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# Impact of risk-dependent interventions on low haemoglobin deferral rates in whole blood donors

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Vox Sanguinis

**Background** Blood donors with a relatively low haemoglobin (Hb) level at their previous donation attempt have an increased risk of Hb deferral at the subsequent donation attempt. The aim of this study was to investigate whether the interventions prolongation of donation interval and/or a dietary advice decrease the Hb deferral rate.

**Methods** 11 897 whole blood donors with Hb levels from below to 0·2 mmol/l above the cut-off level for donation received either no intervention, a prolongation of the donation interval to six or twelve months, a dietary advice, or both. Deferral rates for low Hb levels at the subsequent donation attempt were compared in the different intervention groups. Additionally, the effects of the interventions on Hb deferral risk and donor return for a subsequent donation attempt were analysed using generalized estimating equations.

**Results** The Hb deferral rate was substantially lower in the group that received a prolongation of the donation interval to six months than in the Control Group (12·9% vs. 6·3% in men and 20·4% vs. 13·4% in women). However, the additional benefit of twelve over 6-month interval prolongation was small, and no benefit of a dietary advice showed up. On the other hand, receiving a dietary advice increased the likelihood of donor return for a subsequent donation attempt.

**Conclusion** Implementation of a protocol for the prolongation of donation intervals to six months for donors with Hb levels from below to slightly above the cut-off level for donation may reduce the deferral rate for low Hb levels while keeping donor lapse at a minimum.

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**Key words:** whole blood donors, haemoglobin, Hb deferral, intervention, donation interval, dietary advice.

## Introduction

Blood donors are screened prior to every donation attempt to secure both blood quality and donor health. Donors have to meet certain eligibility criteria, and if these criteria are not met, donors are deferred for donation. One of the eligibility criteria is a minimum haemoglobin (Hb) level. In the Netherlands, these minimum Hb levels are 8·4 mmol/l (13·5 g/dl) for men and 7·8 mmol/l (12·5 g/dl) for women [1]. Substantial numbers of donors are deferred because of low Hb levels. Deferrals are demoralizing for donors and increase the risk of donor lapse [2,3].

Sex-specific prediction models for Hb deferral risk have been developed and externally validated by our research group [4–6]. The strongest predictor in these models was the Hb level at the previous visit to the collection site. Another important predictor was the time interval since that previous visit. In the Netherlands, the minimum

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donation interval is 56 days for both men and women, and the maximum number of whole blood donations allowed per year is five for men and three for women [1]. However, these guidelines may not be sufficient for each individual donor to maintain appropriate Hb levels. In an observational study performed by our research group, we examined Hb deferral rates on the next donation attempt for different combinations of Hb levels and donation intervals [7]. In that study, we observed that, for women with Hb levels 0·1 or 0·2 mmol/l above the cut-off level for donation at their previous donation, the risk of Hb deferral was only below 10% (which we considered a low risk) after a donation interval of at least 1 year, or half a year, respectively. For men with Hb levels 0·1 mmol/l above the cut-off level, the deferral rate was below 10% if they returned at least half a year after their previous donation. Men and women who were deferred because they did not meet the Hb eligibility criteria had deferral rates below 10% if they returned after at least 1 year. In the observational study described above, donors were not appointed to a certain donation interval, and it is therefore hard to draw conclusions about the beneficial effects of dedicated prolongation of donation intervals. An intervention study is necessary to investigate whether implementing a protocol for the prolongation of donation intervals for donors with a high risk of Hb deferral may reduce the deferral rate for low Hb levels.

Another factor which may have a beneficial effect on Hb levels and reduce Hb deferral risk is a high dietary iron intake [8–10].

In the current study, we conducted an intervention trial to investigate the effect of prolongation of donation intervals for donors with a high risk of Hb deferral, that is donors with relatively low Hb levels, on the deferral rate for low Hb levels at the subsequent donation attempt. In addition, we investigated the effect of a dietary advice aiming at increasing dietary iron intake on Hb deferral rates. We hypothesized that prolongation of donation intervals and a dietary advice would decrease the deferral rate for low Hb levels.

## Methods

### Donors

The study was carried out by Sanquin, the Dutch organization that is responsible for safe and efficient blood supply, at fixed collection sites in the north-west (11 sites) and the south-east (16 sites) regions in the Netherlands. Whole blood donors who attempted to donate whole blood at any of these locations between 1 December 2014 and 30 April 2015 (the inclusion period), and who gave their written consent to participate in scientific research at Sanquin, were eligible for the study ($n$ = 63 216). After exclusion (see below), a total of 62 724 donors were included in the study. The study protocol was approved by the Ethical Advisory Board of Sanquin.

### Intervention and control groups

All eligible donors were categorized into six groups. Donors considered at high risk of Hb deferral at the subsequent donation attempt received an intervention, which was different in the six groups (see below). For practical reasons, the different interventions were divided over the different collection sites. At a particular collection site, only one type of intervention was given, but any type of intervention was implemented at more than one collection site. Allocation of donors to the groups was based on the collection site at which they donated blood.

Donors considered at high risk of Hb deferral at the subsequent (second) donation attempt were those with current Hb levels (at the first donation attempt) below, at, or 0·1 or 0·2 mmol/l above the sex-specific cut-off level for donation. In other words, men with Hb levels ≤8·6 mmol/l (13·9 g/dl) and women with Hb levels ≤8·0 mmol/l (12·9 g/dl).

