Manuscript Title: The prevalence and associated mortality of non-anaemic iron deficiency in older adults: a 14 year observational cohort study

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Abstract (186 words)

Background: Iron is central to multiple biological pathways, and treatment of non-anaemic absolute iron deficiency (NAID) is beneficial in certain conditions. However, it is unknown if NAID is associated with increased mortality in older-adults.

Methods: A nationally representative sample of 4451 older-adults from the English Longitudinal Study of Ageing was used. NAID was defined as serum ferritin <30µg/L and haemoglobin ≥120g/L (women) or ≥130g/L (men). Cumulative mortality was estimated by Kaplan Meier method. Unadjusted and adjusted hazard ratios (HR) of mortality were calculated using Cox proportional hazards regression models.

Results: Baseline NAID prevalence was 8.8% (95%CI 8.0%-9.7%). 10.9% (95% CI of 9.7-12.3%) for women and 6.35% for men (95% CI 5.3%-7.5%). The HR for mortality for individuals with NAID compared with non-anaemic individuals without iron deficiency over 14-year follow-up was 1.58 (95% CI 1.29-1.93). This association was independent of all identified demographic, health-related and biological covariates, and robust in multiple sensitivity analyses.

Conclusions: In older-adults in England, NAID is common and associated with an increased mortality rate compared to non-anaemic individuals with normal serum ferritin. The association is principally driven by an excess mortality in women.

Key Words:

Iron deficiency, mortality, non-anaemic, older adults

Background

Iron is essential for normal biological functioning in humans, being required for multiple processes including the biosynthesis of haemoglobin, myoglobin, cytochromes and nitric oxide synthase, mitochondrial function, immune cell growth and proliferation, specific cell mediated effector pathways, DNA synthesis and cell proliferation and regulation. Furthermore, preclinical models suggest impacts related to neurotransmission, brain development and brain metabolism [1]. However, iron deficiency is the most common micronutrient deficiency in the world, affecting over two billion people and is responsible for some of the most common human diseases [1-6]. The most common causes of iron deficiency include insufficient dietary intake or pathological conditions resulting in blood loss or malabsorption [3]. Importantly, safe, low-cost treatment and prevention strategies for iron deficiency are well established.

Although it is well established that iron deficiency anaemia is associated with increased morbidity and mortality [6], the clinical importance of non-anaemic absolute iron deficiency (NAID) is less clear. Iron deficiency, even in the absence of anaemia, has proven clinical relevance in certain conditions. In heart failure, iron deficiency without anaemia is associated with reduced physical performance, reduced maximum exercise capacity [7] and increased risk of hospital readmission[8]. In chronic obstructive pulmonary disease (COPD) patients undertaking pulmonary rehabilitation, it is associated with poorer pre-training aerobic capacity and reduced training responses than individuals with normal iron status [9]. In pregnancy iron deficiency, even without anaemia, is associated with low-birthweight [10]. Furthermore, in non-anaemic heart failure patients with iron deficiency, iron supplementation has improved exercise capacity and quality of life [11]. Additionally, in non-anaemic adolescent women with iron deficiency, iron supplementation can reduce fatigue [12].

However, it remains unclear whether NAID is associated with mortality amongst the general population, as is the case for iron deficiency *with* anaemia [6]. There is preliminary evidence to suggest it may be: in heart failure patients and renal transplant recipients, iron deficiency and mortality have been found to be associated, independent of anaemia [13-15], while in non-anaemic heart failure patients with iron deficiency, iron supplementation has reduced

a composite end point of all-cause death or cardiovascular hospitalization [16]. But whether there is a generalised link between NAID and mortality remains to be determined. Further, the extent of the problem of NAID in the general population is unclear. Various definitions of iron deficiency without anaemia are used in previous research, here we use NAID to refer to absolute iron deficiency using a serum ferritin cut-off of <30µg/L. The NAID definition used here does not include functional iron deficiency as serum transferrin levels were not available. Our specific objectives were to determine prevalence of NAID in older adults and assess whether NAID is associated with increased mortality. We hypothesised that NAID would be present and associated with an increased mortality rate compared with people without NAID. Here we report the prevalence and associated all-cause mortality of NAID in a nationally representative sample older-adults aged ≥50 years in the UK using data from the English Longitudinal Study of Ageing linked with National Health Service (NHS) central register mortality data.

