Postpartum hemorrhage in families

A Norwegian population-based study

Lorentz Erland Linde

Thesis for the degree of Philosophiae Doctor (PhD)
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Scientific environment

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From the bottom of my statistical heart, I encourage all, who get the chance, to go for an expedition with the Maternal-fetal-neonatal research group into the mountains west of Norway. It will be a journey for life, and I assure you that my assumptions are not confounded when saying: you will never regret it.

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Abstract

Background: Postpartum haemorrhage (PPH) is the leading cause of direct maternal morbidity in the world. The trend of PPH occurrence increase in developed countries.
Aim: To explore the risk of recurrent PPH in a woman, through generations and between siblings. Secondly, to study how these risks interact with high birthweight.
Material and methods: With data from the Medical Birth Registry of Norway we performed a population-based cohort study including singleton births (1967–2017). We identified individuals as newborns, parents, grandparents, and siblings. We used multilevel logistic regression to calculate the odds ratios (OR), with 95% confidence interval (CI). We also calculated adjusted population attributable fractions (aPAR).
Results: The PPH recurrence risk was strongest for severe PPH (OR: 6.0; 5.5–6.6). Generational recurrence risk was stronger through the maternal than paternal line. Recurrence between siblings was highest between full sisters (OR 1.47; 1.41–1.52), followed by maternal half-sisters, paternal half-sisters and partners of full brothers. A history of PPH in a woman or birthweight ≥4000 g each accounted for 15% (aPAR) of PPH cases. Maternal, fetal, and obstetric characteristics showed differential associations with PPH types. Recurrence risk was strongest for the same type to reoccur and most pronounced for PPH due to dystocia (aOR: 6.8; 6.3–7.4). PPH due to retained placenta was most often registered as severe and showed the strongest effect of the sex of the neonate: males carried lower risk (aOR: 0.80; 0.78–0.82). Previous cesarean section showed strong association with PPH due to dystocia (aOR of 13.2; 12.5–13.9).
Conclusion: Individual and family history of PPH affected women's risk of PPH in a dose response pattern and consistent with the anticipated proportion of shared genes. This was independent of the risk associated with high birthweight. Our findings implies that genetic or sustained environmental factors contribute to PPH. Retained placenta was the type of PPH most often registered with severe PPH. Dystocia related PPH had strongest recurrence risk and was strongly associated with previous cesarean. This makes these two types of PPH self-appointed for future study on PPH-preventive measures in woman with individual or family history of PPH.

Abstrakt

Bakgrunn: Postpartum blødning (PPB) er den ledende direkte årsaken til verdens mødredødelighet og forekomsten har en økende trend i utviklende land.
Mål: Å studere gjentagelsesrisiko for PPB hos en kvinne, over generasjoner og mellom søsken, samt å utforske hvordan risikoen påvirkes høy fødselsvekt.
Materiale og metode: Med data fra Medisinsk Fødselsregister (MFR) gjennomførte vi en populasjonsbasert studie av enlinger (1967–2017). Vi identifiserte individer som nyfødte, foreldre , besteforeldre og søsken. Vi benyttet multilevel logistisk regresjon for å beregne odds ratio (OR) med 95% konfidensintervall (KI). I tillegg beregnet vi justerte populasjonstilskrivbare fraksjoner.
Resultater: Gjentagelsesrisikoen hos en kvinne var sterkest for alvorlig PPB (OR: 6.0; 5.5–6.6). Gentagelsesrisikoen over generasjoner var sterkere på morssiden enn farssiden av slekten. Gjentagelsesrisikoen mellom søsken var størst mellom helsøstre (OR 1.47; 1.41–1.52), fulgt av maternelle halvsøstre, paternelle halvsøstre og partnere av helbrødre. Tidligere PPB hos en kvinne og fødselseslsvekt ≥4000 g representerte 15 av PPB tilfellene. Maternelle, føtale og obstetriske egenskaper hadde forskjellige assosiasjoner med type-spesifikk PPB. Det var sterkest tendens til at PPB typene gjentok seg selv. Denne effekten var sterkest for dystocirelatert PPB (aOR: 6.8; 6.3–7.4). PPB grunnet retinert placenta var oftest registrert som alvorlig blødning og viste størst effekt av fosterets kjønn; guttefostre hadde lavere risiko for PPB (aOR: 0.80; 0.78–0.82). Tidligere keisersnitt var sterkt assosiert med dystocirelatert PPB (aOR: 13.2; 12.5–13.9).
Konklusjon: Individuell og familiehistorikk med PPB påvirker den fødendes risiko for PPB i et dose-respons mønster og samsvarer med den forventede andelen av delte gener. Risikoen var uavhengig av risikoen assosiert med høy fødselsvekt. Vår studie indikerer at genetiske eller vedvarende miljøfaktorer bidrar til PPB. Retinert placenta var oftest assosiert med alvorlig PPB. Dystocirelatert PPB hadde høyest gjentagelsesrisiko og var sterkt assosiert med tidligere keisersnitt. Dette gjør det naturlig å sette søkelys på disse to typene i fremtidige studier som omhandler PPB og forebyggende tiltak hos kvinner med egen eller familiehistorikk med PPB.

List of Publications

I. Linde LE, Ebbing C, Moster D, Kessler J, Baghestan E, Gissler M, Rasmussen S. (2022) Recurrence of postpartum hemorrhage, maternal and paternal contribution, and the effect of offspring birthweight and sex: a population-based cohort study. Arch Gynecol Obstett. DOI: 10.1007/s00404-021-06374-3

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Contents

Abbrevations

aOR	Adjusted odds ratio
aPAF	Adjusted population attributable fractions
CI	Confidence interval
DIC	Disseminated intravascular coagulation
FIGO	International Federation of Gynecology and Obstetrics
G	Grams
HELLP	Hemolysis, elevated liver enzymes, low platelets
HR	Hazard ratio
ICD	International classification of diseases
IU	International units
IM	Intramuscular
MBRN	Medical Birth Registry of Norway
ML	Milliliter
Nor PD	Norwegian Prescription Database
OR	Odds ratio
PAF	Population attributable fractions
PPH	Postpartum hemorrhage
RERI	Relative excess risk due to interaction
RR	Relative risk

Introduction

The innermost joy of an obstetrician's heart is to deliver a healthy baby to a healthy mother. The magnitude of this intense and clear feeling is proportionate to the sorrow that follows when obstetric disasters occur.

PPH is the leading direct cause of maternal deaths worldwide.[1] In the Norwegian population it was reported 10 deaths due to haemorrhage in labour from 1976–2018, and all occurred before 2012.[2-4] However, the occurrence of PPH is rising in the developed world,[5] and in British maternity services as much as 30% of delivering women experienced PPH in 2008–2009.[6]

Although few patients die due to PPH in Norway, we aimed to utilise the full potential of our population-based datasets to gain knowledge of risk factors and recurrence of PPH. Such knowledge is vital if we aim to prevent or reduce the occurrence of its most feared complication; the death of a newborn child's mother.

Definition of PPH

There are different cut-of values for PPH definitions between different populations.

The International Federation of Gynecology and Obstetrics (FIGO) define PPH as blood loss of more than 500ml within 24 hours of vaginal birth and 1000ml after cesarean section. They also add another option: any blood loss sufficient to compromise haemodynamic stability (which might vary among patients). They categorize PPH into 3 groups: minor (500–1000ml), major (>1000ml) and massive PPH (>2000ml or the need of >4 units of blood regardless of blood loss volume). In addition, FIGO specify PPH during cesarean section as severe if the amount exceeds 1500ml.

In the Medical Birth Registry of Norway (MBRN) PPH is defined as blood loss >500ml during labour or within the first 24 hours after delivery. Blood loss > 1500ml or the need of blood transfusion is defined as severe PPH.

The American College of Obstetrics and Gynecologists have a different cut-off value for PPH and define it as blood loss greater than 1000ml or blood loss accompanied with signs of hypovolemia within the first 24 hours postpartum.[7]

A hemorrhage volume of 500ml might seem insignificant, but during labour the final volume of blood shed is unknown and crossing the limit of 500ml is a “red flag warning” of the potential dangers to come.

Evolutionary perspectives of PPH

Among mammalian taxa, human placentas are among the most invasive.[8] Abrams et al. describes that compared to other mammalian species the placental invasiveness of humans is an important risk factor for the occurrence of PPH. With reference to Rockwell,[9] they also hypothesise that the change to bipedal locomotion may have enhanced the invasiveness of the placenta as a counterbalance to the increased gravitational forces accompanied by such locomotion. Another possible explanation of the human placental invasiveness is the encephalization humans have undergone and the following increased need of nutrients. [8]

Historical perspective

Historical data of PPH occurrence is scarce. This may partly be explained through the cultural phenomenon that men, who most often wrote historical texts, often were banned from delivering rooms. However, the first edition of the book Obstetrics by J. Whitridge Williams, published in 1903, state that the average loss of blood during

labour is 400ml. The book also touches the field of epidemiology when saying: “With the exception of the very rare cases incident to inversion of the uterus, a serious bleeding following the birth of the child is usually due to one of the three causes. Of these the most common is retention of the partly separated placenta or of individual cotyledons; less often is due to deep tears involving the tissues of the birth canal, and very rare instances to defective functioning of the uterine musculature-atony.”[10] Regarding prevention of PPH, Williams mentions that the routine employment of the method of Créde, first described in 1861, had saved thousands of lives, as opposed to traction of the umbilical cord and manual removal of the placenta. [10]

Physiological mechanisms of PPH prevention

The main physiological prevention of PPH is the oxytocin driven contractions of the uterine musculature which, after the delivery of the baby, ensures expulsion of the placenta after birth and the constriction of maternal vessels that supply the placenta bed on the intrauterine surface. An old study demonstrated a peak of oxytocin postpartum, around the point of placental expulsion,[11] which indicate the importance of this contractile function in clearing the uterine cavity for pregnancy products.

Causes of PPH

There are multiple mechanisms by which postpartum hemorrhage may develop and a commonly used mnemonic for the main causes described in literature is 4T’s: Tone (uterine atony), Trauma (laceration, hematoma, inversio uteri or rupture), Tissue (retention of placenta or conceptional products), Thrombin (coagulopathy).

Tone

The postpartum tone of the uterus is mainly ensured by the hormone oxytocin, which is secreted from the pituitary gland and also plays a role in bonding between the mother and the newborn child.[11, 12] Oxytocin receptor availability in the uterus has in animal studies been shown to increase dramatically towards the end of pregnancy,[13] and through these receptors oxytocin leads to a strong contraction of the uterine muscles. After the child is born the effect of this stimuli is expulsion of the placenta and prevention of bleeding from the placenta bed (decidua, area inside the uterus where the placenta has been attached). There are theoretically three mechanisms by which this effect may be interfered:

1. The production in hypothalamus or secretion from pituitary may be reduced or suboptimal.
2. The passage of the hormone through the bloodstream may be inefficient e.g., due to hypovolemia or constriction of vessels (by altered positioning of uterus and maternal body during labour).
3. Reduced effect at uterine level either through alterations at receptor level (receptor availability or receptor effect) or exhaustion of muscle contractility (maternal glycogen depletion, high anaerobic workload or electrolyte disturbances).

The lack of tone is commonly referred to as atony and is in literature the mechanism most commonly reported to be the cause of PPH. Bateman et al. [14] and Widmer et al. [15] reported that 79% and 62% of all registered PPH cases (>500ml and refractory PPH, respectively) where attributable to atony.

Oyelese and Ananth described causes of uterine atony categorize them into three main groups[16]:

- Labour related (Induction of labour, oxytocin use, precipitous labour, prolonged labour, chorioamnionitis)
- Uterine overdistention (Multiple pregnancies, polyhydramnion, macrosomia and placental abruption (concealed))
- Anaesthesia (general anaesthesia with inhaled anaesthetics)

Trauma

Trauma of the birth canal during labour can occur at any level of the internal genital organs. Uterine rupture is defined as tear of the uterine wall. In Nordic countries this is a rare, but severe complication during labour.[17, 18] Likewise, inversio uteri (where the uterus is inversed, for example by drag in a non-detached placenta, and thereby impair the proper contraction of the uterine musculature, is a rare complication.[19] Other more commonly occurring traumas are tear of the birth canal either to the cervix, vagina or the perineum. The Norwegian Society of Gynecology and Obstetrics define perineal tear into 4 categories[20]:

1. Laceration of perineal skin or vaginal epithelium
2. Deep perineal damage, but with sparing of external anal sphincter complex (EAS)
3. Divided into three categories according to involvement of EAS:
   A: <50% of EAS involved
   B: ≥50% of EAS involved
   C: internal anal sphincter involvement.

Paravaginal hematomas are also a potential consequence of obstetric trauma which through its concealed nature may be a challenge to correctly diagnose.

It is a natural consequence that the amount and severity of bleeding associated with the birth trauma is proportionate to the severity of the trauma and the duration of the surgical procedures to obtain hemostasis.

Tissue

“Tissue” is the designation of retained pregnancy products like placenta and membrane tissue within the uterine cavity, which may lead to ineffective contractility and PPH or be retained due to ineffective contractility. The most severe form is described as placenta accreta spectrum (PAS). The diagnosis of PAS can only be made by pathologic examination and implies that the entire uterine wall is included in the sample. PAS is subdivided into three categories: The mildest form is the setting when the placenta is abnormally adherent to the uterine wall (placenta accreta) and is

distinguished from the next two, more severe categories where the placenta has grown into or through the thickness of the myometrium (placenta increta and placenta percreta, respectively). [21] Another situation "tissue" describes is cases where a succenturiate placental lobe may be retained or an iatrogenic tear of the placenta result in retained intrauterine cotyledon or other placental products.

Thrombin

"Thrombin" describes PPH caused by alteration in the homeostasis between clot formation and resolution. The major cause is disseminated intravascular coagulation (DIC) which is a state of platelet depletion as an effect of obstetric complications. Examples of conditions that may lead to DIC are great amount of blood loss, like during placental abruption or severe PPH in general or conditions where platelets are dysfunctional like in Pre-eclampsia/HELLP or acute fatty liver.[22]

Another setting is when there is a previously known coagulopathy in the pregnant woman. However, as such conditions are usually known before the start of labour, they may be accounted for, and the risk for them to occur is minimised.

Risk factors for PPH

According to Kominiarek & Kilpatrick as much as 40% of PPH cases can be predicted by identifiable risk factors. [23]

Maternal age:

Multiple studies have connected maternal age with PPH.[15, 24-27] The association is reported to be linear.

