Transfusion of ever-pregnant donor red blood cells and mortality of male patients

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SUPPLEMENTAL MATERIALS

Title: Transfusion of ever-pregnant donor red blood cells and mortality of male patients

This document contains additional figures and tables for the manuscript “Transfusion of ever-pregnant donor red blood cells and mortality of male patients”.

Contents

Supplemental methods

Exposure

Information was collected on the date of birth of all offspring and the sex of the biological offspring. If the date of birth preceded the date of transfusion, and the child was determined to be biological offspring (which was determined by comparing the date of birth with the date of start of the family relation), the donor was classified as 'ever-pregnant', with sons and/or daughters, respectively.

Three comparisons were performed (outlined in *Figure 1*). Comparison 3 acts as a control comparison for the study hypothesis, because exposure to blood products from female donors with daughters was not expected to be associated with mortality. All exposure information was obtained from the BRP at the date of donation for every female donor, and from the blood bank information system for the male donors.

Comparison 1 can be considered a comprehensive reproduction study of the earlier found association between ever-pregnant donors and mortality, as it uses the same exposure and outcome as have been previously reported in a partially overlapping cohort (period January 1st 2005-September 1st 2015).[1] Comparisons 2 and 3 pertain to different exposures that have not been described elsewhere previously and should therefore be viewed as an independent analysis.[1,2] Analyses were also performed separately for the population aged ≥18 years to have a study population that is comparable with other studies.

Outcome

The study outcome was all-cause mortality. Mortality data were obtained from the hospital administration at the hospital's end of data collection or the administrative end of study (1/1/2019).[1,2]

Covariates

Although the MATER study is an observational study, we expected that the potential for confounding in this study was small. As the information about donor sex and pregnancy is not available to treating physicians, in practice red blood cell units are allocated independently of donor characteristics (notably, sex and parity of the donor).

However, the logistics of the distribution of blood products depend on a number of factors that we consider to be potential confounders (*Figure S1*). Hospital (categorical, six levels) is considered a potential confounder, because it is associated with mortality and can become associated with exposure through geographical differences in product distribution. Year (continuous) is a potential confounder, because (1) mortality risk following transfusions varies over time due to more restrictive transfusion policies becoming the norm, and (2)

characteristics of the donor population vary over time[3,4]. Blood group (categorical variable, 9 levels) is another potential confounder, because it is associated with mortality and because some blood groups are rare, the distribution of donor factors can differ between blood groups. All information on potential confounders was obtained from hospital administration and the R-FACT study at baseline.[2,5]

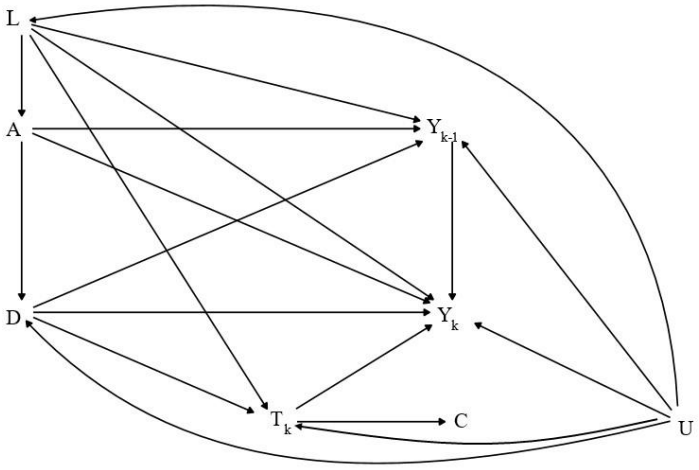


Figure S1. Directed acyclic graph of the effect of product characteristics (donor pregnancy and sex of the offspring) on mortality

In Figure S1, A represents assignment to study arm at time *k-1*. L represents the set of 'center' variables consisting of year of transfusion, hospital and patient blood group. These center variables together influence the receival of a next transfusion and the risk of mortality of the patient, and are therefore a sufficient set for adjustment of the confounding at study start. D is a mediator, here influenced by treatment arm A and on the causal path of A to Y, and stands for the dose of hemoglobin received by the patient after the transfusion at time *k-1*. T_k represents the receival of a next transfusion. C stands for censoring of the patient following receival of the transfusion, and in the population where follow-up is limited to time until mixture of arms, C is conditioned on by design. This conditioning is removed by weighing the population by the inverse probability of censoring weights estimated with T_k. Y_{k-1} and Y_k represent mortality at timepoints *k-1* and *k*, respectively. U is a vector containing all unmeasured covariates that could influence mortality (e.g. disease severity of patients at *k-1* and *k*), hemoglobin dose received (blood bank logistic factors), center variables (patient population differences between centers) and the probability of receiving additional transfusions.

Follow-up

Follow-up started with the first receipt of a transfusion during study period (starting 1/1/2005) and ended when patients were censored, which was at the time of death, time of transfusion from different exposure group, or administrative end of study (1/1/2019), whichever came first. Patients could only contribute follow-up to the analyses if they received all their transfusions from the same exposure category on their first day.

Statistical analysis

To be able to compare the effect of the abovementioned different exposure categories, patients were censored at the time they received a transfusions from a different category than their previously received transfusions. This resulted in patients receiving more transfusions (and thus more likely to have a worse prognosis) being more likely to be censored, a phenomenon known as *informative censoring.*[6] Furthermore, the possibility exists that *treatment-confounder feedback* by hemoglobin present in the blood product further exacerbates the already existing bias in any analysis not adjusted for informative censoring.[7] This is because blood products from female donors have a consistently lower hemoglobin content compared to male donors, and this difference is not adjusted during the production process of red blood cell units in the Netherlands.[8] If chosen as exposure, any variable which affects the hemoglobin dose of the product may lead to bias if not accounted for correctly, because the hemoglobin dose of the product affects (in part) the time to next transfusion, and the number of transfusions is associated with underlying disease severity. As women have a lower normal level of hemoglobin compared to men, treatment-confounder feedback should be accounted for in the analyses.

To correct for both confounding at baseline, and the informative censoring during follow-up and treatment-confounder feedback, inverse probability weighting was applied in three steps. First, a propensity score was estimated based on the identified potential confounders using a logistic model with exposure (i.e., assignment to either exposure arm or reference arm) as the dependent variable. Second, to correct for the censoring upon receiving a transfusion from a different exposure category, a propensity-score weighted pseudo-population was created in which further inverse probability of censoring weights (IPCW) were estimated. Weights were constructed per transfusion day for the first 28 days, and per 4-weekly interval thereafter, using a Cox model with the cumulative number of transfusions as continuous covariate. The IPCW estimator (predicted probability of censoring) corrects for censored subjects by redistributing weights of similar censored and uncensored patients when used to calculate the survival probabilities. As censoring, due to reaching the end of follow-up at the reference date of the hospital, is not influenced by patient characteristics, this information was not included in the censoring model. Instead, we developed a censoring model for time to non-administrative censoring only. Third, the propensity score was multiplied with the censoring score to obtain the final weights.[9-11] Weights were trimmed at a fixed level of 10, to reduce instability of the IPW estimator. Weighted marginal structural Cox models were fitted using the R packages *ipw* and *survey*.[11]

Analyses were stratified by patient sex and age, in line with previous studies.[1,12] Completely separate models were specified for the stratified analyses, in order to be able to model the

relation between the confounders and the outcome in these subgroups with greater detail. We consider age as a proxy for transfusion indication, with young male patients more often receiving transfusions for trauma and massive transfusion.[13] Age categories were defined as 0-17, 18-50, 51-70 and over 70 years of age. This analysis was repeated in the independent cohort of data collected after 1st of September 2015 to the 1st of January 2019, and can be viewed as an effort to independently replicate the previous findings of Caram-Deelder et al. which included data up to 1st of September 2015.[1]

In sensitivity analysis I, hazard ratios were calculated using standard Cox PH survival analysis. This analysis was performed to compare with previous work[1,12] and to empirically assess the necessity of accounting for treatment-confounder feedback. Three ways of specifying the included study population were analyzed (*Figure S2*). In the full cohort analysis, exposures from the concerned reference and exposure could be mixed, and censoring took place when a patient received an exposure from a different exposure category. In the no-mixture cohort, patients were censored when they received a transfusion from a different exposure category than the one of their first transfusion. In the single transfusion cohort, patients were censored when they received a second transfusion. Cox proportional hazards models were fitted, adjusted for:

- cumulative number of transfusions [time-varying, restricted cubic spline with five knots];
- hospital [fixed];
- blood group [fixed];
- calendar year [fixed];
- age of the donor [time-varying, cumulative number of units from donors aged ≥50 years];
- interaction term for cumulative number of transfusions and hospital [time-varying].

