Donor Deferral Due To Low Hemoglobin – An Updated Systematic Review

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Abstract

Background/Objectives: Blood donors attending a donation session may be deferred from donating blood due to a failure to meet low hemoglobin (Hb) thresholds. This costs the blood donor service, and donors, valuable time and resources. In addition, donors who are deferred may have more symptoms and as a direct and/or indirect effect of their experience return rates of donors deferred for low Hb are reduced, even in repeat donors. It is therefore vital that low Hb deferral (LHD) is minimized. The aim of this updated systematic review is to expand the evidence base for factors which affect a donor's risk of deferral due to low Hb.

Materials/Methods: Studies were identified by searching MEDLINE, Embase, *The Cochrane* Library and the WHO International Clinical Trials Registry to March 2019. Demographic data, donor history, hematological/biological factors and the primary outcome of deferral due to low Hb were extracted. Our primary outcome was deferral due to low Hb. Analyses were descriptive and quantitative; pooled odds ratios (ORs) and 95% confidence intervals (CIs) were obtained by meta-analysis using random effects models.

Results: A total of 116 studies met the inclusion criteria. Meta-analysis showed a significantly greater risk of LHD in females compared with males in studies applying universal Hb thresholds for males and females (OR 14.62 95%CI 12.43-17.19) and in those which used sex-specific thresholds (OR 5.73, 95%CI 4.36-7.53). Higher rates of LHD were also associated with increasing age in men, low body weight, shorter inter-donation interval, donors of Hispanic or African descent, higher ambient temperature, donors with low ferritin levels and donation in a fixed donor center. There was conflicting evidence on the effect of new and repeat donor status, and blood group.

Conclusion: This work has strengthened the evidence of the previous review in identifying factors that should be considered in studies of donor deferral and highlighting areas in need of further study, including ABO and Rh blood groups, previous platelet donation, diet, smoking, time of day, and genetic data. These factors may lead to individually tailored donation criteria for safe and efficient donation in the future.

Introduction

Faced with dwindling numbers of new donors, blood services globally need to be able to better understand how to retain donors. One of the main reasons why donors will stop donating blood is because they received a temporary deferral for low hemoglobin (Hb) [1]. While it is widely understood that women are more at risk of being deferred for low Hb than men, there is limited data on the contribution to a donor's risk of low Hb deferral from other demographics, or physical and environmental factors.

A previous systematic review from 2013, which included 55 studies, identified a variety of risk factors that were associated with a higher risk of low Hb deferral (LHD) in blood donors [2]. These included female gender, the season of donation (spring and summer), older male donors, non-white ethnicity, and new donors [2]. Other potential factors identified from individual studies were difficult to evaluate due to the small number of studies reporting each factor.

The objective of this review is to identify new research findings since the previous review was published and re-assess the impact of the factors described in the previous review. This review also now includes a formal quality assessment of all individual studies. The information obtained in this review expands the evidence base of factors that influence LHD in blood donors, and helps to select criteria that should be considered in trials of donor management.

Materials and Methods

The protocol for this review was prospectively registered on PROSPERO (CRD42017071105). The review was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [3]. Full details of the search strategy, eligibility, data extraction and quality assessment are provided in Supplementary Information. Briefly, searches were carried out to March 2019 and identification of eligible studies is shown in Figure 1. Screening for eligibility and data extraction was performed independently in duplicate by two reviewers, one from Oxford and one from Cambridge.

Extracted data included characteristics of study participants (sex, age, ethnicity, weight, number of donations during study, season of donation, type of donor etc.), Hb thresholds for deferral from donation, outcome data (number of donors deferred and/or number of donation attempts resulting in LHD) and any other reported factors which may affect donation. Quality assessment methods were adapted from the RTI Item Bank for assessing risk of bias and confounding in observational studies [4] and are included in Appendix B.

The primary outcome was deferral due to low Hb, and both qualitative and quantitative analyses were performed. Random effects meta-analyses were used to account for the expected clinical and statistical heterogeneity between studies and provide average risk estimates based on unadjusted data which should be interpreted with caution. Summary measures were presented as unadjusted odds ratios (ORs) with 95% confidence intervals (CIs). Heterogeneity was assessed using the I^2 statistic [5]. Statistical analysis was carried out in R v3.4.2 (http://www.r-project.org/) and Review Manager 5.3 [6].

Results

Study selection

The PRISMA study flow diagram is shown in **Figure 1**. After de-duplication by an information specialist (CD), 2518 records were initially screened independently by two reviewers. Of these, 102 eligible records contributed to 76 independent studies. Thus, together with 40 studies from the previous review, 116 studies were included in this update.

