Association between anemia and frailty in 13,175 community-dwelling adults aged 50 years and older in China

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Abstract

Background: Anemia and frailty contribute to poor health outcomes in older adults; however, most current research in lower income countries has concentrated on anemia or frailty alone rather than in combination. The aim of the present study was to investigate the association between anemia and frailty in community-dwelling adults aged 50 years and older in China. Methods: The study population was sourced from the 2007/10 SAGE China Wave 1. Anemia was defined as hemoglobin less than 13g/dL for men and less than 12g/dL for women. A frailty index (FI) was compiled to assess frailty. The association between anemia and frailty was evaluated using a 2-level hierarchical logistic model. Results: The prevalence of anemia was 31.0% (95% CI: 28.4%, 33.8%) and frailty 14.7% (95% CI: 13.5%, 16.0%). In the univariate regression model, presence of anemia was significantly associated with frailty (OR=1.62, 95% CI: 1.39, 1.90) and the effect remained consistent after adjusting for various potential confounding factors including age, gender, residence, education, household wealth, fruit and vegetable intake, tobacco use, alcohol consumption and physical activity (adjusted OR =1.31, 95% CI: 1.09, 1.57). In the linear model, each 1 g/dL increase in hemoglobin concentration was associated with 4% decrease in the odds of frailty after adjusting for several confounding variables (adjusted OR =0.96, 95% CI: 0.93, 0.99). Conclusion: Anemia and low hemoglobin concentrations were significantly associated with frailty. Therefore, health care professionals caring for older adults should increase screening, assessment of causes and treatment of anemia as one method of avoiding, delaying or even reversing frailty.

Background

China has a rapidly growing older adult population along with increasing life expectancy from 44.6 years in 1950 to 75.3 years in 2015, and is projected to reach almost 80 years
by 2050[1]. With ageing populations comes shifts in disease burdens, typically towards chronic non-communicable diseases. Low hemoglobin in older adults increases the risk for a number of poor health outcomes, with anemia defined as hemoglobin less than 13g/dL for men and less than 12g/dL for women[2], increasing the levels of fatigue, cognitive decline and weakening muscle strength[3]. These same factors also contribute to frailty in older adults.

Frailty is a geriatric syndrome that increases vulnerability to stressors and leads to risk of negative outcomes such as falls, dependency, hospitalization and death[4]. While many tools are available to ascertain frailty, two tools are commonly used[5]. Rockwood defined frailty in terms of the accumulation of deficits (frailty index, FI), and generally include 30-40 variables[6]. Fried suggested a frailty phenotype identified by the presence of three or more of five components (unintentional weight loss, weakness, poor endurance and energy, slowness and low physical activity)[7]. The prevalence of frailty varies from 4%-59.1% with different assessment and geographic region[8].

The burden imposed by the co-occurrence of anemia and frailty in older age poses a potential challenge for healthcare systems worldwide. A recent meta-analysis estimated that older persons with anemia had more than double the odds of frailty, although with conflicting results for the two longitudinal studies (2-5 year follow-up) that assessed the association between anemia and frailty[9]. Many of the studies that contributed to these estimates were focused on high-income countries, and used the phenotype criteria[7] to define frailty. To our knowledge, there have been no large representative studies to assess the relationship between anemia and frailty in older community-dwelling populations in China.

The aim of the present study was to investigate the association between anemia and frailty in community-dwelling adults aged 50 years and older from the World Health
Methods

Study population and design

SAGE was a longitudinal cohort study of ageing and older adults in six low- and middle-income countries (China, Ghana, India, Mexico, Russian Federation and South Africa) [10]. The study population was sourced from SAGE China Wave 1 from 2007-2010, using a probability sampling design and a five-stage cluster sampling strategy[11]. SAGE China Wave 1 contacted 1,642 individual respondents aged 18–49 years and 13,367 respondents aged 50+ years. The response rate for the individual questionnaire was 98%, and a final total sample size of 13,175 for this analysis.

SAGE was approved by the World Health Organization's Ethical Review Board (RPC146), and local approval by the ethics review committee of the Chinese Center for Disease Control and Prevention (approval notice 200601). Each respondent signed informed consent.

