Higher Hemoglobin Levels Are Associated With Better Physical Performance Among Older Adults Without Anemia: A Longitudinal Analysis

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Abstract

Background

Anemia is the most common hematological abnormality among older adults, and it is associated with decreased physical performance. But the role of hemoglobin in the absence of anemia remains unclear. Thus, this study aimed to assess the impact of hemoglobin levels on physical performance in Brazilian older adults without anemia.

Methods

The study is longitudinal in that it relies on two waves of the Saúde, Bem-Estar e Envelhecimento (SABE; Health, Well-being, and Aging) study: 2010 and 2015–2016. Mixed-effects linear regression was used to determine the effects of the hemoglobin concentrations on the Short Physical Performance Battery-SPPB over time among the 1,020 who had complete data and did not have anemia in 2010. In the follow-up, there were 562 without anemia. Analyses were stratified by sex.

Results

In analyses adjusted for age, education, grip strength, comorbidities, and body mass index, hemoglobin levels were positively associated with physical performance scores among older women ($\beta = 0.15$, $p < 0.05$) and men ($\beta = 0.18$, $p < 0.05$) without anemia.

Conclusion

Our study demonstrates that higher hemoglobin levels were associated with better physical performance among older men and women without anemia. This finding is important because, in clinical practice, most health professionals focus on the World Health Organization definition of anemia. Our study suggests the importance of hemoglobin levels among older adults, even those without anemia.

Background

It is well-known that anemia, the most common hematological abnormality among older adults, is a major health problem associated with decreased physical performance, reduced mobility, increased functional dependence, and higher mortality (1–6). However, there is some debate whether the criteria adopted by the World Health Organization (WHO) to define anemia are adequate for older adults. Previous studies found disability and mortality risk gradients even within the WHO normal hemoglobin (Hb) range. These studies suggest that Hb levels higher than current cutoffs for anemia treatment might offer a clinical advantage (4, 7, 8). Therefore, it is important to explore more broadly the impact of hemoglobin levels, rather than anemia thresholds, on physical performance.

A limitation in the past studies is that most that analyzed the association between Hb levels on physical function are cross-sectional, and those that have used longitudinal data have focused on the effect of baseline Hb levels on physical function (9–11). Chaves et al. (1) conducted a cross-sectional study with older women from the Women's Health and Aging Studies I and II, which found that mobility difficulty was greater among those participants with lower Hb levels. A study conducted in Australian men described that each 1g/dL increase in Hb was strongly associated with a reduced risk of slow walking speed, poor grip strength, inability to perform chair stands, ADL, and IADL disabilities (12). Tseng et al. (2021) found that slower gait speed was significantly associated with Hb levels, but the associations disappeared when Hb values were dichotomized according to the WHO anemia criteria in Taiwanese older adults (11). Marzban et al. (2021) also showed a short review in their paper with several other studies (10), but none discussed this effect in individuals without anemia.

The few studies that have considered Hb changes have produced conflicting results, and some have analyzed narrow populations. For example, Zakai and colleagues (2005) reported that lower baseline Hb levels and incident anemia were associated with lower gait speeds among women at follow-up even though the change in Hb levels over time was not statistically significant (4). Hirani et al. (2016), in a sample of Australian men, showed that for every 1 g/dL increase in Hb, there was a significant reduction in risk of sarcopenia, slow walking speed, poor grip strength, inability to perform chair stands, and problems with activities of daily living (ADLs) and instrumental activities of daily living (IADLs) (12). Yoshimura et al. (2021) showed that the change in Hb levels was positively associated with the Functional Independence Measure - motor efficacy, but the sample was restricted to stroke patients with anemia who had been hospitalized (13).

Cross-sectional studies in low and middle-income countries (LMIC) have explored the associations between hemoglobin or anemia and several outcomes, such as higher health services utilization, disability, frailty, and mortality (6, 8, 14–16). Still, no longitudinal studies have examined the role of Hb on physical performance. Payne et al. (2018) analyzed cross-sectional data from a population-based study of rural South African men and women aged 40 and over and found that Hb concentration was independently associated with grip strength in women, but not in men, and did not observe associations between Hb and walking speed (9). On the other hand, a study conducted with Iranian older adults found an association between anemia and walking speed only among men in sex-stratified analyses, but they did not analyze continuous Hb levels (10).