Description of Included Studies

A summary of the characteristics of studies can be found in Supplementary Table 1. Of the 116 included studies, the majority of studies (n=80) included single unit red blood cell (RBC)/whole blood donations only. Other donation types included platelets, double red cell and multicomponent donations (Table 1). The studies were carried out in 35 countries across six continents.

Hb deferral thresholds were reported in 85 studies, and four studies used hematocrit (HCT) levels. A universal threshold of 125 g/L was used in 31 studies, while sex-specific thresholds were used in the remaining studies, where reported. The threshold for men was between 120 and 135 g/L, and for women between 110 and 125 g/L. A variety of screening methods for Hb levels were used, including gravimetric using a drop of blood and a copper sulphate solution, venous and capillary spectrophotometric estimation of hemoglobin (Hemocue), and automated analyzer (for example Sysmex analyzers.

Quality Assessment

A summary of risk of bias and confounding components is shown in **Supplementary Figure 1**. The risk of selection bias was low in the majority of included studies. A moderate risk of attrition bias was observed due to some studies failing to report the number of successful donations or deferrals due to other reasons. Few studies adequately reported baseline characteristics of donors. The risk of

attrition bias was lower in new studies, as was the risk of confounding, however few studies performed multivariate analyses and as such the risk of confounding is relatively high.

Supplementary Figure 1

Factors Associated with Low Hemoglobin Deferral (LHD)

Sex

Sex specific LHD rates were reported by 64 studies, and the male to female ratio varied widely, with the percentage of female participants ranging from 1.7 [7] to 100 [8]. Studies from India had significantly fewer female participants (3.96 - 20.2%), whereas studies performed in Europe and the USA generally had more equal proportions of male and female participants. LHD rates were higher in females in all studies. Studies which used universal Hb thresholds for both male and female donors showed a 14-fold increased risk of LHD for females (OR 14.62, 95%CI 12.43-17.19). An increased risk of LHD in females remained for those studies which applied lower Hb thresholds for female donors (OR 5.73, 95%CI 4.36-7.53) (**Figure 2**). High heterogeneity between studies was observed in both analyses (I^2>95%).

Studies that reported male and female deferral numbers separately were stratified by geographical location of study, and results of these meta-analyses are presented in **Supplementary Figure 2**. Notably, differences between studies performed in different geographical settings were observed even when similar Hb thresholds were applied. For example, the increased risk of LHD in females compared with males was significantly higher in studies from Africa (OR 5.24, 95%CI 4.07-6.74) than in European studies (OR 2.85, 95%CI 2.21-3.68) despite both sets of studies using predominantly sex-specific Hb thresholds (where reported). The greatest difference in the risk of LHD between men and women was observed in India (OR 19.11, 95%CI 13.95-26.16).

Ethnicity

Nine studies reported LHD by ethnicity, although there was a lack of consistency in the groups studied [9-16]. In four studies, [9-11, 13] the non-white ethnicities reported were Asian, Black, Hispanic and not stated, whereas in one study [12] donors were categorized as White, Asian, African, unknown and "coloured" and in another study [16], donors were defined as African-American, Hispanic, White and "other". Another study [15] reported deferral rates for Black, Asian, Mixed, Native America, and Native Hawaiian. One study only compared white donors with non-white donors. Five studies reported Hb deferrals by ethnicity separately for male and female donors.

For male donors, four out of five studies observed a significantly higher risk of LHD in African-American/Black donors compared with White donors, with meta-analysis showing an approximate two-fold increased risk (OR 1.94, 95%CI 1.14-3.31) associated with African-American/Black ethnicity. In female donors, the risk of LHD associated with African-American/Black ethnicity was higher and found in all five studies (OR 2.82, 95%CI 1.71-4.65) (**Figure 3A**). In the comparison of Asian and White male donors, the combined risk across four studies was not significant (OR 1.17, 95%CI 0.77-1.78). However, a significantly higher risk of LHD was found in female Asian donors compared with White donors, with an overall 63% increased risk associated with Asian ethnicity (OR 1.63, 95%CI 1.31-2.03) (**Figure 3B**). A similar increased risk of LHD was found in female Hispanic donors compared with female White donors (OR 1.43, 95%CI 1.22-1.68). However, in male donors, there was no evidence that Hispanic ethnicity was associated with an increased risk of LHD (OR 0.74, 95%CI 0.53-1.03) (**Figure 3C**). However, it should be noted that the degree of heterogeneity across studies was high (I^2>88% in all comparisons) and these ORs represent an average increased risk across studies.

Age

LHD by age (years) was reported in 19 new studies [9, 10, 12, 15, 17-31]. In 14 studies which reported results separate for men and women, the general trend across studies for men was for LHD rates to increase with age (**Figure 4**), whereas for women there were fewer deferrals among women over 50 compared to women younger than 50. Some reported that the youngest groups of women had the highest deferral rates [9, 12] while others saw a higher deferral rate for women aged 30-50 [18, 25, 26].

