Long-term Mortality Risks Associated With Mild Anaemia in Older Persons: The Busselton Health Study

Running Head: Mortality and Anaemia

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Key points:

- Anaemia (WHO criteria) was associated with increased all cause and cancer deaths at 10 years and 23 years follow-up in men but not woman

- Cancer deaths primarily reflected prostate and genito-urinary cancer and, to a lesser extent, gastrointestinal cancer

- Anaemia is not just a 'women's problem'

- All anaemia, including mild anaemia, should be investigated in both men and women of middle age and beyond

ABSTRACT

Background

Up to 25 % of older people in the USA and other Western countries are anaemic by World Health Organization (WHO) criteria. The objective of this study was to examine the long-term relationships of haemoglobin concentration with all-cause and cause-specific mortality in a community-based sample of Australian adults surveyed in 1978.

Methods

A community survey of 2,194 adults aged 40+ years in Busselton, Western Australia in 1978 with mortality follow-up to 2001. Cox regression models were used to investigate the relationships of haemoglobin as a continuous measure and anaemia by WHO criteria (women below 12 g/dL (7.5 mmol/L); men below 13 g/dL (8.1 mmol/L)) with all cause, cardiovascular and cancer mortality.

Results

Anaemia was predominantly mild (>10 g/dL) and normocytic. There was increased risk of death from all causes and from cancer for men with low haemoglobin. Cancers were predominantly of the prostate and genito-urinary organs, and to a lesser extent the gastrointestinal tract. There was no increased risk of all cause or cancer death in women.

Conclusion

Mild, normocytic anaemia is associated with survival reductions in middle-aged and older men, where it often occurs with prostate, gastrointestinal and other cancers, and should be investigated to exclude treatable causes.

INTRODUCTION

Community epidemiological studies [1-7] over the past two decades show that many older people in the United States and elsewhere are anaemic by World Health Organization (WHO) criteria [8]. According to a 2004 report of the United States National Health and Nutritional Examination Survey III (NHANES), approximately 10% of Americans 65 years and older are anaemic, rising to 25% of men and 20% of women 85 years and older [7]. High prevalences of anaemia in older people have also been reported in community studies from Europe [1, 5, 9] and Australia [6]. Although at younger ages, anaemia is usually more prevalent in women, higher prevalences of anaemia in older men compared to older women have been found in several community studies, with prevalences as high as 25-45% reported for men aged 80 years or more [1-3, 5, 6, 9].

How serious are the outcomes associated with this widespread anaemia? There is disagreement over the definition, clinical sequelae and management of anaemia in older persons. Such anaemia is often mild and could conceivably have few if any related risks. Average haemoglobin concentrations are lower in older age groups (reviewed [10-13]). Consequently there have been calls to revise anaemia criteria for older people, on the grounds that mild haemoglobin decreases are a normal consequence of healthy ageing and not associated with clinically significant disease risks or unfavorable outcomes [9, 14-17].

However, higher haemoglobin levels have been observed in groups of older people selected to minimize diseases, medications and other factors influencing haematological values [10, 13]. There is also evidence that even mild reductions in haemoglobin may be associated with higher mortality in older people. A European community study of 755 people 85 years or older, with a 10-year follow up, has found anaemia by WHO criteria is associated with increased mortality risks, with the greatest risks occurring in men [5]. Similarly Kikuchi and colleagues [18] reported

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that nursing home residents with anaemia defined as haemoglobin <11 g/dL had significantly lower survival rates than non-anaemic controls. Survival was also greater with increasing haemoglobin concentrations in disabled, community-dwelling women aged 70 to 80 years in the Women's Health and Ageing Study [19]. A large Canadian study of pathology laboratory haemoglobin data for 17,030 community dwelling adults 66 years or older followed for three years found that both very low and very high haemoglobin concentrations were associated with increased mortality [20]. Similar results were obtained in a study of 4089 NHANES III participants followed for 6-12 years, although not all ethnic groups showed mortality increases with high haemoglobin [21].

Anaemia may also have other serious consequences in older people. A 4-year prospective community cohort study of 1146 Americans 65 years or more found that, compared to other participants, people anaemic by WHO criteria showed greater average rates of decline in physical performance (including balance and gait speed). Faster decline in physical performance was in turn associated with greater risks of hospitalization, nursing home admission, subsequent disability and mortality, however these were not examined directly [22]. Similarly in the Women's Health and Ageing Study mobility difficulties were found to be greater at lower haemoglobin concentrations [23].

