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ORIGINAL

Association of iron status with the risk of bloodstream infections: results from the prospective population-based HUNT Study in Norway

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Abstract

Purpose: As iron is essential for both immune function and microbial growth, alterations in iron status could influence the risk of infections. We assessed the associations of iron status with risk of bloodstream infections (BSIs) and BSI mortality.

Methods: We measured serum iron, transferrin saturation (Tsat) and total iron-binding capacity (TIBC) in 61,852 participants in the population-based HUNT2 study (1995–97). Incident BSIs (1995–2011) were identified through linkage with the Mid-Norway Sepsis Register, which includes prospectively registered information on BSI from local and regional hospitals. We assessed the risk of a first-time BSI and BSI mortality with the iron indices using Cox proportional hazards regression analysis.

Results: During a median follow-up of 14.8 years, 1738 individuals experienced at least one episode of BSI, and 370 died within 30 days after a BSI. In age- and sex-adjusted analyses, BSI risk was increased among participants with indices of iron deficiency, serum iron ≤ 2.5th percentile (HR 1.72, 95% CI 1.34–2.21), Tsat ≤ 2.5th percentile (HR 1.48, 95% CI 1.12–1.96) or TIBC ≥ 97.5th percentile (HR 1.46, 95% CI 1.06–2.01). The associations remained similar after adjusting for comorbidities and exclusion of BSI related to cancer, rheumatic illnesses and inflammatory bowel disease. BSI mortality showed similar associations.

Conclusion: Indices of severe iron deficiency are associated with an increased risk of a future BSI.

Keywords: Bacteraemia, Sepsis, Iron, Epidemiology, Population based

Introduction

Bloodstream infections (BSIs) cause sepsis and critical illness and are major causes of morbidity and mortality worldwide [1, 2]. Due to its large impact on global health, there have been increased initiatives to identify modifiable risk factors for BSI [1, 3]. So far, we know that the risk of acquiring BSI depends on both host factors such as social and demographic factors (e.g., age, nutrition, lifestyle and poverty) [1, 4] as well as biologic factors such as host genetic susceptibility, chronic medical disorders (e.g., cancers, obesity, diabetes) [3, 5] and the ability to mount an adequate immune response to the invading bacteria [6]. Moreover, differences in virulence and

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antimicrobial susceptibility of infecting microbes also influence the incidence and mortality of BSI [1].

Recent advances in adaptive and innate immunity have demonstrated an essential role of systemic and cellular iron-regulating mechanisms in protecting hosts from infection [7]. On the other hand, most microbes also depend on iron for their pathogenicity, and some bacteria (e.g., *Escherichia coli*, *Staphylococcus aureus* and *Pseudomonas*) have evolved the ability to scavenge iron from host iron-binding proteins such as transferrin [7]. Iron is tightly bound to transferrin to control the balance between the host's need for iron in cellular metabolism and restricting invading bacteria from obtaining iron [7]. Disturbances in this delicate homeostasis between free iron in serum and transferrin-bound iron could clearly influence the risk of BSI and sepsis [8].

Most studies of the association between disturbances in iron metabolism and risk of infections have been performed in children with iron deficiency anemia in developing countries. While some studies have shown an increased risk of infections such as respiratory tract infections [9], others have found that iron-deficient individuals seem to be less prone to infections such as malaria [10]. There is evidence to suggest a U-shaped relationship indicating that both low and high iron levels could increase infection risk [7, 11]. In the adult western population, few studies exist on the association between iron levels and susceptibility to infections. As most of these studies have used indirect markers of iron levels in serum (e.g., anemia, hypochromasia), there is also a lack of studies on the association between free iron in serum and transferrin-bound iron (i.e., iron status) and the risk of infections.

In this era of rising antibiotic resistance, we need new measures to prevent severe infections [12]. To the best of our knowledge, no study has examined the associations of iron status with the risk and mortality of BSI in a long-term follow-up in the general population. The large Norwegian population-based HUNT2 study cohort has prospective follow-up data on blood culture-positive infections over 15 years used as a specific indicator of sepsis [13, 14]. In this cohort of 61,852 adults, we assessed the association of iron status with risk of BSI and BSI mortality [15].

Take-home message

Bloodstream infections and iron deficiency represent an important burden of disease. Our study assessed iron status and risk of bloodstream infections in the HUNT2 survey with 61,852 individuals and 15 year follow-up, showing increased risk of BSI among individuals with low iron status.