In sensitivity analysis II, when products from female donors with uncertainty about their offspring (due to BRP records being less complete before 1958) were transfused, patients were censored. Sensitivity analysis III was repeated for the independent cohort of patients included after 1st of September 2015 to the 1st of January 2019, and can be viewed as an effort to independently replicate the previous findings of Caram-Deelder et al.[1] Other sensitivity analyses included censoring at the time a product from a donor with both sons and daughters was given (sensitivity analysis IV.), and censoring for both the donor with sons and daughters and the exclusion of never-pregnant women from the exposure groups (sensitivity analysis V.).

Supplemental results

Additional results for the manuscript are presented here. In brief, Table S2 contains donor and patient characteristics for the cohorts used in the sensitivity analyses. Table S3 contains donor

and patient characteristics of the study population aged ≥18 years. Table S4 contains the results for the main analysis for the study population aged ≥18 years.

Results for the analysis stratified by patient age for female patients are reported in Table S5.

Results for the analysis in the independent cohort included after 1st of September 2015 stratified by patient age for male patients are reported in Table S6. Results for the analysis in the independent cohort included after 1st of September 2015 stratified by patient age for female patients are reported in Table S7.

Results for the sensitivity analyses are reported in Tables S8-11. The following figure provides a visual aid for the content of tables S8-11:

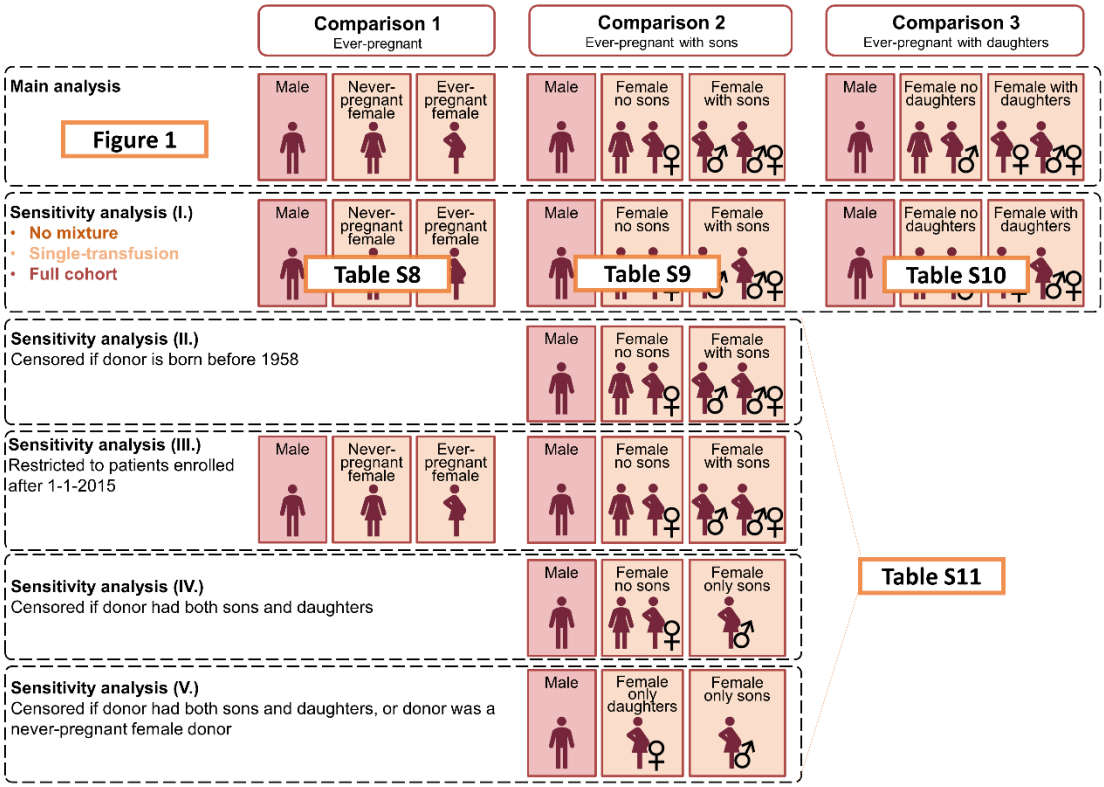


Figure S2. Schematic representation of exposure definition in sensitivity analyses and corresponding tables

Table S12 contains results for the comparison of exposure categories as assigned on the first day for the complete study population.

Table S13 contains the distribution of the weights prior to truncation, for the population of male and female patients in the primary analysis, comparison 1.

Table S14 contains patient and exposure characteristics, including the proportion of patients from each hospital, year, blood group and number of transfusions stratified by sex and age of the patient.

Table S15 contains the proportions of censoring and length of follow-up stratified by sex and age.

Figure S3. Absolute standardized mean differences of patient characteristics for comparison 1