Group 1 served as the Control Group and donors considered at high risk of Hb deferral in this group did not receive any intervention; high-risk donors in all other groups received different interventions. For high-risk donors in Group 2a, the donation interval was prolonged to 6 months. In Group 2b, the donation interval was prolonged to 6 months if the Hb level was 0·2 mmol/l above the cut-off level for donation, or to twelve months if the Hb level was 0·1 mmol/l above the cut-off level or lower. High-risk donors in Group 3 received a dietary advice aiming at increased iron intake. High-risk donors in Groups 4a and 4b received the dietary advice and their donation intervals were prolonged. For donors in Group 4a, the prolongation was 6 months, for donors in Group 4b the prolongation was either 6 or 12 months depending on their Hb level (as described above for Group 2b).

Donors given dietary advice received a small card with concise information about the function of iron and haemoglobin, and about the risk of developing iron deficiency with a blood donation. The card also contained a shortlist of iron-rich food items, divided into food items for breakfast, lunch, dinner and snacks. Furthermore, this card provided a link to a website with more extensive information about iron, iron-rich food items and recipes. Effects of the dietary advice were analysed based on 'intention-to-treat' and adherence to the dietary advice was not measured.

High-risk donors who received an intervention also received an information letter about the study and information on how to opt-out of the study.

## Data

A total of 274 donors opted-out of the study and their data were not used. From the remaining donors ($n$ = 62 942), pseudonymized data of all whole blood donation attempts within 2 years after their first donation attempt in the inclusion period were extracted from the blood bank information system (eProgesa 5.02 MAK system, Paris, France). Data included information on sex, age, Hb level, deferral, date and location of each donation attempt. Hb levels of donors were routinely measured during donor screening in finger stick capillary samples using a photometer (HemoCue, Angelholm, Sweden).

Donors with unknown gender ($n$ = 2), unknown Hb levels ($n$ = 27), donors with a second donation attempt occurring within 56 days, that is the minimum donation interval, ($n$ = 187), and donors visiting different collection sites at their first and second donation attempt ($n$ = 2) were excluded from the analyses. A total of 62 724 donors (29 185 men, 31 539 women) were included in the study. From these donors, extracted data from the first and second (in case a donor returned within 2 years) donation attempt were used. A total of 55 899 donors (89%) (26 724 men, 29 175 women) returned for a second donation attempt within two years after their first donation attempt. This group of donors was used to assess the effect of the interventions on the Hb deferral rate. See Fig. 1 for an overview of the number of included and excluded donors, and the allocation of donors to intervention groups.

### *Dependent variables*

The dependent variable Hb deferral (yes/no) at the second donation attempt was defined as having a Hb level lower than 8·4 mmol/l for men and lower than 7·8 mmol/l for women. In addition, donor return (yes/no) was examined and defined as attempting to donate within 2 years after the first donation attempt.

### *Independent variables*

To study the intervention effects dummy variables indicating whether donors received a 6-month interval prolongation (yes/no), a 12-month interval prolongation (yes/no) and a dietary advice (yes/no) were created.

Besides the interventions, the effects of age, the difference between the Hb level at the first donation attempt and the sex-specific Hb cut-off level (Δ Hb cut-off), Hb deferral at the first donation attempt and seasonality on Hb deferral and/or donor return were examined.

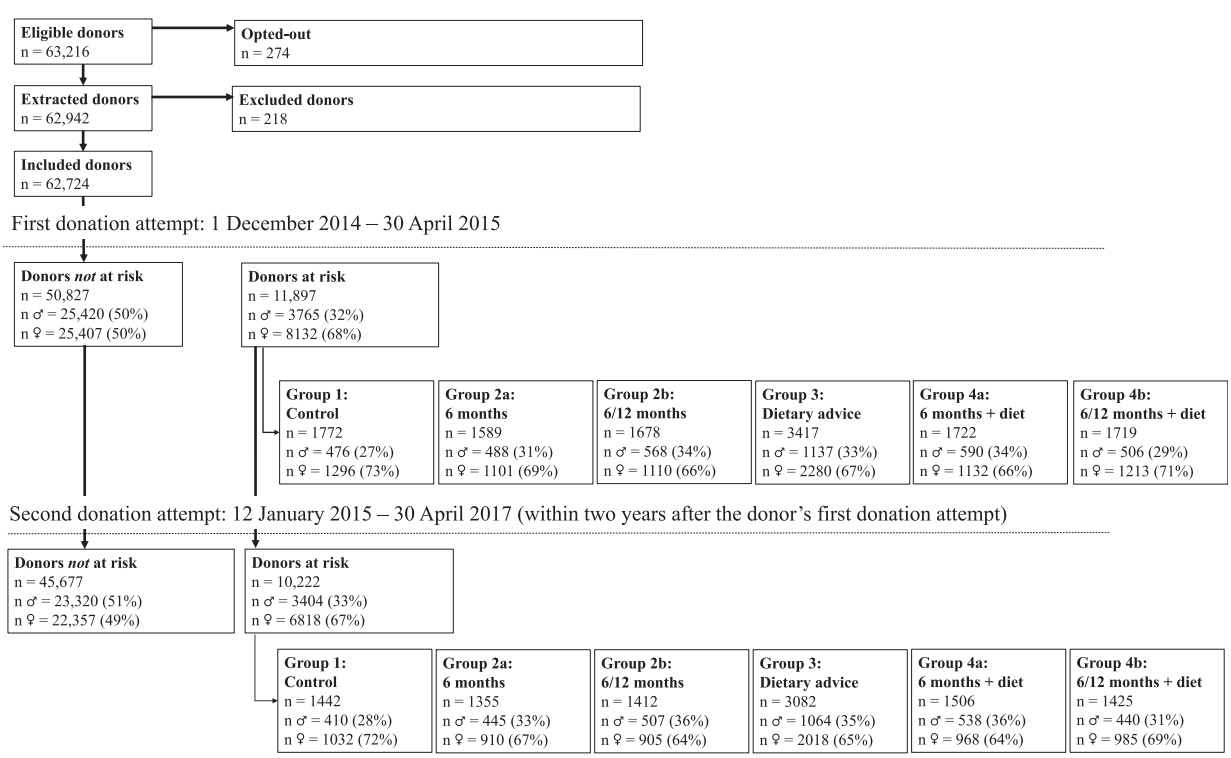


**Fig. 1** Overview of the number of included and excluded donors, and the allocation to interventions (6/12-month prolongation of donation interval and/or a dietary advice).

