in general and in older individuals) suggest that it is 'logic' to use different definitions of anemia in men and women,

our data raise doubts about this logic. Indeed, HRQoL data from our study suggest that the definition of anemia in men – a hemoglobin concentration <13.0 g/dL (8.0 mmol/L) – should also be applied for women older than 60 years. Apparently, the hemoglobin values which start to hamper (physical) functioning do not differ between older men and women. We were not able to study the optimal definition of anemia in perspective of mortality because of the limited number of deaths in our cohort. Martinsson *et al.* observed an increased mortality defining anemia as <14.0 g/dL (8.7 mmol/L) in men and <13.0 g/dL (8.0 mmol/L) in women.²⁷ A recent, large study assessing the effect of hemoglobin concentrations on cardiovascular and all-cause mortality in nearly 300,000 participants showed that men with a hemoglobin concentration in the lower normal range had a higher risk of mortality whereas this was not observed in women.⁴⁵

Our study has some strengths and limitations. It is the first study to investigate the possible effect of anemia on HRQoL in individuals of all ages in a very large cohort from the general population. Additionally, we used information on HRQoL from a large number of participants with a wide range of age, socio-economic status and comorbidities. All subjects were uniformly characterized and were not aware of hemoglobin status when filling out the questionnaires, preventing the outcome of the questionnaire from being affected by the knowledge of a diagnosis of anemia.

Several potential limitations should be acknowledged. As mentioned earlier, the subtypes of anemia might have been misclassified due to a lack of clear classification criteria. Since this is a cross-sectional study, the analyses do not provide information about causality, for example for the fact that despite lower median hemoglobin concentrations in older women than in older men, the impact of anemia on HRQoL occurred at the same hemoglobin concentration. Additionally, given the observational