Methods

Participants

Participants were drawn from the English Longitudinal Study of Ageing: a nationally representative cohort study of adults aged over 50 [17]. Relevant variables for this analysis were measured in wave 2 of ELSA (2004/2005) so core participants who provided data at wave 2 were included and followed up through linkage to mortality data provided from the official records from the National Health Service central register to the latest available data in March 2018 (a 14-year follow-up, with a participant average of 12 years and 2 months). Of the 8,780 core participants assessed in this wave, 8,551 gave consent to data linkage and their records were followed up (97.4%). We excluded individuals (n=2,935) for whom ferritin was unavailable due to a sample not having been taken or due to problems with the sample taken, and a further 249 individuals with a ferritin <30µg/L as this is above the normal range and is likely to represent concurrent inflammation, or, rarely, the presence of hemochromatosis. Thus 5,367 provided usable laboratory data, and 5,070 provided full data on covariates. We further excluded participants with anaemia at baseline (haemoglobin <130g/l for men and <120g/l for women), providing a final sample size of 4,451 (Figure 1). ELSA received ethical approval from the National Research Ethics Service and all participants provided informed consent. There was no specific patient or public involvement relating to the analyses presented here.

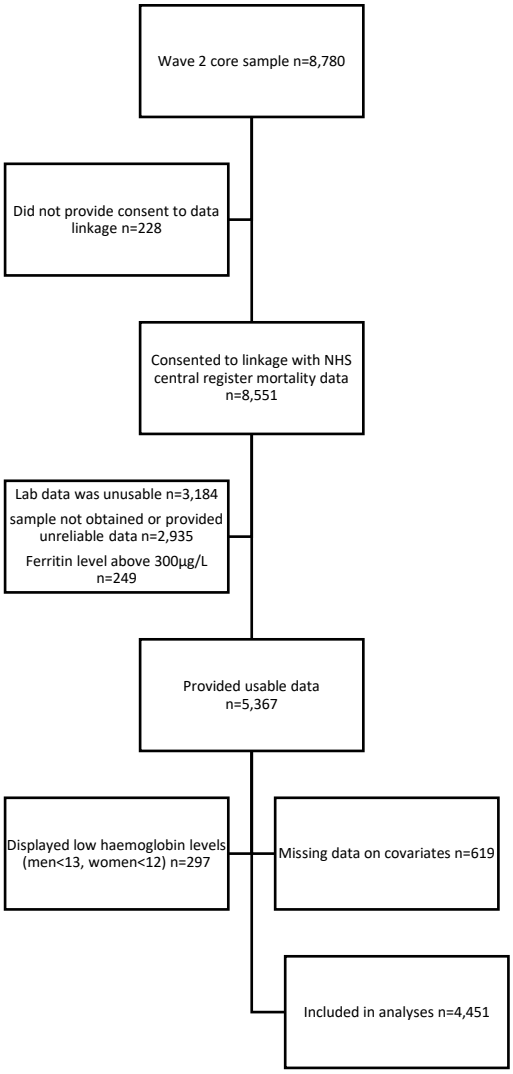

Figure 1: Flow of participants included in the study

Measures

The primary method of data collection in ELSA involves computer assisted interviews completed face-to-face at the participants' normal place of residence. The biological variables used in this study were obtained from blood drawn by a trained healthcare professional, following standard guidelines during a separate home visit. Biological samples were not processed if they did not meet required processing standards including excessive delays in processing or concerns of sample leakage. Full explanation of data collection, protocols and study tools are available at https://www.elsa-project.ac.uk/.