In contrast, mild normocytic anaemia in the absence of apparent inflammation, although showing a trend to lower survival, did not significantly reduce survival in a 5-year follow up study of 52 people aged 65 years or more referred to a geriatric service [16]. It was proposed that apparent mortality was inflated in some previous studies because of failure to correct for clinical disease, failure to restrict analyses to normocytic anaemia or failure to exclude more severe anaemias with haemoglobin <10 g/dL [16]. These authors and others suggest that there is little yield from

investigations of the mild, normocytic anaemia often seen in older subjects in the absence of inflammation [16, 17, 24].

These conflicting findings highlight the need for larger community epidemiological studies of the long-term outcomes of mild anaemia in older subjects. The number of people affected and the potential socioeconomic costs are substantial. In the present study, we investigate mortality risks associated with anaemia over longer follow up periods in community residents aged 40 years or more. Commencing in 1966, people from the Western Australian community of Busselton have participated in a series of comprehensive health surveys (reported elsewhere [e.g. 25, 26]). We have investigated the relationship between anaemia and mortality in the Busselton 1978 survey cohort (2,194 participants) with mortality follow-up until 2001, a maximum of 23 years. To the best of our knowledge, this represents both one of the largest community groups so far investigated for anaemia-related mortality risks and also the longest follow-period so far reported.

METHODS

The study cohort

The target population for the 1978 Busselton survey was all resident adults registered to vote (voter registration is compulsory in Australia) and the overall participation rate was 74%. We have not made any adjustment for non-response in the cohort follow-up analysis.

The 1978 survey cohort was chosen because haemoglobin and a range of clinical variables relevant to disease history were available from this survey. Participants were asked to complete a comprehensive health and lifestyle questionnaire and to undergo various measurements and tests. Smoking and alcohol consumption, asthma, diabetes, history of arthritis, recurrent infections,

thyroid disease, use of anti-hypertensive medication and, in women, menopausal status and number of pregnancies, were obtained by questionnaire.

Height was measured by stadiometer for bare-footed subjects. Weight was measured with subjects in light underclothes. Body mass index was derived as weight (kilograms) divided by the square of height (metres). Systolic and diastolic blood pressures were measured by mercury sphygmomanometer after five minutes rest in a sitting position. Coronary heart disease was determined from the WHO Rose Questionnaire for angina and myocardial infarction and the electrocardiogram together with a self-reported confirmation that a doctor had said they had heart disease. Haemoglobin, mean red cell volume, white cell count, serum cholesterol and triglycerides were determined from a fasting blood sample at the time of survey.

Mortality follow-up

Mortality follow-up to 2001 (23 years total) was available from record linkage to the state death register. Underlying cause of death was coded as cardiovascular diseases for ICD9 390-459 or ICD10 I00-I98 and cancer for ICD9 140-239 or ICD10 C00-C97. There were too few deaths due to other and more specific causes such as colorectal cancer, respiratory diseases and infections for reliable analysis.

Statistical analysis

The relationship of haemoglobin level to mortality was assessed by Cox proportional hazards regression after adjustment for measured confounders. The confounders were age, alcohol consumption, arthritis, asthma, blood pressure, body mass index, coronary heart disease, diabetes, history of cancer other than skin cancer, history of chest, kidney, bladder, throat, sinus or ear

infections, mean red cell volume, smoking, thyroid disease, total and high density lipoprotein (HDL) cholesterol, triglycerides and white cell count.

The analyses are restricted to people aged at least 40 years at survey having data on haemoglobin and confounding variables and with pregnant women and people with body mass index under 16 (i.e. possibly malnourished) excluded, leaving 2,194 people for analysis. Haemoglobin has been analysed as both a continuous variable and a categorical variable with the lowest category defined as those who are anaemic according to WHO criteria (men <13 g/dL or <8.1 mmol/L; women <12 g/dL or <7.5 mmol/L). Anaemia was defined by mean cell volume (MCV) as microcytic (MCV<80 fl), normocytic (MCV 80-100 fl) or macrocytic (MCV>100 fl). Cox regression results for continuous haemoglobin are expressed as a hazard ratio per decrease of 1 g/dL and those for categorical haemoglobin as a hazard ratio in comparison to the referent category. Estimated hazard ratios (relative risk) and 95% confidence intervals are provided. Confidence intervals excluding one are significant at the 5% level of significance. Hazard ratio estimates are presented for all people aged 40+ years and, where feasible, also separately for people aged 75+ years. We have conducted an analysis that uses the maximum available follow-up (up to 23 years) as well as an analysis that restricts follow-up to 10 years.