Methods

Study population

The second Nord-Trøndelag Health Survey (HUNT2, 1995–1997) invited all inhabitants ≥ 20 years old ($n = 93{,}865$) in Nord-Trøndelag county to a clinical examination that included non-fasting blood sampling, and the participants completed questionnaires covering a range of health-related topics [16] (http://www.ntnu.edu/hunt/databank). A total of 65,236 (69.5%) persons participated. Iron status measurements were performed as a population-screening for hereditary hemochromatosis, and the study revealed an estimated hereditary hemochromatosis prevalence of 0.7% [19]. No routine follow-up was carried out in pathologically low iron indices in the HUNT2 study, but later diagnostic and/or treatment cannot be ruled out. For this study, we selected all participants in HUNT2 with baseline measurements of serum iron, transferrin saturation percentage (Tsat) and total iron-binding capacity (TIBC). Using the 11-digit unique personal identification number of Norwegian citizens, the HUNT2 study cohort was linked to the Mid-Norway Sepsis Register with prospectively recorded information on all BSI events at Levanger and St. Olavs hospitals from 1 January 1995, and Namsos hospital was included in the register from 1 September 1999. The HUNT study database is regularly updated with information on site of residence and vital status from the Norwegian population register. Nord-Trøndelag county in central Norway has a population of 130,000 where 70% is served by Levanger hospital and 30% by Namsos hospital, and the tertiary referral center is St. Olavs hospital in Trondheim. The population is stable (net out-migration 0.3% per year) and ethnically homogeneous (97% Caucasians) [17]. Among the 65,236 HUNT2 participants, prior to start of follow-up (which was the entry date in HUNT2 between August 1995–June 1997 for residents having Levanger as their primary hospital and 1 September 1999 for residents having Namsos as their primary hospital) [17], 47 (0.07%) had a positive blood culture, 1140 (1.8%) migrated or died, and 2197 (3.4%) had incomplete information on iron status or comorbidities, leaving 61,852 participants for analysis (see Supplementary Figure 1).

Laboratory measurements

Fresh non-fasting serum samples were analyzed at the Central Laboratory at Levanger hospital using a Hitachi 911 Autoanalyser (Mito, Japan). Iron concentrations were measured after reduction of transferrin with ascorbic acid, complexed with bathophenanthrolin and

quantitated colorimetrically (Boehringer, Germany). TIBC was calculated from serum transferrin analyzed by immunoturbidimetric methodology from DAKO A/S, Denmark. The method was calibrated against the international standard CRM 470. Transferrin saturation percentage was calculated as 100 × (serum iron/2 × TIBC)%. Serum creatinine was analyzed using the Jaffé method (Roche Diagnostics, Germany). eGFR was estimated from recalibrated creatinine values using the Modification of Diet in Renal Disease (MDRD formula), as previously described [18].

Outcome ascertainment

Participants were followed up for BSI identified at the two hospitals (Levanger and Namsos) in Nord-Trøndelag county or at the tertiary referral center, St. Olavs hospital in Trondheim. We used BSI mortality as an indicator of risk of severe BSI and defined death from BSI as death occurring within 30 days after detection of a BSI. Outcome variables were first-time BSI and death from BSI. In participants with multiple positive blood cultures, a new episode of BSI was defined as positive blood culture > 30 days after the previous one. Blood cultures solely with microorganisms commonly associated with skin contamination such as coagulase negative *Staphylococcus* species, *Corynebacterium* species and *Propionibacterium* species were not considered as BSI [19].

Covariates

HUNT2 participants self-reported a range of chronic illnesses including cardiovascular disease (history of myocardial infarction, stroke and/or angina), lung disease (asthma or chronic obstructive pulmonary disease) and diabetes. Chronic kidney disease was defined as estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2. Body mass index (BMI) was calculated as weight (kg) divided by the squared value of height (m^2) and categorized as recommended by WHO (< 18.5, 18.5–24.9, 25–29.9, 30.0–34.9, 35.0–39.9 and ≥ 40.0 kg/m^2). We retrieved information on cancer diagnoses from the Cancer Registry of Norway for all patients with BSI (from 1 January 1953 until 1 January 2014). Information on rheumatic illnesses (e.g., rheumatoid arthritis, ankylosing spondylitis) and inflammatory bowel disease (e.g., ulcerative colitis, Crohn's disease) was retrieved from medical records in patients with BSI. This information had been retrieved for 1216 BSI patients (68%); 1145 were BSI patients at Levanger hospital, and 111 of them had this diagnosis. Thus, the prevalence of rheumatic illness was 0.09%, which correlates with other prevalence studies [20, 21].