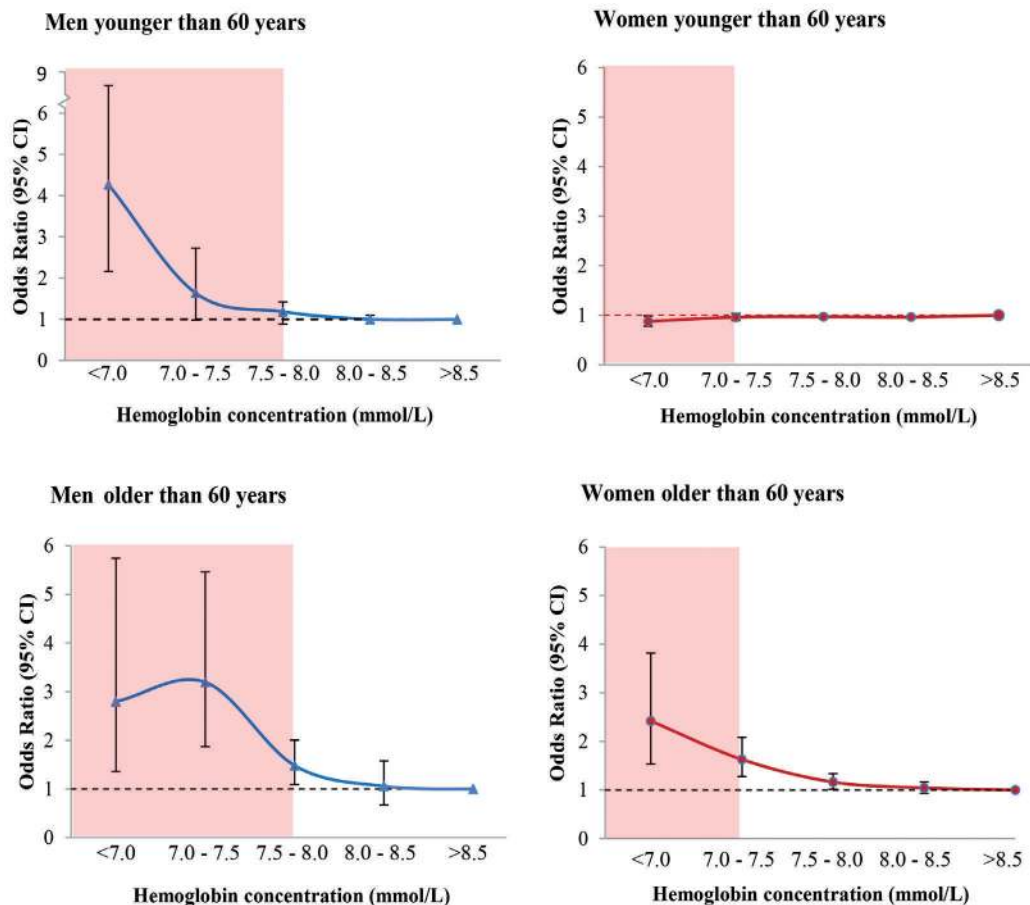


Figure 4. Risk of having a lower total health-related quality of life score than the (sex- and age-specific) 25th percentile cut-off according to hemoglobin concentrations. The red rectangles indicate a hemoglobin concentration below the currently used World Health Organization definition of anemia. 95% CI: 95% confidence interval.

nature of the study, it was not possible to exclude the role of unknown or unmeasured confounding variables. A third limitation is that HRQoL was measured with the RAND-36 questionnaire, which is a generic health status questionnaire and not specifically developed to measure QoL in anemic individuals. Finally, it is possible that the results were influenced by volunteer bias.

This study indicates that anemia is associated with decreased survival and HRQoL, especially that concerning physical health, in individuals older than 60 years. After adjusting for confounding variables the impact of anemia was particularly present in individuals with ACI. These results suggest that older individuals might benefit from treatment to increase their hemoglobin values. Furthermore, this study challenges the sex-dependent definition of anemia in individuals older than 60 years, and suggests that in both men and women older than 60 years, the definition currently used in men [hemoglobin concentration <13.0 g/dL (8.0 mmol/L)] could be applied in perspective of HRQoL.

Acknowledgments

The authors would like to thank all participants of the Lifelines cohort study and everybody involved in the set-up and implementation of the study. We would also like to thank Anneke Geurts-Moespot and Siem Klaver of

Hepcidinanalysis.com, who contributed to the measurement of hepcidin.

Funding

Lifelines has been funded by a number of public sources, notably the Dutch Government, The Netherlands Organization of Scientific Research NOW (grant 175.010.2007.006), the Northern Netherlands Collaboration of Provinces (SNN), the European fund for regional development, Dutch Ministry of Economic Affairs, Pieken in de Delta, Provinces of Groningen and Drenthe, the Target project, BBMRI-NL, the University of Groningen, and the University Medical Center Groningen, the Netherlands. This work was supported by the National Consortium for Healthy Aging, and funds from the European Union's Seventh Framework program (FP7/2007–2013) through the BioSHaRE-EU (Biobank Standardisation and Harmonisation for Research Excellence in the European Union) project, grant agreement 261,433. Lifelines (BRIF4568) is engaged in a Bioresource Research Impact Factor (BRIF) policy pilot study, details of which can be found at: <http://bioshare.eu/content/bioresource-impact-factor>.

This work is part of the MDS-RIGHT activities, which has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement n. 634789 - 'Providing the right care to the right patient with myelodysplastic syndrome at the right time'.

