Using longitudinal data from the Health Survey for England to resolve discrepancies in thresholds for haemoglobin in older adults

Authors: Jennifer Mindell[1], Alison Moody[1], Ayesha Ali[1], Vasant Hirani[1]

[1]Department of Epidemiology and Public Health, University College London, UK

Address correspondence to:

Dr Jennifer Mindell,

Department of Epidemiology and Public Health, UCL, 1-19 Torrington Place, London WC1E 6BT, UK.

email: j.mindell@ucl.ac.uk

Text word count: 2963 (excluding summary, references, acknowledgements, figure legends and tables)

Summary word count: 198

Short title

Thresholds for haemoglobin in older adults in England

Summary

Anaemia increases with age and is common among older people. Due to its relationship with morbidity and mortality, accurate diagnosis is important. Thresholds defining the diagnosis of anaemia have been the subject of considerable scientific debate, with both higher and lower cut-offs proposed. High haemoglobin is also a health risk in some but not all studies. Using nationally representative data of 5,329 adults aged 65+ (Health Survey for England 1998, 2005, 2006), linked to administrative mortality data, this paper describes the relationship between haemoglobin levels and mortality, adjusted for age and other confounders. Among men, a reverse J shaped relationship was observed: relative to the modal group (14– 14.9g/dl), those with 'mild anaemia' of 12–12.9g/dl haemoglobin had a 56% (95% CI 24%-96%) greater mortality hazard, and those with 'severe anaemia', haemoglobin <12g/dl, had an 87% (39%-153%) greater hazard. At the other end of the range, those with haemoglobin of ≥16g/dl had 32% (2%-70%) greater mortality hazard. Haemoglobin levels in women showed a similar but smaller, non-significant pattern: hazard ratio 1.32 (0.91-1.92) for severe anaemia (<11g/dl), and 1.30 (0.95-1.79) for high haemoglobin (≥15g/dl). This research supports the use of the WHO thresholds (13g/dl for men, 12g/dl for women).

Key words

Haemoglobin, anaemia, mortality, older people, survey

Introduction

Anaemia is a common problem, particularly among older people (aged 65 and over) (Beghe *et al*, 2004; Guralnik *et al*, 2004; Craig *et al*, 2007). Although the underlying cause is not identified in up to one in three cases (Penninx *et al*, 2006; Tettamanti *et al*, 2010), many diseases and conditions are associated with anaemia, including cancer, chronic kidney disease, chronic inflammation, congestive heart failure, iron deficiency and other nutritional deficiencies, bone marrow failure and malnutrition (Penninx *et al*, 2006). Anaemia is also associated with depression (Onder *et al*, 2005). The cause of anaemia may affect haemoglobin concentration, with most studies finding that haemoglobin concentrations are lowest in those with iron deficiency anaemia, closest to normal in anaemia of inflammation, with unexplained anaemia in between (Merchang *et al*, 2012).

Regardless of cause, individuals with anaemia have increased mortality (Chaves *et al*, 2004; Zakai *et al*, 2005; Culleton *et al*, 2006; Bross *et al*, 2010) and morbidity, including hospitalization (Penninx *et al*, 2006; Culleton *et al*, 2006), physical disability (Maraldi *et al*, 2006), poor physical function and falls (Penninx *et al*, 2005), and fracture incidence (Chen *et al*, 2010), and more rapid decline in cognitive function (Shah *et al*, 2011). Anaemia affects disease-related mortality, morbidity and quality of life (Spivak *et al*, 2005; Zakai *et al* 2005), independently of prevalent diseases at baseline (Penninx *et al*, 2005; Penninx *et al*, 2006; Shah *et al*, 2011), though some associations are due primarily to comorbidity (Maraldi *et al*, 2006).

However, a several studies have criticized the use of the World Health Organization (WHO) criteria (<13g/dl [<8.1mmol/l] haemoglobin for men, <12g/dl [<7.5mmol/l] haemoglobin for women) for older adults (Isaks et al, 1999; Patel et al, 2009). These criteria were developed in 1968, based on statistical distributions equivalent to two standard deviations below the mean in a reference sample aged <65 years. Thresholds defining anaemia in older populations have been the subject of considerable scientific debate. Some studies used lower, non-sex specific, thresholds for anaemia among the elderly, including <11g/dl (Culleton *et al* 2006) and <11.5g/dl (Joosten *et al* 1992). Riva *et al* (2009) used <10.0 g/dl to differentiate "Severe anaemia", from "Mild anaemia" (>=10 but under the WHO limits). Others have used higher, sex specific thresholds: 0.2g/dl above WHO limits (Beutler and Waalen 2006); and 0.1-2.0g/dl above WHO limits, i.e. "low-normal haemoglobin" (Penninx et al, 2006; Chaves et al, 2002). Additionally, three studies in older adults have shown elevated mortality amongst those in the highest *and* in the lowest quintiles of haemoglobin levels, (Zakai *et al*, 2005; Culleton *et al*, 2006), even after extensive adjustment for other factors (Dharmarajan *et al*, 2005).

This paper investigates which haemoglobin levels are associated with all-cause mortality in adults in the general population and examined the effects of different haemoglobin levels on mortality, to contribute to the debate on the thresholds for harmful haemoglobin levels in older people.