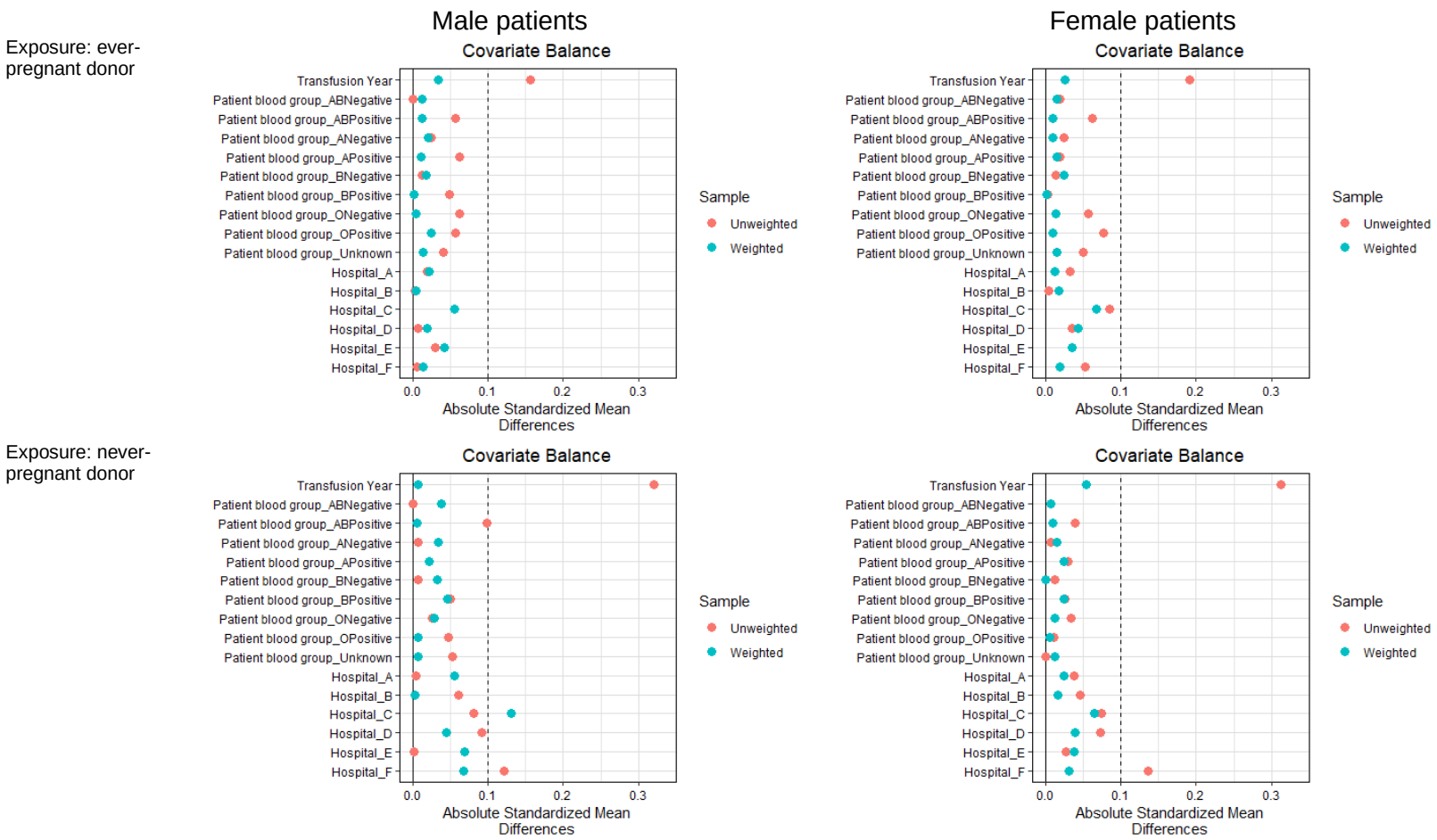


Figure S4. Absolute standardized mean differences of patient characteristics for comparison 1, stratified by patient age, for male patients

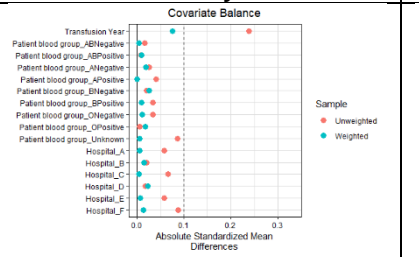
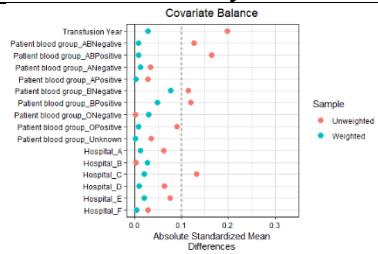
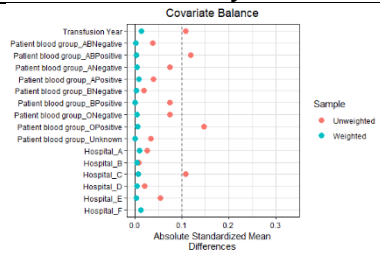
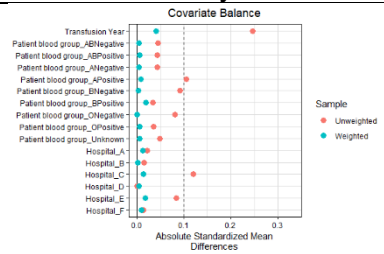
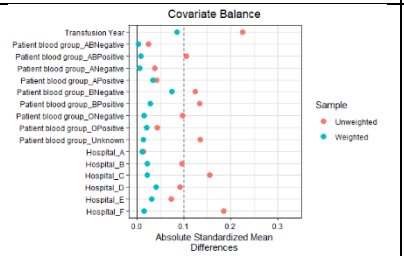
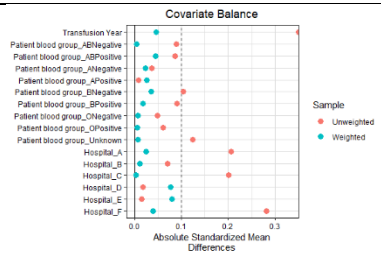
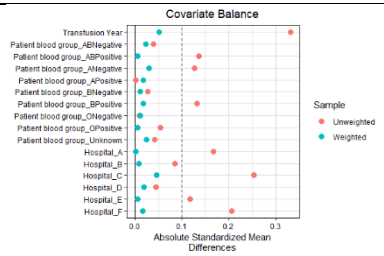
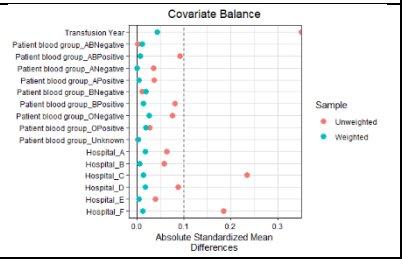
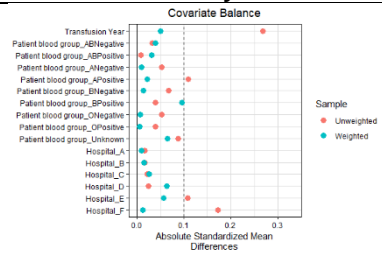
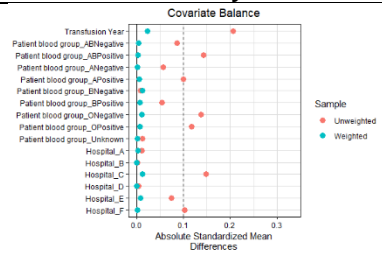
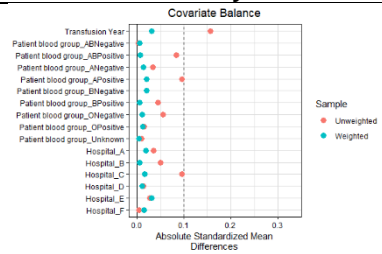
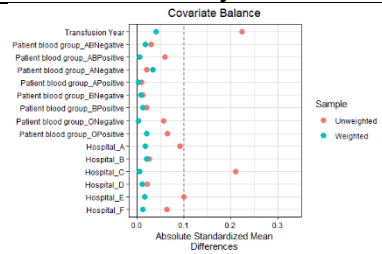
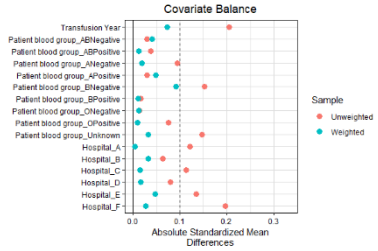
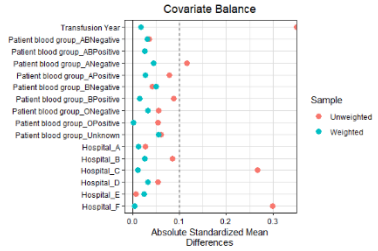
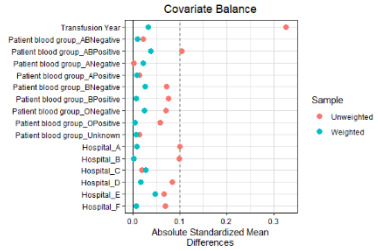
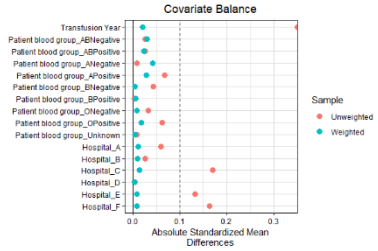
	0-17 y	18-50 y	51-70 y	≥71 y
Exposure: ever-pregnant donor				
Exposure: never-pregnant donor				

Figure S5. Absolute standardized mean differences of patient characteristics for comparison 1, stratified by patient age, for female patients

	0-17 y	18-50 y	51-70 y	≥71 y
Exposure: ever-pregnant donor				
Exposure: never-pregnant donor				

Sensitivity analyses

Sensitivity analyses were performed to verify the previously described assumptions about the data and the used methods, and results can be found in Tables S7-10.