Parity (0, 1, 2, 3 or ≥4) and *grand multipara* (0, 1, 2, 3, 4 or ≥5):

Oyelese and Ananth found no statistical significant association between parity and PPH.[16] Oberg found decreased risk of PPH in multiparous, compared to primiparous

women.[28] These findings highlight the need of examining further pregnancy rate in women with previous PPH.

Maternal history of PPH:
PPH in preceding deliveries of a woman is a known risk factor for PPH[29] (but this risk factor obviously only applies to multiparous women).

Family history of PPH:
Risk assessment of PPH based on family history of PPH is particularly important as it may apply to primiparous women, but studies on how a positive family history of PPH affect the risk of PPH are scarce and with conflicting results. A Swedish study by Oberg et al. found generational recurrence risk of PPH,[30] while a Scottish study did not reveal intergenerational recurrence risk. [31] The same Swedish study also found recurrence between siblings as parent.[30]

Period of birth:
International studies have noted increased trend of PPH occurrence. [5]

Inter-delivery interval:
A short interpregnancy interval has in some studies been associated with adverse perinatal outcomes like preterm birth, low birth weight and small for gestational age, [32-34] but other studies have failed to show this.[35] To our knowledge it has not been associated with risk of PPH.

Mother's country of birth:
Risk factors for PPH may vary among populations,[16, 28] and mother's country of birth may to a certain degree serve as a surrogate variable when exploring the generalizability of our results and to what extent they differ between populations.

Social factors: marital status, level of education:

Subgroups of a population may have different risk profiles for PPH due to differential exposure to sustained environmental factors. Oberg et al. found no effect of marital status, while Nyfløt et al. found that single status was associated with PPH.[28, 36] However, we did not come across studies indicating that other socioeconomical factors are associated with PPH.

Change of father between first and second pregnancy:
A Swedish study explored the effect of change of father on PPH risk and found highest risk of PPH between succeeding pregnancies of intact couples,[30] compared to mothers who had changed partner.

Pregestational and gestational diabetes mellitus:
Both pregestational and gestational diabetes mellitus are risk factors for PPH. [26] Ende et al. hypothesized that the association is caused by the vascular pathology associated with diabetes.[26] Pregnant women in Norway having pregestational diabetes with vascular complications have been recommended to use acetylsalicylic acid from first trimester since 2014,[37, 38] which is a known risk factor for PPH.[39] Another link to PPH is the increased risk of fetal macrosomia, large placenta and polyhydramnios, [40] known risk factor for PPH.[41, 42]

Chronic hypertension:
Hypertensive diseases in pregnancy include chronic hypertension. Hypertension is found to be risk factor for PPH. [14, 26, 43] It has been speculated if endothelial dysfunction in hypertensive disorders affect vasoconstriction negatively.[43]

Pre-eclampsia:
Pre-eclampsia and eclampsia are risk factors for PPH. It has been suggested that angiogenic factors in maternal circulation are associated with both PPH and development of pre-eclampsia.[43] Pre-eclampsia is described to originate from the placenta.[44] Therefore, one may also speculate if the link between pre-eclampsia and PPH is pathological placentation. The development HELLP, which may occur in pre-

eclamptic patients, directly affect platelet number and increase risk of PPH, as described above.[22] Another explanation may be related to the prophylactic prescription of acetylsalicylic acid to pregnant women with previous pre-eclampsia in the Norwegian population since 1999,[45] a medication which increases PPH risk.[39] Lastly, a small proportion of women with pre-eclampsia receive magnesium-sulphate in situations of threatening eclampsia. Magnesium-sulphate is used as seizure prophylaxis and has a post-delivery contractility compromising effect on the uterine muscles.[14]

Bleeding before 13 weeks of gestation

First trimester bleeding and threatened abortion has been associated with PPH due to retained placenta[46] and PPH in general[47], but negatively associated with pre-eclampsia.[43] The link may be pathological placentation. Previous cesarean section has been linked to increased risk of placenta previa (which also may cause first trimester bleeding), and has been accounted as support of a biological dysfunction of the endometrium due to uterine scar.[48] Low implantation of placenta is a risk factor for both first trimester bleeding and PPH.[49]

Birthweight:

Studies have shown that there is association between fetal macrosomia and PPH.[41, 42] The association has been explained through increased distention of the uterus and large uteroplacental (decidual) wound surface.

Multiple gestation:

Ende et al. performed meta-analyses of six studies and concluded that multiple gestation was a risk factor for PPH.[26] The mechanism may be similar to that of macrosomia, with distention of the uterus and large uteroplacental (decidual) wound surface, but Ende et al. underline that association may also be explained by other mechanisms, as higher frequency of multiple gestation after in vitro fertilization. This further connects multiple gestation to PPH, as in vitro fertilization is associated with

higher risk of placenta previa, and implantation of placenta in lower uterine segments.[50]

Fetal sex:
Studies have described sex differences in relation to birthweight, placental weight (and their ratio) and umbilical cord properties,[51-53] but whether fetal sex influence the risk of PPH is unknown.

Velamentous and marginal umbilical cord insertion:
Both velamentous and marginal umbilical cord insertion have been associated with increased risk of PPH.[54]

Operative vaginal delivery (forceps or vacuum):
Operative vaginal delivery is described as an iatrogenic risk factor for PPH through trauma of the genital tract. [16]

Previous cesarean section:
A history of cesarean section has been associated with higher risk of retained placenta in general [25, 55, 56] and atonic PPH,[14] but these findings are not consistent in the literature.[57, 58]

Estimation of blood loss during labour

Blood loss during labour has been estimated and registered, since inception of the medical birth registry, by the midwife or physician who is attending the birth. It is a routine that all blood and other fluids are collected in a jar, at the far end of the delivery bed, and weighed. Blankets which are soaked with blood are also weighted. The amount of amniotic fluid is estimated and subtracted from the total volume. We have no reason to believe that this method has changed during study period.

At caesarean section similar collection of soaked surgical cotton tissue and aspiration of excess fluid is done to estimate blood loss. Also, in the operating theatre the amount of amniotic fluid is estimated.

A study from 1967 claim that blood loss is frequently underestimated.[59] This article was published the same year as MBRN was founded and indicates that blood loss estimation has been a topic of interest in obstetrics for as long as the MBRN has existed. In a validation study with the aim of scrutinizing registrations of severe pregnancy complications between 2008 and 2013, severe PPH was found to be of acceptable quality, with a sensitivity of 87.7% and a positive predictive value of 81.1%.[60] Keeping in mind the results of a study from 2006 that severe PPH is often misclassified as mild PPH,[61] the sensitivity of severe PPH in our study may be considered to be high.

Symptoms of obstetric blood loss

Studies and textbooks state that there are great variety among pregnant women in how much the blood volume increase during pregnancy, and that knowledge of this is scarce.[62, 63] Williams state that the normal increase of blood volume varies between 30 to 60 percent of nonpregnant volume. For multiple gestations this is generally higher and for women with pre-eclampsia it is lower and inverse proportionate with the severity.[63] Zeeman et al. evaluated blood volume of eclamptic women at delivery and found it to increase as little as 10% during pregnancy, but in subsequent normotensive pregnancies the blood volume increase was equal to that of healthy pregnancies.[64] Williams underline that one of the dangers of PPH is the delivering women's late response to bleeding, which makes the physiological changes evident at later stages than in non-pregnant individuals.[63] This knowledge underline the importance of individualized approach when assessing the effect on maternal physiology during PPH. Tamizian and colleagues [65] and Bonnar[66] describe the clinical presentation and physiological response to bleeding. However, Bonnar specify

that the response is related to a delivering woman. These are summarized in the following table:

Amount of blood loss (in percent, %)	Signs/symptoms
10-15% ~ 500–100ml blood loss	Mild tachycardia, palpitations, mild lightheadedness
15-25% ~1000–1500ml blood loss	Tachycardia, tachypnea, sweating, drowsiness
25-35% ~ 1500–2000ml blood loss	Restlessness, pale and clammy skin, oligouria, tachycardia (120–140 beats/minute) (systolic blood pressure 60–80 mmHg)
35-45% ~ 2000–3000ml blood loss	Circulatory collapse, anuria, dyspnea/air hunger, tachycardia (>140 beats/minute) (systolic blood pressure 40–60 mmHg)

Managment of PPH

The Norwegian Society of Gynecology and Obstetrics (NGF) have published guidelines and recommendations for PPH treatment and prophylaxis in 1998, revised in 2008, 2014 and 2020.[37, 38, 67, 68]

Prophylaxis

Throughout the period from 1998 to 2020, NGF have recommended 5 international units (IU) of oxytocin given intramuscularly (i.m.) as prophylaxis of PPH for every delivering women. From 2008 recommendations for “active management of placenta labour” was added to the guidelines.[68] In 2014 specific recommendations for cesarean section was introduced: 3 IU of oxytocin intravenously (i.v.) and in cases with high risk of PPH: tranexamic acid before skin incision.[38] FIGO (International

Federation of Gynecology and Obstetrics) recommends Oxytocin 10 IU as first choice for preventing PPH and where this is not available: carbetocin (heat stable), misoprostol or ergot alkaloids.[69]

The effect of tranexamic acid (Cyklokapron) is debated. A recent published systematic review by Ferrari et al concluded that it has therapeutic effect on PPH, but proof of a prophylactic effect is still limited and therefore prophylactic administration is not supported.[69, 70]

A Cochrane review concluded that uterine massage had no effect on the prophylaxis of PPH. [71] Another Cochrane review did not find sufficient evidence to state if nipple stimulation had effect on reduction of PPH.[72]

In 2008 the NGF added a recommendation to optimize treatment of antenatal anemia to reduce complications of PPH.[68]

Medical treatment of PPH

The NGF recommend the following medication in their medical treatment logarithm of 2020.[37]

Medication	Repeat dosage	Contraindication	Mechanism of action[73]
1. Oxytocin 500 IU in 500ml NaCL/Ringer Acetat. Infusionrate: 150ml/h			Stimulate smooth muscles in uterus, causing contractions.
2. Tranexamic acid (Cyklokapron) 1000mg slow IV infusion	Can be repeated after 30 minutes or as infusion: 1g/8hours		Anti-fibrinolytic (connect to Plasminogen when it transforms to plasmin and reduce the effect of plasmin on fibrin.

3. Methylergometrin 0,2mg (1ml) i.m. or diluted in 9ml 0,9% NaCl slow IV infusion	Can be repeated every 2. Hour to a total of 5 times or total dose of 1,0mg.	Relative: hypertension Absolute: coronary heart disease	Bind oxytocin receptors in the smooth muscles of the uterus. Increase strength and frequency of postpartum contractions
4. 15-methyl-PGF2aALPHA (Prostinfenem) 0,25mg i.m. or intramyometrial	Can be repeated every 15 minutes to a total of 8 times or total dose of 2,0mg.	Relative: asthma Absolute: pulmonal hypertension	Syntetic 15-methyl analogue of prostaglandin F2alpha. Binds prostaglandin E2 receptor and cause uterine contractions.
5. Misoprostol tablet. 0,2mg, 3 tablets sublingually or rectally. (slow absorption)	Can be repeated after 2 hours		Synthetic prostaglandin. Binds prostaglandin receptor and cause uterine contraction.

Surgical management of PPH

Depending on cause of PPH and mode of delivery different surgical procedures are available as treatment options for PPH.

Vaginal operations	
Créde	Exerting strong fundal pressure to increase uterine tone and expel retained placenta, membranes or blood, first described by Carl Siedmund Franz Créde in 1861[10]
Manual removal of placenta	Passing the hand into the uterus, bringing the placenta away

Uterine curettage	To remove smaller placental parts or amniotic membranes, using a Curette
Suturing of obstetric trauma	To obtain surgical hemostasis
Uterine balloon tamponade	To obtain intrauterine pressure and thereby hemostasis. Can be combined with B-Lynch sutures
Transabdominal operations	
B-Lynch sutures	To compress uterus
Ligature of uterine arteries (O'Leary sutures)	To cut blood supply
Peripartum hysterectomy	To remove the uterus with uncontrolled hemorrhage
Other	
Aortic balloon insertion	Inserted by radiologist
Uterine artery embolization (UAE)	Procedure performed by radiologists

Intrauterine balloon is most effective against atonic PPH, and it has been shown that it is less effective against PPH due to PAS and retained products of placenta.[74] It is also more effective after vaginal delivery than after cesarean section.[74]

B-Lynch suture technique was introduced in 1997. Its primary target is to treat PPH and prevent peripartum hysterectomy. It has been most effective against atonic PPH. The sutures are applied during laparotomy. The sutures may be applied alone or accompanied by application of other hemostatic mechanism, for example in combination with a uterine balloon tamponade, commonly referred to as the "uterine sandwich technique".[75]

Vascular ligation is an effective treatment option for PPH but requires explorative laparotomy. The most common is O'Learys technique with ligation of uterine arteries. Other arteries may also be ligated. The desired effect is a reduced local pulse pressure

and blood flow to the uterus. It has a 92% success rate when used as a second-line approach to PPH.[7]

Uterine artery embolization is a treatment option for stable patients where uterotonics fail to induce hemostasis. It is a potentially lifesaving and organ preserving technique, but not universally available -not even in Norway. It has a reported median success rate of 89%.[7] Uterine artery embolization is also a good treatment option in pelvic hematomas or PPH with diffuse origin.

