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BLOOD DONORS AND BLOOD COLLECTION

TRANSFUSION

The effect of ferritin-guided iron supplementation among Danish female first-time blood donors

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Abstract

Background: The identification of blood donors at risk of developing low hemoglobin (Hb) and subsequent intervention is expected to reduce donation-induced iron deficiency and low Hb among blood donors. This study explores the effects of ferritin-guided iron supplementation for female first-time donors implemented in four of five administrative regions in Denmark.

Study Design and Methods: We included 45,919 female first-time donors in this study. Hb values were determined in donations of included donors during a 2-year follow-up period. For each region, an intervention group (after implementation) and a control group (before implementation) were defined. The primary outcome was Hb below the donation threshold (7.8 mmol/L ∼ 12.5 g/dL) at the time of donation, in the control group, and the intervention group, using logistic regression. The secondary outcome was the number of donations per donor given during the follow-up period.

Results: We observed a statistically significant decrease in the risk of female first-time donors experiencing a donation with low Hb after ferritin-guided iron supplementation was introduced: Odds ratio, 0.82; 95% confidence interval (CI), 0.71–0.95. We found a statistically significant increase in the number of donations per donor during the follow-up period after intervention; rate ratio: 1.05, 95% CI: 1.02–1.08.

Discussion: Ferritin-guided iron supplementation led to a significant reduction in the occurrence of low hemoglobin (Hb) levels among Danish female first-time blood donors. The intervention was additionally associated with an increase in the number of donations per donor.

KEYWORDS

blood donation, ferritin, hemoglobin, iron supplementation

1 | INTRODUCTION

Globally, approximately 118 million blood donations are given annually.[1] The Danish blood supply relies on 129,000 voluntary, unpaid blood donors[2] and the safety of the voluntary blood donors is important. Blood donors, especially women of childbearing age, are at risk of iron-deficient erythropoiesis following blood donation, which can lead to low hemoglobin (Hb).[3–5] Iron deficiency has also been associated with symptoms such as decreased physical fitness and fatigue.[6,7] In addition, it could cause longer donation intervals and deferral among blood donors and thereby affect the blood supply.

Ferritin (F) is a cellular iron storage protein and thus a marker of iron stores in plasma. Low F is an important predictor of developing low Hb[8] and is used to identify blood donors at risk of declining Hb.

It has previously been shown that iron supplementation based on F and Hb levels resulted in a lower proportion of donors with low Hb concentration in the Danish Capital Region.[9]

Ferritin-guided iron supplementation is not mandatory in Denmark. Nevertheless, four out of five administrative regions in Denmark decided to implement ferritin-guided iron supplementation between 2011 and 2018 to mitigate the risk of iron depletion and subsequent development of low Hb. The information about and distribution of the iron supplementation was carried out by the blood bank in the region of interest, as shown in Table 1. Due to the absence of a national guideline endorsing ferritin-guided iron supplementation, the algorithms implemented vary across regions. Together with Hb measurements and sex, F is used in algorithms to identify donors with iron deficiency subsequently offered iron supplementation.

This study aimed to explore the effect of ferritin-guided iron supplementation among female first-time blood donors in Denmark. Taking advantage of the stepwise introduction of ferritin-guided iron supplementation in the four regions, we compared the risk of low Hb among female first-time blood donors in the different regions, during 2 years of follow-up before and after the implementation of the regimens.

2 | MATERIALS AND METHODS

2.1 | Study population

Donation data were obtained from the laboratory information systems in the five regional blood centers. We included 45,919 female first-time whole blood donors in our study population between March 1, 2011 and February 1, 2018; 13,043 in the Capital Region, 9019 in Central Denmark Region, 5588 in North Denmark Region, 4762 in the Zealand Region, and 13,507 in South Denmark Region. These numbers represent donors in the main cohort (Table 2) and donors included in the "cohorts of other regions" (Supplementary Table 1). The participants were healthy, unremunerated, voluntary, female first-time whole blood donors. The following participant variables were retrieved: date of birth, sex, Rh and ABO blood type, Hb values, date(s) of donation, and type(s) of donation. Routine F measurements among female first-time blood donors have been introduced in four of the five Danish regions (Capital Region in 2011, North Denmark Region in 2012, Central Denmark Region in 2016, and Zealand Region in 2018). In the Capital Region, ferritin-guided iron supplementation was gradually implemented between March 1, 2011 and September 1, 2011, when implementation was complete (Supplementary Table 2). In South Denmark Region, routine F measurements have not been implemented.

