Low ferritin levels appear to be associated with worsened health in male repeat blood donors

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**Background and objectives** Frequent blood donation depletes iron stores of blood donors. Iron depletion may lead to anaemia, but the health effects of iron depletion without anaemia in healthy blood donors are not well understood. We studied in the FinDonor cohort whether worsening of self-rated health of blood donors during the study period was associated with biomarkers for iron levels or other self-reported changes in lifestyle.

**Materials and methods** We included 1416 participants from the cohort who answered an 89-item questionnaire on their health and lifestyle during their enrolment visit and again at the end of the study. We performed multivariate logistic regression to test if blood donation-related factors affected the probability of reporting worsened health. To set these findings into a more holistic context of health, we subsequently analysed all other questionnaire items with a data-driven exploratory analysis.

**Results** We found that donation frequency in men and post-menopausal women and ferritin level only in men was associated negatively with worsened health between questionnaires. In the exploratory analysis, stable physical condition was the only questionnaire item that was associated negatively with worsened health in both women and men.

**Conclusion** Our results suggest that low ferritin level is associated with worsened health even in non-anaemic repeat donors, although we find that when health is analysed more holistically, ferritin and other factors primarily related to blood donation lose their importance.

**Key words:** blood donation, donor health, self-rated health, iron deficiency, iron deficiency without anaemia, ferritin.

**Introduction**

Blood establishments are responsible of securing a safe blood donation. Donor selection criteria strive to guarantee the quality and safety of the blood components and donor safety. The long history of blood donation as such demonstrates that there are no clear acute or long-term harmful effects related to blood donation. If not properly managed, blood donation leads to iron deficiency anaemia, but this risk is typically well cared for. Lately, concern has been raised regarding the possibility of depletion of iron stores without anaemia, in particular among younger women or frequent donors [1].

Due to the healthy donor effect, blood donors are considered to be healthier than the general population [2]. Healthier individuals get selected by the blood establishment and the donors themselves as donors and are able to maintain the habit from years to decades. For example, among young individuals, better self-perceived mental health, and with the increase in age, better self-perceived physical health are associated with blood donation [3].

Despite these positive associations, blood donors are also considered to be at higher risk of iron deficiency [1, 4, 5], especially as a result of frequent blood donation [1, 6–8]. However, iron deficiency without anaemia has not
been found to be associated with reduced self-perceived health-related quality of life in blood donors [8, 9]. Recently, iron supplementation was found to reduce iron deficiency-related symptoms in non-anaemic Swiss blood donors [10]. Iron levels of Finnish blood donor population are mostly affected by blood donation activity [11]. Importantly, iron supplementation for at-risk groups has been in place since the 1980s in Finland. In addition to donation activity, other factors like age [12], BMI [12, 13] and donation frequency [6, 14] are associated with both blood donors iron status and self-rated health [15].

The factors which influence health are multiple and interactive. According to the World Health Organization constitution: ‘Health is defined as a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity’ [16]. Subjective and objective determinants of health should be used together as they might have different influences on health [17]. In industrialized countries, self-rated health (alternatively self-reported or self-perceived health) is the most relevant measure of one’s general health and robust predictor of objective outcomes, such as mortality [18–20].

The Finnish Red Cross Blood Service (FRCBS) set up the FinDonor 10 000 study in 2015 [21] to investigate the health effects of blood donation with a specific focus on iron status [11]. In the present study, we test if worsening of self-rated health of blood donors during the study period was associated with donation activity, biomarkers for iron levels or self-reported changes in lifestyle.

Material and methods

FinDonor 10 000 was a prospective longitudinal cohort study and ran from the 18 May 2015 to 8 December 2017. An ethical approval (approval number 282/13/03/00/14) for the study was acquired from the Hospital District of Helsinki and Uusimaa Review Board. Details of the FinDonor cohort, sample collection, laboratory analyses and quality issues are described elsewhere [21].