One study from Africa [24] reported deferral rates by age for men and women separately but these were universally very high, with the lowest rate of LHD in any one age group being 27% (in men in their 30s) and the highest 71.4% (in women under 20). Two European studies found that male donors who were deferred for low Hb had a higher mean age (years) than those not deferred, (47 vs 43) [19] (50 vs 46) [20]. In contrast, both studies reported a lower mean age in female deferred donors (38 vs 41) [19], (39 vs 43) [20]. A study from the Netherlands [31] showed via a multivariable logistic regression model an increased risk of LHD for older men and younger women. A US study [10] compared different age groups to those aged 40-49 and found that older men were more likely to be deferred (50-59: OR 1.56; 60+: OR 2.96), and younger men less likely (<30: OR 0.57; 30-39: OR 0.74), with an inverse trend for women (<30: OR 1.09; 30-39: OR 1.00; 50-59: OR 0.73; 60+: OR 0.72). Finally, an Indian study [23] reported that more younger than older donors of both sexes were deferred.

SSeven studies reported the relationship between seasonal or temperature changes and LHD [19, 20, 24, 31-34]. Three of these, two European [19, 20] and one African study [24], reported deferral numbers by season. Meta-analyses of the three studies showed no significant difference in LHD rates between spring and summer months. One other European study noted a significant increase in the LHD rate of donors from 2% in January to 3.5% in July [32]. In addition, a US study [33] reported a deferral rate of approximately 8% when the temperature was above 12 degrees celcius, compared with 6% in winter. A Dutch study [31] performed logistic regression and found that higher LHD was associated with spring and summer compared with autumn and winter, which was more pronounced in men.

In studies that reported deferral numbers separately by sex [19, 20, 24], meta-analysis of each season versus winter showed no significant effects of season in male donors (**Figure 5**). In female donors, evidence from three studies showed a significantly higher risk of LHD in summer donations compared with winter (OR 1.18, 95%CI 1.07-1.30) (**Figure 5**), but no differences associated with either spring or autumn donations.

An additional study from the USA [34] reported percentages of low Hb deferrals for men and women between 2002 and 2004. It found an overall increase in LHD in other seasons compared with winter, which was most pronounced in summer. Looking at sex and age specific deferral rates, older women had a higher increase in deferrals by season compared to younger women, as did older men at a lower magnitude.

Weight

Four studies [9, 10, 13, 35] reported ORs for LHD by weight and sex. One US study [10] found that, compared to people who weighed between 150 and 174lbs, lighter men (OR 1.38) and women (OR 1.13) were deferred at a higher frequency, as were the heaviest women (over 200lbs weight, OR 1.04), although no CIs were reported. Men who were between 175 and 199lbs (OR 0.79) and above 200lbs (OR 0.72) were less likely to be deferred, as were women between 175 and 199lbs (OR 0.98), although the statistical significance of these ORs were not reported. One US study [9] used the same weight categories as the previous study, and showed a marginally significant increase in LHD for the heaviest women (>200lbs) (OR 1.5, 95%CI 1.0 -2.2). In a US study [13], the heaviest age group (>200lbs) was used as the reference group, and logistic regression showed significantly higher deferral rates for both sexes for donors in all lighter weight categories with the exception of female donors who weighed between 150 and 174lbs, who had a marginally lower deferral rate (OR 0.95, 95%CI 0.93-0.97), and females between 175-199lbs (OR 0.92, 95% 0.89-0.94). A Dutch study [35] used age-adjusted ORs and found that, compared to those in the lightest weight category (<60kg),

deferral risk decreased with increasing weight, with the lowest risk for male donors over 100kg (OR 0.22, 95%CI 0.18-0.27).

Donation Characteristics

Donation history was reported using a number of different methods including donation intensity, inter-donation interval and repeat versus new donors (**Table 1**). Evaluation of the association of donation characteristics with low Hb deferral is difficult as there is an effect of selection and also an opposite effect of lowering of iron stores with repeated donation.

Twelve studies reported deferral by donation intensity, either the number of previous donations the donor had made in the past two years expressed as a categorical [9, 10, 13, 21, 36] or continuous [19, 20, 31, 37] variable, or the time since the donor's previous donation [19-21, 38-40].