TABLE 1 Algorithm of ferritin guided iron supplementation among Danish female blood donors.

	Hemoglobin mmol/L	Ferritin µg/L	Iron substitution at diagnosis	Iron substitution at subsequent donations
Capital Region	<7.8	<15	100 × 100 mg	20 × 100 mg
		15–40	60 × 100 mg	20 × 100 mg
	7.8–10.4	<30	60 × 100 mg	20 × 100 mg
		30–60		20 × 100 mg
Central Denmark Region	6.8–7.7	<15	60 × 100 mg	20 × 100 mg
		15–22	20 × 100 mg	20 × 100 mg
	7.8–10.2	<15	60 × 100 mg	20 × 100 mg
		15–22	20 × 100 mg	20 × 100 mg
North Denmark Region	7.0–7.7	<15	40 × 100 mg	40 × 100 mg
		15–40	20 × 100 mg	20 × 100 mg
	7.8–10.2	<15	20 × 100 mg	20 × 100 mg
Zealand Region	6.8–7.7	<15	40 × 100 mg	20 × 100 mg
		15–22	20 × 100 mg	20 × 100 mg
	7.8–10.2	<15	40 × 100 mg	20 × 100 mg
		15–22	20 × 100 mg	20 × 100 mg

Note: mmol/L = 1.6113 g/dL.

2.2 | Design

Hb values were determined in all donations with few exceptions due to missing values (Figure 1). In all regions, the first contact with the blood bank consisted of an inclusion meeting and a blood sample without donation. F and Hb samples were taken before the donation and used in algorithms together with sex to estimate the need for iron supplementation. These algorithms differ between regions (Table 1). We excluded donors who gave at least one donation other than whole blood, for example, plasma, stem cell, or organ donation, during or before the study period. Donors who had donations in two different regions during the study period were also excluded.

For each of the four regions, we defined a primary cohort consisting of an intervention group and a control group. Participants from Central Denmark Region, North Denmark Region, and Zealand Region were included during a 1-year period before and after the implementation of ferritin-guided iron supplementation, respectively. Due to data collection challenges, participants from the Capital Region were included during a 5-month period before and after the implementation of ferritin-guided iron supplementation, respectively. The cohort selection and follow-up process are illustrated in Figure 2.

TABLE 2 Basic characteristics demonstrating pre- and post-implementation cohorts.

	Before implementation	After implementation
N	5729	5279
Cases	8.4%	6.9%
Subsequent donations, median (IQR)	1 (0–3)	1 (0–3)
Region		
Capital Region	1499 (26.2%)	1141 (21.6%)
Central Denmark Region	1897 (33.1%)	1904 (36.1%)
North Denmark Region	932 (16.3%)	972 (18.4%)
Zealand Region	1401 (24.5%)	1262 (23.9%)
Age, median (IQR)	22 (19–31)	22 (19–30)
Hemoglobin (mmol/L), median (IQR)	8.4 (8.1–8.7)	8.4 (8–8.7)

Participants were followed for 2 years after their first contact with the blood bank and all their donations and Hb measurements were registered. Participants were included in the study even if they did not donate any blood in the follow-up period.