During their enrolment visit, participants were asked to fill out an electronic questionnaire about their health and lifestyle at the donation site after donating blood. This questionnaire included 89 questions about general health, current and past medical conditions, dietary habits, smoking, alcohol use, physical activity and sleep. During the 2018 summer, participants received a letter from FRCBS inviting them to answer the questionnaire again from home using a web page. We added questions about educational level, working status and quality of life to this second follow-up questionnaire. We used combined data from participant’s donation history (FRCBS donation database, e-Progesa, MAK-SYSTEM), both questionnaires and laboratory results from the enrolment visit blood samples.

Of the 2584 donors who consented to the study, we excluded 1103 participants because they did not answer both questionnaires. We divided the participants into three different groups: men, post-menopausal and pre-menopausal women. The post-menopausal group was formed by women who were over 45 years of age and reported amenorrhoea. Women under 45 years of age reporting amenorrhoea were excluded from the analyses (N = 38). Women of all ages who reported menstruation formed the pre-menopausal group. Subsequently, we excluded donors who did not answer the question 5: ‘How would you rate your health in general?’ (N = 5), question 27: ‘How much do you weigh?’ (N = 15) in both questionnaires, who had high ferritin (≥400 µg/l), N = 3 or who had high CRP (≥30 mg/l, N = 4) from the analyses.

To test if blood donation-related factors could explain worsening of self-rated health between the two questionnaires, we performed multivariate logistic regression. As a measure of self-rated health we used the commonly used and validated single question: ‘How would you rate your health in general?’ (excellent, very good, good, moderate or poor) [20]. The outcome variable (health_outcome) was defined as reporting worsened health (health_outcome = 1) rather than same or better health in the second questionnaire (health_outcome = 0). As explanatory factors, we used donor characteristics age (years), initial ferritin, initial haemoglobin, initial weight, BMI difference, during study average annual donation frequency and if initial self-rated health was very good (was not very good = 0, was very good = 1) or excellent (was not excellent = 0, was excellent = 1). Full analysis code can be found from [22].

The data were analysed separately for men, post-menopausal women and pre-menopausal women. After estimating p-values and odds ratios (OR) by fitting a model once to the original data, 95% percentile confidence intervals were estimated for ORs, that is effect sizes, with the adjusted bootstrap (BCa) method [23]. These were calculated by sampling with replacement from the original study group a sample of equal size as the original study group 10 000 times. A logistic regression model was fitted each time to the data to calculate 10 000 alternative effect sizes for each donor characteristic. The confidence interval was then calculated and adjusted for non-normality from the distribution of these 10 000 effect sizes.

In the exploratory analysis, we excluded 371 additional participants more who did not answer some of the questions selected for the analysis (see [24] for code). In brief, we first decided to exclude 26 of the 89 questions from the analysis, because they could not be formulated as...
change in quantity between the questionnaires or were related to female reproductive health. For all the remaining 63 questions, 817 donors had provided complete data. Many questions in the questionnaire probe similar topics. We screened if answers of the questions had a correlation of at least 0.5 with answers of some other question and selected among the group of questions correlating with themselves a single question to represent that group (Fig. S2). We selected the question that allowed us to keep as much data as possible and had a balanced distribution to enable modelling. This enabled us to increase the number of donors with complete data to 1045 and augment the models of primary analysis with further donor characteristics (Table S5). The answers to these selected questions were then recoded as change between the two questionnaires. Questions 1–3 have the format ‘Have you ever...?’ and represent single health events (e.g. diagnosis of anaemia). We coded them as ‘0’ for no new event during the study and ‘1’ for a new diagnosis during the study. The rest of the questions asked in both questionnaires can be interpreted as ordered factors. We coded them as change of factor levels between questionnaires, that is ‘decreased’, ‘stable’ or ‘increased’. The additional questions of the follow-up questionnaire were not used. The exploratory analysis was carried out by adding the selected questions to the primary analysis multivariate logistic regression models and refitting the models (see [25] for code).

We carried out all analysis in R ‘a free software environment for statistical computing and graphics’ [26] using tidyverse [27]. In particular, plots were created with library ggplot2 [28], ggbeeswarm [29] and GGally [30], tables with tableone [31] separation in logistic models was identified with safeBinaryRegression [32], collinearity was analysed with function vif() in car [33], and BCa confidence intervals were calculated with boot [34].