There is some evidence that the association between Hb and functionality may be different in men and women. However, the differences according to sex are not adequately explored. For instance, in a study based in Japan, Sawada et al. (2021) showed low Hb was associated with worse scores in IADLs and cognition in women but not in men (17). A study based in China, Li, Chen, and Han (2021) showed that Hb levels predict frailty in women over 60 but not their male peers (18).

Thus, this study aimed to address some of the limitations of past studies. To do so, we assess the impact of hemoglobin levels on physical performance in Brazilian older adults without anemia stratified by sex

using longitudinal data.

Methods

Design and Participants

Data from the Saúde, Bem-Estar e Envelhecimento (SABE; Health, Well-being, and Aging), a multiple-cohort study of Brazilian older adults that began in 2000, are used in this study. SABE is based on a probabilistic sample of adults aged ≥ 60 years residing in the city of São Paulo (n = 2,143). Follow-ups were conducted in 2006, 2010, and 2015–2016. A representative sample of older adults aged 60 to 64 years was added to the study in each new wave. Details on the methodology of the study have been published previously (6, 8). The Research Ethics Committee at the University of São Paulo approved all waves of the SABE Study. Participation was voluntary, and a signed informed consent form was obtained from all participants in each wave. All of the procedures followed the ethical standards of the institutional and national research committee and the 1964 Helsinki declaration.

For this study, we focus on the last two waves as blood samples were first collected in 2010. In 2010, there were 1,344 participants aged 60 and older, but 89 had incomplete data on blood parameters and 133 on selected variables. Another 102 were anemic. Therefore, the 2010 sample is restricted to 1,020 individuals. In 2015, 634 individuals who were reinterviewed had complete data on covariates. Among these, 72 developed anemia, leaving a total of 562 to be included in the follow-up.

Measures and procedures

Data collection included face-to-face interviews using a standardized questionnaire, measurement of anthropometric data and physical performance, and collection of physiological specimens of blood and urine.

The outcome measure, physical performance, was assessed in both waves using the Short Physical Performance Battery - SPPB (19, 20). The total SPPB score is the sum of the scores on the three tests and ranges from 0 to 12: standing balance (the ability to maintain feet side-by-side, semi-tandem, and tandem positions for 10 seconds each), walking speed (for 3 m at their usual pace), and ability to rise from a chair (stand up from a sitting position once with arms folded at the chest).

Hemoglobin concentration (g/dL) was collected at both waves and analyzed at the laboratory of the Hospital of the Medical School at the University of São Paulo using an ADVIA 120 system (Siemens Healthcare Diagnostics, Germany). Anemia was defined using the WHO cutoffs – hemoglobin < 12 g/dL for women and < 13 g/dL for men (21), and anemic individuals were excluded from the analysis.

Covariates were measured in the baseline. We included age, education (in years of schooling), health status, grip strength, and body mass index (BMI). Health status was assessed based on self-reported chronic conditions diagnosed by a physician. We combined these conditions into two groups: 1) the number of cardiometabolic diseases (diabetes, hypertension, stroke, and cardiovascular disease)

because of their interaction with anemia in physical function (22), and 2) the number of other self-reported chronic conditions (cancer, chronic pulmonary disease, osteoarthritis, and osteoporosis). Grip strength was assessed using the highest value obtained between two attempts using a hand-held dynamometer (Takei Kiki Kogyio TK 1201), with the participant in a sitting position, with elbow and forearm resting in the table, and with palm facing up. BMI was calculated by dividing weight (in kilograms) by height (in meters) squared (kg/m^2). Weight was measured using a calibrated scale, and height was measured using a stadiometer fixed to a plain wall, both with the individuals barefoot and wearing light clothing.