References

- McLean E, Cogswell M, Egli I, Wojdyla D, de Benoist B. Worldwide prevalence of anaemia, WHO Vitamin and Mineral Nutrition Information System, 1993-2005. *Public Health Nutr.* 2009;12(4):444-454.
- Stevens GA, Finucane MM, De-Regil LM, et al. Global, regional, and national trends in haemoglobin concentration and prevalence of total and severe anaemia in children and pregnant and non-pregnant women for 1995-2011: a systematic analysis of population-representative data. *Lancet Glob Health.* 2013;1(1):e16-25.
- Gaskell H, Derry S, Moore A, McQuay HJ. Prevalence of anaemia in older persons: systematic review. *BMC Geriatr.* 2008;8:1.
- Guralnik JM, Eisenstaedt RS, Ferrucci L, Klein HG, Woodman RC. Prevalence of anemia in persons 65 years and older in the United States: evidence for a high rate of unexplained anemia. *Blood.* 2004;104(8):2263-2268.
- Penninx BW, Pluijm SM, Lips P, et al. Late-life anemia is associated with increased risk of recurrent falls. *J Am Geriatr Soc.* 2005;53(12):2106-2111.
- Penninx BW, Pahor M, Cesari M, et al. Anemia is associated with disability and decreased physical performance and muscle strength in the elderly. *J Am Geriatr Soc.* 2004;52(5):719-724.
- Culleton BF, Manns BJ, Zhang J, Tonelli M, Klarenbach S, Hemmelgarn BR. Impact of anemia on hospitalization and mortality in older adults. *Blood.* 2006;107(10):3841-3846.
- Dharmarajan TS, Pankratov A, Morris E, et al. Anemia: its impact on hospitalizations and length of hospital stay in nursing home and community older adults. *J Am Med Dir Assoc.* 2008;9(5):354-359.
- Penninx BW, Pahor M, Woodman RC, Guralnik JM. Anemia in old age is associated with increased mortality and hospitalization. *J Gerontol A Biol Sci Med Sci.* 2006;61(5):474-479.
- Halawi R, Moukhaider H, Taher A. Anemia in the elderly: a consequence of aging? *Expert Rev Hematol.* 2017;10(4):327-335.
- Chaves PH, Ashar B, Guralnik JM, Fried LP. Looking at the relationship between hemoglobin concentration and prevalent mobility difficulty in older women. Should the criteria currently used to define anemia in older people be reevaluated? *J Am Geriatr Soc.* 2002;50(7):1257-1264.
- Beutler E, Waalen J. The definition of anemia: what is the lower limit of normal of the blood hemoglobin concentration? *Blood.* 2006;107(5):1747-1750.
- Farag YM, Keithi-Reddy SR, Mittal BV, et al. Anemia, inflammation and health-related quality of life in chronic kidney disease patients. *Clin Nephrol.* 2011;75(6):524-533.
- Ferrari M, Manea L, Anton K, et al. Anemia and hemoglobin serum levels are associated with exercise capacity and quality of life in chronic obstructive pulmonary disease. *BMC Pulm Med.* 2015;15:58.
- Wasada I, Eguchi H, Kurita M, et al. Anemia affects the quality of life of Japanese cancer patients. *Tokai J Exp Clin Med.* 2013;38(1):7-11.
- Kraai IH, Luttik ML, Johansson P, et al. Health-related quality of life and anemia in hospitalized patients with heart failure. *Int J Cardiol.* 2012;161(3):151-155.
- Stolk RP, Rosmalen JG, Postma DS, et al. Universal risk factors for multifactorial diseases: LifeLines: a three-generation population-based study. *Eur J Epidemiol.* 2008;23(1):67-74.
- Klijns B, Scholtens S, Mandemakers JJ, Snieder H, Stolk RP, Smidt N. Representativeness of the LifeLines cohort study. *PLoS One.* 2015;10(9):e0137203.
- VanderZee K I K I. Psychometric qualities of the RAND 36-Item Health Survey 1.0: a multidimensional measure of general health status. *Int J Behav Med.* 1996;3(2):104-122.
- Blanc B, Finch CA, Hallberg L, et al. Nutritional anaemias. Report of a WHO scientific group. *World Health Organ Tech Rep Ser.* 1968;405:5-37.
- Mast AE, Blinder MA, Gronowski AM, Chumley C, Scott MG. Clinical utility of the soluble transferrin receptor and comparison with serum ferritin in several populations. *Clin Chem.* 1998;44(1):45-51.
- Lopez A, Cacoub P, Macdougall IC, Peyrin-Biroulet L. Iron deficiency anaemia. *Lancet.* 2016;387(10021):907-916.
- Kroot JJ, Laarakkers CM, Geurts-Moespot AJ, et al. Immunochemical and mass-spectrometry-based serum hepcidin assays for iron metabolism disorders. *Clin Chem.* 2010;56(10):1570-1579.