Statistical analyses

Levels of serum iron, Tsat and TIBC were categorized into values ≤ 2.5th percentile (low) or ≥ 97.5th percentile (high); the values in between were categorized into quintiles. The HUNT study population is representative of the Norwegian adult population, and we therefore based our iron values on the distribution in the entire cohort. For each category of iron indices, we used the Stata *stcompadj* command to estimate the age-adjusted cumulative incidence of first-time BSI, accounting for death as a competing risk. For each outcome, we used Cox regression analysis to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) by categories of the iron indices using the middle quintile as reference. In the analysis of BSI risk, participants were followed until their first BSI, migration out of Nord-Trøndelag county, death or end of follow-up at 31 December 2011, whichever occurred first. In the analyses of BSI mortality, participants were followed until migration out of Nord-Trøndelag county, death or 31 December 2011, whichever occurred first. The proportional hazards assumption was examined using log-log plots and tests of Schoenfeld residuals. In a first model we adjusted for age (using attained age as the time scale) [22] and sex (by stratification). In a second model we additionally adjusted for BMI and chronic illnesses as these conditions may increase the risk of BSI [3], can cause "anemia of chronic disease" and altered iron status [23]. In a separate analysis, we omitted potentially cancer-related BSI from the outcome definition, indicated by a cancer diagnosis within 5 years prior to a BSI or 2 years after. Both cancer and cancer treatment could confound iron status and BSI risk. In a sensitivity analysis, we excluded the first 2 years of follow-up after HUNT2 participation from the follow-up to reduce possible confounding by prevalent but unknown disease at the time of serum measurements. Another sensitivity analysis was performed to investigate the impact of rheumatic illnesses and inflammatory bowel disease. We omitted BSI potentially related to this group of diseases from the outcome definition in 1145 cases of BSI at Levanger hospital, and Cox regression models were performed solely in participants having Levanger as their primary hospital ($n = 43{,}280$). All analyses were performed with Stata version 15.1 (Statacorp, Texas, USA).

Ethics

This study was approved by the Regional Committee for Medical and Health Research Ethics of Central Norway (REK no 2012/153), and all participants signed an informed consent.

Results

Among 61,852 participants, 1738 (2.9%) experienced at least one episode of BSI during median follow-up of 14.8 years, and 370 (0.6%) persons died from BSI. This corresponds to an incidence rate of 221/100,000 person-years and mortality rate of 47/100,000 person-years. Participants who experienced BSI were more likely to be male, older and obese (Table 1).

Table 1 Baseline characteristics of the study population at inclusion to HUNT 2, *n* = 61,852

	***n* (%)**
BSI during follow-up	1738 (2.8)
Sex (female)	32,847 (53.1)
	Median (IQR)
Age	49.8 (36.3–63.2)
	Mean (SD)
BMI kg/m^2	26.3 (4.1)
Comorbidities	
Cardiovascular disease	4567 (7.4)
Chronic renal disease	2612 (4.2)
Lung disease	2157 (3.5)
Diabetes	1734 (2.8)
Serum iron (μmol/l), mean 16.5 (SD 6.3)	
Low ≤ 6	2202 (3.5)
7–12	14,169 (22.9)
13–15	12,950 (20.9)
16–17	8510 (13.8)
18–21	12,749 (20.6)
22–31	9975 (16.1)
High ≥ 32	1297 (2.1)
Transferrin saturation percentage (Tsat), mean 27.4 (SD 11.3)	
Low ≤ 9	1974 (3.2)
10–20	14,634 (23.7)
21–25	12,906 (20.9)
26–30	11,572 (18.7)
31–36	10,040 (16.2)
37–52	9050 (14.6)
High ≥ 53	1676 (2.7)
Total iron-binding capacity (TIBC) (μmol/l)[a], mean 61.5 (SD 9.2)	
High ≥ 82	1685 (2.7)
69–81	10,068 (16.3)
64–68	10,855 (17.6)
60–63	11,782 (19.1)
56–59	11,955 (19.33)
47–55	13,664 (22.1)
Low ≤ 46	1843 (3.0)