Peripartum hysterectomy is a lifesaving procedure where the uterus is removed. Literature state that the first time it was performed, with survival of both mother and child, was in Italy 1876 by professor Eduardo Porro.[76] In 2016 Campbell et al.[77] reported that the world wide occurrence of peripartum hysterectomy varies greatly among populations from 0.2/1000[78] to 10.5/1000 [79] deliveries. The Nordic Obstetric Surveillance Study reported an overall peripartum hysterectomy rate of 3.5/10 000 from 2009–2012.[17]

This thesis at a glance

What is already known	What this thesis adds
PPH occurrence has a rising trend lines in the world.[5, 6]	Shows trend line of PPH with rising occurrence in the Norwegian population 1967–2017.
Further pregnancy rate may be affected by adverse pregnancy outcomes, exemplified by placental abruption.[80]	Estimates further pregnancy rate after PPH.
A large fetus and a history of PPH in a preceding delivery are both known risk factor for PPH.[29, 81]	Shows how high birthweight interact with recurrence risk of general PPH in a woman.
Paternal contribution to fetal characteristics like birthweight is shown,[82] but studies has failed to do so regarding PPH.[30]	Shows paternal contribution to PPH.
Generational recurrence risk of PPH is indicated,[30] but results are diverging. [31]	Confirms generational recurrence risk of PPH using population data. Shows how birthweight of the neonate influence and interact with generational recurrence risk of PPH.
Recurrence between siblings has been shown in a Swedish study.[30]	Confirms recurrence of PPH between siblings. Shows how birthweight of neonate influence and interact with recurrence risk of PPH between siblings.
The occurrence of type specific PPH rates vary considerably between populations[14, 15, 28] and literature	Describes distribution of mild and severe PPH cases among types of PPH.

mainly focus on PPH due to uterine atony [24-26] and retained placenta.[57]	
Previous PPH in a woman is a known risk factor for recurrence of general PPH.[29] PPH has also been associated with demographic factors,[28, 36, 55, 56, 81, 83] obstetric history,[55] pregnancy-related factors,[28] and complications related to the fetus, the placenta, membranes and umbilical cord. [84]	Explores risk factors for type specific PPH and explores the recurrence risk of type specific PPH.
Studies have described sex differences in relation to birthweight, placental weight, and umbilical cord properties.[51-53]	Shows sex-differences in risk of PPH in general and in different PPH types.
Previous cesarean section has been linked to atonic PPH,[14]and retained placenta in general, [25, 55, 56] but the findings are not consistent in literature.[57, 58]	Shows how a previous cesarean affect the risk of the different type specific PPH in the Norwegian population.
Maternal age increases the risk of PPH in general and PPH due to atony.[15, 24-27]	Shows how the age of mother is associated with the different type-specific causes of PPH.
We know both PPH anamnesis and high birthweight are risk factors for PPH.[29, 81]	Quantify population attributable fractions of PPH caused by PPH anamnesis and current high birthweight

Aims of the thesis

The overall aim of the study was to increase understanding of the risks of PPH using population data from MBRN and administrational registries. With emphasis on risk of recurrent PPH in a woman, through generations and between siblings, this will provide answers to expecting women and their families, and clarify questions of hereditary impact of PPH and can increase the knowledge on which we select women for the right level of labour care.

Specific aims:
First, to explore a woman's risk of PPH, with emphasis on recurrence, and how it is affected by medical and pregnancy characteristics including previous obstetric anamnesis with focus on PPH and type-specific PPH. Secondly, to study how a family anamnesis of PPH affects the risk of PPH. Thirdly, to explore how PPH anamnesis in a woman or her family interacts with the risk of PPH associated with high birthweight. Lastly, to explore the population attributable fractions of PPH due to high birthweight and PPH anamnesis.

Materials and methods

Data Sources

The Medical Birth Registry of Norway (MBRN)

The Norwegian Directorate of Health established the MBRN in 1967. The aim of the registry is surveillance of maternal and perinatal health in the population and it is mandatory to register all births and stillbirths in Norway (after the 16th week of gestation, 12 weeks since 2001) into the registry.[85] MBRN is one of the oldest health registries in the world.[85] From the inception the University of Bergen was responsible for the registry, but from 2002 the Norwegian Institute of Public Health are responsible. For our studies we were provided birth records from 1967–2017, with a total of 3 003 025 registered births. Through this period the registry has been upgraded at several times, but the most comprehensive upgrade was performed in 1999 when a revised version of the original notification form (appendix I) was implemented with new variables including data on maternal smoking (appendix II).

Throughout the last decades the MBRN has been a respected source of information and has given ground for multiple epidemiological studies. Among these are studies of validation of cesarean section,[86] mode of delivery after cesarean section,[87] birth-defects,[88, 89] and maternal medical conditions such as diabetes, epilepsy and asthma.[90] Several generation based studies has also been carried out on the basis of MBRN data on outcome like preterm birth,[91] pre-eclampsia,[92] obstetric anal sphincter injuries,[93] and polyhydramnios.[94] Generational data from MBRN has, until now, not been used to study PPH.

Regarding quality of the MBRN data, a Norwegian study found variables of severe postpartum hemorrhage, eclampsia, HELLP and hysterectomy to be of adequate quality for epidemiological research.[60] MBRN has been the main source of data in this thesis.

Statistics Norway

Information on the parental education level and country of birth were provided by Statistics Norway and linked with the birth registry using the unique national identification number of each birth.

Central Population Registry

Information on parents was provided by the Central Population Registry of Norway for individuals born after 1954.[95] This made it possible to construct a population-based pedigree for family aggregation.

Record linkage

Recurrence in same woman

To assess the recurrence risk of PPH in a mother we prepared two different datasets. Those who had their first birth in 1967 or later were included.

Dataset 1. When analysing recurrence of PPH in a mother we linked her first and succeeding births in the registry (up to a maximum of three births for each mother).

Dataset 2. When analysing the effect of birthweight on recurrence of PPH, we increased the sample size to gain more statistical power by identified pairs of first and second, second and third, and third and fourth births in the same mother, which totaled 1 479 584 pairs of births.

Recurrence between generations

Generational information was revealed by identifying the individual both as a newborn and as a mother or father. We restricted the generational files to the first three births in the second generation, yielding 1 002 687 mother–offspring pairs, 841 164 father–offspring pairs and 761 011 both-parents–offspring triads.

Recurrence between siblings

To study recurrence between siblings as parents, we aligned the generational information of siblings. Thus, each record included birth registry data for four births: (i) the birth of the parent, (ii) the birth of its offspring, (iii) the birth of the parent's

sibling and (iv) the birth of the sibling's offspring (i.e. the parent's niece/nephew). A parent and its sibling's offspring constituted an aunt/uncle–niece/nephew pair, who share on average 25% of their genes, whereas pairs of siblings and pairs of their offspring (cousin pairs) share 50% and 12.5% of their genes, respectively. If the parent had more than one sibling, we selected the niece/nephew born immediately before the birth of the parents' offspring. Thus, each record in the file included the chronology of the family history. We restricted the analyses to fewer than six records for each pair of siblings. This left 909 584 sibling–offspring pairs available to explore whether the intergenerational recurrence of PPH and the recurrence of PPH between siblings is influenced by a history of PPH in other family members. Similarly, maternal and paternal half-sisters were identified.

Study design and populations

The *source population* were all deliveries registered in the MBRN from 1967–2017. For all three papers we performed population-based cohort studies and selected the *study population*: all singleton births with spontaneous onset or induction of labour (irrespective of cesarean or vaginal delivery as endpoint) from 1967–2017 with gestational age birth of ≥22 weeks.

Paper I: Recurrence of postpartum hemorrhage, maternal and paternal contribution, and the effect of offspring birthweight and sex: a population-based cohort study
This study aiming to evaluate, firstly: the recurrence risk of PPH in a woman using the datasets described above as "dataset 1" and secondly: how birthweight in actual birth affected this recurrence risk, using the file "dataset 2". We also explored of there were difference in further pregnancy rate among those who experienced, and did not experience PPH, and used Cox proportional hazards regression of time from the first delivery. Last, we estimated proportions of all cases of PPH attributable to previous PPH and current birthweight (>4000 g), adjusted population attributable fractions (aPAF).

Paper II: Recurrence of postpartum hemorrhage in relatives: A population-based cohort study

In this study we aimed to explore the recurrence of PPH between first- and second-generation deliveries linking the file as described above in the section "recurrence between generations". We also explored the generational effect of PPH in the mother and the fathers' own births separately. Next, we used the same generational files to explore the recurrence risk between full sisters, maternal- and paternal- half-sisters and partners of full brothers.

We then performed combined analyses. We studied the association between birthweight in current delivery (2nd generation), PPH in 1st generation and the risk of PPH in 2nd generation. At last we studied the association between birthweight in current delivery (2nd generation), PPH in a whole sister's delivery (2nd generation) and the risk of PPH in 2nd generation.

Paper III: Risk factors and recurrence of cause-specific postpartum hemorrhage: A population-based study

Paper III used the architecture similar to "recurrence in same woman", but when studying cause-specific recurrence of PPH we used only the two first deliveries of a woman. First, we described the distribution of different potential risk factors and severity grades of the different subtypes of PPH. Secondly, we explored risk factors for the different subtypes of PPH. Third, we explored the recurrence risk of the different subtypes of PPH. At last, we performed a more thorough exploration of the risk of dystocia related PPH in second delivery.

Outcome and independent variables, including possible confounders

Outcome variables

PPH

The main outcome variable was PPH defined as the loss of more than 500 mL of blood during labour or within 24 hours postpartum (in the thesis referred to as PPH). Prior to the update of MBRN PPH was recorded by plain text and from 1999 by using check boxes.

Severe PPH

From 1999, PPH of more than 1500 mL or the need for blood transfusion (regardless of bleeding volume) were additionally recorded (severe PPH). Severe PPH was notified by using check box.[85]

PPH subtypes

The PPH types studied in the third manuscript "Risk factors and recurrence of cause-specific postpartum hemorrhage: A population-based study" were defined as PPH combined with each of the following complications:

1 Retained placenta and/or membranes:

Defined as lack of expulsion of the placenta within 30 minutes of delivery,[96]or the retention of membranes.
Before 1999 this was notified to the MBRN by plain text.
From 1999 it was either recorded by check boxes or by plain text as: manual removal of the placenta, uterine curettage or abnormally invasive placenta.

2 Uterine atony:

Defined as failure of the uterus to contract adequately following delivery.[97]
Prior to the update PPH was recorded by plain text and from 1999 by using check boxes.

3 Obstetric trauma:

Obstetric trauma was notified to the MBRN as perineal laceration (1st–4th degree) Prior to the update PPH was recorded by plain text and from 1999 by using check boxes.
An additional option was to notify by plain text as other obstetric trauma or inversio uteri.

4 Dystocia:

Dystocia is defined by the Word Health Organization as duration of labor with spontaneous onset extends beyond the normal duration defined (based on observational studies from 1973–2018).[98] First stage (time from five centimeters to full cervical dilatation) 12 and 10 hours in first and subsequent labours, respectively. Second stage (time from full cervical dilatation to birth) 3 and 2 hours in first and subsequent labours, respectively. Before 1999 it has been notified to the MBRN by plain text as protracted labor or cephalopelvic disproportion. From 1999 it has been notified by check boxes.

5 Undefined PPH cause:

PPH without recorded category.

6 Placental abruption:

Notified in the MBRN before 1999 by plain text, and from 1999 by check box.

7 Placenta previa:

Notified in the MBRN before 1999 by plain text, and from 1999 by check box.

Independent variables and possible confounding factors:

The main independent variables were:

History of PPH

In paper I and paper III PPH in a previous delivery

In paper II a history of PPH was defined as PPH in 1st generation delivery (of either the mother or the father or both).

Birthweight in the current delivery was categorized: <4000g (reference), 4000–4499g, 4500–4999g, ≥5000g. We used birthweight <4000g as reference, because proportions of PPH stabilized with birthweights decreasing below 4000g.

Period of birth

To explore effects of secular changes we divided the population into periods according to year of delivery. When doing so we had to account for the different outcome variables and its distribution over the study period. Recurrence in the same women would have a more evenly distribution throughout the study period than outcomes in second generation, which naturally would cluster in the latter half of the study period.

When analysing recurrence in the same mother (paper I and paper III), the period of birth was divided into five groups with approximately equal durations (1967–1977, 1978–1987, 1988–1997, 1998–2007 and 2008–2017).

When analysing recurrence between relatives (paper II), the period was divided into groups with approximately equal numbers of records (between generations: 1967–2001, 2002–2010 and 2011–2017; between pairs of siblings: 1967–2002, 2003–2007, 2008–2011, 2012–2014 and 2015–2017).

Maternal age was categorized into the following groups: <20 years, 20–24 years, 25–29 years, 30–34 years, 35–39 years or ≥40 years. The date of birth is part of the Norwegian identification number and thereby implemented into MBRN.

Parity (0, 1, 2, 3 or ≥4). *Grand multipara* (≥5).

Inter-delivery interval was defined as the number of years between 2 deliveries (<1 year, 1 to <2 years, 2 to <3 years, 3 to <4 years, 4 to <5 years or ≥5 years).
Marital status married/registered partner, cohabitating, not married/alone, divorced/separated/widow, not defined. Cohabitating was introduced into MBRN in 1982. Before this, cohabitating women were registered as single.

Mother's country of birth Constructed by linking information from Statistics Norway. The variable is categorized as Norway (88.7% of the total study population (2663806/3003025) or eight WHO regions **(**11.3% of the total study population (339219/3003025))[99] [(A) high-income countries, (B) Central Europe, Eastern Europe and Central Asia, (C) sub-Saharan Africa, (D) North Africa and Middle East, (E) South Asia, (F) Southeast Asia, East Asia and Oceania, (G) Latin America and Caribbean or (H) unknown or stateless].

Level of education (available until 2013) (≤7 years, 8–10 years, 11–12 years, 13–17 years, ≥18 years, or no information).

Further, we investigated whether the occurrence and recurrence of PPH were influenced by maternal conditions such as:
pregestational and gestational diabetes mellitus, chronic hypertension, pre-eclampsia, operative vaginal delivery (forceps or vacuum), shoulder dystocia

We also explored the possible effect of the following factors on recurrence risk of PPH: fetal sex, change of father between first and second pregnancy, bleeding before 13 weeks of gestation, previous cesarean section.

Methods

Statistical analysis

In all articles we used logistic regression analyses to calculate odds ratios (ORs) with 95% confidence intervals (CIs) for PPH in the actual birth as the outcome.
The statistical analyses were performed using SPSS (version 25) and MLwiN (version 3.05)

Main exposures and outcome variables

In paper I we used PPH as main outcome variable. A previous PPH was the main exposure variable. We also assessed the interaction between birthweight in current delivery and previous PPH as exposure variables.

In Paper II PPH with previous PPH in relatives (between generations and between siblings) was the main exposure variable. In later analyses we also assessed the interaction between birthweight in the current delivery and family history of PPH as exposure variables.

In paper III the main outcome was type-specific PPH. We used variables related to demographic characteristics, obstetrical history (including previous type specific PPH), pregnancy and fetal complications, and placental/ membranes/ umbilical cord characteristics as exposures.

Accounting for hierarchical nature of the data

We accounted for the hierarchical nature of the family data by performing multilevel regression analyses in which the data were divided into different levels—in analyses including pairs of births of the same parent: current delivery (level 1) and parent (level 2); in generational analyses: current delivery (level 1), parent (level 2) and grandparent (level 3); and in analysis of pairs of siblings: current delivery (level 1), sibling pair (level 2) and sibship (level 3). Possible confounding variables were included if they

were associated with PPH in both the current and previous births of the same parent or relative(s).