Two European studies found that the number of previous donations lessened LHD risk in both men and women, with a greater association in men [19, 20]. However, the third concluded that for men, LHD deferral increased as the number of donations increased. One US study [9] found no effect of donation history, while the other [10] reported ORs below 1 for donors who had seven or more donations in the past two years. A Brazilian study [18] found that, for women in particular, the proportion of donation attempts that became low HCT deferrals increased to above 0.3 for those with seven donations in the past, compared with a proportion of around 0.1 or less for those with one or two previous donations. These results for women in particular contrast with the earlier US studies, which found that women who donated more often were at a lower risk of deferral, and that only men who had donated once or twice in the past year had a significantly reduced risk of deferral [13, 21].

Eight studies reported an association between LHD and time since previous donation [9, 18-21, 38-40]. Four European studies found that men had a reduced chance of LHD the longer they waited to donate, however the results for women were inconsistent [19, 20, 38, 40]. A US study [21] reported no significant association for donors who had returned to donate 24 weeks or less since their previous donation compared with those who returned between 24 and 36 weeks, however those who waited longer between donations were significantly less likely to be deferred. A South African study [39] found no significant effect of donation interval. A Brazilian study [18] found that in male donors aged >44y, the time since previous donation had little effect on LHDs, whilst younger male donors saw a decrease in low HCT deferrals until around 10 months since their previous donation. Results for female donors were similar, although the proportion of low HCT deferrals was higher for

all age groups than for men. A US study [9] found that donors who waited 13 weeks or less were significantly more likely to be deferred for low Hb than those who waited 26 weeks or longer.

Two studies [41, 42] reported the effect of minimum inter-donation interval on LHDs. A US study [41] found that, after increasing the minimum inter-donation interval from eight to twelve weeks, the LHD rate was reduced from 12.5% to 10.2% (p<0.0001). A Canadian study [42] also found that after raising its minimum donation interval from 56 to 84 days, deferral rates fell from 13% to 9.5%.

Fifteen studies [15, 21, 28-30, 39, 43-51] reported LHD for new and repeat donors. Meta-analysis of 13 studies which reported LHD rates found no difference in the risk of LHD between new and repeat donors (OR 0.80, 95%CI 0.58-1.10) (**Figure 6**). In addition, a study from Thailand [47] reported only deferral percentages for repeat and new donors and found a higher percentage of LHDs for regular donors than new donors, whereas a study from the Caribbean [49] observed the opposite effect. The risk of LHD in new and repeat donors is likely to be confounded by the number and intensity of donations in individual studies which may contribute to the high heterogeneity observed across studies.**Previous Hemoglobin Levels**

Six studies reported the relationship between a donor's previous Hb or HCT level and the likelihood of LHD [18-21, 36, 52]. Two European studies [19, 20] applied logistic regression and showed a reduced risk of LHD in donors who were not deferred at their previous visit. A third study [37] found that men whose Hb increased between visits were less likely to be deferred than those whose Hb levels had decreased. In another study from the Netherlands [52] there was a higher risk of LHD for donors whose Hb levels were stable across visits, while donors class III and IV (whose initial Hb levels were higher but experienced a sharper decline) had a lower risk of deferral. In a US study [21], donors who had previous Hb levels below the reference group of ≥145 g/L had a higher risk of LHD, while previously deferred donors (Hb <125 g/L) were more likely to be deferred due to low Hb. Finally, a Brazilian study [18] compared initial HCT levels with those in the visit immediately before a low HCT deferral over a maximum 11 years of study and found that women whose initial HCT was <41 were three times more likely to be deferred than those who had initial HCT>43, and men with low initial HCT were almost six times more likely to be deferred. There was a similar relationship when examining the donor's HCT level at their previous visit.

Iron Status Interventions

Four interventional studies [53-56] investigated whether interventions to improve a donor's iron status affected their likelihood to be deferred for low Hb.

One Indian study [53] gave deferred donors information on diet, and recommended oral iron supplementation. Of the 68.8% of donors who returned to donate, 85% were successful. A Danish study [54] directed iron supplementation to those that were considered to potentially benefit and saw a significant decrease in the male LHD percentage from 0.92 to 0.55 (p=0.03).

A randomized trial from the USA of iron intervention strategies [55] found that the LHD rate in donors who received oral iron (19mg or 38mg) was lower (2.7%) than in those who received placebo (6.1%). Furthermore, the LHD rate in donors who received a ferritin status letter which either recommended they continue donation (Ferritin>26ug/L) or took iron supplementation/delayed donation (Ferritin≤26ug/L) was lower (4.1%) than in those who received a letter with no such information/advice (9.8%).

Another randomized trial from Germany [56] comparing 50mg iron, 20mg food supplement or no iron found a higher rate of LHD in those who did not take iron supplements compared to those who did (OR 5.03, 95%CI 1.52-16.69). A significant effect was found from the combined treatment groups (OR 6.56, 95%CI 2.32-18.53).