Statistical analysis

Descriptive statistics (weighted means and standard errors) were used to assess the differences in physical performance and selected variables by sex. Sample weights were used to adjust for the complex sampling design. The association between hemoglobin concentration and SPPB scores was analyzed using a repeated mixed-effects linear regression with robust standard errors (23). Repeated mixed-effects regressions handle nested data inherent to repeated observations within individuals to allow for an unequal number of observations across individuals. SPPB score and hemoglobin concentration were treated as continuous variables. Random effects for the intercept were included to allow individuals to vary in the initial level of physical performance. The model included year, age, sex, years of schooling, grip strength, number of cardiometabolic diseases, the total number of other chronic conditions, and BMI. We present the regression coefficients, confidence intervals, and p-values. All regressions were stratified by sex because preliminary analyses indicated a statistically significant interaction between Hb levels and sex. Based on the results of the adjusted regression models, we calculated the predicted scores of SPPB given various levels of hemoglobin concentration by gender. All data analyses were conducted using the statistical software Stata/SE 16.1.

Results

Table 1 displays some selected characteristics of participants at the baseline. Most of the evaluated population was female. Women were less educated, had more health conditions, lower grip strength, higher BMI values, lower hemoglobin, and lower SPPB scores in 2010.

Table 1
Weighted mean and standard errors of selected characteristics of older adults (≥ 60 years old) according to sex in the baseline. SABE Study. São Paulo, Brazil, 2010.

Characteristics	Total (n = 1020)	Women (n = 666)	Men (n = 354)	*p*
Age	69.5 (0.6)	69.8 (0.7)	69.0 (0.6)	0.081
Education (in years)	5.3 (0.3)	5.0 (0.4)	5.8 (0.4)	0.003
Number of cardiometabolic conditions	1.2 (0.04)	1.2 (0.04)	1.1 (0.06)	0.042
Number of other chronic conditions	0.7 (0.03)	0.9 (0.04)	0.3 (0.04)	< 0.001
Grip strength (kg)	25.7 (0.4)	20.6 (0.4)	33.5 (0.5)	< 0.001
BMI (kg/m^2)	28.4 (0.2)	29.2 (0.3)	27.3 (0.2)	< 0.001
Hemoglobin concentration (g/dL)	14.4 (0.05)	13.9 (0.05)	15.2 (0.07)	< 0.001
SPPB score	9.2 (0.1)	9.0 (0.1)	9.6 (0.1)	< 0.001

SE = Standard Error; 95% CI = 95% Confidence Interval; SPPB = Short Physical Performance Battery; BMI = body mass index

Table 2 shows the results of the adjusted mixed-effects linear models. Higher hemoglobin levels were associated with higher physical performance scores among older women (β = 0.15, p = 0.036) and men (β = 0.18, p = 0.038). There were reductions in mean levels of SBBP among men and women over time. Higher age was negatively associated with SBBP levels. Higher grip strength was associated with higher SBBP levels. Education was also positively associated with physical performance. Cardiometabolic diseases, as well as other diseases, were negatively associated with SPPB levels. Among women, BMI was negatively associated with SPPB changes.

Table 2
Repeated mixed-effects linear models for longitudinal changes in physical function (SPPB score) as a function of hemoglobin changes over five years in Brazilian older adults, by sex. SABE Study. São Paulo, Brazil, 2010–2015.