Written informed consent was obtained from all participants. The mortality follow-up linkage was approved by the Confidentiality of Health Information Committee of Western Australia and all protocols and analyses were approved by the Human Research Ethics Committee of the University of Western Australia.

Declaration of Source of Funding

RESULTS

The cohort included 1,025 men with 554 deaths, 279 cardiovascular deaths and 145 cancer deaths, and 1,169 women with 437 deaths, 227 cardiovascular deaths and 110 cancer deaths during the full 23 year follow-up period. There were 92 men (91 deaths during follow-up) and 102 women (101 deaths during follow-up) who were aged 75 years and older at baseline. There were a total of 207 deaths among men and 153 among women during the first 10 years of follow-up. The average age at survey was 60 years for men and 59 years for women. For men, the average haemoglobin level was 15.2 g/dL (SD 1.0 g/dL) and 16 were anaemic by WHO criteria (prevalence 1.6%), with a range of 11.2-12.9 g/dL. For women, the average haemoglobin level was 13.9 g/dL (SD 0.9 g/dL) and there were 29 (prevalence 2.5%) with anaemia with a range of 9.4-11.9 g/dL. Prevalence was higher in older than in middle-aged groups with 6.7% of men and 9.5% of women aged 80+ years being anaemic. Table 1 shows the number with anaemia by age group. The characteristics of the participants for the full cohort and for those with anaemia are presented in Table 2.

The multivariate-adjusted hazard ratios for haemoglobin from Cox regression analyses are displayed in Table 3. Using the full 23 years of follow-up, there is evidence of increased risk of death from all causes and increased risk of cancer death for men with lower haemoglobin. The continuous trend model estimates that the risk of death increases by a factor of 1.13 per 1 g/dL decrease in haemoglobin (p = .01) and the categorical model estimates a relative risk of 1.74 (p = .07) for anaemic men compared to men with haemoglobin 13.0-15.9 g/dL. Similarly, the relative risk of cancer death is 1.24 per 1 g/dL decrease (p = .02) and 4.70 (p <.001) for the anaemic group compared to men with haemoglobin 13.0-15.9 g/dL. Men with high haemoglobin (16.0+ g/dl) had lower (albeit not statistically significant) risk of all cause death and cancer death than men with haemoglobin 13.0-15.9 g/dL supporting a monotonic relationship rather than a U-shaped relationship. Hazard ratios from a Cox model with five haemoglobin categories also support a monotonic relationship (see the figure Appendix 1 in the supplementary data on the journal website http://www.ageing.oxfordjournals.org).

There is no increased risk of cardiovascular death in men and no increased risk of all cause death, cardiovascular death or cancer death in women. The pattern of relative risks is largely unchanged when mortality follow-up is restricted to 10 years or the cohort is restricted to those aged 75+ years in 1978 although the confidence intervals are wider, due to smaller numbers of deaths. Similar patterns of relative risk are also seen when the analysis is restricted to men with normocytic anaemia compared to non-anaemic men. The hazard ratios (95% confidence interval) for the multivariate model fitted to the full cohort of males (aged 40+ years) for normocytic anaemia in relation to all cause mortality and cancer mortality were 2.54 (1.24, 5.24) and 5.28 (2.01, 13.88) respectively.

The cancers to which death was attributed in the anaemic men were predominantly neoplasms of the prostate/genito-urinary organs (accounting for half of the total cancer deaths) and gastrointestinal cancers (accounting for a quarter of the total cancer deaths).

DISCUSSION/COMMENT

This prospective analysis of haemoglobin in relation to mortality for a population-based cohort from Busselton, Australia, provides evidence that men with low haemoglobin have increased risk of all-cause death and cancer death. Effects were not restricted solely to the older participants. While risks were greater in the older age group (75 years or more), significant risks were also found in the full group (40 years or more).

Anaemia in men was typically mild (>10 g/dL haemoglobin) and predominantly normocytic yet still associated with substantially reduced survival. Proposals that little may be gained from investigations for older people with normocytic anaemia have been based partly on shorter studies over 1-5 years, frequently with high proportions of women [16, 24]. While anaemia is often viewed as mostly affecting women [19], the prevalence and mortality risks of anaemia in older men in the Busselton survey was, in general, similar to or higher than in women. While some studies have not observed gender differences [e.g. 20], our observations are consistent with other studies, including NHANES II, which observed higher prevalence [1-3, 5, 9, 27] and sometimes higher mortality risk [5, 18] in older men. Gender differences in anaemia prevalence in NHANES II may in part reflect differences in anaemia subtype prevalence [27], a factor which might also explain some of the differences between studies in gender-specific mortality risks. Differences in the prevalence and management of prostate cancer may also contribute.