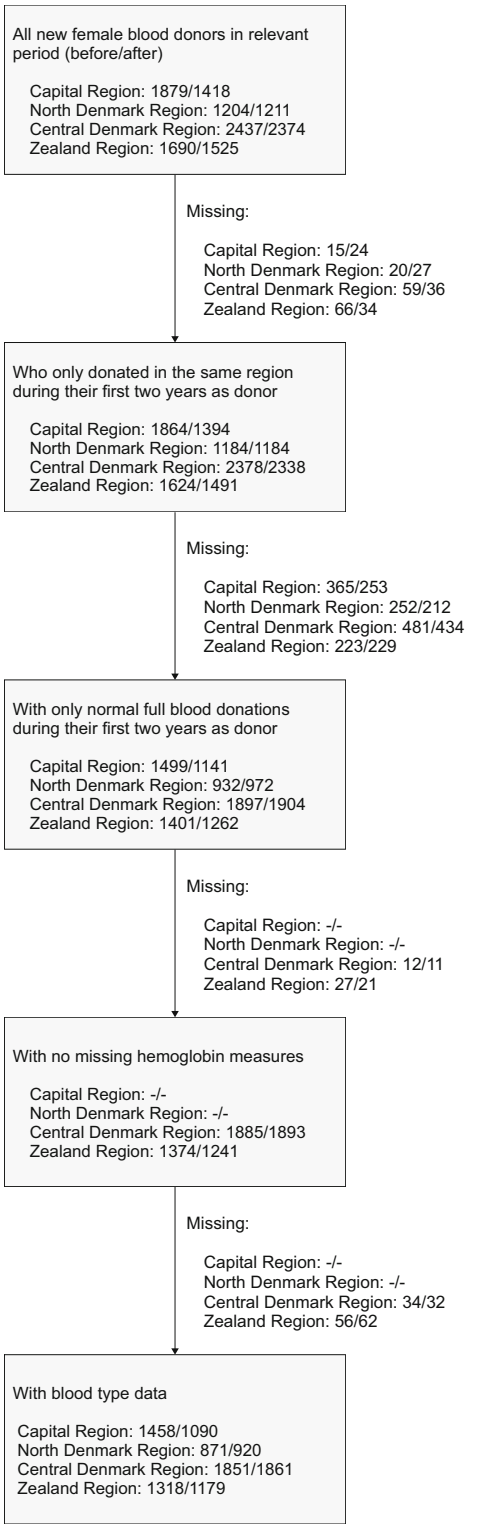


FIGURE 1 Description of missing donors by analysis.

* Within five of the correct value - the correct value is not displayed due to person data protection concerns

Our primary outcome was Hb below the donation threshold (7.8 mmol/L ~ 12.5 g/dL) in the 2-year follow-up period. Participants who experienced at least one donation with low Hb in the follow-up period were defined as cases. Our secondary outcome was the number of donations per donor given during the follow-up period.

We defined four primary cohorts, each consisting of a control group and an intervention group as mentioned above. Thus, there was one primary cohort for each of the