Donation Setting

Four studies [21, 57-59] compared donor deferral rates at fixed and mobile collection points. A study from the UAE [58] reported LHD rates for fixed centers versus mobile sites of 25.3% and 14.4% respectively. Meta-analysis of the remaining three studies showed a significant increase in the risk of LHD for those who donated at fixed compared to mobile sites (OR 1.14, 95%CI 1.03-1.27) (**Figure 7**).

Blood Group

LHD by blood group was analyzed in three studies [15, 24, 31]. An African study [24] found a significant association between LHD and AB blood group (AB vs O: OR 4.12, 95%CI 1.81-9.4) but not A or B blood groups. A US study [15] reported ORs by blood group compared to O negative, both before and after changes to the criteria for blood donation in the USA. In both time periods, there was a significantly higher risk of deferral for those in blood group A+, while blood groups AB+ and B+ had a lower risk of deferral. Finally, a Dutch study [31] analyzed blood group O- compared to others, and did not find a significant difference in deferral rates.

Other Factors

A number of other factors were only considered in single studies. Briefly, a higher risk of LHD was reported as significantly associated with donors' Hb non-consistent recovery time [52], replacement (versus voluntary) donation [60], afternoon/evening (versus morning) donation [32] and specific

genetic polymorphisms [61]. Other factors which were investigated but not found to be significantly associated with LHD included smoking [9], diet [48], and Rh positive blood group [24].

Discussion

This review has identified 116 studies which investigated the effect of various factors with deferral of donors due to failure to meet minimum Hb thresholds. Random effects meta-analyses and qualitative syntheses of results have shown that female sex, ethnicity, age, weight, seasonality, donation intensity, iron interventions and historical Hb levels can all affect a donor's risk of being deferred for low Hb.

All blood donor deferrals have cost and healthcare implications and have a negative effect on donor motivation to donate in the future. If blood collection services can reduce deferral rates, especially those due to low Hb, they may maximize donor return and reduce costs. It is well known that clear differences exist in the rates of deferral of donors due to low Hb between men and women, with women significantly more likely to be deferred than men. Our meta-analysis confirms that clear differences exist in deferral rates between male and female donors irrespective of whether minimum Hb thresholds for donation are defined universally for male and female donors, or whether sex-specific thresholds are used. Reasons for these differences in deferral rates between males and females have been suggested to include both physiological and social causes. Premenopausal female donors have lower iron stores resulting from the effects of menstruation and pregnancy [62]. In contrast, men have increased testosterone levels which are associated with higher Hb levels [63]. Males are also more likely to be cigarette smokers [64] and cigarette smoking increases carboxyhemoglobin resulting in increased Hb levels [65]. The need for different Hb donation thresholds for male and female donors therefore appears to be warranted. Indeed, the US Food and Drug Administration recently changed the Hb threshold for donation from a universal threshold of 125 g/L to sex-specific thresholds of 130 g/L for men and 125 g/L for women [66]. However, sex-specific Hb thresholds only provide a benchmark and cannot account for the many other factors that affect the risk of LHD and which may differ in their associated risk between male and female donors. The effect of other factors therefore can only reliably be evaluated by stratification of donors by gender. However, the lack of consistent reporting within individual studies prohibits accurate risk estimates and separate analyses for male and female donors are clearly warranted in future studies, as is controlling for other risk factors (e.g. adjustment or stratification in multivariable analyses).

The effect of the ethnicity of a prospective donor's risk of deferral from donation due to low Hb has been described previously [9-16]. Our results confirm that both male and female African-American donors are at higher risk of LHD than White donors, although the differential risk of deferral appears to be higher in female than male donors. Female donors of either Asian or Hispanic ethnicity are

also at higher risk of LHD than their White counterparts, although the evidence in male Asian or Hispanic donors is inconclusive. The deferral rates for different populations show wide variation (Supplementary Table 1). Although these absolute rates are not directly comparable due to the different Hb thresholds applied and other differences in eligibility criteria, the LHD rates in female donors compared to males in studies which use identical Hb thresholds show wide variation according to the country of study, again suggesting that a donor's ethnicity affects his/her ability to meet minimum Hb thresholds for donation. Variation in Hb levels between Black and White populations is well established [67]. Different minimum Hb thresholds for male and female donors according to ethnic origin have been suggested [68].