Materials and Methods

Participants

The Health Survey for England (HSE) is an annual, cross-sectional survey of a nationally representative sample of adults and children living in private households in England (Mindell *et al*, 2012). Each year, core modules of questions and measurements are supplemented by population boosts and/or or additional topics. In 1998 and 2006, modules were included on cardiovascular disease and physical activity; in 2005, the HSE focused on the health, risk factors, and determinants of health of people aged 65+ (Erens *et al*, 2000; Craig *et al*, 2007; Craig *et al*, 2008).

Data collection

The sampling design and method have been described in detail elsewhere (Erens *et al*, 2000; Craig *et al*, 2007; Craig *et al*, 2008). A random sample was selected each year using a two-stage, stratified process. After sending a letter, an interviewer visited the address to recruit the participants and conduct the interviews, using computer-assisted personal interviewing (CAPI).

Household-level socio-demographic data included equivalised household income (income adjusted for the number of adults and children in the household). Individual-level socio-demographic data (occupational social class and years of education) were supplemented by questions about general self-reported health, smoking, (other health behaviours had been measured in non-comparable ways in different survey years), and doctor-diagnosed cardiovascular conditions (CVD, namely stroke, myocardial infarction,

angina, dysrhythmia, heart murmur or other heart condition, not asked of half the sample aged 65+ in 2006).

Participants were also asked whether they had “any longstanding illness, disability or infirmity”. Those who replied ‘yes’ were asked whether this had limited their daily activities or the work that they could do in any way. The interviewer also measured height and weight. After the interviewer visit, non-fasting blood samples were obtained from consenting adults during a nurse visit. For participants who gave consent for their data to be linked to NHS records, their identifying information was sent to the NHS, to be flagged as an HSE participant. The mortality data for all flagged respondents was extracted in January 2011, stating for each person whether or not they had died, and if so, when.

Blood samples were posted to the Department of Clinical Biochemistry at the Royal Victoria Infirmary, Newcastle for analysis. Haemoglobin was measured on Abbott Diagnostics Cell-Dyn 4000 analysers. Further details of laboratory measurements and of quality control are available elsewhere (Erens *et al*, 2000; Craig *et al*, 2007; Craig *et al*, 2008).

Ethical approval

Ethical approval for the three surveys was obtained from the London Multi-centre Research Ethics Committee (MREC) prior to the surveys. All participants gave oral consent to be interviewed and have measurements made, and written consent to have blood samples taken and mortality data linked to the survey data.

Statistical analysis

Analyses in this paper include participants aged 65+ from HSE 1998, 2005 and 2006, who had given consent for their data to be linked to mortality data, and had provided a valid haemoglobin sample (Table 1). Haemoglobin levels vary by race/ethnicity and the impact on mortality of a given level may also vary (Denny *et al* 2006; Patel *et al* 2007; Dong *et al* 2008; Patel *et al* 2009). As numbers from non-white groups were too small for separate analysis (1.5% were non-white), this paper is restricted to data from people of a white ethnic background. Overall, 51% of those interviewed who were included in the analysis.

Haemoglobin results were grouped in two ways: by sex-specific quintile, and by bands defined by 1g/dl relative to the WHO criteria for each sex (haemoglobin <13g/dl [<8.1mmol/l] in men and <12g/dl [<7.5mmol/l] in women). People taking iron or other hematinics were also excluded from these analyses. With the data available, it was not possible to distinguish the cause of anaemia, therefore only haemoglobin results were used for the categorization.

Non-response weighting was introduced to HSE in 2003, as with other UK government surveys, because of falling response rates. Variables enabling adjustment for complex survey design were also introduced at that time. Except when describing participants' characteristics (Table 2), the data were weighted for non-response to the blood sample, so that although some groups tended to be over or under-represented in a, the survey and b, the blood sample, this was corrected in the analysis (using weights provided for

2005 and 2006, and a weight of 1 for the 1998 sample), and the complex survey design accounted for in the analysis: data from 1998 were ascribed dummy variables for strata and sampling point.

Survival analysis was carried out using STATA version 12 to estimate the hazard of death in the substantially censored data (by the end of follow-up, 5-13 years post-interview, 72% of the sample were censored, i.e. still alive). Cox's regression was used to estimate the hazard ratio of time to death post-interview for each quintile of haemoglobin relative to the middle quintile and also for each 1g/dl group relative to the modal group whilst controlling for other significant factors. Preliminary analysis showed marked sex differences, so analyses were conducted separately by sex. All analyses were adjusted for age using five-year age groups to 85+.

Socio-economic factors (education, income, and social class), smoking, BMI, longstanding illness, and self-reported doctor-diagnosed CVD were assessed in univariate analyses then significant variables considered in multivariate Cox regression. Age at leaving full-time education explained more of the variation in outcome than other socio-economic factors. CVD was not significant when longstanding illness, age and haemoglobin group were included; and since longstanding illness was available for the full sample, but CVD asked only of half the 2006 sample, CVD was not included in the final models. Kaplan-Meier survival curves were prepared comparing participants in the different haemoglobin bands. Adjacent, central bands with similar hazard ratios were combined to limit the number of curves displayed (see Figure 2).