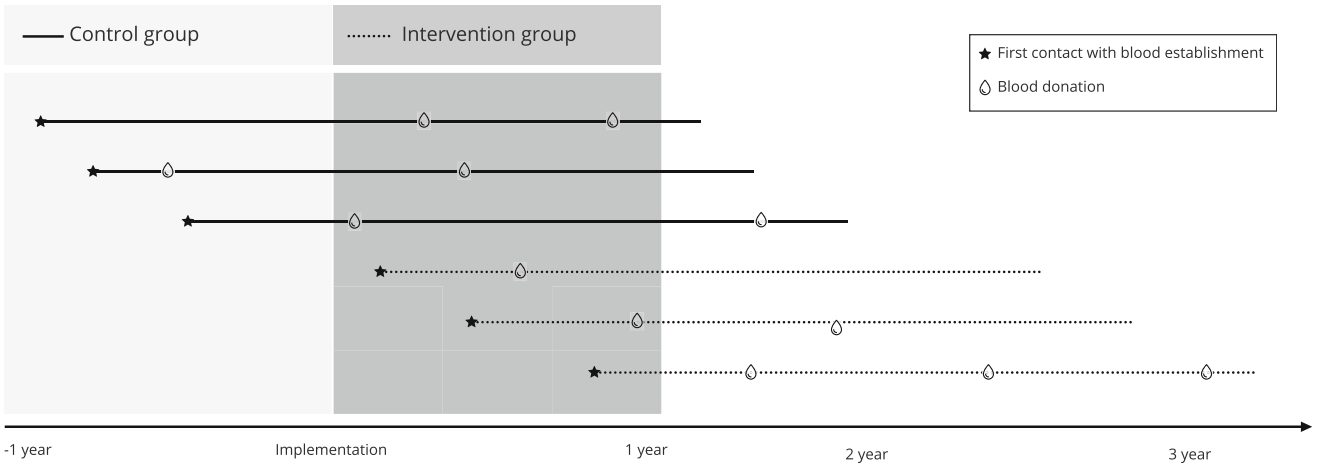


FIGURE 2 Cohort selection process and follow-up time.

regions in which the ferritin-guided iron supplementation had been implemented (Capital Region, Central Denmark Region, North Denmark Region, and Zealand Region). The population of these cohorts were all female first-time whole blood donors, and the study implementation intervals and follow-up periods were defined from when the ferritin-guided iron supplementation had been implemented in the given region (Supplementary Table S2). For each of these four primary cohorts, an extra reference cohort was defined, "cohorts of other regions," in order to compare the effect of the ferritin-guided iron supplementation between a region of intervention and regions without intervention in the same time period (Supplementary Table S1).

2.3 | Statistics

To answer the main research question, we compared the ratio of odds of being a case (i.e., participants experiencing at least one low Hb measurement within the first 2 years of first blood donation) using logistic regression analysis to calculate odds ratios and 95% confidence intervals (CI). The analysis was conducted, both as a crude analysis and adjusted for donor age and blood type. The analysis was also conducted for the pooled cohort of all four regions, while adjusting for the region.

In order to better control for the number of donations given by each donor in the follow-up period, and the time between donations, we conducted a Cox proportional hazards analysis with donation number as the underlying time scale. The analysis was performed, both as a crude analysis and adjusted for age at inclusion (as blood donor), blood type, time since last donation, and time since inclusion. The analysis was also conducted for the pooled cohort of all four regions, while adjusting for the region.

The implementations of F measurements in the four regions were distributed over a period coinciding with a national decrease in the number of whole blood donations. Accordingly, the number of whole blood donations in the first 2 years as a female blood donor also decreased over time (Figure 3).

To control for the national time-specific change in number of blood donations, or other unknown time-related covariates during the study period, we compared each primary cohort to their corresponding "cohort of other regions" using a logistic regression. As with the main analysis, the case status was the outcome. The group (control vs. intervention) and cohort (primary cohort vs. "cohort of other regions") were the predictors along with an interaction between the group and the cohort. The focus of this analysis was to test if the change in ratio of cases was bigger in the region with the implementation, than in the cohort of other regions expressed by the coefficient for the interaction and the corresponding odds ratio. We also included an analysis controlling for blood type and age of the donor.

To evaluate whether ferritin-guided iron supplementation might affect the blood supply, we compared the number of donations per donor between the two groups in each primary cohort using a Poisson regression—both a crude analysis with no covariates, and an adjusted analysis correcting for blood type and age of donor. All statistical analyses were performed in R version 4.1.3.[10]

2.4 | Ethics

The use of administrative blood donor data were approved as part of the DBDS protocol by the Zealand Regional Committee on Health Research Ethics (SJ-740) and the Data Protection Agency (P-2019–99). The data were pseudonymized before analysis.

