Title: Frequent blood donation and offspring birth weight – a next generation association?

Authors:

Andreas S. Rigas¹, Ole B. Pedersen², Erik Sørensen¹, Lise W. Thørner¹, Margit H. Larsen¹, Louis M. Katz³, Kaspar Nielsen⁴, Kjell Titlestad⁵, Gustaf Edgren⁶,⁷, Klaus Rostgaard⁸, Christian Erikstrup⁹, Henrik Hjalgrim⁸,¹⁰, Henrik Ullum¹

Affiliations:

¹ Department of Clinical Immunology, Copenhagen University Hospital, Denmark
² Department of Clinical Immunology, Næstved Hospital, Denmark.
³ America’s Blood Centers, Washington DC, USA
⁴ Department of Clinical Immunology, Aalborg University Hospital, Denmark
⁵ Department of Clinical Immunology, Odense University Hospital, Denmark
⁶ Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Sweden
⁷ Department of Cardiology, Södersjukhuset, Stockholm, Sweden
⁸ Department of Epidemiology Research, Statens Serum Institut, Denmark.
⁹ Department of Clinical Immunology, Aarhus University Hospital, Denmark.
¹⁰ Department of Haematology, Copenhagen University Hospital, Denmark.

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Corresponding author and reprints:
Henrik Ullum, MD, PhD, Professor
Department of Clinical Immunology
Copenhagen University Hospital
Blegdamsvej 9
2100 Copenhagen Ø
Denmark
Telephone: +45 35453545
E-mail: henrik. ullam@regionh.dk

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Abstract:

Background
The prevalence of iron depletion is high among pre-menopausal women who donate blood frequently. Studies in non-donor populations indicate that iron deficiency anemia is associated with an increased risk of low birth weight. This prompts concerns that iron deficiency induced by frequent blood donation might impair subsequent fetal development.

Aim
To assess whether pre-pregnancy donation intensity affects birth weight of singletons born at term (gestational week 38 or later) to nulliparous female donors in Denmark.

Methods
We identified 293,897 first live singleton births to Danish women between 1997 and 2012 with complete information on: gestational age, birth weight, child sex, parental age, maternal smoking status during pregnancy, and parental education length, and annual income. Linear regression analysis was applied with birthweight as outcome,
number of donations within three years prior to pregnancy as explanatory variable, and confounding variables as described.

Results

Birthweight among children of low intensity donors (n=22,120) was 12.6 g (95% CI: 6.7-18.6) higher than non-donors (n=268,253) after controlling for the abovementioned factors. The higher birthweight among low intensity donors can be explained by the healthy donor effect. In fully adjusted analyses, birthweight among children of high intensity donors (n=3,524) was 20.2 g (95% CI: 5.1-35.3 g) lower compared with low intensity donors. This reduced birthweight among high intensity donors compared to low intensity donors may reflect blood donation induced iron deficiency.

Conclusion

Our results show that high pre-pregnancy donation intensity is inversely associated with birth weight of singletons born at term to nulliparous women.
Introduction:

The World Health Organization lists iron deficiency as one of the top 10 global health risks\(^1\). Iron is pivotal to several physiological processes\(^2\) and most notably iron deficiency can lead to iron deficiency anemia\(^3\). Thus, anemia is also a global health challenge and especially children and women of child-bearing age are at risk\(^4\). While several dietary and physiological factors affect iron stores\(^5,6\), its strongest predictor among blood donors is the number of recent blood donations\(^5\). Indeed, in the Danish Blood Donor Study 38% of young frequently donating women have iron deficiency\(^5\). Accordingly, women donating frequently are at a considerable risk of iron deficiency\(^5\).

In non-donor populations, maternal iron deficiency during pregnancy has been linked to an increased risk of offspring being born small for gestational age\(^7\). Consistent with this, iron supplementation during pregnancy has been found to reduce the risk of low birth
weight\textsuperscript{8}, and total iron intake in the first trimester has been positively associated with birth weight\textsuperscript{9}. Further emphasising the importance of maternal iron status, animal studies suggest that maternal iron deficiency may impair offspring neurological development and cognitive function\textsuperscript{10-16}; and in humans iron deficiency with anemia may affect hippocampal morphogenesis\textsuperscript{17}. Low birth weight is in itself a risk factor for later cardio-vascular disease\textsuperscript{18,19}.