Results

Response rates by survey year and sex are provided in Table 1. Among the sample available for survival analysis, 2446 men and 2863 women aged 65+ provided usable blood samples. Participant characteristics (unweighted and without adjustment for complex survey design) are presented in Table 2. The prevalence of anaemia (weighted for non-response) was 14% for men and 11% for women, including 5% of men and 3% of women with haemoglobin more than 1g/dl below WHO thresholds. Anaemia prevalence increased with age, from 6% of men aged 65-69, to 31% of those aged 85+, and from 5% to 22% of women. High haemoglobin levels (haemoglobin ≥ 3g/dl above the WHO anaemia threshold) decreased with age, from 13% to 6% among men, and 9% to 4% among women. The modal haemoglobin band was 1-2g/dl above the WHO threshold for both sexes (mean 14.4g/dl in men, 13.4g/dl in women).

Figure 1, panels A and B, show hazard ratios for time to death by quintile of haemoglobin level, adjusted for other significant factors. For men, only the lowest quintile differed significantly from the middle quintile. For women, no quintile was significantly different from the middle quintile. As categorization by haemoglobin band appears to be more discriminating (panels C and D), the rest of this paper focuses on the haemoglobin bands.

When adjusted only for age, the highest hazard ratio among men was for the lowest haemoglobin group, <12 g/dl (HR 2.19, 95%CI 1.66–2.90). Mild anaemia (haemoglobin 12.0-12.9 g/dl) was also a significant risk (1.64, 1.31–2.06), as was high haemoglobin (≥ 16g/dl, HR 1.35, 1.04–1.74). For women, only those with more severe anaemia (<11g/dl)

had a significant risk (age-adjusted HR. 1.61, 1.08–2.41). Unlike men, neither women with mild anaemia (11.0-11.9 g/dl) nor with high haemoglobin (≥ 15g/dl) had significantly raised hazard ratios (p=0.06 in both cases), but the sample sizes and number of deaths among these groups were smaller for women than men.

When additional variables were added to the model, lower education, current or previous smoking, having a limiting longstanding illness, and being underweight were also associated with mortality (being overweight was associated with survival among women only). After adjustment for these factors, the significance and magnitude of the risk posed by high or low haemoglobin fell slightly for both men and women, but remained significant for men. For men, the highest hazard ratio remained for those with more severe anaemia, <11g/dl (HR 1.87, CI 1.39–2.53). Mild anaemia (haemoglobin 11.0-11.9g/dl) was also a significant risk (1.56, 1.24–1.96), as was high haemoglobin (≥ 16g/dl (1.32 1.02–1.70, Figure 1C). For women, after adjustment for multiple factors, no haemoglobin band showed significant difference from the reference group, although a non-significant U-shaped association was seen (Figure 1D).

Kaplan-Meier curves showed that survival was worst for men with more severe anaemia but was also worse for those with mild anaemia or high haemoglobin, compared with those whose baseline haemoglobin was 0-3g/dl above the WHO thresholds (Figure 2A). For women, no significant differences were seen (Figure 2B).

Discussion

Anaemia is of concern because of the morbidity and mortality associated both with the abnormally low haemoglobin level and with the underlying cause(s) of the anaemia, a condition which is common and increases with age (Beghe *et al* 2004; Guralnik *et al* 2004; Craig *et al* 2007). As the population ages and the prevalence of anaemia increases, an understanding of these associations is essential. We have shown that for men, both mild and more severe anaemia were significantly associated with reduced survival, compared with normal haemoglobin, defined using WHO thresholds. The group with the highest levels of haemoglobin (≥ 16g/dl) also had a significantly raised adjusted hazard ratio. It is unclear whether any U shaped or reverse J shaped effect on mortality operates through the same causal pathways at both high and low values. Although anaemia was significantly associated with mortality only in men among these HSE participants, a similar relationship was seen in women but the 95% confidence intervals were wide.

Greater detail about the relationship between haemoglobin level and mortality hazard can be seen using haemoglobin bands than quintiles. This is probably because the lowest and highest quintiles each included people with normal haemoglobin levels, which we have shown was not associated with mortality in our study.

Although the presence of ‘low normal’ haemoglobin levels has previously been associated with increased morbidity and mortality (Zakai *et al* 2005; Penninx *et al* 2006), there was no association between survival and ‘low normal’ haemoglobin in HSE

participants. Our study provides reassurance that the current WHO thresholds are neither too low, unlike some studies' conclusions (Zakai *et al* 2005; Patel *et al* 2009), nor too high, as proposed by others (Joosten *et al* 1992; Isaks *et al* 1999; Culleton *et al* 2006; Patel *et al* 2009).

The main strengths of the study are that it includes a large nationally-representative sample, rather than being a local population or one collected through use of healthcare services. The study includes the use of standardised methods for ascertaining haemoglobin status and relevant confounding factors. It is only the second study to examine a nationally-representative sample of free-living older people.