3 | RESULTS

Basic characteristics of the study population are presented in Table 2 and Supplementary Table 1. In pooled analyses, we observed a decrease in risk of experiencing a donation with low Hb after implementation of ferritin-guided iron supplementation (Table 3). In analyses stratified by region, the decrease was found in the Capital

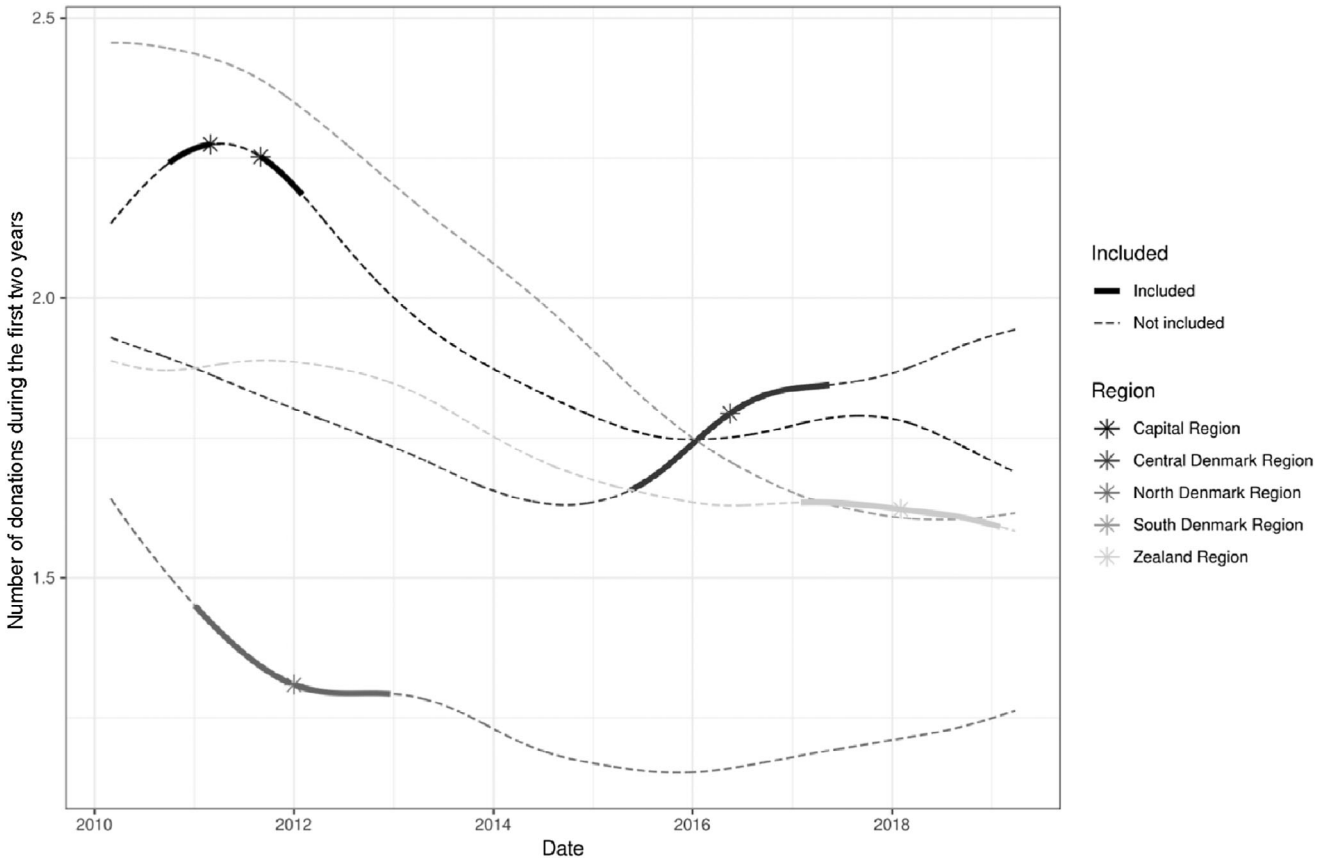
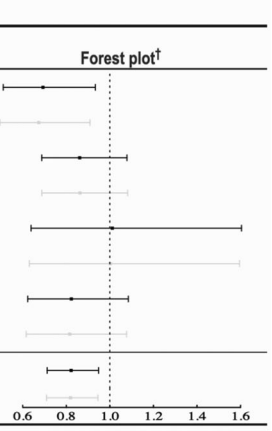


FIGURE 3 Smoothed number of national whole blood donations during the first 2 years as a blood donor for female donors.