This prompts concern that blood donation-induced iron deficiency in pregnant women who have previously been blood donors could adversely affect foetal growth and subsequent offspring health. So far, this issue has been addressed only in a recent Canadian study, reporting no association between pre-pregnancy donation intensity and low birth weight\textsuperscript{20}. However, consistent with the expressed concern, a sub-analysis in the Canadian study indicated that exemption from donation because of anaemia was associated with a borderline statistically significantly increased risk of low birth weight in the offspring.

Continued vigilance to ensure the good health of blood donors is paramount for blood banking and transfusion medicine. We therefore took advantage of nationwide registers in Denmark to repeat the Canadian study on a larger scale and with more detailed donation data.
**Materials**

We identified first-born singletons born in Denmark in the period 1997-2012 and their parents in the Danish Civil Registration System which holds status and dates of vital events: i.e. birth and, when relevant, dates of immigration/emigration and death, and family status for all individuals living in Denmark since 1968\(^\text{21}\). Using the personal identification number unique to all Danish citizens as key, we obtained information from the population-based Medical Birth Registry\(^\text{22}\) on gestational age, mode of delivery (caesarean section yes/no), birth weight, and maternal smoking status during the pregnancy for the entire cohort of children. From other registries\(^{23-25}\), information on parental length of education and annual income in the year preceding the birth was ascertained.

We then linked this cohort of parents with data from the Danish portion of the Scandinavian Donation and Transfusion (SCANDAT)\(^\text{26}\) database to identify blood donors and their respective blood donation history.

**Statistical analyses**

We have previously found that number of donations in the preceding three years is the strongest predictor of iron level among Danish blood donors compared with multiple other physiological and dietary factors\(^5\). Therefore, we used SCANDAT data on donation history to construct such a variable for all parents for the three years preceding gestation of the identified children *by back-calculating from gestational age at birth*. Similar measures were produced for time windows of five and seven years preceding
the pregnancy, respectively. Lastly, total number of donations before the pregnancy was also calculated. We stratified donors by donation activity into high intensity donors (those with two or more annual donations in the considered time window before pregnancy, i.e. at least 6 donations in a three year time window), and low intensity donors (those with at least one donation in the investigated time window, i.e. one to five donations in a three year window). Non-donors were defined as individuals with no records of blood donation before pregnancy.

As birth weight is closely related to gestational age and premature birth is associated with a wide range of different illnesses, we chose to investigate only children born after gestational week 37, i.e. at term.

The following variables were included as potential confounders in our analyses in order to adjust for amongst others socio-economic status and the healthy donor effect:

maternal smoking status during pregnancy (yes/no), maternal (dichotomized at age 30 years) and paternal (continuous) ages, maternal and paternal lengths of education (continuous), maternal and paternal annual incomes (standardized to year 2000 and ranked from -0.5 to 0.5; i.e. the individual with lowest income ranked as -0.5 and the individual with highest income ranked as 0.5, and everyone in between dependent on income), mode of delivery, and year of birth (dichotomized at year 2005). Analyses also included offspring sex.

The distribution of the investigated factors was assessed by histograms. For the three primary groups: high intensity donors, low intensity donors, and non-donors; the study
population were described using means (SD) for normally distributed data, with medians (25 percentile and 75 percentile) for non-normally distributed data, and with proportions for binary data. Correspondingly, differences between groups were compared by a t-test for normally distributed data, a rank test for non-normally distributed data, and with a chi square test for binary data.

Linear regression models were constructed with birth weight as outcome and number of donations by the mothers in the three years preceding the first pregnancy either on continuous or a categorical (none, low intensity, high intensity) scale adjusted for maternal age, maternal smoking during pregnancy and gestational age or for the entire wider array of potential confounders listed above.