Sensitivity analyses

We used sensitivity analyses to assess the impact of unmeasured confounders on the recurrence of PPH between deliveries in the same mother, generations and sisters.[100] We performed a Markov-chain Monte-Carlo simulation[101] with the prior assumption that adding an influential, unmeasured confounder to known confounder(s) would zero out the recurrence risk, which decreased the regression coefficient (β; standard deviation) for the main exposure variable of PPH to 0; 0.05, corresponding to an OR of 1 with a 95% CI of 0.9 to 1.1.

Populational attributable fractions (PAF)

To estimate the proportion of all cases of PPH attributable to previous PPH and any category of birthweight ≥4000 g in the current delivery, adjusted population attributable fractions (aPAFs) were calculated as the proportion of those exposed among all cases:[102]

aPAF= $pd\,\frac{aRR-1}{aRR}$ and 1– $\sum_{i=0}^{k} \frac{pd_i}{aRR_i}$

for two or more exposure categories, respectively, where pd_i is the proportion of PPH cases in the i^{th} exposure category among all cases, and aRR_i is the adjusted relative risk in the i^{th} exposure category compared with the unexposed group (reference, i=0). We calculated aPAF for PPH in the same mother with a history of PPH or birthweight (<4000g, 4000–4499g, 4500–4999g and ≥5000g) in the current delivery as the exposure variable. To facilitate comparisons of aPAF with a history of PPH and birthweight in the current delivery, we restricted these calculations to parous females. Similarly, we calculated the aPAF of PPH in the second generation and second sisters (in pairs of sisters) with a family history of PPH.

Further pregnancy rate

To assess likelihoods of a further delivery after PPH, we calculated further pregnancy rate, defined as the percentage of women who had a subsequent delivery after the first,[80] and used Cox proportional hazards regression of time to a subsequent delivery, adjusting for possible confounding factors in the previous delivery.

Assesment of interactions

Assessment of interaction can be done by a mathematical approach which evaluate the effect of two separate exposures or variables on an outcome. In "Modern epidemiology" by Rothman this is thoroughly described.[103] Briefly summarized, Rothman describe how to calculate a quantity referred to as: relative excess risk due to interaction (RERI). RERI is a measure of additive effect modification or interaction, and is (when calculated from ORs) OR_{11}-OR_{10}-OR_{01}-1, where OR=OR_{11} is the OR when both dichotomous exposures=1, and OR_{10} and OR_{01} when one exposure=1. If the result of this equation is "positive" there is positive interaction or more than additivity. If it is "zero" there is no interaction or exactly additivity. If it is "negative" there is negative interaction or less than additivity.

Ethical consideration

The study was approved by the Regional Committee for Medical and Health Research Ethics (2013/1484) and the registry owners (the Medical Birth Registry of Norway, the Norwegian Institute of Public Health, Statistics Norway and the Norwegian Tax Administration).

Consent to participate: Not applicable

Consent for publication: Not applicable

Main results

PPH in general

PPH was registered in 10% of the deliveries (n=277 746), and there was an increasing trend of the occurrence of PPH during the study period.

Trend of PPH

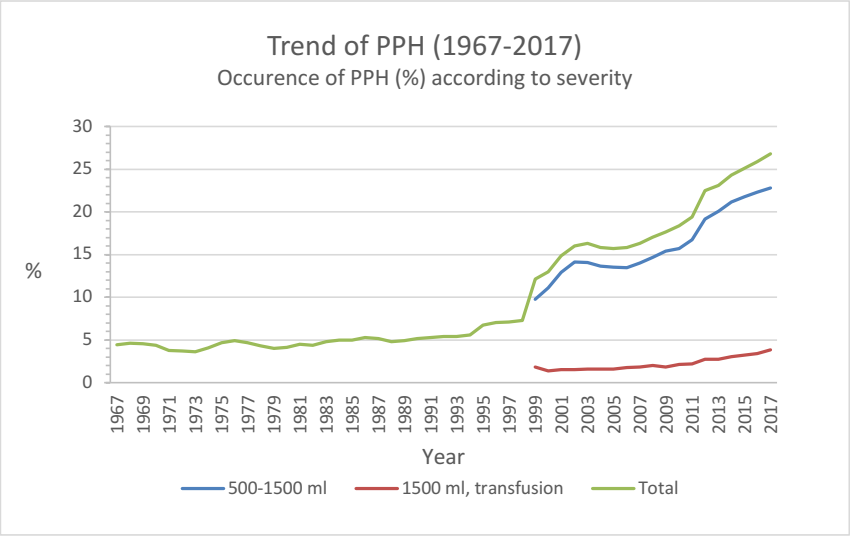


Figure 1. Trend of PPH (1967–2017)

During the study period (1967–2017) the occurrence of PPH has raised less than 4.4% to more than 26.8%. After the implementation of a new registration form and specification of severity of PPH in 1999 the slope became steeper. The occurrence of mild PPH increased more than severe PPH.

Logistic regression and sensitivity analyses found that ORs for the recurrence of PPH changed only marginally after adjusting for known possible confounders except the period of birth which moderately decreased the effects on recurrence. Therefore, in the final regression analyses we mainly adjusted for birth year period only.

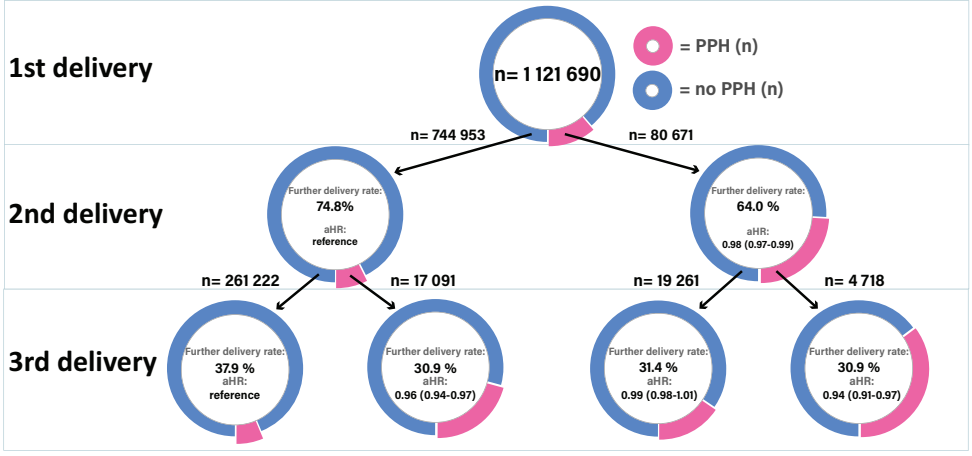
Recurrence of PPH in the same woman

We found that history of PPH in a woman's preceding delivery affected the risk of PPH in subsequent deliveries. There was a threefold increased risk of PPH in the second delivery if a woman experienced PPH in her first delivery. For women with three deliveries, we found the highest risk of PPH in the third delivery if both preceding deliveries were affected by PPH. From 1999, when severe PPH was registered, we found strongest recurrence risk for severe PPH in second delivery, compared to mild PPH.

Subsequent delivery rate

Subsequent delivery rate was affected by PPH. Women who had experienced PPH had a lower subsequent delivery rate compared to woman who had not experienced PPH.

Figure 2. Further delivery rate and adjusted Hazard ratios (aHR) in women with a history of postpartum hemorrhage (PPH) compared to women without [104]



Paternal effect of PPH recurrence

Exploring the paternal effect on PPH risk we found that men who fathered children with different women had a significantly increased risk of recurrent PPH (OR>1). Adjustment for birthweight did not affect the association.

Effect of fetal sex on risk of PPH

The overall risk of PPH was lower in deliveries where the sex of the newborn was male. This association was strengthened by adjustment for birthweight.

Cause-specific PPH

Distribution of PPH types

There was great variation in the occurrence between the different PPH causes. 42.0% were without specified cause of PPH, 23.4% were due to atony, 12.0% dystocia, 11.4% retained pregnancy products, and 9.2% were due to obstetric trauma. Placental abruption and placenta previa were registered as cause of PPH in 1.2% and 0.8%, respectively.

The distribution of severe PPH, registered after 1999, showed a different distribution: Severe PPH (registered after 1999, 28 149 type specific cases) showed a different distribution with 25.8% caused by atony and 25.7% were caused by retained placenta. The following causes, in decreasing order, were undefined bleeding cause 21.5%, dystocia 14.1%, obstetric trauma 9.2%, placenta previa 1.8% and placental abruption 1.8%.

Retained placenta were more often registered with severe PPH (29.3%) compared with other categories of PPH. Only 6.4% of registrations with undefined cause of PPH were severe.

Distribution of maternal, pregnancy and birth characteristics in types of PPH

The distribution of PPH of maternal, pregnancy and birth characteristics varied among the different types of PPH.

As example, young women were more often registered with PPH due to obstetric trauma. Nulliparity were more common in women with PPH caused by dystocia and

obstetric trauma. High birthweight was more common in PPH caused by dystocia, atony and obstetric trauma.

Risk of type specific postpartum hemorrhage according to maternal, pregnancy and birth characteristics

The risk of the different type specific PPH categories were associated with different maternal, pregnancy and birth characteristics. For example, maternal age was strongest associated with PPH due to dystocia, primiparity was strongest associated with PPH related to dystocia and obstetric trauma, while birthweight was strongest associated with PPH due to dystocia.

Retained placenta was associated with placenta anomalies: velamentous and marginal umbilical cord insertion.

The effect of fetal sex on type-specific PPH

We found an effect of fetal sex on type specific PPH. There was lower risk of PPH due to retained placenta, atony and PPH of undefined cause (in decreasing order) if the newborn was a boy. Adjustment for birthweight did not affect these results. The effect was present also in PPH due to obstetric trauma, but only significant when comparing birthweight groups between 3000 and 4499g. In unadjusted analyses we found an association between male sex and PPH due to dystocia, but the association disappeared after stratification according to birthweight. For placenta previa the risk of PPH was independent of fetal sex, while for PPH due to placental abruption the risk of PPH was higher in pregnancies with male fetuses.

Risk of type specific postpartum hemorrhage (PPH>500ml) in the second delivery according to PPH types in the first delivery and pregnancy- and birth characteristic

In general, there was an increased risk for the type specific PPH to recur from the first to the second delivery. The recurrence risk was highest for dystocia related PPH. In

decreasing order the following where PPH due to retained placenta and/or membranes, atony and obstetric trauma. The lowest recurrence risk was found for PPH of undefined cause.

We explored how a previous cesarean affected the risk of PPH subtypes and found it to be strongest associated to PPH due to dystocia, and the association was particularly stronger than for the other subtypes of PPH. In sub analyses we wanted to explore if this effect was similar in primiparous women, as the "previous cesarean group" could mimic primiparity with regards to delivering properties, but we found that this effect was even stronger in women with a previous cesarean than in primiparous women.

The recurrence risk of PPH between family members

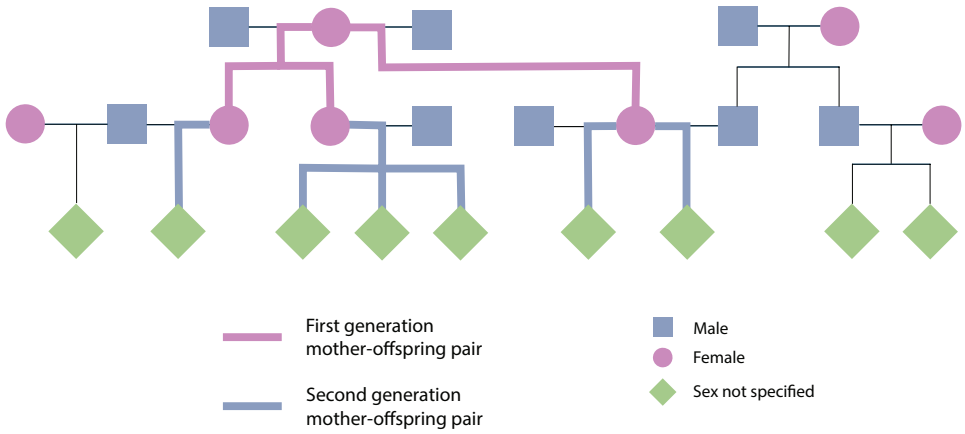
Based on results from sensitivity analyses and exploration of potential confounders, in the final analyses we generally presented unadjusted ORs of inter-generational recurrence and in analyses of recurrence between siblings we only adjusted for period of birth. After we excluded cesarean sections in our analysis ORs of recurrence between relatives were slightly stronger.

Transgenerational recurrence of PPH

We found that there was an increased transgenerational recurrence risk of PPH. Mothers who themselves were born in deliveries with PPH had increased risk of PPH when they gave birth. The association was stronger for severe PPH (in second generation). When stratifying second generation according to year of birth into groups of approximately equal number of deliveries, we found that the recurrence risk decreased through the study period, while the absolute risk increased.

Exploring the parental differentiated transgenerational effect we found that the recurrence risk was stronger through the maternal than the paternal line, and strongest if both parents were born in deliveries with PPH.

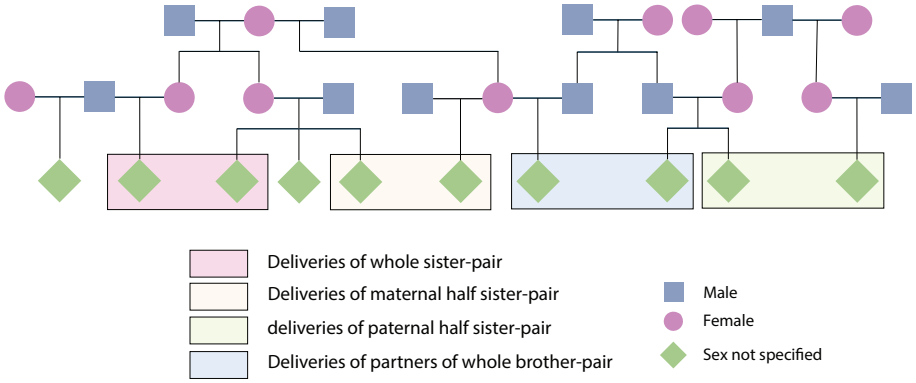
Figure 3. Family pedigree with relations explored in analyses of recurrence between generations[105]



Recurrence of PPH between siblings

Utilizing generational data, we explored if there was a pattern of recurrence of PPH between siblings. We found that the recurrence risk followed a pattern similar to the numbers of shared genes between the family members. The strongest association was found between full sisters, followed by maternal half-sisters, paternal half-sisters and with lowest recurrence risk; partners of whole brothers.