Sensitivity analysis I was performed on the full cohort, the no-mixture of exposure cohort and the single-transfusion cohort, which are reported on in *Table S7* (comparison 1), *Table S8* (comparison 2) and *Table S9* (comparison 3). Of these, exposure to ever-pregnant donors, ever-pregnant donors with sons and ever-pregnant donors with daughters was not associated with mortality in the full cohort (comparison 1: HR 1.02 (1.00-1.05); comparison 2: HR 1.01 (95% CI 0.98-1.05); comparison 3: HR 1.03 (95% CI 0.99-1.06)). In the no-mixture cohort, exposure to ever-pregnant donors was significantly associated with mortality (HR 1.05 (95% CI 1.00-1.09), but exposure to ever-pregnant donors with sons and ever-pregnant donors with daughters was not (comparison 2: HR 1.04 (95% CI 0.98-1.10); comparison 3: HR 1.04 (95% CI 0.98-1.11)). The single-transfusion cohort had the comparatively largest effect sizes for exposure to ever-pregnant donors, ever-pregnant donors with sons and ever-pregnant donors with daughters (comparison 1: HR 1.14 (95% CI 1.02-1.28); comparison 2: HR 1.11 (95% CI 0.98-1.26); comparison 3: HR 1.13 (95% CI 0.99-1.28)). Of note, these analyses are performed with exposure as a continuous variable as opposed to the main analysis, and the HRs should be interpreted as the HR for a one-unit increase in the exposure category, compared to reference.

Results for sensitivity analyses II-V can be found in *Table S10*. Exposure to ever-pregnant donors with sons born after 1958 was not associated with mortality (HR 0.87 (95% CI 0.76-1.00)). Exposure to ever-pregnant donors and ever-pregnant donor with sons was not associated with mortality in the study population included after September 1st 2015 (comparison 1: HR 0.87 (95% CI 0.68-1.11)); comparison 2: HR 0.83 (95% CI 0.63-1.10)). Exposure to ever-pregnant donors with sons, without daughters, was not associated with mortality (HR 0.94 (95% CI 0.78-1.13)).

Supplemental tables

Table S1. Censored patients and follow-up of patients in the complete dataset and primary analysis, by exposure group

	Complete dataset*		Primary analysis	
Characteristics	**Male patients**	**Female patients**	**Male patients**	**Female patients**
Number of patients	N=48,538	N=50,138	N=28,115	N=28,710
Arm: male	36,439†	37,762†	18,367	18,964
Arm: ever-pregnant	20,905†	21,219†	6,274	6,218
Arm: never-pregnant	14,347†	14,712†	3,474	3,528
Number of patients censored on day 1, (%)	-	-	20,423 (42%)	21,428 (43%)
Number of patients censored during follow-up, (%)	-	-	8,246 (29%)	8,030 (28%)
Arm: male, (%)	-	-	3,447 (42%)	3,376 (42%)
Arm: ever-pregnant, (%)	-	-	2,874 (35%)	2,722 (34%)
Arm: never-pregnant, (%)	-	-	1,925 (23%)	1,932 (24%)
Follow-up, median (IQR), days‡	1,081 (230-2,415)	1,372 (373-2,662)	151 (6-1,597)	434 (11-2,007)
Arm: male	1,380 (337-2,691)	1,609 (496-2,849)	244 (9-1,817)	617 (22-2,227)
Arm: ever-pregnant	1,142 (298-2,388)	1,383 (427-2,499)	48 (4-1,208)	170 (4-1,592)
Arm: never-pregnant	1,064 (308-2,221)	1,111 (348-2,260)	33 (3-1,020)	120 (3-1,247)

*In the complete dataset, all follow-up from patients is included and no censoring takes place

†In the complete dataset, patients could receive different exposures on day 1, and these can therefore classified into multiple arms.

Table S2. Patient and transfusion characteristics for the Sensitivity Analyses

Characteristics	Full cohort		No-donor mixture cohort*		Single-transfusion cohort†	
	Male patients	Female patients	Male patients	Female patients	Male patients	Female patients
Number of patients	N=42,996	N=44,850	N=28,115	N=28,710	N=17,403	N=16,705
Number of deaths, (%)	15,817 (37%)	13,557 (30%)	4,280 (15%)	4,008 (14%)	1,610 (9%)	1,420 (9%)
Follow-up, median (IQR), days‡	606 (40-2,078)	978 (112-2,421)	151 (6-1,597)	434 (11-2,007)	18 (2-1,142)	28 (2-1,326)
Person-time, sum in years	137,590	171,123	69,558	85,898	34,037	35,343
Age of patients, median (IQR), years	65 (49-75)	65 (41-77)	64 (39-75)	65 (36-77)	62 (2-74)	63 (11-77)
0 to 17	6,490 (15%)	5,246 (12%)	5,931 (21%)	4,819 (17%)	5,386 (31%)	4,345 (26%)
18 to 50	4,726 (11%)	8,888 (20%)	2,644 (9%)	4,865 (17%)	1,278 (7%)	1,983 (12%)
51 to 70	16,086 (37%)	12,921 (29%)	9,687 (34%)	7,787 (27%)	5,058 (29%)	4,064 (24%)
≥71	15,694 (37%)	17,795 (40%)	9,853 (35%)	11,239 (39%)	5,681 (33%)	6,313 (38%)
Transfusions of red blood cell units per patient, median (IQR)	2 (2-4)	2 (2-4)	2 (1-2)	2 (1-2)	1 (1-1)	1 (1-1)
Units of red blood cells transfused, Number (%)§	136,586	130,552	49,992	51,052	17,403	16,705
female donor, never-pregnant	15,404 (11%)	15,480 (12%)	4,467 (9%)	4,648 (9%)	2,776 (16%)	2,704 (16%)
female donor, ever-pregnant, male offspring	24,226 (18%)	22,892 (18%)	6,602 (13%)	6,721 (13%)	3,382 (19%)	3,292 (20%)
female donor, ever-pregnant, no male offspring	23,114 (17%)	22,762 (17%)	6,644 (13%)	6,749 (13%)	3,930 (23%)	3,730 (22%)
male donor	88,779 (65%)	84,438 (65%)	36,662 (73%)	37,447 (73%)	10,028 (58%)	9,622 (58%)

* Consists of all the follow-up time during which patients either received all their red blood cell transfusions exclusively from one exposure category: female donors without a history of pregnancy (never-pregnant donors), female donors with a history of pregnancy (ever-pregnant donors, with or without sons), or male donors. The main analysis uses this cohort definition.
† Consists of patients with only a single red blood cell transfusion during the period in which they were followed up. Follow-up time will be censored at the time this inclusion criterion was violated.
‡ Median follow-up time is defined as the longest time any patient is in one of the comparisons. Exposure categories are: female donors without a history of pregnancy (never-pregnant donors), female donors with a history of pregnancy (ever-pregnant donors, with or without sons), male donors.
§ Includes units from female donors with offspring of unknown sex

Table S3. Patient and transfusion characteristics for the analysis with patients aged ≥18 years

Characteristics	Complete dataset		Main analysis*	
	Male patients	Female patients	Male patients	Female patients
Number of patients	41,857	44,743	22,184	23,891
Number of deaths, (%)	17,482 (42%)	14,709 (33%)	3,993 (18%)	3,777 (16%)
Follow-up, median (IQR), days‡	956 (193-2,299)	1,309 (349-2,626)	95 (5-1,305)	393 (9-1,907)
Person-time, sum in years	157,340	195,710	49,169	69,219
Age of patients, median (IQR), y	68 (58-76)	68 (52-78)	69 (59-77)	69 (55-79)
18 to 50	5,626 (13%)	10,295 (23%)	2,644 (12%)	4,865 (20%)
51 to 70	18,412 (44%)	14,636 (33%)	9,687 (44%)	7,787 (33%)
≥71	17,819 (43%)	19,812 (44%)	9,853 (44%)	11,239 (47%)
Transfusions of red blood cell units per patient, median (IQR)	3 (2-7)	3 (2-5)	2 (1-2)	2 (1-2)
Units of red blood cells transfused, Number (%)§	276,985	224,547	41,175	43,851
female donor, never-pregnant	46,566 (17%)	37,771 (17%)	3,719 (9%)	3,951 (9%)
female donor, ever-pregnant, male offspring	53,957 (19%)	43,375 (19%)	5,146 (12%)	5,503 (13%)
female donor, ever-pregnant, no male offspring	16,902 (6%)	13,822 (6%)	1,730 (4%)	1,721 (4%)
male donor	157,658 (57%)	127,954 (57%)	30,492 (74%)	32,561 (74%)

* Consists of all the follow-up time during which patients either received all their red blood cell transfusions exclusively from one exposure category: female donors without a history of pregnancy (never-pregnant donors), female donors with a history of pregnancy (ever-pregnant donors, with or without sons), or male donors. The main analysis uses this cohort definition.
† Consists of patients with only a single red blood cell transfusion during the period in which they were followed up. Follow-up time will be censored at the time this inclusion criterion was violated.
‡ Median follow-up time is defined as the longest time any patient is in one of the comparisons. Exposure categories are: female donors without a history of pregnancy (never-pregnant donors), female donors with a history of pregnancy (ever-pregnant donors, with or without sons), male donors.
§ Includes units from female donors with offspring of unknown sex.

Table S4. Mortality Hazard Ratio of Male and Female Transfusion Recipients in the Analysis with Patients Aged ≥18 Years, Comparisons 1, 2 and 3

Donor category	Male recipients			Female recipients		
	No. of Deaths	No. of Recipients	HR (95% CI)	No. of Deaths	No. of Recipients	HR (95% CI)
Comparison 1						
Male (reference)	2,881	14,665	1 (reference)	2,752	16,028	1 (reference)
Female, ever-pregnant	744	4,696	0.99 (0.92-1.09)	636	4,935	0.95 (0.87-1.05)
Female, never-pregnant	368	2,823	0.87 (0.78-0.98)	389	2,928	1.03 (0.92-1.16)
Comparison 2						
Male (reference)	2,881	14,665	1 (reference)	2,752	16,028	1 (reference)
Female, ever-pregnant with sons	468	3,135	0.98 (0.88-1.08)	423	3,353	0.99 (0.89-1.11)
Female, never-pregnant with sons	604	4,173	0.95 (0.86-1.04)	577	4,315	0.98 (0.89-1.08)
Comparison 3						
Male (reference)	2,881	14,665	1 (reference)	2,752	16,028	1 (reference)
Female, ever-pregnant with daughters	465	3,191	0.99 (0.89-1.10)	396	3,292	0.91 (0.82-1.02)
Female, never-pregnant with daughters	607	4,154	0.93 (0.85-1.02)	591	4,398	1.00 (0.90-1.10)

Table S5. Mortality Hazard Ratio of Female Transfusion Recipients Exposed to Red Blood Cell Transfusions From Female (Never-Pregnant or Ever-Pregnant) vs Male Donors Stratified by Patient Age

Donor category	0-17 y			18-50 y			51-70 y			≥71 y			p value for interaction
	No. of Deaths	No. of Recipients	HR (95% CI)	No. of Deaths	No. of Recipients	HR (95% CI)	No. of Deaths	No. of Recipients	HR (95% CI)	No. of Deaths	No. of Recipients	HR (95% CI)	
Comparison 1													
Male (reference)	152	2,936	1 (reference)	180	3,425	1 (reference)	858	5,232	1 (reference)	1,714	7,371	1 (reference)	
Female, ever-pregnant	50	1,283	0.76 (0.54-1.06)	37	895	1.02 (0.71-1.48)	188	1,647	0.86 (0.72-1.02)	411	2,393	0.94 (0.84-1.06)	0.6797
Female, never-pregnant	29	600	1.33 (0.73-2.40)	24	545	1.36 (0.85-2.16)	104	908	0.85 (0.68-1.03)	261	1,475	1.01 (0.87-1.18)	0.0150
Comparison 2													
Male (reference)	152	2,936	1 (reference)	180	3,425	1 (reference)	858	5,232	1 (reference)	1,714	7,371	1 (reference)	
Female, ever-pregnant with sons	34	955	0.69 (0.47-1.03)	28	592	1.28 (0.84-1.96)	121	1,118	0.87 (0.71-1.08)	274	1,643	0.97 (0.84-1.11)	0.2440
Female, never-pregnant with sons	43	899	1.10 (0.75-1.62)	38	827	1.26 (0.87-1.83)	167	1,383	0.88 (0.73-1.06)	372	2,105	0.94 (0.83-1.06)	0.0686
Comparison 3													
Male (reference)	152	2,936	1 (reference)	180	3,425	1 (reference)	858	5,232	1 (reference)	1,714	7,371	1 (reference)	
Female, ever-pregnant with daughters	30	936	0.64 (0.43-0.97)	20	586	0.88 (0.54-1.43)	125	1,150	0.84 (0.68-1.03)	251	1,556	0.90 (0.78-1.04)	0.8156
Female, never-pregnant with daughters	46	907	1.15 (0.75-1.77)	31	833	1.07 (0.71-1.60)	163	1,374	0.89 (0.74-1.07)	397	2,191	1.00 (0.88-1.13)	0.1313

Table S6. Mortality Hazard Ratio of Male Transfusion Recipients Exposed to Red Blood Cell Transfusions From Female (Never-Pregnant With or Ever-Pregnant) vs Male Donors Stratified by Patient Age for Patients included after 1st of September 2015

Donor category	0-17 y			18-50 y			51-70 y			≥71 y			p value for interaction
	No. of Deaths	No. of Recipients	HR (95% CI)	No. of Deaths	No. of Recipients	HR (95% CI)	No. of Deaths	No. of Recipients	HR (95% CI)	No. of Deaths	No. of Recipients	HR (95% CI)	
Comparison 1													
Male (reference)	36	626	1 (reference)	24	321	1 (reference)	138	1,207	1 (reference)	243	1,325	1 (reference)	
Female, ever-pregnant	14	321	0.77 (0.40-1.47)	14	107	2.45 (1.13-5.30)	39	453	0.81 (0.54-1.20)	78	534	1.01 (0.75-1.36)	0.0027
Female, never-pregnant	4	135	0.93 (0.29-3.02)	3	94	0.92 (0.25-3.40)	29	382	0.73 (0.46-1.14)	64	398	1.21 (0.88-1.64)	0.2249
Comparison 2													
Male (reference)	36	626	1 (reference)	24	321	1 (reference)	138	1,207	1 (reference)	243	1,325	1 (reference)	
Female, ever-pregnant with sons	11	243	0.83 (0.40-1.72)	10	72	2.44 (1.04-5.70)	26	309	0.88 (0.55-1.41)	50	374	0.90 (0.63-1.29)	0.0155
Female, never-pregnant with sons	7	213	0.86 (0.34-2.13)	7	122	1.28 (0.52-3.15)	44	542	0.91 (0.59-1.39)	92	559	1.16 (0.89-1.52)	0.5243
Comparison 3													
Male (reference)	36	626	1 (reference)	24	321	1 (reference)	138	1,207	1 (reference)	243	1,325	1 (reference)	
Female, ever-pregnant with daughters	14	253	0.98 (0.51-1.89)	8	77	2.22 (0.94-5.27)	26	316	0.76 (0.48-1.21)	58	382	1.12 (0.82-1.55)	0.0342
Female, never-pregnant with daughters	5	205	0.81 (0.28-2.32)	7	122	0.97 (0.37-2.54)	40	507	0.80 (0.54-1.20)	78	551	1.01 (0.76-1.35)	0.7276

Table S7. Mortality Hazard Ratio of Female Transfusion Recipients Exposed to Red Blood Cell Transfusions From Female (Never-Pregnant or Ever-Pregnant) vs Male Donors Stratified by Patient Age for Patients included after 1st of September 2015

Donor category	0-17 y			18-50 y			51-70 y			≥71 y			p value for interaction
	No. of Deaths	No. of Recipients	HR (95% CI)	No. of Deaths	No. of Recipients	HR (95% CI)	No. of Deaths	No. of Recipients	HR (95% CI)	No. of Deaths	No. of Recipients	HR (95% CI)	
Comparison 1													
Male (reference)	19	483	1 (reference)	18	571	1 (reference)	113	1,008	1 (reference)	163	1,304	1 (reference)	
Female, ever-pregnant	9	276	0.88 (0.25-3.09)	4	187	0.72 (0.24-2.22)	42	408	1.26 (0.85-1.88)	53	530	1.06 (0.73-1.55)	0.7541
Female, never-pregnant	9	139	2.10 (0.66-6.72)	4	146	1.31 (0.40-4.27)	23	275	0.89 (0.54-1.47)	50	412	1.10 (0.74-1.62)	0.0174
Comparison 2													
Male (reference)	19	483	1 (reference)	18	571	1 (reference)	113	1,008	1 (reference)	163	1,304	1 (reference)	
Female, ever-pregnant with sons	6	194	0.87 (0.23-3.27)	3	121	1.00 (0.28-3.64)	27	275	1.30 (0.80-2.10)	38	370	1.25 (0.82-1.93)	0.9437
Female, never-pregnant with sons	13	218	1.67 (0.60-4.63)	9	206	1.69 (0.71-4.03)	33	393	0.80 (0.48-1.31)	63	562	1.05 (0.67-1.65)	0.0192
Comparison 3													
Male (reference)	19	483	1 (reference)	18	571	1 (reference)	113	1,008	1 (reference)	163	1,304	1 (reference)	
Female, ever-pregnant with daughters	7	208	0.98 (0.28-3.44)	3	121	0.87 (0.25-3.08)	28	304	1.15 (0.72-1.83)	31	360	0.81 (0.52-1.27)	0.5285
Female, never-pregnant with daughters	12	203	1.85 (0.65-5.25)	5	214	1.03 (0.36-2.92)	33	279	0.91 (0.58-1.43)	69	563	1.08 (0.76-1.54)	0.0395

Table S8. Comparison 1: Mortality Hazard Ratio of Male and Female Transfusion Recipients Exposed to Red Blood Cell Transfusions From Female (Never-Pregnant or Ever-Pregnant) Donors vs Male Donors (Sensitivity Analysis I.)

Donor category	Male recipients			Female recipients		
	No. of Deaths	No. of Recipients	HR (95% CI)	No. of Deaths	No. of Recipients	HR (95% CI)
Full cohort						
Female, ever-pregnant analysis						
Male (reference)	7,203	29,879	1 (reference)	6,517	30,916	1 (reference)
Female, ever-pregnant	4,958	19,771	1.02 (1-1.05)	4,299	19,726	1.02 (1-1.05)
Female, never-pregnant analysis						
Male (reference)	4,850	26,162	1 (reference)	4,850	26,162	1 (reference)
Female, never-pregnant	2,403	11,467	1.02 (0.97-1.06)	2,364	11,888	1.03 (0.99-1.07)
No mixture of exposure						
Male (reference)	3,068	18,367	1 (reference)	2,904	18,964	1 (reference)
Female, ever-pregnant	823	6,274	1.05 (1-1.09)	686	6,218	1 (0.95-1.04)
Female, never-pregnant	389	3,474	1.00 (0.93-1.08)	418	3,528	1.08 (1.01-1.16)
Single-transfusion						
Male (reference)	911	10,028	1 (reference)	823	9,622	1 (reference)
Female, ever-pregnant	447	4,599	1.14 (1.02-1.28)	353	4,379	1.01 (0.89-1.15)
Female, never-pregnant	252	2,776	1.03 (0.90-1.19)	244	2,704	1.13 (0.98-1.31)

Table S9. Comparison 2: Mortality Hazard Ratio of Male and Female Transfusion Recipients Exposed to Red Blood Cell Transfusions From Female (Never-Pregnant With Male Offspring or Ever-Pregnant With Male Offspring) Donors vs Male Donors (Sensitivity Analysis I.)

Donor category	Male recipients			Female recipients		
	No. of Deaths	No. of Recipients	HR (95% CI)	No. of Deaths	No. of Recipients	HR (95% CI)
Full cohort						
Female, ever-pregnant with sons analysis						
Male (reference)	5,698	26,426	1 (reference)	5,245	27,433	1 (reference)
Female, ever-pregnant	3,149	14,006	1.01 (0.98-1.05)	2,798	14,019	1.04 (1-1.08)
Female, never-pregnant, no sons analysis						
Male (reference)	6,266	28,032	1 (reference)	5,871	29,281	1 (reference)
Female, never-pregnant with sons	3,843	16,560	1.03 (1-1.07)	3,587	17,017	1.02 (0.98-1.05)
No mixture of exposure						
Male (reference)	3,068	18,367	1 (reference)	2,904	18,964	1 (reference)
Female, ever-pregnant with sons	519	4,301	1.04 (0.98-1.10)	457	4,308	1.02 (0.96-1.09)
Female, never-pregnant with sons*	645	5,209	1.04 (0.98-1.10)	620	5,214	1.03 (0.98-1.09)
Single-transfusion						
Male (reference)	911	10,028	1 (reference)	823	9,622	1 (reference)
Female, ever-pregnant with sons	320	3,382	1.11 (0.98-1.26)	261	3,292	1 (0.87-1.15)
Female, never-pregnant with sons*	371	3,930	1.08 (0.96-1.22)	329	3,730	1.11 (0.97-1.26)

* Combined category of products from Female, never-pregnant donors and Female, ever-pregnant donors without sons.

Table S10. Comparison 3: Mortality Hazard Ratio of Male and Female Transfusion Recipients Exposed to Red Blood Cell Transfusions From Female (Never-Pregnant With Female Offspring or Ever-Pregnant With Female Offspring) Donors vs Male Donors (Sensitivity Analysis I.)

Donor category	Male recipients			Female recipients		
	No. of Deaths	No. of Recipients	HR (95% CI)	No. of Deaths	No. of Recipients	HR (95% CI)
Full cohort						
Female, ever-pregnant with daughters analysis						
Male (reference)	5,663	26,336	1 (reference)	5,209	27,337	1 (reference)
Female, ever-pregnant with daughters	3,120	13,902	1.03 (0.99-1.06)	2,731	13,913	1.01 (0.98-1.05)
Female, never-pregnant with daughters analysis						
Male (reference)	6,301	28,083	1 (reference)	5,889	29,375	1 (reference)
Female, never-pregnant with daughters*	3,877	16,691	1.02 (0.99-1.05)	3,622	17,144	1.02 (0.99-1.05)
No mixture of exposure						
Male (reference)	3,068	18,367	1 (reference)	2,904	18,964	1 (reference)
Female, ever-pregnant with daughters	525	4,367	1.04 (0.98-1.11)	426	4,228	0.96 (0.89-1.02)
Female, never-pregnant with daughters*	644	5,183	1.03 (0.98-1.08)	637	5,305	1.04 (0.99-1.09)
Single-transfusion						
Male (reference)	911	10,028	1 (reference)	823	9,622	1 (reference)
Female, ever-pregnant with daughters	333	3,460	1.13 (0.99-1.28)	262	3,234	0.99 (0.87-1.14)
Female, never-pregnant with daughters*	358	3,852	1.07 (0.95-1.21)	328	3,788	1.11 (0.97-1.26)

* Combined category of products from Female, never-pregnant donors and Female, ever-pregnant donors without daughters.