Measures

Anemia

Blood hemoglobin concentrations were derived from dry blood spot samples and examined using standardized ELISA techniques at the Shanghai Municipal Centre for Disease Control and Prevention Laboratory. The World Health Organization’s (WHO) definition of anemia was used: hemoglobin less than 13g/dL for men and less than 12g/dL for women[2].

Frailty

Frailty was defined using the deficit accumulation approach. A frailty index (FI) was constructed as the proportion of deficits present out of 40 variables available in the SAGE database, including self-rated health, 9 medically diagnosed conditions, 4 medical symptoms, 13 functional activities assessments, 10 activities of daily living (ADLs), body
mass index (BMI, calculated as weight/height\(^2\)(kg/m\(^2\))), grip strength and gait speed [12]. Individual scores ranged from 0 (no deficits) to 1 (highest level of deficits in all variables). The FI cut-off value of 0.2 was defined as approaching a frail state[12].

**Other covariates**

SAGE used a standardized survey instrument to collect sociodemographic information and behavioral risk factors based on the WHO STEPwise approach to Surveillance (WHO STEPS, WHO 2005). Socio-demographic variables included age, sex, education, rural/urban residence, and household wealth. Age was categorized into four groups: 50 to 59 years; 60 to 69 years; 70 to 79 years; and 80 years or older. Highest level of education completed was classified into six categories using an international classification scheme (No formal education; less than primary; primary school completed; secondary school completed; high school completed; college completed and above) for use in this analysis[13]. The household wealth was generated using an asset-based approach and included possession of assets and dwelling characteristics[14], with the resulting wealth quintiles ranging from quintile 1 (Q1, poorest) to quintile 5 (Q5, wealthiest) households.

Non-communicable disease risk factors included alcohol and tobacco consumption, insufficient fruit and vegetable intake and low physical activity levels. Tobacco use was classified into four groups: never smoker, not current smokers, current smokers (not daily) and current daily smokers. Alcohol consumption was categorized into four groups: never drinker, non-heavy drinkers, infrequent heavy drinkers and frequent heavy drinkers according to the number of standard drinks consumed in a given week. Physical activity was measured by the Global Physical Activity Questionnaire (GPAQ) and three categories were generated: low, moderate and high levels[15]. Fruit and vegetable consumption was calculated by the number of daily servings eaten. Five or more servings were defined as sufficient daily intake (equivalent to at least 400 grams per day), fewer than five servings
was categorized as insufficient[16].

**Statistical methods**

Statistic analyses were conducted using STATA SE version 14.1 (Stata Corp, College Station, TX). The population prevalence of anemia and frailty was calculated by using normalized weights. Weights were based on selection probability, non-response, and post-stratification adjustments. A 2-level hierarchical logistic model was used to evaluate the association between anemia and frailty using STATA command “melogit”. We also included hemoglobin concentration as a continuous variable in the model (models 3 and 4) to see if there was an association between hemoglobin concentration and frailty. Covariates of interest included age, gender, residence, education, household wealth, fruit and vegetable intake, tobacco use, alcohol consumption and physical activity. P < 0.05 from two-sided statistical tests was considered statistically significant.

**Results**

The sociodemographic characteristics of samples are shown in Table 1. A total of 13,175 individuals aged 50 and older were included in the analysis. The proportion of women (50.2%) was higher than men (49.8%) in the study, with small sex differences by age groups. The overall mean age was 62.6 years (SE 0.2). The majority of the respondents were between 50 and 59 years old (44.9%), nearly half of all respondents (47.3%) lived in an urban area. Fifty-eight percent had completed primary school or higher. The prevalences of lowest and highest wealth quintile were 16.3% and 21.8% respectively. The mean Hb level was 13.3±3.0 g/dL, being 14.0±3.0 g/dL in men and 12.8±2.8 g/dL in women respectively (2633 of anemia was missing). Overall prevalence of anemia was 31.0% (95% CI: 28.4%, 33.8%) (Table 2). By gender, 31.7% of men and 30.3% of women were found to be anemic (F=3.103, P=0.048). The prevalence of anemia among rural dwelling respondents (19.4 %) was lower than in urban areas (46.3%) (F=76.318,
P<0.001). Anemia prevalence was higher in older age groups. Higher wealth individuals had higher anemia rates, reaching 39.7\% (95\%CI: 34.1\%, 45.5\%) in the richest group. In contrast, the prevalence of anemia decreased (F=4.656, P<0.001) at higher levels of education.