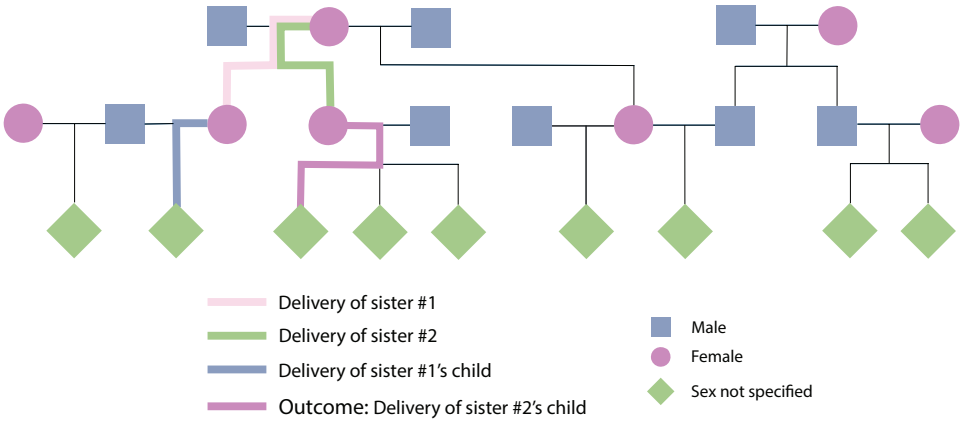
Figure 4. Family pedigree with relations explored in analyses of recurrence between siblings[105]



Combined effects of PPH in relatives

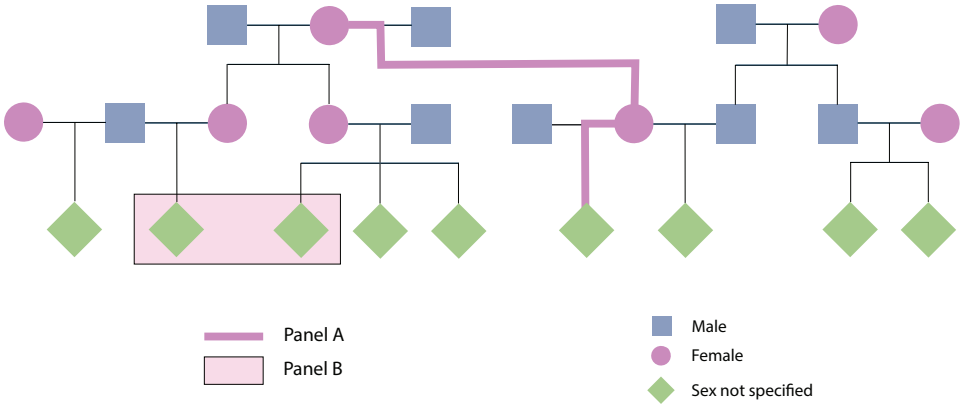
Exploring the combined effect of the recurrence risk of PPH in the transgenerational aspect and recurrence risk of PPH between siblings, we found that the risk of PPH in a delivering woman increased with the number of relatives previously exposed to PPH. Adjustment for possible confounders had negligible effect on the risk estimates, and consequently the results were presented unadjusted.

Figure 5. Family pedigree with relations explored in analyses of combined effect of PPH in relatives[105]



The association between birthweight and recurrence risk of PPH

Figure 6. Family pedigree with relations explored in analyses of the association between birthweight and recurrence of PPH in relatives[105]



Combined effect of birthweight in actual pregnancy and PPH anamnesis in a delivering woman

When combining information of PPH in previous delivery with high birthweight in actual pregnancy we found that they gave a slightly more that additive effect on the risk of PPH.

Table 1: Evaluation of interaction between a history of PPH (>500 ml) in a mother and birthweight ≥ 4500g in the current delivery on occurrence of PPH

Birthweight in current delivery	PPH in mother's previous delivery	PPH in current delivery								
		Total	PPH (*n*)	%	aOR[a]	95% CI		aOR[a]	95% CI	
<4500g	No	68616	1092241	6.3	**1**	Reference		**1**	Reference	
≥4500g	No	6610	50076	13.2	2.37	2.31	2.44	2.38	2.31	2.45
<4500g	Yes	20564	95196	21.6	3.00	2.95	3.06	1	Reference	
≥4500g	Yes	2464	7731	31.9	5.71	5.43	6.00	1.87	1.77	1.97

[a] aOR, OR adjusted for marital status, period (1967–1977, 1978–1987, 1988–1997, 1998–2007 and 2008–2017), maternal age, parity and WHO region of maternal birth

Measuring the effect modification on additive scale gave: Relative excess risk due to interaction: 95% CI: 1.3 (1.0–1.6). Measure of effect modification on multiplicative scale: OR of multiplicative interaction: 0.80 (0.76–0.85). These results show a slightly more that additive effect of interaction between the effect of PPH in a preceding delivery and high birthweight in actual pregnancy.

The combined effect of birthweight in actual pregnancy and history of PPH in relatives

We explored how recurrence risk of PPH was affected by birthweight in the current pregnancy and postpartum hemorrhage in relatives (recurrence between generations and between pairs of sisters). We found that the birthweight in the current delivery and a history of PPH in a mother's relatives (her mother or sisters) had independent effects on subsequent PPH.

Population attributable fractions

Exploring the population attributable fractions of history of PPH in parous woman we found that 14.4% was attributable to a history of PPH (with no previous PPH as the reference).

Studying parous and primiparous women independently we found that 15% of all PPH cases in both groups was attributable to any birthweight above 4000 g in the current delivery.

When exploring population attributable fractions of PPH in women with aspect to generational recurrence risk we found that among PPH deliveries in the second generation 1.9% (aPAF=1.9%) was attributable to PPH in the previous generation. In the same group 14.2% were attributable to high birthweight in current delivery.

Exploring population attributable fractions for recurrence between siblings we found that aPAF for pairs of sisters was 5.0% for a history of PPH in the first sister, while among PPH in the same group of deliveries 14.6% was attributable to high birthweight in the current delivery.

Discussion

Epidemiology is defined as systematic search for the cause of diseases. [106] A common approach in epidemiological research is to study a subset of a population and extrapolate the results with the aim of defining properties of the total population. Consequently, the general evaluation of epidemiological research is focusing on the representability of the selected subset.

There are different types of validity. Epidemiology is defined as systematic search for the cause of diseases. [106] A common approach in epidemiological research is to study a subset of a population and extrapolate the results with the aim of defining properties of the total population. Consequently, the general evaluation of epidemiological research is focusing on the representativity of the selected subset.

The MBRN dataset holds information of all deliveries in Norway, but this does not liberate it from errors, and the validity of our results should therefore be thoroughly discussed. We evaluated internal and external validity separately.

The internal validity reflects the correctness of the results and is influenced by:
- Random error
- Systematic error
    -selection bias
    -information bias
-Confounding
The external validity reflects the ability to extrapolate the results beyond the studied subset or population and is dependent on high internal validity.

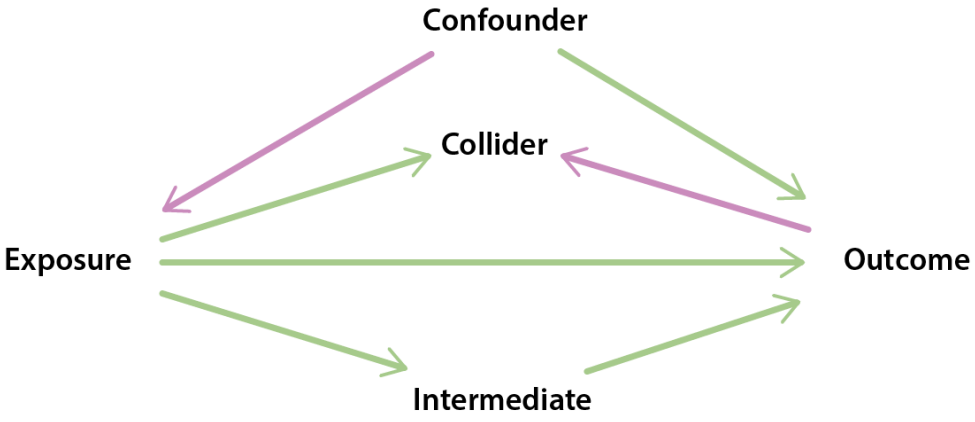


Figure 7. Directed acyclic graph

Directed acyclic graph is a tool commonly used to visualize confounding effects, by known or unknown variables, on the relationship between the exposure and outcome. "Open paths" should be adjusted for, while closed paths (like the collider-path) should not be adjusted for, as this would result in confounding.

Study design

In the hierarchy of evidence-based medicine randomized controlled trials is considered as gold-standard for exploring causality. However, such studies require extreme level of precision with low level of risk for the study objects or patients to be ethically approved.

In observational data, where information is already collected, the patients or population studied are not exposed to risk by performing the study and consequently requirements for level of precision may be reduced. This principle is thoroughly explained by Hernan,[107] who encourage researchers to do observational studies, repeat them in multiple populations and do meta-analyses to increase the precision (and tighten confidence intervals).

With this in mind and with regards to our aim of studying PPH, which is the major cause of direct maternal deaths worldwide,[1] a population based cohort study is that of choice when observational data, like the MBRN database, are available.

Outcome measure

In our study we performed logistic regression analyses, with Odds Ratio (OR) as outcome measure. An alternative to this is binominal regression analyses with Relative Risk (RR) as outcome measure.

A major difference between the two, RR (ratio of risks) and OR (ratio of odds), lies within the denominators of risks and odds, and is described by Holcomb et al.[108] Risk's denominator contains all cases, while odds's denominator contains the number of cases without the outcome. This gives the two outcome measures different statistical and mathematical properties.[109] A consequence is that OR, compared to RR, tend to overestimate associations when the occurrence of the outcome become high. However, they will always cross the level of significance (1) at the same values of the outcome. In everyday statistical work it is recommended to choose RR when occurrence of the outcome exceeds 10–20%.[108] The general occurrence of PPH in our study population was 10% (277 746 out of 2 790 090). In later years of the study period and in some groups with high risk of recurrence (recurrence of PPH when PPH in two previous deliveries) the occurrence of PPH exceeds these percentages, but to make the results of the individual analyses comparable to each other we chose to be consistent and used OR as outcome measure throughout the thesis.

Validity of the study

According to "Modern Epidemiology", by Rothman, there are three major threats to validity: confounding, selection bias and generalizability, and information bias.[103]

To evaluate validity is the approach used to define the ability of a study to predict an outcome in a target population. Target population is defined as the population for whom the information gained from the study is relevant,[103] which in our study are present and future expecting women.

Internal validity refers to the degree to which the effect measured is representative for the source population and that the cause-effect relationship cannot be explained by other factors. It can be affected by random error, bias and confounding.

External validity is dependent on internal validity but ensures generalizability of the results beyond the source population.

Internal validity

Selection bias

Using population data reduces the effect of selection bias to a minimum, but in our study of PPH we selected a study population with spontaneous start or induction of labour. The rationale behind this selection was to increase relevance for the clinicians and midwifes. Thus, we excluded all deliveries that were planned for cesarean section. The excluded group may include medical indicated cesarean sections, or sections performed due to maternal wish or preference. Medical indications for cesarean section may be two or more previous cesareans, placenta previa, transverse lie of the fetus, placental abruption or fetal indications. These cases may be scheduled to hospital settings with higher degree of medical resources available and we therefore consider it less representative for the general population.

We performed additional analyses with selections both including and excluding all cesarean deliveries. With regards to recurrence off PPH in general, the inclusion of all cesareans strengthened rather than attenuated our risk estimates.

As multiple gestation is a risk factor for PPH,[26] we only selected singleton births.

The rationale for including only gestational age of ≥22 weeks was to exclude abortions.

Information bias

With regards to MBRN data information bias may represent bias related to the collection of data (registration bias). Since the data were prospectively collected through national standardized forms the effect of recall bias could be regarded as negligible.

The trend of PPH occurrence during the study period, shown in figure 1, show a marked increase in occurrence around year 1999, which coincides with the most comprehensive update of the notification forms of the MBRN, including specification of PPH severity. The increase also coincides with the implementation of activity-based financing of the Norwegian health services in 1997,[110] where the occurrence of complications, like PPH, could allocate higher subsidies from the health trust. In combination these changes may induce what is referred to as a Hawthorne effect in literature,[111] where study participants (in this setting the persons who register PPH) increase performance in response of being studied, observed, or measured.

Misclassification is a concern of registry data, but in our study on recurrence we expect such misclassification to be equal in exposed and non-exposed individuals and therefore this would be considered as non-differential misclassification.

Studies claim that visual estimation of PPH tend to underestimate bleeding volume.[59, 61] In line with this is our observation that registration of especially PPH of undefined cause (which mainly represent mild cases of PPH), has increased after the change in notification form and implementation of activity-based financing in 1999. Further, a validation study scrutinizing cases of severe PPH between 2008 and 2013, found the registrations to be of acceptable quality, with a sensitivity of 87.7% and a

positive predictive value of 81.1%.[60] Thus, we consider the sensitivity of severe PPH in our study to be high and argue that the general sensitivity of PPH registrations have improved during the study period.

Confounding

To account for confounding has been one of the major tasks in performing and interpreting our analyses. The risk profile for PPH is comprehensive and we can only directly account for known variables registered in MBRN and other databases linked to the MBRN.

To serve as a confounder the variable must be associated with both the exposition and the outcome.[103] This is visualized in figure 7. In all analyses we have explored the effect of adjustment for age, parity and birth year separately and together. Concerning recurrence risk of PPH in general we also explored the effect of adjustment for social factors like marital status, mother's country of birth and level of education (available until 2013). When analysing cause-specific recurrence risk we explored the effect of stratification between term and preterm deliveries.

Birth year periods

As shown in figure 1 the occurrence of PPH has changed through the study period. Year of birth is a continuous variable, which can be categorized, and to account for the change in occurrence of PPH through the study period in our analyses both adjustment and stratification could be suitable.[112] Such effects from a time varying covariate or exposure are commonly called *effect modification* or *interaction*.[103] The rationale behind this is that the association varies with the value of time, similar to the interaction of PPH anamnesis and the value of birthweight, which we discuss in this thesis. Rothman state that effect-measure modification in epidemiological studies not necessarily should be considered as confounding, as they may be part of a natural variation. However, our interpretation is that the quality of PPH registration in MBRN

has improved during the study period and that adjustment or stratification for year of birth should be done.