We did not observe the U-shaped or reverse J-shaped curves with increased mortality risks at higher Hb levels that have been seen in some studies [20, 21]. Increased mortality with higher Hb may be in part attributable to atherosclerotic cardiovascular events and factors such as increases in Hb with smoking may also need to be taken into account [28].

In general, anaemia prevalence for both men and women was lower in the 1978 Busselton cohort than in either the 1988-1994 United States NHANES III study [7] or an Australian study of Sydney community residents 75 years or older, surveyed in 1997 [6]. However prevalence was comparable to data obtained in 1976-1980 in the NHANES II study, where 3.4% of men and 3.7% of women of age 45-64 years were anaemic based on Hb below a 95% reference range [27]. It is unclear whether the higher prevalence seen in the later studies reflects generalised increases in anaemia prevalence over time in countries such as Australia and the US. Both the prevalence and the consequences of anaemia in older people will depend on many factors including age, gender, etiology and clinical interventions, as well as socioeconomic status, diet and other lifestyle and environmental factors.

The mortality risks for different populations will reflect in part the proportions of anaemias with different etiologies within a population at a particular time. In the NHANES III analysis, approximately a third of anaemias were attributed to nutritional deficiencies (iron, vitamin B12 or folate), a third were deemed anaemias of chronic inflammation (also termed anaemias of chronic disease) or renal failure and the remaining third were of unknown etiology [7]. While etiologies could not be examined in depth in our study, the findings support contentions that anaemia in older people is attributable primarily to malnutrition or to underlying infectious, inflammatory, neoplastic or other disease rather than 'normal ageing' [2, 5, 12, 29]. Even mild anaemia may provide an early warning signal for occult cancer or reflect or contribute to cardiovascular disease or other serious health conditions. Of note, cancers of the prostate and genito-urinary organs

were the predominant forms of cancer contributing to mortality in anaemic men, and this should be taken into account when investigating anaemia in older male patients. The relatively low mortality attributable to gastrointestinal cancers might partly reflect more aggressive investigation for these cancers in anaemic older people. Anaemia due to treatment, hypogonadism, malnutrition or other factors is recognized to be common in patients with advanced prostate cancer, where it is associated with poor prognosis [30]. As far as we are aware, prostate cancer has not previously been highlighted in community studies of anaemia as an important factor contributing to reduced survival in men with mild anaemia.

In conclusion, mild anaemia is associated with significantly increased mortality in middle-aged and older men and should be investigated to exclude treatable causes. Further studies are required to ascertain the optimal investigation strategies for each gender.

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Table 1. Number of subjects with anaemia by age group

Age group	All	No anaemia	Microcytic anaemia	Normocytic anaemia	Macrocytic anaemia
MEN					
40-49	228	226	0	2	0
50-59	271	269	0	1	1
60-69	295	290	1	4	0
70-79	201	196	2	2	1
80-89	28	26	1	1	0
90+	2	2	0	0	0
Total	1025	1009	4	10	2
WOMEN					
40-49	284	273	7	4	0
50-59	353	347	1	5	0
60-69	317	312	2	3	0
70-79	173	170	1	2	0
80-89	37	34	0	3	0
90+	5	4	0	1	0
Total	1169	1140	11	18	0

Table 2. Characteristics of subjects overall and separately for those with anaemia.

	Anaemic men (n=16)	All men (n=1,025)	Anaemic women (n=29)	All women (n=1,169)
Age (years)	68 (11)	60 (11)	60 (15)	59 (11)
Haemoglobin (mg/dL)	12.3 (0.6)	15.2 (1.0)	11.2 (0.7)	13.9 (0.9)
Mean cell volume	88 (9)	90 (4)	83 (10)	89 (5)
Arthritis (%)	44	38	52	45
Asthma (%)	0	5	3	5
History of non-skin cancer (%)	19	3	3	4
History of chest infection (%)	12	9	3	6
History of kidney/bladder infection (%)	12	2	17	9
History of ear/sinus/throat infections (%)	31	16	7	19
Thyroid disease (%)	0	1	7	8
Coronary heart disease (%)	25	13	17	10
Diabetes (%)	6	3	3	3
Smoking (%) (never/ex/light/heavy)	38/44/12/6	24/47/14/14	79/14/3/3	63/20/7/10
Alcohol (%) (never/ex/light/heavy)	19/19/50/12	9/8/52/30	45/10/34/10	26/10/53/11
Body mass index (kg/m2)	25.1 (3.4)	26.1 (3.2)	25.5 (5.5)	25.5 (4.1)
Total cholesterol (mmol/L)	5.1 (1.2)	6.1 (1.2)	6.1 (1.4)	6.3 (1.3)
HDL cholesterol (mmol/L)	1.5 (0.5)	1.4 (0.3)	1.6 (0.3)	1.7 (0.4)
Triglycerides (mmol/L)	1.43 (0.51)	1.52 (1.04)	1.22 (0.80)	1.25 (0.71)
Diastolic BP (mmHg)	73 (13)	78 (13)	76 (13)	77 (12)
Systolic BP (mmHg)	137 (28)	140 (21)	138 (25)	139 (23)
White cell count	68 (24)	71 (19)	61 (20)	65 (18)
Post menopause (%)			55	76
Number pregnancies (%) 0/1-3/4+			21/39/41	11/45/44

