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Published in:
Journal of Nutrition, Health and Aging

DOI:
10.1007/s12603-022-1836-2

J Nutr Health Aging.2022;26(9):864-871
Published online August 27, 2022, https://doi.org/10.1007/s12603-022-1836-2

Original Research

Iron Deficiency and Incident Infections among Community-Dwelling Adults Age 70 Years and Older: Results from the DO-HEALTH Study

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Abstract

OBJECTIVES: To assess if baseline iron deficiency, with or without anemia, is associated with incident infections over 3 years among community-dwelling older adults.

DESIGN: Prospective secondary analysis of DO-HEALTH, a 3-year randomized, double-blind controlled trial.

SETTING AND PARTICIPANTS: 2157 community-dwelling adults age 70+ from 5 European countries with good cognitive function and mobility and no major health events in the 5 years prior to enrollment

Measurements: Incident infections, their severity and type were recorded every 3 months throughout the 3-year follow-up. Iron deficiency was defined as soluble transferrin receptor (sTfR) levels > 28.1 nmol/l and anemia as hemoglobin levels < 120 g/l for women and 130 g/l for men. We applied negative binomial mixed effects regression models with random effects for countries, and controlling for treatment allocation, age, sex, body mass index, polypharmacy, number of comorbidities, smoking status, living situation, alcohol intake, frailty status, and physical activity levels. A pre-defined stratified analysis was performed to explore if the associations between iron deficiency and infections were consistent by baseline anemia status.

RESULTS: In total, 2141 participants were included in the analyses (mean age 74.9 years, 61.5% of women, 26.8% with iron deficiency). Across all participants, baseline iron deficiency was not associated with incident overall infections, but was associated with a 63% greater rate of incident severe infections requiring hospitalization (incidence rate ratio [IRR] 1.63, 95% Confidence Interval [CI] 1.11-2.41, p=0.01). This association was more pronounced among the 2000 participants who did not have anemia at baseline (IRR=1.80, 95% CI 1.20-2.69, p=0.005).

CONCLUSION: Based on this prospective study among generally healthy European community-dwelling older adults, iron deficiency was not associated with the incidence rate of overall infections but may increase the incidence of severe infections. Intervention studies are needed to prove the causality of this observation.

Key words: Iron deficiency, anemia, infections, older adults, DO-HEALTH.

Introduction

Iron deficiency is the most common nutritional deficiency worldwide and is defined as the depletion of total-body iron (1). Iron deficiency and iron deficiency anemia cause an important disease burden, affecting populations of all ages and sexes (2). While data on their prevalence in the older population remain scarce, a recent large study reported a substantial prevalence of iron deficiency (up to 35.3%) among 2141 generally healthy European community-dwelling older adults (3).

Iron metabolism in the human body is tightly regulated to avoid both cellular damage associated with iron overload and anemia associated with iron deficiency (4). Iron also plays an important role in immunity. In the innate system, macrophages effectively restrict iron availability to microbial invaders while in vitro studies report that iron restriction impairs T-cell proliferation in the acquired system (5, 6). Notably, iron has been suggested to be essential for the replication of many pathogens, including viruses, bacteria, some protozoa and fungi species (4, 7, 8). Creating a state of low serum iron ("hypoferremia") in mice by administrating an iron-clearing agent (hepcidin, the iron-regulatory hormone or a hepcidin agonist) protects against lethal sepsis caused by certain extracellular pathogens (9). These findings suggest that iron may play a supportive role in both the immune defense of the host, but also the proliferation of the pathogens; this may explain a U-shaped relationship observed in animal models indicating both iron deficiency and iron overload may increase the risk of infection (10).

As people live longer, they are at an increased risk for infections due to chronic health conditions and the aging of the immune system, so called immunosenescence (11). Since infections are key drivers of morbidity and mortality in older adults (12), reducing their incidence by identifying modifiable risk factors is of value. However, a limited number of studies have investigated the association between iron status and the incidence of infections. While some of these studies suggested iron deficiency or iron deficiency anemia was associated with

Received June 17, 2022
Accepted for publication June 26, 2022

a lower risk of infections (13), others found a neutral (14) or increased risk (15-18).