Genetic factors may explain some of the variation between donors of different ethnic groups in their susceptibility to LHD, although few studies have investigated the effect of genotypes on LHD. Different Hb genotypes which occur at varying frequencies in different populations may be associated with lower Hb levels, for example α-thalassemia traits that occur at high frequencies of 20% or more in some populations [69]. Polymorphisms in the HFE and TMPRSS6 genes have been shown to be associated with lower Hb levels [61] and ethnic variation in the frequency of mutations in both genes has been identified [70, 71]. Ethnic variation may also arise from nutritional differences. For example, a vegetarian diet has been suggested to occur more often in the Indian population [72] with particularly high frequencies in certain religious groups. The European Vegetarian Union have reported vastly different proportions of vegetarians in different countries [73]. The effect of blood group on LHD is inconclusive with conflicting results obtained from three trials. However, analysis of low Hb deferral by blood group is confounded by different frequency of donation as many blood services recall donors with RH negative groups and O and A ABO groups more often than RH positive and A and AB ABO blood group donors.

There is considerable evidence that increasing age is associated with a higher risk of LHD deferrals in males. Some explanation can be gained from the decreasing testosterone levels and thus reduced Hb levels with age [63, 74, 75]. The effect of age of LHD in women is less clear, with some studies reporting high LHD rates in younger women whilst others found an association between LHD and age. This is likely explained by the combined effects of menstruation and pregnancy in younger women alongside menopausal effects in older women. A large population-based US study found a pronounced increase in the prevalence of anemia with increasing age and suggested that key causes for this were likely to be nutritional deficiencies and chronic disease [74].

The increased risk of LHD observed in warmer months observed in several studies may be attributed to transient hemodilution as blood flow to the skin increases as an element of the heat balance

mechanism [76]. Other indirect factors influencing Hb level have been proposed, including nutrition, physical activity and viral infections [35]. It may be that a change in minimum Hb thresholds for donation according to ambient temperature could be possible, but a detailed understanding of the degree of change in Hb associated with different seasons/temperatures and the relationship between these changes and iron stores would be required before this can be considered further.

A lower risk of LHD has also been observed with increasing body weight [9, 10, 13, 35]. It has been suggested that heavier individuals might be expected to have a greater absolute blood volume and so would donate proportionally less of their total iron stores than a lighter person, with a lesser impact of loss of iron through donation [13]. However, the effect of weight on LHD is likely to be confounded by gender and age as well as lower iron stores as BMI increases [77] which may explain some inconsistency in the findings of individual studies.

Donation characteristics associated with LHD include previous donation [15, 21, 28-30, 39, 43-51], frequency of donations [9, 18-21, 38, 40-42], and previous deferral due to low Hb [19, 20] although results are conflicting and apparent differences exist between male and female donors. Evaluation of the association of donation characteristics with low Hb deferral is difficult as there is an effect of selection and an opposite effect of lowering of iron stores with repeated donation. Shorter inter-donation intervals have been associated with higher frequency of iron deficiency, lower Hb, and higher rates of deferral [10, 78, 79]. As males have typically two to four times greater iron stores than females [62], it would be expected that males are better suited to high intensity donation than women. The historical 8-week inter-donation interval used in the USA has recently been brought into question. An AABB Association Bulletin recommended that consideration should be given to increasing inter-donation intervals in some circumstances, in particular for young and/or female donors, in order to reduce iron deficiency in blood donors [80], although no formal change has been implemented [66]. A recent large trial of donors in the UK randomized to 8, 10, or 12 week (men) or 12, 14, or 16 week (women) inter-donation intervals over two years found that although shorter inter-donation intervals increased the risk of LHD, shorter inter-donation intervals were associated with a higher mean number of successful donations in both men and women over the trial duration [77].

Oral iron supplementation has been shown to reduce the risk of LHD, elevating Hb and iron stores in blood donors [81]. However, the prospect of implementing iron supplementation in blood donors is a matter of some controversy [82, 83]. Depleted iron stores are more common in female and young donors as well as those who donate regularly [84], and it has been suggested that low iron is associated with cognitive impairment [85]. Targeted iron supplementation in these high risk groups

has been recommended [86]. However, this comes with cost implications, associated adverse effects and compliance issues as well as possible health risks associated with regular iron intake [83]. Alternative strategies have been suggested [86]. These include extending inter-donation intervals, limiting donations in young donors (as implemented in Australia where the minimum age for donation has been increased from 16 to 18 years [87], and introducing serum ferritin testing as part of donor eligibility to donate in order to identify those individuals with low iron stores, as implemented in donors aged 16-18 years by Vitalant and the American Red Cross in the US [88, 89]. It remains to be seen which approach can best balance the health of donors against maintaining adequate blood supplies.