To account for a difference in Hb level between the first and second donation attempt due to a seasonality effect (in case the second donation attempt occurred in a different season than the first donation attempt), a variable representing the season in which both donation attempts occurred was used for the analyses. Donors were included between 1 December 2014 and 30 April 2015; thus, the first donation attempt occurred only in winter and spring. The second donation attempt could occur in all seasons. The seasonality variable was therefore categorized as follows: 'First in winter, second in fall/winter', 'First in spring, second in fall/winter', First in spring, second in spring/summer', and 'First in winter, second in spring/summer' (reference category). For the seasonal classification, we used the meteorological seasons rather than the astronomical seasons.

### Statistical analyses

Mean values and standard deviations (SD) of Hb levels, as well as deferral rates for low Hb and return rates, were calculated for the six different groups. Values were calculated for each group in total, and separately for donors who were considered at high risk of Hb deferral in each group.

Next, binary logistic generalized estimating equations (GEE) analyses were performed on donors who were considered at high risk of Hb deferral at the first donation attempt and who returned for a second donation attempt, to assess the effect of the interventions on Hb deferral at the second donation attempt. In the GEE analyses, the subjects were nested within the collection sites to control for collection site variance.

Three models were fitted. First, the effects of demographic variables on Hb deferral were assessed, including age, Δ Hb cut-off at the first donation attempt and Hb deferral at the first donation attempt, as well as the effect of seasonality of the two donation attempts (Model 1). Next, the intervention variables 6-month interval prolongation, 12-month interval prolongation and dietary advice were added (Model 2). To explore possible interaction effects, another model was fitted including the interaction terms 6-month prolongation * dietary advice and 12-month prolongation * dietary advice (Model 3). Regression coefficients and odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for the independent variables. The performance of the different models was compared using the Corrected Quasi Likelihood under Independence Model Criterion (QICC). A lower QICC indicates a better model performance. After the analyses were performed on donors who were considered at high risk of Hb deferral, the same analyses were performed on the whole study population, to assess whether implementation of the intervention strategies would have a significant impact on the number of Hb deferrals in the total donor population.

Lastly, the effects of the interventions on return rates of all donors who were considered at high risk of Hb deferral at the first donation attempt were studied. Hereto, binary logistic GEE models were fitted using donor return as outcome variable. Again, three models were fitted. In model 1, the effects of the demographic variables age and Hb deferral at the first donation attempt were assessed. In model 2, the intervention variables were added, and in model 3, a possible interaction between the interventions prolongation of donation interval and dietary advice was additionally examined.

All analyses were performed for men and women separately. The analyses were performed with SPSS, Version 23, SPSS, Inc., Chicago, IL.

## Results

Baseline characteristics of the whole study population at the first donation attempt are presented in Table 1. A total of 11 897 donors (19.0%) were considered at high risk for Hb deferral. Table 2 presents an overview of Hb levels and Hb deferral rates at the second donation attempt, as well as the difference scores compared to the first donation attempt, of donors who were considered at high risk of Hb deferral at their first donation attempt. Donor return rates are also presented in Table 2. In all groups, mean Hb levels were higher and Hb deferral rates were lower at the second donation attempt compared to the first donation attempt. The increase in mean Hb level and decrease in Hb deferral rate were larger in groups in which the donation interval was prolonged compared to the Control Group and the group that received a dietary advice without prolongation of the donation interval.

### GEE analyses: effect of the interventions on Hb deferral rates in men

Table 3 shows the model parameters for men at risk of Hb deferral (upper part) and all men (lower part). For both subgroups, Model 2 had the lowest QICC and fitted the data best (QICC change from Model 1 = −38 for men at risk and −26 for all men). According to Model 2, for men at risk of Hb deferral, age was unrelated to the risk of Hb deferral. Men with higher Hb levels at the first donation attempt and men who were deferred at the first donation attempt had a lower risk of Hb deferral at the second donation attempt. For men with a first donation attempt in winter, those who returned in fall or winter had a lower risk of Hb deferral than those who returned in spring or summer. More importantly, controlled for the