Further, recent reviews highlighted the important burden of iron deficiency, with or without anemia and its consequences on functional outcomes, cardiovascular disease, all-cause mortality, and depression among older adults (2, 19). However, robust evidence regarding an association between iron deficiency and infection rates is still lacking (20).

Therefore, the aim of this study was to assess if, and to what extent, iron deficiency with or without anemia, was associated with the incidence of infections, their type and severity over three years in a large cohort of generally healthy older adults from five European countries.

Methods

Study population

The present study is an observational, prospective, secondary analysis of the DO-HEALTH trial. The original study was a three-year randomized, double-blind, placebo-controlled 2x2x2 factorial design clinical trial designed to test the effect of vitamin D 2000 IU daily, omega-3 1g daily, and a simple home-based strength exercise program on blood pressure, fractures, muscle function, cognition, and infections (21). A total of 2157 community-dwelling individuals aged 70 years and older were recruited from seven centers in five European countries: Zurich, Basel, Geneva (Switzerland), Berlin (Germany), Innsbruck (Austria), Toulouse (France) and Coimbra (Portugal). Inclusion criteria were absence of major health events in the five years prior to enrollment, sufficient mobility, and good cognitive status. Further details are provided elsewhere (22).

Outcomes

Incidence of infections was assessed every three months, during in-person interviews by phone or during yearly clinical visits. Upon each contact, the participants were asked whether any infection, with or without fever, had occurred. In case a participant had experienced an infection, a detailed infection questionnaire developed in two pilot trials to DO-HEALTH was applied (23, 24). Verification was conducted by an independent physician board using all available information, including symptoms, treatment received, and, if available, general practitioner diagnosis and hospitalization record (21, 22).

Incident infections were summed for each participant across the entire three-year follow-up. Infections were further categorized by severity (requiring a physician visit, requiring hospitalization), and infection type for the most commonly occurring infections (lower respiratory, upper respiratory, gastrointestinal, urinary).

Definition of iron deficiency and anemia

Iron parameters and hemoglobin concentration were measured at baseline using fasting serum samples. We used soluble transferrin receptor (sTfR) levels as a clinical marker of iron deficiency since this parameter is not influenced by inflammation (25), chronic diseases, or age (26, 27). The threshold of more than 28.1 nmol/L was used to define iron deficiency as it was previously validated in older adults (28-30). sTfR levels were measured with Tina-quant Transferrin ver.2 test on a cobas c 502 analyser (Roche) using an Immunoturbidimetric assay. Anemia was defined as hemoglobin levels less than 120 g/L for women and less than 130 g/L for men according to the WHO guidelines (31).

Baseline covariates

Participants' characteristics including age, sex, tobacco consumption, and body mass index (BMI) were collected at baseline. Alcohol consumption (g/day) was derived from the Food Frequency Questionnaire (32). Number of comorbidities were assessed with the self-administered comorbidity questionnaire (33). Frailty status (robust, at least pre-frail) was determined according to Fried criteria (34). Polypharmacy was defined as the use of five or more medications. Physical activity levels (0, 1-2, ≥3 times per week) were measured using the Nurses' Health Study questionnaire (35).

Statistical analysis

Baseline demographic and clinical characteristics were compared between iron deficient and non-iron deficient participants using t tests for continuous variables and Chi-square tests for categorical variables. Negative binomial mixed effects regression models were used to assess the association between iron deficiency and infection rate. All models were adjusted for treatment allocation (vitamin D, omega-3 fatty acids, exercise), age (36), BMI (37), sex (38), polypharmacy (39), number of comorbidities (39), tobacco consumption (40), living alone, alcohol consumption (41), frailty status (42), and physical activity levels (43) with a random effect for country of residence (Switzerland, Germany, Austria, France and Portugal). An offset of the logarithm of participant follow-up time was included in all models. Incidence rate ratios (IRR) were calculated to determine the effect of iron deficiency on infection rate, interpreted as an IRR below 1 indicating a protective association, and above 1 indicating a deleterious association of iron deficiency on infection rate. A pre-defined stratified analysis was performed to explore if the associations between iron deficiency and infections were consistent by baseline anemia status.