A primary threshold of serum ferritin <30µg/L was used to define iron deficiency as this has been reported as the most sensitive and specific test for the identification of iron deficiency [3]. We identified confounding variables by using Directed Acyclic Graphs (DAGs). Demographic confounders identified included gender, age (continuous

variable), marital status (married or cohabiting vs never married, divorced, separated or widowed), ethnicity (white vs other due to the low number of ethnic minority groups), educational attainment (no qualifications or NVQ level 1, GCE/O Level, A level or other higher education, and degree), employment status (currently working part-time or full-time vs not working), wealth (in quintiles, as per previous precedent which has been shown to be a robust indicator of socio-economic status and living standard in the ELSA population [18]).

Health related confounders included self-reported doctor diagnosis of any of the following chronic diseases (heart failure, 'heart attack', 'other heart problem (not covered by given categories)', angina, diabetes, stroke, dementia, arthritis, Parkinson's disease, and chronic lung disease such as chronic bronchitis and asthma), frequency of alcohol consumption (less than once per week, one to four times per week, and five to seven times per week), self-reported sedentary behaviour (hardly ever or never do sports or activities of mild, moderate, or vigorous intensity vs more frequency physical activity), and cognition (using an average of standardised scores of memory, executive function, processing speed and orientation in time) [19].

Biological covariates included C-reactive protein (mg/L) (CRP) and fibrinogen in (g/L).

Statistical analysis

Prevalence was calculated using weighted proportions to ensure the sample was representative of the English population. Cumulative mortality was estimated by Kaplan Meier method and both unadjusted and adjusted hazard ratios of mortality were calculated using Cox proportional hazards regression models to estimate hazard ratios (HRs) and 95% confidence intervals. Survival time was measured in months from baseline (the data of the wave 2 interview) to death, censoring (the date of the last interview prior to drop out), or latest-available follow-up (165 months from baseline). Model 1 was unadjusted, model 2 adjusted for demographic variables (gender, age, marital status, ethnicity, educational attainment, employment status and wealth), model 3 additionally adjusted for health-related variables (comorbidities, frequency of alcohol consumption, sedentary lifestyle and cognition) and model 4 additionally adjusted for biological covariates (CRP and fibrinogen levels). Analyses were stratified by age and gender, and with these adjustments made, the proportionate hazards assumption was met (as tested using the

Schoenfeld Residuals Test). All analyses were weighted using inverse probability weights to ensure national representation and to take account of differential non-response. To try and ascertain whether the relationship was stronger for certain causes of death, we re-categorised death by cause using ICD-10 codes into four main categories (cancer, respiratory, cardiovascular disease, and other) and re-ran analyses to ascertain if results varied by cause of death. Only two participants were omitted due to unknown cause of death.

In addition to the main analysis described above, we carried out several sensitivity analyses. First, we tested alternative thresholds of ferritin <40, 50, 60, 70 and 100µg/L. Second, we tested whether there was a moderating effect of either age or gender by including interaction terms. Third, in order to account for potential reverse causality (whereby participants had unidentified health conditions that might have affected their iron levels and pre-disposed them to premature mortality), we (i) excluded deaths in the two years following baseline, and (ii) excluded participants with diabetes, kidney problems or heart failure at baseline. As NAID could be a precursor to anaemia, thereby meaning that anaemia in fact explains any association with mortality, we also excluded any participants who went on to develop anaemia at 4 or 8-year follow-up (the two subsequent waves where blood samples were taken). We also considered that those with low iron might be on anticoagulants or antiplatelet medications and have major comorbidities, which could explain any association with mortality, so we excluded participants on blood-thinning medication. As we did not have any direct measure of renal impairment we excluded any participants on antihypertensive medication as hypertension is a common cause of renal impairment. Finally, we excluded anybody with a history of cancer and, in order to explore whether other health behaviours could explain the findings, we adjusted for past or current smoking habits.