TABLE 3 Logistic regression analysis of women experiencing low hemoglobin during the first 2 years as donor.

Intervention group, of blood donors starting after implementation of feritin measures, compared to control group of blood donors starting after implementation compared to before implementation.

Region	Cases Before (%)	Cases After (%)	Crude analysis Odds ratio (95%-CI)	Crude analysis P-value	Adjusted analysis* Odds ratio (95%-CI)	Adjusted analysis* P-value	Forest plot†
Capital Region	8.98%	6.40%	0.693 (0.510 - 0.934)	0.017	0.673 (0.495 - 0.909)	0.011	
Central Denmark Region	9.44%	8.24%	0.861 (0.687 - 1.078)	0.193	0.863 (0.688 - 1.082)	0.201	
North Denmark Region	3.98%	4.02%	1.011 (0.638 - 1.604)	0.963	1.002 (0.631 - 1.595)	0.993	
Zealand Region	9.24%	7.74%	0.823 (0.623 - 1.085)	0.169	0.816 (0.616 - 1.077)	0.152	
All‡	**8.38%**	**6.95%**	**0.822 (0.712 - 0.948)**	**0.007**	**0.819 (0.709 - 0.945)**	**0.006**	

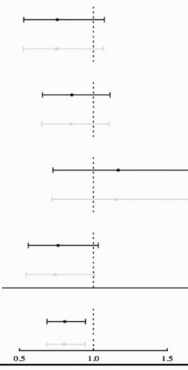


* The adjusted analyses are adjusted for age and blood type
† A forest plot of odds ratios,
– Crude
– Adjusted
‡ Data from the above four regions combined into one analysis. The region is included as a linear covariate in both the crude and in the adjusted analysis.

TABLE 4 Logistic regression analysis of women experiencing low hemoglobin during the first 2 years as donor.

Investigation of interaction between group (before (reference) and after the implementation of feritin measures), and cohort (Cohort of regions with non overlapping study period (refernece) and region with the feritin measure implementation).

Region	Before implementation n (Crude/Adjusted)	Before implementation Ratio (95%-CI)	After implementation n (Crude/Adjusted)	After implementation Ratio (95%-CI)	Interaction Odds-ratio (p-value) - Crude	Interaction Odds-ratio (p-value) - Adjusted*	Forest plot†
Capital Region compared to Central Denmark Region, Zealand Region and South Denmark Region collectively as 'Other'.							
Capital Region	1459 / 1459‡	8.98% (7.62% - 10.56%)	1094 / 1094‡	6.40% (5.09% - 8.01%)	0.756 (0.529 - 1.074)	0.751 (0.525 - 1.069)	
Other	1887 / 1853	12.93% (11.49% - 14.52%)	2219 / 2187	11.99% (10.70% - 13.41%)			
Central Denmark Region compared to Capital Region, North Denmark Region and South Denmark Region collectively as 'Other'.							
Central Denmark Region	1885 / 1851	9.44% (8.20% - 10.85%)	1893 / 1861	8.24% (7.08% - 9.57%)	0.855 (0.656 - 1.113)	0.849 (0.651 - 1.106)	
Other	5451 / 5282	7.54% (6.87% - 8.27%)	5965 / 5765	7.59% (6.95% - 8.29%)			
North Denmark Region compared to Central Denmark Region, Zealand Region and South Denmark Region collectively as 'Other'.							
North Denmark Region	929 / 871	3.98% (2.90% - 5.45%)	969 / 920	4.02% (2.95% - 5.46%)	1.168 (0.726 - 1.881)	1.158 (0.719 - 1.866)	
Other	4746 / 4662	12.75% (11.83% - 13.73%)	5648 / 5565	11.23% (10.43% - 12.08%)			
Zealand Region compared to Capital Region, North Denmark Region and South Denmark Region collectively as 'Other'.							
Zealand Region	1374 / 1318	9.24% (7.82% - 10.89%)	1241 / 1179	7.74% (6.37% - 9.36%)	0.761 (0.559 - 1.033)	0.742 (0.545 - 1.009)	
Other	6332 / 6096	7.28% (6.67% - 7.95%)	6489 / 6152	7.83% (7.20% - 8.51%)			
Pooled analysis.							
This	5647 / 5498	8.38% (7.68% - 9.13%)	5197 / 5050	6.95% (6.29% - 7.67%)	0.806 (0.686 - 0.947)	0.802 (0.682 - 0.942)	
Other	14211 / 13780	9.04% (8.58% - 9.53%)	19931 / 19284	9.15% (8.75% - 9.55%)			