All analyses were performed using SAS v9.4. Two-sided p-values < .05 were considered statistically significant.

Ethics approval and informed consent

The Cantonal Ethical Committee of the Canton of Zurich approved this ancillary analysis (BASEC N° 2018–01755). Informed consent was obtained from all individual participants included in the study.

Table 1. Baseline characteristics of the study participants, overall and by iron status

Characteristic	Overall (n=2141)	Iron deficiency[a] (n=573)	No iron deficiency[a] (n=1568)	P value[b]
Women, No. (%)	1317 (61.5)	363 (63.4)	954 (60.8)	0.29
Men, No. (%)	824 (38.5)	210 (36.7)	614 (39.2)	
Age (years)	74.9 (4.5)	75.6 (4.7)	74.7 (4.3)	<.001
BMI, kg/m^2	26.3 (4.3)	27.1 (4.5)	26 (4.2)	<.001
Alcohol, g/day[c]	8.9 (11.7)	7.7 (11.1)	9.3 (11.9)	0.008
Current smokers, No. (%)	125 (5.8)	14 (2.4)	111 (7.1)	<.001
Live alone, No. (%)	897 (41.9)	242 (42.2)	655 (41.8)	0.85
Physical activity, No. (%)[d]				0.009
None	372 (17.4)	123 (21.5)	249 (15.9)	
1-2 times per week	644 (30.1)	170 (29.7)	474 (30.3)	
>=3 times per week	1123 (52.5)	280 (48.9)	843 (53.8)	
Frailty status, No. (%)[e]				0.007
Robust	1124 (53.3)	272 (48.4)	852 (55.1)	
At least pre-frail	985 (46.7)	290 (51.6)	695 (44.9)	
Polypharmacy, No. (%)[f]	575 (26.9)	191 (33.3)	384 (24.5)	<.001
Iron supplementation, No. (%)	120 (5.6)	37 (6.5)	83 (5.3)	0.30
Number of comorbidities[g]	1.7 (1.4)	2 (1.5)	1.6 (1.4)	<.001
Hemoglobin, g/L	139.8 (12.4)	139.3 (14.2)	139.9 (11.7)	0.35
Anemia, No. (%)[h]	140 (6.5)	63 (11.0)	77 (4.9)	<.001
Countries, No. (%)				
Austria	198 (9.3)	55 (9.6)	143 (9.1)	0.02
France	299 (14)	73 (12.7)	226 (14.4)	
Germany	346 (16.2)	92 (16.1)	254 (16.2)	
Portugal	293 (13.7)	101 (17.6)	192 (12.2)	
Switzerland	1005 (46.9)	252 (44.0)	753 (48.0)	

All values are presented as mean (SD), unless otherwise noted; Abbreviations: BMI, body mass index; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; a. Iron deficient defined as a soluble transferrin receptor (sTfR) measurement greater than 28.1 nmol/L at the baseline assessment; b. Differences between iron deficient and non iron deficient participants was assessed by an independent t test for continuous variables and Chi-square test for categorical variables; c. Alcohol consumption (g/day) was derived from the Food Frequency Questionnaire; d. Frequency of physical activity (0, 1–2, ≥3 times per week) was measured using the Nurses' Health Study questionnaire; e. Frailty status was defined using the Fried Physical Frailty Phenotype which evaluates five criteria: fatigue (self-reported), unintentional weight loss (self-reported loss more than 5% of total body weight), reduced physical activity (self-reported), slowness (impaired walking speed) and weakness (low grip strength). Participants are classified as at least pre-frail when one or more of the criteria are presented, and otherwise classified as robust; f. Polypharmacy was defined as the concomitant use of 5 or more medications; g. Self-reported number of comorbidities was assessed by the Sangha questionnaire, range 0-13; h. Anemia was defined as hemoglobin <130 g/L for men and <120 g/L for women.