Our analysis has a number of key limitations. Firstly, the risk estimates presented in this review are unadjusted for potential confounding factors. The risk estimates obtained from random-effects meta-analyses are therefore average estimates only and should be interpreted with caution. Clearly, individually tailored donation criteria will be most effective when considering a number of factors simultaneously and the inter-dependency of those factors will determine the most effective criteria to be assessed. A number of studies have performed multivariate analysis and report results adjusted for a range of potential confounding factors including age, sex, ethnicity, weight, season, ambient temperature, blood group, inter-donation interval, number of prior donations and use of iron supplementation [9, 10, 13, 15, 19, 31, 34, 35, 61, 77, 90]. However, the disparity in factors adjusted for between individual studies precluded meta-analysis of these adjusted results. A more flexible approach might be gained through meta-regression, allowing individual study characteristics to be included as covariates, thus assessing the effect of study level characteristics on effect size estimates. Adjustment for confounding factors can be incorporated into the regression model, thus allowing interpretation of the extent to which such factors affect the effect size. However, the most powerful approach is the large trial which measures a wide range of factors to be evaluated in a multivariate analysis approach using sophisticated statistical modelling techniques. The factors identified in this review provide a basis for the design of such trials, with due attention given to gender, age and ethnicity in particular.

Secondly, a high degree of heterogeneity exists across studies and care should be taken over the interpretation and reporting of summary estimates given this high heterogeneity. Key sources of heterogeneity include minimum Hb donation thresholds and differences in the ratio of male to female donors in individual studies. The determination of Hb levels in prospective donors included a variety of methods which included both venous and capillary blood measurements, leading to varying levels of imprecision and bias across studies. Thirdly, the number of donations included in

each study as well as donation and deferral history is likely to introduce further heterogeneity in the likelihood of deferral at the point of study. Multiple donation attempts, whether successful or unsuccessful, could lead to differences in the underlying distribution of Hb levels, and thus the risk of LHD. Finally, despite the clear evidence for differences in the risk of LHD between male and female donors, many studies reported results for male and female donors combined, limiting the ability to assess the sex-specific effect of other factors.

Given the vast array of factors which appear to affect a donor's ability to meet Hb thresholds, individually tailored donation criteria may improve the retention of donors and increase blood supply overall. However, tailoring donation frequency will require the development of sophisticated mathematical models in prospective studies and this could be an important area for donor research in the future. We suggest that future prospective studies of LHD should incorporate the factors identified in this study, and appropriate statistical modelling methods should be used. This may lead to the identification of specific sub-groups of prospective donors which can then be subject to tailored donation criteria and/or iron supplementation.

This systematic review has highlighted a number of factors which affect a donor's ability to meet minimum Hb donation thresholds. A donor's sex, age, ethnicity, weight, donation history and inter-donation interval as well as ambient temperature and donation setting affect the risk of LHD. Other potential factors which may influence LHD include diet, smoking, blood group and genetic factors but further evidence is required. In conclusion, large prospective studies are needed, with an emphasis on collecting a wide spectrum of data on participant demographics, ethnicity and donation characteristics and using appropriate statistical models to establish the combined effect of these multiple factors on LHD in blood donors.

Acknowledgments

Conflicts of Interest

Prof. David Roberts is joint principal investigator of the INTERVAL study. There are no other conflicts of interest.

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Table 1: Deferral results by donation characteristics.

Study	Donation Group	Hb Deferral Rate (%) (males/females)	OR (95% CI) (male/female)
Donation Intensity			
Baart 2012	Number of whole blood donations in past two years		
	Continuous	n/r	1.14 (1.12-1.15)/0.92 (0.9-0.93)
Baart 2014	Number of whole blood donations in past two years		
	Continuous	n/r	0.97/0.9
Baart 2016	Number of whole blood donations in past two years		
	Continuous	n/r	0.97/0.9
Cable 2012	Number of whole blood donations in past two years		
	1-3	12.26	1
	4-6	11.23	0.9 (0.7-1.3)
	7-9	9.07	1 (0.8-1.3)
	10+	5.17	1 (0.9-1.4)
Custer et al 2012 and	Number of whole blood donations during previous 12 months		
Mast et al 2010	0	1·3/18·2	1
	1	1·1/17·5	0·72 (0·67–0·77)/0·99 (0·98–1·01)
	2	1·5/18·1	0·84 (0·79–0·90)/1·07 (1·05–1·09)
	3	2·1/18·1	1·04 (0·97–1·11)/1·09 (1·06–1·12)
	4	2·3/16·4	1·08 (1·01–1·15)/0·97 (0·94–1·00)
	5	2·6/13·4	1·07 (0·99–1·16)/0·76 (0·73–0·80)
	≥6	2·8/8·8	1·00 (0·89–1·13)/0·45 (0·40–0·51)
De Kort 2019	Number of whole blood donations in past two years		
	Continuous	n/r	0.025/0.015
Spencer 2016	Number of whole blood donations in past two years		
	0	n/r	1
	1-3	n/r	1.02
	4-6	n/r	1
	7-9	n/r	0.83
	10+	n/r	0.59
Zanella et al 1989	Annual Rate of Donation		
	M: <2/year	M: trend is to fall over the 16 donations.	
	F: <1.5/year	F: trend is to rise over the 18 donations.	
	M: 2–3/year	M: trend is to fall over 23 donations (slight rise in 18-21 year olds).	
	F: 1·5–2·5/year	F: stable over 11 donations then varies.	
	M: >3/year	M: falls over the 22 donations.	
	F: >2·5/year	F: falls to 12 donations then rises.	
Inter-donation Interval			
Baart 2014	Time since previous donation per month smaller than one year		
	Continuous	n/r	0.89/0.9