The analyses where we have performed stratification are presented in tables in our papers. In analyses where we have performed adjustments for periods, which was the most powerful confounder, we created new variables with birth year strata of approximately equal number of deliveries and according to the outcome variables distribution throughout the study period. Consequently, outcomes in second generation are clustered with shorter intervals in the latter half of the study period, while recurrence in the same woman is more evenly distributed: recurrence in a woman: 1967–1977, 1978–1987, 1988–1997, 1998–2007 and 2008–2017; between generations: 1967–2001, 2002–2010, and 2011–2017; between pairs of siblings: 1967–2002, 2003–2007, 2008–2011, 2012–2014, and 2015–2017.

Social and demographic factors

Adjustment for the social factor as marital status and level of education (available until 2013) where carried out with the aim of accounting for potential factors of PPH that where socially determined, but this had negligible effect on our risk estimates. However, this does not rule out that social or environmental factors influence our recurrence risk estimates, but to a negligible degree, as indicated by our sensitivity analyses.

Mother's country of birth

In the table "supporting information S1" of *Paper I* we presented the distribution of PPH according to ethnicity. To account for possible effects of country of birth we performed analyses with adjustments for mother's country of birth, but these analyses failed to affect our risk estimates. Reasons for this might be either that recurrence risk is not affected by ethnicity or that the non-Norwegian representation in the dataset (14.8% with non-Norwegian origin) makes them statistically outnumbered.

Confounding by medication:

Acetylsalicylic acid a is a known risk factor for PPH [39] and has been used prophylactically to reduce the risk of pre-eclampsia in the Norwegian population since 1999.[45] Tranexamic acid is used to prevent PPH, but has not been routinely used during the study period.[113] To explore the possible effects of these medications has been beyond the scope of this study. However, for future studies information of prescribed anticoagulants could be directly accounted for if data from the Norwegian Prescription Database (Nor PD) were included.

Residual confounding:

Residual confounding caused by unmeasured confounding factors cannot be ruled out in our results. Our sensitivity analyses indicated that this was not present.

External validity (generalisability)

Reported risk and occurrence of PPH vary among populations.[16] This might be due to difference in handling modifiable risk factors or it may be differences in genetic or sustained environmental factors associated with ethnicity. Statistically it may also be due to differential definitions of PPH. The relatively homogenous ethnic Norwegian population studied may reduce the generalizability of our results. However, the finding that recurrence risks were not affected by immigration status support the generalizability to other populations.

Regarding *Paper III* and type-specific occurrence and recurrence risk the diagnostic codes utilized to describe causes of PPH differ among studies and populations. However, such challenges should be met with an effort to unite and carry out meta-analyses.

Precision of the study

A main strength of the population-based design of this study is the size of the study population with n=2 790 090, which increase precision of ORs and tighten the confidence intervals.

Discussion of the results

PPH in general

Trend of PPH

Our data show that the time-trend of PPH is approaching 30% occurrence in the later years of the study period. This corroborates with increasing trend of PPH in developed countries.[5] A study from UK reported PPH in more than 30% of deliveries at their maternity services during 2008 and 2009.[6]

Recurrence of PPH in same woman

PPH in preceding deliveries of a woman is a known risk factor for PPH,[29] but solely apply to parous women. In our study we found strong recurrence risk of PPH when we studied 794 000 women with two deliveries and 282 000 women with three deliveries. These findings are consistent with the results of a Swedish study examining recurrence risk in the first three deliveries of 583 000 Swedish women.[28] A study from New South Wales studying 125 000 women with two deliveries also concluded the same.

Stillbirth is a known risk factor for PPH[114] and the mechanism is possibly through alteration of the normal mechanisms of births. Consequently, it was expected that an association between stillbirth and PPH in parous women without previous PPH would be found. However, the lack of association in women with previous PPH remains more challenging to explain and has not been previously reported. The finding may represent a phenomenon referred to as index event bias.[115] This is supported by a more detailed exploration of our results (*Paper I* Supporting information table S2)

which show that 20.9% of stillbirths in the recurrent-PPH-group experienced PPH, while only 10.8% of stillbirths in women with no previous PPH experienced PPH in present delivery. Nevertheless, it cannot be ruled out that stillbirth have different pathophysiological mechanisms in the two groups.

Subsequent delivery rate

Our finding of reduced further pregnancy rate in women with PPH was a new finding. However, it was not evident before five and three years after the first and second delivery, respectively. These differences could potentially affect our estimates of PPH recurrence risk, but divergence of the cumulative hazard ratio graphs was delayed, and we therefore believe the effect on recurrence risk estimates are negligible. Further pregnancy rate as phenomenon has been studied after obstetric complications other than PPH. It was increased after perinatal demise,[116] and reduced after placental abruption.[117] After fetal demise an increased further pregnancy rate may be caused by parental need or wish for a new child, while the reduction after severe obstetric complication may be associated with fear and traumatic experience from the complication. Similar mechanisms may come into play after PPH. To explore this further was beyond the scope of our study.

Paternal effect of PPH recurrence

Our finding that the maternal recurrence risk was higher when the father was the same in subsequent pregnancies is in line with a Swedish study.[30]

We explored the paternal contribution to PPH further and found significant higher recurrence risk (OR>1) in deliveries where the father had changed partner. Such analyses did not reach statistical significance in a Swedish study.[30] It is probable that this inter-study difference is due to the larger sample in our study.

Effect of fetal sex on risk of PPH

Sex differences has been explored for different variables and is present in birthweight, placental weight (and their ratio) and umbilical cord properties.[51-53] We did not expect to find that delivering a female neonate would carry a higher risk of PPH. The effect was present also after adjusting for birthweight. This finding is both novel and challenging to explain, but the explanation may lie in the placenta. It may be that placenta of female fetuses have different physical, vascular or invasive properties that may increase the risk of PPH. The effect of fetal sex on PPH risk is interesting from a biological, and possibly evolutionary perspective,[8] and generates new research questions into sex differences in the placenta.

Cause-specific PPH

Distribution of PPH types

The distribution of the different types of PPH varies markedly between different studies and populations. This is especially true for PPH caused by atony and retained placenta. Bateman et al. [14] and Widmer et al. [15] reported that 79% and 62% of all registered PPH cases (>500ml and refractory PPH, respectively) were due to atony. This contrasts our finding that 23% of PPH were due to atony, which is more consistent with a Swedish study that found 41% of PPH were due to atony (>1000ml).[28] PPH due to retained placenta is more comparable between studies. We found 11.4% were due to retained placenta, which is in line with results from an American study by Bateman et al.[14] 33.5% of PPH cases were due to retained placenta in the study of Oberg et al. (with definition of PPH as blood loss >1000 ml) and is comparable to our results in severe PPH where 25.7% were due to retained placenta.[15] The interstudy differences are interesting and we cannot rule out that they represent genetic or physiological differences. They may also be caused by differences in medical cultural and management of delivering women. However, the most likely explanation is differences in coding and registration of bleeding. Some studies are based on older ICD-codes,[14] where definitions of PPH types are less specific compared to what we have utilised. This applies especially to PPH due to

dystocia. As dystocia may result in uterine fatigue and atony it is assumable that PPH due to dystocia may have been classified as atony in studies where dystocia is not recorded in the databases. This may partly explain some of the marked interstudy differences found concerning occurrence of PPH due to atony.[14]

PPH associated with retained placenta had the highest occurrence of severe PPH. We do not have exact information of placenta accreta spectrum in our dataset or in the population, but it is reasonable to assume that some cases of placenta accreta spectrum cases are contributing to the cases of severe PPH in the retained placenta group. To explore this further, was beyond the scope of our study. Another explanation of the high rate of severe PPH in the retained placenta group is the need of surgical intervention in treatment of the retained products. This may consume extra time and allow more blood to be lost, as opposed to atony which in most cases are sufficient and effectively treated with medications. We encourage time-to-surgery scrutiny in future studies.

Risk of type specific postpartum hemorrhage according to maternal, pregnancy and birth characteristics

We found association between increasing maternal age and all types of PPH. The strongest effect was found for PPH caused by dystocia. Previous studies have primarily reported association between maternal age and PPH caused by atony,[15, 24-27] but association between maternal age and retained placenta, regardless of PPH, has been reported.[27]

Parity showed strongest association with PPH due to dystocia. 76% of the cases were primiparas. This is in line with previous knowledge that nulliparas have higher risk of dystocia.[118] Parity showed strongest association with PPH due to dystocia. 76% of the cases were primiparas. This is in line with previous knowledge that nulliparas have higher risk of dystocia.[118]

High birthweight has been strongly associated with PPH.[29, 41, 104] What our study added was that the associations varied according to type of PPH. The strong association between birthweight and PPH due to dystocia has not been described in previous studies. There was also a strong association between birthweight and PPH due to birth canal lacerations and uterine atony. A previously described mechanism of how macrosomia cause PPH is through increased distention of the uterus and a large utero-placental wound surface.[15, 81, 104, 119] Another explanation for the association with PPH is that fetal macrosomia may cause dystocia or atony and lead to the need of operative vaginal delivery, resulting in surgical bleeding. With regards to PPH due to birth canal trauma macrosomia may increase tension on maternal tissue during labor and lead to increased risk of obstetric trauma with accompanied blood loss.[120]

First trimester bleeding was associated with PPH caused by retained placenta and is in line with previous studies indicating that retained placenta (irrespective of PPH)[46] and PPH in general[47] are associated with threatened abortion.

The effect of fetal sex on type-specific PPH

It is well known that sex differences exist in properties of placenta, umbilical cord and birthweight, [52, 53, 121-123] and in *Paper I* we found sex differences with regards to PPH in general. Therefore, it was not surprising that this effect was present in type-specific PPH. The strongest effect was present in PPH caused by retained placenta. This was a new finding, but is in line with previous knowledge that delivery of girls carries higher risk of retained placenta in general. [55, 57] Our finding with association between delivering a girl and PPH due to atony has been described in a previous study.[124] That PPH due to placental abruption is associated with delivering a boy is in line with the risk of placental abruption in general is associated with male sex, [124] and may be regarded as the opposite effect seen concerning PPH due to retained placenta where delivery of a girl increases the risk. The same difference applies to pre-eclampsia,[125] although not consistently.[124] This support a suspicion

that there are sex differences in depth of placentation and that transformation of spiral arteries in pregnancies with male fetuses may be more inadequate.[126-128]

Risk of type specific postpartum hemorrhage (PPH>500ml) in the second delivery according to PPH types in the first delivery and pregnancy- and birth characteristic

When studying recurrence of type specific PPH we found highest risk for the same types of PPH to recur in second delivery. The strongest recurrence risk was found for PPH due to dystocia, which to our knowledge is a new finding. Dystocia, with and without PPH, has only been explored in previous studies with focus on risk factors for PPH. [129-132] A possible explanation for the high recurrence risk associated with PPH due to dystocia may be linked to sustained genetic or environmental factors, like tendency to deliver large babies or fetopelvic disproportion, with need of operative delivery and thereby cause PPH through surgical bleeding.

As expected, the lowest recurrence risk was found for PPH without specific cause. This is plausible since the category was dominated by mild cases and thereby corroborates with the concept that a mild phenotype of a polygenic trait or disease is generally less prone to recur than a severe phenotype. [133] It is a finding that suggest that most of these cases were correctly assigned to the group.

Another factor that affected recurrence risk was the change of father, which slightly reduced the risk of PPH caused by obstetric trauma and atony and undefined bleeding cause. This effect persisted also after adjustment for inter-delivery interval, which could be expected to be longer for women who had changed partners. The finding is in line with our result that there was a slight paternal effect on recurrence risk of PPH in general.[104]

Inter-delivery interval had negligible effect on PPH in general, [104] but after categorization into sub-types of PPH we revealed some diversity. There was an

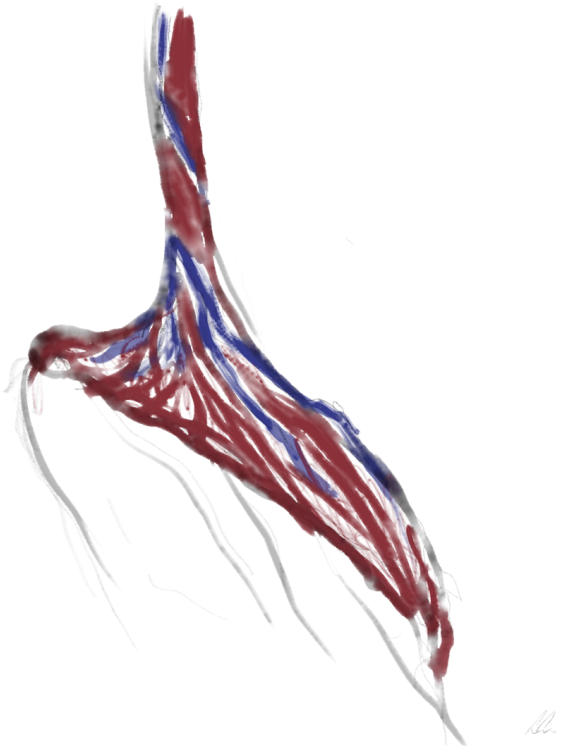
increased risk of PPH due to retained placenta when the inter-delivery was less than on year. One may speculate if a short inter-delivery interval is associated with favorable environment for deeper placentation.

It is an international concern that cesarean rates are high,[134] we therefore explored the effect of a previous cesarean on the risk of type specific PPH. Studies have linked previous cesarean to risk of retained placenta in general [25, 55, 56] and atonic PPH,[14] but not consistently.[57, 58] In our results all types of PPH were associated to previous cesarean, but three types stood out; PPH due to dystocia, retained placenta and atony, with a strongest association to PPH due to dystocia. As PPH due to dystocia is widely ignored in literature we performed further explorative analyses and included nulliparous women. The rationale for this was to use the nulliparous group as a control for the effect of no previous dilation of the cervix (which may be the case for many women with previous cesarean) in the development of dystocia in women with previous cesarean. The risk of PPH due to dystocia in previous cesarean section was higher than in nulliparous women. This indicates that the effect of no previous vaginal delivery of the cervix only partly can explain the association. Other explanations may be sustained genetic or environmental factors causing dystocia with PPH (like macrosomia or fetopelvic disproportion) or it may be caused by a direct effect of ineffective labor contractions due to uterine scar, or combination of both. These effects are either stronger than the effect of no previous cervical dilation (which may prolonged labour and exhaust uterine contractions) or they are additional effects. The theory of sustained genetic or environmental factors is supported by our finding that PPH due to dystocia was the type of PPH most likely to recur from first to second delivery. With regards to the high risk of PPH due to retained placenta after cesarean section one may speculate if this is related to the tendency of abnormal invasion of placenta to occur in women with previous cesarean section.[48]

We found a dose-response-pattern between PPH due to retained placenta and velamentous and marginal umbilical cord insertion, with strongest association to velamentous cord insertion (which is the most severe form of umbilical cord insertion

pathology among the two). This support the biological plausibility of our results and that pathological placentation is linked to PPH. The umbilical cord conditions are possible to diagnose by ultrasonography during pregnancy,[135] and should be accounted for when assessing PPH risk in delivering women.