Results

Baseline characteristics of the study population

Of the 2,157 DO-HEALTH trial participants, 2,141 had recorded baseline sTfR with a median follow-up of 2.99 (IQR 2.97-3.00) years (Table 1). Among those with baseline iron deficiency, 2.0% of participants (42/2141) did not have any recorded follow-up. The overall prevalence of iron deficiency and anemia at baseline was 26.8%, and 6.5% respectively. The mean age of participants was 74.9 years (SD 4.5), 61.5% were women, 46.7% were at least pre-frail, and 5.6% were taking iron supplements. Iron deficient participants were older (p=0.001), had a higher BMI (p<0.001), more comorbidities (p<0.001), were more likely to be at least pre-frail (p=0.007), had a higher prevalence of anemia (p<0.001). No significant difference between iron and non-iron-deficient participants was noted in terms of sex, hemoglobin levels, living situation, and iron supplementation.

Incident infections over the three-year follow-up

A total number of 6,175 infections were documented over the three-year follow-up. Unadjusted incidence rates indicate that on average, participants had one infection per year (Incidence Rate [IR]=1.05 per person year, 95% CI 1.01-1.08), and one infection requiring a physician visit every two years (IR=0.50, 95% CI 0.48-0.53). Infections requiring hospitalization occurred in 2.7% of all infections (IR=0.03, 95% CI 0.02-0.03). There was one death related to an infection.

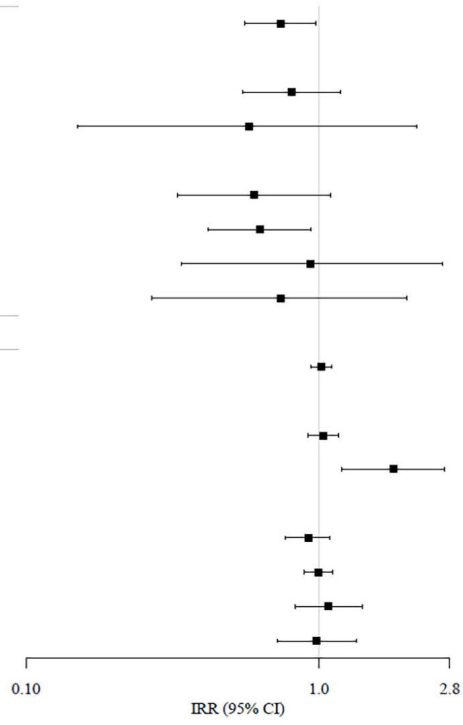
Table 2. Baseline iron deficiency and incidence rates of infection, by severity and type

Infection Type[a]	No. of Infections		Crude Incidence Rate (95% CI)[b]		Crude IRR (95% CI)[c]	Adjusted IRR (95% CI)[c,d]	P value
	Iron deficiency[e] (n=573)	No iron deficiency[e] (n=1568)	Iron deficiency[e] (n=573)	No iron deficiency[e] (n=1568)			
Overall infection [a]	1623	4552	1.03 (0.96, 1.11)	1.05 (1.00, 1.09)	0.98 (0.91, 1.07)	1.00 (0.92, 1.08)	0.91
Severity of infection							
Req. physician visit	810	2151	0.52 (0.47, 0.57)	0.50 (0.47, 0.53)	1.04 (0.93, 1.16)	1.03 (0.91, 1.15)	0.67
Req. hospitalization	64	105	0.04 (0.03, 0.06)	0.02 (0.02, 0.03)	1.72 (1.17, 2.51)	1.63 (1.11, 2.41)	0.01
Type of infection							
Lower respiratory	261	810	0.17 (0.14, 0.19)	0.19 (0.17, 0.20)	0.89 (0.75, 1.06)	0.89 (0.75, 1.06)	0.19
Upper respiratory	694	2036	0.44 (0.40, 0.48)	0.47 (0.44, 0.50)	0.94 (0.84, 1.05)	0.97 (0.86, 1.08)	0.56
Gastrointestinal	109	288	0.07 (0.06, 0.09)	0.07 (0.06, 0.08)	1.04 (0.81, 1.35)	1.06 (0.82, 1.38)	0.63
Urinary	169	437	0.11 (0.08, 0.14)	0.10 (0.09, 0.12)	1.06 (0.80, 1.42)	0.96 (0.71, 1.29)	0.79