Additionally, as a sensitivity analysis to increase our statistical power, we used multiple imputation by chained equations using identified confounders as predictor variables to impute missing data from covariates (n=619), generating 50 imputed datasets to bring the sample size back to 5,070. Finally, in our main analyses, we used semi-parametric methods. But as these did not estimate the baseline hazard, we also tested whether results were consistent when using a parametric model. As the hazard function showed similarities to a monotonic increasing distribution, we used a Weibull proportional hazards model, with Akaike's information criterion and Bayesian

information criterion and Wald test for κ=1 showing best fit compared to alternative parametric proportional hazards models tested. All analyses were carried out using Stata Version 14 (Statacorp). All sensitivity analyses show results from fully-adjusted models.

Results

Cohort Characteristics

Of the 4,451 participants, 389 had NAID using a ferritin cut-off of <30µg/L. This equated to 8.8% of the population (95%CI 8.0%-9.7%). For women, 10.9% of them had NAID (95%CI 9.7%-12.3%) while for men 6.3% of them had NAID (95%CI 5.3%-7.5%). Amongst those aged 50-65, there was a 9.7% prevalence (95%CI 8.6%-11.0%), whilst for those aged 65 and above the prevalence was 7.8% (95%CI 6.7%-9.1%). Those with NAID were more likely to be female but there were no other demographic differences from the rest of the population. They showed a pattern of less frequent alcohol consumption and had lower levels of CRP and slightly lower levels of fibrinogen. Table 1 shows the demographics of the sample.

Tracking was possible for the following 14 years and during this time, there were 1,124 deaths (25.3%). Amongst those with ferritin ≥30µg/L, there were 21.0 deaths per 100 person-years (95%CI 19.8-22.4), whereas for those with ferritin <30µg/L, there were 25.5 deaths per 100 person-years (95%CI 21.3-30.7).

Time to event analyses for all-cause mortality

Amongst individuals with NAID (ferritin <30µg/L) there were 58% more deaths over the 14 year follow-up period compared to those without (fully-adjusted model: HR 1.58, 95%CI 1.29-1.93). This association was independent of all identified demographic, health-related and biological covariates and consistent across all models (see Table 2). Figure 2 shows a dose-response relationship depending on level of ferritin used to determine NAID.

When exploring associations with specific cause of death, there were 58% more deaths from cancer amongst those with NAID (HR 1.58, 95%CI 1.14-2.20) and 114% more deaths from respiratory causes (HR 2.14, 95%CI 1.30-3.50).

But there was less convincing evidence of more deaths from other causes (HR 1.52, 95%CI 0.94-2.46) and no evidence of death from cardiovascular causes (HR 1.24, 95%CI 0.81-1.90) (see Table 3).