One limitation of this paper is that people living in institutions were excluded. This group has lower haemoglobin levels and a higher prevalence of anaemia (Bajekal 2002) than the general population but their prevalence of 'low normal' haemoglobin has not been investigated. In HSE 2000, blood samples were obtained from 627 residents of care homes. Overall, 38% of men and 30% of women had anaemia (using WHO criteria), while 24% and 25% respectively had 'low normal' haemoglobin. The prevalence of 'low normal' haemoglobin is not markedly different, although anaemia was far more common in residents of care homes. However, the care home residents in HSE 2000 were much older: 44% of men and 60% of women aged 65+ living in care homes who provided blood samples in HSE 200 were aged 85+, compared with 7% and 8% of men and women aged 65+ in HSE 2005. Also, no information was available on other related nutritional deficiency states, dietary intakes or on dosage of iron in multivitamin supplements.

Longstanding illness was chosen as an explanatory variable for survival rather than self-reported health to avoid reverse causality of poor subjective health due to anaemia. When factors associated with reduced survival were added into the model, education, smoking, BMI, and longstanding illness were each associated with survival; their inclusion reduced the effect of more severe anaemia in men by 20%, from HR 2.19 to 1.87 (20% is the difference between log 2.19 and log 1.87). The addition of these factors reduced the effect of 'mild' anaemia by 11% and the effect of high haemoglobin by 2%. No serum creatinine data were available, so we were unable to adjust for chronic kidney disease, which would affect both mortality and haemoglobin levels.

Although only half the participants aged 65 and over in HSE 2005 gave a blood sample, results were weighted to adjust for known characteristics that differed between participants in the interview who did and did not give a blood sample, in addition to the basic non-response weighting. There was no attempt to weight for non-consent to data linkage. However, among those giving a blood sample, the consent rate was very high (92%), so this is unlikely to a major source of response bias.

Numbers were too small to investigate whether using the lower Joostens criteria to define anaemia in older people identified a group at higher risk, however given the sex differences found in our analysis, this supports the use of sex-specific thresholds.

Another limitation was that there were too few participants from non-white ethnic groups to examine ethnic differences in this relationship. The prevalence of anaemia, defined by

WHO criteria, is higher in African Americans than Caucasians (Denny *et al* 2006, Dong *et al* 2008). In some studies, the age-adjusted mortality risk ratio did not differ by sex or race, using the WHO criteria, (Denny *et al* 2006, Dong *et al* 2008) but others found that WHO-defined anaemia was associated with mortality only in white not black adults aged 71-82y; mortality rates in black men were higher only in those whose haemoglobin was below 2g/dl below the WHO threshold (i.e. <11.0g/dl) (Patel *et al* 2007). Significantly raised mortality hazard ratio was found in whites but not blacks with 'low normal' haemoglobin (Dong *et al* 2008). The NHANES III data found that mortality was raised below race-specific thresholds of 0.2g/dl above the WHO thresholds in Mexican Americans, and 0.7g/dl below the threshold in non-Hispanic blacks (Patel *et al* 2009).

Unlike previous reports, our study does not support screening to identify older individuals with 'low normal' haemoglobin. We have confirmed the adverse effect of anaemia and also of high haemoglobin in men on survival, independently of other major risk factors, but did not find any such effect in women. Further studies or longer follow-up of the HSE participants will be required to assess whether this is a problem of low numbers and therefore limited power to confirm the association, or whether there are other explanations, such as differential association between mortality and only some types of anaemia (Semba *et al* 2007).

Acknowledgments

We are grateful to the participants in the HSE, the field staff, colleagues at the National Centre for Social Research (NatCen), and Emanuela Falaschetti for her help with statistical analysis.

Contribution

JM had the idea for the paper and wrote the first draft; AM conducted the analyses; AA and VH contributed to the literature review; all authors contributed to interpreting the results and revising earlier drafts and approved the final paper.

Conflict of interest disclosure

JM and AM are, and VH was, funded to work on the Health Survey for England.

Reference

Bajekal M. (2002) Health Survey for England 2000. Care homes and their residents. London: The Stationery Office, 2002.

Beghe C, Wilson A, Ershler WB. (2004) Prevalence and outcomes of anemia in geriatrics: a systematic review of the literature. The American Journal of Medicine, **116 (7A)**, S3-S10.

Bross MH, Soch K, Smith-Knuppel T. (2010) Anemia in older persons. American Family Physician. **85**, 480-7.

Beutler E, Waalen J. (2006) The definition of anemia: what is the lower limit of normal of the blood hemoglobin concentration? Blood, **107(5)**, 1747-50

Chaves PHM, Xue QL, Guralnik JM, Ferrucci L, Volpato S, Fried LP. (2004) What constitutes normal hemoglobin concentration in community-dwelling disabled older people? Journal of the American Geriatrics Society, **52**, 1811-6.

Chaves PHM, Ashar B, Guralnik JM, Fried LP. (2002) 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 re-evaluated? Journal of the American Geriatrics Society, **50**, 1257-1264.

Chen Z, Thomson CA, Aickin M, Nicholas JS, van Wyck D, Lewis CE, Cauley JA, Bessford T, and Short list of Women's Health Initiation (WHI) Investigators. (2010) The relationship between incidence of fractures and anemia in older multiethnic women. Journal of the American Geriatrics Society, **58**, 2337-44.