Illustration 1. Pathological umbilical cord insertion



The recurrence risk of PPH between family members

Our research group has previously reported family aggregation of complications as pre-eclampsia, obstetric anal sphincter injuries and placental abruption. They are transmitted and run primarily through the maternal line.[93, 136, 137]

The risk estimates of PPH recurrence between family members were stronger if we included only vaginal deliveries. This is consistent with results from the Swedish population, [28] but to increase relevance for a setting in the delivery-rooms, where the risk of acute cesarean always is present, we presented data with selection of deliveries with spontaneous start or induction of labour, regardless of delivery mode.

Transgenerational recurrence of PPH

Transgenerational recurrence was explored through the maternal and paternal line. Our results of maternal contribution are in line with previous knowledge from the Swedish population,[30] but are in conflict with a generational study using two Scottish birth-cohorts to explore the effect.[31] The inter-study difference is challenging to explain, but one may speculate if unclear definition of PPH in one of the utilized Scottish cohorts has attenuated the generational effect. The paternal transgenerational effect corroborates with our own results of recurrence risk of PPH in fathers who changed partners.

If extrapair paternity affect our risk estimates of recurrence through the paternal line will remain unrevealed, but extrapair paternity is reported to be low (<2%),[138] and are likely equally distributed in males born with PPH, compared to without PPH, which makes the effect non-differential.

Recurrence of PPH between siblings

Our findings that the recurrence of PPH between siblings follows a dose-response pattern according to the anticipated number of shared genes increase the biological plausibility of our results. It is further supported by consistency with the results of a Swedish study.[30]

Combined effects of PPH in relatives

The combined approach with data accounting for recurrence risk both through generations and between siblings, has not been published before. Also, these results showed a dose-response pattern according to the anticipated proportions of shared genes, which substantiates the biological plausibility of our results. The results were robust for confounding, even for adjustment for birth year period which only affected the risk estimates negligibly, likely because a confounder must be related to both the exposition and outcome to be able to confound.

The association between birthweight and recurrence risk of PPH

There is a known association between current fetal macrosomia and PPH,[81] but the possible interaction between fetal birthweight and PPH anamnesis in a woman, through generations and between siblings has not been explored previously.

There were significant differences in risks of PPH according to previous PPH and current birthweight when comparing births in the same woman, between generations and sisters (table 2, paper I, and table 4, paper II). As expected from differential proportions of shared genes and environmental factors, the effect of previous PPH in the same woman was stronger than that between generations and siblings. However, the effects of current birthweight in the same woman, between generation and sisters were similar, even without adjusting for parity, although the effects in the same woman were restricted to multiparity, as opposed to the generational- and sibling analyses.

The interaction between a history of PPH and current birthweight shown in table 1 seems to be similar for generations and sisters (table 4, paper II). When giving a collective interpretation of the analyses in a woman, through generations and between siblings there is a tendency for the effect of PPH anamnesis to be most prominent when comparing the lower weight groups, while for the higher weight groups this effect seems to be overridden by the added risk effect of PPH due to macrosomia.

Population attributable fractions

Population attributable fractions of PPH and birthweight has not been previously studied. The effect of PPH anamnesis on PAF is strongest for recurrence (in the same women), and PAF's are essentially equal for birthweight and previous PPH in a woman.

That PAFs for PPH due to birthweight in the analyses of recurrence risk in a woman, through generations and between siblings are comparable supports the biological plausibility of the results, since data used in a woman is spread throughout the study period (1967–2017), while the data used for the analyses through generations and between siblings is primarily distributed in the latter half of the study period (as they are found in the second generation).

Conclusions and implications

Paper I

The risks of PPH in a woman's second or third delivery increased with the number of previous deliveries with PPH. The recurrence risk was modulated by birthweight, showed a moderate paternal effect and was influenced by offspring sex. There was a slightly reduced further pregnancy rate in women with previous PPH, but this likely had small effect on recurrence risk. Despite the increasing trend of PPH, the recurrence risks were similar throughout the 50-year study period.

Paper II

There was an increased recurrence risk of PPH between generations and siblings (as parents), and the risk was higher among relatives with a closer genetic relationship. These risks were modulated by birthweight in the present pregnancy and was stronger through the maternal than the paternal line of transmission. The results indicates that there is a genetic component in the etiology of PPH.

Paper III

Maternal, fetal and obstetric characteristics had differential effects and the recurrence risk differed considerably between the different PPH types. PPH due to retained placenta was most frequently registered with severe PPH, the only type affected by inter-delivery interval and showed strongest effect of sex; delivery of a boy was associated with lower risk of PPH. PPH due to dystocia had the highest recurrence risk in a succeeding delivery and was the type of PPH with strongest association to a previous cesarean section. This indicates that PPH due to dystocia, which is widely ignored in literature, is of major importance for the risk assessment of PPH recurrence.

The results of this thesis add to the understanding of recurrence risk of PPH and suggest that PPH can be inherited. The overall pattern of our results indicates that recurrence risk of PPH followed a dose-response pattern proportionate to the

anticipated number of shared genes and severity of bleeding. The results also followed the pattern of polygenic theory of inheritance, that a phenotype of severe trait has higher recurrence rate.[133] This strengthens the biological plausibility of our results.

In a clinical setting the results may be integrated into risk assessment and aid clinicians in the selection of women at higher risk of PPH. For the Norwegian population the development of an online PPH-risk scoring tool could be appropriate. Specific efforts should be made to reduce time-to-treatment in situations where risk of retained placenta is increased. For women with previous cesarean, efforts could be made to reduce the high risk of dystocia related PPH. Future study should assess possible benefits of special follow-up or planned cesarean section in a subsequent pregnancy, to decrease the risk of recurrent PPH[139].

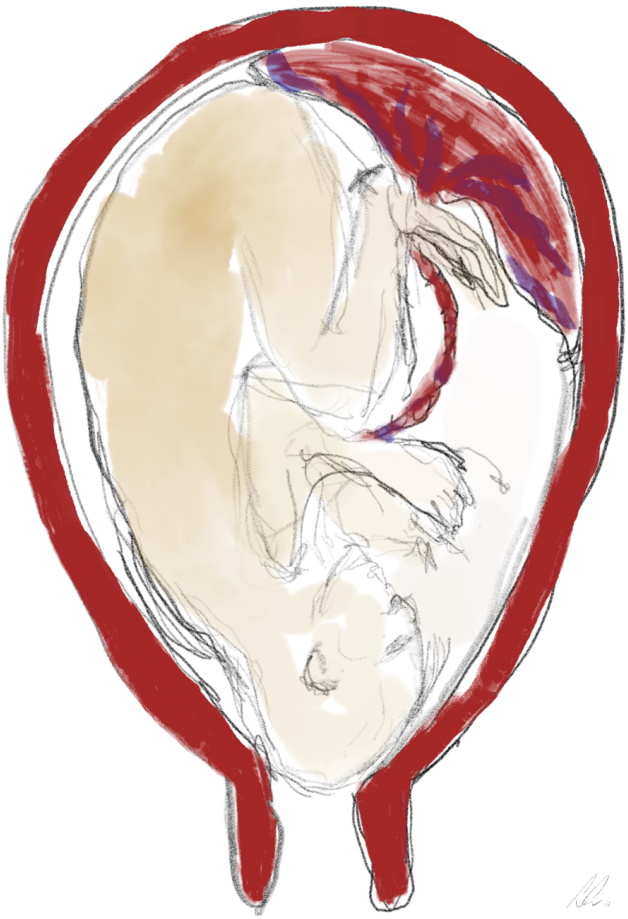
Our results increase the understanding of one of the most feared complications to human delivery and may give answers to expecting women and their families. The results may aid clinicians when assessing risk of PPH in mothers with a history of PPH and indicate where PPH-preventive measures can most be effective.

Suggestions for future research

The scrutiny of a field gives answers to some research questions and provides a breeding ground for others. In this matter this thesis is no exception.

1. Investigate if recurrence patterns between relatives vary according to type-specific PPH.
2. Perform a clinical study with aim of evaluating time-to-treatment when placenta is retained, independent of PPH. In a second phase efforts could be done to reduce time-to-treatment and assess if this measure has effect on occurrence of severe PPH due to retained placenta.
3. Explore if further pregnancy rate varies according to type of PPH.
4. To perform genetic epidemiological studies, GWAS genome wide association studies, to explore if there are genetic variants associated with the recurrence risk between relatives.
5. Explore if there is interplay between PPH due to dystocia and maternal pelvic anatomy.
6. Explore risk of type specific PPH according to Robson groups, with aim of tailoring the knowledge of this thesis to a clinical setting by approaching a widely known terminology.
7. Explore the effect of maternal anticoagulation therapy on PPH occurrence by crossing data from Norwegian Prescription Database.
8. Explore recurrence pattern of fetal macrosomia between relatives, which has been strongly associated with PPH in our results.
9. Implement risk assessment scoring systems for PPH, based on risk of occurrence and recurrence in a woman, through generations and between siblings, and in future studies evaluate if pre-labour risk assessment decrease occurrence and severity of PPH.

Illustration 2. “This thesis at a glance”



Source of data

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Table and Figure Captions

Appendices

Appendix I. Notification form, the Medical Birth Registry of Norway, 1967–1998

STATENS HELSETILSYN
Postboks 8128 Dep.
0032 OSLO

Medisinsk registrering av fødsel

Sendes 9. dag etter fødselen til fylkeslegen (stadsfysikus) i det fylket der moren er bosatt.

Merk: Det skal fylles ut blankett for hvert barn (foster). Dør barnet etter fødselen, skal det også fylles ut legeerklæring om dødsfall, og/eller dødsfallet meldes til skifteretten (lensmannen).

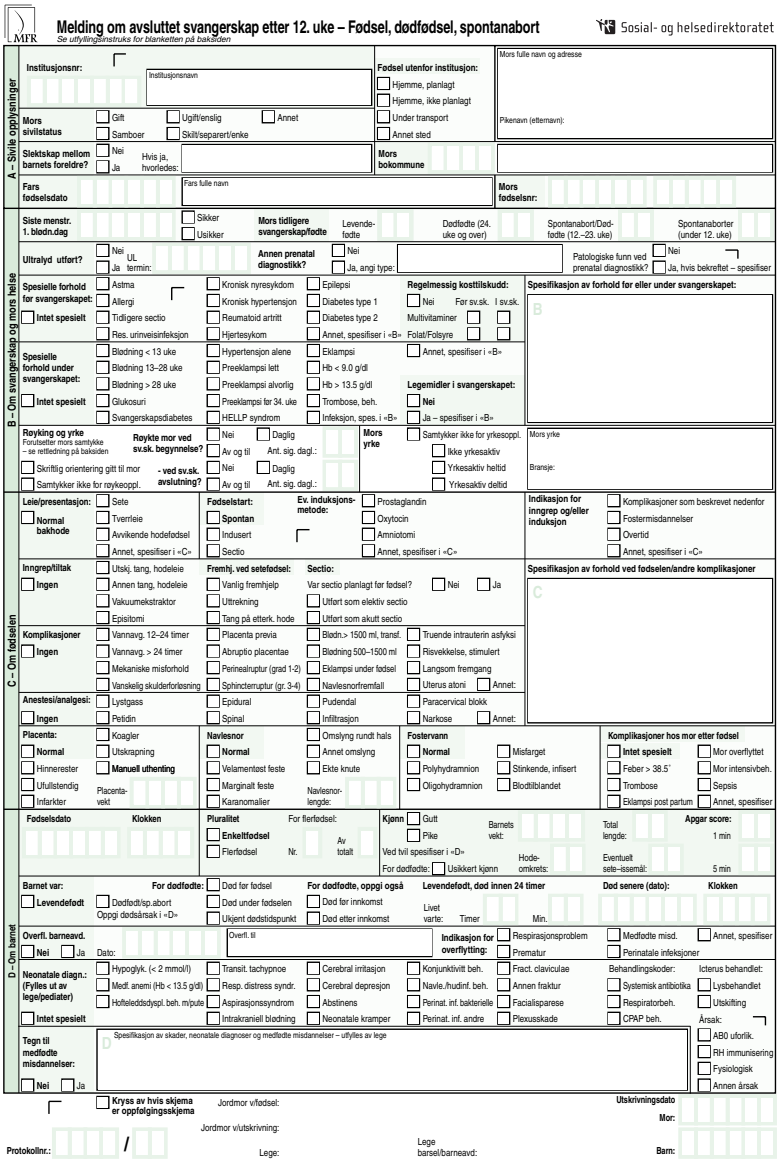
Barnet	Barnet var: 1 ☐ Levende født 2 ☐ Dødfødt foster	Født dag, mnd., år	Klokkeslett	Personnr.	Skriv ikke her
	1 ☐ Enkel 2 ☐ Tvilling 3 ☐ Trilling 4 ☐ Firling		Kjønn: 1 ☐ Gutt 2 ☐ Pike		
	Etternavn, alle fornavn (bare for levendefødte)				
	Fødested. Navn og adresse på sykehuset/fødehjemmet		Kommune		
Faren	Etternavn, alle fornavn		Født dag, mnd., år	Bostedskommune	
Moren	Etternavn, alle fornavn. Pikenavn			Født dag, mnd., år	
	Bosted. Adresse		Kommune		
	Ekteskapelig status: 1 ☐ Ugift 6 ☐ Samboende 2 ☐ Gift 3 ☐ Enke 4 ☐ Separert 5 ☐ Skilt			Ekteskapsår (gifte)	
	Antall tidligere fødte (før denne fødselen)	Levende fødte	Av disse i live	Dødfødte	
	Er moren i slekt med faren? 1 ☐ Nei 2 ☐ Ja. Hvilket slektskapsforhold:				
Morens helse **før** svangerskapet	1 ☐ Normal 2 ☐ Sykdom (spesifiser):				
			Siste menstruasjons første blødningsdag		
Morens helse **under** svangerskapet	1 ☐ Normal 2 ☐ Komplikasjoner (spesifiser):				
Ble fødselen provosert	1 ☐ Nei 2 ☐ Ja				
Inngrep under fødselen	1 ☐ Nei 2 ☐ Ja (spesifiser):				
	Inngrepet utført av: 1 ☐ Lege 2 ☐ Jordmor				
Komplikasjoner i forbindelse med fødselen	1 ☐ Nei 2 ☐ Ja (spesifiser):				
Fostervann, placenta og navlesnor	1 ☐ Normalt 2 ☐ Patologisk (spesifiser):				
Barnets tilstand	Bare for levende fødte. Tegn på asfyksi? 1 ☐ Nei 2 ☐ Ja		Apgarscore etter 1 min.	etter 5 min.	
	For levende fødte og dødfødte. Tegn på medfødt anomali, på skade eller sykdom? 1 ☐ Nei 2 ☐ Ja. Hvilke:				
	Lengde (i cm)	Hode-omkr. (i cm)	Vekt (i g)	For døde innen 24 timer Livet varte i: Timer / Min	
	For dødfødte. Døden inntrådte 1 ☐ Før fødselen 2 ☐ Under fødselen. Dødsårsak:				
				Seksjon? 1 ☐ Nei 2 ☐ Ja	
Alvorlige arvelige lidelser i slekten	1 ☐ Nei 2 ☐ Ja Sykdommens art og hos hvilke slektninger:				

Sted (sykehusets stempel) — Dato — Jordmor — Lege

IK - 1002.