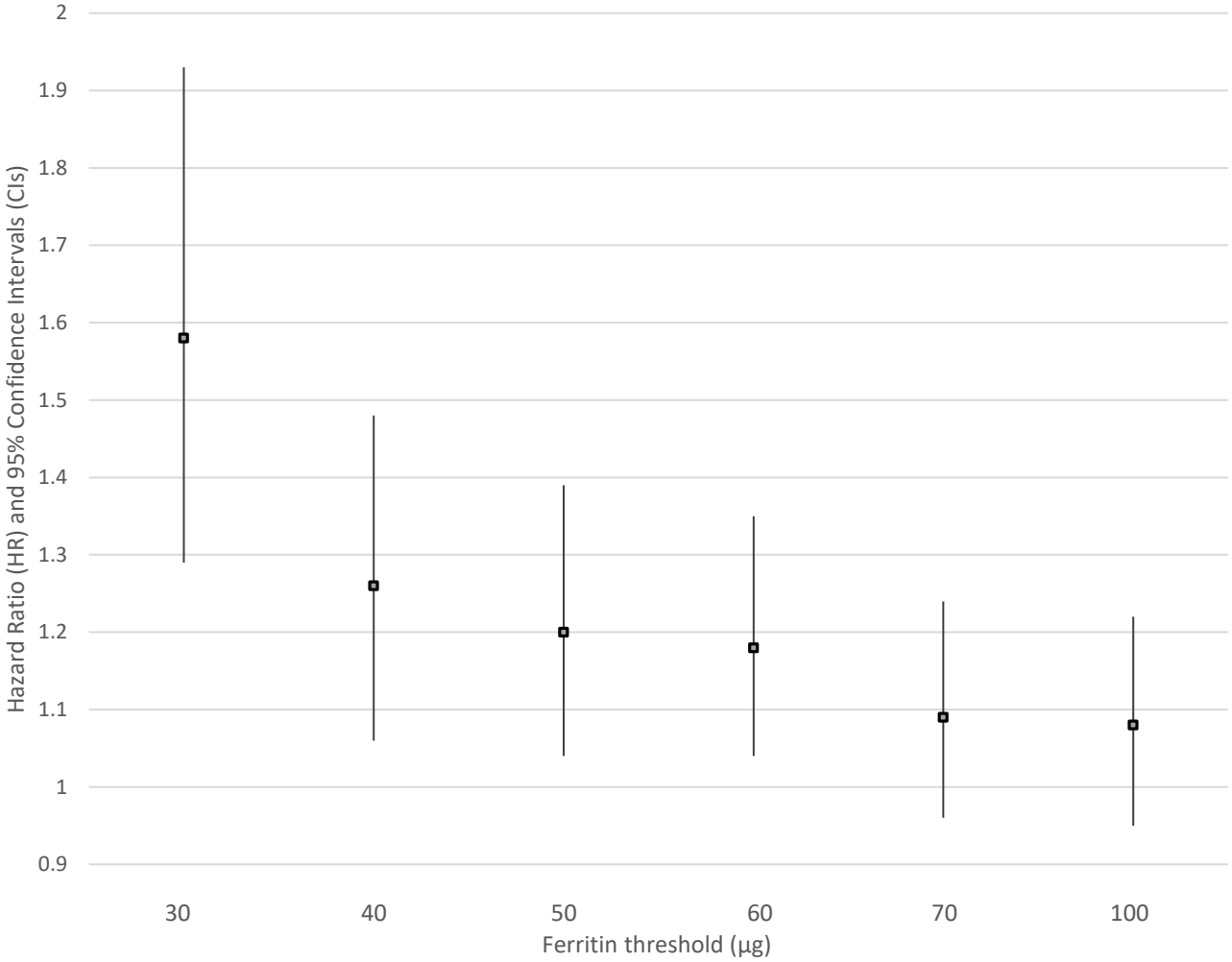

Figure 2: Hazard ratios (with confidence intervals) for different cut-offs of ferritin

Sensitivity analyses

There was no evidence of any moderation of this association by age (interaction term HR=1.00, 95%CI 0.98-1.02). There was also only slight evidence of a stronger association in women than in men (interaction term HR=1.44, 95%CI 0.94-2.21). Results were maintained when excluding those who died within two years of baseline (HR=1.45, 95%CI 1.17-1.80, n=4,374), when excluding those with diabetes, kidney problems or heart failure (HR=1.56, 95%CI 1.27-1.93, n=4,345), when excluding participants who went on to develop anaemia (HR=1.65, 95%CI 1.32-2.05, n=4,395), when excluding those on anti-thrombotic medication (HR=1.36, 95%CI 1.07-1.72, n=3,941) or antihypertensive medication (HR=1.63, 95%CI 1.30-2.06, n=3,851), when excluding people with a history of cancer

(n=299) (HR=1.62, 95%CI 1.30-2.01, n=4,152), and when adjusting for past or current smoking habits (HR=1.48, 95%CI 1.21-1.82). Imputing missing data to bring the sample back to 5,070 did not alter the significance of results (HR=1.39, 95%CI 1.15-1.68). A Weibull proportionate hazards model also produced very similar results (HR=1.47, 95%CI 1.20-1.80).