Table 3. Effects of haemoglobin concentration on mortality Multivariate-adjusted* hazard ratios for haemoglobin (Hb) in relation to all cause mortality, cardiovascular mortality and cancer mortality in subjects aged 40+ years and in the group aged 75+ years using full 23 years follow-up and when follow-up is restricted to 10 years. Table shows hazard ratio (95% confidence interval).

| | MEN | | | WOMEN | | |
	Continuous Hb (1 g/dL decrease)	<13.0 vs. 13.0-15.9	16.0+ vs. 13.0-15.9	Continuous Hb (1 g/dL decrease)	<12.0 vs. 12.0-14.9	15.0+ vs. 12.0-14.9
ALL DEATHS						
Age 40+ cohort 23 years	1.13 (1.03, 1.24)	1.74 (0.95, 3.21)	0.91 (0.73, 1.14)	1.00 (0.89, 1.12)	1.59 (0.89, 2.86)	1.16 (0.86, 1.56)
Age 40+ cohort 10 years	1.19 (1.03, 1.37)	1.64 (0.73, 3.70)	0.83 (0.56, 1.22)	1.04 (0.86, 1.25)	2.24 (1.00, 4.99)	1.10 (0.66, 1.82)
Age 75+ cohort 23 years	1.30 (0.99, 1.70)	1.17 (0.29, 4.66)	0.84 (0.37, 1.88)	1.10 (0.85. 1.43)	0.68 (0.22, 2.12)	0.95 (0.29, 3.16)
Age 75+ cohort 10 years	1.46 (1.07, 2.00)	1.88 (0.41,8.56)	0.88 (0.35, 2.20)	1.06 (0.77, 1.45)	0.63 (0.16,2.52)	0.71 (0.15, 3.42)
CARDIOVASCULAR DEATHS						
Age 40+ cohort 23 years	1.03 (0.90, 1.17)	0.65 (0.19, 2.24)	1.13 (0.84, 1.53)	1.05 (0.90, 1.24)	1.70 (0.78, 3.70)	0.92 (0.58, 1.46)
Age 40+ cohort 10 years	0.98 (0.79, 1.20)	0.32 (0.04, 2.84)	1.15 (0.70, 1.89)	0.99 (0.76, 1.30)	1.41 (0.42, 4.72)	1.08 (0.48, 2.42)
Age 75+ cohort 23 years	1.10 (0.70, 1.73)	0.60 (0.04, 8.88)	1.08 (0.37, 3.11)	1.08 (0.77, 1.52)	0.34 (0.07, 1.69)	0.54 (0.08, 3.51)
CANCER DEATHS						
Age 40+ cohort 23 years	1.24 (1.03, 1.48)	4.70 (2.08, 10.59)	0.73 (0.45, 1.17)	0.88 (0.70, 1.11)	**	**

Age 40+ cohort 10 years	1.48 (1.15, 1.92)	6.71 (2.35, 19.15)	0.55 (0.23, 1.34)	0.78 (0.52, 1.17)	**	**
Age 75+ cohort 23 years	1.95 (0.96, 3.98)	44.4 (1.23, 1602)	0.43 (0.04, 4.18)	3.35 (0.71, 15.9)	**	**

* Adjusted for age, alcohol consumption, arthritis, asthma, blood pressure, body mass index, coronary heart disease, diabetes, history of cancer other than skin cancer, history of chest, kidney, bladder, throat, sinus or ear infections, mean red cell volume, smoking, thyroid disease, total and high density lipoprotein (HDL) cholesterol, triglycerides and white cell count.

** Insufficient cancer deaths for relative risk estimation