**Table 1** Characteristics of all donors (both at risk and not at risk for Hb deferral) at the first donation attempt

| | Intervention group | | | | | |
|---|---|---|---|---|---|---|
| **Characteristic** | **1** | **2a** | **2b** | **3** | **4a** | **4b** |
| Men (*n* = 29 185) | *n* = 3904 | *n* = 3314 | *n* = 3684 | *n* = 8509 | *n* = 4646 | *n* = 5128 |
| Age (years) | 45 (±15) | 48 (±14) | 49 (±13) | 49 (±14) | 51 (±13) | 51 (±13) |
| Seasonality | | | | | | |
| Winter | 3014 (77) | 2598 (78) | 2918 (79) | 6662 (78) | 3668 (79) | 3927 (77) |
| Spring | 890 (23) | 716 (22) | 766 (21) | 1847 (22) | 978 (21) | 1201 (23) |
| Hb level (mmol/l) | 9·4 (±0·7) | 9·3 (±0·6) | 9·3 (±0·6) | 9·4 (±0·7) | 9·4 (±0·7) | 9·4 (±0·7) |
| Δ Hb cut-off (mmol/l) | 1·0 (±0·7) | 0·9 (±0·6) | 0·9 (±0·6) | 1·0 (±0·7) | 1·0 (±0·7) | 1·0 (±0·7) |
| Hb deferral | 65 (1·7) | 78 (2·4) | 75 (2·0) | 205 (2·4) | 110 (2·4) | 89 (1·7) |
| At risk for Hb deferral at next donation attempt | 476 (12·2) | 488 (14·7) | 568 (15·4) | 1137 (13·4) | 590 (12·7) | 506 (9·9) |
| Women (*n* = 33 539) | *n* = 4917 | *n* = 4377 | *n* = 4185 | *n* = 9384 | *n* = 5041 | *n* = 5635 |
| Age (years) | 38 (±15) | 42 (±15) | 44 (±14) | 42 (±15) | 45 (±14) | 44 (±14) |
| Seasonality | | | | | | |
| Winter | 3080 (63) | 2844 (65) | 2705 (65) | 6168 (66) | 3258 (65) | 3550 (63) |
| Spring | 1837 (37) | 1533 (35) | 1480 (35) | 3216 (34) | 1783 (35) | 2085 (37) |
| Hb level (mmol/l) | 8·5 (±0·6) | 8·5 (±0·6) | 8·4 (±0·6) | 8·5 (±0·6) | 8·5 (±0·6) | 8·5 (±0·6) |
| Δ Hb cut-off (mmol/l) | 0·7 (±0·6) | 0·7 (±0·6) | 0·6 (±0·6) | 0·7 (±0·6) | 0·7 (±0·6) | 0·7 (±0·6) |
| Hb deferral | 322 (6·5) | 230 (5·3) | 235 (5·6) | 563 (6·0) | 298 (5·9) | 261 (4·6) |
| At risk for Hb deferral at next donation attempt | 1296 (26·4) | 1101 (25·2) | 1110 (26·5) | 2280 (24·3) | 1132 (22·5) | 1213 (21·5) |

Data are presented as mean (±SD) or as *n* (%).

**Table 2** Hb levels and Hb deferral rates at the second donation attempt, and return rates, of donors considered at high risk of Hb deferral at their first donation attempt

| **Group** | **Intervention** | ***n*** | **Hb level (mmol/l)** | **Δ Hb (mmol/l)*** | **Hb deferral rate** | **Δ Hb deferral*** | **Donor return rate** |
|---|---|---|---|---|---|---|---|
| Men | | 3404 | | | | | |
| 1 | Control Group, no intervention | 410 | 8·8 (±0·5) | 0·3 (±0·6) | 12·9 | –0·5 | 86 |
| 2a | 6-month prolongation | 445 | 8·9 (±0·5) | 0·4 (±0·5) | 6·3 | –9·2 | 91 |
| 2b | 6 or 12-month prolongation† | 507 | 9·0 (±0·6) | 0·5 (±0·6) | 4·5 | –8·1 | 89 |
| 3 | Dietary advice | 1064 | 8·8 (±0·6) | 0·3 (±0·6) | 14·2 | –3·3 | 94 |
| 4a | Dietary advice + 6-month prolongation | 538 | 8·9 (±0·5) | 0·5 (±0·6) | 9·9 | –8·7 | 91 |
| 4b | Dietary advice + 6 or 12-month prolongation† | 440 | 9·0 (±0·6) | 0·6 (±0·7) | 5·9 | –9·1 | 87 |
| Women | | 6818 | | | | | |
| 1 | Control Group, no intervention | 1032 | 8·0 (±0·5) | 0·3 (±0·6) | 20·4 | –3·6 | 80 |
| 2a | 6-month prolongation | 910 | 8·1 (±0·4) | 0·3 (±0·5) | 13·4 | –6·4 | 83 |
| 2b | 6 or 12-month prolongation† | 905 | 8·2 (±0·5) | 0·4 (±0·5) | 10·9 | –9·1 | 82 |
| 3 | Dietary advice | 2018 | 8·0 (±0·5) | 0·3 (±0·6) | 20·8 | –3·2 | 89 |
| 4a | Dietary advice + 6-month prolongation | 968 | 8·1 (±0·5) | 0·4 (±0·5) | 14·6 | –9·5 | 86 |
| 4b | Dietary advice + 6 or 12-month prolongation† | 985 | 8·2 (±0·5) | 0·4 (±0·6) | 9·8 | –9·0 | 81 |

Data are presented as mean (±SD) or as %.

*Δ: delta, difference in Hb level and Hb deferral rate between second and first donation attempt.