Results

After the exclusions detailed in Materials and Methods, we were able to include 1416 donors (589 men, 353 post-menopausal and 474 pre-menopausal women) of the FinDonor cohort. The time interval between answering the two questionnaires varied from 12 months to 39 months (Fig. S1). We found a slight cohort level trend towards the donors reporting worse health in the second compared to the first questionnaire, in particular in pre-menopausal women (Table 1).

To evaluate whether exclusion of donors from the data sets used for the hypothesis testing and explorative analysis could bias results from them, completion rates by initial health status (Table S1) and evolution of health status (Fig. S3) were analysed. Overall, self-reported health of 15% of women had improved and 54% reported same and 31% worsened health (14%, 57% and 29%, respectively, in men) with similar percentages in the explorative

| Characteristic | Men | Post-menopausal women | Pre-menopausal women |
|---------------|-----|-----------------------|----------------------|
| n             | 589 | 353                   | 474                  |
| Age (years)   | 47.65 (13.20) | 58.58 (5.57) | 35.51 (10.04) |
| Initial weight (kg) | 85.23 (14.38) | 71.09 (12.86) | 70.74 (14.06) |
| BMI difference (second - first) (mean (SD)) | 0.23 (1.39) | 0.28 (1.53) | 0.90 (1.91) |
| Initial haemoglobin (g/l) (mean (SD)) | 150.38 (9.64) | 138.07 (8.03) | 135.28 (7.80) |
| Initial ferritin (µg/l) (median [IQR]) | 41.00 (25.00, 68.00) | 33.00 (21.00, 51.00) | 25.00 (16.00, 41.00) |
| During study donation frequency (yearly) (mean (SD)) | 3.00 (1.40) | 2.41 (0.94) | 1.92 (0.96) |
| Initial health rating (%) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Poor          | 15 (2.5) | 6 (1.7) | 9 (1.9) |
| Satisfactory  | 175 (29.7) | 142 (40.2) | 156 (32.9) |
| Good          | 294 (49.9) | 146 (41.4) | 236 (49.8) |
| Very good     | 105 (17.8) | 59 (16.7) | 73 (15.4) |

| Final health rating (%) |
|-------------------------|
| Poor                      | 2 (0.3) | 1 (0.3) | 2 (0.4) |
| Satisfactory              | 36 (6.1) | 30 (8.5) | 28 (5.9) |
| Good                      | 213 (36.2) | 136 (38.5) | 195 (41.1) |
| Very good                 | 256 (43.5) | 149 (42.2) | 192 (40.5) |
| Excellent                 | 82 (13.9) | 37 (10.5) | 57 (12.0) |
sub-cohort. In women, the completion rate tends to increase with improved initial health, unlike in men.

Our primary goal was to test whether blood donation-related factors could explain worsened self-rated health between the two questionnaires. To this end, we selected from the literature plausible donation-related factors [11, 35] and constructed logistic multivariate regression models to test the specific hypothesis of whether these factors could be associated with worsened donor health.

Results of the multivariate logistic regression models are presented in Fig. 1 and their numeric values in Table S2. The model included separate factors for worsening of higher health ratings (‘Initial health rating Very good’ and ‘Initial health rating Excellent’, Fig. 1 and Table 1). These factors were found to be the most influential, with odds ratios of worsened health between the two questionnaires from 4 to 19 in different study groups. Initial weight was found to be positively associated with worsened health in all groups. Initial ferritin and during study donation frequency were found to associate negatively with worsened health in men. Among post-menopausal women, during study donation frequency was also found to associate negatively with worsened health. The BMI difference (BMI in second – BMI in first questionnaire) in post-menopausal women was found to associate positively with worsened health. The most visible mean difference was seen in initial weight of men, where donors that reported worsened health had a mean initial weight of 88.8 kg and for stable and improved health 84.2 and 82 kg, respectively (Fig. 2).

To further verify that the above results are not confounded by initial health rating of donors, we repeated the above analysis stratified by initial health (Tables S3 and S4 and Fig. S4). The negative association of ferritin with worsened health was detected in men with ‘Very good’ or ‘Excellent’ initial self-reported health.