Craig R, Mindell J (eds.) (2007) The Health Survey for England 2005: The Health of Older Adults. London, The NHS Information Centre.

Craig R, Mindell J. (eds.) (2008) Health Survey for England 2006. London, The NHS Information Centre.

Culleton BF, Manns BJ, Zhang J, Tonelli M, Hemmelgam BR. (2006) Impact of anemia on hospitalization and mortality in older adults. Blood, **107**, 3841-6.

Denny SD, Kuchibhatia MN, Cohen HJ. (2006) Impact of anemia on mortality, cognition, and function in community-dwelling elderly. The American Journal of Medicine, **119**, 327-34.

Dharmarajan TS, Pais W, Norkus EP. (2005) Does anemia matter? Anemia, morbidity, and mortality in older adults: need for greater recognition. Geriatrics, **60**, 22-7.

Dong X, de Leon CM, Artz A, Tang Y, Shah R, Evans D. (2008) A population-based study of hemoglobin, race, and mortality in elderly persons. The Journals of Gerontology (A), **63A**, 873-8.

Erens B, Primatesta P. (2000) Health Survey for England 1998: Cardiovascular disease. London: TSO.

Gaskell H, Derry S, Moore RA, McQuay. (2008) Prevalence of anaemia in older persons: a systematic review. BMC Geriatrics, **8**, 1

Guralnik JM, Eisenstaedt RS, Ferrucci L, Klein HG, Woodman RC. (2004) Prevalence of anemia in persons 65 years and older in the United States: evidence for a high rate of unexplained anemia. Blood, **104**, 2263-8.

Isaks GI, Westendorp RGJ, Knook DL. (1999) The definition of anaemia in older persons. Journal Of The American Medical Association, **281**, 1714-1717.

Joosten E, Pelemans W, Hiele M, Noyen J, Verhaeghe R, Boogaerts MA. (1992) Prevalence and causes of anaemia in a geriatric hospitalized population. Gerontology, **38**, 111-117.

Maraldi C, Ble A, Zuliani G, Guralnik JM, Mussi C, Fellin R, Volpato S. (2006) Association between anemia and physical disability in older patients: role of comorbidity. Aging Clinical and Experimental Research, **18**, 485-92.

Merchang AA, Roy CN. (2012) Not so benign haematology: anaemia of the elderly. British Journal of Haematology, **156**, 173–185.

Mindell JS, Biddulph J, Hirani V, Stamatakis E, Craig R, Shelton N. (2012) The Health Survey for England (Cohort paper). International Journal of Epidemiology. doi: 10.1093/ije/dyr199.

Nilsson-Ehle H, Jagenburg R, Landahl S, Svanborg A. (2000) Blood haemoglobin declines in the elderly: implications for reference intervals from age 70 to 88. European Journal of Haematology. **65**, 297-305.

Onder G, Penninx BWJH, Cesari M, Bandinelli S, Lauretani F, Bartali B, Gori AM, Pahor

M, Ferrucci L. (2005) Anemia is associated with depression in older adults: results from the InCHIANTI Study. The Journals of Gerontology (A), **60A**, 1168-72.

Patel KV, Harris TB, Faulhaber M, Angleman SB, Connelly S, Bauer DC, Kuller LH, Newman AB, Guralnik JM (2007) Racial variation in the relationship of anemia with mortality and mobility disability among older adults. Blood, **109**, 4663-70.

Patel KV, Longo DL, Ershier WB,Yu B, Semba RD, Ferrucci L, Guralnick JM. (2009) Haemoglobin concentration and the risk of death in older adults: differences by race/ethnicity in the NHANES III follow-up. British Journal of Haematology, **1445**, 514-23.

Penninx BWJH, Pluijm SMF, Lips P, Woodman R, Miedama K, Guralnik JM, Deeg DJH. (2005) Late-life anemia is associated with increased risk of recurrent falls. Journal of the American Geriatrics Society. **53**, 2106-11.

Penninx BWJH, Pahor M, Woodman RC, Guralnik JM. (2006) Anemia in old age is associated with increased mortality and hospitalization. The Journals of Gerontology (A). **61A**, 474-9.

Riva E, Tettamenti M, Mosconi P, Apolone G, Gandini F, Nobili A, Tallone MV, Detoma P, Giacomin A, Clerico M, Templa P, Guala A, Fasolo G, Lucca U. (2009) Association of mild anemia with hospitalization and mortality in the elderly: the Health and Anaemia population-based study. Haematologica, **94**, 22-8.

Semba RD, Ricks MO, Ferrucci L, Xue QL, Chaves P, Fried LP, Guralnik JM. (2007) Types of anemia and mortality among older disabled women living in the community: the Women's Health and Aging Study I. Aging Clinical and Experimental Research, **19**, 259-264

Shah RC, Buchman AS, Wilson RS, Leurgans SE, Bennett DA. (2011) Hemoglobin level in older persons and incident Alzheimer disease. Neurology, **77**, 219-26.

Spivak JL. (2005) Anemia in the elderly: Time for new blood in old vessels? Archives of Internal Medicine, **165**, 2187-2189.