†The donation interval was prolonged to six months if the Hb level was 0·2 mmol/l above the sex-specific cut-off level for donation, or to twelve months if the Hb level was 0.1 mmol/l above the cut-off level or lower.

seasonality parameter and the demographic parameters, prolongation of the donation interval to six months or twelve months decreased the risk of Hb deferral, but receiving a dietary advice did not. A contrast analysis showed that prolongation of the donation interval to twelve months was more beneficial than prolongation of the donation interval to six months; however, the difference was small (contrast variable = –0·03, $P = 0·005$). An

**Table 3** Effects of demographic characteristics and interventions on Hb deferral risk for men

| | Model 1 | | Model 2 | |
|---|---|---|---|---|
| **Parameters** | **Beta (SE)** | **OR (95% CI)** | **Beta (SE)** | **OR (95% CI)** |
| Men at risk ($n$ = 3404) | | | | |
| Intercept | −2·010 (0·291) | 0·134 (0·076–0·237) | −1·884 (0·306) | 0·152 (0·083–0·277) |
| *Demographic characteristics* | | | | |
| Age (years) | 0·006 (0·005) | 1·006 (0·997–1·016) | 0·008 (0·005) | 1·008 (0·999–1·018) |
| Δ Hb cut-off (mmol/l) | −1·784 (0·399)*** | 0·168 (0·077–0·367)*** | −1·892 (0·393)*** | 0·151 (0·069–0·330)*** |
| Hb deferral at first donation attempt | −0·749 (0·279)** | 0·473 (0·273–0·817)** | −0·806 (0·289)** | 0·477 (0·254–0·787)** |
| Seasonality | | | | |
| First in winter, second in fall/winter | −0·861 (0·207)*** | 0·423 (0·282–0·635)*** | −0·656 (0·216)** | 0·519 (0·340–0·793)** |
| First in spring, second in fall/winter | −0·264 (0·171) | 0·768 (0·549–1·075) | −0·372 (0·177)* | 0·689 (0·487–0·975)* |
| First in spring, second in spring/summer | −0·867 (0·276)** | 0·420 (0·245–0·721)** | −0·827 (0·288)** | 0·437 (0·248–0·769)** |
| First in winter, second in spring/summer (reference) | | | | |
| *Intervention* | | | | |
| 6-month prolongation of donation interval | | | −0·491 (0·140)*** | 0·612 (0·465–0·806)*** |
| 12-month prolongation of donation interval | | | −1·069 (0·207)*** | 0·343 (0·229–0·515)*** |
| Dietary advice | | | 0·219 (0·130) | 1·244 (0·964–1·606) |
| All men ($n$ = 26 724) | | | | |
| Intercept | −2·237 (0·199) | 0·107 (0·072–0·158) | −2·200 (0·206) | 0·111 (0·074–0·166) |
| *Demographic characteristics* | | | | |
| Age (years) | 0·008 (0·003)* | 1·008 (1·002–1·014)* | 0·009 (0·003)** | 1·009 (1·002–1·015)** |
| Δ Hb cut-off (mmol/l) | −2·715 (0·095)*** | 0·066 (0·055–0·080)*** | −2·703 (0·094)*** | 0·067 (0·056–0·081)*** |
| Hb deferral at first donation attempt | −1·460 (0·178)*** | 0·323 (0·164–0·329)*** | −1·487 (0·179)*** | 0·226 (0·159–0·321)*** |
| Seasonality | | | | |
| First in winter, second in fall/winter | −0·464 (0·146)** | 0·629 (0·472–0·837)** | −0·404 (0·146)** | 0·668 (0·502–0·889)** |
| First in spring, second in fall/winter | 0·154 (0·113) | 1·167 (0·935–1·457) | 0·136 (0·114) | 1·146 (0·917–1·433) |
| First in spring, second in spring/summer | −0·498 (0·206)* | 0·608 (0·406–0·909)* | −0·480 (0·207)* | 0·619 (0·412–0·929)* |
| First in winter, second in spring/summer (reference) | | | | |
| *Attempted to donate at a collection site having had implemented the following intervention* | | | | |
| 6-month prolongation of donation interval | | | −0·239 (0·093)** | 0·787 (0·657–0·944)** |
| 6 or 12-month prolongation of donation interval[†] | | | −0·443 (0·099)*** | 0·642 (0·529–0·780)*** |
| Dietary advice | | | 0·188 (0·083)* | 1·207 (1·026–1·421)* |

Beta, regression coefficient; CI, confidence interval; OR, odds ratio = exp(beta); SE, standard error.

*Significant predictive effect: * $P < 0·05$, ** $P < 0·01$, *** $P < 0·001$.

[†]The donation interval was prolonged to six months if the Hb level was 0·2 mmol/l above the sex-specific cut-off level for donation, or to twelve months if the Hb level was 0·1 mmol//l above the cut-off level or lower.

interaction effect between prolongation of the donation interval and a dietary advice was not observed. The performance of Model 3 was worse compared to Model 2 (QICC change from Model 2 = +8). Model 3 is therefore not shown.

For all men, according to Model 2, the risk of Hb deferral was lower at collection sites that had implemented any type of the intervention prolongation donation intervals, compared to collection sites that had not implemented the intervention prolongation of donation intervals. No differences in Hb deferral risk were observed between collection sites that had implemented a 6-month interval prolongation and collection sites that had implemented a 6 or 12-month interval prolongation (contrast variable = −0·0007, $P$ = 0·072). Also, a slight increase in Hb deferral risk was found at collection sites that had implemented the dietary advice intervention, compared to collection sites that had not implemented this intervention. Interaction effects were not observed and addition of interaction terms in Model 3 decreased the model fit (QICC change from Model 2 = +2).