Given the multiple determinants of health, we wanted to find out how do the effects of the studied blood donation-related factors compare to the effects of the rich FinDonor health questionnaire data. For this exploratory analysis, we included 1045 donors (Table S5). Results of the analyses are presented in Fig. 3 (numeric values in Fig. 1

### Associations of donor characteristics to worsened self-reported health from hypothesis-based multivariate regression

The standardized coefficients (circle), their bootstrapped 95% BCa confidence intervals (thick line) and whether the factor was significant (Bonferroni-corrected $P < 0.05$ in the initial regression models, filled circle) or not (non-filled circle). Ferritin is presented as log(ferritin)/log(2), that is a unit increase corresponds to doubling of ferritin. Weight, age and haemoglobin were divided by 5, that is a unit increase corresponds to 5 kg, 5 years or 5 g/l, respectively. [Colour figure can be viewed at wileyonlinelibrary.com]

### Distributions of selected donor characteristics divided by change in self-reported health

Each individual shown as an open circle in a dot plot and overlaid with a boxplot where the central line shows the median and upper and lower edges of the box 25th and 75th percentiles, respectively. [Colour figure can be viewed at wileyonlinelibrary.com]
Table S6). Size of the data set was found to be limiting for analysis of post-menopausal women and pre- and post-menopausal women were combined into one group. After data-driven exclusion of donor characteristics, the two models included 31 donor characteristics, which covered 26 individual questions (initial self-rated health used twice), two laboratory values (ferritin and haemoglobin) and two values from donation registry (age and during study donation frequency). Of these donor characteristics, 11 had a Bonferroni-corrected p-value below 0.05 in the model fitted to non-bootstrapped data in at least one study group. These 11 are included in Fig. 3. As in the hypothesis testing models, the ‘Initial health rating Very good’ and ‘Initial health rating Excellent’ variables had the largest coefficients. Of other factors included also in the hypothesis testing model, ‘during study donation frequency’ was negatively associated with worsened health in men and women and ‘initial weight’ positively associated for men. The directions of associations between donor characteristics and worsened health were consistent between the hypothesis testing and exploratory models. However, the confidence intervals of all these coefficients, except donation frequency in women, crossed zero indicating that their direction of effect could not be estimated with 95 % certainty by the models. In men and women, an equal answer to question, ‘21. How would you rate your current physical condition?’ in both questionnaires, in comparison to having answered an inferior level in the second questionnaire than in the first, was negatively associated with worsened health (OR of 0.13 [CI: 0.08–0.043] in men; OR of 0.32 [CI: 0.19–0.67] in women, Fig. 3: row ‘Physical condition stable’). In addition, significant p-values were detected for questions related to elevated cholesterol, tiredness, physical symptoms, condition and activity, but in most cases the direction of the effects could not be estimated with 95% certainty.

Discussion
The FinDonor 10 000 cohort represents the Finnish blood donors well despite an over-representation of active
donors [21]. In the present publication, we studied only the FinDonor participants that answered both the enrolment and follow-up questionnaire. Highly educated and permanently employed people are over-represented in this population [21]. These factors are known to have a mostly positive effect on health [17, 36]. The health of non-anaemic iron-deficient blood donors is a concern for the blood donation community. According to enrolment ferritin 5% of men, 10% of post-menopausal and 21% of pre-menopausal women of the 1416 participants were iron-deficient (ferritin < 15 μg/l). Hence, our study might not have sufficient numbers of non-anaemic iron-deficient blood donors to be applicable to this subpopulation. Furthermore, we found that among women the initial health status correlated with completion rate of the second questionnaire (Table S1). Among women and men, only 3–4% of donors had a two level drop in health (Fig. S3). Hence, our data might be biased to detect only associations with moderate worsening in health.