Abbreviations: CI, confidence interval; IRR, incidence rate ratio; Req.: requiring; a. Infections were assessed every 3 months. Participants were asked whether any infection with or without fever had occurred. Every case of infection was confirmed through medical records; b. Incidence rate per one person year; c. Incidence rate ratio expressed as the ratio of incidence rates of iron deficient participants compared to non-iron deficient participants. Values less than one indicates a protective association of iron deficiency on infection rate, while values greater than one indicates a detrimental association of iron deficiency on infection rate; d. Negative binomial regression model adjusted for treatment effects (vitamin D, omega-3 fatty acids, exercise), age, BMI, sex, polypharmacy, comorbidity count, smoking status, living alone, alcohol, frailty status (robust, at least pre-frail), and activity level (none, 1-2 times per week, ≥3 times per week) with a random effect for country. 35 observations were excluded from adjusted models due to missing covariate information; e. Iron deficiency defined as a soluble transferrin receptor (sTfR) measurement greater than 28.1 nmol/L at the baseline assessment. Person years of follow-up was 1581.1 years for the iron deficient group and 4344.9 years for non-iron-deficient group

Figure 1. Baseline iron deficiency and incidence rates of infections by baseline anemia status

	No. of infections Iron deficiency | No iron deficiency[a]	Adjusted IRR (95% CI)[d,e]	P−values
Participants with anemia at baseline (n=140)[b]			
Any infection[c]	153 | 239	0.74 (0.56, 0.98)	0.03
Severity of infections			
Req. physician visit	91 | 134	0.81 (0.55, 1.19)	0.29
Req. hospitalization	5 | 10	0.58 (0.15, 2.16)	0.41
Type of infections			
Lower respiratory	22 | 47	0.60 (0.33, 1.10)	0.10
Upper respiratory	59 | 108	0.63 (0.42, 0.94)	0.02
Gastrointestinal	8 | 10	0.94 (0.34, 2.64)	0.91
Urinary	20 | 24	0.74 (0.27, 2.00)	0.55
Participants without anemia at baseline (n=2000)[b]			
Any infection[c]	1470 | 4309	1.02 (0.94, 1.11)	0.69
Severity of infections			
Req. physician visit	719 | 2015	1.04 (0.92, 1.17)	0.51
Req. hospitalization	59 | 95	1.80 (1.20, 2.69)	0.005
Type of infections			
Lower respiratory	239 | 762	0.92 (0.77, 1.09)	0.33
Upper respiratory	635 | 1925	1.00 (0.89, 1.12)	0.99
Gastrointestinal	101 | 278	1.08 (0.83, 1.41)	0.58
Urinary	149 | 413	0.98 (0.72, 1.34)	0.91