Variables	**Men**		**Women**	
	β	95% CI	β	95% CI
Fixed				
Hemoglobin concentration (g/dL)	0.18*	(0.01, 0.35)	0.15*	(0.01, 0.28)
Year	-1.97***	(-2.33, -1.62)	-1.86***	(-2.07, -1.64)
Age	-0.05***	(-0.08, -0.02)	-0.12***	(-0.14, -0.10)
Education	0.09***	(0.04, 0.14)	0.07***	(0.04, 0.10)
Cardiometabolic conditions	-0.24*	(-0.45, -0.03)	-0.39***	(-0.57, -0.22)
Other chronic conditions	-0.17	(-0.50, 0.15)	-0.19*	(-0.38, 0.00)
Grip Strength	0.08***	(0.05, 0.10)	0.07***	(0.04, 0.09)
BMI (kg/m^2)	-0.04	(-0.10, 0.01)	-0.03*	(-0.06, -0.01)
Constant	10.63***	(6.53, 14.74)	16.74***	(14.14, 19.34)
Random				
Intercept	1.29	(1.01, 1.66)	1.41	(1.26, 1.58)
Residual	1.68	(1.46, 1.93)	1.50	(1.38, 1.64)
BIC	2348.6		4487.62	
AIC	2301.57		4433.09	
95% CI = 95% Confidence Interval; BMI = body mass index; AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion				
*p < 0.05; **p < 0.01; ***p < 0.001				

Table 3 presents the adjusted predicted scores of SPPB given various levels of Hb concentration by gender, based on the regression models found in Table 2. Results indicate that those with higher Hb concentrations have higher SBBP scores.

Table 3
Predicted scores of Short Physical Performance Battery (SBBP) for older men and women in Brazil. SABE Study. São Paulo, Brazil, 2010–2015.

	Men		Women	
Hemoglobin concentration (g/dL)	SBBP score	95% CI	SBBP score	95% CI
11	-	-	-	-
12	-	-	7.8	(7.5, 8.1)
13	8.4	(7.9, 8.8)	8.0	(7.8, 8.2)
14	8.5	(8.3, 8.8)	8.1	(8.0, 8.3)
15	8.7	(8.5, 8.9)	8.3	(8.1, 8.5)
16	8.9	(8.6, 9.1)	8.4	(8.1, 8.7)
17	9.1	(8.7, 9.4)	8.6	(8.1, 9.0)
18	9.2	(8.7, 9.8)	8.7	(8.1, 9.3)
95% CI = 95% Confidence Interval				

Discussion

In our results, Hb levels were positively associated with SPPB in older adults without anemia – those with higher Hb levels presented better physical performance. To our knowledge, this is the first study to analyze this association in older adults without anemia in LMIC. Our results confirm previous findings by Hirani and colleagues' in which increases in Hb levels are associated with better physical performance indicators, but their results were limited to men in Australia. We show that this finding is also relevant for older women. Therefore, even among older populations without anemia, lower levels of Hb are associated with worse physical performance.

Previous authors have already suggested that the WHO criteria for defining anemia in adults may not be adequate for older populations. These optimal Hb cutoffs for clinical decision-making were defined mainly based on statistical distribution considerations using apparently healthy people, rather than being developed through considerations of inflammation, the high prevalence of chronic conditions in older adults, and the physiological reduction in Hb concentration in the oldest old, factors that would shift the Hb distribution (1, 24–26).

One cause of the association between Hb and physical performance is the fact that Hb is responsible for tissue oxygenation, and lower Hb values can lead to local hypoxia in skeletal muscle and reduced muscle function (11). This effect is usually described in people with anemia. However, we found that lower Hb levels, even without anemia, can lead to lower physical function. This finding has not been underexplored in the literature. Zakai et al. (4) suggested that functional decline may occur in close temporal

association with hemoglobin decline, reinforcing that analyzing Hb levels may be more informative than only diagnosing anemia, as we showed here.

Steensma and Tefferi (2007) discussed that formal definitions of anemia do not always address the complex relationship between Hb level and health outcomes. Many factors can affect a healthy person's Hb value, including ethnic background, altitude of residence, smoking status, and physiologic fluctuations of plasma volume. Hence, the interpretation of blood count results remains the responsibility of the ordering physician, who should also refer to a patient's baseline Hb level when a previous measurement is available (24). In the same study, Steensma and Tefferi point out that a growing body of medical literature supports a "low-normal" Hb level associated with a broad range of poorer health-related outcomes. For example, a previous cross-sectional study using data from the 2010 wave of SABE study showed that at a concentration of 12 g/dL, the probability of mobility difficulty was 9.1%. But at higher levels, the probability of mobility decreased by 7.4% at 13 g/dL and 6.1% at 14 g/dL (8). Furthermore, the association was consistent in both men and women (8).