To provide a frame of reference for the analyses of maternal donations, we repeated this using paternal donation intensity as predictor of offspring birth weight. In these analyses, mothers were required to be non-donors.

Supplemental analyses included similar models with donation intensity interval windows of five and seven years, respectively, and with total number of donations before the first pregnancy. Moreover, longitudinal data analyses on all recorded births for each women using fixed effects models, random effects models and between-within models were applied on all pregnancies in the observed period. Models built were evaluated via Akaike’s information criterion and Bayesian information criterion. Due to clustering on maternal level, robust standard errors were used. These models were adjusted for the most important factors evaluated via the linear regression models;
and therefore, we adjusted for maternal age (binary), calendar year (binary), smoking status (binary), child sex (binary), parity (discrete ordinal scale), and donor status (yes/no). As exposure, we used either donation activity per year in a 3-year window leading up to pregnancy or a binary variable indicating whether six or more donations (High frequency donor) were made in a 3-year period before pregnancy. The fixed effects models controls for all time-invariant factors\textsuperscript{27}, for example height and to some degree weight; and the effects of donation activity should resemble the within effect. The random effects model also computes effect sizes for variables that do not change over time\textsuperscript{27}, and the effect of donation activity should resemble the between effect. The between-within model is a mixture of these two models. Moreover, several supplementary analyses with either different modelling of covariates or conditioned on a specific donation pattern were performed. Lastly, as SCANDAT\textsuperscript{26} may be biased due to missing data donation records in its early years (established in 1980) from a few parts of Denmark, we evaluated the same models without the first three years; and thereby reducing the risk of left truncation. Therefore, we considered only children born since year 2000 in these sub-analyses.

A p-value below 0.05 was considered statistically significant.

The statistical software program STATA (\url{www.stata.com}) was used for the analyses.

**Results**

We identified 293,897 first live singleton at term births to Danish women between 1997 and 2012. Of the mothers, 91.3\%, 7.5\%, and 1.2\% were non-donors, low frequency donors, and high frequency donors, respectively (Table 1).
Maternal donors were generally older, less likely to consume tobacco during their pregnancy, and had longer educations compared with maternal non-donors (Table 1). Moreover, the registered spouse of the maternal donors were older and had longer education compared with the registered spouses of the maternal non-donors.

High frequency maternal donors were on average 1 year older and had a longer education compared with low frequency maternal donors. However, no statistically significant difference in the proportion of active tobacco users during pregnancy was observed between low and high frequency maternal donors (Table 1). Further, registered spouses of high frequency maternal donors were on average older and had longer educations compared with registered spouses of low frequency maternal donors.

Low intensity donors gave birth to larger babies (mean: 3538g; SD: 470) than both non-donors (mean: 3508g; SD: 480; p<0.001) and high intensity donors (mean: 3512g; SD: 464; p=0.002) (Table 1).

From 1997 until 2012 the proportion of active tobacco users during pregnancy decreased for both donors and non-donors, the maternal age at first pregnancy rose for both donors and non-donors, and, lastly, the average offspring birthweight for both donors and non-donors declined slightly but statistically significantly. Further, donation intensity prior to the first pregnancy also changed over the investigated period; a small rise in number of donations prior to the first pregnancy was observed (data not shown).

In linear regression analysis adjusted for gestational age, maternal age, and smoking status, each additional annual donation by the mother within the three-year pre-
pregnancy window reduced birth weight by 14.6 g (95%CI: 7.4-21.8). In the fully
adjusted model, each donation per year made by the mother within the three-year pre-
pregnancy window reduced birth weight by 10.5 g (95%CI: 3.3 – 17.7). Inverse
associations were similarly observed in analyses using five- and seven-year donation
intensity windows, respectively, and in analyses using cumulative number of donations
as exposure (Table 2), as well as in analyses including a wider array of potential
confounders. No interactions were observed between donation intensity and maternal
age, smoking status, or calendar year.