Baart 2016	Time since previous donation per month smaller than one year		
	Continuous	n/r	0.87/1.11
Custer 2014	Time since previous donation in weeks		
	8-16	n/r	1.5 (1.4-1.6)
	16-20	n/r	1.2 (1.05-1.3)
	20-24	n/r	1.2 (1.1-1.3)
	24-36	n/r	1
	36-52	n/r	0.8 (0.7-0.9)
	52+	n/r	0.7 (0.7-0.8)
Muon 2018	Interdonation Interval		
	<3 months	4.4/40.4	3.58 (3.22-3.99)/8.48 (7.95-9.06)
	3-4 months	1.8/13	1.39 (1.26-1.54)/1.87 (1.76-1.99)
	4-5 months	1.6/9.9	1.23 (1.12-1.36)/1.38 (1.32-1.43)
	5-6 months	1.5/8.9	1.16 (1.07-1.25)/1.22 (1.18-1.26)
	≥6 months	1.3/7.4	1/1
Van den Berg 2019	Interdonation Interval		
	≤3 months	1.98/13.95	1.18 (0.52-2.69)/0.94 (0.63-1.41)
	3 to 6 months	2.37/16.88	1.41 (0.65-3.05)/1.14 (0.83-1.56)
	>6 months	1.68/14.78	1/1
Zeimann et al 2006	Interdonation Interval		
	<6 months	6·3	0·70 (0·56–0·87)
	6 to 11 months	6·2	0·68 (0·54–0·86)
	12 to 23 months	7·7	0·87 (0·67–1·13)
	≥24 months	8·8	1

New vs Repeat

Afzal 2016	New	1.04/41.99	1/1
	Repeat	4.77/37.82	4.58 (3.8-5.52)/0.85 (0.9-0.95)
Al Shaer 2017	New	14.27	1
	Repeat	6.68	0.47 (0.45-0.49)
Bakrim 2018	New	9.69	1
	Repeat	8.6	0.89 (0.79-1)
Custer 2004	New	0·7/12·6	1/1
	Repeat	0·5/10·3	0·69 (0·47–1·03)/0·80 (0·76–0·85)
Custer 2012	New	8·8	1
	Repeat	8·1	0·87 (0·86–0·88)
Goncalez 2013	New	7·9	1
	Repeat	3·9	0·47 (0·47–0·48)
Klausa 2013	New	38.46	1
	Repeat	39.58	1.03 (0.46-2.29)
Kouao 2012	New	2·6	1
	Repeat	4·0	1·61 (1·23–2·11)
Ngoma 2013	New	14.14	1

	Repeat	7.29	0.52 (0.49-0.55)
Ngoma 2014	New	10.54	1
	Repeat	12.5	1.09 (0.99-1.19)
Perez 2018	New	1/14	1/1
	Repeat	2.76/15.27	2.75 (2.6/2.91)/1.09 (1.07/1.11)
Van den Berg 2019	New	1.55/19.01	1/1
	Repeat	1.98/13.28	1.28 (0.31-5.34)/0.65 (0.46-0.93)
Wilkinson 1982	New	1·2/17·6	1/1
	Repeat	1·0/13·2	0·78 (0·75–0·81)/0·71 (0·70–0·72)

Figure Legends

Figure 1: PRISMA flow diagram of study selection

Figure 2: Meta-analyses of low Hb deferral for females compared with males stratified by universal or sex-specific deferral thresholds.

Figure 3: Meta-analysis of low hemoglobin deferral by ethnicity. A: Black or African-American vs White; B: Asian vs White; C: Hispanic vs White.

Figure 4: Study-specific correlates between percentage of deferrals and age groups, by sex.

Figure 5: Meta-analysis of low hemoglobin deferral by season. A: Spring vs Winter; B: Summer vs Winter; Autumn vs Winter.

Figure 6: Meta-analysis of low hemoglobin deferral, repeat versus new donors

Figure 7: Meta-analysis of low hemoglobin deferral, fixed versus mobile donation sites