Discussion

In a representative population sample, the prevalence of NAID in adults aged 50+ living in England was 8.8%. Amongst individuals with NAID there were 58% more deaths over a 14 year follow up period, compared with non-anaemic people with normal serum ferritin levels. These associations were robust to multiple sensitivity analyses. The excess mortality seen was predominantly driven by cancer and respiratory causes. It was not possible to ascertain how long NAID was present before baseline, hence, the excess mortality seen may have resulted from the cumulative impact of many years of iron deficiency. To our knowledge this is the first prospective study to examine associations between NAID and mortality in a representative population sample of older adults.

Several limitations warrant discussion. Firstly, as a prospective observational study, causality cannot be assumed. However, the findings are consistent with previous studies from basic science to disease specific clinical trials, in that they suggest dysfunction of biological pathways with clinically relevant implications related to iron deficiency. Furthermore, the robustness of our findings despite multiple sensitivity analyses supports our conclusions. Second, as we studied a nationally geographically representative sample of older adults in England, it includes predominantly white Europeans, hence our findings cannot be uncritically extended to non-white European populations or to countries with different social and economic systems. Third, it was not documented which individuals were taking supplementary iron, or conversely who, through dietary preference might have had a low iron diet. However, as we excluded people with anaemia from the analyses, and most current clinical guidelines only suggest assessing and treating iron status for people with anaemia, it is reasonable to consider any impact of this confounder to be minimal. Fourth, we used self-reported doctor diagnoses of other health conditions rather than results from full clinical assessment. However previous research suggests that self-reported diagnoses correspond reasonably well

with physician diagnoses in similarly aged adults and is therefore justifiable in large cohort studies [20]. Fifth, we did not have specific data on renal impairment, inflammatory bowel disease (IBD) or gastrointestinal/gynaecological cancers, which can all increase iron deficiency and mortality; therefore we conducted sensitivity analyses removing people with related conditions. The prevalence of IBD is 0.5-1% [21], while the incidence rate of bowel cancer is 71/100,000 [22] hence any impact on results is likely to be minimal. Further, excluding patients who died within two years of study entry, or with a history of cancer, did not change our conclusions. However, it remains a possibility, that some individuals with no history of cancer, had an undiagnosed cancer at baseline, which both caused NAID and caused their death occurring two years or more after their baseline assessment. Sixth, as additional markers of iron status where not available, such as transferrin and transferrin saturation, it was not possible to investigate functional iron deficiency in addition to absolute iron deficiency. Finally, we lack information on whether patients with NAID also had other symptoms such as bleeding or weight loss.

In addition to the previous research on non-anaemic iron deficiency stated above, the present data build on studies investigating serum ferritin (rather than NAID specifically). One previous study involving 788 postmenopausal women found no relationship with mortality [23], but another study did find increased mortality in women [24], whilst a third study found increased excess mortality specifically in black men with a serum ferritin <50 μg/L[25]. However, in addition to the results being mixed, sample sizes in these previous studies have been much smaller than in this study. Future replications of this finding in other large-scale cohort studies are thus encouraged.

In conclusion, we demonstrate, in a nationally representative sample of older adults, that NAID is common and there are substantially more deaths amongst individuals with NAID. These findings have important implications for further research including interventional trials, particularly as previous interventional trials have shown treating NAID can improve clinical outcomes in certain patient groups. Of note, high levels of serum ferritin can lead to adverse outcomes [24, 26-28], hence careful selection of iron deficient individuals would be required, together with optimisation of the dose of iron to be given. Although side effects of oral iron are frequent, considered overall iron replacement is safe and inexpensive. Therefore, future studies should further investigate the relationship found

here, which in turn could justify interventional trials testing the potential benefits of iron replacement for older adults with NAID.

Declarations

Funding

For this analysis, DF was supported by the Wellcome Trust [205407/Z/16/Z] and KP was supported by National Institute for Health Research Academic Clinical Fellowship award and the Imperial College Clinician Investigator Scholarship. The funders had no say in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. This publication presents independent research. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

Authors' contributions

All the authors participated in designing the study, writing the manuscript, and making the decision to submit the manuscript for publication. KP and DF analysed the data and vouch for its accuracy.