Abbreviations: CI, confidence interval; IRR, incidence rate ratio. Req.: requiring; a. Iron deficiency defined as a soluble transferrin receptor (sTfR) measurement greater than 28.1 nmol/L at the baseline assessment; b. Anemia was defined as hemoglobin <130 g/L for men and <120 g/L for women; Sample sizes: Anemic, iron deficient (n=63); anemic, non-iron deficient (n=77); non anemic, iron deficient (n=510); non anemic, non-iron deficient (n=1490). Person years of follow-up: Anemic, iron deficient (174.25 years); anemic, non-iron deficient (203.01 years); non anemic, iron deficient (1406.81 years); non anemic, non-iron deficient (4138.86 years); One participant was missing anemia status; c. Infections were assessed every 3 months. Participants were asked whether any infection with or without fever had occurred. Every case of infection was confirmed through medical records; d. Negative binomial regression model adjusted for treatment effects (vitamin D, omega-3 fatty acids, exercise), age, BMI, sex, polypharmacy, comorbidity count, smoking status, living alone, alcohol, frailty status (robust, at least pre-frail), and activity level (none, 1-2 times per week, ≥3 times per week) with a random effect for country. 36 observations were excluded from adjusted models due to missing covariate information; e. Incidence rate ratio expressed as the ratio of incidence rates of iron deficient participants compared to non-iron deficient participants. Values less than one indicates a protective association of iron deficiency on infection rate, while values greater than one indicates a detrimental association of iron deficiency on infection rate.

Baseline iron deficiency and incidence rates of infection

Overall, iron deficiency was not associated with the incidence of overall infections (IRR=1.00, 95% CI 0.92-1.08, p=0.91). When considering the severity of infections, we did not find any significant association between iron deficiency and the incidence of infections which required a physician visit (IRR=1.03, 95% CI 0.91-1.15, p=0.67). However, participants who were iron deficient at baseline had a 63% greater incidence rate of infections requiring hospitalization (IRR=1.63, 95% CI 1.11-2.41, p=0.01), compared to non-iron-deficient individuals. There was no significant difference in the incidence rates of lower respiratory, upper respiratory, gastrointestinal, or urinary infections between iron and non-iron deficient participants (Table 2).

Stratified analysis by baseline anemia status

At baseline, 510 participants (23.8%) were iron deficient without being anemic, 77 (3.6%) had anemia without iron deficiency, and 63 (2.9%) had iron deficiency with concomitant anemia.

Among the 140 participants with anemia at baseline, iron deficiency was associated with a 26% lower incidence rate of overall infection (IRR = 0.74, 95% CI 0.56-0.98, P=0.03). However, we did not find any significant association between iron deficiency and the incidence of infections requiring a physician visit or hospitalization. Regarding infection type, iron deficiency was associated with a 37% lower incidence rate of upper respiratory infections (IRR = 0.63, 95% CI 0.42-0.94, P=0.02). The incidence rates of lower respiratory, gastrointestinal, or urinary infections were not statistically significant between iron deficient and non-iron-deficient participants (Figure 1).

Among the 2000 participants without anemia at baseline, iron deficiency was neither associated with the incidence of overall infection (IRR = 1.02, 95% CI 0.94-1.11, P=0.69) nor with the incidence of infections requiring a physician (IRR = 1.04, 95% CI 0.92-1.17, P=0.51). However, individuals with iron deficiency had an 80% greater incidence of infections requiring hospitalization (IRR = 1.80, 95% CI 1.20-2.69, P=0.005), compared to their non-iron-deficient counterparts. Regarding infection type, iron deficiency was not associated with the incidence of lower respiratory, upper respiratory, gastrointestinal, or urinary infections (Figure 1).

Discussion

To the best of our knowledge, the present study is the first to investigate the association between iron deficiency, with or without anemia, and the severity and types of infections in a large cohort of generally healthy and active European community-dwelling older adults. On average, independently of their baseline iron status, participants had one infection per year, and one infection requiring a physician visit every two years. Overall, we found that the presence of iron deficiency at baseline was not associated with a greater incidence rate of overall infection over the three-year follow-up. Similarly, baseline iron deficiency was not associated with a higher incidence of a specific type of infection. However, participants with iron deficiency at baseline had a 63% greater incidence rate of infections requiring hospitalizations when compared to their non-iron-deficient counterparts, even after adjustment on key potential confounders.

While these findings appear to be partly in line with current knowledge on the relationship between iron status and susceptibility to infections, their direct comparison remain limited for several reasons. So far, studies on the association between disturbances in iron metabolism and infections reported conflicting results, pointing toward either a decreased susceptibility to infection in the presence of iron deficiency (13) or an increased risk of infection in children and adult populations (16-18). Further, the paucity of clinical evidence on iron status and infections among adults has been highlighted in a systematic review published in 2013 including four studies among 676 individuals admitted to intensive care unit, who underwent surgery or were pregnant (44). Tansarli et al. concluded that the limited available evidence suggested that individuals with iron deficiency might be more susceptible to different types of infections compared to those with normal iron status (44). However, the authors highlighted major limitations in the existing studies including their limited sample size, the lack of adjustment for possible confounders, and the heterogeneity in the study populations (44). More recently, a Norwegian population-based study among 61,852 individuals with a mean age of 49.8 years investigated the relationship between iron status and the risk of bloodstream infections over 15 years of follow-up (45). The authors reported that iron deficiency defined as serum iron levels below the 2.5th percentile was associated with a 1.7 increased risk of blood stream infection, after adjustment on age, sex, BMI and comorbidities (45). Of note, these results were independent of anemia status.

The lack of consensus in the definition of iron deficiency across studies is an additional point that precludes the comparison of our results with the literature. Iron deficiency is most commonly assessed by ferritin (46). Over the last years, this biomarker has been criticized, as it is also influenced by inflammatory conditions due to its additional function as an acute-phase protein, which might bias findings when studying infection susceptibility (47). In this regard, the use of sTfR levels to define iron deficiency in our study population of older adults might be more suitable to investigate iron deficiency and its association with adverse outcomes including infections.

Given the limited evidence on the association between iron deficiency and susceptibility to infections among generally healthy older adults, our large multicenter prospective study contributes valuable insight on the topic. Our findings are further held mechanistically by the well-established and important role of iron in innate and acquired immunity (5). Numerous studies in adults and children have shown that iron deficient individuals have defective immune function, particularly T-cell activity (20). In addition, individuals with iron deficiency were found to have reduced bactericidal activity

of macrophages and decreased ability to produce inflammatory cytokines (20). While there is convincing evidence from pre-clinical and immunological studies that iron deficiency impairs cell-mediated immunity, further studies are needed to disentangle the immune-related effects of iron deficiency from other factors.

Anemia may also play a relevant role in the association between iron metabolism disturbance and incidence of infections. In our pre-defined stratified analysis by baseline anemia status, iron deficiency was associated with a 26% lower incidence rate of overall infections among participants with anemia. Clinical evidence on the association between iron deficiency anemia and infections remains limited and makes the comparison between studies difficult. The reduction in the incidence of overall infection among individuals with iron deficiency anemia was mostly driven by the 37% lower incidence of upper respiratory infections. This reduction may be explained from a pathophysiological point of view by a lactoferrin-mediated mechanism at mucosal surfaces. This is as part of the innate immune system limits iron availability to pathogenic microorganisms (4). Further research in this field is required as in literature, studies examining iron deficiency and susceptibility to acute respiratory infections have predominantly focused on young children in developing countries and report contradictory findings on whether iron deficiency is a risk (13) or protective (48) factor for acute respiratory infections. However, the small number of DO-HEALTH participants with iron deficiency anemia limits the scope of our conclusions.

Overall, our findings suggest that iron deficiency may be a promotor of severe infections requiring hospitalizations in generally healthy older adults without anemia. After identifying the underlying cause of iron deficiency, targeted management might be initiated such as education on dietary sources of iron or supplementation (49, 50). Further interventional studies are needed to investigate whether treating iron deficiency could efficiently reduce the incidence of severe infections among older adults.