## GEE analyses: effect of the interventions on Hb deferral rates in women

Table 4 shows the model parameters for women at risk of Hb deferral (upper part) and all women (lower part). Also for both female subgroups, Model 2 had the lowest QICC

**Table 4** Effects of demographic characteristics and interventions on Hb deferral risk for women

| | Model 1 | | Model 2 | |
|---|---|---|---|---|
| **Parameters** | **Beta (SE)** | **OR (95% CI)** | **Beta (SE)** | **OR (95% CI)** |
| Women at risk ($n$ = 6818) | | | | |
| Intercept | −0·959 (0·123) | 0·383 (0·301–0·488) | −0·808 (0·132) | 0·446 (0·344–0·578) |
| *Demographic characteristics* | | | | |
| Age (years) | −0·013 (0·002)*** | 0·987 (0·983–0·992)*** | −0·011 (0·002)*** | 0·989 (0·985–0·994)*** |
| Δ Hb cut-off (mmol/L) | −1·193 (0·186)*** | 0·303 (0·211–0·436)*** | −1·218 (0·189)*** | 0·296 (0·204–0·428)*** |
| Hb deferral at first donation attempt | −0·253 (0·130) | 0·776 (0·601–1·002) | −0·268 (0·132)* | 0·765 (0·590–0·991)* |
| Seasonality | | | | |
| First in winter, second in fall/winter | −0·540 (0·110)*** | 0·583 (0·469–0·724)*** | −0·373 (0·114)** | 0·689 (0·551–0·861)** |
| First in spring, second in fall/winter | −0·025 (0·086) | 0·975 (0·824–1·155) | −0·085 (0·089) | 0·919 (0·771–1·095) |
| First in spring, second in spring/summer | −0·442 (0·114)*** | 0·643 (0·514–0·803)*** | −0·410 (0·122)** | 0·664 (0·523–0·843)** |
| First in winter, second in spring/summer (reference) | | | | |
| *Intervention* | | | | |
| 6-month prolongation of donation interval | | | −0·378 (0·083)*** | 0·685 (0·583–0·806)*** |
| 12-month prolongation of donation interval | | | −0·660 (0·103)*** | 0·517 (0·423–0·632)*** |
| Dietary advice | | | 0·005 (0·069) | 1·005 (0·878–1·151) |
| All women ($n$ = 29 175) | | | | |
| Intercept | −0647 (0·087) | 0·524 (0·442–0·621) | −0·572 (0·092) | 0·565 (0·471–0·677) |
| *Demographic characteristics* | | | | |
| Age (years) | −0·018 (0·002)*** | 0·982 (0·979–0·985)*** | −0·017 (0·002)*** | 0·983 (0·980–0·986)*** |
| Δ Hb cut-off (mmol/l) | −2·076 (0·067)*** | 0·125 (0·110–0·143)*** | −2·064 (0·066)*** | 0·127 (0·111–0·144)*** |
| Hb deferral at first donation attempt | −0·776 (0·096)*** | 0·460 (0·381–0·556)*** | −0·791 (0·096)*** | 0·454 (0·376–0·547)*** |
| Seasonality | | | | |
| First in winter, second in fall/winter | −0·547 (0·087)*** | 0·579 (0·487–0·687)*** | −0·480 (0·088)*** | 0·619 (0·521–735)*** |
| First in spring, second in fall/winter | −0·013 (0·058) | 0·987 (0·881–1·106) | −0·036 (0·059) | 0·964 (0·860–1·082) |
| First in spring, second in spring/summer | −0·497 (0·087)*** | 0·608 (0·513–0·722)*** | −0·487 (0·088)*** | 0·615 (0·517–0·730)*** |
| First in winter, second in spring/summer (reference) | | | | |
| *Attempted to donate at a collection site having had implemented the following intervention* | | | | |
| 6-month prolongation of donation interval | | | −0·204 (0·059)*** | 0·816 (0·727–0·915)*** |
| 6 or 12-month prolongation of donation interval† | | | −0·397 (0·061)*** | 0·672 (0·597–0·757)*** |
| Dietary advice | | | 0·055 (0·049) | 1·057 (0·960–1·163) |

Beta, regression coefficient; CI, confidence interval; OR, odds ratio = exp(beta); SE, standard error.

*Significant predictive effect: *$P$ < 0·05, **$P$ < 0·01, ***$P$ < 0·001.

†The donation interval was prolonged to 6 months if the Hb level was 0·2 mmol/l above the sex-specific cut-off level for donation, or to 12 months if the Hb level was 0·1 mmol//l above the cut-off level or lower.

and fitted the data best (QICC change from Model 1 = −55 for women at risk and −43 for all women). According to Model 2, for women at risk of Hb deferral, age was negatively related to the risk of Hb deferral. Women with higher Hb levels at the first donation attempt and women who were deferred at the first donation attempt had a lower risk of Hb deferral at the second donation attempt. For women with a first donation attempt in winter, those who returned in fall or winter had a lower risk of Hb deferral than those who returned in spring or summer. Controlled for the seasonality parameter and the demographic parameters, prolongation of the donation interval to 6 or 12 months decreased the risk of Hb deferral, but receiving a dietary advice did not. Prolongation of the donation interval to 12 months was more beneficial than prolongation of the donation interval to 6 months; however, the difference was small (contrast variable = −0·03, $P$ = 0·011). Interaction effects were not observed and addition of interaction terms in Model 3 decreased the model performance (QICC change from Model 2 = +5).

For all women, according to Model 2, the risk of Hb deferral was lower at collection sites that had implemented any type of the intervention prolongation donation intervals, compared to collection sites that had not implemented the intervention prolongation of donation intervals. Even in the whole group of female donors, implementation of a 6 or 12-month interval prolongation was slightly more beneficial than implementation of only 6-month interval prolongation (contrast variable = −0·005, $P$ = 0·005). No difference in Hb deferral risk was

found between collection sites that had implemented the intervention dietary advice and collection sites that had not implemented this intervention. Interaction effects were not observed and addition of interaction terms in Model 3 decreased the model fit (QICC change from Model 2 = +3).