Frailty prevalence was 14.7\% (95\%CI: 13.5\%, 16.0\%), being higher in women (17.4\%) than men (11.9\%)(F=52.933, P<0.001) (Table 3). The 80+ age group had the highest prevalence of frailty (41.2\%). Compared with urban respondents, rural dwellers had higher levels of frailty (15.6\%). Lower education and wealth levels were associated with higher frailty (P<0.001).

Table 4 shows the associations between anemia and frailty for all respondents. In the univariate regression model (model 1), presence of anemia was significantly associated with frailty (OR=1.62, 95\% CI: 1.39, 1.90) and the effect attenuated only slightly after adjusting for various potential confounding factors including age, gender, residence, education, household wealth, fruit and vegetable intake, tobacco use, alcohol consumption and physical activity (model 2) (adjusted OR =1.31, 95\% CI:1.09, 1.57). Further, we included hemoglobin concentration in the linear models (models 3 and 4) to examine the associations, and found each 1 g/dL increase in hemoglobin concentration was associated with 4\% decrease in the odds of frailty after adjusting for age, gender, residence, education, household wealth, fruit and vegetable intake, tobacco use, alcohol consumption and physical activity (adjusted OR =0.96, 95\% CI: 0.93, 0.99).

Discussion

This study reported the prevalences of anemia and frailty and the two conditions combined in a large population of older Chinese adults. The prevalences of both conditions were higher at older ages and in individuals with lower education levels. In addition, anemia was significantly associated with frailty, where each 1 g/dL increase in hemoglobin
concentration was related with 4% decrease in the odds of frailty after adjusting for several variables. As far as we know, this was the first paper addressing the association between anemia and frailty among community-dwelling adults aged 50 years and older in China.

While estimates of anemia prevalence differ considerably, with reported prevalence ranging from 2.9% to 61% in older men and from 3.3% to 41% in older women [17], the prevalence was generally higher in men than in women and increased with advancing age[17,18]. Anemia prevalence was 14.1% for men and 10.2% for women aged 65 and older in the US National Health and Nutrition Examination Survey (NHANES 2013–2016) [19]. An Australian epidemiologic study had anemia estimates of 14.6% among men aged 70+ years[20]. Thirty-eight percent of community-dwelling people aged 60 years and older had anemia in a small study in India[21]. Likewise, 38.1% of older adults had anemia in the Singapore Longitudinal Ageing Studies (SLAS)[22]. Our analyses indicated that the prevalence of anemia was 31.0% (95%CI: 28.4-33.8%) in China, which was higher in men, older people, lower levels of education, and those lived in urban area and with higher wealth, being inverse of the results among older Mexican adults[23]. It indicated that living area and wealth may modifies the probability of being in the different nutritional conditions, which related with anemia. In addition, the different population, sampling programs and hemoglobin test methods may also contribute to the difference between these studies.

Attention to the measurement and impact of frailty in older age has increased substantially over the past decade. The deficit accumulation approach has been well tested in different populations. For example, the overall weighted prevalence of frailty was 9.9% in the community-dwelling older population (60+ years) derived from the China Comprehensive Geriatric Assessment Study (CCGAS), based on the Comprehensive
Geriatric Assessment Frailty Index[24]. The physical frailty phenotype approach was used in an analysis of the China Health and Retirement Longitudinal Study (CHARLS), resulting in 7% of adults aged 60 years or older being classified as frail[25]. In our study, the frailty index resulted in 14.7% (95%CI: 13.5-16.0%) of community-dwelling residents aged 50+ years being classified as frail, higher than the two studies mentioned which use somewhat different frailty criteria.

Anemia reduces the oxygen-carrying capacity, which can result in tissue hypoxia and lead to a number of poor outcomes, including reduced submaximal and maximal aerobic capacity, failing muscle strength, cognitive impairment and development of frailty[26-28], which related to vulnerability and some negative outcomes. Several previous studies have examined the interaction between anemia and frailty among older people in high income countries. A case-control study in Baltimore (USA) firstly explored the relationship between anemia and frailty, showing an inverse correlation between interleukin-6 (IL-6) and hemoglobin or hematocrit in the frail group, suggesting that frail subjects have evidence of inflammation and lower hemoglobin and Hematocrit levels[29]. Data from the Women’s Health and Aging Studies (WHAS) I and II found that mildly low and low-normal hemoglobin levels were associated with increased frailty, and the risk of frailty increased at statistically significant levels for anemia adjusted for age, race, and education[30-31].