BSI bloodstream infection, *IQR* interquartile range, *BMI* body mass index, *SD* standard deviation

[a] High values of TIBC indicate iron deficiency

In age- and sex-adjusted analyses, BSI risk was increased among participants with indices of iron deficiency: low serum iron (HR 1.72, 95% CI 1.34–2.21), low Tsat (HR 1.48, 95% CI 1.12–1.96) or high TIBC (HR 1.46, 95% CI 1.06–2.01). The associations remained essentially similar after adjustments for BMI and chronic illnesses and also after exclusion of cancer-related BSI ($n = 368$) from the outcome definition (Table 2). In a sensitivity analysis where we omitted BSI-related rheumatic illnesses and inflammatory bowel disease ($n = 111$) from the outcome definition, the associations remained essentially similar (Supplementary Table 1). The results were also similar when we started follow-up 2 years after baseline (Supplementary Table 2), showing that the increased risk of BSI in iron-deficient subjects is not only present shortly after the time of diagnosis. The cumulative incidence curves also confirm that the excess risk at indices of iron deficiency continued throughout the follow-up period (Fig. 1). There was no association between indices of high iron levels and increased risk of BSI and no association between differences in iron status between the 2.5th and 97.5th percentiles and BSI risk (Table 2).

Analyses of BSI mortality showed similar associations as those we observed for a first-time BSI, but the low number of BSI deaths precluded precise estimates. Thus, age- and sex-adjusted BSI mortality was increased among participants with low serum iron (HR 1.52, 95% CI 0.86–2.66), low Tsat (HR 1.41, 95% CI 0.75–2.67) and high TIBC (HR 1.67, 95% CI 0.76–3.68), and the associations did not attenuate after adjustment for BMI and comorbidities (Table 3).

Discussion

In this large population-based cohort, indices of iron deficiency were associated with increased risk of a future BSI. Interestingly, individuals who were iron depleted continued to have an increased risk of BSI during a 15-year follow-up, even after adjusting for chronic medical disorders and excluding BSIs that occurred in relation to malignancies and chronic inflammatory disorders. To the best of our knowledge, our study is the first to show an increased risk of future BSI in individuals with iron depletion not related to cancers or chronic illnesses.

Former studies on the association between iron status and risk of infection have indicated a U-shaped risk profile where both iron deficiency and excess iron are linked to increased infection risk [7, 11]. To explore this hypothesis, we categorized our iron indices into quintiles using the middle quintile as reference and in the extreme ends ≤ 2.5th percentile or ≥ 97.5th percentile. A reason why we see no clear association between high iron status and risk of infection in our study could be that the low number of BSI cases in the high iron status categories precluded precise estimates of the associations between

Table 2 Associations of indices of iron status with risk of bloodstream infection

Indices of iron status	Risk of first-time BSI, adjusted for age and sex				Risk of first-time BSI, adjusted for age, sex, BMI and comorbidities[a]		Risk of non-cancer related BSI[b], adjusted for age, sex, BMI and comorbidities[a]		
	Years at risk	No. BSI	HR	95% CI	HR	95% CI	No. BSI	HR	95% CI
Serum iron (μmol/l)	786527	1738					1370		
Low ≤ 6	27125	83	1.72	1.34–2.21	1.71	1.33–2.20	71	1.79	1.36–2.35
7–12	177840	418	1.08	0.93–1.27	1.06	0.90–1.24	334	1.03	0.87–1.23
13–15	164480	383	1.01	0.87–1.19	1.01	0.86–1.19	294	0.96	0.80–1.15
16–17	108973	246	1.00	Reference	1.00	Reference	199	1.00	Reference
18–21	163237	344	0.97	0.83–1.15	0.98	0.84–1.16	272	0.97	0.81–1.16
22–31	128313	236	0.91	0.76–1.09	0.93	0.78–1.12	178	0.88	0.72–1.08
High ≥ 32	16555	28	1.06	0.72–1.57	1.06	0.72–1.57	22	1.05	0.68–1.63
Transferrin saturation percentage (Tsat)									
Low ≤ 9	24676	59	1.48	1.12–1.96	1.45	1.10–1.91	48	1.40	1.03–1.91
10–20	184421	432	1.11	0.96–1.28	1.08	0.93–1.24	342	1.02	0.87–1.19
21–25	164506	357	0.95	0.82–1.10	0.94	0.81–1.09	278	0.88	0.75–1.04
26–30	147447	345	1.00	Reference	1.00	Reference	284	1.00	Reference
31–36	128719	275	0.92	0.79–1.08	0.94	0.80–1.10	210	0.88	0.74–1.06
37–52	115412	236	0.90	0.77–1.07	0.93	0.79–1.10	183	0.89	0.74–1.07
High ≥ 53	21344	34	0.84	0.59–1.20	0.86	0.60–1.22	25	0.78	0.52–1.18
Total iron-binding capacity (TIBC) (μmol/l)									
High ≥ 82	21553	43	1.46	1.06–2.01	1.36	0.99–1.87	35	1.34	0.94–1.91
69–81	128767	225	0.95	0.80–1.12	0.92	0.78–1.09	183	0.93	0.77–1.12
64–68	139549	283	0.94	0.80–1.10	0.93	0.80–1.09	208	0.86	0.72–1.03
60–63	151071	346	1.00	Reference	1.00	Reference	274	1.00	Reference
56–59	152182	345	0.92	0.79–1.07	0.93	0.81–1.09	283	0.97	0.82–1.15
47–55	171521	428	0.92	0.79–1.05	0.95	0.82–1.09	337	0.95	0.81–1.11
Low ≤ 46	21881	68	1.00	0.77–1.30	1.04	0.80–1.35	50	0.98	0.72–1.32