Analyses considering strata of donation intensities as predictors of birth weight
produced similar results (Table 3). Specifically, among the female donors high donation
intensity was associated with a 20.2 g (95%CI: 5.1-35.3) lower offspring birth weight
compared with low donation intensity in adjusted analyses. The effect size of high
donation intensity on birthweight corresponds approximately to a 1/6 of the effect of
active tobacco smoking during pregnancy on birthweight (effect of smoking= -122.5g ;
95%CI: -140.1 to -104.9). The effect size of active tobacco smoking was derived from
the linear regression models by including smoking status as a binary variable. Similar
effect sizes were observed when examining: five-year and seven-year time periods
(Table 3).

In similarly adjusted linear regression models, offspring of high and low intensity
paternal donors (1-5 and 6+ donations 3 years pre-pregnancy) who were spouses to non-
donors weighed the same at birth (regression coefficient: -2.3g; 95%CI: -19.8 to 15.1;
Mothers in these analyses were all non-donors. In general, maternal donors gave birth to heavier children than non-donors (Supplementary Table 1). However, the observed effect is largely driven by low frequency donors.

Further, we evaluated all births (i.e. both first and later born children) between 1997-2012 by applying fixed effects models, random effects models, and between-within models with robust standard errors due to clustering on maternal level. As presented in supplementary Table 2, the effect of 1 extra donation per year resulted in a decrease of 10 g in birth weight; while high donation activity (at least 6 donations) prior to pregnancy was associated with a reduction in birth weight of 38.8 g (95%CI: 19.6 - 58.1). Generally, fixed effects models adjust for all un-observables that do not change over time; for example height and to some degree weight. Moreover, with a similar approach, the random effects model yielded comparable results; and the effect of donor status (donor vs non-donor) was an increase in birth weight of 45.8 g (95%CI: 42.7 – 49.0). Combining these two approaches in a between-within model resulted in similar results (supplementary Table 2), where the within effect evaluates the effect on an individual level, while between effect evaluates the effect on a population level.

**Further, due to the incremental changes in birthweight because of donation intensity, extra sub-analyses were performed with the aim of evaluating whether donation intensity was also associated with an increased risk of low birth weight (<2500 g) since clinical implications exists at this threshold18,19. Analyses indicate a statistically non-significant increased odds ratio of low birth weight if being a high frequency donor**
compared with low frequency donors (OR = 1.07; 95%CI: 0.78-1.47). However, only 1.3-1.4% of children were defined as low birth weight, thereby, reducing the power of the analyses. Moreover, supplementary analyses with either a different modelling of covariates or analyses conditioned on specific donation activity, yielded similar direction of association between donation intensity and birthweight and with effect sizes of similar magnitude (supplementary table 3).

Lastly, main analyses were performed without the first three years of birth data to evaluate whether any effect of left truncation was present. Results from these sub-analyses yielded similar results (results not shown).
Discussion

We used nation-wide data on birth characteristics and parental blood donation history to ascertain the association between pre-pregnancy donation intensity and birthweight among first born full term singletons. Our analyses showed that while offspring of female blood donors on average weighed more than offspring of non-donating women, among donating women blood donation intensity in the pre-pregnancy period was inversely associated with birth weight. Specifically, as evaluated by linear regression analysis in female blood donors, each additional annual blood donation in the three-year period before pregnancy was associated with a 10.5 g decrease in offspring birthweight. Moreover, supplementary analyses evaluating all births in the observed period yielded the same direction of associations of similar magnitude. This further corroborates our findings from our primary analyses.

The above findings illustrate the inherent challenge to studies of health effects of blood donors, coined “the healthy donor effect”\textsuperscript{28}. Accordingly, the observed higher birth weight of blood donor offspring compared with other new born children could be construed as evidence that blood donations do not influence offspring health. However, our analyses showed that this difference compared with non-donors was largely explained by the group of low frequency donors. In contrast, the mean birth weights of offspring of high intensity donors (3512 g; SD: 464 g) and of non-donors (3508 g, SD: 480 g) did not differ (p=0.62), which also reflects the magnitude of the effect of donation intensity on birth weight as the healthy donor effect would result in a larger
birthweight for donors compared with non-donors as indicated by the difference between low frequency donors and non-donors.