Tettamanti M, Lucca U, Gandini F, Recchia A, Mosconi P, Apolone G, Nobill A, Tallone MV, Detoma P, Giacomin A, Clerico M, Tempia P, Savola L, Fasolo G, Ponchio L, Della Porta MG, Riva E. (2010) Prevalence, incidence and types of mild anemia in the elderly: the “Health and Anemia” population-based study. Haematologica, **95**, 1849-56.

World Health Organization. (1968) Nutritional Anaemias: Report of a WHO Scientific Group. WHO Technical Reports Series 405. Geneva, Switzerland: WHO.

Zakai NA, Katz R, Hirsch C, Shlipak MG, Chaves PHM, Newman AB, Cushman M. (2005) A prospective study of anemia status, hemoglobin concentration, and mortality in an elderly cohort. The Cardiovascular Health Study. Archives of Internal Medicine, **165**, 2214-20.

Table 1 Response to haemoglobin sample and data linkage, by survey year

	n	% of interviewed	% of eligible for blood sample
1998			
Household response rate to interview	74%		
Individual response rate (within cooperating households)	97%		
Interviewed	3199		
Consented to mortality data & data able to be matched	2634	82	
Agreed nurse visit	2888	90	
Nurse visit completed	2702	84	
Eligible for haemoglobin blood sample	2505		
Agreed blood sample	2277	71	91
Valid haemoglobin result obtained	2089	65	83
Mortality records matched and valid haemoglobin result	2048	64	82
2005			
Household response rate to interview	71%		
Individual response rate (within cooperating households)	97%		
Interviewed	4118		
Consented to mortality data & data able to be matched	2642	64	
Agreed nurse visit	3392	82	
Nurse visit completed	3070	75	
Eligible for haemoglobin blood sample	2772		
Agreed blood sample	2393	58	86
Valid haemoglobin result obtained	2107	51	76
Mortality records matched and valid haemoglobin result	1839	45	66
2006			
Household response rate to interview	68%		
Individual response rate (within cooperating households)	96%		
Interviewed	3175		
Consented to mortality data & data able to be matched	2518	79	
Agreed nurse visit	2599	82	
Nurse visit completed	2381	75	
Eligible for haemoglobin blood sample	2112		
Agreed blood sample	1815	57	86
Valid haemoglobin result obtained	1607	51	76
Mortality records matched and valid haemoglobin result	1442	45	68

Table 2 Participant Characteristics

	Men				Women			
	1998	**2005**	**2006**	**Total**	**1998**	**2005**	**2006**	**Total**
N included in analysis	947	855	664	2,466	1,101	984	778	2,863
	%	%	%	%	%	%	%	%
Haemoglobin								
More than 1g/dl below WHO limit [a]	5	4	4	5	4	2	2	3
0.1 - 1g/dl below WHO limit	10	7	7	8	8	8	6	7
Anaemia (WHO criteria)[a]	16	11	11	13	11	10	8	10
0 - 0.9g/dl above WHO limit	19	19	20	19	25	21	19	22
1 - 1.9g/dl above WHO limit	33	29	30	31	36	37	39	37
2 - 2.9g/dl above WHO limit	24	28	27	26	22	24	25	24
3g/dl or more above WHO limit	9	14	11	11	6	8	8	7
Lowest quintile	23	19	19	21	23	19	17	20
2nd quintile	22	19	20	20	24	22	21	22
3rd quintile	23	21	23	22	18	18	20	19
4th quintile	17	20	19	19	18	21	22	20
Highest quintile	16	21	19	18	17	20	20	19
Age								
65-69	35	35	35	35	30	31	36	32
70-74	26	28	30	28	24	29	25	26
75-79	20	21	18	20	24	19	19	21
80-84	12	10	12	12	14	13	12	13
85+	7	6	5	6	8	8	8	8
mean age	73.4	73.2	73.1	73.3	74.3	73.9	73.5	73.9
s.e. mean	0.21	0.22	0.24	0.13	0.20	0.21	0.24	0.12
Longstanding illness								
None	34	31	30	32	33	31	31	32
Non-limiting	23	32	31	28	23	27	27	25
Limiting	43	37	39	40	45	42	42	43
BMI								
Normal (18.5 - 24.9kg/m2)	25	24	21	24	30	26	26	28
Underweight (<18.5kg/m2)	1	0	1	1	2	1	1	1
Overweight (25.0 - 29.9 kg/m2)	49	46	48	47	38	36	37	37
Obese I (30.0 - 34.9kg/m2)	15	18	21	18	18	19	20	19
Obese II (≥ 35kg/m2)	3	4	3	3	5	8	8	7
Missing	7	8	7	7	6	10	8	8
Cigarette smoking status								
Never smoked	22	26	29	26	43	49	51	47
Ex-smoker	64	63	60	63	42	41	39	41
Current smoker	13	10	12	12	15	10	9	12
Missing	0	0	0	0	0	0	0	0
Cardiovascular disease								
No CVD [b]	53	61	65	58	55	60	62	58
Doctor-diagnosed CVD [b]	47	39	35	42	45	40	37	41
Missing	0	0	0	0	0	0	1	0
Age at leaving fulltime education								
≥ 16 years	26	39	40	34	27	36	40	34
<16 years	72	60	60	64	72	62	59	65
Missing	2	2	0	1	2	2	0	1
Occupational social class								