- Ganji V, Kafai MR. Population prevalence, attributable risk, and attributable risk percentage for high methylmalonic acid concentrations in the post-folic acid fortification period in the US. *Nutr Metab (Lond).* 2012;9(1):2.
- Guralnik JM, Eisenstaedt RS, Ferrucci L, Klein HG, Woodman RC. Prevalence of anemia in persons 65 years and older in the United States: evidence for a high rate of unexplained anemia. *Blood.* 2004;104(8):2263-2268.
- Weiss G, Goodnough LT. Anemia of chronic disease. *N Engl J Med.* 2005;352(10):1011-1023.
- Martinsson A, Andersson C, Andell P, Koul S, Engstrom G, Smith JG. Anemia in the general population: prevalence, clinical correlates and prognostic impact. *Eur J Epidemiol.* 2014;29(7):489-498.
- Eisele L, Durig J, Broecker-Preuss M, et al. Prevalence and incidence of anemia in the German Heinz Nixdorf Recall Study. *Ann Hematol.* 2013;92(6):731-737.
- Endres HG, Wedding U, Pittrow D, Thiem U, Trampisch HJ, Diehm C. Prevalence of anemia in elderly patients in primary care: impact on 5-year mortality risk and differences between men and women. *Curr Med Res Opin.* 2009;25(5):1143-1158.
- Stauder R, Thein SL. Anemia in the elderly: clinical implications and new therapeutic concepts. *Haematologica.* 2014;99(7):1127-1130.
- Willems JM, den Elzen WP, Vlasveld LT, et al. No increased mortality risk in older persons with unexplained anaemia. *Age Ageing.* 2012;41(4):501-506.
- Lucca U, Tettamanti M, Mosconi P, et al. Association of mild anemia with cognitive, functional, mood and quality of life outcomes in the elderly: the "Health and Anemia" study. *PLoS One.* 2008;3(4):e1920.
- Thein M, Ershler WB, Artz AS, et al. Diminished quality of life and physical function in community-dwelling elderly with anemia. *Medicine (Baltimore).* 2009;88(2):107-114.
- Bang SM, Lee JO, Kim YJ, et al. Anemia and activities of daily living in the Korean urban elderly population: results from the Korean Longitudinal Study on Health and Aging (KLoSHA). *Ann Hematol.* 2013;92(1):59-65.
- Langer AL, Ginzburg YZ. Role of hepcidin-ferroportin axis in the pathophysiology, diagnosis, and treatment of anemia of chronic inflammation. *Hemodial Int.* 2017;21 (Suppl 1):S37-S46.
- Weiss G, Goodnough LT. Anemia of chronic disease. *N Engl J Med.* 2005;352(10):1011-1023.
- Ferrucci L, Penninx BW, Volpato S, et al. Change in muscle strength explains accelerated decline of physical function in older women with high interleukin-6 serum levels. *J Am Geriatr Soc.* 2002;50(12):1947-1954.
- Olivares M, Hertrampf E, Capurro MT, Wegner D. Prevalence of anemia in elderly subjects living at home: role of micronutrient deficiency and inflammation. *Eur J Clin Nutr.* 2000;54(11):834-839.
- Kimel M, Leidy NK, Mannix S, Dixon J. Does epoetin alfa improve health-related quality of life in chronically ill patients with anemia? Summary of trials of cancer, HIV/AIDS, and chronic kidney disease. *Value Health.* 2008;11(1):57-75.
- Roger SD, Jassal SV, Woodward MC, Soroka S, McMahon LP. A randomised single-blind study to improve health-related quality of life by treating anaemia of chronic kidney disease with Aranesp(R) (darbepoetin alfa) in older people: STIMULATE. *Int Urol Nephrol.* 2014;46(2):469-475.
- Boccia R, Lillie T, Tomita D, Balducci L. The effectiveness of darbepoetin alfa administered every 3 weeks on hematologic outcomes and quality of life in older patients with chemotherapy-induced anemia. *Oncologist.* 2007;12(5):584-593.
- Agnihotri P, Telfer M, Butt Z, et al. Chronic anemia and fatigue in elderly patients: results of a randomized, double-blind, placebo-controlled, crossover exploratory study with epoetin alfa. *J Am Geriatr Soc.* 2007;55(10):1557-1565.
- Vagetti GC, Barbosa Filho VC, Moreira NB, Oliveira V, Mazzardo O, Campos W. Association between physical activity and quality of life in the elderly: a systematic review, 2000-2012. *Rev Bras Psiquiatr.* 2014;36(1):76-88.
- Molzahn A, Skevington SM, Kalfoss M, Makaroff KS. The importance of facets of quality of life to older adults: an international investigation. *Qual Life Res.* 2010;19(2):293-298.
- Lee G, Choi S, Kim K, et al. Association of hemoglobin concentration and its change with cardiovascular and all-cause mortality. *J Am Heart Assoc.* 2018;7(3).