In our sample of 1416 blood donors, we found that men (n = 589) rated their health slightly better or the same as women (Table 1), supporting results of studies in general populations [17, 18]. We also saw a slight overall trend towards worsened health in the second questionnaire in comparison to the first questionnaire (Table 1). However, we have shown that there was no consistent individual-level trend for worsened health in the FinDonor cohort, rather random variation or regression to the mean [21]. To capture the effect that the highest health rating cannot improve and the possible regression to the mean effects, the model included separate factors for initial high health ratings (‘Initial health rating Very good’ and ‘Initial health rating Excellent’, Fig. 1 and Table 1). We found that these donor characteristics had the strongest associations with the worsened self-rated health between questionnaires. Capturing variation related to the baseline health ratings in the enrolment questionnaire is important to correctly estimate the effect sizes of other factors, although it reveals little of the actual causes of worsened health. Donors replied to the first questionnaire at the donation site after donating blood. Consequently, healthy registration effect [15] or warm glow [37] was likely to have been present. Hence, the initial high health rating factors in the model were likely to capture also these effects.

We detected that initial weight was positively associated with worsened health in all groups. The OR for women was 1.4 meaning that a 5 kg increase in initial weight increases the odds of reporting worsened health by 40%. The difference in BMI (second – first) was positively associated with worsened health in post-menopausal women (Fig. 1, Table S2). Results are in accordance with previous studies about weight stability and obesity avoidance to stay healthy [38].

We found that in men and post-menopausal women, during study donation frequency was negatively associated with worsened self-rated health (Fig. 1, Table S2). The result is similar to that of Donor InSight blood donor study [15] and is likely to be related to the healthy donor effect.

We detected that in men initial ferritin level was negatively associated with worsened health. (Fig. 1, Table S2). To our knowledge, such association between ferritin and evolution of self-rated health has not been reported before. Hence, higher iron stores, reported by higher ferritin levels, might help to maintain health even in non-anaemic male repeat blood donors. In women, the completion rate was found to be higher if the initial health rating was higher. In the stratified analysis, the ferritin association is only detected in men with ‘very good’ or ‘excellent’ initial self-reported health. Hence, it seems possible that we are unable to detect the ferritin association in women due to selection bias.

To allow interpretation of the primary hypothesis-based analysis of donor characteristics associated with worsened health in a more comprehensive context of health, we carried out a secondary exploratory analysis which included as many donor characteristics from our donor health and lifestyle questionnaire as possible given limitations of data availability (Fig. 3, Table S6). In this analysis, we found that stable physical condition was the only donor characteristic for which direction of effect could be reliable estimated for men and women. In addition for women, ‘increase of interference of physical symptoms’ was positively and ‘increase of physical condition’ and ‘stable ability of heavy activity’ were negatively associated with worsened health. These results are in accordance with previous results about healthy lifestyle, for example physical activity is positively associated with good self-rated health and unhealthy lifestyle with ill-health [39] and that active lifestyle is associated with better self-rated health [40, 41].

Blood donors are considered to be healthy but the definition and perception of health is complex and involves several factors such vitality and physical and mental health [36, 42]. Also, health-damaging behaviours may serve to promote pleasure, relieve stress or even enhance mental health [43]. Some particular health components may be more important to an individual when they assess their health, while others are less consequential [42], for example, possible mild symptoms caused by low iron stores in otherwise healthy non-anaemic donors might be compensated by the positive feelings from blood donation [44]. Also, impact of iron metabolism to health at large is actively debated. Low iron stores may even be beneficial in some cases [45, 46].

In conclusion, our results suggest that low iron stores, reported to be low ferritin levels, could be associated with
worsened health even in non-anaemic repeat donors. This raises concern over iron store management of active donors, but the results also imply that when health is analysed more holistically, blood donation-related factors lose their importance.

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Conflict of interest

There are no conflicts identified.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1 Distribution of time between questionnaires in the study groups.
Figure S2 Correlations between answers of questionnaire items.
Figure S3 Health status evolution between questionnaires.
Figure S4 Forest plot of hypothesis testing stratified by initial health.
Table S1 Completion rates by level of self-rated health at the first visit.
Table S2 ORs from the hypothesis testing model.
Table S3 Population characteristics of hypothesis testing stratified by initial health.
Table S4 ORs from hypothesis testing stratified by initial health.
Table S5 Population characteristics of exploratory analysis.
Table S6 ORs from the explorative model.