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The English Longitudinal Study of Ageing was developed by a team of researchers based at the University College London, NatCen Social Research, the Institute for Fiscal Studies and the University of Manchester. The data were collected by NatCen Social Research. The funding is provided by National Institute of Aging Grant R01AG017644 and a consortium of UK government departments coordinated by the National Institute for Health Research.

The authors would like to acknowledge that we are in a climate emergency. As such, the potential impact of this research will only be possible if the climate emergency is urgently addressed.

Competing interests

Professor Polkey's institution has received research funding from Vifor for partial support of a trial evaluating the efficacy of iron replacement in patients with Chronic Obstructive Pulmonary Disease (NCT03050424). The trial sponsor for that trial is Royal Brompton & Harefield NHS Foundation Trust, not Vifor.

The other authors have no conflicts of interest to declare.

Tables

Table 1: Descriptive characteristics of the sample compared by presence of NAID

	No iron deficiency (n=4,062)	NAID (n=389)	p
Age, μ (SD)[a]	65.3 (9.0)	64.6 (9.5)	.13
Gender, % female[b]	54.9%	68.4%	<.001
Marital status, % living as a couple [b]	73.2%	69.2%	.089
Ethnicity, % white [b]	98.8%	99.2%	.49
Educational attainment, % [c]			.14
No qualifications/NVQ1/CSE	38.1%	42.7%	

Qualifications at age 16/GCE/NVQ2	19.2%	16.7%	
Qualifications at age 18/A level/NVQ3	29.9%	29.3%	
Further qualifications/degree	12.9%	11.3%	
Occupational status, % working [b]	36.0%	35.5%	.85
Wealth, % in lowest quintile [b]	14.8%	16.7%	.32
Comorbidities, % with one or more[b]	46.6%	47.0%	.88
Frequency of alcohol consumption, % [c]			<.001
Less than once a week	36.2%	48.3%	
1-4 days a week	39.2%	37.8%	
5-7 days a week	24.5%	13.9%	
Sedentary lifestyle, % [b]	3.1%	3.1%	.99
Cognition, % in lowest quintile[b]	14.1%	15.2%	.55
CRP levels, μ (SD)[a]	3.8 (6.4)	2.8 (3.2)	.005
Fibrinogen levels, μ (SD)[a]	3.2 (0.7)	3.1 (0.6)	.005

[a] One-way ANOVA; [b] Chi-square test; [c] Wilcoxon-Mann Whitney test

Table 2: Hazard Ratios with robust standard errors from Cox proportional hazards analyses showing time to death amongst adults aged 50+ with ferritin <30 μg/L

	HR (SE)	95%CI	P
Model 1	1.55 (0.16)	1.27-1.89	<.001
Model 2	1.48 (0.15)	1.22-1.81	<.001
Model 3	1.49 (0.15)	1.22-1.83	<.001
Model 4	1.58 (0.16)	1.29-1.93	<.001

Model 1 was unadjusted, model 2 adjusted for demographic variables (gender, age, marital status, ethnicity, educational attainment, employment status and wealth), model 3 additionally adjusted for health-related variables (comorbidities, frequency of alcohol consumption, sedentary lifestyle and cognition) and model 4 additionally adjusted for biological covariates (CRP and fibrinogen levels).

Table 3: Hazard Ratios with robust standard errors from Cox proportional hazards analyses showing time to death amongst adults aged 50+ with ferritin <30 μg/L split by type of death

	HR (SE)	95%CI	P
Cancer deaths (deaths=386)	1.58 (0.27)	1.14-2.20	.006
Respiratory deaths (deaths=172)	2.14 (0.54)	1.30-3.50	.003
CVD deaths (deaths=300)	1.24 (0.27)	0.81-1.90	.32
Other deaths (deaths=255)	1.52 (0.37)	0.94-2.46	.091

Models adjusted for demographic variables (gender, age, marital status, ethnicity, educational attainment, employment status and wealth), health-related variables (comorbidities, frequency of alcohol consumption, sedentary lifestyle and cognition) and biological variables (CRP and fibrinogen levels).

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