### GEE analyses: effect of the interventions on donor return rates

Table 5 shows the model parameters for men (upper part) and women (lower part) at risk of Hb deferral. For both men and women, Model 3 had the lowest QICC and fitted the data best (QICC change from Model 2 = −16 for men and −14 for women). According to these models, for both men and women, age was positively related to return, and Hb deferral was negatively related to return. In men, prolongation of the donation interval to six months and receiving a dietary advice had a positive effect on donor return. The negative interaction effect of a 6-month interval prolongation and a dietary advice indicate that the combined effect of these interventions was less positive as the sum of the separate effects. However, the combination of a 6-month interval prolongation and a dietary advice still resulted in a net positive effect on donor return. The combination of a 12-month interval prolongation and a dietary advice resulted in a net negative effect on donor return.

In women, receiving a dietary advice had a positive effect on donor return; however, a significant positive effect of a 6-month interval prolongation was not observed. Instead, prolongation of the donation interval to 12 months had a borderline significant negative effect on donor return. Interaction effects of interval prolongation and a dietary advice were negative. The combination of a 6-month interval prolongation and a dietary advice resulted in a net positive effect on donor return, whereas the combination of a 12-month interval prolongation and a dietary advice resulted in a net negative effect on donor return.

## Discussion

The current study shows that prolongation of donation intervals to 6 months for both male and female donors with Hb levels from below to 0·2 mmol/l above the cut-off level for donation decreases the risk of Hb deferral at the subsequent donation substantially. For men, the Hb deferral rate was 12·9% in the group that received a prolongation of the donation interval to 6 months and 6·3% in the Control Group; for women, the Hb deferral rates in these groups were 20·4% and 13·4%, respectively. The additional benefit of twelve over 6-month interval prolongation for donors with Hb levels from below to 0·1 mmol/l above the cut-off value for Hb deferral was small. For the group in which donors received a 6 or 12-month interval prolongation, depending on their Hb level, the Hb deferral rate was 4·5% in men and 10·9% in women. In contrast to the beneficial effect of prolongation of donation intervals, we could not find evidence that attempting to improve dietary iron intake in donors by providing a dietary advice could decrease the risk of Hb deferral at the subsequent donation.

The observed beneficial effect of prolongation of donation intervals is in line with findings of previous studies showing that longer donation intervals are associated with lower deferral rates for low Hb levels [7,11,12]. Several studies have reported that diet is at most weakly related to iron status in blood donors [8–10]. As adherence to the dietary advice was not measured, a simple explanation for not finding a beneficial effect of a dietary advice could be that the donors did not adhere to the advice. Although a beneficial effect of iron supplementation is mentioned in the literature [13–15], it is important to note that the dietary advice did not mention the possibility of using iron supplements, as this is not in line with the current policy of Sanquin. Data on iron intake, either from foods or from iron supplements, by the donors, were not available. A potential alternative explanation for the lack of a beneficial effect of the dietary advice could be that donors already consumed a diet that complied with the dietary advice, causing a ceiling effect. Either way, the results show that providing a dietary advice as was done in this study is not beneficial as a policy to reduce the number of Hb deferrals.

Although providing a dietary advice was not effective in decreasing Hb deferral rates, this intervention did have a positive effect on donor return rates. On the other hand, prolongation of the donation interval, which was successful in decreasing the risk of Hb deferral, decreased the likelihood of donor return when the prolongation period was twelve months. The combination of a dietary advice and a 6 or 12-month interval prolongation did not further decrease the Hb deferral risk, but it increased the likelihood of donor return.

Thus, prolongation of donation intervals to 6 months could be sufficient to decrease the risk of Hb deferral for most donors, while keeping donor lapse at a minimum. However, a 6-month interval prolongation may introduce a possible complication, as donors with relatively low Hb levels in winter who return after 6 months in spring or summer still have a higher risk of Hb deferral. This seasonality effect is in line with previous studies in which higher Hb deferral rates were reported in summer than in winter [16,17]. Thus, seasonality should also be taken into account when implementing a protocol to decrease Hb deferral.

Implementation of a protocol for the prolongation of donation intervals, whether or not taking seasonality into

**Table 5** Effects of demographic characteristics and interventions on donor return for donors considered at high risk of Hb deferral