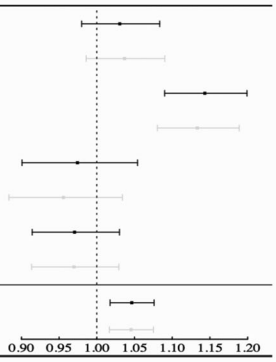


* Adjusted for donor age and blood type.
† Legend:
– Crude
– Adjusted
‡ Within five of the correct value - the correct value is not displayed due to person data protection concerns.

TABLE 5 Poisson regression analysis of number of donations during the first 2 years as donor for female donors.

Intervention group, of blood donors starting after implementation of feritin measures, compared to control group of blood donors starting after implementation compared to before implementation.

Region	Mean number of donations before	Mean number of donations after	Crude analysis Rate ratio (95%-CI)	Crude analysis P-value	Adjusted analysis* Rate ratio (95%-CI)	Adjusted analysis* P-value	Forest plot†
Capital Region	2.31	2.38	1.030 (0.980 - 1.083)	0.242	1.037 (0.986 - 1.090)	0.159	
Central Denmark Region	1.66	1.90	1.143 (1.090 - 1.199)	0.000	1.133 (1.080 - 1.189)	0.000	
North Denmark Region	1.33	1.29	0.974 (0.901 - 1.054)	0.516	0.956 (0.883 - 1.034)	0.259	
Zealand Region	1.66	1.61	0.970 (0.914 - 1.030)	0.324	0.970 (0.914 - 1.029)	0.312	
All‡	1.78	1.82	1.046 (1.018 - 1.076)	0.001	1.045 (1.017 - 1.075)	0.002	



* The adjusted analysis are adjusted for age and blood type
† A forrest plot of rate ratios,
– Crude
– Adjusted
‡ The data from all of the four above regions combined in one analysis. The region is included as a linear covariate i both the crude and the adjusted analysis.

Region with tendencies to a similar effect in the Central Denmark and Zealand Regions (Table 3). Similar results were observed in Cox regression analysis, showing a significantly lower hazard in the "after cohort." These findings remained consistent in both the pooled analysis and in separate analyses for the Capital Region and the Central Denmark Region (Supplementary Table 3).

In a pooled analysis, we found a decrease in risk of experiencing a donation with low Hb after implementation of ferritin-guided iron supplementation in the primary cohort compared with "the cohort of other regions" (Table 4).

During the study period, there was an overall decrease in the number of whole blood donations given, in the first 2 years as a blood donor (Figure 3). To ascertain that the effect of the intervention was not due to lower donation intensity over time, we assessed the average number of donations per female first-time blood donor during the study period. We found an increase in the number of donations after implementation of ferritin-guided iron supplementation in a pooled analysis including all four regions (Table 5). In analyses stratified by region, a significant increase in the number

of donations after implementation was found in Central Denmark Region (Table 5).

We found no difference between the ratio of female first-time donors with low Hb at their first donation before compared with after implementation (Supplementary Table 4).

4 | DISCUSSION

Among Danish female first-time blood donors, implementation of ferritin-guided iron supplementation was associated with a decrease in risk of experiencing a donation with low Hb, during a 2-year follow-up period. The implementation of ferritin-guided iron supplementation was associated with an increase in whole blood donations in the follow-up period.