Another important aspect of our study is the specificity of the relationship between Hb concentrations and physical function, which was consistent even after adjusting for age, years of education, number of chronic cardiometabolic conditions, number of other chronic diseases, grip strength, and BMI, showing an independent association. Those covariates included in our analyses were largely discussed in the literature as risk factors for worse physical function and disability. Some functional decline is expected with advanced age, even without disease, but this decline is slow and gradual (27). Some authors point out that other factors are determinants for this decline, such as education (8, 28, 29). It is also well known that physical function decline is higher with chronic diseases (30, 31). Our analysis also opted to consider cardiometabolic conditions separately because it was already discussed that those conditions have an important interaction with anemia in physical function (13, 22). We also adjusted for grip strength, which is one of the main indicators of physical decline in older ages (32–35), as well as higher BMI, which several publications have indicated, is a risk factor for poor physical performance, mainly in walking and chair-stand tests (27, 32, 36, 37).

We also performed sensitivity analyses to ensure that our results are robust. In analyses including all participants (those with and without anemia), results were similar, showing that the relationship between Hb levels and SPPB scores is consistent across a wider Hb range.

Interpretation of our results should consider some limitations. First, as with any other aging cohort, the loss to follow-up and death during the period is considerable. Another study based on SABE data shows that anemia predicts mortality among participants (6); lower hemoglobin values among the non-anemic may as well. This suggests that our study underestimates the effects of Hb on physical performance. Another limitation is that the time between the two measurements (five years) is considerably long, which could mask shorter fluctuations.

But our study has several strengths. First, it is the first study with a large representative sample of community-dwelling older adults in an LMIC, where a nutritional transition is still ongoing, and the causes

and consequences of lower levels of Hb may represent a heavy burden in health services. Also, our analyses considered the levels of Hb over time in physical function, which is less common as even longitudinal studies typically consider Hb levels only at the baseline. We also showed effects stratified by sex which is important to target health care actions specifically for men and women. Most importantly, we showed that the effects of Hb levels are consistent in non-anemic individuals, which may alert health professionals to the importance of evaluating changes in Hb levels in all older adults, even without the formal diagnosis of anemia.

Conclusions

In conclusion, our study demonstrates that non-anemic older adults with higher hemoglobin levels presented better physical performance. This result is important because, in clinical practice, most health professionals do not stay alert if Hb level drops but does not reach the WHO-defined anemia threshold. We raise the possibility that therapeutic interventions (such as improvement in nutritional intake, treatment of possible causes of lower levels of Hb, treatment of chronic conditions that may be impacting Hb levels, or pharmacological approaches to correct iron deficiency) may be taken with reductions of Hb levels, even before anemia is diagnosed, to maintain physical function.

Abreviations

ADL: Activities of Daily Living; AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; BMI: body mass index; CI: Confidence Interval; Hb: hemoglobin; IADL: Instrumental Activities of Daily Living; low and middle-income countries, LMIC; SABE Study: Saúde, Bem-Estar e Envelhecimento (Health, Well-being, and Aging Study); SE: Standard Error; SPPB: Short Physical Performance Battery; WHO: World Health Organization.

Declarations

Ethics approval and consent to participate

The Research Ethics Committee at the University of São Paulo approved all waves of the SABE Study. Participation was voluntary, and a signed informed consent form was obtained of all participants in each wave. All of the procedures followed the ethical standards of the institutional and national research committee and the 1964 Helsinki declaration.

Consent for publication

Not applicable.

Availability of data and materials

The datasets on which the conclusions of this manuscript rely are not available publicly. The datasets used and/or analyzed during the current study are available from YAOD, PI of SABE Study (yedaenf@usp.br), on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

LPC conceived the study, proposed the study design. LPC and FCDA performed data analysis, interpretation and drafted the manuscript. YAOD is the PI of the SABE Study. All authors helped draft the manuscript and interpretation, reviewed and approved the submitted manuscript.

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