Another cross-sectional and longitudinal study in older Australian men also suggested that anemia may contribute to the development of frailty[20]. Recent studies including both older men and women indicated that older anemic adults were more likely to be frail, with the association between lower levels of hemoglobin and number of frailty criteria showing dose-response effect[32-34]. However, another contrasting result suggested having anemia contributed to a weak but significantly lower chance of worsening frailty[35]. In our study, we used 40 variables to construct a Frailty Index and observed that both
anemia and lower concentrations of hemoglobin were associated with frailty. Some studies have suggested that age-associated chronic inflammation is an explanatory factor in the relationship between anemia and frailty. In older adults, anemia and frailty may share a pathophysiological pathway with chronic inflammatory processes, resulting from immunosenescence-associated changes and increased oxidative stress[36-38].

Gabriele[39] described a close connection between inflammaging, anemia, and frailty, where comorbidities and inflammaging contribute to anemia of chronic inflammation (ACI), which was the most frequent type of anemia in older adults. Considering the etiopathogenetic mechanisms of inflammation, some interventions such as dietetic approach and physical exercise that can moderate oxidative stress and chronic inflammation may prevent anemia, frailty and their negative impact on functional performance and quality of life. Another study reported that a high intake of dietary total antioxidant capacity (TAC) was inversely related with frailty, and the intake of green tea, vegetable and fruits which contributed to TAC was also associated with lower odds of frailty[40]. Our results also indicated sufficient intake of vegetables and fruit and moderate to high levels of physical exercise had protective effects against frailty.

There were a few limitations in our study. Firstly, we used cross-sectional data from SAGE China Wave 1, it cannot provide causal direction in the relationship between anemia and frailty. Results from SAGE China Waves 2 and 3 may provide an opportunity to examine the direction of this relationship we identified. Secondly, we used self-report for some items to construct Frailty Index, which may be influenced by recall bias, although self-reported health questions are widely applied in population studies. Thirdly, the missing data for haemoglobin may have also contributed to selection bias. We analyzed the distribution of the missing data of Hb and found that total of missing values were randomly distributed across five income groups, but there were significant differences
between rural and urban across five income groups, that might be the reason why higher wealth individuals had higher anemia rates. However, our study was based on a large, national probability sample of older adults of both genders in China. We do not expect these missing values to have impacted the results or interpretations. Furthermore, the results indicated a quantitative relationship between hemoglobin concentration and frailty.

Conclusions

In conclusion, anemia and frailty were prevalent in China dwelling adults aged 50 years and older, and we also found that anemia and lower levels of hemoglobin concentration were significantly associated with frailty. Therefore, health care professionals caring for older adults may want to improve their recognition and treatment of anemia in their patient populations. Attention at the primary care level may reduce this risk for frailty, disability, hospitalization and mortality. This way, effective policies, early screening and health interventions can be employed for avoiding, delaying or even reversing frailty in a rapidly growing population in China.

Declarations

**Ethics approval and consent to participate**

SAGE was approved by the World Health Organization's Ethical Review Board (RPC146), and local approval by the ethics review committee of the Chinese Center for Disease Control and Prevention (approval notice 200601). Each respondent signed informed consent.

**Consent for publication:** not applicable.

**Availability of data and material**

The datasets supporting the conclusions of this article are available upon request in the
website of WHO
(http://apps.who.int/healthinfo/systems/surveydata/index.php/catalog/sage).

**Competing Interests:**
The authors have no conflicts of interest to declare.

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**Authors' contributions**
FW, PK, YFG and YZ designed, implemented the conduct of this study. YL, CZL and WJW examined the blood hemoglobin concentrations. YR, YFG and YS conceived of the analysis. YR and YFG contributed to the statistical analyses and drafted the manuscript. SYS, ZZH and GL contributed to the editing of initial draft. All authors read and approved the final manuscript.

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Tables

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