Globally, different strategies are used to mitigate the risk of low Hb among blood donors including prolongation of donation intervals[11] and ferritin-guided iron supplementation to at-risk-donors.[12] The risk of adverse events to iron supplementation and number of available donors must be in focus.[13]

In Denmark, ferritin-guided iron supplementation has been gradually introduced since 2011. A beneficial effect of iron supplementation has been shown in the literature,[14,15] also with lower iron doses than administered in Denmark.[16]

We found an overall effect of ferritin-guided iron supplementation on low Hb donations among first-time female blood donors. This result was also found when comparing the region of intervention with the corresponding regions with no intervention. Both pre- and post-implementation cohorts was used in the corresponding regions to ensure that effects seen in the region of investigation were not due to other, national trends, such as a decrease in the number of whole blood donations given or other time-related covariates. Regions in which ferritin-guided iron supplementation had already been implemented were therefore valid to be included in the comparison, as long as there was no overlapping intervention time. Replication of our observations in other cohorts is warranted.

In Denmark, low F is treated with 100 mg iron tablets and the number of tablets varies according to F, Hb, and the local algorithm as shown in Table 1. In other countries, tablets with a lower content of iron or iron-rich dietary advice are recommended. Tablets with lower iron content have also been used in randomized studies demonstrating similar effects as tablets with 100 mg.[16] Lower doses of iron might minimize adverse events of iron intake, for example, gastrointestinal distress, and thereby increase donor iron intake compliance. Investigation of donor compliance regarding intake of iron supplementation is a focus for further studies. Furthermore, this study solely evaluated the effects of implementing ferritin-guided iron supplementation and did not assess potential adverse events, such as the possibility of supplementation masking other diseases. However, these potential adverse events should be investigated in future research.

In this study, it was shown that in conjunction with implementation of ferritin-guided iron supplementation, the number of donations among female first-time blood donors increased. Number of donors experiencing low Hb did not increase, as could be expected due to shorter donation intervals. This could be a result of the iron supplementation, which helps to restore donor iron stores faster and consequently increase the resilience of more frequent donations. However, this finding was not consistent across all regions and a comparison between the different ferritin-guided iron management strategies is warranted. Importantly, this study showed that ferritin-guided iron supplementation did not cause fewer donations among female first-time blood donors in a 2-year follow-up period across all regions.

One region, North Denmark Region, had a lower percentage of female first-time blood donors developing low Hb than the other regions. However, this region also had the lowest number of donations per donor in the follow-up period, which was thought to explain the low percentage of cases. The number of donations before and after implementation in this region did not differ, as also mentioned above.

We included donors in our study, even if they did not donate any blood in the follow-up period, "zero-donors." We opted for this approach because the absence of donations during the follow-up period could be attributed to the outcome of the Hb measurement performed during the initial visit to the donation facility. Our objective was to examine the donor's behavior rather than focusing solely on individual donations. Therefore, it was considered essential to include these "zero-donors" in both the pre- and post-implementation stages to avoid potential bias in the results.

4.1 | Strengths and limitations

The study is an observational study using historic comparisons. The stepwise introduction of ferritin-guided iron supplementation in Denmark allowed us to assess the changes in each region at a time and use regions with no change in procedure in the current study period as a reference. The study is a national study and includes a relatively large study population, which is also a strength.

Seemingly, the numbers are too small to allow firm conclusions to be made about whether differences in intervention effects between regions are real and can be attributed to the different algorithms for iron supplementation.

5 | CONCLUSION

In Danish female first-time blood donors, ferritin-guided iron supplementation was associated with decreased risk of low Hb during a 2-year follow-up period. The implementation of ferritin-guided iron supplementation was associated with an increase in the number of donations per donor during the follow-up period.

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CONFLICT OF INTEREST STATEMENT

Christian Erikstrup has received an unrestricted research grant from Abbott Diagnostics. All other authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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