The inverse association between donation activity and offspring birth weight among the female donors could of course reflect a behavioural gradient between more and less active donors that is unrelated to iron deficiency and donation activity. While intuitively, one would assume such bias to reflect better health among the more active donors, we carried out parallel analyses for offspring of male blood donors to examine this. In these analyses, blood donation intensity did not associate with offspring birth weight. If similar selection mechanisms for becoming and remaining blood donors apply to men and women, this finding would favour a causal mechanism underlying the association between maternal pre-pregnancy donation intensity and offspring birth weight, possibly mediated by iron-depletion. However, the clinical implications of the marginally reduced birthweight have yet to be evaluated.

We cannot readily explain the contrasting findings between the present investigation and those of a recent Canadian investigation reporting no adverse effect of maternal pre-pregnancy donation but note a few differences in study designs and in sample size. Firstly, in our main analysis we considered only first-born singletons in our analyses, whereas the Canadian investigation applied no such restriction. There is an inverse relationship between parity and iron stores. Moreover, blood donors are not allowed to donate while pregnant or when breastfeeding. Therefore, pre-pregnancy donation
intensity may be affected, and in Denmark a notable drop in donation activity is seen for women in their late twenties and early thirties most likely due to pregnancy(ies), maternity leave (nursing), and possibly work-life balance with young children. We do not know whether the same trends for donation activity is observed in Canada, but if so the interpretation of donation activity of multiparous women prior to pregnancy may be biased.

Secondly, we only considered children born at term. Gestational age is a strong predictor of birth weight and even though model adjustment for gestational age is possible, the risk of residual confounding is greater; and investigating only children born at term gives a unique insight into the effect of pre-pregnancy donation activity without the bias of pre-term births.

Thirdly, the two studies employed different main outcomes (risk of low birth weight vs. birth weight). Therefore, our investigation using birthweight on a continuous scale would have greater statistical power compared with using risk of low birthweight as outcome. However, sub-analyses indicate a non-statistically significant increased odds ratio of low birth weight if being a high frequency donor compared with low frequency donors (OR = 1.07; 95%CI: 0.78-1.47). However, only 1.3-1.4% of children were defined as low birth weight, thereby, reducing the power of the analyses.
Co-variate information was largely similar in the Canadian and our study; differences comprised the lack of information on maternal smoking status during pregnancy and information on annual income in the Canadian study. However, these factors did not affect magnitude of the effect of donation activity in our study.

In Canada, donors are allowed to donate up to six times per year, but high frequency donors were defined as those donating at least 3 donations in a 2-year period leading up to the first observed pregnancy in the study period (1.5 donations per year), and thereby constituting approximately 20% of the included active donors with at least 1 donation in the observed time-period. However, when applying the same criteria for high donation frequency as in our study (at least 2 donations per year), the proportion of high frequency donors in the Canadian study was 9.9% compared with a proportion of 13.7% of high frequency donors in the present study. Therefore, it appears that the donation frequency in the Canadian study was somewhat lower than in the current study.

The literature on birth weight in non-donor populations is quite clear; observational studies suggest that maternal anaemia during pregnancy is associated with lower birth weight\textsuperscript{31,32}. Moreover, trials with supplemental iron during pregnancy indicate that the risk of low birth weight decreases\textsuperscript{8}, and total iron intake in the first trimester has been positively associated with birth weight\textsuperscript{9}. The mechanism for this association, however, has not been elucidated\textsuperscript{32}.
Our investigation has several strengths, including a large sample size and independent and unbiased information as ascertained from national registers on both exposures and potential confounders, few of which proved relevant to our analyses. However, our study has also limitations. In particular, we did not include information on maternal body mass index in our analyses, which might therefore have confounded the observed difference between low frequency donors and non-donors since female blood donors weigh more than non-donating women\(^3\). However, we observed no association between BMI and donation intensity in the Danish Blood Donor Study (unpublished findings).