BSI bloodstream infection, *BMI* body mass index, *HR* hazard ratio, *CI* confidence interval

[a] Comorbidities: cardiovascular events, chronic renal disease, lung disease and diabetes

[b] The outcome is first-time BSI except cancer-related BSI, indicated by a cancer diagnosis within 5 years prior to BSI or 2 years after

iron excess and increased risk of BSI. Moreover, all subjects with high iron status in HUNT2 were scheduled for further examinations, and those diagnosed with hereditary hemochromatosis were followed closely at the hospital for this condition thereafter.

In line with our findings, a systematic review reported that five out of six studies found higher occurrence of infections among patients with iron deficiency [24]. There are several plausible pathophysiologic explanations for an increased risk of BSI at low iron levels. Recent work has shown that iron plays a crucial role in the hypoxia-inducible-factor (HIF) transcription factor/prolyl hydroxylase domain pathway. HIFα induces a number of aspects of host immune function, from boosting phagocyte microbicidal capacity to driving T cell differentiation and cytotoxic activity [25]. Indeed, reduced T cell function [26], reduced bactericidal activity of macrophages [27] and decreased ability to produce inflammatory cytokines [28] have been shown in iron-depleted persons.

Our study suggests that the immune defense mechanisms may be relatively more depressed than the ability of bacteria to sequester iron in low iron environments, resulting in a net increased risk of BSI in iron-deficient individuals.

Major strengths of our study include its large size, the population-based design and long-term follow-up. Information on potential confounding factors such as chronic illnesses and malignancies, as well as linkage to microbiologic records, also add strength to our study. Moreover, in a sensitivity analysis we showed that the increased risk of BSI among iron-depleted subjects still was present after excluding the BSI events during the first 2 years of follow-up, which reduces the possibility that confounding from preclinical disease may explain the association and indicates that iron deficiency could be persistent in our subjects.

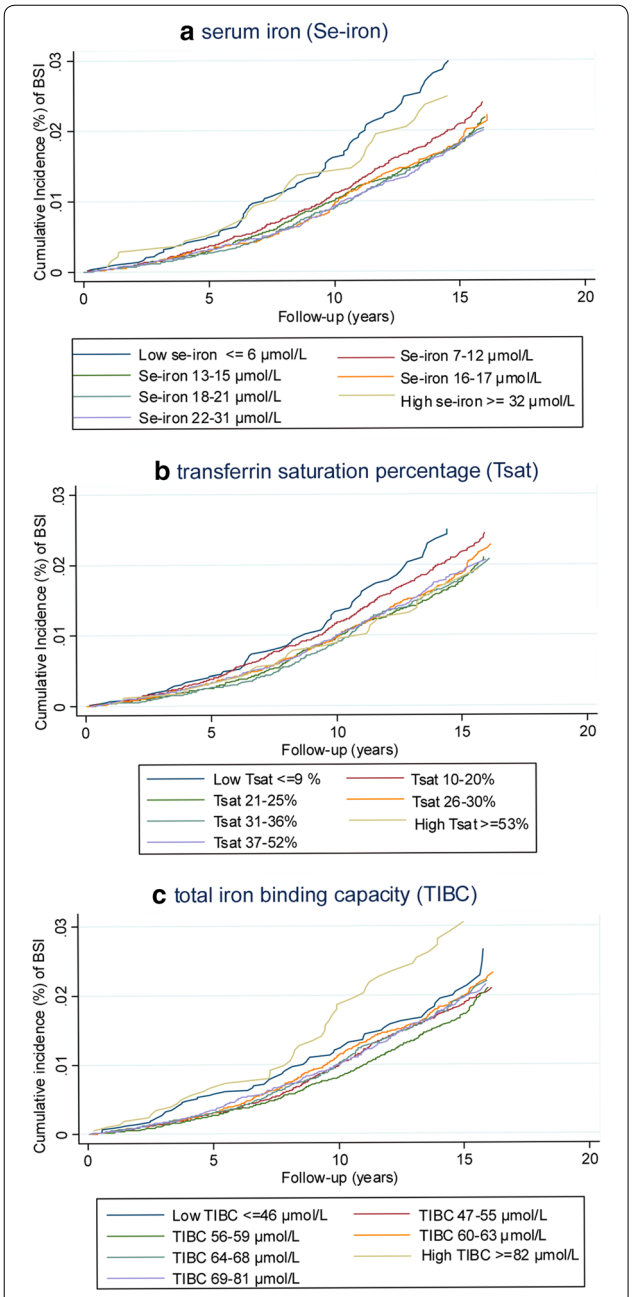

Fig. 1 Age-adjusted cumulative incidence of BSI associated with levels of serum iron (**a**), transferrin saturation percentage (**b**) and total iron-binding capacity (**c**), estimated for age 49.8 years (the mean age of the total population)

Iron status in the context of infection risk must take in account anemia of chronic disease, counting for 20% of anemias in the elderly (≥65 years) [29]. We have therefore adjusted for these confounding factors by adjusting for chronic illnesses, age and BMI, as these factors could influence both BSI risk and iron status [3, 23]. By retrieving data from the Cancer Registry of Norway, we also obtained valid and essentially complete information on cancer diagnoses among BSI cases. Importantly, the associations between low iron status and increased BSI risk remained similar after these adjustments. Also in sensitivity analyses leaving out patients with rheumatic illnesses and inflammatory bowel, we obtained similar results to the main analysis.

Linkage to microbial records with information on bacterial species enabled us to exclude pathogens commonly associated with contamination of blood cultures. The majority of positive blood cultures in this material are thus likely to represent serious infections. Although we did not have clinical information about the course of infection for all participants, a review of medical records of the patients with *S. aureus* and *Streptococcus pneumoniae* BSI in this cohort has shown that ~98% met the 2001 sepsis criteria [13, 14]. Thus, we find it likely that the patients with BSI clinically could be characterized as septic.

There are some limitations of our study. One is that our definition of BSI mortality as any death occurring within 30 days after detection of a BSI could be confounded by other causes of death not being related to the event of BSI. The lack of information on ferritin and hemoglobin concentrations is also a limitation. Ferritin is widely accepted as a standardized assessment of global iron stores, but is largely influenced by inflammation [30]. Hemoglobin concentration becomes abnormal only in long-standing iron deficiency and is influenced by a wide range of medical conditions [30]. Some studies have shown that Tsat or TIBC alone is an alternative diagnostic test for iron deficiency [31, 32]. We believe that our study has proved that serum iron, Tsat and TIBC, although prone to diurnal variation and fasting status, are useful for studying the association between iron metabolism and the future risk of BSI.

Another limitation is the one single measurement of the iron indices in our study and that we do not have measurements at the time when BSI was acquired. As iron status was measured up to 15 years before the outcome, it could have changed during the follow-up period, possible by later identification and correction by supplementation. However, any potential misclassification of iron indices caused by diurnal variation, non-fasting blood sampling or the single measurement would most likely be non-differential, i.e., not related to later risk of BSI, and is therefore likely to have led to underestimation of the associations. In nutritional surveys among adults from Norway during the same period as our study, the intake of iron was below the recommended daily amount [33], suggesting that iron deficiency was stable at the population level. A recent population study from

Table 3 Associations of indices of iron status with BSI mortality[a]