Our study has several strengths. It took advantage of data collected in the DO-HEALTH trial, the largest European study on aging that included and followed 2157 community-dwelling older adults over three years. Also, the occurrence of infections were assessed and documented prospectively, with a validated protocol for each incident infection, ascertained by in-person interviews every three months, throughout the three-year trial period and confirmed by an independent physician. Moreover, we defined iron deficiency using sTfR as a valid and reliable biomarker which is not influenced by inflammatory states, chronic diseases, and malignancies. However, a few limitations need consideration. Since our study was conducted among generally healthy and physically active community dwelling older adults, our results may not be generalizable to less active, more vulnerable, or institutionalized older adults. Consistently, the prevalence of anemia at baseline was very low. Therefore, further studies are needed to confirm the associations between iron disturbance and infection by anemia status. Further, the potential for false positive results may exist since we did not adjust for multiple comparison testing. At last, given the observational design of our study and despite adjustments on several potential confounders, we cannot exclude the possibility that the observed associations between iron deficiency and infections may be explained in part by residual confounding.

Conclusion

Our prospective study suggests that iron deficiency, without anemia, may be associated with severe infections requiring hospitalizations among generally healthy European community-dwelling older adults. Intervention studies are needed to prove the causality of this observation.

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Funding sources: This analysis of the DO-HEALTH data set was funded by an independent and investigator-initiated grant funded by Vifor Pharma. The DO-HEALTH study was funded by the Seventh Research Framework Program of the European Commission (Grant Agreement n°278588; PI Prof. Heike A. Bischoff-Ferrari, MD, DrPH), and within this framework, also by the University of Zurich (Chair for Geriatric Medicine and Aging Research), DNP, Roche, NESTEC, Pfizer and Streuli. The funding/supporting organizations had no role in the design and conduct of DO-HEALTH, including collection, management, analysis, and interpretation of the data, as well as preparation, review, or approval of the manuscript, or decision to submit the manuscript for publication.

Conflicts of interest: DRS reports personal fees from Danube University of Krems, US Department of Defense, European Society of Anesthesiology, Korean Society for Patient Blood Management, Korean Society of Anesthesiologists, Network for the Advancement of Patient Blood Management, Haemostasis and Thrombosis, Bayer AG, Zürich, B. Braun Melsungen AG, Boehringer Ingelheim GmbH, Bristol-Myers-Squibb, CSL Behring GmbH, Celgene International II Sàrl, Daiichi Sankyo AG, Haemonetics, Instrumentation Laboratory (Werfen), LFB Biomédicaments, Merck Sharp & Dohme, PAION Deutschland

GmbH, Pharmacosmos A/S, Pfzer AG, Pierre Fabre Pharma, Portola Schweiz GmbH, Roche Diagnostics International Ltd, Sarstedt AG & Co., Shire Switzerland GmbH, Tem International GmbH, Vifor Pharma, Vifor (International) AG, Zuellig Pharma Holdings. DRS's academic department is receiving grant support from the Swiss National Science Foundation, the Swiss Society of Anesthesiology and Reanimation (SGAR), the Swiss Foundation for Anesthesia Research, Vifor SA and Vifor (International) AG. DRS is co-chair of the ABC-Trauma Faculty, sponsored by unrestricted educational grants from Novo Nordisk Health Care AG, CSL Behring GmbH, LFB Biomédicaments, and Octapharma AG. LA is currently an employee of MSD, Switzerland. As part of the DO-HEALTH independent and investigator-initiated clinical trial, HABF reports as the PI of the DOHEALTH trial, grants from European Commission, from University of Zurich, from NESTEC, from PFIZER Consumer Healthcare, from Streuli Pharma, plus nonfinancial support from DSM Nutritional Products and nonfinancial support from Roche Diagnostics. Further, Prof. Bischoff-Ferrari reports speaker fees from Wild, Pfzer, Vifor, Mylan, Roche Diagnostics, and independent and investigator-initiated grants from Pfizer and from Vifor. All other authors declare no competing interests.

Acknowledgements: We thank all the members of the DO-HEALTH Research Group, and we are grateful to the patients for their participation in, and commitment to, this study

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How to cite this article: P. Lanz, M. Wieczorek, A. Sadlon, et al. Iron Deficiency and Incident Infections among Community-Dwelling Adults Age 70 Years and Older: Results from the DO-HEALTH Study. J Nutr Health Aging.2022;26(9):864-871; https://doi.org/10.1007/s12603-022-1836-2