**Conclusion**

Our results show that high pre-pregnancy donation intensity is inversely associated with birth weight of singletons born at term to nulliparous women. The incremental changes in birth weight associated with incremental changes in donation intensity appears not to be reflected in an increased risk of low birth weight. However, more research is warranted. We suggest that the relation to iron depletion and the clinical impact of the differences identified be clarified. All donors should understand the potential impact of blood donation on iron stores. Options to prevent or reduce iron depletion in female donors of childbearing age include: Restricting the number of allowable annual donations to conform with our low intensity cohort; measurement of iron stores and
response to levels consistent with iron depletion; and/or facilitating access to replacement iron for those donors who desire continuing high intensity donation.

Table 1:

<table>
<thead>
<tr>
<th>Variables</th>
<th>Non donor (1)</th>
<th>Low frequency donor (2)</th>
<th>High frequency donor (3)</th>
<th>1vs2</th>
<th>1vs3</th>
<th>2vs3</th>
</tr>
</thead>
<tbody>
<tr>
<td>N percent</td>
<td>268,253</td>
<td>22,120</td>
<td>3,524</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mater age*</td>
<td>27.6 (4.5)</td>
<td>28.2 (3.9)</td>
<td>29.3 (3.9)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoker (%)</td>
<td>19.1</td>
<td>10.3</td>
<td>9.6</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.20</td>
</tr>
<tr>
<td>Education in years (mater) †</td>
<td>14 (13;16)</td>
<td>14 (13;16.5)</td>
<td>14.5 (13.8;16.5)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Paternal age*</td>
<td>30.2 (5.5)</td>
<td>30.6 (4.9)</td>
<td>31.6 (5.0)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Education in years (pater) †</td>
<td>14 (13;15)</td>
<td>14.5 (13;16)</td>
<td>14.5 (13.5;16)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.026</td>
</tr>
<tr>
<td>Birth weight*</td>
<td>3508 (480)</td>
<td>3538 (470)</td>
<td>3512 (464)</td>
<td>&lt;0.001</td>
<td>0.62</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Legend Table 2: Characteristics of the study population. *Mean with standard deviation †Median and 25 and 75 percentiles. Non-donors were defined as having no previous donation activity; Low-frequency donors were defined as having at
least 1 donation and less than 6 donations 3 years prior to the first pregnancy; high-frequency donors were defined as having at least 6 donation 3 years prior to the first pregnancy. All mothers were nulliparous women and gave birth to a live singleton after the completion of gestational week 37.

Table 2:

<table>
<thead>
<tr>
<th>Time span before birth</th>
<th>RC</th>
<th>95%CI</th>
<th>p</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 years (1 extra donation per year)</td>
<td>-10.5</td>
<td>-17.7; -3.3</td>
<td>0.004</td>
<td>25,644</td>
</tr>
<tr>
<td>5 years (1 extra donation per year)</td>
<td>-8.7</td>
<td>-16.0; -1.5</td>
<td>0.018</td>
<td>33,449</td>
</tr>
<tr>
<td>7 years (1 extra donation per year)</td>
<td>-10.7</td>
<td>-19.2; -2.3</td>
<td>0.013</td>
<td>37,305</td>
</tr>
<tr>
<td>No period (per extra donation)</td>
<td>-1.2</td>
<td>-2.1; -0.4</td>
<td>0.005</td>
<td>45,930</td>
</tr>
</tbody>
</table>

Legend: Results from the linear regression analysis with birth weight (g) as outcome (RC = regression coefficient) and adjusted as explained in the statistical section.

Table 3:

<table>
<thead>
<tr>
<th>Time span before birth</th>
<th>RC</th>
<th>95%CI</th>
<th>p</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 years (at least 6 donations)</td>
<td>-20.2</td>
<td>-35.3; -5.1</td>
<td>0.009</td>
<td>25,644</td>
</tr>
</tbody>
</table>
Legend: Results from the linear regression analysis with birth weight (g) as outcome (RC = regression coefficient) and adjusted as explained in the statistical section. * due to an extremely low number of individuals with at least 14 donations in 7 years, we chose a cut-off which still reflect high donation intensity and which also had sufficient power for these analyses.

References:


