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BLOOD IN, BLOOD OUT: ASPECTS OF BLOOD TRANSFUSIONS AND DONATIONS IN THE REALMS OF OBSTETRIC CARE AND BEYOND

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Blood in, Blood out: Aspects of blood transfusions and donations in the realms of obstetric care and beyond

Thesis for Doctoral Degree (Ph.D.)

By

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“Blood is a juice of rarest quality.”

MEPHISTOPHELES (I)

To my family.

Popular science summary of the thesis

Blood transfusions are a cornerstone of modern medicine, often used to manage life-threatening bleeding during childbirth. Their availability depends on the generosity of numerous healthy individuals who, without personal gain donate blood. However, much about transfusions remains unknown. Do we use blood products to the same extent today as before? What is the risk of needing another transfusion in a future delivery if one was required in the first? Are there long-term consequences for the mother of being transfused during childbirth? Could blood donation before pregnancy affect a woman's health or her baby? This doctoral thesis explores these questions through four large-scale Swedish population studies utilizing national health and blood donation registries.

Our first study examined patterns and trends in red-cell transfusion use in obstetric care in Sweden. The study included 1.6 million births between 2003 and 2017 and indicated that transfusion rates among women in delivery remained relatively stable over time. However, the number of high-volume transfusions declined, low-volume transfusions became more common, and the total number of blood units used per delivery decreased. The overall transfusion rate was surprisingly high—3 percent—compared to other high-income countries. Most transfusions occurred on the day of delivery, but they were also administered several days later. The study revealed considerable differences in transfusion practices between hospitals, even after adjusting for maternal risk factors. Our results suggest that there may be room for harmonizing transfusion decisions and practices, although further research is needed to clarify these discrepancies.

Previous studies have revealed that a significant risk factor for transfusion during delivery is having received one previously. Our second study examined the impact of transfusion recurrence by analyzing data from 825,000 women who had multiple deliveries between 2000 and 2017. We found that women who received a transfusion during their first childbirth were five times more likely to be transfused during their next delivery than those who did not. Certain pregnancy complications, particularly those having to do with the placenta, preeclampsia, and iron deficiency, further increase this risk. We also observed that having a sister who had received a transfusion in childbirth slightly increased the odds of needing one, suggesting a possible familial or genetic influence.

Receiving a transfusion affects the immune system in ways not fully understood. Studies have connected blood transfusions to an increased risk of autoimmune diseases and lymphoma. In our third study, we followed over one million women up to 25 years after childbirth from 1987 and forward to find out whether receiving a transfusion during delivery affected the risk of certain immune-related diseases. We found that transfused women had a slightly higher risk of developing some disorders, such as lupus and systemic sclerosis. However, we found no increased risk for lymphoma or rheumatoid arthritis. These findings suggest a potential association between transfusions and long-term effects on the immune system. That said, it is a complex relationship to investigate, and more research approaches are needed to confirm these findings.

In the fourth study, we turned our focus to blood donors. Female blood donors who donate frequently are at a high risk of developing iron deficiency, as it is challenging to replenish lost iron, and women typically do not have large iron stores to begin with. Iron deficiency, in turn, is connected to an increased risk of pregnancy complications affecting both mother and child. We investigated 2.5 million deliveries between 1985 and 2017 and compared pregnancy and delivery complications in women who had donated blood before pregnancy, both amongst themselves and non-donating women. Overall, donors had fewer complications and slightly heavier babies than non-donors, likely reflecting the "healthy donor effect," where donors are healthier than the average population. However, comparisons among donors revealed a different pattern. Women who had donated eight times or more in the five years before pregnancy had lower-birth-weight babies and higher risks of complications like preterm birth and preeclampsia compared to those donating only once or twice. These findings suggest that frequent donations in reproductive age may carry risks that warrant a discussion on policies for female blood donors planning for pregnancy.

Taken together, these studies address essential aspects of blood transfusions and donations in the context of obstetric care and beyond. They emphasize the importance of safe and consistent transfusion practices, the necessity of considering transfusion history in prenatal care, and the potential risks associated with iron depletion in frequent blood donors. We believe that the findings offer valuable guidance on protecting maternal and neonatal health for healthcare professionals, blood banks, and policymakers.

Abstract

Blood transfusion therapy is a cornerstone of modern obstetric care, commonly administered during childbirth to manage acute hemorrhage. Meanwhile, blood donation represents a vital public health act sustained by healthy individuals, many of whom are women of reproductive age. This thesis examines red-cell transfusion and whole blood donation from multiple perspectives, including clinical patterns, recurrence, long-term outcomes, and the effects of pre-pregnancy donation on maternal and offspring health. It combines four register-based cohort studies using Swedish health data and blood donation data integrated within the SCANDAT3-S database to evaluate how blood, both received and given, intersects with maternal and neonatal health.

Aims

- To describe the patterns and temporal trends of red-cell transfusion use in obstetric care in Sweden.
- To assess the risk of recurrent transfusion in delivery.
- To investigate whether red-cell transfusion during childbirth is associated with long-term risks of autoimmune disease and non-Hodgkin lymphoma.
- To evaluate whether blood donation before pregnancy is associated with adverse maternal or neonatal outcomes.

Study I. Transfusion practices in obstetric care in Sweden have evolved, but national-level data on usage patterns remain limited. This study analyzed a nationwide cohort of 1.6 million deliveries in Sweden between 2003 and 2017. In addition to describing overall transfusion patterns, we examined temporal trends and volume using logistic regression. For analyses of inter-hospital variations in transfusion rates, we used direct standardization to the year 2003, adjusting for parity and maternal age. Overall, 3 percent of women were transfused annually, and there were no considerable changes over the study period. We saw an increasing proportion of low-volume and a decline in high-volume transfusions. The most common number of red-cell units transfused per delivery was two, reflecting a broader pattern where even-numbered transfusions—particularly two or four units—dominated clinical practice. We saw substantial variation in the proportion of transfused deliveries across hospitals.

Summary: While overall transfusion rates remained stable, hospital-level variation and the use of paired units may signal inappropriate use and warrant further investigation.

Study II. Although transfusion during childbirth is typically viewed as an event determined by the specific circumstances of each delivery, some women experience repeated transfusions across deliveries. We analyzed a nationwide cohort of 825,000 women with deliveries between 2000 and 2017 to investigate the recurrence of transfusion. We used logistic regression to estimate the odds ratios of requiring a repeated transfusion in relation to specific risk factors. Women transfused in their first delivery were overall approximately five times more likely to be transfused in their second delivery (adjusted odds ratio [aOR] 5.4, 95% confidence intervals [CI]; 5.0-5.8) than non-transfused, non-hemorrhaged women. The overall odds of repeat transfusion were similar regardless of hemorrhage diagnosis in the first delivery. When considering specific subtypes, we saw the most pronounced recurrence risk associated with prior diagnoses of atony (aOR 6.7; 95% CI 6.1–7.4), placental retention (aOR 4.4; 95% CI, 3.8–5.1), and caesarian section with hemorrhage (aOR 6.8; 95% CI, 5.8–8.0). Certain conditions in the second pregnancy (e.g., preeclampsia, placenta previa, iron deficiency anemia) increased the odds of recurrence. Having a sister transfused in childbirth was associated with higher odds of transfusion in childbirth (aOR 1.8; 95% CI, 1.5–2.1).

Summary: A prior transfusion is a strong risk factor for future transfusion, underscoring the importance of individualized risk management.

Study III. The long-term effects of obstetric transfusion on immune-mediated conditions remain poorly understood. In this study, we followed a large register-based cohort of over one million women, starting in 1987, for up to 25 years to assess the risk of autoimmune disease and non-Hodgkin lymphoma. Cox proportional hazard models were used, adjusting for both fixed and time-dependent maternal factors. To reduce the risk of reverse causation, a six-month lag period was applied before the start of follow-up after each delivery. Transfusion in childbirth was modestly associated with increased risks for later diagnosis of systemic lupus erythematosus (SLE) (adjusted hazard ratio [aHR] 1.38; 95% CI, 1.01-1.87) and systemic sclerosis (aHR 1.89; 95% CI, 1.21-3.21), but not associated with risk of non-Hodgkin lymphoma or rheumatoid arthritis. However,

the absolute risk difference at 25 years was slight. Sensitivity analyses, applying various stratifications and restrictions, generally supported the main findings.

Summary: Although the absolute risk difference was small, transfusion in childbirth was associated with an increased risk of developing SLE and systemic sclerosis.

Study IV. While blood donors are typically healthier than the general population, frequent donation may deplete iron stores and influence pregnancy outcomes. We analyzed a register-based cohort of 2.5 million deliveries between 1985 and 2017 to investigate any potential adverse effects of blood donations on pregnancy and childbirth. We used mixed-effects linear models to estimate birth weight by donation intensity, and logistic regression was applied to assess maternal and neonatal outcomes. When comparing births to non-donors to those to women who donated at least once within five years of delivery, we found that donors were less likely to experience adverse pregnancy outcomes and that the birth weight of their offspring was slightly higher. However, when considering only donors, high-frequency donors (≥9 donations within five years of delivery) had lower birth weight babies and higher risks of preeclampsia (aOR 1.18; 95% CI, 1.06–1.31), preterm birth (aOR 1.33; 95% CI, 1.22–1.45), and SGA infants (aOR 1.17; 95% CI, 1.03–1.34) than low-frequency donors (1-2 donations). Specific temporal analyses using interaction terms supported the notion of a biological effect. Sensitivity analyses confirmed the main findings.

Summary: High-frequency whole blood donation before pregnancy may have adverse effects on maternal health and neonatal outcomes.

In conclusion, the thesis reveals that transfusion and donation intersect with maternal health. It underscores the need for consistent transfusion practices, monitoring for recurrence risk, awareness of potential long-term immune effects, and cautious iron management in frequent female donors.

LIST OF SCIENTIFIC PAPERS

I. Brynolf A., Zhao J., Wikman A., Öberg S., Sandström A., Edgren G. (2021), *Patterns of red-cell transfusion use in obstetric practice in Sweden 2003-2017: A nationwide study*. Vox Sang, 116: 821-830. doi: 10.1111/vox.13074. Epub 2021 Feb 2. PMID: 33528029

II. Brynolf A, Sandström A, Edgren G. *Risk of recurrent red-cell transfusion in delivery: A nationwide longitudinal study*. BJOG. 2024 Mar;131(4):455-462. doi: 10.1111/1471-0528.17672. Epub 2023 Sep 25. PMID: 37749750.

III. Brynolf A, Sandström A, Hjalgrim H, Edgren G. *Association Between Red-Cell Transfusion in Childbirth and Long-Term Risk of Lymphoma and Autoimmune Disease: A Swedish Nationwide Cohort Study*. Am J Hematol. 2025 Apr;100(4):735-739. doi: 10.1002/ajh.27610. Epub 2025 Jan 27. PMID: 39868856.

IV. Brynolf A, Sandström A, Öberg S, Toss F, Edgren G. *Whole blood donations before delivery and the risk of adverse pregnancy, delivery, and neonatal outcomes: A Swedish longitudinal cohort study*. MANUSCRIPT.

CONTENTS

List of abbreviations

This thesis aims to minimize the use of abbreviations, as its author finds them generally unbearable.

°C	Degrees Celsius
ABO	The most important system for blood group classification
AMTSL	Active management of the third stage of labor
BMI	Body-mass index
CI	Confidence intervals
DNA	Deoxyribonucleic acid
E.g.	Exempli gratia (for example)
Hb	Hemoglobin
(a)HR	(adjusted) Hazard ratio
ICD	International Classification of Diseases
IL	Interleukin
IVF	In vitro fertilization
LISA	The Longitudinal Integration Database for Health Insurance and Labour Market Studies
MBR	The Medical Birth Register
NHL	Non-Hodgkin lymphoma
NPR	National Patient Register
(a)OR	(adjusted) Odds ratios
PBM	Patient blood management
RA	Rheumatoid arthritis
SAGM	Saline-adenine-glucose-mannitol solution
SCANDAT	Scandinavian donations and transfusions database
SGA	Small-for-gestational-age
SLE	Systemic lupus erythematosus
Th	T-helper cell
TRALI	Transfusion-related acute lung injury
TRIM	Transfusion-related immunomodulation
IUFD	Intra-uterine fetal demise

1 Introduction

In 1818, obstetrician James Blundell described early whole-blood transfusions for postpartum hemorrhage as an "experimental remedy," offering the "only remaining chance for life" (2). In the following centuries, fundamental discoveries—including ABO and Rhesus blood groups, sodium citrate for blood storage, and the antiglobulin test, fractioning into blood components—substantially improved transfusion safety (3-7).

Today the administration of concentrated red blood cell units is a widely used treatment for hemorrhage and anemia, with the primary goal of restoring the blood's oxygen-carrying capacity (8). Although safer than ever before, red-cell transfusions still carry medical risks, including infections and immunological reactions (9). From a systems perspective, blood is also a costly and finite resource—its collection, processing, and storage require substantial infrastructure, and overuse may strain availability for patients with critical needs (10-14). Hence, healthcare systems have adopted "patient blood management" (PBM) strategies, emphasizing restrictive transfusion criteria, blood-sparing surgical techniques, and iron supplementation to minimize blood use (15-17). In parallel, reduced red-cell utilization has been observed in Sweden, England, the United States, China, and the European Union (18-24).

When we transfuse younger women in Sweden with red-cell units, it is most commonly in an obstetric context (21). Red-cell transfusions can certainly be imperative and life-saving in these settings. However, they are also used for relative indications, such as postpartum anemia in the hemodynamically stable patient. In this scenario, red-cell transfusion may be considered optional, as there are viable alternatives, such as iron supplementation. For clinicians, it is crucial to avoid administering unnecessary or marginally indicated transfusions. Besides medical risks and costs associated with red-cell transfusions shared among all patient groups (25), blood exposure increases the risk of alloimmunization, which may complicate future pregnancies (26, 27). Moreover, the long-term immunological consequences of maternal transfusion in childbirth remain incompletely understood. Thus, while contemporary transfusion practices are far removed from Blundell's original "experimental remedy," the balancing risks and benefits remain as important today.

1.1 Rationale and scope

This thesis examines temporal trends, hospital-level variations, and risk factors associated with obstetric transfusions in Sweden, including recurrence across pregnancies. Additionally, it examines potential long-term health implications of transfusions, with a focus on their associations with autoimmune diseases and non-Hodgkin lymphoma. Finally, the thesis examines whether blood donation, which frequently results in profound iron deficiency, impacts maternal and neonatal health. By addressing these realms, we aim to inform clinical practice and policy, thus promoting safer future transfusion and donation practices.

2 Background

In this chapter, we aim to provide a brief overview of the clinical and public health contexts necessary to interpret the studies that provide the foundation for this thesis.

2.1 The red-cell transfusion

Being central to this thesis, the red-cell transfusion deserves a standalone introduction. A standard red-cell unit is usually derived from 450 mL of whole blood and contains approximately 200 to 250 mL of red blood cells suspended in an additive solution, stored at 2–6°C for up to 42 days. Additives typically include saline-adenine-glucose-mannitol (SAGM) to preserve red-cell viability (28). The hematocrit (the percentage of whole blood volume composed of red blood cells) is about 55 to 60 percent, and each unit contains roughly 200 to 250 mg of iron. The overwhelming majority of all units are "allogeneic," meaning that the treatment exposes the recipient to blood from a donor other than themselves. Donor exposure is unique per unit, meaning that multi-unit transfusions correspond to multiple donor exposures, a consideration with immunologic relevance.

To minimize the risk of febrile non-hemolytic transfusion reactions, alloimmunization, and the transmission of certain infections, all red-cell units are subjected to leukocyte reduction. This process reduces the white blood cell count to less than 5×10^6 per unit, and its implementation has been gradual in high-income settings since the late 1990s (29).

2.2 Iron metabolism and maternal-fetal needs

Mammal iron metabolism is a complex process involving multiple pathways and organ systems (30-32). It is used for hemoglobin (Hb) synthesis, the primary oxygen-carrying protein in red blood cells, as well as for cellular processes, including energy production and immune function.

2.2.1 Iron deficiency and its diagnosis

Body iron is predominantly stored in red blood cells and may thus be lost during hemorrhage (32). Prolonged insufficient iron intake or absorption may

compromise erythropoiesis, the process by which the bone marrow replenishes red blood cells. What follows is iron deficiency anemia, characterized by low hemoglobin levels (with a concentration of less than 120 g/L for non-pregnant women and 130 g/L for men) in combination with depleted iron stores (33).

However, hemoglobin levels as a lone laboratory test are insufficient for diagnosing iron deficiency, as a low value reflects the result of depletion rather than its onset. Iron-deficient erythropoiesis—a state where red-cell production is limited by inadequate iron supply—may occur even before anemia is evident. Thus, it is possible to maintain hemoglobin levels even in cases of iron depletion (34). Ferritin is a large, hollow protein that efficiently stores iron (mainly in the liver and spleen) when it is not currently transported or utilized. The fraction of ferritin in circulation reflects body iron stores (32), and clinicians commonly consider the level of plasma ferritin as a marker of iron deficiency in an otherwise healthy individual (35).

Table 1. WHO criteria for iron deficiency and anemia in pregnancy (36).

Parameter	WHO threshold for deficiency	Brief description
Hemoglobin (Hb)	<110 g/L In Sweden, 105g/L is considered normal in the second trimester (37)	Iron-containing protein in red blood cells, responsible for oxygen transport. Concentration drops only after iron stores are depleted. A concentration below the threshold is defined as anemia.
Ferritin	<30 ng/mL The definition <15 ng/mL is also seen in the literature.	Ferritin is a globular protein complex that stores iron in a safe, soluble, and non-toxic form inside cells. A fraction of it is found in circulation and reflects iron stores in otherwise healthy Individuals. It serves as a marker for the early detection of iron deficiency.
Transferrin saturation	<20% (iron/transferrin × 100)	Transferrin is the iron transport protein in the blood. Transferrin saturation reflects iron availability for erythropoiesis.

2.2.2 Iron demands in pregnancy

Iron demands increase substantially during pregnancy due to the expansion of maternal blood volume, fetal growth, and placental development (38). Since it is not synthesized endogenously and is poorly absorbed compared to other nutrients, adequate intake and optimal absorption conditions are crucial.

It is estimated that a singleton pregnancy typically requires 500 to 1,000 mg of additional iron, with daily needs rising from less than 1 mg per day in the first trimester to approximately 7.5 mg daily in the third (39). Although absorption is enhanced during pregnancy, dietary intake rarely meets the increased needs. Women would thus ideally enter pregnancy with an iron reserve of approximately 500 mg, a threshold seldom achieved due to menstruation and suboptimal dietary intake (35). To bridge the gap, the World Health Organization (WHO) recommends universal iron supplementation during pregnancy (30 to 60 mg per day) (36). However, an individualized approach is also feasible in high-income settings (40).

Studies indicate that 40–55 percent of European women of reproductive age have insufficient iron stores. As a result, approximately one-third of these women develop iron deficiency anemia in the third trimester (41) or earlier. For example, a recent UK study found that 42 percent of non-anemic women were iron deficient already in the first trimester (42). There are also significant variations within countries due to dietary, socioeconomic, and ethnic factors (43).

Following the discontinuation of general iron fortification in Sweden, a follow-up study found that the prevalence of iron deficiency among teenage girls increased from 37 to around 45 percent (44). A recent survey confirmed an iron deficiency prevalence of nearly 40 percent among Swedish female adolescents and close to 70 percent among their vegetarian or vegan peers (45). To our knowledge, there are no contemporary large-scale studies on the prevalence of iron deficiency among pregnant women in Sweden.

2.2.3 Supplemental iron recommendations within antenatal care

If initiated during antenatal care, iron supplementation taken as prescribed may help prevent iron-deficient anemia and alleviate iron deficiency during the second and third trimesters (46). Current Swedish national guidelines recommend measuring ferritin and hemoglobin levels at the first antenatal visit (around gestational weeks 8–11) (47). A ferritin level below 30 ng/L prompts daily supplementation with 100 mg of iron, while borderline or sufficient stores (30-150 ng/L) lead to a recommendation of 100 mg every other day. Ferritin may be reassessed if anemia is later detected through routine hemoglobin testing, which is typically performed one to two times during the second and third trimesters. In

case of iron deficiency anemia in the late third trimester, intravenous iron may be considered (48). In previous guidelines, lower ferritin thresholds for starting supplementation are described (49). A 2003 questionnaire study revealed low compliance to the former national guideline, which recommended 100 mg of iron daily for all pregnant women, with only 41 percent of midwives and 28 percent of pregnant women reporting adherence (50).

2.2.4 Maternal and offspring implications of iron deficiency

From a maternal perspective, iron deficiency increases physiological vulnerability during pregnancy and delivery. Studies have also revealed associations between maternal iron deficiency or iron deficiency anemia and adverse obstetric outcomes, including small-for-gestational-age (SGA) infants, preterm birth, cesarean section, low Apgar scores (less than 7 at 5 minutes), and an increased likelihood of maternal red-cell transfusion (51-54).

Table 2. Adverse events associated with maternal iron deficiency or iron deficiency anemia.

Outcome	Definition (55, 56)
Preterm birth	Birth occurs before 37 completed weeks of gestation.
Intrauterine fetal demise (IUFD)	Death of the fetus in utero after 22 completed weeks of gestation (or ≥500g in weight).
Low birth weight (LBW)	Birth weight is less than 2,500 grams, regardless of gestational age.
Apgar score	A scoring system (0–10) assessing newborn well-being at 1 and 5 minutes after birth based on heart rate, respiratory effort, muscle tone, reflex response, and color.
Small for gestational age (SGA) infant	Infant with a birth weight below the 10th percentile for gestational age and sex.
Preeclampsia	A pregnancy complication characterized by new-onset hypertension (≥140/90 mmHg) and proteinuria (≥300 mg/24h) or organ dysfunction after 20 weeks of gestation.

The interpretation of the effects of maternal iron status on fetal development is more complex. Although iron deficiency and anemia in children are associated with impaired cognitive development (57, 58), systematic reviews have not demonstrated clear associations between iron supplementation in pregnancy and improved neurodevelopmental outcomes in the offspring (59, 60). Moreover, biochemical markers of iron status in the fetus do not reliably reflect maternal iron

deficiency or anemia, inferring that the fetus "takes what it needs" and maintains adequate iron levels regardless of maternal status (61-63).

However, the evidence is mixed, and relatively recent reviews suggest that maternal iron stores do influence neonatal and childhood iron stores and metabolism in the offspring (64, 65). For example, a correlation has been observed between low maternal iron stores and fetal iron stores at birth (66) and in the first year of life (67, 68). This, in turn, may impact central nervous system development (69, 70). Notably, maternal iron deficiency may have different effects on the fetus depending on the trimester in which it occurs. A retrospective Swedish study found an association between maternal anemia in early pregnancy, in contrast to anemia diagnosed late in pregnancy, and an increased risk of neuropsychiatric disorders (71). Similarly, a retrospective study of medical records found an inverse relationship between early pregnancy hematocrit (reflecting iron stores) and birth weight and fetal growth ratio but no association during the second or third trimester (72). The finding may be of particular importance, as previously mentioned, iron deficiency laboratory tests are typically not drawn before the first visit in antenatal care (at the end of the first trimester).

Importantly, maternal iron deficiency and anemia are also associated with varying degrees of socioeconomic vulnerability and food insecurity, which complicates comparisons between countries and the estimation of biological effects (58, 73).

2.3 Postpartum hemorrhage

Pregnancy induces significant hematological changes, notably a physiological anemia resulting from a disproportionate increase in plasma volume relative to red-cell mass. During pregnancy, the hemoglobin level is naturally lower due to this dilution. As a result, a reduced nadir (the lowest physiological point) compared to the non-pregnant state is not necessarily indicative of deficiency (74, 75). These hematological adaptations in pregnancy enhance fetal oxygenation and reduce maternal thrombotic risks (76). After delivery, the maternal hematocrit normalizes gradually over four to six months through hormonal shifts and diuresis (77).

2.3.1 Definitions and incidence

Normal blood loss at delivery is less than 500 mL. Excessive blood loss after delivery – postpartum hemorrhage – is common and remains a significant cause of preventable maternal mortality in low and middle-income countries and maternal morbidity worldwide (78-81). Most often, postpartum hemorrhage occurs within the first 24 hours of delivery (82).

Table 3. Post-partum hemorrhage definitions (55, 56, 82, 83).

Category	Description	Swedish ICD-10	Common cause
Primary	Blood loss ≥500 mL within 24h of delivery. ≥1000 mL denotes severe postpartum hemorrhage	Blood loss >1,000 ml within 24h, with separate ICD coding for excessive hemorrhage at caesarian section	Uterine atony, retained placenta, genital trauma
Secondary	24h–6 weeks postpartum		Placental remains, infection

Globally, postpartum hemorrhage is estimated to affect 6 to 11 percent of deliveries, with severe hemorrhage in 1 to 3 percent (81). However, different definitions, recording practices, and the lack of nationwide data considerably hamper international comparisons of incidence. In Sweden, for example, only blood loss of 1,000 ml or above is registered as postpartum hemorrhage, reflecting a more clinically relevant definition in the generally healthy obstetric population (56). Interestingly, Sweden has seen a rise in postpartum hemorrhage diagnoses of 37 percent between 2000 and 2016 (84), and its coding is recently validated and of high quality (85). The increasing incidence of postpartum hemorrhage in recent decades has also been reported in high-income settings such as the Netherlands, the United States, Canada, Australia, Switzerland, and Ireland (86-91).

2.3.2 Risk factors for postpartum hemorrhage

Uterine atony (the failure of the uterus to contract effectively after childbirth) remains the leading cause of postpartum hemorrhage, followed by retained placenta, genital tract trauma, and coagulopathies (92, 93). Notably, a recent systematic review and meta-analysis of over 300 studies confirmed uterine atony as the leading cause of postpartum hemorrhage, accounting for over 70 percent of cases (94). Notably, the review identified several strong risk factors—including anemia (adjusted odds ratio [aOR] 2.36), previous postpartum

hemorrhage, multi-fetal pregnancy, offspring birth weight of more than 4,500 g, and placenta previa. The finding that nearly 8 percent of postpartum hemorrhage cases involve multiple concurrent causes further underscores the complexity of postpartum blood loss and supports a multifactorial approach in both prevention and management strategies. In contrast, commonly cited factors such as obesity, induction of labor, or prolonged second stage presented inconsistent associations (94, 95).

2.3.3 Postpartum anemia

Hemoglobin levels may fluctuate significantly due to physiological changes after delivery, including blood loss and fluid shifts, making nadir difficult to establish early postpartum (96). Hence, the WHO defines postpartum anemia as a hemoglobin level of less than 110 g/L at one week postpartum and less than 120 g/L at eight weeks (97). In clinical practice in Sweden, most women do not stay in the hospital for a week, which makes the interpretation of anemia diagnoses at discharge difficult. Postpartum anemia can manifest as fatigue, mood disturbances, depression, cognitive difficulties, and reduced mother-infant bonding—factors that can substantially affect maternal well-being (98-101). The condition is primarily driven by postpartum hemorrhage, fueled by concomitant iron deficiency and anemia during pregnancy (35, 96).

2.4 Transfusion strategies in obstetric care

The WHO aptly defines the appropriate use of blood products as "the transfusion of safe blood products only to treat a condition leading to significant morbidity or mortality that cannot be prevented or managed effectively by other means" (102).

2.4.1 Transfusions in the actively bleeding patient

In cases of severe acute obstetric hemorrhage, red-cell transfusion undoubtedly saves lives and serves as a bridge to hemostasis alongside surgical or pharmacological interventions (103-105). The immediate goal is to stabilize hemodynamics and preserve organ function rather than normalizing hemoglobin levels (8). Clinical management typically integrates bundle care interventions along with individual patient factors. Factors that guide management include

perceived hemodynamics, measures of tissue oxygenation, and estimated blood loss, rather than solely relying on hemoglobin thresholds (82, 106, 107).

Naturally, preventing postpartum hemorrhage is a cornerstone in reducing the need for red-cell transfusions in Sweden and elsewhere. The internationally recommended strategy includes “active management of the third stage of labor” (AMTSL), which comprises the administration of uterotonic drugs (typically oxytocin), controlled cord traction, and uterine massage (79). However, temporal trends in clinical management and implementation of such protocols in Sweden, while critical, fall outside the scope of this thesis.

2.4.2 Transfusions in the hemodynamically stable patient

A recent Cochrane systematic review investigated treatment for postpartum anemia (108). Although most evidence was of low or very low quality, the authors concluded that "the effect of red blood cell transfusion compared to intravenous iron on mortality, fatigue, and breastfeeding is very uncertain."

Few randomized trials compare red-cell transfusion to other interventions in the hemorrhaged parturient. However, a Dutch randomized non-inferiority trial by Prick et al. (2014) compared non-intervention with a restrictive transfusion strategy in otherwise healthy women with postpartum hemorrhage exceeding 1000 ml and hemoglobin levels between 48 and 79 g/L 12-24h after delivery. The trial yielded similar physical fatigue scores and clinical outcomes in both study arms (109). In a follow-up study, authors found that transfusions incurred higher costs without any meaningful health-related quality-of-life benefits (110). Retrospective observational studies have also linked low-volume transfusions with prolonged hospitalization, increased morbidity, and lower breastfeeding rates (111-113), though these findings may be vulnerable to residual confounding. A small pilot study comparing red-cell transfusion with intravenous iron in women with severe post-partum hemorrhage found that the patients receiving iron therapy had overall more favorable outcomes, displaying replete iron stores and higher hemoglobin levels in weeks 3 to 12 postpartum (114). Contemporary international clinical guidelines promote restrictive policies, recommending transfusion only at hemoglobin levels below ~70 g/L and encouraging oral or intravenous iron as an alternative treatment when feasible (17, 115, 116).

2.5 Obstetric transfusion epidemiology and variability

Transfusion rates are not determined solely by unquestionable clinical need. They also reflect local practices, institutional norms, and system-level capacity. However, our understanding is hampered by a lack of nationwide, reliable data on transfusions. This section provides a brief overview of national and inter-hospital patterns of red-cell use in obstetric care, including trends in massive transfusion and unit administration strategies.

2.5.1 Overall red-cell use in obstetric care

While red-cell utilization has declined in many medical and surgical specialties, the obstetrics domain has followed a slightly different course. In fact, obstetric transfusion rates increased in many high-income settings, often mirroring rising rates of postpartum hemorrhage and maternal morbidity (91, 117-124). However, there are signs of stabilization. In the United States, for example, the incidence of hemorrhage increased markedly, although transfusion rates peaked around 2011 and have declined modestly since (125). Similar trajectories have been noted in Switzerland (126) and Australia (127), where rates stabilized after an earlier increase. Contrary to the general trend, a 2016 nationwide study from the Netherlands reported a decreasing incidence of maternal red-cell transfusions during delivery (86).

Massive transfusions, commonly defined as the administration of more than 10 red blood cell units within 24 hours, represent extreme clinical scenarios with fatal consequences if not promptly and adequately addressed. However, incidence and management strategies seem to vary markedly across high-income settings (128). In Sweden and Denmark, obstetric-related cases account for roughly 6 percent of all massive transfusions (129). A regional study from Stockholm (1990–2011) showed a 30 percent increase in massive transfusion incidence over time, reaching 5.3 per 10,000 deliveries (104). Although hemorrhage-related mortality in obstetric settings is very rare in Scandinavian countries (129-131), massive blood loss may cause severe maternal morbidity, and complications such as myocardial ischemia can occur in the setting of severe anemia (132).

2.5.2 Appropriateness, hospital variation, and unit use

There are several ways to evaluate the appropriateness of individual red-cell transfusions in clinical practice, and this is generally challenging due to the limited

clinical detail in administrative data (133). However, several studies have claimed evidence of inappropriate red-cell use in retrospective audits of obstetrical settings (134-136). In our datasets, we lack the clinical nuance to consider individual transfusions. Therefore, we opted to investigate two larger-scale measures of use: the distribution of use and hospital variation in use.

A reasonable starting point when considering transfusions is to administer a single red-cell unit and reassess before administering more. Nonetheless, a phenomenon known as the "double-unit bias" may lead to routine administration of two units without interim evaluation (137). Since the marginal benefit of a second unit is often limited, this practice may result in unnecessary transfusions. A "single-unit transfusion policy," where each unit is followed by clinical and laboratory reassessment, has been advocated for decades as a safer and more resource-conscious strategy (138), and its adoption could substantially impact overall red-cell use at the population level (139). Importantly for the patient, each red-cell unit represents a separate exposure to a donor, and doubling the number of units administered also doubles the recipient's exposure to foreign antigens.

Differences in transfusion practice are not limited to countries or regions—considerable variation exists between hospitals. These variations naturally reflect differences in case mix and valid clinical decisions. However, they may also signal under or over-transfusion utilization, making inter-hospital comparisons valuable when investigating transfusion use. Thus, adjusted comparisons have revealed unwarranted discrepancies in transfusion rates across various clinical settings (140-143), including obstetrics (144-146), which merits further investigation.

2.5.3 Study rationale

Despite international efforts to optimize transfusion practices, national-level data on obstetric transfusion use in Sweden remain limited. The paucity of data makes it challenging to evaluate whether evolving global guidelines have influenced local practices or how consistently they are applied across hospitals. *Study I* addresses this gap by examining national trends, unit administration strategies, and inter-hospital variation in the use of obstetric transfusions.

2.6 Who is at risk for recurrent transfusions—and why?

A subset of women experience repeated transfusions across pregnancies, suggesting persistent or unrecognized vulnerabilities. This section examines known clinical risk factors, potential familial or hematologic predispositions, and the limitations of registry data in assessing recurrence risk.

2.6.1 Risk factors for transfusion during delivery

Red-cell transfusions in delivery typically arise from significant blood loss due to postpartum hemorrhage, often due to placental complications (127, 147, 148). Known risk factors for transfusion thus closely mirror those for severe postpartum hemorrhage, including placental complications (retention or malformations), multiple gestation, prematurity, coagulopathy, and cesarean delivery (149-152). Emergency cesareans notably carry substantially higher transfusion rates than planned procedures, likely due to prolonged labor, anesthesia considerations, and unexpected placental or maternal complications (153). Attempts at vaginal birth after cesarean also increase transfusion risk compared to planned repeat cesareans (154). It remains unclear to what extent postpartum hemorrhage overall reflects undiagnosed coagulopathies within the population, but unexpected massive bleeding may indicate an underlying previously unrecognized hematological disorder (155). There may also be genetic factors that contribute to the risk of recurrent hemorrhage (156). Notably, many women experiencing significant postpartum hemorrhage and transfusion lack identifiable risk factors, underscoring the unpredictability and clinical challenge (95, 147, 150). The predictive models for postpartum transfusion may be argued to have limited clinical utility (157-160).

Concomitant iron deficiency and anemia may increase the risk of maternal transfusions at delivery by lowering the clinical threshold for transfusion, and potentially contribute to recurrence in subsequent deliveries (158, 161). In regions with high anemia prevalence, studies show that prepartum anemia strongly influences transfusion practices (51, 162). The extent to which prepartum iron deficiency and anemia contribute to transfusion rates in Sweden, a high-income country with free-of-charge universal antenatal care, is, to our knowledge, unknown.

2.6.2 Study rationale

While several clinical risk factors for obstetric transfusion are well established, the recurrence of these factors across deliveries remains poorly understood. Some women appear more vulnerable to repeated transfusions, potentially due to unrecognized hematologic or familial factors. Our comprehensive, long-standing registry database offers an opportunity to explore recurrence patterns at scale. *Study II* assesses the risk of transfusion recurrence and investigate whether specific maternal or clinical characteristics can help identify women at elevated risk.

2.7 Long-term health after obstetric transfusions

Beyond immediate outcomes, transfusion may have long-term immunological consequences. This section addresses biological hypotheses and methodological concerns in interpreting long-term risks associated with transfusion exposure.

2.7.1 Known immunological hazards associated with transfusions

There are known non-infectious complications, particularly immunological reactions, associated with red-cell transfusion. Clinical manifestations such as febrile non-hemolytic transfusion reaction and transfusion-related acute lung injury (TRALI) range from mild to severe (163-168). Although exceedingly rare, fatal transfusion errors due to human error or blood incompatibility still occur (169, 170).

The incidence of these serious transfusion events in the obstetric population is not well delineated (165, 171-173). For women of reproductive age maternal alloimmunization—where maternal antibodies target fetal red-cell antigens, potentially causing hemolytic disease in the newborn—is a particularly relevant hazard. While alloimmunization may occur spontaneously, red-cell transfusions increase this risk (26, 174).

2.7.2 Immune effects of transfusion

Several hypotheses exist regarding the immunological effects of red-cell transfusions, particularly in individuals with existing or incipient autoimmune diseases (175, 176).

Transfusions are known to induce immunosuppression or modulation—an effect termed transfusion-related immunomodulation (TRIM) (177). This paradoxical phenomenon was historically observed through reduced rates of organ rejection following transfusion in transplant recipients (178). While it is speculated that TRIM may increase susceptibility to postoperative infections (e.g., pneumonia), randomized trials have yet to confirm such associations conclusively (178). There may also be a connection between an increased risk of red-cell transfusion-associated alloimmunization and underlying or incipient autoimmune disease, although causal pathways are challenging to establish (179). Other mechanisms of interest are that transfused donor antigens might resemble host antigens, triggering autoimmunity through molecular mimicry (180). In obstetric patients, specific immunomodulatory effects of red-cell transfusions have been noted, including suppressed T-helper cell activity (a type of white blood cell that plays a central role in coordinating the immune response) and increased levels of interleukin-10 (IL-10), an anti-inflammatory cytokine (181).

However, broader questions remain regarding how or if such immunologic alterations contribute to the clinical manifestations of subsequent inflammatory or autoimmune disorders.

Table 4. Diseases associated with transfusions. Prevalence and incidence (per year) in Sweden.

Disease	Brief description	Disease prevalence and incidence
Non-Hodgkin lymphoma (NHL)	A diverse group of malignant lymphomas affecting B-/T-cells. It includes aggressive and indolent subtypes and commonly affects lymph nodes but may involve extranodal sites. Risk increases with age and immune dysfunction (182).	*Incidence*: Approximately 20 per 100,000 individuals (nationwide). *Prevalence:* Has increased in recent decades due to a rising incidence and improved survival rates. *Female-to-male ratio*: slightly more common in men than in women. *Peak onset age*: 65–75 (183).
Systemic lupus erythematosus (SLE)	A chronic autoimmune disease involving multiple organ systems, characterized by autoantibody production and immune complex deposition (184).	*Prevalence (in women)*: 122 per 100,000 (regional data) *Incidence (in women):* 4.8 per 100,000. *Female-to-male ratio:* Approximately 7:1. *Female proportion:* 86.1% of cases *Mean age at diagnosis*: 43.7 years (185)
Rheumatoid arthritis (RA)	A systemic autoimmune disorder targeting synovial joints that leads to chronic inflammation, joint destruction, and extra-articular manifestations (186).	*Prevalence (in women)*: 940 per 100,000 (nationwide). *Incidence (in women)*: 56 per 100,000 women per year. *Female-to-male ratio*: Approximately 2:1. *Peak onset age*: 70–79 years for both sexes (187).
Systemic sclerosis	A connective tissue disease featuring widespread vascular abnormalities and excessive collagen deposition in skin and internal organs. It includes limited and diffuse subtypes (188).	*Prevalence*: 22.7 per 100,000 (nationwide) *Incidence*: 11.9 per 1,000,000 person-years. *Female-to-male ratio*: 5:1. *Female proportion*: 84% of prevalent cases, 80% of incident cases *Peak onset age*: 70–79 years for both sexes (189).

2.7.3 Challenges when studying transfusion outcomes

Many studies investigating transfusion-related outcomes encompass older, chronically ill populations (e.g., malignancy, cardiac disease, major surgeries) (190–192), in which transfusions often indicate disease severity, complicating causal interpretation of any effects associated with red-cell transfusions (193–195). Furthermore, older patients have limited lifespans post-transfusion. Typically, transfusion recipients are 65 years or older, with higher standardized

mortality rates compared to non-recipients (196-198). This, in turn, effectively restricts observation periods for autoimmune diseases with long latency periods. Thus, confounding by indication and competing risks remain critical methodological challenges in transfusion research. Collectively, the evidence regarding transfusion-associated autoimmune or malignant outcomes remains limited, inconsistent, and of varying quality (199-201).

2.7.4 Study rationale

Obstetric transfusion recipients represent a younger, healthier cohort, typically exposed to red-cell transfusion due to acute hemorrhage rather than chronic disease. This unique context presents an opportunity to examine transfusion-related immune outcomes with reduced confounding and extensive post-exposure observation periods. Given the predominance of women in autoimmune disease incidence and the biological plausibility of immune modulation following transfusion, we believe the aim of *study III*, which studies long-term risks in this population, is both relevant and timely.

2.8 Blood donation: effects on maternal and neonatal health

Blood donation is a critical public health contribution. However, repeat donations may impact iron reserves in the donor. Approximately half of Swedish blood donors are women (202), and, as discussed more extensively previously in this section, low iron stores may bring harm to female donors who become pregnant. This section provides a brief examination of the physiological effects of donation on iron stores and the challenges in distinguishing biological effects from confounding factors resulting from the donor's health status.

2.8.1 Blood donations and effects on iron stores

One whole blood donation (approximately 450 mL) removes between 200 and 250 mg of body iron. Frequent blood donation increases the risk of iron deficiency, particularly among premenopausal women who are already experiencing menstrual losses and dietary constraints (203-205). However, iron deficiency may pass unnoticed since hemoglobin level screening at the donation site (equivalent to 120–125 g/L or more) does not guarantee adequate iron reserves (206). For example, nearly 40 percent of frequent donors in Denmark

presented with ferritin levels below the iron deficiency threshold (less than 15 ng/mL), indicating that they were virtually iron-depleted (207).

Iron supplementation after donation is often recommended or provided and may be effective. However, donor adherence to this regimen is variable (208, 209). Thus, the WHO and the Association for the Advancement of Blood and Biotherapies (AABB) recommend routine ferritin measurement for blood donors in addition to hemoglobin testing (210, 211). Although efforts are underway to address this aspect of donor safety (212, 213), high donation frequency remains a strong predictor of donor iron deficiency (205).

In Sweden, specifically, female blood donors are permitted to donate whole blood three times (occasionally four) annually, with a minimum interval of 122 days between donations. They must meet a hemoglobin threshold of 125 g/L (214). Ferritin measurement is taken at baseline, while follow-up use of this measurement varies regionally. These measures contrast with more liberal policies in countries like the United States, where women may donate up to six times a year (215), with no universal recommendation for ferritin testing at first donation. In Europe, donor iron management strategies vary significantly, from minimal testing in the United Kingdom to proactive, ferritin-guided donation protocols in Denmark and the Netherlands (212, 216).

Table 5. Donor recommendations in selected countries.

Country	Minimum age	Donation interval	Postpartum deferral	Additional testing
Sweden	18 years	≥ 3-4 months	9 months	Ferritin testing at the first visit, varying follow-up according to regional policy
United States	16 years	≥ 8 weeks	≥ 6 weeks	No uniform recommendations
Denmark	17 years	≥ 3 months	6 months	Ferritin testing at the first visit and if Hb is below the deferral limit.
The Netherlands	18 years	≥ 4 months	6 months	Ferritin testing at the first visit and the fifth whole blood donation repeatedly

2.8.2 Challenges in research on blood donors

Studies on delivery and neonatal outcomes consistently indicate similar or better pregnancy outcomes among blood donors than non-donors (217-220). However, it would be implausible that blood donations *per se* lead to better pregnancy and delivery outcomes. Hence, results may reflect residual confounding due to the "healthy donor effect"—individuals who donate blood tend to be healthier than the general population due to self-selection and eligibility screening criteria (221, 222). Thus, the actual impact of donation-induced iron deficiency on maternal and neonatal outcomes remains unclear.

2.8.3 Study rationale

With access to detailed, long-standing national data on both blood donation and pregnancy outcomes, *study IV* aims to evaluate whether frequent pre-pregnancy blood donation is associated with adverse outcomes for the mother or child while accounting for the donor's health status. Understanding these risks is vital for guiding safe donation policies for women of reproductive age.

3 Research aims

The overall aim of this thesis was to explore aspects of red-cell transfusions in obstetrics and the effects of blood donations before delivery, more specifically:

Study I investigates temporal trends and the distribution of red-cell transfusion in a contemporary Swedish cohort

Study II examines the risk of recurrent red-cell transfusion in delivery

Study III investigates whether red-cell exposure in delivery is associated with an increased long-term risk of non-Hodgkin lymphoma and autoimmune disease.

Study IV examines whether blood donation before pregnancy is associated with increased risks for both mothers and their offspring.

4 Materials and methods

Sweden maintains several high-quality nationwide registers that enable the linkage of individual-level clinical, demographic, and socioeconomic data. These registers, managed primarily by the National Board of Health and Welfare and Statistics Sweden, are widely used in epidemiological research. In addition, specialized disease-specific and quality-of-care registers, such as the Swedish Intensive Care Register and the National Diabetes Register, complement national registers by offering detailed clinical data for selected conditions (223).

4.1 The personal registration number

Introduced in 1947 and standardized to a 10-digit format in 1967, the Swedish personal identification number ("personnummer") is assigned to all residents of Sweden. It encodes the individual's date of birth, a three-digit serial number (odd for males, even for females), and a check digit. Reporting all births to the Swedish Tax Agency is mandatory within one month postpartum. Upon registration, individuals granted temporary residence for more than one year are also assigned a personal identification number. Those without residency permits may receive a coordination number ("samordningsnummer") instead (224). Patients lacking valid identification at the time of care may be issued a temporary number, which can later be linked to their official personal ID in medical records. Such data, however, is not always captured in national health statistics. The personal identification number enables individual-level linkage across registers and is foundational to register-based epidemiology in Sweden (225, 226).

4.2 The SCANDATs

Until the late 1970s, blood transfusions in Sweden were predominantly unfractionated, collected by small-scale, independent blood banks (227). Early on, computer techniques, relying on punch cards, were used to manage the administrative and medical data within the blood banks (228). Along with the centralization and professionalization of the service followed fractionation and blood component therapy, and the development of methodologies that further improve blood safety (227, 229-232). The SCANDAT databases leverage early computerization to compile comprehensive "vein-to-vein" records of blood

donations and transfusions in Sweden, dating back to 1968, and in Denmark, from the 1980s. Nationwide data in Sweden have been available since 1996 (202).

The first version of SCANDAT was compiled between 2002 and 2004 through collaboration between academic institutions and regional blood services, linking donor and recipient data using personal identification numbers, primarily to study cancer risks in blood recipients and donors (233-235). SCANDAT2 was an update of the original database, compiling data up to 2012, while SCANDAT3 included data up to 2017. All studies in this thesis leverage the comprehensive SCANDAT3-S database (figure 1).

Although not a formal national quality register, SCANDAT3-S provides standardized, high-resolution data from all blood banks and transfusion laboratories in Sweden, enabling traceability of over 97 percent of transfusions and nearly all donations to uniquely identifiable individuals. It also includes individuals tested for blood group antigens for whatever clinical reason, resulting in a population base of approximately 8 million people. Additionally, SCANDAT3-S is pseudonymized and securely linked to multiple nationwide health and population registers, which facilitates large-scale, individual-level analysis of transfusion exposures and health outcomes.

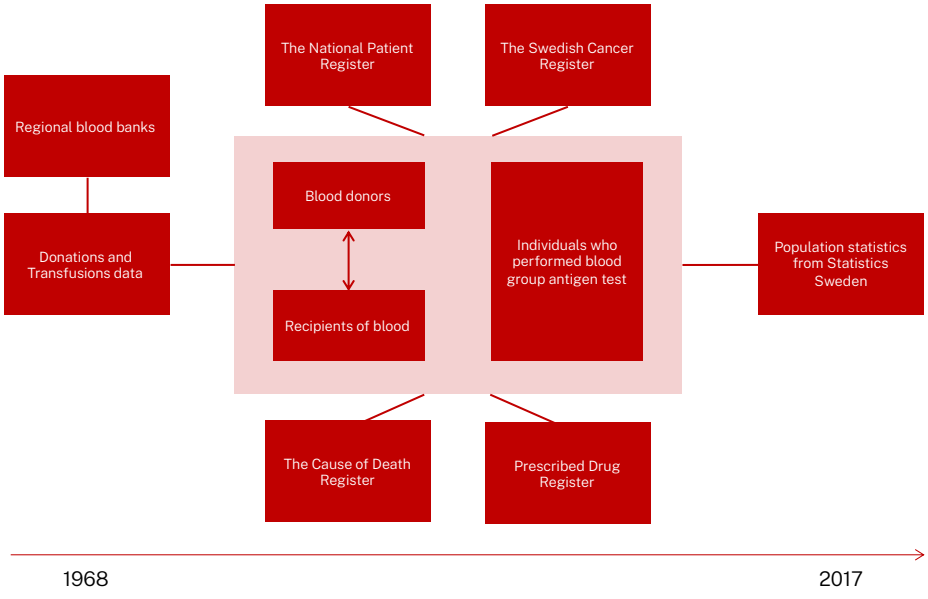

Figure 1. Schematic structure of SCANDAT3-S.

Although SCANDAT3-S provides unique opportunities, it has its limitations. Its completeness makes any comparison with population-based or regional studies challenging. Additionally, it lacks documented indications for transfusion. Instead, these must be inferred from diagnosis and procedure codes, introducing potential misclassification and confounding. The long-standing, large volume of data also raises challenges related to data quality, including entry errors, coding inconsistencies, and temporal changes. Moreover, as SCANDAT3-S was not nationwide until 1996, we manually adjusted the analysis database to ensure complete alignment between exposure and outcome data in *studies III* and *IV*, which each covered more extended periods. Further technical and historical details are available in other sources (202, 236-238).

4.3 Swedish National Board of Health and Welfare registers

The Swedish Medical Birth Register (MBR) is a nationwide database established in 1973, containing records of approximately 5 million live births from gestational week 22+0 and beyond (239). Stillbirths were initially recorded from week 28+0 but have been included from week 22+0 since 2008. The register captures about 98 percent of all deliveries in Sweden. It provides standardized, individual-level information on antenatal care, gestational age, maternal health conditions, delivery procedures, and neonatal outcomes, using the International Statistical Classification of Diseases (ICD-7-10) and procedure codes ("Klassifikation av vård-/ kirurgiska åtgärder," KVÅ and KKÅ). Data collection begins at the first antenatal visit—typically in the first trimester—and continues through delivery, postnatal discharge, or pregnancy loss. Since 2007, digital reporting has become the predominant method. Completeness is ensured through routine cross-checks between recorded personal identification numbers and birth records from the Total Population Register (kept by Statistics Sweden) (240). Discrepancies trigger validation queries from the National Board of Health and Welfare. The register also includes births to non-residents, which can occasionally result in a higher recorded number of births than that reported in the Total Population Register. Despite its high validity, the register has limitations. Missing data are common for certain variables, for instance, tobacco use in late pregnancy, especially snuff use. Demographic variables may be incomplete for mothers lacking a personal identification number. Additional inaccuracies or contradictions occasionally arise but are typically corrected upon detection.

Despite these limitations, the register remains one of Sweden's most widely used and validated sources for perinatal epidemiology, underpinning over 1,000 published studies (241). The register was the key source for maternal comorbidity and outcomes, as well as neonatal outcomes, in all studies.

The Swedish National Patient Register (NPR), maintained by the National Board of Health and Welfare, is a nationwide database covering virtually all hospital admissions in Sweden. It encompasses both public and private facilities and contains detailed records on patient demographics, admission and discharge dates, diagnostic codes (based on ICD classifications), surgical and medical procedures, and discharge outcomes. The NPR was established in the 1960s and attained full nationwide coverage for inpatient care in 1987. Since 2001, the register has also included data on outpatient specialist visits. These additions have enabled comprehensive longitudinal tracking of healthcare utilization, disease incidence, and treatment patterns across the Swedish population. Linkage through unique personal identification numbers enables integration with other national registers, substantially enhancing the value of the register for epidemiological research and the evaluation of health services. The NPR is widely used in research, routinely validated through quality control procedures, and externally assessed for coverage, coding accuracy, and reliability (242, 243). We retrieved comorbidity and outcome data from the NPR for *studies II* and *III*

The Swedish Prescribed Drug Register is a national database established in 2005, collecting individual-level data on all prescriptions dispensed at community pharmacies in Sweden. Although hospital-administered medications are excluded, this register allows linkage with other national registers, facilitating detailed analyses of medication usage and outcomes over extended periods (244). In *study III*, we used the register to identify the use of immunomodulatory or cytostatic medication.

The Swedish Cancer Register systematically compiles nationwide data on all incident cancer cases in Sweden. It includes standardized information on tumor characteristics, diagnoses, and treatments (245). The register serves as a source of outcome data in s*tudy III* (NHL).

4.4 Statistics Sweden registers

Statistics Sweden maintains several key registers critical for administrative functions and research infrastructure.

The Total Population Register provides demographic data for all residents, including personal identifiers, birth and death dates, marital status, and historical addresses, serving as a fundamental resource for population statistics and medical research (240).

The Multi-generation register links indexed individuals (born in 1932 and later and alive in 1961) to their biological parents and extended familial networks, enabling studies of intergenerational dynamics and genetic-environmental interactions. (246).

The Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA) consolidates longitudinal data on employment, education, income, and social security from multiple sources. It supports analyses of labor market participation and socioeconomic conditions, serving as a key data source for research on health outcomes related to socioeconomic status (247).

We use information from registers maintained by Statistics Sweden on demographic and socioeconomic covariates in *studies II*, *III*, and *IV*—including education, income, country of birth, migration, and mortality. In *study II*, we identified sibling relationships using the Multi-generation Register.

4.5 Study design

This chapter provides a consolidated description of the methodological framework underlying the four studies included in this thesis. It summarizes key aspects of study design, exposure and outcome definitions, and covariate selection. Its purpose is to enhance transparency, facilitate comparability, and provide an overview of shared methodological principles.

For specific details, please refer to the individual study.

Table 6. Overview of studies included in the thesis.

	Study I	Study II	Study III	Study IV
Design	Nationwide cohort	Nationwide cohort	Cohort (nationwide from 1996)	Cohort (nationwide from 1996)
Period	2003–2017	2000–2017	1987–2017	1985–2017
Participants	1,599,659 births	825,451 women	1,043,713 women	2,650,417 births
Main exposure		Prior red-cell transfusion in delivery	Red-cell transfusion in delivery	Whole blood donations before delivery
Primary outcome	Patterns of red-cell transfusion	Recurrent maternal red-cell transfusion	NHL, SLE, RA, and systemic sclerosis	Birth weight, SGA, preterm delivery, IUFD, maternal transfusion, and preeclampsia

4.5.1 Study sources

All four studies in this thesis are based on prospectively collected, linked, and pseudonymized data from nationwide Swedish health and population registers gathered within the SCANDAT3-S database. We describe these registers in sections 4.2 to 4.4.

4.5.2 Populations

Study I included all women aged 15 to 50 years who had a registered delivery in Sweden between 2003 and 2017, with each delivery treated as an independent observation. In the analysis of variation between hospitals, only delivery wards with more than 500 births per year were included, which comprised 42 general hospitals accounting for 97.8% of all recorded births.

Study II consisted of women aged 18 to 49 and included up to three consecutive births between 2000 and 2017. We excluded women with missing personal identification numbers, incomplete delivery dates, and emigration before first delivery or in between births. In a specific analysis, we included only women with singleton deliveries who received transfusions during their first delivery.

Study III included women aged 18 to 50 who had delivered their first child between 1987 and 2017. Women with a prior diagnosis of autoimmune disease, lymphoma, or any transfusion history unrelated to delivery were excluded. Follow-up commenced six months after delivery and continued until a diagnosis of outcome, censoring, death, or the end of the study. Within this study, we also created a matched sub-cohort to facilitate the estimation of absolute risk differences.

Study IV included all singleton births from 1985 to 2017 in women aged 18 to 50, excluding deliveries to women who had emigrated prior to giving birth. When using a five-year exposure window for blood donation, we included only births with full registry coverage in the preceding five years (e.g., the earliest inclusion date was 1 January 1990). For analyses requiring a five-year exposure window pre- and post-delivery, we included only births from the earliest of 1 January 1990 up to 31 December 2012. Thus, we included subsets of the cohort in specific analyses, depending on the temporal availability of data surrounding each delivery.

4.5.3 Exposure and outcome definitions

Across all studies, red-cell transfusion in temporal proximity to childbirth was a key variable, although its role as an exposure or outcome and the corresponding time windows differed.

In *study I*, the occurrence of red-cell transfusion within 14 days before or after delivery was the primary outcome used to describe overall transfusion patterns. We also considered the outcome in volume categories, analyzing it in relation to maternal and obstetric variables, calendar time, and hospital level.

In *study II*, red-cell transfusion was both an exposure (occurring at first delivery) and an outcome (at subsequent deliveries), defined as occurring from one day before to seven days after delivery. We stratified by the presence of postpartum hemorrhage (overall and by subtype) and whether transfusion was required, allowing for a separate evaluation of recurrence risks compared to non-

hemorrhaged, non-transfused women. In a separate analysis, we estimated the overall risk of transfusion in delivery among women with a sister who had a history of transfusion in delivery compared to those without a transfused sister.

In study *III*, red-cell transfusion was the exposure of interest, defined as occurring any number of times with any number of units from three days before to seven days after delivery. We updated exposure status at each delivery, and women who received transfusions during any delivery were categorized as "transfused" from that point forward. Outcomes included incident diagnoses of specified autoimmune diseases (SLE, systemic sclerosis, or RA) or non-Hodgkin lymphoma.

In *study IV*, we considered exposure as blood donation within five years of delivery, with donation intensity classified into three categories: low (1–2 donations), moderate (3–8 donations), and high (≥9 donations). We also analyzed timing and donation intensity, treating pre- and post-delivery donations as discrete events ranging from 1 to 15. Maternal transfusion served as one outcome (of several), defined as a recorded transfusion within seven days before or after delivery. Maternal outcomes also included preeclampsia, preterm birth, fetal demise, and postpartum hemorrhage. Neonatal outcomes included birth weight, low Apgar score (less than 7 at 5 minutes), and small-for-gestational-age (SGA) status.

4.5.4 Covariates and comorbidities

All studies included a core set of maternal and pregnancy-related covariates, though specific categorizations and modeling strategies varied by study objective.

Commonly included variables that we adjusted for were parity, body mass index (BMI, kg/m²), gestational age, fetal presentation, mode of delivery, delivery onset, hospital type (with three levels), and individual hospital (with 60 in total). Mentioned covariates were categorized to reflect clinical relevance and optimize statistical modeling. For example, gestational age was typically grouped into preterm, term, or post-term categories, and we classified delivery mode as spontaneous vaginal, instrumental vaginal, elective cesarean, or emergency cesarean. Maternal age and calendar year are significant covariates that we generally model as splines (with equally or manually placed knots, typically 5), allowing for non-linearity.

In *study II*, maternal comorbidities included both chronic and transient conditions such as diabetes (gestational and non-gestational), hypertensive disorders, various anemias, hemoglobinopathies (e.g., sickle cell disease, thalassemia), bleeding disorders (e.g., von Willebrand disease, idiopathic thrombocytopenic purpura), SLE, and chronic kidney disease. Chronic conditions were considered persistent across subsequent pregnancies following the initial diagnosis. Transient conditions, such as iron deficiency anemia, were only considered if diagnosed within nine months preceding delivery, allowing for differentiation between ongoing and resolved issues.

In *studies III* and *IV*, we also aimed to account for confounding and biases through socioeconomic variables. We included education level (ranging from non-completion of compulsory schooling to university degree), household income (categorized into percentiles), and birth origin as indicators of socioeconomic status, alongside health behaviors such as tobacco use and early pregnancy, as well as BMI (captured in antenatal visits).

4.6 Statistical approach

Each study used statistical models tailored to its specific research aims. The table below outlines the primary models applied and their justification.

Table 7. Overview of the statistical modeling applied in the thesis.

	Statistical model	Justification for model choice
Study I	Descriptive statistics, logistic regression, spline modeling, and direct standardization.	It allows flexible modeling of time trends and adjusted comparisons between hospitals, which helps characterize volume and transfusion patterns.
Study II	Logistic regression with robust standard errors.	Appropriate for binary outcome (recurrent transfusion), accounts for clustering through robust standard errors, and provides interpretable effect estimates and absolute risks.
Study III	Cox proportional hazards regression matched sub-cohort for cumulative incidence.	Enables time-to-event analysis for rare outcomes. Matching increases efficiency in estimating absolute risk differences while adjusting for major confounders.
Study IV	Mixed-effects linear regression, logistic regression, spline modeling, interaction analysis.	Models addressed repeated measures per woman. Splines capture non-linear dose-response. Robust methods mitigate cluster-related underestimation of variance in logistic regression analyses.

All processing and analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC, USA). Results from all regression analyses were presented with 95% confidence intervals (CI).

Repeated measurements refer to multiple observations of the same individual over time, allowing for the analysis of temporal trends and within-individual changes in exposures or covariates. Repeated measurements can introduce specific analytical challenges, including correlation between observations within the same individual, requiring appropriate statistical approaches to account for such correlations. Failure to appropriately handle these correlated data points can result in underestimated standard errors, inflated statistical significance, and potential misinterpretation of findings. Therefore, specialized statistical models, such as mixed-effects models or generalized estimating equations, are necessary to analyze and interpret repeated-measurement data correctly. We used mixed models with random intercepts to account for the correlation among multiple deliveries from the same woman in linear regression analyses, such as those on birth weight. In all our studies, we adopt robust variance estimators in logistic regression models as a practical alternative to adjust for residual clustering. Although we apply appropriate measures for handling repeated measurements,

women generally only contribute with a small number of deliveries, making it a less significant issue in practice.

4.6.1 Descriptive statistics, standardization, and temporality

In *study I*, the statistical analyses were primarily descriptive, aimed at characterizing overall patterns of obstetric red-cell transfusion in Sweden. We categorized deliveries based on transfusion status and stratified them further by the number of units administered: low (1–2 units), medium (3–9 units), and high (≥10 units), conveying clinical severity. Categorical variables, including demographic and gestational characteristics, were summarized using frequencies and percentages. Continuous variables were described with medians and interquartile ranges to convey central tendencies and variability.

The total number of units transfused per delivery day was calculated to investigate the volume and distribution of red-cell use. We also examined the distribution of unit counts per delivery and the corresponding cumulative proportion of total red-cell units administered.

We assessed the change in the proportion of transfused deliveries over time using logistic regression. The relationship between transfusion probability and year of delivery was modeled using a restricted cubic spline with five equally spaced knots, as this approach allowed for the flexible modeling of potentially non-linear relationships. Additional stratified analyses using parity, mode of delivery, and transfusion volume categories explored subgroup variation. We also modeled the likelihood of transfusion as a function of maternal age, using a spline with manually placed knots (for better fit).

Direct standardization methods were applied to assess variation between hospitals. Transfusion rates, presented as the number of transfusions per 1,000 deliveries, were standardized to the 2003 population distribution by maternal age and parity.

4.6.2 Logistic regression and risk of recurrent transfusion

In *study II,* we described the cohort according to characteristics and comorbidities in first, second, and third deliveries. We used logistic regression to model the odds ratios of overall risk of recurrent transfusion. Further, we applied a similar model to consider transfusion in a second delivery in relation to a history

of postpartum hemorrhage with or without concomitant transfusion, compared to non-hemorrhaged, non-transfused women. In women with three or more deliveries, we considered the risk of transfusion in each subsequent delivery with regard to their transfusion history.

Additional analyses included only women with singleton deliveries who had been transfused at their first delivery. In this subcohort, we also applied a logistic model to calculate the odds ratios for transfusion in second and third delivery, stratifying maternal comorbidities, obstetric complications, and events in prior deliveries.

Finally, we assessed familial aggregation, and the presence of a transfused sister was included as a predictor of transfusion.

All models were adjusted for potential confounders, including maternal BMI, birth origin, blood group, hospital level, and year of delivery. Maternal age and calendar year were modeled using restricted cubic splines with five knots. We included interaction terms to explore potential effect modification in women with recurrent transfusions. Robust sandwich estimators were employed to produce standard errors valid under within-subject clustering.

4.6.3 Cox regression, rare outcomes, and long-term follow-up

Study III assessed the long-term association between maternal red-cell transfusion during childbirth and the subsequent development of SLE, systemic sclerosis, RA, and NHL. We used Cox proportional hazards regression to estimate unadjusted and adjusted hazard ratios, with time since the most recent delivery as the underlying timescale. We chose this timescale to align follow-up with the biologically relevant window after childbirth, allowing for consistent modeling across women delivering at different ages and in various periods.

Entry into the cohort was determined by the date of the first recorded birth. The exposure was defined as any red-cell transfusion within three days before and seven days after delivery. Exposure status was treated as time-updated and irreversible (i.e., once exposed, women remained exposed throughout the study period). To minimize reverse causation, follow-up began six months postpartum and was uniformly delayed following each subsequent delivery. Outcomes were defined as the first registered diagnosis of NHL, SLE, systemic sclerosis, or RA. Follow-up continued until any outcome occurred, or censoring due to emigration,

diagnosis of human immunodeficiency virus (HIV) infection, in vitro fertilization (IVF) procedures, diagnosis of pregnancy-related endocrine disorders, the study's conclusion, or death. We also censored women who received blood products other than red-cells in delivery or any blood products in a non-obstetric setting.

The adjusted model included time-varying covariates updated at each delivery, such as maternal age and year of delivery (modeled as splines), parity, BMI, mode of delivery, preeclampsia, tobacco use, and hospital tier. When considering education and income, we carried forward the highest attainment. We treated birth origin and ABO blood group as fixed covariates, updated only at the time of study entry.

It is challenging to verify the proportional hazards assumption in these extensive datasets. However, we found this assumption to hold by examining the distributions of martingale residuals as a function of follow-up time for each of the four outcomes.

The cumulative incidence and its difference were estimated at 25 years using a matched sub-cohort (1:10 ratio). We matched on maternal age (within ±3 years), parity, delivery year (within ±2 years), and hospital tier. While this approach improves computational efficiency and interpretability, it introduces potential bias if the matching process disproportionately includes or excludes individuals based on their underlying risk. As such, the cumulative incidence estimates from the matched sub-cohort may not fully reflect incidence in the full population. This trade-off was considered appropriate, given the rarity of outcomes and the aim to provide both estimated absolute risk estimates and relative measures.

Sensitivity analyses explored robustness to reverse causation (via alternate latency periods), transfusion volume (1–2 vs. ≥3 units), calendar period, delivery mode, and preeclampsia.

4.6.4 Mixed model analyses and splines

Study IV assessed the relationship between whole blood donation before pregnancy and maternal and neonatal outcomes. Descriptive statistics were used to compare maternal and pregnancy characteristics between ever-donors and non-donors. For continuous outcomes such as birth weight, we applied linear

mixed-effects regression with a random intercept for each woman to account for repeated deliveries. Binary outcomes—including preeclampsia, preterm birth, SGA status, fetal demise, Apgar below 7 at 5 minutes, postpartum hemorrhage, and maternal transfusion—were analyzed using logistic regression models with robust standard errors. We excluded births with missing outcome information from analyses of the specific outcome.

Among women who donated within five years prior to delivery, donation frequency was examined both categorically (1–2, 3–8, ≥9 donations) and continuously (1 to 15 donations) using restricted cubic splines with five equally placed knots to capture non-linear dose-response patterns. We adjusted the models for maternal age and year of delivery (modeled as restricted cubic splines with five equally spaced knots), parity, BMI, tobacco use, birth origin, income, education, and hospital.

To specifically address "the healthy donor effect," we conducted a secondary analysis that incorporated a ten-year window around birth (five years before and after delivery). The aim was to compare births in which the parturient had donated an equal number of times – either exclusively before or after delivery. Since only pre-delivery donations would biologically affect pregnancy and delivery outcomes, the births of women who donated only after delivery served as a comparison. To achieve this, we included an interaction term (the ratio of pre-delivery donations to total donations) in the model. Using this term, we compared delivery outcomes among women with identical total donation counts but differing donation timing in relation to delivery (all donations prior to or all donations postpartum). Events we hypothesize might influence future donation behavior (such as fetal demise, postpartum hemorrhage, and maternal transfusion) were excluded from this analysis.

Sensitivity analyses included restriction analysis of birth weight in relation to donation intensity for term births, as well as alternative parameterizations of donation intensity.

5 Ethical considerations

5.1 Rationale and guiding principles

All medical research, including explorations of prospectively collected administrative data such as ours, must be grounded in the core principles of medical ethics: respect for autonomy, beneficence, non-maleficence, and justice. These principles, articulated in documents such as the Declaration of Helsinki (248) and the Council for International Organizations of Medical Sciences (CIOMS) guidelines (249), form the ethical foundation for research involving human data, even when individual informed consent is waived. We believe our research is well compliant with these principles.

5.2 General ethical considerations in register-based research

Large-scale register-based epidemiological studies enable investigations of rare events, long-term outcomes, and population-wide exposures that would be infeasible or unethical to study using experimental designs. These types of studies present specific challenges. Key ethical concerns include the absence of individual consent, the risk of re-identification, and the potential for unauthorized access to or leakage of data.

In Sweden, as in other Nordic countries, individual informed consent is not required for register-based research involving pseudonymized data. This practice is grounded in legal frameworks and long-standing research ethics praxis, supported by the ethical principle of maximizing public benefit. According to international guidelines, waiving consent may be justified when research poses minimal risk and holds significant social value, as is the case with large-scale epidemiological studies using securely managed health registers.

We address specific concerns regarding the risk of re-identification and information leakage through rigorous data protection protocols. For instance, all personal identifiers were removed prior to data access through a pseudonymization process in which national registration numbers were replaced with unique, non-identifiable codes. The key is securely stored by the Swedish Board of Health and Welfare, allowing additional linkages only under regulated

conditions. Hence, we performed all analyses on pseudonymized data and reported as aggregated results, reducing the risk of individual identification.

In addition to pseudonymization, we applied robust digital and physical data security measures throughout the research process. Access to data was restricted to authorized personnel using secure virtual private network (VPN) connections. Multi-factor authentication and encrypted storage were standard, and institutional firewalls, along with multiple layers of login and access control, protected all systems. Secure computing environments ensured compliance with national cybersecurity guidelines and university-level data handling protocols.

Beyond these concerns, we consider it an ethical imperative to use high-quality health data for the public good. The collection, maintenance, and governance of Swedish health registers represent a substantial investment of public resources and trust. As such, researchers are responsible for conducting methodologically sound, policy-relevant, high-quality studies that justify this investment. Thus, the responsible use of sensitive health data is a matter of stewardship, ensuring that the knowledge gained serves the greater good of society.

5.3 Study-specific ethical reflections

This specific research was approved by both the Regional Ethics Committee in Stockholm (reference 2018/167-31) and the Swedish Ethical Review Authority (reference 2023-07671-01). All handling complied with national and European Union data protection regulations, including the General Data Protection Regulation (GDPR).

All our studies, which aim to investigate signs of unnecessary exposure to blood products and actively search for their adverse effects, address ethical principles. However, we believe that the potential harms of whole blood donation before pregnancy deserve specific mention. Blood donation is an altruistic act—voluntary, uncompensated, and socially encouraged. Although blood donations benefit society, the possibility of iron depletion and related complications in blood donors must be carefully weighed against these goods. It imposes a heightened moral responsibility on researchers to rigorously examine whether donation practices may inadvertently place certain groups, such as women of reproductive age or their offspring, at increased risk.

6 Results

This section summarizes the main findings of the articles included in this thesis. For detailed results and analyses, please refer to the individual papers.

6.1 Study I

This nationwide observational cohort study, conducted in Sweden from 2003 to 2017, encompassed 1,599,659 deliveries among 959,686 women aged 15–50 years, with maternal red-cell transfusions administered in 3.0% of all deliveries.

6.1.1 Maternal characteristics and transfusion patterns

Compared with non-transfused cases, women receiving transfusions were at baseline more frequently nulliparous and more likely to experience preterm or post-term deliveries, instrumental or cesarean deliveries, and multifetal pregnancies. Across the study period, 139,424 red-cell units were recorded as administered. The overall use of red-cell units decreased over time, from 90 to 80 per 1,000 deliveries.

Nearly half of all transfusion events involved the administration of three units or fewer. Specifically, 62% of transfused deliveries received a 2-unit transfusion, while approximately 25% received more than three units (figure 2). Approximately 52.1% were used in transfusion events involving a total of three units or less.

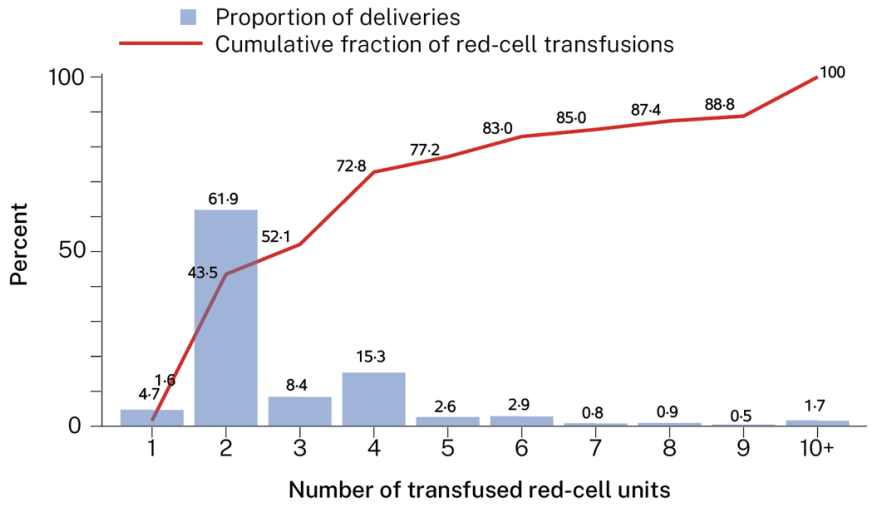

Figure 2. The distribution of blood use. Bars illustrate the number of red-cell transfusions per delivery. The solid line represents the cumulative proportion of all transfused red-cell units.

Regarding the timing of administration, 42% of units were administered on the day of delivery, 30% on the day after, and an additional 20% on or after the third postpartum day (figure 3).

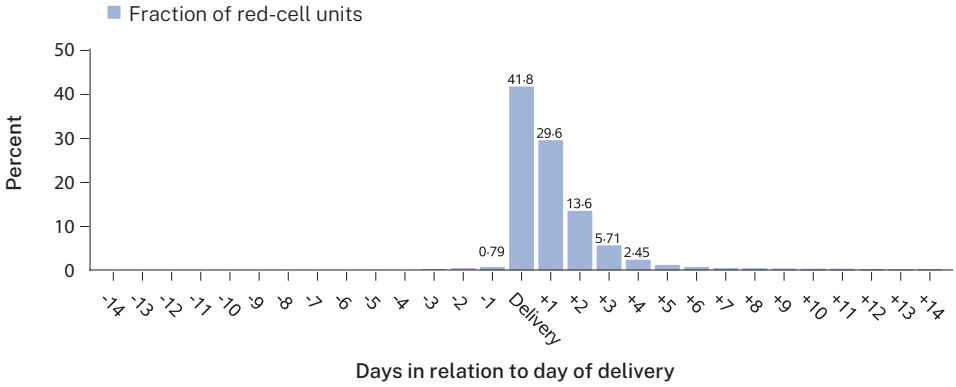

Figure 3. The distribution of red-cell unit usage in percent in relation to the day of delivery.

6.1.2 Temporal trends and standardization analysis

Although the proportion of transfused deliveries remained stable at approximately 30 per 1,000, a shift in transfusion volumes was observed over time (figure 4a). The incidence of low-volume transfusions (1–2 units) increased from 17 to 22 per 1000 deliveries, whereas moderate-volume (3–9 units) and high-volume (≥10 units) transfusions declined from 10 to 7.6 and from 0.7 to 0.3 per 1,000 deliveries, respectively (figure 4b).

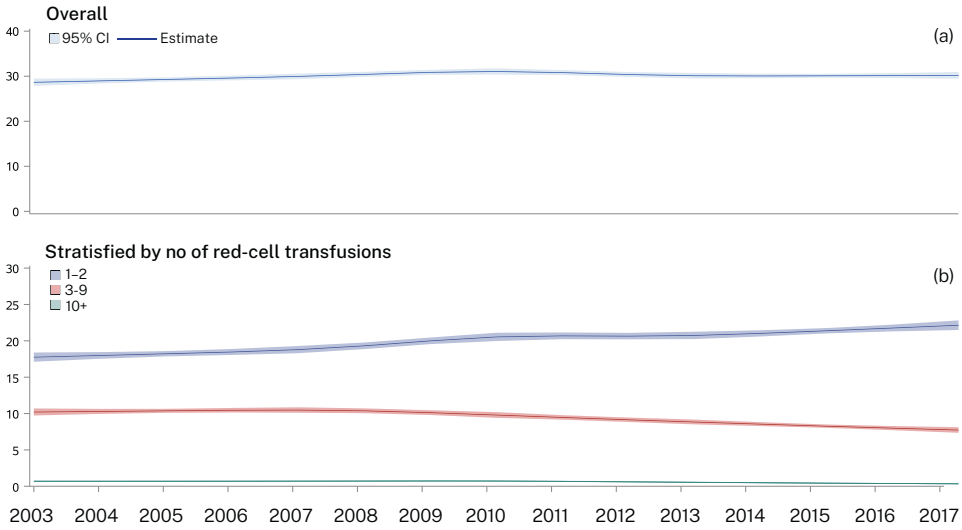

Figure 4. The proportion of deliveries in which red-cell transfusion occurred as a function of time for (a) the entire cohort and subdivided (b) according to the total number of administered red-cell units.

The analysis of variability (standardized to the 2003 population regarding maternal age and parity) revealed substantial inter-hospital variability, with transfusion rates ranging from 20 to 54 per 1,000 deliveries (figure 5).

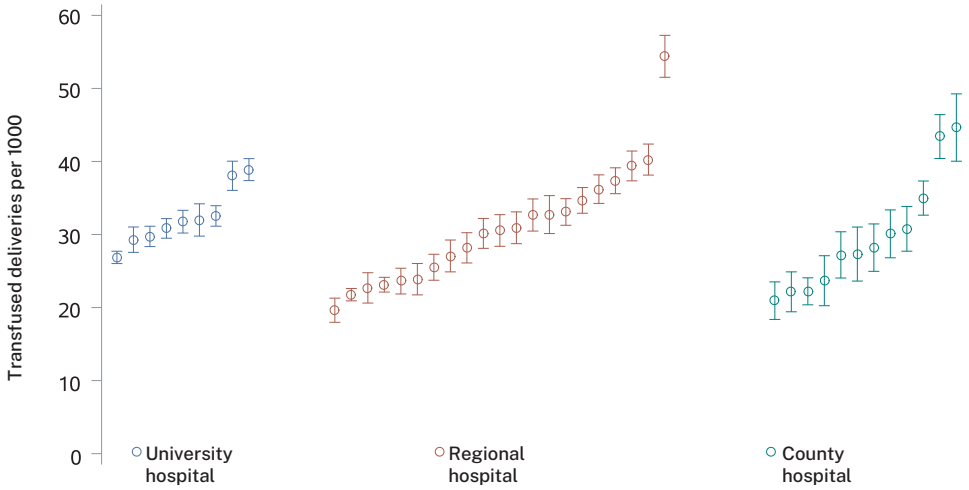

Figure 5. The hospital-specific number of transfused deliveries per 1,000 live births. Each circle represents an individual hospital, and the error bars represent the 95% confidence limits.

6.2 Study II

This study encompassed 825,451 women with 1,419,909 deliveries, and maternal red-cell transfusion was recorded in 3.0% of deliveries. Of these, 30,244 (3.8%) occurred in the first, 10,606 (2.1%) in the second, and 2,195 (1.8%) in the third delivery. Postpartum hemorrhage diagnosis was seen in 7.9%, 6.2%, and 5.6% of first, second, and third deliveries, respectively. Among the transfused individuals, 70.7%, 75.1%, and 74.4% in first, second, and third deliveries had a concomitant diagnosis of postpartum hemorrhage. Among women diagnosed with iron deficiency anemia, transfusion occurred in 9.8%, 6.0%, and 5.6% of deliveries in the first, second, and third deliveries, respectively. Among women with other hematological abnormalities, a large proportion were transfused in delivery.

6.2.1 Recurrence risk in relation to prior hemorrhage

The study demonstrated a striking overall recurrence risk for transfusion in delivery. In second deliveries, women with no prior transfusion or diagnosis of postpartum hemorrhage exhibited a transfusion rate of 1.7%. In contrast, for those who received a red-cell transfusion in the first delivery, 8.7% were transfused again in the subsequent delivery. Among women who received transfusions in both their first and second deliveries, 15.5% were transfused again in their third delivery. It corresponded to an adjusted odds ratio (aOR) of 11.5 (95% CI, 7.9–16.6) compared with women who had not received any previous transfusions.

Furthermore, we investigated the risk of transfusion in the second delivery, stratified by the presence of prior hemorrhage (and subtype) with or without transfusion (table 8). A prior diagnosis of hemorrhage without transfusion was associated with increased odds (aOR 2.4; 95% CI, 2.2–2.6) for transfusion in the second delivery compared to the reference of non-hemorrhaged, non-transfused women. However, the presence of a transfusion in the first delivery, regardless of hemorrhage, further increased the odds of transfusion in the second delivery compared to the reference (aOR 5.4; 95% CI, approximately 4.9–6.0).

Almost all subtypes of postpartum hemorrhage without transfusion conferred increased odds of transfusion in the next delivery compared to the reference. However, the most pronounced risk estimates were seen in women with hemorrhage and prior transfusion, especially those with atony (aOR 6.7; 95% CI, 6.1-7.4) and hemorrhage after cesarean section (aOR 6.8; 95%, CI 5.8-8.0).

Table 8. Risk of red-cell transfusion in a second delivery, in relation to previous transfusion, postpartum hemorrhage diagnosis, and obstetric transfusions in their sisters.

Events in the first delivery	Second delivery	aOR
	No. of transfused (% of all)/not transfused	(95% CI)[a]
Any diagnosis of hemorrhage		
No postpartum hemorrhage, no transfusion	8,029 (1.7)/458,950	1.0 (ref.)
Postpartum hemorrhage, no transfusion	998 (4.1)/23,612	2.4 (2.2–2.6)
No postpartum hemorrhage, with transfusion	431 (8.7)/4,506	5.4 (4.9–6.0)
Postpartum hemorrhage, with transfusion	1,106 (8.7)/11,635	5.4 (5.0–5.8)
Specific types of hemorrhage		
No postpartum hemorrhage, no transfusion	8,029 (1.7)/458,950	1.0 (ref.)
Atony, no transfusion	220 (5.1)/4,136	3.1 (2.7–3.6)
Atony, with transfusion	546 (10.6)/4,608	6.7 (6.1–7.4)
Placental retention, no transfusion	280 (3.3)/8,154	1.9 (1.7–2.2)
Placental retention, with transfusion	229 (7.4)/2,872	4.4 (3.8–5.1)
Laceration, no transfusion	74 (2.6)/2,790	1.4 (1.1–1.8)
Laceration, with transfusion	107 (5.1)/2,002	3.1 (2.5–3.8)
Unspecified hemorrhage, no transfusion	80 (3.8)/2,044	2.3 (1.8–2.9)
Unspecified hemorrhage, with transfusion	50 (7.2)/646	4.4 (3.3–6.0)
Delayed hemorrhage, no transfusion	10 (1.6)/608	0.9 (0.5–1.8)
Delayed hemorrhage, with transfusion	29 (6.1)/449	3.9 (2.7–5.7)
Hemorrhage after cesarean, no transfusion	311 (5.6)/5,279	3.3 (2.9–3.7)
Hemorrhage after cesarean, with transfusion	185 (11.1)/1,487	6.8 (5.8–8.0)
Obstetric transfusions in sister		
Overall	10,564 (2.1)	
Female sibling with no transfusion in delivery	1,636 (2.1)	1.0 (ref.)
Female sibling with transfusion in delivery	146 (3.5)	1.8 (1.5–2.1)
No female sibling with delivery	8,782 (2.1)	1.0 (0.9–1.1)

a. *Odds ratios adjusted for maternal age (spline), year of delivery (spline), BMI, hospital level, country of birth, and blood group.*

6.2.2 Familial influence

Additionally, we observed a familial component (table 8). Women with a sister who had received a transfusion during delivery were at moderately increased odds of transfusion herself (aOR 1.8; 95% CI, 1.5–2.1).

6.2.3 Risk factors for recurrent transfusion

Thus, women who were transfused in the first delivery had an increased baseline risk of transfusion. We specifically examined risk factors for recurrence in the stratum of women who had received a transfusion in a first singleton delivery (table 9). Events such as the manual evacuation of the placenta (aOR 1.3; CI 95 %, 1.2-1.5), retained placenta (aOR 1.4; CI 95 %, 1.3-1.5), and caesarian section (aOR 1.4; CI 95 %; 1.2-1.6) increased the risk of new transfusion compared to women without these complications. Similarly, recurrent transfusion was more likely in women with a diagnosis of preeclampsia (aOR 2.2; CI 95 %, 1.7-2.7), placenta previa (aOR 5.0; CI 95 %, 3.8-6.7), other placental abnormalities (aOR 7.5; CI 95 %, 3.8-6.7), and preterm delivery (aOR 5.0; CI 95 %, 3.8-6.7) in second delivery, compared to women without such events.

Among women with iron deficiency anemia diagnosed before the second delivery, we saw a modestly increased risk for recurrent transfusion (aOR 1.9; 95% CI, 1.2-3-3). However, the number of individuals in this analysis was small.

Table 9. Risk of recurrent red-cell transfusion at delivery in subsequent singleton deliveries in women with red-cell transfusion in the first singleton delivery, in relation to gestational comorbidity and events.

	Second delivery		Third delivery	
	Transfused (%)	aOR (95% CI)[a]	Transfused (%)	aOR (95% CI)[a]
Deliveries with transfusion	1,458 (8.6)	-	204 (5.8)	-
Comorbidity[b]				
Pre-eclampsia	83 (16.0)	2.2 (1.7–2.7)	13 (8.7)	1.8 (1.0–3.3)
Gestational hypertension	17 (8.6)	0.9 (0.6–1.7)	4 (9.8)	1.9 (0.7–5.6)
Gestational diabetes	44 (9.9)	1.2 (0.9–1.7)	7 (5.7)	1.1 (0.5–2.4)
Iron-deficiency anemia	6 (13.6)	1.9 (1.2–3.3)	9 (20.0)	4.1 (1.8–9.1)
Other anaemia	4 (7.7)	1.7 (1.1–2.7)	5 (10.2)	1.9 (0.8–1.5)
Prepartum factors[b]				
Intrauterine fetal death	5 (8.9)	0.9 (0.3–2.3)	0 (0.0)	n/a

In vitro fertilization	59 (13.5)	1.6 (1.2–2.1)	7 (8.9)	1.8 (0.8–4.0)
Antepartum hemorrhage	15 (20.0)	2.3 (1.2–4.8)	4 (19.0)	2.8 (0.8–9.8)
Non-cephalic presentation	255 (10.9)	1.4 (1.2–1.5)	44 (9.8)	1.9 (1.4–2.8)
Placenta praevia	74 (31.5)	5.0 (3.8–6.7)	14 (29.2)	4.8 (2.2–10.2)
Placental abnormality	13 (43.3)	7.5 (3.6–17.6)	5 (62.5)	n/a
Preterm delivery	136 (16.4)	2.4 (2.0–2.6)	24 (12.6)	2.4 (1.4–3.9)
Post-term delivery	108 (10.6)	1.3 (1.0–1.6)	15 (8.3)	1.5 (0.8–2.6)
Intrapartum factors[b]				
Dystocia	161 (15.1)	2.0 (1.7–2.4)	10 (10.1)	1.8 (0.9–3.6)
Offspring weight >4500g	163 (12.9)	1.6 (1.3–1.9)	27 (9.9)	2.0 (1.3–3.1)
Mode of delivery[c]				
Spontaneous vaginal	922 (7.9)	1.0 (ref.)	127 (5.1)	1.0 (ref.)
Emergency cesarean	216 (16.1)	2.3 (2.0–2.8)	37 (18.4)	4.7 (3.1–7.2)
Planned caesarean	229 (6.9)	0.9 (0.8–1.0)	36 (4.9)	1.0 (0.7–1.5)
Instrumental	90 (14.9)	1.9 (1.5–2.4)	4 (7.8)	1.7 (0.6–4.8)
Events in the previous delivery[b]				
Dystocia	499 (8.9)	1.1 (1.0–1.2)	72 (5.9)	1.0 (0.8–1.4)
Manual exploration of the uterus	533 (10.1)	1.3 (1.2–1.5)	81 (7.2)	1.3 (1.0–1.8)
Retained placenta	521 (10.4)	1.4 (1.3–1.5)	84 (7.7)	1.5 (1.1–2.0)
Postpartum hemorrhage	1,049 (8.5)	1.0 (0.9–1.3)	149 (5.8)	0.9 (0.7–1.3)
Cesarean	431 (10.8)	1.4 (1.2–1.6)	71 (6.4)	1.1 (0.8–1.5)
Unassisted vaginal delivery	672 (7.9)	1.2 (1.1–1.3)	161 (5.7)	1.2 (0.8–1.7)

a. *aOR, odds ratio adjusted for maternal age at delivery, body mass index (BMI), hospital level, year of delivery, country of birth, and blood group.*

b. *Variables are binary and non-cases act as reference.*

c. *Mutually exclusive variable.*

6.3 Study III

In this cohort study of 1,043,713 women with 1,999,013 deliveries, 4.1% of the women received at least one red-cell transfusion during childbirth.

6.3.1 Long-term risk of adverse outcomes

Relative to non-transfused women, those who were transfused experienced a modestly increased long-term risk of certain autoimmune diseases (table 10). The adjusted hazard ratios (aHRs) were 1.38 (95% CI, 1.01–1.87) for SLE and 1.89 (95% CI, 1.12–3.21) for systemic sclerosis. The corresponding cumulative incidence differences at 25 years of follow-up were 0.09% (95% CI, 0.01 to 0.18%) and 0.08% (95% CI, −0.01 to 0.10%), respectively. In contrast, the risks for NHL and RA were not elevated (aHR 0.86; 95% CI, 0.53-1.40 and 1.07; 95% CI, 0.92–1.24, respectively).

Table 10. Incidence rates, events per person-years, and unadjusted and adjusted cause-specific hazard ratios for the diagnosis of NHL, SLE, systemic sclerosis, or RA in relation to red-cell exposure during delivery.

Diagnosis group	Incidence rate[a]	Events / person-years	Unadjusted HR (95% CI)	Adjusted HR[b] (95% CI)
Non-Hodgkin lymphoma				
Transfusion in delivery	4.0	17/420,460	0.93 (0.57–1.50)	0.86 (0.53–1.40)
No transfusion in delivery	4.6	540/11,805,084	1.00 (ref)	1.00 (ref)
Systemic lupus erythematosus				
Transfusion in delivery	10.2	43/420,460	1.46 (1.07–1.98)	1.38 (1.01–1.87)
No transfusion in delivery	7.0	824/11,805,084	1.00 (ref)	1.00 (ref)
Systemic sclerosis				
Transfusion in delivery	3.6	15/420,460	2.05 (1.21–3.45)	1.89 (1.12–3.21)
No transfusion in delivery	1.8	208/11,805,084	1.00 (ref)	1.00 (ref)
Rheumatoid arthritis				
Transfusion in delivery	44.0	185/420,460	1.13 (0.98–1.31)	1.07 (0.92–1.24)
No transfusion in delivery	39.5	4,666/11,805,084	1.00 (ref)	1.00 (ref)

a. *Per 100,000 person-years.*

b. *Adjusted for maternal age (spline), year of delivery (spline), parity, blood group, birth origin, BMI, smoking, smoking, snuff use, income, level of education, hospital level, mode of delivery, and preeclampsia in any delivery.*

We found no overall risk of death associated with red-cell transfusion in delivery (aHR 0.99; 95% CI, 0.80–1.21).

6.3.2 Sensitivity and dose-response analyses

Sensitivity analyses were performed by stratifying according to the accumulated number of transfused units, calendar period, mode of delivery, and the delay in the start of postpartum follow-up (figure 6).

Among women receiving 1–2 units, the aHR for SLE was 1.25 (95% CI, 0.85–1.84), whereas for those receiving three or more units, it increased to 1.66 (95% CI, 1.01–2.73). Similar patterns were observed for systemic sclerosis, with adjusted HRs of 1.83 (95% CI, 0.97–3.47) and 2.03 (95% CI, 0.84–4.92), respectively. The point estimates for the two exposure categories were statistically non-significant for all outcomes.

Stratified analyses by calendar period revealed no clear temporal trends, and interaction tests between time period and red-cell exposure were non-significant for all outcomes. As expected, statistical power was lower in earlier years. Varying the start of follow-up for each postpartum period had little effect on the adjusted hazard ratios for NHL, SLE, and RA. However, for systemic sclerosis, initiating follow-up immediately after childbirth yielded a higher hazard ratio (aHR 1.98; 95% CI, 1.19–3.30) compared to starting one or two years postpartum (aHR 1.66; 95% CI, 0.95–2.91, and aHR 1.51; 95% CI, 0.82–2.78, respectively).

Stratification by cesarean section did not materially affect the results for NHL, systemic sclerosis, or RA. For SLE, the association was attenuated among those with cesarean delivery (aHR 1.21; 95% CI, 0.71–2.05). Interaction tests between red-cell transfusion and cesarean section were non-significant for all outcomes. Excluding patients with preeclampsia had minimal impact on the results, and we observed no significant interactions.

Overall, sensitivity analyses affirmed the primary results and suggested that maternal red-cell transfusion during the peripartum period is modestly associated with a long-term increased risk of certain autoimmune conditions.

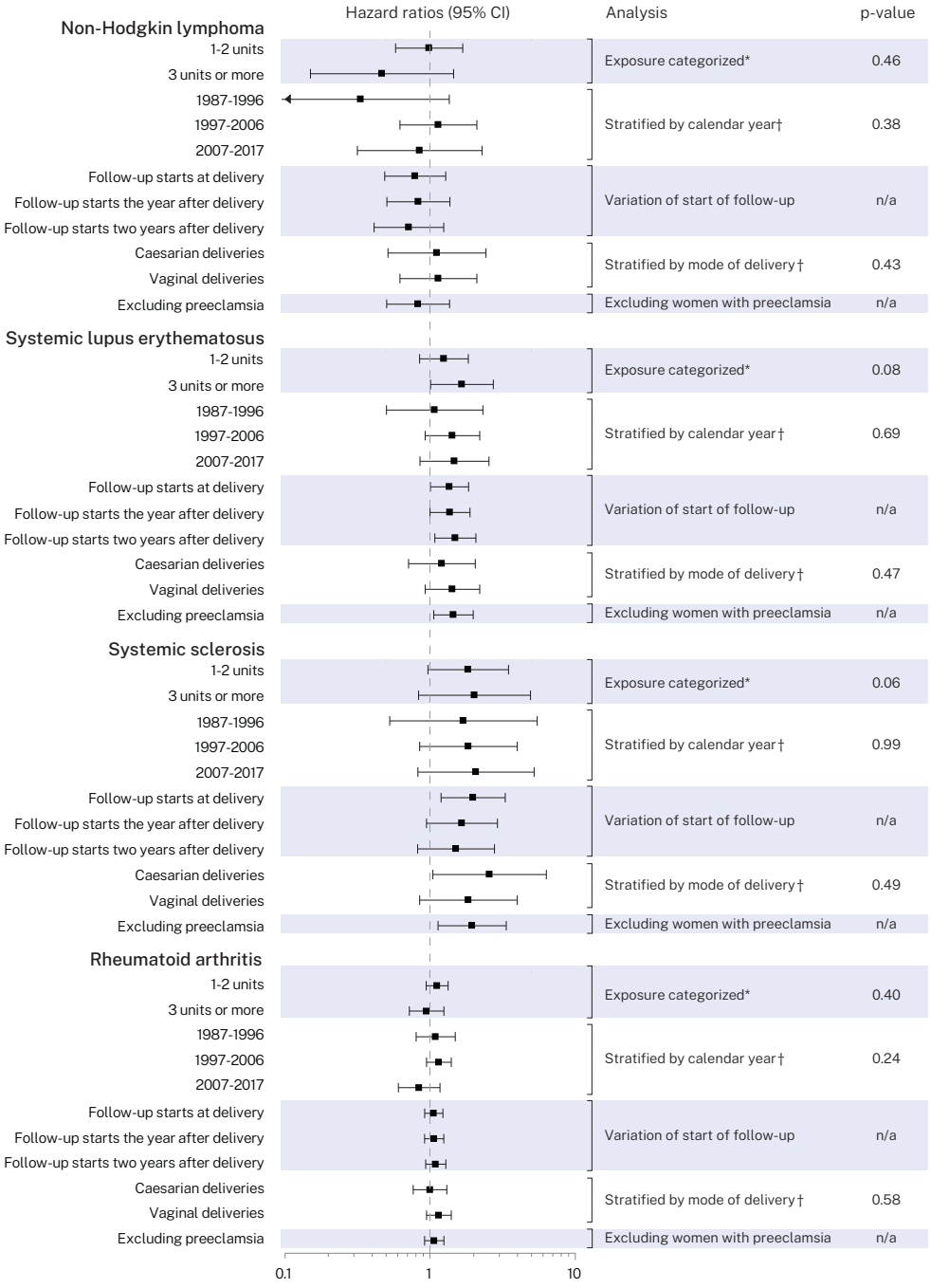
Hazard ratios (95% CI)
Analysis
p-value
Non-Hodgkin lymphoma
1-2 units
3 units or more
Exposure categorized*
0.46
1987-1996
1997-2006
2007-2017
Stratified by calendar year†
0.38
Follow-up starts at delivery
Follow-up starts the year after delivery
Follow-up starts two years after delivery
Variation of start of follow-up
n/a
Caesarian deliveries
Vaginal deliveries
Stratified by mode of delivery†
0.43
Excluding preeclamsia
Excluding women with preeclamsia
n/a
Systemic lupus erythematosus
1-2 units
3 units or more
Exposure categorized*
0.08
1987-1996
1997-2006
2007-2017
Stratified by calendar year†
0.69
Follow-up starts at delivery
Follow-up starts the year after delivery
Follow-up starts two years after delivery
Variation of start of follow-up
n/a
Caesarian deliveries
Vaginal deliveries
Stratified by mode of delivery†
0.47
Excluding preeclamsia
Excluding women with preeclamsia
n/a
Systemic sclerosis
1-2 units
3 units or more
Exposure categorized*
0.06
1987-1996
1997-2006
2007-2017
Stratified by calendar year†
0.99
Follow-up starts at delivery
Follow-up starts the year after delivery
Follow-up starts two years after delivery
Variation of start of follow-up
n/a
Caesarian deliveries
Vaginal deliveries
Stratified by mode of delivery†
0.49
Excluding preeclamsia
Excluding women with preeclamsia
n/a
Rheumatoid arthritis
1-2 units
3 units or more
Exposure categorized*
0.40
1987-1996
1997-2006
2007-2017
Stratified by calendar year†
0.24
Follow-up starts at delivery
Follow-up starts the year after delivery
Follow-up starts two years after delivery
Variation of start of follow-up
n/a
Caesarian deliveries
Vaginal deliveries
Stratified by mode of delivery†
0.58
Excluding preeclamsia
Excluding women with preeclamsia
n/a
0.1
1
10

Figure 6. Adjusted hazard ratios from sensitivity analyses exploring the risk of a diagnosis of NHL, SLE, systemic sclerosis, or RA in relation to red-cell exposure in delivery. All comparisons are in relation to non-transfused women.

All analyses were, if applicable, adjusted for maternal age (spline), parity, blood group, birth origin, early pregnancy BMI, smoking, smoking, snuff use, income, level of education, hospital level, year of delivery (spline), delivery mode, and preeclampsia.

† Separate analyses of the effect of red-cell transfusion on disease outcome per subgroup stratum, where no transfusion in delivery acts as reference (not shown).

** Categorization of the total number of red-cell transfusions into categories "no transfusion" (reference, not shown), "1-2 units" or "3 units or more".*

6.4 Study IV

This cohort comprised 2,551,685 singleton deliveries in Sweden from 1985 to 2017, of which 306,970 (12.0%) were to women who had previously donated blood.

6.4.1 Donor characteristics and baseline comparisons

Blood donors differed from non-donors across key characteristics. Donors were more likely to be Swedish-born to Swedish parents (84.3% vs. 67.3%), older (median age 32 vs. 30 years), had greater educational attainment (54.9% vs. 32.0% with ≥3 years of university education) and income (16.6% vs. 9.7% above the 90th percentile). They also had slightly higher median BMI (24 vs. 23) and were less likely to smoke. When comparing deliveries among recent donors (within five years of delivery) to never donors, the donor offspring had a marginally higher mean birth weight (adjusted estimate; 3,488 g vs. 3,454 g; mean difference 34 g; 95% CI, 32–37 g), and the donor had lower odds of preeclampsia, preterm birth, intrauterine fetal death, SGA infants, low offspring Apgar score, and maternal transfusion.

6.4.2 Donation intensity and dose-response patterns

When we restricted the analyses to births from only donors, a dose-response pattern emerged (table 11). Adjusted mean birth weights were gradually lower with higher donation intensity: 3,613 g in women with 1–2 previous donations, 3,603 g in women with 3–8 prior donations, and 3,585 g in women with ≥9 donations within five years of delivery. We also observed increased odds of preeclampsia (aOR 1.18; 95% CI, 1.06–1.31), preterm birth (aOR 1.33; 95% CI, 1.22–1.45), and SGA infants (aOR 1.17; 95% CI, 1.03–1.34). For fetal demise, low Apgar scores, postpartum hemorrhage, and maternal transfusion, point estimates for aORs were above 1, but confidence intervals included the null.

Table 11. Associations between the number of blood donations five years before pregnancy and birth weight as well as with the risk of adverse delivery and neonatal outcomes.

	Donations before pregnancy	Deliveries	Birthweight, g (95% CI)	Birthweight, g (95% CI)[a]	Birthweight difference, g (95% CI)[a]
Birthweight	1-2	81,967	3,593 (3,589-3,597)	3,613 (3,593-3,633)	0.0 (ref)
	3-8	86,584	3,565 (3,561-3,568)	3,603 (3,583-3,624)	+10 (4-16)
	9+	10,675	3,477 (3,467-3,487)	3,585 (3,563-3,607)	+28 (17-38)

		Deliveries (% outcome)	Odds ratio (95% CI)	Odds ratio (95% CI)[a]
Preeclampsia	1-2	79,825 (2.8)	1.00 (ref)	1.00 (ref)
	3-8	84,105 (3.0)	1.10 (1.04-1.17)	1.03 (0.97-1.09)
	9+	10,244 (4.3)	1.56 (1.41-1.73)	1.18 (1.06-1.31)
Delivery < 37 weeks of gestation	1-2	78,456 (4.4)	1.00 (ref)	1.00 (ref)
	3-8	82,636 (4.7)	1.07 (1.02-1.12)	1.05 (1.00-1.10)
	9+	10,006 (6.5)	1.49 (1.37-1.62)	1.33 (1.22-1.45)
Fetal demise	1-2	81,882 (0.3)	1.00 (ref)	1.00 (ref)
	3-8	86,497 (0.3)	1.09 (0.91-1.30)	1.05 (0.88-1.27)
	9+	10,663 (0.3)	1.27 (0.89-1.81)	1.16 (0.81-1.66)
Small-for-gestational age infant	1-2	80,583 (1.8)	1.00 (ref)	1.00 (ref)
	3-8	85,039 (2.0)	1.07 (1.00-1.14)	1.03 (0.96-1.11)
	9+	10,418 (2.6)	1.43 (1.26-1.63)	1.17 (1.03-1.34)
Apgar < 7 at 5 minutes	1-2	81,171 (1.1)	1.00 (ref)	1.00 (ref)
	3-8	85,794 (1.1)	0.97 (0.89-1.06)	0.92 (0.84-1.00)
	9+	10,533 (1.6)	1.38 (1.16-1.62)	1.12 (0.94-1.33)
Postpartum hemorrhage	1-2	76,168 (7.2)	1.00 (ref)	1.00 (ref)
	3-8	80,506 (7.2)	1.00 (0.96-1.03)	0.99 (0.96-1.03)
	9+	9,859 (7.9)	1.09 (1.01-1.18)	1.02 (0.95-1.10)
Peripartum maternal transfusion	1-2	80,295 (2.2)	1.00 (ref)	1.00 (ref)
	3-8	84,791 (2.3)	1.03 (0.96-1.09)	0.98 (0.92-1.05)
	9+	10,379 (3.0)	1.37 (1.22-1.55)	1.12 (0.99-1.26)

a. *Adjusted for maternal age (spline), year (spline), BMI, parity, birth origin, smoking in early pregnancy, level of education, income bracket, and hospital.*

When modeling donations as discrete events, a similar pattern appears with lower birth weight accompanying increasing donation intensity (figure 7). Compared to women with only one donation in the previous five years, the relationship between donations and birth weight was modest until approximately eight donations, at which a visual inflection point may be perceived. The adjusted birth weight point estimates for deliveries to a woman with 15 donations in the previous five years were -74 g (95% CI, -139 to -11 g) compared to deliveries to a woman with only one donation in the same time frame.

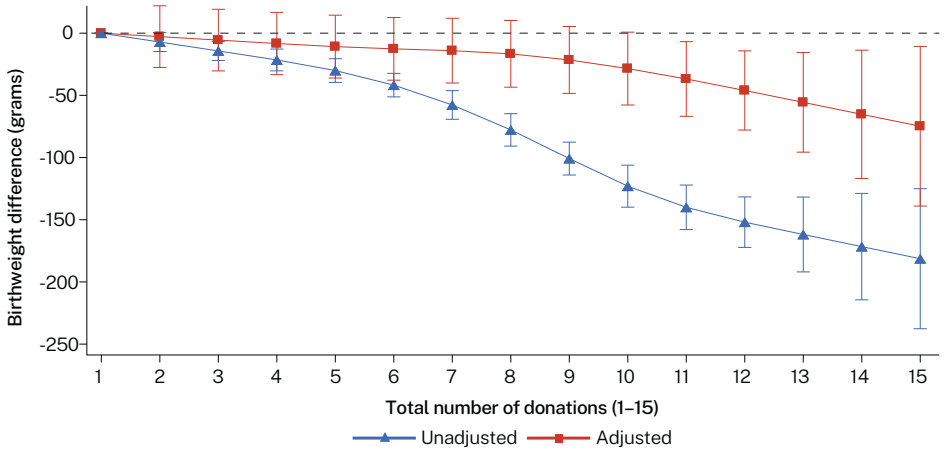

Figure 7. The difference in birth weight in relation to the number of whole blood donations within five years before delivery, compared to women with only one previous donation.

Displaying unadjusted (blue line) and adjusted (red line) analyses. Adjustments for maternal age (spline), year of delivery (spline), parity, body mass index (BMI), birth origin, smoking in early pregnancy, level of education, income bracket, and delivery hospital.

6.4.3 Sensitivity analyses

Our secondary analyses aimed to evaluate the biological rationale and robustness of the findings.

When comparing women with equal donation counts, those who donated exclusively before delivery had considerably lower offspring birth weights than those who only donated after delivery (figure 8). The difference increased with the increasing intensity of donations. For example, the mean adjusted birth weight of children born to women who exclusively donated blood 15 times before delivery was 152 g lower (95% CI, -244 to -60 g) than in children born to women who exclusively donated blood 15 times after delivery. When comparing women who

had only one donation before or after delivery, however, we found no meaningful difference.

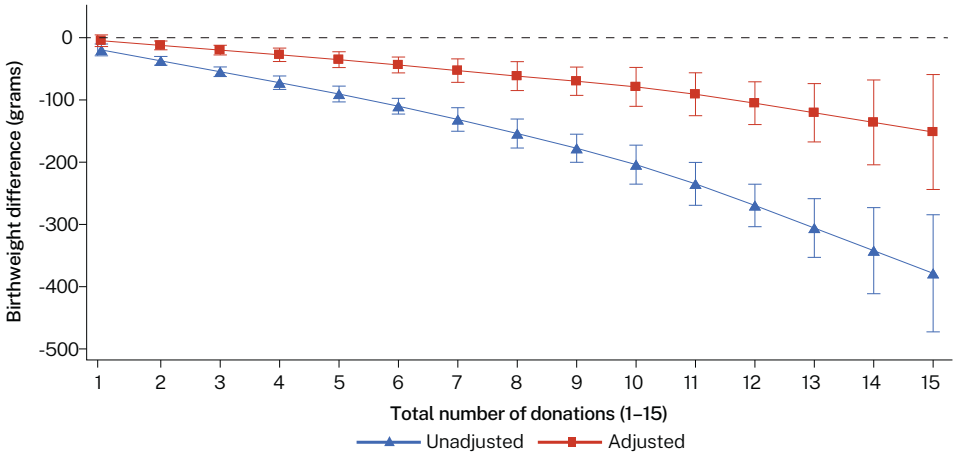

Figure 8. The difference in birth weight in relation to the total number of donations before or after delivery, comparing women with the same number of donations before and after delivery.

Displaying unadjusted (blue line) and adjusted (red line) analyses. Analyses were adjusted for maternal age (spline), year of delivery (spline), parity, BMI, birth origin, smoking in early pregnancy, level of education, income bracket, and delivery hospital.

Similar results were seen in models considering the risks of preeclampsia (aOR 1.70; 95% CI, 0.65–4.47) and preterm birth (aOR 2.31; 95% CI, 1.07-4.97) for women with 15 donations before delivery, as compared to those donating only after delivery. No associations were observed for women who donated only once. There were no clear associations of any risk increase of having an SGA infant or an infant with an Apgar score of less than 7 at 5 minutes.

When restricting analyses to term pregnancies, we observed a slight attenuation in the reduction in birth weight, indicating that the increased risk of prematurity explains some of the effects of donations. However, since prematurity may be in the causal chain, stratification introduces (collider) bias, and the result should be interpreted with caution. Alternative parameterization of the spline variable as a categorical variable did not substantially alter findings.

7 Methodological considerations

The registers used in this thesis are robust, long-standing, comprehensive, and have nationwide coverage, with minimal loss to follow-up. Their extensive size and scope enable the study of rare exposures and outcomes with sufficient statistical power, allowing for longitudinal follow-up of individuals over extended periods.

Our studies rely exclusively on data already present in these registers, thereby limiting our analyses to the information that is recorded. In some instances, we lack clinical or socioeconomic nuances. While prospective experimental designs such as randomized controlled trials or primary data collection might offer more granularity, they are impractical or ethically unfeasible for the research questions addressed in this thesis.

7.1 Sources of error

In retrospective observational research, especially register-based cohort studies, a central methodological goal is to approximate causal inference—an approach rooted in the philosophical idea of estimating the effect of an exposure on an outcome while accounting for confounding and bias (250-252). This involves engaging with "theoretical counterfactuals," by which we mean hypothetical scenarios representing what would have happened to the same individual had they not been exposed, assuming all other factors remained unchanged. These counterfactuals underpin causal inference by providing a benchmark against which observed outcomes are interpreted.

Because we cannot observe both the exposed and unexposed states in the same individual, we aim to identify two groups that are sufficiently similar to allow for a meaningful comparison. Adjustment helps reduce confounding, thereby making the comparison more closely resemble the counterfactual scenario. However, we do not live in this perfect counterfactual world. In this chapter, we address a selection of possible sources of error that are particularly relevant to our research questions. These include issues related to confounding, bias, misclassification, and limitations inherent to the data sources used. For the specific limitations, please refer to each study.

7.1.1 Confounding

Confounding is a factor that distorts the relationship between the exposure and the outcome, creating a spurious association or obscuring a true one. It should be of significant concern in all retrospective observational health research (253, 254).

7.1.1.1 Residual confounding

Residual confounding refers to the distortion of causality that persists even after adjustment, often due to unmeasured confounding, misclassification, crude measurement, or incomplete modeling (255). In *study IV*, we find that women who donated blood within five years before delivery exhibited slightly better outcomes than those who never donated—a pattern likely driven by residual confounding, as a biologically protective effect of blood donation is implausible. There may also be confounding within the donor population, as donors may not be as comparable as we model them to be. In most studies of blood donors, repeat donations seem most closely associated with good health (256), and perceived or *de facto* health issues predict future donation behavior (257). Hence, an active donor may differ profoundly from a lapsed donor in ways we do not capture. In *study IV*, residual confounding due to these reasons is likely to have led to underestimation rather than an exaggeration of any true association. The remediation of such confounding requires a high level of suspicion and a plethora of well-constructed analyses, each attempting to address the research question from a different perspective.

7.1.1.2 Confounding by indication

Confounding by indication occurs when the reason for receiving treatment (the indication) is associated with the outcome, making it difficult to separate the effect of the treatment from the underlying condition that prompted it (254). It is particularly challenging in transfusion research. For example, red-cell transfusions are associated with increased long-term morbidity and mortality in many disease groups, such as esophageal cancer (258), major abdominal surgery (192), and cardiac surgery (190, 191). However, since sicker patients are more likely to receive transfusions and also more likely to experience poor outcomes, it is difficult to disentangle the effect of the transfusion itself (193-195).

Women who receive transfusions during childbirth are typically younger and healthier than the general transfused population, offering a unique setting to study immunologic outcomes with less background illness. In *study III*, we use this assumption to minimize confounding from baseline health. However, there is still a risk of confounding since transfused women often experience severe obstetric complications such as massive hemorrhage, preeclampsia, or infection—conditions that may themselves influence future immune function or increase the risk of autoimmune disease independent of transfusion. As a result, any association we observe between transfusion and later autoimmune disease might partly reflect the underlying complication rather than the transfusion itself. While we adjust for known risk factors, residual confounding may persist due to unmeasured or imperfectly captured aspects of obstetric morbidity, which may distort our risk estimates.

7.1.2 Biases

Bias refers to systematic errors in the design, data collection, analysis, or interpretation of studies that lead to incorrect or misleading conclusions (252). Unlike confounding, which involves distortion of an association due to a third factor related to both exposure and outcome, biases directly impact internal validity by introducing inaccuracies or misrepresentations in measurement or selection processes. Internal validity reflects the degree to which the observed associations in a study are trustworthy and free from systematic error. Maintaining internal validity ensures that findings accurately reflect genuine causal relationships rather than artifacts of bias. Only when internal validity is reasonably assured can we consider the generalizability of the results—the extent to which findings apply to other populations or settings.

7.1.2.1 Selection bias

Selection bias refers to systematic differences in characteristics between individuals included in the study and those excluded, which can potentially lead to results that are not representative of the target population (259). In the context of all our studies, selection bias might arise due to differential registration completeness or selective reporting across different hospitals, regions, or over time. Moreover, individuals with certain health conditions or from specific demographic groups may be systematically underrepresented or overrepresented due to variations in healthcare utilization, documentation

practices, or reporting accuracy. Such bias can impact the generalizability and internal validity of the study findings. However, having nationwide registers and a generally inclusive healthcare system alleviates these issues, especially when compared to research from countries lacking such structures.

A classic example of selection bias is the "healthy donor effect." Blood donor selection criteria (medical history, hemoglobin screening, self-reported wellness) create a distinctively healthier donor pool than the general population. The group is more likely to engage in health-conscious behaviors, smoke less, and have better access to healthcare (257, 260, 261). Active donors may self-select by pausing their donations due to health issues, further intensifying selection bias. Consequently, observational studies may report misleadingly beneficial health associations of blood donations (221, 262) since these nuances are not captured in study sources.

7.1.2.2 Information bias and misclassification

Information bias refers to systematic errors in the measurement or classification of exposures, outcomes, or covariates. A key subtype is misclassification, which occurs when individuals are incorrectly categorized. Misclassification can be non-differential (equally likely across groups, usually biasing results toward the null) or differential (where errors differ between groups, potentially distorting estimates in unpredictable directions).

In our studies, non-differential misclassification is the most probable scenario. For example, lifestyle factors such as smoking and BMI are often missing or misreported, but the errors are unlikely to differ systematically between exposure groups.

The use of registry data over more than three decades introduces other forms of information bias. In *study III*, evolving diagnostic criteria for autoimmune diseases and non-Hodgkin lymphoma may affect outcome ascertainment. These time-related inconsistencies may systematically differ between periods but are expected to be unrelated to exposure status (non-differential), which likely biases the results toward the null. However, transfusion practices (including the introduction of universal leukocyte reduction) have changed, potentially altering exposure effects across different calendar periods. To address this, we adjusted

for the calendar year and performed sensitivity analyses using interaction terms and stratifying by periods.

In *study II*, we relied on registry discharge diagnoses to infer causes of transfusion using a hierarchical classification. It may introduce misclassification, as we lack clinical nuance, and multiple causes of bleeding may coexist. In some transfused women with no hemorrhage diagnosis recorded, the reason might be underreporting. The diagnosis of "anemia" at discharge also lacked specificity—it may reflect pre-existing anemia, postpartum bleeding, or a combination, complicating interpretation. Additionally, under-registration of mild or transient conditions (e.g., iron deficiency, minor bleeding events) may underestimate their contribution to transfusion recurrence.

The SCANDAT databases used in *studies III* and *IV* were not nationwide prior to 1996, and early data may be incomplete in certain regions. Despite efforts to harmonize data and exclude births with incomplete exposure ascertainment, residual misalignment remains possible—another form of exposure misclassification.

Finally, in *study III*, we excluded women who were transfused in non-obstetric contexts. If these transfusions reflected early signs of autoimmune disease (e.g., anemia), this exclusion could lead to informative censoring and under-ascertainment of outcomes. However, such transfusions were rare and unlikely to substantially bias results in this relatively healthy cohort.

7.1.2.3 Surveillance bias

Surveillance bias is a specific type of information bias. It refers to a systematic distortion in outcomes due to differences in monitoring, testing, or follow-up intensity between exposed and non-exposed groups. In the context of *study III*, surveillance bias could occur if women who experience significant postpartum hemorrhage and receive transfusions subsequently undergo more frequent medical assessments or inquiries, leading to an increased likelihood of earlier diagnosis of conditions such as SLE.

7.1.2.4 Reverse causation

Reverse causation is a specific type of bias and measurement error in which the outcome affects the risk of the exposure. Specifically, "protopathic bias" occurs

when a treatment or exposure is initiated in response to early symptoms of a disease that has not yet been diagnosed. For example, a study found that individuals receiving red-cell transfusions within a year have a significantly higher risk of developing solid and non-solid cancer than controls, a finding likely due to precancerous conditions or undiagnosed disease (233).

In *study III*, the premise is that most obstetric red-cell recipients are in otherwise good health, especially compared to the average recipient of red-cell transfusions. However, this is not necessarily true for all obstetric patients receiving red-cell transfusions. Since inflammatory diseases have long latency, obstetric complications may be an early sign of an underlying but undiagnosed disease (263-265). For example, chronic inflammation due to an undiagnosed disease may suppress hematopoiesis and lower hemoglobin levels, resulting in anemia and increasing the likelihood of transfusion (266).

To mitigate protopathic bias, we initiated a follow-up with a six-month latency, as it is unlikely that any causal link between autoimmune disease and transfusion would manifest itself within half a year of birth. In such cases, reverse causation is at least much more likely. Moreover, in randomly selected individuals, we also manually reviewed the recorded diagnoses in the National Patient Register and the Medical Birth Register to identify anomalies that might suggest an undiagnosed disease in individuals later diagnosed with SLE and systemic sclerosis. Although we did not find signs of irregularities or convincing evidence of an increased risk for RA (a disease with similar features), reverse causation remains a concern.

7.1.3 Power and random error

Statistical power refers to the ability to detect true associations, while random error represents chance variation that reduces the precision of effect estimates. Both power and random error are of particular concern when studying rare exposures and outcomes, as in studies of red-cell transfusion during childbirth and subsequent autoimmune disease (*study III*) or high-frequency blood donation and uncommon pregnancy outcomes (*study IV*). Despite utilizing nationwide registers with large overall sample sizes, the absolute number of some events remains low, leading to wide confidence intervals and potentially limiting the ability to detect modest associations. In our studies, this increases the risk of

false-negative findings and renders less precise estimates, especially in subgroup analyses. Accordingly, findings related to rare exposures or outcomes should be interpreted cautiously.

On a philosophical note, even with nationwide data, we are not describing a finite population but estimating parameters that may extend beyond the specific dataset observed. The Swedish population could be viewed as a sample from a theoretical infinite population. Confidence intervals, therefore, are essential due to sampling variability and because they reflect uncertainties arising from model assumptions, unmeasured confounding, and the theoretical counterfactuals central to causal inference.

8 Findings and implications

This chapter summarizes the main findings from the four studies presented in this thesis, which we discuss in detail in the respective papers.

8.1 Patterns and trends in red-cell transfusion practice

Our study demonstrated a stable rate of obstetric red-cell transfusions in Sweden between 2003 and 2017. The trend roughly aligns with observations from the United States and Australia (125, 127). However, this overall stability masks an internal shift: the proportion of low-volume transfusions (1–2 units) has increased while the proportion of larger transfusions has declined. A similar pattern has been observed in Switzerland (126). Thus, our findings do not support an increase in the incidence of massive transfusions nationwide in Sweden, previously described in the Stockholm region (104), which is reassuring. The overall proportion of patients receiving transfusions remained consistent, although the number of units used decreased over time (from 90 to 80 units per 1,000 deliveries). We may speculate that these findings, taken together, reflect a general trend of reduced use of blood products also being observed within the realm of obstetrics.

A surprising finding was the overall transfusion rate of 3 percent, which sets Sweden apart and on the higher end among high-income countries. In studies, baseline transfusion rates differ substantially between countries, ranging from 1 percent in the United States, Switzerland, and France to approximately 2 percent in Australia (117, 126, 145, 267, 268). In the Nordic region, we also see substantial variation despite similar health systems and clinical guidelines. In Denmark, transfusion rates among low-risk primiparous were around 2 percent, increasing to 3 percent among cesarean deliveries from 2001 to 2009, with variations depending on obstetric risk categories (269). In Finland, national rates rose slightly from 1.8 to 2.2 percent from 2006 to 2008, with some central hospitals reporting rates of up to 4 percent (270). Norwegian data from 2011 to 2018 suggest lower transfusion rates—around 1 percent—though differing definitions complicate direct comparisons (271). Although it is challenging to compare transfusion rates, we believe our findings warrant further investigation into the underlying factors that drive transfusion in obstetric patients in Sweden.

Advanced maternal age is a recognized risk factor for adverse delivery outcomes (272, 273), and our findings support the notion that it is also associated with a non-linear increase in the probability of transfusion risk.

8.1.1 Appropriateness and timing

We did not aim to evaluate appropriateness at the individual level in this study. However, our findings raise questions about overall patterns.

First, we see a predominance of two-unit transfusions. In fact, the use of two units dwarfs that of single unit use (63 versus 4 percent, respectively), and we observe a curious general tendency to use an even (2 or 4) rather than an odd (1 or 3) number of red-cell units. Single-unit use is not always explicitly recommended in guidelines (274), but studies on single-unit transfusion policies suggest that they are effective and safe in the obstetric population (275, 276). If implemented on a large scale, it may impact red-cell utilization more than lowering laboratory thresholds for transfusion (237), effectively reducing blood product exposure.

Second, we observe that a significant proportion of transfusions occur on the days following delivery. We cannot rule out late critical bleeding events or that the first day after delivery is temporally close to the actual delivery (due to restrictions in available data). However, it is reasonable to suspect transfusions in anemic but hemodynamically stable patients, which may deviate from guidelines and indicate redundant exposure to blood products.

8.1.2 Hospital variability

We observed considerable hospital variability in the proportion of deliveries in which transfusions occurred, which remained after adjusting for maternal age and parity. This variation, ranging from 20 to 54 transfused deliveries per 1,000, aligns with previously mentioned international research showing significant variability in obstetrics (96, 97) and non-obstetrics (141, 142) settings. Patterson et al. (2014) examined hospital-level variation in obstetric red-cell transfusion rates across New South Wales, Australia. The study found a fourfold difference between hospitals, with 73 percent of the variation explained by differences in case mix, obstetric interventions, and hospital characteristics—suggesting that clinical practice and institutional factors significantly influence transfusion use (146). Our findings underscore the need for continued efforts to review transfusion

practices locally and for follow-up research to understand better the factors that drive variation between hospitals in Sweden.

In summary, Sweden shows stable but relatively high obstetric transfusion rates, with a shift toward lower volumes and substantial hospital variation. These patterns raise questions about the consistency and appropriateness of practice, warranting further investigation.

8.2 Risk of recurrence of maternal transfusion during delivery

Our study demonstrated that a history of red-cell transfusion during delivery potently predicts recurrent transfusion in subsequent pregnancies. Specifically, women who received a red-cell transfusion during their first delivery had markedly higher rates of subsequent transfusion than those without (8.7 versus 1.7 percent in the second delivery). It escalated further in women who experienced transfusions in both their first and second deliveries, in which 15.5 percent were transfused in the third delivery, corresponding to an aOR of 11.5 (95% CI; 7.9-16.6).

The findings were consistent with previous studies, showing elevated recurrence risks for both postpartum hemorrhage and transfusion. Ford et al. (2007) found a threefold higher risk of recurrence after one hemorrhage event, rising to fivefold after two prior events, with an even greater risk (>11-fold) for severe hemorrhage requiring transfusion (277). Similarly, Patterson et al. (2018) reported a nearly fivefold increased risk of recurrent transfusion among women with a history of transfusion during childbirth (278), findings echoed by Thams et al. in Denmark (sevenfold increase in odds of recurrence) (279).

Specific obstetric risk factors influence recurrence risk, notably retained placenta, which strongly predicts recurrent severe hemorrhage involving transfusions (159, 280). In our study, women with a previous diagnosis of postpartum hemorrhage had increased odds of red-cell transfusion in a subsequent delivery, the risk being notably higher among those who had received a transfusion during the first event. The finding persisted across all major hemorrhage subtypes, including uterine atony, placental retention, and lacerations, and was most pronounced when transfusion had occurred alongside atony (aOR 6.7; 95% CI 6.1-7.4) or cesarean section (aOR 6.8; 95% CI 5.8-8.0). Our study aligns with those of Öberg et al. (2014) (156), who reported an overall increased recurrence risk across hemorrhage types but differed from Linde et al. (280), who found that recurrence

risk varied significantly depending on the underlying cause, with the highest risks associated with dystocia, retained placenta, and atony.

8.2.1 Beyond hemorrhage, other variabilities

We found that women with comorbidity, especially hematological abnormalities, were transfused to a larger extent than the general population. While most women entering pregnancy are healthy, this finding communicates the importance of considering baseline risk in parturients with comorbid conditions in clinical management (153).

We also found that the overall risk of recurrent transfusion in the second delivery was similar in women regardless of previous diagnosis of hemorrhage. The finding aligns with Patterson et al. (2018), who found that a woman with red-cell transfusion in first birth and absent diagnosis of postpartum hemorrhage was as likely to be transfused in second birth and at increased risk of adverse outcomes (e.g., isoimmunization) (278). In our material, approximately more than 7 out of 10 transfused women also had a diagnosis of postpartum hemorrhage. Although we cannot rule out misclassification, it may signal that prior transfusion without recorded hemorrhage marks underlying vulnerabilities—possibly related to iron stores, coagulation, or vascular factors—predispose to recurrent hemorrhage (150, 161).

Women transfused in the first delivery with subsequent diagnosis of iron deficiency anemia were at an increased risk of recurrent transfusion in the second delivery (aOR 1.9, 95% CI; 1.2-3.3). The absolute numbers were small and likely did not accurately reflect the true prevalence. Combined with the limitation that we lack the indication of transfusion (which may have been influenced by prepartum conditions), this exacerbates the risk of underestimating the influence of iron deficiency anemia on the outcome. However, iron deficiency, with or without anemia, stands out as a modifiable risk in practice and one in which a predelivery intervention may alter the chain of causality, resulting in postpartum anemia with or without the need for transfusion. The finding that women with a transfused sister had an increased risk (aOR 1.8, 95% CI; 1.5-2.1) supports the notion that familial or heritable factors may contribute to a persistent biological or possibly genetic predisposition (156, 281, 282).

Additionally, clinical practices vary at the hospital level, as demonstrated in *study I,* and this may contribute to variability in recurrence rates across hospitals. However, we did not assess inter-hospital differences in the present study, although this is an interesting topic for further investigation.

In summary, women who have received a prior transfusion during delivery are significantly more likely to require a transfusion in their subsequent delivery than non-transfused parturients, regardless of the indication for the initial transfusion. Thus, she should be subject to meticulous pre-delivery planning in any subsequent pregnancy to avoid blood loss and allogeneic blood product exposure, including the addressing of any modifiable risk factors.

8.3 Long-term disease risk after red-cell transfusion in childbirth

Our study demonstrated study that red-cell transfusions during childbirth are associated with a modestly increased long-term risk of developing SLE and systemic sclerosis, with no apparent association with RA or NHL. The adjusted hazard ratios were 1.38 (95% CI, 1.01–1.87) for SLE and 1.89 (95 % CI, 1.12–3.21) for systemic sclerosis—and the findings persisted through sensitivity analyses, although the absolute cumulative incidence differences at 25 years were minor. Previous investigations speculate that transfusion-related immunomodulation and the persistence of foreign cells can influence immune responses in the long term (177, 283). Our findings may support the hypothesis that the immunomodulatory effects of transfusion contribute to the development of autoimmune conditions in susceptible women.

8.3.1 Autoimmune diseases

Investigations into the long-term associations between red-cell transfusions and autoimmune diseases or malignancies have yielded mixed results. Rogers et al. (2012) followed 4,721 women over approximately 15 years and found a nearly two-fold increase in autoimmune diseases (including RA, SLE, and Sjögren's syndrome) among previously transfused women (incidence rate ratio [IRR] ~1.9; 95% CI, 1.4–2.7) (176). One Swedish case-control study, using regional data from southern Sweden on females (2002), reported an uncertain association between prior transfusions and SLE (OR 2.3; 95% CI, 0.9–5.8) (201). In a similar study design, Symmons et al. (1997) identified notably increased odds specifically for RA among

transfused individuals (OR 4.8; 95% CI, 1.3–18), although the study also highlighted smoking and obesity as concurrent risk factors (284). In contrast, Cerhan et al. observed no increased risk of RA associated with prior transfusion in a prospective cohort study of older women (relative risk [RR] 0.72; 95% CI, 0.48–1.08), illustrating inconsistent evidence that may be due to differences in study design or population (199).

Our null finding on the risk of RA after red-cell transfusion in this large-scale database with robust exposure and outcome data recording is reassuring. Less reassuring is that the increased risk of SLE seems consistent within our analyses. As previously mentioned, we acknowledge that there is an inherent risk of protopathic bias in that undiagnosed SLE at the time of delivery may affect the risk of exposure to blood products. It could be argued that this risk is also present in RA, but SLE is usually diagnosed at an earlier age than RA (ages 45 versus 70) (185, 187), which may exacerbate the risk of reverse causation.

8.3.2 Microchimerism and risk of systemic sclerosis

Microchimerism—persistent donor cells within the recipient's circulation—has been documented in transfused trauma patients (285) and specific pediatric populations (286). The phenomenon is seen naturally following pregnancy, with a bi-directional flow of cells through the umbilical cord, and fetal cells may circulate in the mother after decades (287). Its role in the etiology of autoimmunity has sparked scientific interest (288-290), notably so after the finding that women with systemic sclerosis exhibit male fetal DNA in blood and skin to a significantly higher degree compared to healthy controls (291, 292). Postpartum transfusions potentially exacerbate immune reactions by adding a source of foreign cells and antigens. One hypothesis is that the pregnancy state skews the mother's immunity toward tolerance (to protect the fetus), which might initially dampen reactions to transfused cells. However, as this tolerance wanes after delivery, abnormal immune responses may emerge. Although theoretically plausible, stable donor-derived microchimerism post-transfusion has not been demonstrated in obstetric patients (293).

Our study found a small but consistently increased risk of systemic sclerosis following red-cell exposure. However, we found the risk to be vulnerable to modulation in follow-up, with a longer latency followed by an attenuated risk. Also,

anemia often accompanies systemic sclerosis (264). Thus, similarly to SLE, one must consider the risk of reverse causation and confounding.

8.3.3 Non-Hodgkin lymphoma risk

Around the turn of the century, researchers observed a rise in the incidence of non-Hodgkin lymphoma (294-296). Blood transfusions were implicated in some materials, but populations and designs were heterogeneous, and many studies yielded null findings (297-300). Of particular interest in this thesis is a Swedish cohort study by Anderson et al. (1998), which examined postpartum transfusions and their associations with NHL. They found no increased incidence of NHL among transfusion recipients compared to non-recipients (301). However, a more recent meta-analysis by Cerhan et al. (2019), pooling results from 14 studies, reported a slight overall increased risk for NHL associated with transfusion history (RR ~1.2), particularly in cohort studies (RR ~1.34), suggesting that transfusions might modestly influence lymphoma risk (302). In the present study, we found no palpable relationship between the risk of NHL after red-cell transfusion, which is comforting. However, long-term follow-up and excellent coverage, we had limited power to detect differences between groups.

Lastly, we found no increased risk of death associated with transfusion in childbirth (aHR 0.99; 95% CI, 0.80-2.21), underscoring that the transfused obstetric patient differs systematically from the typical transfusion recipient (198).

In summary, we found small but persistent associations between the later diagnosis of systemic sclerosis and SLE and red-cell transfusion during childbirth. No such associations were perceived for RA and NHL. It is prudent to explicitly refer to these findings as "associations" rather than implying evidence of causal pathways, as more studies of robust methodology are needed to confirm the findings.

8.4 Consequences of blood donations prior to delivery

Our study demonstrated several important findings relevant to the health of female blood donors. First, we observed a pronounced healthy donor effect, where donors had more favorable pregnancy outcomes than non-donors, even after adjusting for multiple confounders, which strengthens the hypothesis that

the “healthy donor effect” applies to this population. Second, higher donation intensity was consistently associated with adverse pregnancy and offspring outcomes when the analyses were restricted to donors only. When comparing births to women with different donation frequencies (≥9 vs. 1–2) in the five years before delivery, we found an increased risk of preeclampsia (aOR 1.18; 95% CI, 1.06–1.31), preterm birth (aOR 1.33; 95% CI, 1.22–1.45), and SGA infants (aOR 1.17; 95% CI, 1.03–1.34) and lower birth weight. Importantly, continuous dose-response models revealed a threshold-like effect: birth weight declined gradually with donation frequency but more steeply after approximately eight donations.

8.4.1 Blood donors and pregnancy outcomes

Depleted iron stores are common among female premenstrual blood donors (206, 207, 303). Given the essential role of iron in pregnancy and fetal development, there is legitimate concern that frequent blood donations prior to pregnancy and childbirth could adversely affect maternal and neonatal health.

However, existing studies thus generally report neutral or positive associations between pre-pregnancy blood donation and maternal and neonatal outcomes. For instance, studies from Canada and China reported no increased risk of adverse pregnancy outcomes among donors compared to non-donors (219, 304). Similarly, our results also suggest a lower risk of delivery complications among donors compared to never donors. However, we attribute this to underlying health and socioeconomic status differences.

When comparing donors alone, the findings are more nuanced. Germain et al. (2016) found no important difference in birth outcomes for donors with low to moderate frequency two years prior to birth (220). Two Danish studies further explored outcomes related to neonatal health and scholastic attainment. While high-frequency blood donation was mildly associated with a lower birth weight in a dose-response pattern in nulliparous women, the overall distribution of birth weight and the risk of low birth weight were not adversely impacted (218). Offspring of blood donors displayed slightly better scholastic attainment than non-donors, with no difference observed between high- and low-frequency maternal donation (217).

Our study builds upon and extends evidence from prior research by involving multiparous women and allowing for analyses at both extremes of donation.

Furthermore, we contribute a novel analysis comparing delivery outcomes for parturients with the same number of donations but varying timing in relation to delivery. We found that women who exclusively donated blood 15 times before delivery gave birth to infants with a mean weight 152 g lower (95% CI, -244 to -60 g) than those who donated the same number of times exclusively after delivery. Similar timing-related differences were observed for preterm birth (aOR 2.31; 95% CI, 1.07–4.97) and preeclampsia (aOR 1.70; 95% CI, 0.65–4.47), while no such patterns were evident for women with only one donation. The findings thus support a biologically plausible mechanism—likely related to donation-induced iron depletion—beyond residual confounding from healthier donor characteristics.

8.4.2 Consequences of current blood donation practices

In Sweden, female blood donors are permitted to donate up to three times per year, and ferritin levels are routinely measured at first donation (214). Additionally, Sweden provides comprehensive, free-of-charge antenatal care, ensuring early identification and management of pregnancy complications and comorbidities. If we observe the effects of blood donation or transfusion on maternal or neonatal outcomes within our robust healthcare system, it would be of particular interest to examine these associations in other settings, such as the United States, where donation frequency can be as high as six times annually for women. Additionally, its antenatal care system is less comprehensive, which may lead to increased risks of unrecognized or unmanaged complications.

Successful attempts with individual-based ferritin-guided blood donation have been demonstrated in Denmark and the Netherlands (212, 216), but no universal implementation exists. In Sweden, blood donors receive iron supplements with varying adherence, and the use of ferritin as guidance for regular donors is a matter of local protocol. While observed effect sizes in our study are modest, they are consistent, dose-dependent, and most pronounced in high-intensity donors. At the population level, such shifts may contribute meaningfully to neonatal morbidity and maternal risk in specific subgroups. Further investigation of these findings seems urgent, preferably through studies addressing the “healthy donor effect” through sophisticated conditional regression models, applying within-between subject methodology.

9 Conclusions

This thesis examines the use, outcomes, and long-term implications of red-cell transfusion. We believe that the four studies collectively contribute to a deeper understanding of contemporary transfusion practices, recurrence patterns, potential long-term risks, and the consequences of pre-pregnancy blood donation.

Study I. Overall, the rate of red blood cell transfusions during delivery in Sweden remained stable at approximately 3 percent from 2003 to 2017. However, notable shifts were observed toward increased low-volume transfusions and decreased use of higher-volume transfusions. The two-unit transfusion dominates, and a large proportion of units are transfused the days after delivery. Significant and persistent hospital variability was evident even after standardizing for maternal risk factors. These findings highlight potential inconsistencies in clinical decision-making and underscore the need for further research to elucidate these differences.

Study II. A prior obstetric transfusion strongly predicts recurrence, with transfused women exhibiting a fivefold increased risk of needing transfusion again in subsequent deliveries. Notably, this heightened risk persists even in the absence of documented hemorrhage, indicating underlying vulnerabilities. Additional factors, including placental abnormalities and familial predisposition, further elevate the recurrence risk. These findings underscore the importance of individualized pre-delivery risk assessment, intensified surveillance for women at risk, and proactive management of iron deficiency and other correctable or modifiable risk factors in subsequent pregnancies.

Study III. Red-cell transfusion at childbirth was associated with a modest but consistent increase in long-term risk for specific autoimmune diseases, notably SLE and systemic sclerosis. No similar increase was observed for RA or NHL. Although these findings represent minor absolute risk differences, they highlight the inherent challenges in assessing transfusion safety, particularly in detecting subtle immune-mediated effects. Continued vigilance and further research into the immunological consequences of transfusions are crucial to inform clinical decision-making more effectively.

Study IV. Frequent blood donation before pregnancy was associated with modest but consistent increases in adverse pregnancy outcomes, including higher risks of preterm birth, preeclampsia, and lower offspring birth weight, particularly among women donating nine or more times in the five years preceding pregnancy. These outcomes likely reflect depleted maternal iron stores, emphasizing the importance of reviewing current blood donation safety guidelines. Specifically, donor management policies for reproductive-age women may require revision. It is the responsibility of blood-collecting organizations to incorporate measures such as routine iron status screening or longer intervals between donations to protect maternal and neonatal health.

10 Points of perspective

The results presented in this thesis offer several avenues for further research and clinical development.

First, whether red-cell transfusion rates have truly plateaued in Sweden warrants closer attention. While our findings suggest increased restraint in transfusion volumes, closer adherence to guidelines may further reduce the use of blood products. A more detailed examination of hospital-level variability in transfusion rates would also serve an important purpose. Future work should incorporate refined case-mix adjustment, measures of obstetric hemorrhage severity, and institutional practices to better identify whether observed differences reflect appropriate clinical management or inconsistent adherence to guidelines. If confirmed, such variability would motivate systematic audits, guideline harmonization, and quality improvement efforts with a focus on equity.

Second, the consistent finding that a history of transfusion is a strong predictor of recurrence, in ours and other studies, underscores the need for targeted interventions for women with transfusions in delivery. In more granular data, it would be interesting to explore whether modifiable transfusion-related risk factors, foremost iron deficiency and anemia, also tend to recur, as they may be targets for intervention. Moreover, trials investigating whether active, individualized management plans for previously transfused women can reduce the likelihood of recurrence would provide a clear patient benefit.

Third, our findings on the risk of autoimmune disease after transfusion illustrate the methodological challenges of researching long-term immunological complications. While we found a small increased risk of SLE and systemic sclerosis, causal inference remains limited by confounding and uncertainties in temporality. Nonetheless, our study represents one of the most comprehensive attempts to examine autoimmune risk following obstetric transfusion, utilizing extensive epidemiological data, and provides a valuable foundation for more targeted immunological investigations.

Finally, the observed association between frequent blood donation and adverse pregnancy outcomes raises critical questions for donor policy. Further investigation is urgently needed, utilizing complementary approaches such as within-individual designs, sibling comparisons, paternal donation as a control, and long-term follow-up of offspring, including cognitive outcomes. However, even the mere suggestion of harm from blood donations must be dealt with promptly. Organizations responsible for donor recruitment and communication must take an active role in ensuring that potential reproductive risks are clearly conveyed and proactively managed.

In sum, these efforts may contribute to safer, more equitable maternal care.

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12 Use of generative AI

The AI-assisted tool ChatGPT (OpenAI, GPT-4, version June 2024) was used during the preparation of this comprehensive summary (“kappa”) to ensure consistency in language and terminology. All content was critically reviewed and edited by the author to ensure accuracy, relevance, and appropriate tone.

I take full responsibility for the content of the “kappa”/comprehensive summary of the thesis.

13 References

1. Goethe JWv. Faust: A Tragedy. 1889:50.
2. Blundell J. Some account of a Case of Obstinate Vomiting, in which an attempt was made to prolong Life by the Injection of Blood into the Veins. Journal of the Royal Society of Medicine. 1819;10(Pt 2):296-311.
3. Coombs RR, Mourant AE, Race RR. A new test for the detection of weak and incomplete Rh agglutinins. British journal of experimental pathology. 1945;26(4):255-66.
4. Robertson LB. The Transfusion of Whole Blood: A Suggestion for Its More Frequent Employment in War Surgery. Br Med J. 1916;2(2897):38-40.
5. Landsteiner K, Wiener AS. Studies on an agglutinogen (Rh) in human blood reacting with anti-rhesus sera and with human isoantibodies. J Exp Med. 1941;74(4):309-20.
6. Robertson OH. Transfusion with preserved red blood cells. Br Med J. 1918;1(2999):691-5.
7. Robertson OH. A Method of Citrated Blood Transfusion. Br Med J. 1918;1(2991):477-9.
8. Carson JL, Triulzi DJ, Ness PM. Indications for and Adverse Effects of Red-Cell Transfusion. N Engl J Med. 2017;377(13):1261-72.
9. Jacobs JW, Diaz M, Arevalo Salazar DE, Tang A, Stephens LD, Booth GS, et al. United States blood pricing: A cross-sectional analysis of charges and reimbursement at 200 US hospitals. American Journal of Hematology. 2023;98(7):E179-E82.
10. Kacker S, Frick KD, Tobian AAR. The costs of transfusion: economic evaluations in transfusion medicine, Part 1. Transfusion (Philadelphia, Pa). 2013;53(7):1383-5.
11. Kacker S, Frick KD, Tobian AAR. Data and interpretation: economic evaluations in transfusion medicine, Part 4. Transfusion (Philadelphia, Pa). 2013;53(10):2130-3.
12. Kacker S, Frick KD, Tobian AAR. Constructing a model: economic evaluations in transfusion medicine, Part 3. Transfusion (Philadelphia, Pa). 2013;53(9):1885-7.
13. Kacker S, Frick KD, Tobian AAR. Establishing a framework: economic evaluations in transfusion medicine, Part 2. Transfusion (Philadelphia, Pa). 2013;53(8):1634-6.
14. Glenngard AH, Persson U, Soderman C. Costs associated with blood transfusions in Sweden--the societal cost of autologous, allogeneic and perioperative RBC transfusion. Transfus Med. 2005;15(4):295-306.
15. Goodnough LT, Shander A. Patient blood management. Anesthesiology. 2012;116(6):1367-76.

16. Mehra T, Seifert B, Bravo-Reiter S, Wanner G, Dutkowski P, Holubec T, et al. Implementation of a patient blood management monitoring and feedback program significantly reduces transfusions and costs. Transfusion. 2015;55(12):2807-15.

17. Waters JH. Patient blood management in obstetrics. Int Anesthesiol Clin. 2014;52(3):85-100.

18. Chung K-W, Basavaraju SV, Mu Y, van Santen KL, Haass KA, Henry R, et al. Declining blood collection and utilization in the United States. Transfusion. 2016;56(9):2184-92.

19. Goel R, Chappidi MR, Patel EU, Ness PM, Cushing MM, Frank SM, et al. Trends in Red Blood Cell, Plasma, and Platelet Transfusions in the United States, 1993-2014. JAMA. 2018;319(8):825-7.

20. Ellingson KD, Sapiano MRP, Haass KA, Savinkina AA, Baker ML, Chung KW, et al. Continued decline in blood collection and transfusion in the United States-2015. Transfusion. 2017;57 Suppl 2:1588-98.

21. Auvinen MK, Zhao J, Lassen E, Lubenow N, Seger Mollen A, Watz E, et al. Patterns of blood use in Sweden from 2008 to 2017: A nationwide cohort study. Transfusion. 2020;60(11):2529-36.

22. Tinegate H, Chattree S, Iqbal A, Plews D, Whitehead J, Wallis JP, et al. Ten-year pattern of red blood cell use in the North of England. Transfusion. 2013;53(3):483-9.

23. Tang B, Zhang Y, Xu X, Yu X, Ma L, Huang Y. Temporal trends and geographic variations in perioperative red blood cell transfusion in major surgical procedures from 2013 to 2018 in China. Vox Sang. 2023;118(7):567-76.

24. Scrofani C, le Tallec, D., Rautmann, G. The collection, testing and use of blood and blood components in Europe. 2016.

25. Ness PM, Triulzi DJ, Carson JL. Adverse Effects of Red-Cell Transfusion. N Engl J Med. 2018;378(1):97-8.

26. Zalpuri S, Zwaginga JJ, le Cessie S, Elshuis J, Schonewille H, van der Bom JG. Red-blood-cell alloimmunization and number of red-blood-cell transfusions. Vox sanguinis. 2012;102(2):144-9.

27. MacGregor SN. Alloimmunization in Pregnancy: Implications for the Fetus and Neonate. NeoReviews. 2024;25(11):e742-e6.

28. Alliance SSB. Förutsättningar för blodkomponentframställning 2025 [Available from: https://transfusion.se/framstallning-och-anvandning/.

29. Bassuni WY, Blajchman MA, Al-Moshary MA. Why implement universal leukoreduction? Hematology/Oncology and Stem Cell Therapy. 2008;1(2):106-23.

30. Guo S, Frazer DM, Anderson GJ. Iron homeostasis: transport, metabolism, and regulation. Current opinion in clinical nutrition and metabolic care. 2016;19(4):276-81.

31. Beard JL, Connor JR. Iron status and neural functioning. Annual review of nutrition. 2003;23:41-58.

32. Linder MC. Mobilization of Stored Iron in Mammals: A Review. Nutrients. 2013;5(10):4022-50.

33. Brugnara C. Iron deficiency and erythropoiesis: new diagnostic approaches. Clin Chem. 2003;49(10):1573-8.

34. Tang P, Wang H. Regulation of erythropoiesis: emerging concepts and therapeutic implications. Hematology. 2023;28(1):2250645.

35. Milman N. Prepartum anaemia: prevention and treatment. Ann Hematol. 2008;87(12):949-59.

36. WHO. Guideline: Daily iron and folic acid supplementation in pregnant women. 2012.

37. Kunskapsstöd för vårdgivare. Anemi under graviditet och post partum [Internet]. 2023 [2023 [cited 2025 May 26].].

38. Georgieff MK. Iron deficiency in pregnancy. Am J Obstet Gynecol. 2020;223(4):516-24.

39. Milman N, Bergholt T, Byg KE, Eriksen L, Graudal N. Iron status and iron balance during pregnancy. A critical reappraisal of iron supplementation. Acta Obstet Gynecol Scand. 1999;78(9):749-57.

40. Milman NT. Effects of iron supplementation to iron depleted and iron replete pregnant Danish women: Defining criteria for identification of women who can manage without supplements: A randomized, placebo-controlled study. Journal of neonatal-perinatal medicine. 2023;16(3):547-62.

41. Milman N, Taylor CL, Merkel J, Brannon PM. Iron status in pregnant women and women of reproductive age in Europe. Am J Clin Nutr. 2017;106(Suppl 6):1655S-62S.

42. Auerbach M, Abernathy J, Juul S, Short V, Derman R. Prevalence of iron deficiency in first trimester, nonanemic pregnant women. J Matern Fetal Neonatal Med. 2021;34(6):1002-5.

43. Nybo M, Friis-Hansen L, Felding P, Milman N. Higher prevalence of anemia among pregnant immigrant women compared to pregnant ethnic Danish women. Ann Hematol. 2007;86(9):647-51.

44. Sjöberg A, Hulthén L. Comparison of food habits, iron intake and iron status in adolescents before and after the withdrawal of the general iron fortification in Sweden. Eur J Clin Nutr. 2015;69(4):494-500.

45. Stubbendorff A, Borgström Bolmsjö B, Bejersten T, Warensjö Lemming E, Calling S, Wolff M. Iron insight: exploring dietary patterns and iron deficiency among teenage girls in Sweden. Eur J Nutr. 2025;64(3):107.

46. Byg KE, Milman N, Agger AO. Correlations Between Iron Status Markers During Normal Pregnancy in Women with and without Iron Supplementation. Hematology. 1999;4(6):529-39.

47. Socialstyrelsen. Nationella riktlinjer 2025: Graviditet, förlossning och tiden efter. 2025.

48. Johansson A, Johannsmeyer A, Segeblad, B, Zdolsek B, Jansson Å. SFOG-råd Handläggning av järnbristanemi under graviditet. 2021.

49. Wesstrom J. Kvinnor i fertil ålder behöver ofta järntillskott. Läkartidningen. 2015.

50. Wulff M, Ekström EC. Iron supplementation during pregnancy in Sweden: to what extent is the national recommendation followed? Acta Obstet Gynecol Scand. 2003;82(7):628-35.

51. Drukker L, Hants Y, Farkash R, Ruchlemer R, Samueloff A, Grisaru-Granovsky S. Iron deficiency anemia at admission for labor and delivery is associated with an increased risk for Cesarean section and adverse maternal and neonatal outcomes. Transfusion. 2015;55(12):2799-806.

52. Srour MA, Aqel SS, Srour KM, Younis KR, Samarah F. Prevalence of Anemia and Iron Deficiency among Palestinian Pregnant Women and Its Association with Pregnancy Outcome. Anemia. 2018;2018:9135625.

53. Martí A, Peña-Martí G, Muñoz S, Lanas F, Comunian G. Association between prematurity and maternal anemia in Venezuelan pregnant women during third trimester at labor. Arch Latinoam Nutr. 2001;51(1):44-8.

54. Alwan NA, Cade JE, McArdle HJ, Greenwood DC, Hayes HE, Simpson NA. Maternal iron status in early pregnancy and birth outcomes: insights from the Baby's Vascular health and Iron in Pregnancy study. Br J Nutr. 2015;113(12):1985-92.

55. Socialstyrelsen. Internationell statistisk klassifikation av sjukdomar och relaterade hälsoproblem – Systematisk förteckning, svensk version 2025 (ICD-10-SE). 2025.

56. SFOG. Diagnoshandbok för Kvinnosjukvården.; 2010.

57. Lozoff B, Brittenham GM, Wolf AW, McClish DK, Kuhnert PM, Jimenez E, et al. Iron deficiency anemia and iron therapy effects on infant developmental test performance. Pediatrics (Evanston). 1987;79(6):981-95.

58. Lozoff B, Jimenez E, Smith JB. Double burden of iron deficiency in infancy and low socioeconomic status: a longitudinal analysis of cognitive test scores to age 19 years. Arch Pediatr Adolesc Med. 2006;160(11):1108-13.

59. Larson LM, Phiri KS, Pasricha SR. Iron and Cognitive Development: What Is the Evidence? Ann Nutr Metab. 2017;71 Suppl 3:25-38.

60. Jayasinghe C, Polson R, van Woerden HC, Wilson P. The effect of universal maternal antenatal iron supplementation on neurodevelopment in offspring: a systematic review and meta-analysis. BMC Pediatr. 2018;18(1):150.

61. Lanzkowsky P. The influence of maternal iron-deficiency anaemia on the haemoglobin of the infant. Arch Dis Child. 1961;36(186):205-9.

62. Harthoorn-Lasthuizen EJ, Lindemans J, Langenhuijsen MM. Does iron-deficient erythropoiesis in pregnancy influence fetal iron supply? Acta Obstet Gynecol Scand. 2001;80(5):392-6.

63. Türkay S, Tanzer F, Gültekin A, Bakici MZ. The influence of maternal iron deficiency anaemia on the haemoglobin concentration of the infant. J Trop Pediatr. 1995;41(6):369-71.

64. Radlowski EC, Johnson RW. Perinatal iron deficiency and neurocognitive development. Frontiers in human neuroscience. 2013;7:585-.

65. Rao R, Georgieff MK. Iron in fetal and neonatal nutrition. Semin Fetal Neonatal Med. 2007;12(1):54-63.

66. Gaspar MJ, Ortega RM, Moreiras O. Relationship between iron status in pregnant women and their newborn babies. Investigation in a Spanish population. Acta Obstet Gynecol Scand. 1993;72(7):534-7.

67. Colomer J, Colomer C, Gutierrez D, Jubert A, Nolasco A, Donat J, et al. Anaemia during pregnancy as a risk factor for infant iron deficiency: report from the Valencia Infant Anaemia Cohort (VIAC) study. Paediatr Perinat Epidemiol. 1990;4(2):196-204.

68. Savoie N, Rioux FM. Impact of maternal anemia on the infant's iron status at 9 months of age. Can J Public Health. 2002;93(3):203-7.

69. Roncagliolo M, Garrido M, Walter T, Peirano P, Lozoff B. Evidence of altered central nervous system development in infants with iron deficiency anemia at 6 mo : delayed maturation of auditory brainstem responses. The American journal of clinical nutrition. 1998;68(3):683-90.

70. Congdon EL, Westerlund A, Algarin CR, Peirano PD, Gregas M, Lozoff B, et al. Iron deficiency in infancy is associated with altered neural correlates of recognition memory at 10 years. J Pediatr. 2012;160(6):1027-33.

71. Wiegersma AM, Dalman C, Lee BK, Karlsson H, Gardner RM. Association of Prenatal Maternal Anemia With Neurodevelopmental Disorders. JAMA Psychiatry. 2019:1-12.

72. Turgeon O'Brien H, Santure M, Maziade J. The Association of Low and High Ferritin Levels and Anemia with Pregnancy Outcome. Can J Diet Pract Res. 2000;61(3):121-7.

73. Wen S, Nisenbaum R, Weyand AC, Tang GH, Auerbach M, Sholzberg M. High prevalence of iron deficiency and socioeconomic disparities in laboratory screening of non-pregnant females of reproductive age: A retrospective cohort study. Am J Hematol. 2024;99(8):1492-9.

74. Chandra S, Tripathi AK, Mishra S, Amzarul M, Vaish AK. Physiological changes in hematological parameters during pregnancy. Indian J Hematol Blood Transfus. 2012;28(3):144-6.

75. De Leeuw NK, Lowenstein L, Hsieh YS. Iron deficiency and hydremia in normal pregnancy. Medicine (Baltimore). 1966;45(4):291-315.

76. Cerneca F, Ricci G, Simeone R, Malisano M, Alberico S, Guaschino S. Coagulation and fibrinolysis changes in normal pregnancy. Increased levels of procoagulants and reduced levels of inhibitors during pregnancy induce a hypercoagulable state, combined with a reactive fibrinolysis. Eur J Obstet Gynecol Reprod Biol. 1997;73(1):31-6.

77. Taylor DJ, Lind T. Red cell mass during and after normal pregnancy. Br J Obstet Gynaecol. 1979;86(5):364-70.

78. Collaborators GBDMM. Global, regional, and national levels of maternal mortality, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016;388(10053):1775-812.

79. WHO. Recommendations for the Prevention and Treatment of Postpartum Haemorrhage. Geneva 2012.

80. Cresswell JA, Alexander M, Chong MYC, Link HM, Pejchinovska M, Gazeley U, et al. Global and regional causes of maternal deaths 2009-20: a WHO systematic analysis. Lancet Glob Health. 2025;13(4):e626-e34.

81. Say L, Chou D, Gemmill A, Tuncalp O, Moller AB, Daniels J, et al. Global causes of maternal death: a WHO systematic analysis. Lancet Glob Health. 2014;2(6):e323-33.

82. Mavrides E AS, Chandraharan E, Collins P, Green L, Hunt BJ, Riris S, Thomson AJ on behalfof the Royal College of Obstetricians and Gynaecologists. . Prevention and Management of Postpartum Haemorrhage: Green-top Guideline No. 52. BJOG. 2017;124(5):e106-e49.

83. Organization WH. WHO recommendations for the prevention and treatment of postpartum haemorrhage. 2012.

84. Ladfors LV, Muraca GM, Zetterqvist J, Butwick AJ, Stephansson O. Postpartum haemorrhage trends in Sweden using the Robson ten group classification system: a population-based cohort study. BJOG. 2022;129(4):562-71.

85. Ladfors LV, Muraca GM, Butwick A, Edgren G, Stephansson O. Accuracy of postpartum hemorrhage coding in the Swedish Pregnancy Register. Acta Obstet Gynecol Scand. 2021;100(2):322-30.

86. van Stralen G, von Schmidt Auf Altenstadt JF, Bloemenkamp KWM, van Roosmalen J, Hukkelhoven CWPM. Increasing incidence of postpartum hemorrhage: the Dutch piece of the puzzle. Acta obstetricia et gynecologica Scandinavica. 2016;95(10):1104-10.

87. Mehrabadi A, Liu S, Bartholomew S, Hutcheon JA, Kramer MS, Liston RM, et al. Temporal trends in postpartum hemorrhage and severe postpartum hemorrhage in Canada from 2003 to 2010. Journal of obstetrics and gynaecology Canada : JOGC = Journal d'obstetrique et gynecologie du Canada : JOGC. 2014;36(1):21-33.

88. Reale SC, Easter SR, Xu X, Bateman BT, Farber MK. Trends in Postpartum Hemorrhage in the United States From 2010 to 2014. Anesth Analg. 2020;130(5):e119-e22.

89. Ford JB, Patterson JA, Seeho SKM, Roberts CL. Trends and outcomes of postpartum haemorrhage, 2003-2011. BMC pregnancy and childbirth. 2015;15:334-.

90. Kaelin Agten A, Passweg D, von Orelli S, Ringel N, Tschudi R, Tutschek B. Temporal trends of postpartum haemorrhage in Switzerland: a 22-year

retrospective population-based cohort study. Swiss Med Wkly. 2017;147:w14551.

91. Lutomski JE, Byrne BM, Devane D, Greene RA. Increasing trends in atonic postpartum haemorrhage in Ireland: an 11-year population-based cohort study. BJOG. 2012;119(3):306-14.

92. Oyelese Y, Ananth CV. Postpartum hemorrhage: epidemiology, risk factors, and causes. Clinical obstetrics and gynecology. 2010;53(1):147-56.

93. Weeks A. The prevention and treatment of postpartum haemorrhage: what do we know, and where do we go to next? BJOG. 2015;122(2):202-10.

94. Yunas I, Islam MA, Sindhu KN, Devall AJ, Podesek M, Alam SS, et al. Causes of and risk factors for postpartum haemorrhage: a systematic review and meta-analysis. Lancet. 2025;405(10488):1468-80.

95. Ende HB, Lozada MJ, Chestnut DH, Osmundson SS, Walden RL, Shotwell MS, et al. Risk Factors for Atonic Postpartum Hemorrhage: A Systematic Review and Meta-analysis. Obstet Gynecol. 2021;137(2):305-23.

96. Milman N. Postpartum anemia I: definition, prevalence, causes, and consequences. Ann Hematol. 2011;90(11):1247-53.

97. WHO. Guideline: Iron supplementation in postpartum women. Report. Geneva; 2016.

98. Beard JL, Hendricks MK, Perez EM, Murray-Kolb LE, Berg A, Vernon-Feagans L, et al. Maternal iron deficiency anemia affects postpartum emotions and cognition. J Nutr. 2005;135(2):267-72.

99. Murray-Kolb LE, Beard JL. Iron deficiency and child and maternal health. Am J Clin Nutr. 2009;89(3):946S-50S.

100. Corwin EJ, Murray-Kolb LE, Beard JL. Low hemoglobin level is a risk factor for postpartum depression. J Nutr. 2003;133(12):4139-42.

101. Bergmann RL, Richter R, Bergmann KE, Dudenhausen JW. Prevalence and risk factors for early postpartum anemia. Eur J Obstet Gynecol Reprod Biol. 2010;150(2):126-31.

102. WHO. The Clinical use of blood in medicine, obstetrics, paediatrics, surgery and anaesthesia, trauma and burns. Geneva 2001 2001. Report No.: 9241545380.

103. Greene RA, McKernan J, Manning E, Corcoran P, Byrne B, Cooley S, et al. Major obstetric haemorrhage: Incidence, management and quality of care in Irish maternity units. Eur J Obstet Gynecol Reprod Biol. 2021;257:114-20.

104. Thurn L, Wikman A, Westgren M, Lindqvist PG. Massive blood transfusion in relation to delivery: incidence, trends and risk factors: a population-based cohort study. BJOG. 2019;126(13):1577-86.

105. Weeks AD. Tranexamic acid for postpartum haemorrhage: a major advance. Lancet Glob Health. 2018;6(2):e132-e3.

106. Hare GMT, Alli A, Jiang H, Mazer CD. How low can you go: Restrictive transfusion strategies in major surgery and physiological triggers. Best Practice & Research Clinical Anaesthesiology. 2023;37(4):477-85.

107. Butwick AJ, Goodnough LT. Transfusion and coagulation management in major obstetric hemorrhage. Curr Opin Anaesthesiol. 2015;28(3):275-84.

108. Jensen MCH, Holm C, Jørgensen KJ, Schroll JB. Treatment for women with postpartum iron deficiency anaemia. Cochrane Database Syst Rev. 2024;12(12):Cd010861.

109. Prick BW, Jansen AJ, Steegers EA, Hop WC, Essink-Bot ML, Uyl-de Groot CA, et al. Transfusion policy after severe postpartum haemorrhage: a randomised non-inferiority trial. BJOG. 2014;121(8):1005-14.

110. Prick BW, Duvekot JJ, van der Moer PE, van Gemund N, van der Salm PC, Jansen AJ, et al. Cost-effectiveness of red blood cell transfusion vs. non-intervention in women with acute anaemia after postpartum haemorrhage. Vox Sang. 2014;107(4):381-8.

111. Chessman J, Patterson J, Nippita T, Drayton B, Ford J. Haemoglobin concentration following postpartum haemorrhage and the association between blood transfusion and breastfeeding: a retrospective cohort study. BMC Res Notes. 2018;11(1):686.

112. Drayton BA, Patterson JA, Nippita TA, Ford JB. Red blood cell transfusion after postpartum haemorrhage and breastmilk feeding at discharge: A population-based study. Aust N Z J Obstet Gynaecol. 2016;56(6):591-8.

113. Patterson JA, Nippita TA, Randall D, Irving DO, Ford JB, Obstetric Transfusion Steering G. Outcomes associated with transfusion in low-risk women with obstetric haemorrhage. Vox Sang. 2018;113(7):678-85.

114. Holm C, Thomsen LL, Norgaard A, Langhoff-Roos J. Single-dose intravenous iron infusion versus red blood cell transfusion for the treatment of severe postpartum anaemia: a randomized controlled pilot study. Vox Sang. 2017;112(2):122-31.

115. Munoz M, Stensballe J, Ducloy-Bouthors AS, Bonnet MP, De Robertis E, Fornet I, et al. Patient blood management in obstetrics: prevention and treatment of postpartum haemorrhage. A NATA consensus statement. Blood Transfus. 2019;17(2):112-36.

116. Song KH, Choi ES, Kim HY, Ahn KH, Kim HJ. Patient blood management to minimize transfusions during the postpartum period. Obstetrics & gynecology science. 2023.

117. Patterson JA, Roberts CL, Bowen JR, Irving DO, Isbister JP, Morris JM, et al. Blood transfusion during pregnancy, birth, and the postnatal period. Obstet Gynecol. 2014;123(1):126-33.

118. Mehrabadi A, Hutcheon JA, Lee L, Kramer MS, Liston RM, Joseph KS. Epidemiological investigation of a temporal increase in atonic postpartum haemorrhage: a population-based retrospective cohort study. BJOG. 2013;120(7):853-62.

119. Shehata N, Chasse M, Colas JA, Murphy M, Forster AJ, Malinowski AK, et al. Risks and trends of red blood cell transfusion in obstetric patients: a retrospective

study of 45,213 deliveries using administrative data. Transfusion. 2017;57(9):2197-205.

120. Pettersen S, Falk RS, Vangen S, Nyflot LT. Exploring trends of severe postpartum haemorrhage: a hospital-based study. BMC Pregnancy Childbirth. 2023;23(1):363.

121. Knight M, Callaghan WM, Berg C, Alexander S, Bouvier-Colle MH, Ford JB, et al. Trends in postpartum hemorrhage in high resource countries: a review and recommendations from the International Postpartum Hemorrhage Collaborative Group. BMC Pregnancy Childbirth. 2009;9:55.

122. Sheldon WR, Blum J, Vogel JP, Souza JP, Gulmezoglu AM, Winikoff B, et al. Postpartum haemorrhage management, risks, and maternal outcomes: findings from the World Health Organization Multicountry Survey on Maternal and Newborn Health. BJOG. 2014;121 Suppl 1:5-13.

123. Khan KS, Wojdyla D, Say L, Gulmezoglu AM, Van Look PF. WHO analysis of causes of maternal death: a systematic review. Lancet. 2006;367(9516):1066-74.

124. Callaghan WM, Creanga AA, Kuklina EV. Severe maternal morbidity among delivery and postpartum hospitalizations in the United States. Obstet Gynecol. 2012;120(5):1029-36.

125. Corbetta-Rastelli CM, Friedman AM, Sobhani NC, Arditi B, Goffman D, Wen T. Postpartum Hemorrhage Trends and Outcomes in the United States, 2000-2019. Obstet Gynecol. 2023;141(1):152-61.

126. Zdanowicz JA, Schneider S, Mueller M, Tschudi R, Surbek D. Red blood cell transfusion in obstetrics and its implication for patient blood management: a retrospective analysis in Switzerland from 1998 to 2016. Arch Gynecol Obstet. 2021;303(1):121-8.

127. Jegasothy E, Patterson J, Randall D, Nippita TA, Simpson JM, Irving DO, et al. Assessing the effect of risk factors on rates of obstetric transfusion over time using two methodological approaches. BMC Med Res Methodol. 2018;18(1):139.

128. McCall SJ, Henriquez D, Edwards HM, van den Akker T, Bloemenkamp KWM, van der Bom J, et al. A total blood volume or more transfused during pregnancy or after childbirth: Individual patient data from six international population-based observational studies. PLoS One. 2021;16(1):e0244933.

129. Halmin M, Chiesa F, Vasan SK, Wikman A, Norda R, Rostgaard K, et al. Epidemiology of Massive Transfusion: A Binational Study From Sweden and Denmark. Crit Care Med. 2016;44(3):468-77.

130. Green L, Knight M, Seeney FM, Hopkinson C, Collins PW, Collis RE, et al. The epidemiology and outcomes of women with postpartum haemorrhage requiring massive transfusion with eight or more units of red cells: a national cross-sectional study. BJOG. 2016;123(13):2164-70.

131. Colmorn LB, Petersen KB, Jakobsson M, Lindqvist PG, Klungsoyr K, Kallen K, et al. The Nordic Obstetric Surveillance Study: a study of complete uterine rupture,

abnormally invasive placenta, peripartum hysterectomy, and severe blood loss at delivery. Acta Obstet Gynecol Scand. 2015;94(7):734-44.

132. Karpati PC, Rossignol M, Pirot M, Cholley B, Vicaut E, Henry P, et al. High incidence of myocardial ischemia during postpartum hemorrhage. Anesthesiology. 2004;100(1):30-6; discussion 5A.

133. Audet AM, Goodnough LT, Parvin CA. Evaluating the appropriateness of red blood cell transfusions: the limitations of retrospective medical record reviews. Int J Qual Health Care. 1996;8(1):41-9.

134. So-Osman C, Cicilia J, Brand A, Schipperus M, Berning B, Scherjon S. Triggers and appropriateness of red blood cell transfusions in the postpartum patient--a retrospective audit. Vox sanguinis. 2010;98(1):65-9.

135. Parker J, Thompson J, Stanworth S. A retrospective one-year single-centre survey of obstetric red cell transfusions. Int J Obstet Anesth. 2009;18(4):309-13.

136. Stephens B, Sethna F, Crispin P. Postpartum obstetric red cell transfusion practice: A retrospective study in a tertiary obstetric centre. Aust N Z J Obstet Gynaecol. 2018;58(2):170-7.

137. Cauldwell M, Shamshirsaz A, Wong TY, Cohen A, Vidaeff AC, Hui SK, et al. Retrospective surveys of obstetric red cell transfusion practice in the UK and USA. Int J Gynaecol Obstet. 2017;139(3):342-5.

138. Allen JG. The case for the single transfusion. N Engl J Med. 1972;287(19):984-5.

139. Yang WW, Thakkar RN, Gehrie EA, Chen W, Frank SM. Single-unit transfusions and hemoglobin trigger: relative impact on red cell utilization. Transfusion. 2017;57(5):1163-70.

140. Holmqvist J, Brynolf A, Zhao J, Halmin M, Hollenberg J, Martensson J, et al. Patterns and determinants of blood transfusion in intensive care in Sweden between 2010 and 2018: A nationwide, retrospective cohort study. Transfusion. 2022;62(6):1188-98.

141. Goodnough LT, Johnston MF, Toy PT. The variability of transfusion practice in coronary artery bypass surgery. Transfusion Medicine Academic Award Group. JAMA. 1991;265(1):86-90.

142. Qian F, Osler TM, Eaton MP, Dick AW, Hohmann SF, Lustik SJ, et al. Variation of blood transfusion in patients undergoing major noncardiac surgery. Annals of surgery. 2013;257(2):266-78.

143. Ozier Y, Pessione F, Samain E, Courtois F, French Study Group on Blood Transfusion in Liver T. Institutional variability in transfusion practice for liver transplantation. Anesth Analg. 2003;97(3):671-9.

144. Hutcheon JA, Chapinal N, Skoll A, Au N, Lee L. Inter-hospital variation in use of obstetrical blood transfusion: a population-based cohort study. Bjog. 2020;127(11):1392-8.

145. Merriam AA, Wright JD, Siddiq Z, D'Alton ME, Friedman AM, Ananth CV, et al. Risk for postpartum hemorrhage, transfusion, and hemorrhage-related morbidity at

low, moderate, and high volume hospitals. J Matern Fetal Neona. 2018;31(8):1025-34.

146. Patterson JA, Roberts CL, Isbister JP, Irving DO, Nicholl MC, Morris JM, et al. What factors contribute to hospital variation in obstetric transfusion rates? Vox Sang. 2015;108(1):37-45.

147. Bateman BT, Berman MF, Riley LE, Leffert LR. The epidemiology of postpartum hemorrhage in a large, nationwide sample of deliveries. Anesth Analg. 2010;110(5):1368-73.

148. Enright S, Varadkar S, Demaio A, Flynn C, Ni Ainle F, Hehir MP. Antecedents of red cell transfusion in a large contemporary obstetric cohort. J Perinat Med. 2019;47(2):195-9.

149. Ruiz-Labarta FJ, Aracil Rodríguez R, Sáez Prat A, Pérez Burrel L, Pina Moreno JM, Sánchez Rodríguez M, et al. Red Blood Cell Transfusion after Postpartum Hemorrhage: Clinical Variables Associated with Lack of Postpartum Hemorrhage Etiology Identification. J Clin Med. 2023;12(19).

150. Reyal F, Sibony O, Oury JF, Luton D, Bang J, Blot P. Criteria for transfusion in severe postpartum hemorrhage: analysis of practice and risk factors. Eur J Obstet Gynecol Reprod Biol. 2004;112(1):61-4.

151. Castaman G, James PD. Pregnancy and delivery in women with von Willebrand disease. Eur J Haematol. 2019;103(2):73-9.

152. James AH, Jamison MG. Bleeding events and other complications during pregnancy and childbirth in women with von Willebrand disease. J Thromb Haemost. 2007;5(6):1165-9.

153. Rottenstreich A, Regev N, Levin G, Ezra Y, Yagel S, Sompolinsky Y, et al. Factors associated with postcesarean blood transfusion: a case control study. J Matern Fetal Neonatal Med. 2020:1-8.

154. Pont S, Austin K, Ibiebele I, Torvaldsen S, Patterson J, Ford J. Blood transfusion following intended vaginal birth after cesarean vs elective repeat cesarean section in women with a prior primary cesarean: A population-based record linkage study. Acta Obstet Gynecol Scand. 2019;98(3):382-9.

155. Veen CSB, van der Reijken IS, Jansen AJG, Schipaanboord CWA, Visser W, de Maat MPM, et al. Severe postpartum haemorrhage as first presenting symptom of an inherited bleeding disorder. Haemophilia. 2019;25(6):1051-8.

156. Oberg AS, Hernandez-Diaz S, Palmsten K, Almqvist C, Bateman BT. Patterns of recurrence of postpartum hemorrhage in a large population-based cohort. Am J Obstet Gynecol. 2014;210(3):229 e1-8.

157. Chen H, Cao B, Yang J, Ren H, Xia X, Zhang X, et al. Construction and effect evaluation of prediction model for red blood cell transfusion requirement in cesarean section based on artificial intelligence. BMC Med Inform Decis Mak. 2023;23(1):213.

158. Ahmadzia HK, Wiener AA, Felfeli M, Berger JS, Macri CJ, Gimovsky AC, et al. Predicting risk of peripartum blood transfusion during vaginal and cesarean delivery: A risk prediction model. Journal of neonatal-perinatal medicine. 2023.

159. Wikkelso AJ, Hjortoe S, Gerds TA, Moller AM, Langhoff-Roos J. Prediction of postpartum blood transfusion--risk factors and recurrence. J Matern Fetal Neonatal Med. 2014;27(16):1661-7.

160. Richards DS, Ilstrup SJ, Esplin MS, Dizon-Townson D, Butler AM, Einerson BD. Risk factor stratification for urgent and nonurgent transfusion in patients giving birth. American journal of obstetrics & gynecology MFM. 2024;6(11):101506.

161. VanderMeulen H, Strauss R, Lin Y, McLeod A, Barrett J, Sholzberg M, et al. The contribution of iron deficiency to the risk of peripartum transfusion: a retrospective case control study. BMC Pregnancy Childbirth. 2020;20(1):196.

162. Lew E, Lional KM, Tagore S. Obstetric red cell transfusion in a high-volume tertiary hospital: a retrospective cohort study. Singapore Med J. 2022;64(5):307-12.

163. Bolton-Maggs PH, Cohen H. Serious Hazards of Transfusion (SHOT) haemovigilance and progress is improving transfusion safety. Br J Haematol. 2013;163(3):303-14.

164. Bolton-Maggs PHB. Serious hazards of transfusion - conference report: celebration of 20 years of UK haemovigilance. Transfus Med. 2017;27(6):393-400.

165. Thurn L, Wikman A, Westgren M, Lindqvist PG. Incidence and risk factors of transfusion reactions in postpartum blood transfusions. Blood Adv. 2019;3(15):2298-306.

166. Roubinian N. TACO and TRALI: biology, risk factors, and prevention strategies. Hematology Am Soc Hematol Educ Program. 2018;2018(1):585-94.

167. Sachs UJ. Pathophysiology of TRALI: current concepts. Intensive Care Med. 2007;33 Suppl 1:S3-S11.

168. Panch SR, Montemayor-Garcia C, Klein HG. Hemolytic Transfusion Reactions. N Engl J Med. 2019;381(2):150-62.

169. Murphy MF, Stanworth SJ, Yazer M. Transfusion practice and safety: current status and possibilities for improvement. Vox Sang. 2011;100(1):46-59.

170. Vamvakas EC, Blajchman MA. Blood still kills: six strategies to further reduce allogeneic blood transfusion-related mortality. Transfus Med Rev. 2010;24(2):77-124.

171. Teofili L, Bianchi M, Zanfini BA, Catarci S, Sicuranza R, Spartano S, et al. Acute lung injury complicating blood transfusion in post-partum hemorrhage: incidence and risk factors. Mediterr J Hematol Infect Dis. 2014;6(1):e2014069.

172. Haldar R, Samanta S. Post-partum sequential occurrence of two diverse transfusion reactions (transfusion associated circulatory overload and transfusion related acute lung injury). J Emerg Trauma Shock. 2013;6(4):283-6.

173. Agergaard CN, Haunstrup TM, Fjordside AL, Baech J, Steffensen R, Nielsen KR. Severe antibody-mediated transfusion-related acute lung injury in an obstetric patient following transfusion of fresh frozen plasma from a non-transfused male blood donor. Clinical case reports. 2021;9(6):e03818.

174. Sugrue RP, Moise KJ, Federspiel JJ, Abels E, Louie JZ, Chen Z, et al. Maternal red blood cell alloimmunization prevalence in the United States. Blood Advances. 2024;8(16):4311-9.

175. Goubran H, Ragab G, Seghatchian J, Burnouf T. Blood transfusion in autoimmune rheumatic diseases. Transfus Apher Sci. 2022;61(6):103596.

176. Rogers MA, Levine DA, Blumberg N, Fisher GG, Kabeto M, Langa KM. Antigenic challenge in the etiology of autoimmune disease in women. J Autoimmun. 2012;38(2-3):J97-j102.

177. Blajchman MA. Immunomodulation and blood transfusion. American journal of therapeutics. 2002;9(5):389-95.

178. Siemionow M, Agaoglu G. Role of Blood Transfusion in Transplantation: A Review. Journal of reconstructive microsurgery. 2005;21(8):555-64.

179. Ryder AB, Hendrickson JE, Tormey CA. Chronic inflammatory autoimmune disorders are a risk factor for red blood cell alloimmunization. Br J Haematol. 2016;174(3):483-5.

180. Saleh RM, Zefarina Z, Che Mat NF, Chambers GK, Edinur HA. Transfusion Medicine and Molecular Genetic Methods. Int J Prev Med. 2018;9:45.

181. Jiao C, Zheng L. Blood transfusion-related immunomodulation in patients with major obstetric haemorrhage. Vox Sang. 2019;114(8):861-8.

182. Armitage JO, Gascoyne RD, Lunning MA, Cavalli F. Non-Hodgkin lymphoma. The Lancet. 2017;390(10091):298-310.

183. Ekberg S, K ES, Glimelius I, Nilsson-Ehle H, Goldkuhl C, Lewerin C, et al. Trends in the prevalence, incidence and survival of non-Hodgkin lymphoma subtypes during the 21st century - a Swedish lymphoma register study. Br J Haematol. 2020;189(6):1083-92.

184. Tsokos GC. Systemic lupus erythematosus. N Engl J Med. 2011;365(22):2110-21.

185. Arkema EV, Saleh M, Simard JF, Sjöwall C. Epidemiology and Damage Accrual of Systemic Lupus Erythematosus in Central Sweden: A Single-Center Population-Based Cohort Study Over 14 Years From Östergötland County. ACR open rheumatology. 2023;5(8):426-32.

186. Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. The Lancet. 2016;388(10055):2023-38.

187. Eriksson JK, Neovius M, Ernestam S, Lindblad S, Simard JF, Askling J. Incidence of rheumatoid arthritis in Sweden: a nationwide population-based assessment of incidence, its determinants, and treatment penetration. Arthritis Care Res (Hoboken). 2013;65(6):870-8.

188. Denton CP, Khanna D. Systemic sclerosis. Lancet. 2017;390(10103):1685-99.

189. Westerlind H, Bairkdar M, Gunnarsson K, Moshtaghi-Svensson J, Sysojev A, Hesselstrand R, et al. Incidence and prevalence of systemic sclerosis in Sweden, 2004-2015, a register-based study. Semin Arthritis Rheum. 2022;53:151978.

190. Bhaskar B, Dulhunty J, Mullany DV, Fraser JF. Impact of blood product transfusion on short and long-term survival after cardiac surgery: more evidence. Ann Thorac Surg. 2012;94(2):460-7.

191. Woldendorp K, Manuel L, Srivastava A, Doane M, Bassin L, Marshman D. Perioperative transfusion and long-term mortality after cardiac surgery: a meta-analysis. General thoracic and cardiovascular surgery. 2023;71(6):323-30.

192. Elwood NR, Martin AN, Turrentine FE, Jones RS, Zaydfudim VM. The negative effect of perioperative red blood cell transfusion on morbidity and mortality after major abdominal operations. American journal of surgery. 2018;216(3):487-91.

193. Vamvakas EC. Establishing causation in transfusion medicine and related tribulations. Transfus Med Rev. 2011;25(2):81-8.

194. Middelburg RA, van de Watering LM, van der Bom JG. Blood transfusions: good or bad? Confounding by indication, an underestimated problem in clinical transfusion research. Transfusion. 2010;50(6):1181-3.

195. Isbister JP, Shander A, Spahn DR, Erhard J, Farmer SL, Hofmann A. Adverse blood transfusion outcomes: establishing causation. Transfus Med Rev. 2011;25(2):89-101.

196. Wallis JP, Wells AW, Matthews JN, Chapman CE. Long-term survival after blood transfusion: a population based study in the North of England. Transfusion. 2004;44(7):1025-32.

197. Kleinman S, Marshall D, AuBuchon J, Patton M. Survival after transfusion as assessed in a large multistate US cohort. Transfusion (Philadelphia, Pa). 2004;44(3):386-90.

198. Borkent-Raven BA, Janssen MP, van der Poel CL, Schaasberg WP, Bonsel GJ, van Hout BA. Survival after transfusion in the Netherlands. Vox sanguinis. 2011;100(2):196-203.

199. Cerhan JR, Saag KG, Criswell LA, Merlino LA, Mikuls TR. Blood transfusion, alcohol use, and anthropometric risk factors for rheumatoid arthritis in older women. Journal of rheumatology. 2002;29(2):246-54.

200. Maguire-Boston EK, Suman V, Jacobsen SJ, Moore SB, Habermann TM, Cerhan JR, et al. Blood transfusion and risk of non-Hodgkin's lymphoma. Am J Epidemiol. 1999;149(12):1113-8.

201. Bengtsson AA, Rylander L, Hagmar L, Nived O, Sturfelt G. Risk factors for developing systemic lupus erythematosus: a case–control study in southern Sweden. British journal of rheumatology. 2002;41(5):563-71.

202. Zhao J, Rostgaard K, Hjalgrim H, Edgren G. The Swedish Scandinavian donations and transfusions database (SCANDAT3-S) - 50 years of donor and recipient follow-up. Transfusion. 2020;60(12):3019-27.

203. Finch CA, Cook JD, Labbe RF, Culala M. Effect of Blood Donation on Iron Stores As Evaluated by Serum Ferritin. Blood. 1977;50(3):441-7.

204. Milman N. Serum ferritin in Danes: studies of iron status from infancy to old age, during blood donation and pregnancy. Int J Hematol. 1996;63(2):103-35.

205. Cable RG, Glynn SA, Kiss JE, Mast AE, Steele WR, Murphy EL, et al. Iron deficiency in blood donors: the REDS-II Donor Iron Status Evaluation (RISE) study. Transfusion. 2012;52(4):702-11.

206. Baart AM, van Noord PAH, Vergouwe Y, Moons KGM, Swinkels DW, Wiegerinck ET, et al. High prevalence of subclinical iron deficiency in whole blood donors not deferred for low hemoglobin. Transfusion. 2013;53(8):1670-7.

207. Rigas AS, Sørensen CJ, Pedersen OB, Petersen MS, Thørner LW, Kotzé S, et al. Predictors of iron levels in 14,737 Danish blood donors: results from the Danish Blood Donor Study. Transfusion. 2014;54(3 Pt 2):789-96.

208. Karregat JHM, Ekroos S, Castrén J, Arvas M, van den Hurk K. Iron status in Dutch and Finnish blood donor and general populations: A cross-cohort comparison study. Vox Sanguinis. 2024;119(7):664-74.

209. Kiss JE, Brambilla D, Glynn SA, Mast AE, Spencer BR, Stone M, et al. Oral Iron Supplementation After Blood Donation: A Randomized Clinical Trial. JAMA. 2015;313(6):575-83.

210. WHO. Blood donor selection: guidelines on assessing donor suitability for blood donation [Available from: https://iris.who.int/handle/10665/76724.

211. Biotherapies AftAoB. Iron management among blood donors [Available from: https://www.aabb.org/news-resources/resources/transfusion-medicine/iron-management-among-blood-donors.

212. Meulenbeld A, Ramondt S, Sweegers MG, Quee FA, Prinsze FJ, Hoogendijk EO, et al. Effectiveness of ferritin-guided donation intervals in whole-blood donors in the Netherlands (FIND'EM): a stepped-wedge cluster-randomised trial. Lancet. 2024;404(10447):31-43.

213. Sweegers MG, Zalpuri S, Quee FA, Huis In 't Veld EMJ, Prinsze FJ, Hoogendijk EO, et al. Ferritin measurement IN Donors-Effectiveness of iron Monitoring to diminish iron deficiency and low haemoglobin in whole blood donors (FIND'EM): study protocol for a stepped wedge cluster randomised trial. Trials. 2020;21(1):823.

214. GeBlod. Blodgivning i Sverige [Internet] 2025 [[cited 2025 May 24].]. Available from: www.geblod.nu.

215. American Red Cross. Eligibility requirements [Internet]. 2025 [[cited 2025 May 24].]. Available from: https://www.redcrossblood.org/donate-blood/how-to-donate/eligibility-requirements.html.

216. van den Hurk K, Arvas M, Roberts DJ, Castrén J, Erikstrup C. Whole Blood Donor Iron Management Across Europe: Experiences and Challenges in Four Blood Establishments. Transfusion Medicine Reviews. 2024;38(4):150860.

217. Rigas AS, Pedersen OB, Rostgaard K, Sørensen E, Erikstrup C, Hjalgrim H, et al. Frequent blood donation and offspring scholastic attainment: an assessment of long-term consequences of prenatal iron deficiency. Transfusion. 2019;59(5):1717-22.

218. Rigas AS, Pedersen OB, Sorensen E, Thorner LW, Larsen MH, Katz LM, et al. Frequent blood donation and offspring birth weight-a next-generation association? Transfusion. 2019;59(3):995-1001.

219. Chasse M, Tinmouth A, Goldman M, O'Brien SF, Hawken S, Murphy MSQ, et al. Evaluating the Clinical Effect of Female Blood Donors of Child-Bearing Age on Maternal and Neonatal Outcomes: A Cohort Study. Transfus Med Rev. 2020;34(2):117-23.

220. Germain M, Delage G, Robillard P, Katz LM, Gregoire Y. The association between frequency of blood donation and the occurrence of low birthweight, preterm delivery, and stillbirth: a retrospective cohort study. Transfusion. 2016;56(11):2760-7.

221. Atsma F, de Vegt F. The healthy donor effect: a matter of selection bias and confounding. Transfusion. 2011;51(9):1883-5.

222. Shehu E, Hofmann A, Clement M, Langmaack AC. Healthy donor effect and satisfaction with health: The role of selection effects related to blood donation behavior. Eur J Health Econ. 2015;16(7):733-45.

223. Emilsson L, Lindahl B, Koster M, Lambe M, Ludvigsson JF. Review of 103 Swedish Healthcare Quality Registries. J Intern Med. 2015;277(1):94-136.

224. Personnummer och samordningsnummer (Personal identity number and coordination number). Stockholm. 2008.

225. Adami H-O. Sweden: A paradise for epidemiologists? The Lancet (British edition). 1996;347(9001):588.

226. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbom A. Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. European journal of epidemiology. 2009;24(11):659-67.

227. Högman CF. Swedish Transfusion Medicine in a Ten-year Perspective-A Brief Review. Upsala journal of medical sciences. 1988;93(2):189-92.

228. Högman CF, Ramgren O. Computer System for Blood Transfusion Service. Transfusion. 1970;10(3):121-32.

229. Gallo RC, Montagnier L. The discovery of HIV as the cause of AIDS. N Engl J Med. 2003;349(24):2283-5.

230. van der Poel CL. Hepatitis C virus and blood transfusion: past and present risks. Journal of Hepatology. 1999;31:101-6.

231. Dwyre DM, Fernando LP, Holland PV. Hepatitis B, hepatitis C and HIV transfusion-transmitted infections in the 21st century. Vox Sanguinis. 2011;100(1):92-8.

232. Vakkila J, Myllyla G. Amount and type of leukocytes in 'leukocyte-free' red cell and platelet concentrates. Vox Sang. 1987;53(2):76-82.

233. Hjalgrim H, Edgren G, Rostgaard K, Reilly M, Tran TN, Titlestad KE, et al. Cancer incidence in blood transfusion recipients. J Natl Cancer Inst. 2007;99(24):1864-74.

234. Edgren G, Hjalgrim H, Reilly M, Tran TN, Rostgaard K, Shanwell A, et al. Risk of cancer after blood transfusion from donors with subclinical cancer: a retrospective cohort study. The Lancet. 2007;369(9574):1724-30.

235. Edgren G, Reilly M, Hjalgrim H, Tran TN, Rostgaard K, Adami J, et al. Donation frequency, iron loss, and risk of cancer among blood donors. J Natl Cancer Inst. 2008;100(8):572-9.

236. Edgren G. Blood donors' long-term health: implications for transfusion safety: Karolinska institutet; 2007.

237. Edgren G, Rostgaard K, Vasan SK, Wikman A, Norda R, Pedersen OB, et al. The new Scandinavian Donations and Transfusions database (SCANDAT2): a blood safety resource with added versatility. Transfusion. 2015;55(7):1600-6.

238. Zhao J. Bloody big data : ensuring the health of blood donors and transfused patients with health registers: Inst för medicin, Solna / Dept of Medicine, Solna; 2022.

239. Welfare TNBoHa. Statistical register's production and quality National Medical Birth Register. 2021. Report No.: Item number: 2021-9-7547 Version 1.

240. Ludvigsson JF, Almqvist C, Bonamy AK, Ljung R, Michaelsson K, Neovius M, et al. Registers of the Swedish total population and their use in medical research. Eur J Epidemiol. 2016;31(2):125-36.

241. Cnattingius S, Källén K, Sandström A, Rydberg H, Månsson H, Stephansson O, et al. The Swedish medical birth register during five decades: documentation of the content and quality of the register. European journal of epidemiology. 2023;38(1):109-20.

242. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. BMC Public Health. 2011;11:450.

243. Everhov Å H, Frisell T, Osooli M, Brooke HL, Carlsen HK, Modig K, et al. Diagnostic accuracy in the Swedish national patient register: a review including diagnoses in the outpatient register. Eur J Epidemiol. 2025.

244. Wallerstedt SM, Wettermark B, Hoffmann M. The First Decade with the Swedish Prescribed Drug Register - A Systematic Review of the Output in the Scientific Literature. Basic Clin Pharmacol Toxicol. 2016;119(5):464-9.

245. Barlow L, Westergren K, Holmberg L, Talbäck M. The completeness of the Swedish Cancer Register: a sample survey for year 1998. Acta Oncol. 2009;48(1):27-33.

246. Ekbom A. The Swedish Multi-generation Register. Methods Mol Biol. 2011;675:215-20.

247. Ludvigsson JF, Svedberg P, Olen O, Bruze G, Neovius M. The longitudinal integrated database for health insurance and labour market studies (LISA) and its use in medical research. Eur J Epidemiol. 2019;34(4):423-37.

248. World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Participants. Jama. 2025;333(1):71-4.

249. van Delden JJ, van der Graaf R. Revised CIOMS International Ethical Guidelines for Health-Related Research Involving Humans. JAMA. 2017;317(2):135-6.

250. Lipsky AM, Greenland S. Causal Directed Acyclic Graphs. JAMA : the journal of the American Medical Association. 2022;327(11):1083-4.

251. Rothman KJ, Greenland S. Causation and causal inference in epidemiology. Am J Public Health. 2005;95 Suppl 1:S144-50.

252. Lash TL, VanderWeele, T. J., Haneuse, S., Rothman, K. J. Modern Epidemiology 4th Edition. : Wolter Kluwer; 2021.

253. Greenland S, Morgenstern H. Confounding in health research. Annual review of public health. 2001;22:189-212.

254. D'Onofrio BM, Sjolander A, Lahey BB, Lichtenstein P, Oberg AS. Accounting for Confounding in Observational Studies. Annu Rev Clin Psychol. 2020;16:25-48.

255. Liang W, Zhao Y, Lee AH. An investigation of the significance of residual confounding effect. Biomed Res Int. 2014;2014:658056.

256. Ullum H, Rostgaard K, Kamper-Jorgensen M, Reilly M, Melbye M, Nyren O, et al. Blood donation and blood donor mortality after adjustment for a healthy donor effect. Transfusion. 2015;55(10):2479-85.

257. Rigas AS, Skytthe A, Erikstrup C, Rostgaard K, Petersen MS, Hjalgrim H, et al. The healthy donor effect impacts self-reported physical and mental health - results from the Danish Blood Donor Study (DBDS). Transfus Med. 2019;29 Suppl 1:65-9.

258. Boshier PR, Ziff C, Adam ME, Fehervari M, Markar SR, Hanna GB. Effect of perioperative blood transfusion on the long-term survival of patients undergoing esophagectomy for esophageal cancer: a systematic review and meta-analysis. Diseases of the esophagus : official journal of the International Society for Diseases of the Esophagus. 2018;31(4).

259. Stuckless S, Parfrey PS. Bias in Clinical Research. Methods Mol Biol. 2021;2249:17-34.

260. Atsma F, Veldhuizen I, de Vegt F, Doggen C, de Kort W. Cardiovascular and demographic characteristics in whole blood and plasma donors: results from the Donor InSight study. Transfusion. 2011;51(2):412-20.

261. Vahidnia F, Hirschler NV, Agapova M, Chinn A, Busch MP, Custer B. Cancer Incidence and Mortality in a Cohort of US Blood Donors: A 20-Year Study. J Cancer Epidemiol. 2013;2013:814842.

262. Atsma F, Veldhuizen I, Verbeek A, de Kort W, de Vegt F. Healthy donor effect: its magnitude in health research among blood donors. Transfusion. 2011;51(8):1820-8.

263. Vanarsa K, Ye Y, Han J, Xie C, Mohan C, Wu T. Inflammation associated anemia and ferritin as disease markers in SLE. Arthritis Res Ther. 2012;14(4):R182.

264. Gachet B, Jouvray M, Koether V, Collet A, Morell-Dubois S, Sanges S, et al. Prevalence, causes, and clinical associations of anemia in patients with

systemic sclerosis: A cohort study. J Scleroderma Relat Disord. 2024;9(3):203-9.

265. Tsuda S, Sameshima A, Sekine M, Kawaguchi H, Fujita D, Makino S, et al. Pre-conception status, obstetric outcome and use of medications during pregnancy of systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and inflammatory bowel disease (IBD) in Japan: Multi-center retrospective descriptive study. Mod Rheumatol. 2020;30(5):852-61.

266. Fraenkel PG. Anemia of Inflammation: A Review. Med Clin North Am. 2017;101(2):285-96.

267. Fingar KR, Hambrick MM, Heslin KC, Moore JE. Trends and Disparities in Delivery Hospitalizations Involving Severe Maternal Morbidity, 2006-2015. Healthcare Cost and Utilization Project (HCUP) Statistical Briefs. Rockville (MD)2006.

268. Bonnet MP, Deneux-Tharaux C, Dupont C, Rudigoz RC, Bouvier-Colle MH. Transfusion practices in postpartum hemorrhage: a population-based study. Acta Obstet Gynecol Scand. 2013;92(4):404-13.

269. Holm C, Langhoff-Roos J, Petersen KB, Norgaard A, Diness BR. Severe postpartum haemorrhage and mode of delivery: a retrospective cohort study. BJOG. 2012;119(5):596-604.

270. Jakobsson M, Gissler M, Tapper AM. Risk factors for blood transfusion at delivery in Finland. Acta Obstet Gynecol Scand. 2013;92(4):414-20.

271. Al-Zirqi I, Vangen S, Forsen L, Stray-Pedersen B. Prevalence and risk factors of severe obstetric haemorrhage. BJOG. 2008;115(10):1265-72.

272. Cleary-Goldman J, Malone FD, Vidaver J, Ball RH, Nyberg DA, Comstock CH, et al. Impact of maternal age on obstetric outcome. Obstet Gynecol. 2005;105(5 Pt 1):983-90.

273. Frederiksen LE, Ernst A, Brix N, Braskhoj Lauridsen LL, Roos L, Ramlau-Hansen CH, et al. Risk of Adverse Pregnancy Outcomes at Advanced Maternal Age. Obstet Gynecol. 2018;131(3):457-63.

274. Shih AW, Liu A, Elsharawi R, Crowther MA, Cook RJ, Heddle NM. Systematic reviews of guidelines and studies for single versus multiple unit transfusion strategies. Transfusion. 2018;58(12):2841-60.

275. Hamm RF, Perelman S, Wang EY, Levine LD, Srinivas SK. Single-unit vs multiple-unit transfusion in hemodynamically stable postpartum anemia: a pragmatic randomized controlled trial. Am J Obstet Gynecol. 2021;224(1):84 e1- e7.

276. Chan KL, Mak WMV, Tam YH, Lee HKK. Change in Patient-Reported Outcomes in Single-Unit Transfusion Comparable with Double-Unit Transfusion. Blood. 2016;128(22):2636.

277. Ford JB, Roberts CL, Bell JC, Algert CS, Morris JM. Postpartum haemorrhage occurrence and recurrence: a population-based study. Med J Aust. 2007;187(7):391-3.

278. Patterson JA, Nippita T, Randall DA, Irving DO, Ford JB, Obstetric Transfusion Steering G. Outcomes of subsequent pregnancy following obstetric transfusion in a first birth. PLoS One. 2018;13(9):e0203195.

279. Thams AB, Larsen MH, Rasmussen SC, Jeppegaard M, Krebs L. Incidence of postpartum hemorrhage and risk factors for recurrence in the subsequent pregnancy. Arch Gynecol Obstet. 2022.

280. Linde LE, Rasmussen S, Moster D, Kessler J, Baghestan E, Gissler M, et al. Risk factors and recurrence of cause-specific postpartum hemorrhage: A population-based study. PLoS One. 2022;17(10):e0275879.

281. Linde LE, Ebbing C, Moster D, Kessler J, Baghestan E, Gissler M, et al. Recurrence of postpartum hemorrhage, maternal and paternal contribution, and the effect of offspring birthweight and sex: a population-based cohort study. Arch Gynecol Obstet. 2022.

282. Linde LE, Ebbing C, Moster D, Kessler J, Baghestan E, Gissler M, et al. Recurrence of postpartum hemorrhage in relatives: A population-based cohort study. Acta Obstet Gynecol Scand. 2021;100(12):2278-84.

283. Utter GH, Reed WF, Lee TH, Busch MP. Transfusion-associated microchimerism. Vox Sang. 2007;93(3):188-95.

284. Symmons DPM, Bankhead CR, Harrison BJ, Brennan P, Silman AJ, Barrett EM, et al. Blood transfusion, smoking, and obesity as risk factors for the development of rheumatoid arthritis. Results from a primary care-based incident case-control study in Norfolk, England. Arthritis and rheumatism. 1997;40(11):1955-61.

285. Reed W, Lee TH, Norris PJ, Utter GH, Busch MP. Transfusion-associated microchimerism: a new complication of blood transfusions in severely injured patients. Semin Hematol. 2007;44(1):24-31.

286. Assennato SM, Owusu-Ofori S, Osei-Akoto A, Lambert NC, Allain JP. Microchimerism in Ghanaian children recipients of whole blood transfusion for severe anaemia. Vox Sang. 2019;114(2):162-70.

287. Bianchi DW, Zickwolf GK, Weil GJ, Sylvester S, DeMaria MA. Male fetal progenitor cells persist in maternal blood for as long as 27 years postpartum. Proc Natl Acad Sci U S A. 1996;93(2):705-8.

288. Adams Waldorf KM, Nelson JL. Autoimmune Disease During Pregnancy and the Microchimerism Legacy of Pregnancy. Immunological investigations. 2008;37(5-6):631-44.

289. O'Donoghue K. Fetal microchimerism and maternal health during and after pregnancy. Obstet Med. 2008;1(2):56-64.

290. Fjeldstad HE, Johnsen GM, Staff AC. Fetal microchimerism and implications for maternal health. Obstet Med. 2020;13(3):112-9.

291. Artlett CM, Smith JB, Jimenez SA. Identification of Fetal DNA and Cells in Skin Lesions from Women with Systemic Sclerosis. The New England journal of medicine. 1998;338(17):1186-91.

292. Nelson JL, Furst DE, Maloney S, Gooley T, Evans PC, Smith A, et al. Microchimerism and HLA-compatible relationships of pregnancy in scleroderma. Lancet. 1998;351(9102):559-62.

293. Bloch EM, Busch MP, Lee TH, Montalvo L, Matthews Y, Bird A, et al. Microchimerism in the transfused obstetric population. Vox Sang. 2014;107(4):428-30.

294. Alexander FE. Blood transfusion and risk of non-Hodgkin lymphoma. Lancet. 1997;350(9089):1414-5.

295. Brandt L, Brandt J, Olsson H, Anderson H, Moller T. Blood transfusion as a risk factor for non-Hodgkin lymphoma. Br J Cancer. 1996;73(9):1148-51.

296. Sandin S, Hjalgrim H, Glimelius B, Rostgaard K, Pukkala E, Askling J. Incidence of Non-Hodgkin's Lymphoma in Sweden, Denmark, and Finland from 1960 through 2003: an Epidemic That Was. Cancer Epidemiology, Biomarkers & Prevention. 2006;15(7):1295-300.

297. Adami J, Nyren O, Bergstrom R, Ekbom A, McLaughlin JK, Hogman C, et al. Blood transfusion and non-Hodgkin lymphoma: lack of association. Ann Intern Med. 1997;127(5):365-71.

298. Zhang Y, Holford TR, Leaderer B, Boyle P, Zahm SH, Owens PH, et al. Blood transfusion and risk of non-Hodgkin's lymphoma in Connecticut women. Am J Epidemiol. 2004;160(4):325-30.

299. Chow EJ, Holly EA. Blood transfusions and non-Hodgkin's lymphoma. Epidemiol Rev. 2002;24(2):269-79.

300. Cerhan JR. New epidemiologic leads in the etiology of non-Hodgkin lymphoma in the elderly: the role of blood transfusion and diet. Biomed Pharmacother. 1997;51(5):200-7.

301. Anderson H, Brandt L, Ericson A, Olsson H, Moller T. Blood transfusion at delivery and risk of subsequent malignant lymphoma in the mother. Vox Sang. 1998;75(2):145-8.

302. Cerhan JR, Kane E, Vajdic CM, Linet MS, Monnereau A, Bernstein L, et al. Blood transfusion history and risk of non-Hodgkin lymphoma: an InterLymph pooled analysis. Cancer Causes Control. 2019;30(8):889-900.

303. Salvin HE, Pasricha SR, Marks DC, Speedy J. Iron deficiency in blood donors: a national cross-sectional study. Transfusion. 2014;54(10):2434-44.

304. Lu G, Zhu Z, Lu Y, Shen J, Yu Q, Gao L, et al. The influence of blood donation before pregnancy on neonatal birth weight. PLoS One. 2022;17(6):e0269367.