Non-manual	47	50	53	50	51	60	60	57
Manual	52	49	46	50	42	36	36	38
Missing	1	0	0	1	6	3	4	5
Equivalised household income								
Highest quintile [c]	6	9	8	8	4	5	6	5
2nd highest quintile	12	11	10	11	8	8	7	8
3rd quintile	22	19	23	21	18	18	20	19
2nd lowest quintile	27	24	29	27	36	22	37	31
Lowest quintile	19	21	13	18	17	28	12	20
missing	14	15	16	15	17	20	18	18
Vital status at end of follow-up period								
Died	54	19	15	32	47	13	10	25
Survived	46	81	85	68	53	87	90	75

[a] WHO criteria for anaemia: haemoglobin <13.0g/dl for men, <12.0g/dl for women

[b] CVD: Cardiovascular conditions including stroke, myocardial infarction, angina, dysrhythmia, heart murmur or other heart condition

[c] Equivalised household income (taking account of the number and age of householders); quintiles based on the whole core survey sample (all ages) for each survey year.

Table 3 Adjusted hazard ratios for mortality associated with bands of haemoglobin level

	adjusted for age only			adjusted for multiple factors 1		
	Hazard ratio	Confidence interval		Hazard ratio	Confidence interval	
Men						
Haemoglobin:						
more than 1g/dl below WHO limit [a]	2.19	1.66	2.90	1.87	1.39	2.53
0.1 - 1 g/dl below WHO limit [a]	1.64	1.31	2.06	1.56	1.24	1.96
0 - 0.9 g/dl above WHO limit [a]	1.08	0.88	1.34	1.08	0.88	1.34
1 - 1.9 g/dl above WHO limit [a]	1			1		
2 - 2.9 g/dl above WHO limit [a]	0.86	0.70	1.06	0.90	0.73	1.11
3 g/dl or more above WHO limit [a]	1.35	1.04	1.74	1.32	1.02	1.70
Women						
Haemoglobin:						
more than 1g/dl below WHO limit [a]	1.61	1.08	2.41	1.32	0.91	1.92
0.1 - 1 g/dl below WHO limit [a]	1.30	0.99	1.72	1.22	0.93	1.61
0 - 0.9 g/dl above WHO limit [a]	1.05	0.86	1.29	1.04	0.85	1.28
1 - 1.9 g/dl above WHO limit [a]	1			1		
2 - 2.9 g/dl above WHO limit [a]	1.02	0.84	1.23	1.02	0.84	1.24
3 g/dl or more above WHO lim [a] it	1.37	0.99	1.91	1.30	0.95	1.79

Adjusted for age-group, age at leaving full-time education, smoking status, limiting or non-limiting longstanding illness, and BMI category.