| | Model 1 | | Model 2 | | Model 3 | |
|---|---|---|---|---|---|---|
| **Parameters** | **Beta (SE)** | **OR (95% CI)** | **Beta (SE)** | **OR (95% CI)** | **Beta (SE)** | **OR (95% CI)** |
| Men at risk ($n$ = 3765) | | | | | | |
| Intercept | 1·518 (0·221) | 4·563 (2·961–7·030) | 1·511 (0·237) | 4·531 (2·847–7·213) | 1·164 (0·243) | 3·203 (1·990–5·155) |
| *Demographic characteristics* | | | | | | |
| Age (years) | 0·016 (0·004)*** | 1·016 (1·007–1·025)*** | 0·015 (0·004)*** | 1·016 (1·007–1·025)*** | 0·015 (0·004)** | 1·015 (1·006–1·024)** |
| Hb deferral at first donation attempt | −0·479 (0·133)*** | 0·619 (0·477–0·804)*** | −0·463 (0·133)** | 0·629 (0·484–0·817)** | −0·463 (0·134)** | 0·630 (0·484–0·819)** |
| *Intervention* | | | | | | |
| 6-month prolongation of donation interval | | | −0·001 (0·135) | 0·999 (0·766–1·302) | 0·561 (0·195)** | 1·753 (1·195–2·571)** |
| 12-month prolongation of donation interval | | | −0·457 (0·144)** | 0·633 (0·478–0·839)** | 0·067 (0·197) | 1·069 (0·727–1·573) |
| Dietary advice | | | 0·230 (0·117) | 1·258 (1·000–1·582) | 0·832 (0·178)*** | 2·298 (1·621–3·258)*** |
| *Interaction terms* | | | | | | |
| 6-month prolongation * dietary advice | | | | | −0·979 (0·261)*** | 0·376 (0·225–0·627)*** |
| 12-month prolongation * dietary advice | | | | | −0·958 (0·275)*** | 0·384 (0·224–0·657)*** |
| Women at risk ($n$ = 8132) | | | | | | |
| Intercept | 0·696 (0·090) | 2·005 (1·682–2·391) | 0·689 (0·099) | 1·992 (1·640–2·421) | 0·527 (0·104) | 1·694 (1·380–2·078) |
| *Demographic characteristics* | | | | | | |
| Age (years) | 0·026 (0·002)*** | 1·027 (1·022–1·031)*** | 0·027 (0·002)*** | 1·028 (1·023–1·032)*** | 0·027 (0·002)*** | 1·027 (1·023–1·032)*** |
| Hb deferral at first donation attempt | −0·383 (0·067)*** | 0·682 (0·598–0·777)*** | −0·373 (0·067)*** | 0·689 (0·603–0·786)*** | −0·386 (0·068)*** | 0·692 (0·606–0·790)*** |
| *Intervention* | | | | | | |
| 6-month prolongation of donation interval | | | −0·116 (0·073) | 0·891 (0·773–1·027) | 0·165 (0·103) | 1·179 (0·964–1·443) |
| 12-month prolongation of donation interval | | | −0·486 (0·077)*** | 0·615 (0·529–0·715)*** | −0·214 (0·110) | 0·807 (0·650–1·002) |
| Dietary advice | | | 0·239 (0·061)*** | 1·270 (1·126–1·432)*** | 0·546 (0·095)*** | 1·727 (1·433–2·081)*** |
| *Interaction terms* | | | | | | |
| 6-month prolongation * dietary advice | | | | | −0·527 (0·141)*** | 0·590 (0·448–0·779)*** |
| 12-month prolongation * dietary advice | | | | | −0·505 (0·151)** | 0·603 (0·449–0·812)** |

Beta, regression coefficient; CI, confidence interval; OR, odds ratio = exp(beta); SE, standard error.
*Significant predictive effect: *$P < 0·05$, **$P < 0·01$, ***$P < 0·001$.

account, may not only reduce the deferral rate for low Hb levels, but may also improve donor health. However, despite this beneficial effect for donors, not all donors are pleased with prolongation of their donation interval. A total of 274 donors opted-out of the study, mostly because they were highly motivated to donate again as soon as possible, for example because a family member needed a blood transfusion. When implementing a protocol for the prolongation of donation intervals, it is important to provide donors with information that such a policy is beneficial to their health.

The current study benefited from the application of an intervention trial design and a large study population. However, the study population consisted mainly of Dutch donors, caution should therefore be given for the application of these results to donors with different nationalities or different ethnicities. Possible confounding factors were both clustering of regional collection sites and individual donor physician differences. For example, Sanquin's donor physicians are allowed to prolong donation intervals for individual donors if they think it is necessary, and differences between donor physicians in these practises exist [18]. In this study, we assumed individual donor physician differences to be at least distributed evenly across the intervention groups. However, the collection sites in each intervention group were not randomly distributed across the Netherlands, but clustered by region. Interferences due to regional factors, such as the level of urbanization, may have influenced the results. Similar differences between collection sites might exist not only in the Netherlands but also elsewhere. Even though the GEE analyses handle at least part of the variation in the data due to collection sites, future intervention or implementation studies would benefit from a completely random selection and distribution across the country.

Effects of interventions aimed to decrease Hb deferral rates were examined at a group level. It might be more efficient to develop a method which is able to assess on an individual level whether a donor could benefit from an intervention. For example, by assessing for each individual donor whether the donor has a high Hb 'set-point' or is able to quickly re-establish healthy Hb levels [19] or has a genetic predisposition for high or low Hb levels [20]. Hb levels are currently routinely measured during donor screening in order to assess the iron status of blood donors. It should be kept in mind that Hb levels start to decrease only in an advanced stage in the development of iron deficiency. Measurement of other iron parameters with which iron deficiency can be detected in an earlier stage, such as ferritin, an indicator of iron stores, or zinc protoporphyrin, could be used to assess the iron status of donors and may also improve the prediction of Hb deferral for each individual donor [21–24], and may therefore also be useful for the individual allocation of interventions to prevent Hb deferral.

In conclusion, this study showed that prolongation of donation intervals to six months for men with Hb levels of 8·6 mmol/l or lower and for women with Hb levels of 8·0 mmol/l or lower decreased the risk of Hb deferral at the subsequent donation substantially, whereas it did not have a negative effect on donor return for a subsequent donation attempt. Receiving a dietary advice was not effective in decreasing Hb deferral rates; however, this intervention had a positive effect on donor return rates. Implementation of a protocol for the prolongation of donation intervals to 6 months for donors with Hb levels from below to slightly above the cut-off level for donation may reduce the deferral rate for low Hb levels while keeping donor lapse at a minimum.

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## Conflicts of interest

The authors declare no conflicts of interest.

## Author contributions

M.B. designed the research, analysed the data, interpreted the results and wrote the manuscript. K.H. interpreted the results and critically reviewed the manuscript. W.K. designed the research, interpreted the results and critically reviewed the manuscript. E.H. analysed the data, interpreted the results and critically reviewed the manuscript.

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