Indices of iron status	BSI mortality, adjusted for age and sex				BSI mortality, adjusted for age, sex, BMI and comorbidities[b]		Non-cancer related BSI mortality[c], adjusted for age, sex, BMI and comorbidities[b]		
	Years at risk	No. BSI deaths	HR	95% CI	HR	95% CI	No. BSI deaths	HR	95% CI
Serum iron (μmol/l)	786527	370					222		
Low ≤ 6	27125	16	1.52	0.86–2.66	1.54	0.89–2.69	7	1.06	0.47–2.39
7–12	177840	99	1.11	0.80–1.54	1.07	0.77–1.48	64	1.05	0.70–1.58
13–15	164480	89	1.00	0.72–1.40	1.00	0.72–1.39	54	0.94	0.62–1.43
16–17	108973	58	1.00	Reference	1.00	Reference	37	1.00	Reference
18–21	163237	62	0.75	0.52–1.07	0.77	0.54–1.10	36	0.72	0.45–1.14
22–31	128313	42	0.69	0.47–1.04	0.72	0.48–1.07	22	0.63	0.37–1.07
High ≥ 32	16555	4	0.70	0.25–1.19	0.70	0.25–1.93	2	0.62	0.15–2.56
Transferrin saturation percentage (Tsat)									
Low ≤ 9	24676	11	1.41	0.75–2.67	1.39	0.73–2.61	3	0.64	0.20–2.07
10–20	184421	102	1.24	0.92–1.67	1.18	0.88–1.59	68	1.29	0.88–1.89
21–25	164506	79	0.97	0.71–1.32	0.94	0.69–1.29	46	0.92	0.61–1.38
26–30	147447	76	1.00	Reference	1.00	Reference	45	1.00	Reference
31–36	128719	64	0.97	0.70–1.35	1.00	0.72–1.40	37	1.01	0.65–1.56
37–52	115412	33	0.57	0.38–0.85	0.59	0.39–0.89	21	0.67	0.40–1.13
High ≥ 53	21344	5	0.59	0.24–1.45	0.60	0.24–1.49	2	0.44	0.11–1.83
Total iron-binding capacity (TIBC) (μmol/l)									
High ≥ 82	21553	7	1.67	0.76–3.68	1.47	0.67–3.25	6	1.81	0.76–4.33
69–81	128767	49	1.32	0.90–1.93	1.26	0.86–1.85	31	1.20	0.75–1.93
64–68	139549	67	1.36	0.95–1.93	1.34	0.94–1.91	33	0.98	0.62–1.57
60–63	151071	57	1.00	Reference	1.00	Reference	38	1.00	Reference
56–59	152182	77	1.21	0.86–1.70	1.25	0.94–1.81	47	1.14	0.74–1.75
47–55	171521	102	1.24	0.90–1.72	1.30	0.94–1.81	61	1.16	0.77–1.75
Low ≤ 46	21881	11	0.90	0.47–1.72	0.95	0.50–1.81	6	0.75	0.32–1.79

BSI bloodstream infection, *BMI* body mass index, *HR* hazard ratio, *CI* confidence interval

[a] Death from BSI was defined as death within 30 days after an episode of BSI

[b] Comorbidities: cardiovascular events, chronic renal disease, lung disease and diabetes

[c] The outcome is BSI mortality except cancer-related BSI mortality, indicated by a cancer diagnosis within 5 years prior to BSI or 2 years after

Portugal found a high prevalence of iron deficiency and that it was largely undiagnosed [34].

Although our study adds weight to the growing body of evidence linking iron deficiency and risk of infections, we should be careful recommending iron supplements in individuals with mild-to-moderate iron deficiency to prevent infections. While there are studies suggesting that iron supplementation may decrease the risk for some infections [35], a recent systematic review showed increased susceptibility to infections with intravenous versus oral or no iron administration [36]. The controversies shown in iron supplemental studies demonstrate how delicate iron homeostasis is and that iron supplement should be given with caution.

In summary, we show an increased risk of BSI in individuals with low iron status in a 15-year follow-up study. As iron deficiency and BSI represent an important burden of disease globally, our findings suggest increased research on the effect of identifying and correcting iron deficiency to prevent BSI and sepsis.

Electronic supplementary material

The online version of this article (https://doi.org/10.1007/s00134-018-5320-8) contains supplementary material, which is available to authorized users.

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Compliance with ethical standards

Conflicts of interest
Nothing to declare.

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