a WHO criteria for anaemia: haemoglobin <13.0g/dl for men, <12.0g/dl for women

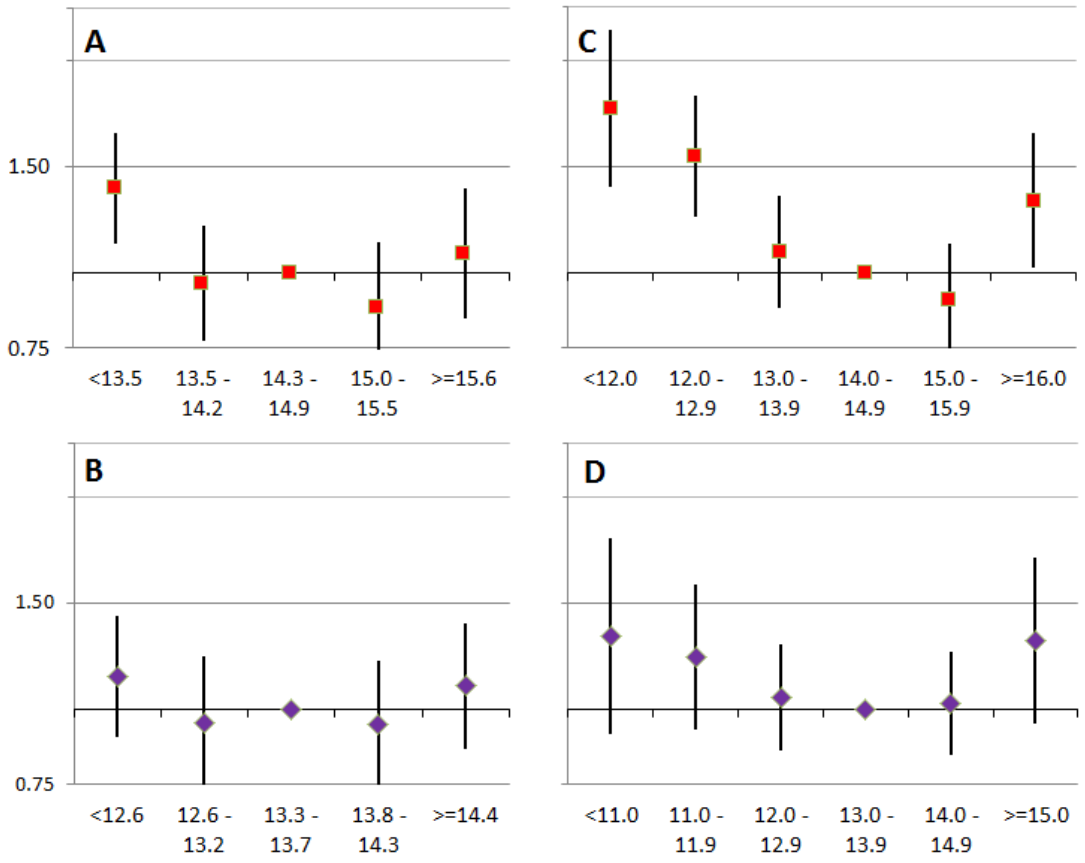

Figure 1. Mortality by haemoglobin level. Adjusted hazard ratios for mortality by haemoglobin quintiles for men (A) and women (B); and by 1g/dl band for men (C) and women (D).

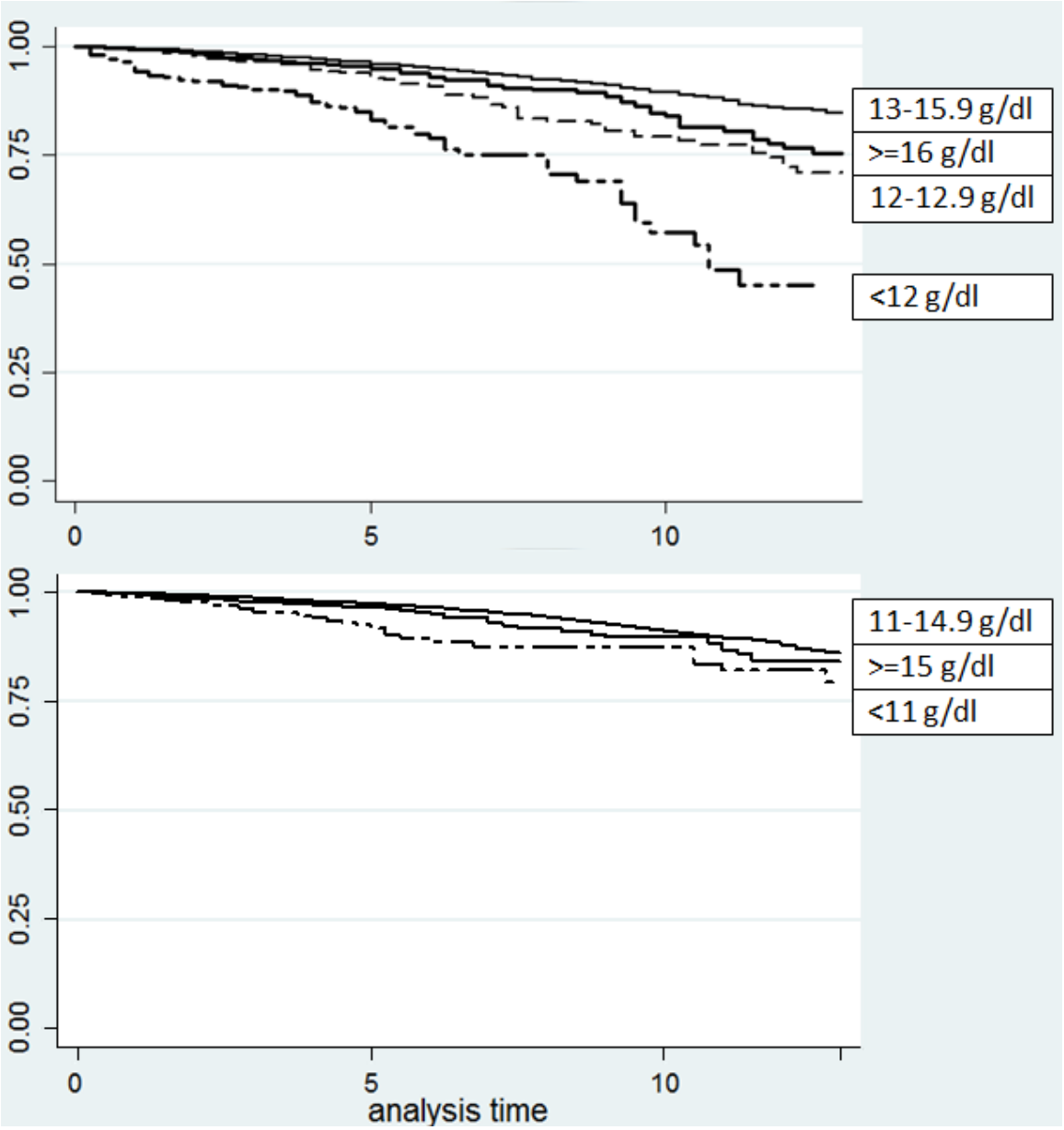

Figure 2. Survival by haemoglobin level. Adjusted Kaplan-Meier curves by haemoglobin level for men (top) and women (bottom).