Table S11. Mortality Hazard Ratio of Male and Female Transfusion Recipients Exposed to Red Blood Cell Transfusions From Female (Never-Pregnant or Ever-Pregnant) Donors vs Male Donors (Sensitivity Analyses II. to VI.)

Donor category	Male recipients			Female recipients		
	No. of Deaths	No. of Recipients	HR (95% CI)	No. of Deaths	No. of Recipients	HR (95% CI)
II. Comparison 2, censored if donor born before 1958						
Male (reference)	3,068	18,367	1 (reference)	2,904	18,964	1 (reference)
Female, ever-pregnant with sons	247	2,399	0.87 (0.76-1.00)	225	2,385	0.88 (0.76-1.03)
Female, never-pregnant with sons*	465	4,054	0.88 (0.78-0.99)	474	4,052	0.99 (0.88-1.12)
III. Comparison 1, patients enrolled after 1-9-2015						
Male (reference)	441	3,479	1 (reference)	313	3,366	1 (reference)
Female, ever-pregnant	145	1,415	0.87 (0.68-1.11)	108	1,401	1.10 (0.79-1.51)
Female, never-pregnant	100	1,009	1.06 (0.76-1.46)	86	972	1.12 (0.82-1.53)
Comparison 2, patients enrolled after 1-9-2015						
Male (reference)	441	3,479	1 (reference)	313	3,366	1 (reference)
Female, ever-pregnant with sons	97	998	0.83 (0.63-1.10)	74	960	1.22 (0.82-1.81)
Female, never-pregnant with sons*	150	1,436	0.97 (0.75-1.25)	118	1,379	1.21 (0.83-1.79)
IV. Comparison 2, censored if donor had both sons and daughters						
Male (reference)	3,068	18,367	1 (reference)	2,904	18,964	1 (reference)
Female, ever-pregnant, only sons	127	1,161	0.94 (0.78-1.13)	106	1,190	0.88 (0.71-1.09)
Female, never-pregnant with sons*	645	5,209	0.94 (0.86-1.03)	620	5,214	0.97 (0.88-1.06)
V. Comparison 2, censored if donor was Female, never-pregnant or if donor had both sons and daughters						
Male (reference)	3,068	18,367	1 (reference)	2,904	18,964	1 (reference)
Female, ever-pregnant, only sons	127	1,161	0.94 (0.78-1.13)	106	1,190	0.88 (0.71-1.09)
Female, ever-pregnant, only daughters	143	1,235	1.00 (0.83-1.21)	98	1,125	0.78 (0.63 -0.97)

* Combined category of products from Female, never-pregnant donors and Female, ever-pregnant donors without sons.

Table S12. Exposure Group Assignment of Transfusion Recipients on Day 1 for Comparison 1 Stratified by Patient Age and Sex

Exposure category (day 1 assignment)	0-17 y		18-50 y		51-70 y		≥71 y	
	Male	Female	Male	Female	Male	Female	Male	Female
	N=6,679	N=5,392	N=5,621	N=10,291	N=18,409	N=14,636	N=17,813	N=19,810
Male	3,701 (55%)	2,935 (54%)	1,802 (32%)	3,424 (33%)	6,408 (35%)	5,232 (36%)	6,453 (36%)	7,369 (37%)
Female, ever-pregnant	1,577 (24%)	1,283 (24%)	518 (9%)	895 (9%)	2,045 (11%)	1,647 (11%)	2,130 (12%)	2,393 (12%)
Female, never-pregnant	651 (10%)	598 (11%)	323 (6%)	545 (5%)	1,232 (7%)	908 (6%)	1,268 (7%)	1,475 (7%)
Mixture	750 (11%)	576 (11%)	2,978 (53%)	5,427 (53%)	8,724 (47%)	6,849 (47%)	7,962 (45%)	8,573 (43%)

Table S13. Weights distribution of primary analysis, comparison 1

Population	Min.	Max.	0.5th percentile	99.5st percentile
Male patients, female ever-pregnant exposure	0,487292	51,05472	0,627831	1,692817
Male patients, female never-pregnant exposure	0,308522	4,166463	0,504654	1,687214
Female patients, female ever-pregnant exposure	0,456485	958,0321	0,587501	2,263018
Female patients, female never-pregnant exposure	0,316219	21132,81	0,504492	2,502784

Table S14. Patient characteristics before IPW, stratified by patient age and sex

Characteristics		0-17 y		18-50 y		51-70 y		≥71 y	
		Male patients	Female patients	Male patients	Female patients	Male patients	Female patients	Male patients	Female patients
Hospital, N (%)									
	1	118 (2%)	96 (2%)	668 (12%)	1,373 (13%)	3,495 (19%)	2,882 (20%)	3,921 (22%)	4,407 (22%)
	2	266 (4%)	229 (4%)	512 (9%)	1,241 (12%)	2,159 (12%)	1,774 (12%)	2,666 (15%)	3,420 (17%)
	3	216 (3%)	190 (4%)	578 (10%)	2,106 (20%)	2,983 (16%)	2,603 (18%)	4,075 (23%)	5,182 (26%)
	4	2,002 (30%)	1,524 (28%)	1,518 (27%)	2,363 (23%)	3,905 (21%)	2,881 (20%)	2,663 (15%)	2,603 (13%)
	5	3,540 (53%)	2,914 (54%)	1,650 (29%)	2,286 (22%)	3,822 (21%)	3,006 (21%)	2,818 (16%)	2,667 (13%)
	6	539 (8%)	442 (8%)	700 (12%)	926 (9%)	2,048 (11%)	1,490 (10%)	1,676 (9%)	1,533 (8%)
Year, N (%)									
	2005	173 (3%)	124 (2%)	160 (3%)	324 (3%)	433 (2%)	297 (2%)	401 (2%)	464 (2%)
	2006	268 (4%)	213 (4%)	218 (4%)	517 (5%)	720 (4%)	513 (4%)	621 (3%)	748 (4%)
	2007	469 (7%)	352 (7%)	397 (7%)	742 (7%)	1,059 (6%)	814 (6%)	972 (5%)	1,087 (5%)
	2008	498 (7%)	396 (7%)	394 (7%)	775 (8%)	1,243 (7%)	979 (7%)	1,144 (6%)	1,374 (7%)
	2009	507 (8%)	422 (8%)	492 (9%)	861 (8%)	1,395 (8%)	1,105 (8%)	1,416 (8%)	1,704 (9%)
	2010	605 (9%)	459 (9%)	486 (9%)	843 (8%)	1,440 (8%)	1,204 (8%)	1,501 (8%)	1,709 (9%)
	2011	562 (8%)	465 (9%)	449 (8%)	857 (8%)	1,469 (8%)	1,180 (8%)	1,476 (8%)	1,806 (9%)
	2012	664 (10%)	521 (10%)	551 (10%)	1,025 (10%)	1,790 (10%)	1,406 (10%)	1,711 (10%)	1,943 (10%)
	2013	577 (9%)	507 (9%)	535 (10%)	917 (9%)	1,797 (10%)	1,334 (9%)	1,617 (9%)	1,808 (9%)
	2014	607 (9%)	496 (9%)	520 (9%)	856 (8%)	1,637 (9%)	1,418 (10%)	1,580 (9%)	1,655 (8%)
	2015	604 (9%)	506 (9%)	482 (9%)	876 (9%)	1,796 (10%)	1,437 (10%)	1,693 (10%)	1,732 (9%)
	2016	439 (7%)	356 (7%)	377 (7%)	694 (7%)	1,409 (8%)	1,234 (8%)	1,431 (8%)	1,573 (8%)
	2017	444 (7%)	344 (6%)	392 (7%)	730 (7%)	1,605 (9%)	1,257 (9%)	1,648 (9%)	1,694 (9%)
	2018	264 (4%)	234 (4%)	173 (3%)	278 (3%)	619 (3%)	458 (3%)	608 (3%)	515 (3%)
Blood group, N (%)									
	AB Rh−	32 (0%)	25 (0%)	41 (1%)	57 (1%)	95 (1%)	79 (1%)	107 (1%)	117 (1%)
	AB Rh+	191 (3%)	159 (3%)	197 (4%)	376 (4%)	546 (3%)	465 (3%)	538 (3%)	577 (3%)
	A Rh−	285 (4%)	234 (4%)	304 (5%)	627 (6%)	1,289 (7%)	1,037 (7%)	1,223 (7%)	1,391 (7%)

	A Rh+	1,731 (26%)	1,351 (25%)	1,897 (34%)	3,507 (34%)	6,543 (36%)	5,223 (36%)	6,403 (36%)	7,065 (36%)
	B Rh−	79 (1%)	59 (1%)	72 (1%)	181 (2%)	255 (1%)	216 (1%)	269 (2%)	268 (1%)
	B Rh+	528 (8%)	449 (8%)	587 (10%)	1,023 (10%)	1,567 (9%)	1,314 (9%)	1,334 (7%)	1,586 (8%)
	O Rh−	320 (5%)	255 (5%)	371 (7%)	618 (6%)	1,290 (7%)	935 (6%)	1,270 (7%)	1,442 (7%)
	O Rh+	1,947 (29%)	1,539 (29%)	2,087 (37%)	3,884 (38%)	6,779 (37%)	5,340 (36%)	6,650 (37%)	7,361 (37%)
	Unknown	1,568 (23%)	1,324 (25%)	70 (1%)	22 (0%)	48 (0%)	27 (0%)	25 (0%)	5 (0%)
No. of transfusions received during follow-up, N (%)									
	1 unit	2,879 (43%)	2,296 (43%)	521 (9%)	930 (9%)	2,160 (12%)	1,906 (13%)	2,279 (13%)	2,729 (14%)
	2 units	1,370 (21%)	1,144 (21%)	1,450 (26%)	4,319 (42%)	5,246 (28%)	4,856 (33%)	5,447 (31%)	7,557 (38%)
	≥ 3 units	2,432 (36%)	1,955 (36%)	3,655 (65%)	5,046 (49%)	11,006 (60%)	7,874 (54%)	10,093 (57%)	9,526 (48%)

Table S15. Censored patients and follow-up of patients in the complete dataset and primary analysis, by exposure group stratified by patient age and sex

	0-17 y				18-50 y			
	Complete dataset*		Primary analysis		Complete dataset*		Primary analysis	
Characteristics	**Male patients**	**Female patients**	**Male patients**	**Female patients**	**Male patients**	**Female patients**	**Male patients**	**Female patients**
Number of patients	N = 6,681	N = 5,395	N = 5,931	N = 4,819	N = 5,626	N = 10,295	N = 2,644	N = 4,865
Arm: male	4,330†	3,427†	3,702†	2,936†	4,515†	8,242†	1,803†	3,425†
Arm: ever-pregnant	2,107†	1,655†	1,578†	1,283†	2,707†	4,765†	518†	895†
Arm: never-pregnant	974†	872†	651†	600†	1,980†	3,403†	323†	545†
Number of patients censored on day 1, (%)	-	-	750 (11%)	576 (11%)	-	-	2,982 (53%)	5,430 (53%)
Number of patients censored during follow-up, (%)	-	-	688 (12%)	482 (10%)	-	-	975 (37%)	1,698 (35%)
Arm: male, (%)	-	-	295 (43%)	214 (44%)	-	-	410 (42%)	709 (42%)
Arm: ever-pregnant, (%)	-	-	262 (38%)	178 (37%)	-	-	336 (34%)	568 (33%)
Arm: never-pregnant, (%)	-	-	131 (19%)	90 (19%)	-	-	229 (23%)	421 (25%)
Follow-up, median (IQR), days‡	1,831 (741-2,928)	1,837 (729-2,892)	767 (17-2,374)	778 (17-2,366)	1,463 (371-2,719)	1,887 (730-3,051)	96 (5-1,557)	1,008 (22-2,556)
Arm: male	2,015 (877-3,060)	2,048 (918-3,058)	1,046 (27-2,604)	1,094 (28-2,631)	1,639 (551-2,814)	2,125 (966-3,280)	179 (7-1,785)	1,242 (54-2,776)
Arm: ever-pregnant	1,584 (707-2,676)	1,716 (743-2,624)	395 (10-1,935)	329 (10-1,928)	1,014 (224-2,199)	1,866 (758-2,877)	22 (4-939)	611 (4-2,197)
Arm: never-pregnant	1,781 (797-2,712)	1,737 (793-2,724)	307 (8-1,968)	330 (10-2,030)	1,336 (418-2,148)	1,392 (569-2,502)	22 (3-1,264)	328 (3-1,587)

*In the complete dataset, all follow-up from patients is included and no censoring takes place

†In the complete dataset, patients could receive different exposures on day 1, and these can therefore classified into multiple arms.

Table S15. Censored patients and follow-up of patients in the complete dataset and primary analysis, by exposure group stratified by patient age and sex (continued)

	51-70 y				≥ 71 y			
	Complete dataset*		Primary analysis		Complete dataset*		Primary analysis	
Characteristics	**Male patients**	**Female patients**	**Male patients**	**Female patients**	**Male patients**	**Female patients**	**Male patients**	**Female patients**
Number of patients	N = 18,412	N = 14,636	N = 9,687	N = 7,787	N = 17,819	N = 19,812	N = 9,853	N = 11,239
Arm: male	14,160†	11,236†	6,408†	5,232†	13,434†	14,857†	6,454†	7,371†
Arm: ever-pregnant	8,308†	6,409†	2,047†	1,647†	7,783†	8,390†	2,131†	2,393†
Arm: never-pregnant	5,843†	4,553†	1,232†	908†	5,550†	5,884†	1,268†	1,475†
Number of patients censored on day 1, (%)	-	-	8,725 (47%)	6,849 (47%)	-	-	7,966 (45%)	8,579 (43%)
Number of patients censored during follow-up, (%)	-	-	3,087 (32%)	2,270 (29%)	-	-	3,496 (35%)	3,580 (32%)
Arm: male, (%)	-	-	1,292 (42%)	948 (42%)	-	-	1,450 (41%)	1,505 (42%)
Arm: ever-pregnant, (%)	-	-	1,067 (35%)	769 (34%)	-	-	1,209 (35%)	1,207 (34%)
Arm: never-pregnant, (%)	-	-	728 (24%)	553 (24%)	-	-	837 (24%)	868 (24%)
Follow-up, median (IQR), days‡	1,014 (223-2,370)	1,129 (286-2,492)	118 (5-1,498)	300 (10-1,737)	776 (132-2,059)	1,133 (272-2,428)	77 (4-1,078)	294 (6-1,652)
Arm: male	1,348 (339-2,679)	1,385 (395-2,654)	187 (7-1,673)	410 (19-1,966)	909 (137-2,229)	1,233 (302-2,549)	141 (6-1,290)	447 (15-1,903)
Arm: ever-pregnant	1,219 (278-2,529)	1,268 (325-2,452)	40 (3-1,242)	122 (4-1,377)	714 (124-1,893)	1,090 (291-2,237)	21 (2-686)	81 (3-1,198)
Arm: never-pregnant	895 (304-2,210)	962 (285-2,198)	33 (3-837)	92 (3-1,104)	739 (129-1,748)	837 (216-1,848)	17 (2-673)	66 (2-966)

*In the complete dataset, all follow-up from patients is included and no censoring takes place

†In the complete dataset, patients could receive different exposures on day 1, and these can therefore classified into multiple arms.

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