50 000 5.96

Appendix II. Notification form, the Medical Birth Registry of Norway, 1999–



MFR

Melding om avsluttet svangerskap etter 12. uke – Fødsel, dødfødsel, spontanabort

Se utfyllingsinstruks for blanketten på baksiden

Sosial- og helsedirektoratet

A – Sivile opplysninger

Institusjonsnr: / Institusjonsnavn

Fødsel utenfor institusjon: Hjemme, planlagt; Hjemme, ikke planlagt; Under transport; Annet sted

Mors fulle navn og adresse

Pikenavn (etternavn):

Mors sivilstatus: Gift; Samboer; Ugift/enslig; Skilt/separert/enke; Annet

Slektskap mellom barnets foreldre? Nei; Ja. Hvis ja, hvorledes:

Mors bokommune

Fars fødselsdato

Fars fulle navn

Mors fødselsnr:

B – Om svangerskap og mors helse

Siste menstr. 1. blødn.dag: Sikker; Usikker

Mors tidligere svangerskap/fødte: Levendefødte; Dødfødte (24. uke og over); Spontanabort/Dødfødte (12.–23. uke); Spontanaborter (under 12. uke)

Ultralyd utført? Nei; Ja. UL termin:

Annen prenatal diagnostikk? Nei; Ja, angi type:

Patologiske funn ved prenatal diagnostikk? Nei; Ja, hvis bekreftet – spesifiser

Spesielle forhold for svangerskapet: Intet spesielt; Astma; Allergi; Tidligere sectio; Res. urinveisinfeksjon; Kronisk nyresykdom; Kronisk hypertensjon; Reumatoid artritt; Hjertesykom; Epilepsi; Diabetes type 1; Diabetes type 2; Annet, spesifiser i «B»

Regelmessig kosttilskudd: Nei; Før sv.sk.; I sv.sk.; Multivitaminer; Folat/Folsyre

Spesifikasjon av forhold før eller under svangerskapet: B

Spesielle forhold under svangerskapet: Intet spesielt; Blødning < 13 uke; Blødning 13–28 uke; Blødning > 28 uke; Glukosuri; Svangerskapsdiabetes; Hypertensjon alene; Preeklampsi lett; Preeklampsi alvorlig; Preeklampsi før 34. uke; HELLP syndrom; Eklampsi; Hb < 9.0 g/dl; Hb > 13.5 g/dl; Trombose, beh.; Infeksjon, spes. i «B»; Annet, spesifiser i «B»

Legemidler i svangerskapet: Nei; Ja – spesifiser i «B»

Røyking og yrke. Forutsetter mors samtykke – se rettledning på baksiden

Skriftlig orientering gitt til mor

Samtykker ikke for røykeoppl.

Røykte mor ved sv.sk. begynnelse? Nei; Daglig; Av og til; Ant. sig. dagl.:

– ved sv.sk. avslutning? Nei; Daglig; Av og til; Ant. sig. dagl.:

Mors yrke: Samtykker ikke for yrkesoppl.; Ikke yrkesaktiv; Yrkesaktiv heltid; Yrkesaktiv deltid

Mors yrke

Bransje:

C – Om fødselen

Leie/presentasjon: Normal bakhode; Sete; Tverrleie; Avvikende hodefødsel; Annet, spesifiser i «C»

Fødselstart: Spontan; Indusert; Sectio

Ev. induksjonsmetode: Prostaglandin; Oxytocin; Amniotomi; Annet, spesifiser i «C»

Indikasjon for inngrep og/eller induksjon: Komplikasjoner som beskrevet nedenfor; Fostermisdannelser; Overtid; Annet, spesifiser i «C»

Inngrep/tiltak: Ingen; Utskj. tang, hodeleie; Annen tang, hodeleie; Vakuumekstraktor; Episiotomi

Fremhj. ved setefødsel: Vanlig fremhjelp; Uttrekning; Tang på etterk. hode

Sectio: Var sectio planlagt før fødsel? Nei; Ja. Utført som elektiv sectio; Utført som akutt sectio

Spesifikasjon av forhold ved fødselen/andre komplikasjoner: C

Komplikasjoner: Ingen; Vannavg. 12–24 timer; Vannavg. > 24 timer; Mekaniske misforhold; Vanskelig skulderforløsning; Placenta previa; Abruptio placentae; Perinealruptur (grad 1-2); Sphincterruptur (gr. 3-4); Blødn.> 1500 ml, transf.; Blødning 500–1500 ml; Eklampsi under fødsel; Navlesnorfremfall; Truende intrauterin asfyksi; Risvekkelse, stimulert; Langsom fremgang; Uterus atoni; Annet:

Anestesi/analgesi: Ingen; Lystgass; Petidin; Epidural; Spinal; Pudendal; Infiltrasjon; Paracervical blokk; Narkose; Annet:

Placenta: Normal; Hinnerester; Utullstendig; Infarkter; Koagler; Utskrapning; Manuell uthenting; Placentavekt

Navlesnor: Normal; Velamentøst feste; Marginalt feste; Karanomaller; Omslyng rundt hals; Annet omslyng; Ekte knute; Navlesnorlengde:

Fostervann: Normal; Polyhydramnion; Oligohydramnion; Misfarget; Stinkende, infisert; Blodtilblandet

Komplikasjoner hos mor etter fødsel: Intet spesielt; Feber > 38.5°; Trombose; Eklampsi post partum; Mor overflyttet; Mor intensivbeh.; Sepsis; Annet, spesifiser

D – Om barnet

Fødselsdato / Klokken

Pluralitet: Enkeltfødsel; Flerfødsel. For flerfødsel: Nr.; Av totalt

Kjønn: Gutt; Pike; Ved tvil spesifiser i «D»; For dødfødte: Usikkert kjønn

Barnets vekt:

Hodeomkrets:

Total lengde:

Apgar score: 1 min; 5 min

Eventuelt sete–issemål:

Barnet var: Levendefødt; For dødfødte: Dødfødt/sp.abort. Oppgi dødsårsak i «D»

For dødfødte, oppgi også: Død før fødsel; Død under fødselen; Ukjent dødstidspunkt; Død før innkomst; Død etter innkomst

Levendefødt, død innen 24 timer: Livet varte: Timer; Min.

Død senere (dato): Klokken

Overfl. barneavd.: Nei; Ja. Dato:

Overfl. til

Indikasjon for overflytting: Respirasjonsproblem; Prematur; Medfødte misd.; Perinatale infeksjoner; Annet, spesifiser

Neonatale diagn.: (Fylles ut av lege/pediater) Intet spesielt; Hypoglyk. (< 2 mmol/l); Medf. anemi (Hb < 13.5 g/dl); Hofteleddsdyspl. beh. m/pute; Transit. tachypnoe; Resp. distress syndr.; Aspirasjonssyndrom; Intrakraniell blødning; Cerebral irritasjon; Cerebral depresjon; Abstinens; Neonatale kramper; Konjunktivitt beh.; Navle-/hudinf. beh.; Perinat. inf. bakterielle; Perinat. inf. andre; Fract. claviculae; Annen fraktur; Facialisparese; Plexusskade; Behandlingskoder: Icterus behandlet; Systemisk antibiotika; Lysbehandlet; Respiratorbeh.; Utskifting; CPAP beh.; Årsak: AB0 uforlik.; RH immunisering; Fysiologisk; Annen årsak

Tegn til medfødte misdannelser: Nei; Ja

D: Spesifikasjon av skader, neonatale diagnoser og medfødte misdannelser – utfylles av lege

IS-1002 23011 07.06. Arvtord Grafisk.

Kryss av hvis skjema er oppfølgingsskjema

Jordmor v/fødsel:

Jordmor v/utskrivning:

Lege:

Lege barsel/barneavd:

Utskrivningsdato

Mor:

Barn:

Protokollnr.:

I

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ORIGINAL ARTICLE

Recurrence of postpartum hemorrhage, maternal and paternal contribution, and the effect of offspring birthweight and sex: a population-based cohort study

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Abstract

Purpose This study examines individual aggregation of postpartum hemorrhage (PPH), paternal contribution and how offspring birthweight and sex influence recurrence of PPH. Further, we wanted to estimate the proportion of PPH cases attributable to a history of PPH or current birthweight.

Methods We studied all singleton births in Norway from 1967 to 2017 using data from Norwegian medical and administrational registries. Subsequent births in the parents were linked. Multilevel logistic regression was used to calculate odds ratios (ORs) with 95% confidence intervals (CI) for PPH defined as blood loss > 500 ml, blood loss > 1500 ml, or the need for blood transfusion in parous women. Main exposures were previous PPH, high birthweight, and fetal sex. We calculated adjusted population attributable fractions for previous PPH and current high birthweight.

Results Mothers with a history of PPH had three- and sixfold higher risks of PPH in their second and third deliveries, respectively (adjusted OR 2.9; 95% CI 2.9–3.0 and 6.0; 5.5–6.6). Severe PPH (> 1500 ml) had the highest risk of recurrence. The paternal contribution to recurrence of PPH in deliveries with two different mothers was weak, but significant. If the neonate was male, the risk of PPH was reduced. A history of PPH or birthweight ≥ 4000 g each accounted for 15% of the total number of PPH cases.

Conclusion A history of PPH and current birthweight exerted strong effects at both the individual and population levels. Recurrence risk was highest for severe PPH. Occurrence and recurrence were lower in male fetuses, and the paternal influence was weak.

Keywords Adjusted population attributable fraction · Birthweight · Fetal sex · Inter-delivery interval · Paternal contribution · Postpartum hemorrhage

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Abbreviations

aOR	Adjusted odds ratio
CI	Confidence interval
OR	Odds ratio
PPH	Post-partum hemorrhage

Introduction

Postpartum hemorrhage (PPH) is the main direct cause of maternal death worldwide [1], and its incidence is increasing in developed countries [2]. In 2008–2009 PPH occurred in more than 30% of deliveries in UK maternity services [3]. PPH may occur due to uterine atony, genital-tract trauma, placenta-related complications, coagulation disorders or uterine distention caused by a large fetus, multiple

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pregnancies and polyhydramnios [4, 5]. Augmentation of labor, a previous caesarean section, chronic maternal hypertension and a previous PPH are also identified risk factors [3, 5, 6].

High birthweight is both a strong and a generally increasingly common risk factor for PPH [7, 8], but has not been studied systematically as a modifier in the recurrence of PPH. The paternal influence on PPH, which is mediated through the fetus and the placenta, has been studied, but with inconsistent results [9], and it is unknown if there is an effect of the offspring sex on occurrence and recurrence. Differential likelihoods of having a subsequent delivery after deliveries with and without PPH could potentially influence the recurrence risk estimates. This has not been addressed previously. Further, PPH recurrence has only been studied from an individual rather than a population perspective. Performing such studies requires large, longitudinal datasets.

We used nationwide medical and administrational registries to investigate the maternal and paternal contributions to recurrence risk of PPH and temporal variation in recurrence. We assessed the likelihood of having a subsequent delivery after PPH and studied how recurrence is influenced by birthweight and offspring sex. Further, we estimated the proportions of PPH cases in parous women that are attributable to a history of PPH and high birthweight in the current delivery.

Materials and methods

Data sources

The Medical Birth Registry of Norway was established in 1967, since when it has been mandatory to register information of all births in Norway [10]. In 1999, a revised version of the notification form was implemented with new variables, including data on maternal smoking. We included singleton pregnancies with a gestational age at birth of ≥ 22 weeks. Gestational age was estimated from the last menstrual period and was based on ultrasonography when data for the last menstrual period were lacking. First, we analyzed deliveries with spontaneous onset or the induction of labor. We then performed analyses with two different selections: (1) including all deliveries and (2) excluding caesarean deliveries. Information on the parental education level and country of birth were provided by Statistics Norway and linked with the birth registry using the unique national identification number of each birth.

Record linkage

From 1967 to 2017, 3,003,025 births were registered. We linked subsequent births in the parents. To assess the recurrence risk of PPH in a mother, we linked her first and succeeding births in the registry (to a maximum of three births for each mother). Those who had their first birth in 1967 or later were included. The same dataset was used to explore subsequent delivery rate in women with and without a history of PPH. To assess the recurrence risk of PPH through a man who fathered children with different women, we linked birth records of his first and second child. When analyzing the effect of birthweight on recurrence, we identified pairs of first and second, second and third, and third and fourth births in the same mother, which totaled 1 479 584 pairs of births.

Outcome variables

The main outcome variable was PPH defined as the loss of more than 500 ml of blood during labor or within 24 h postpartum (hereafter referred to as PPH). From 1999, PPH of more than 1500 ml or the need for blood transfusion (regardless of bleeding volume) were additionally recorded (severe PPH). PPH was notified on forms in free text prior to 1999, and thereafter using check boxes [10].

Independent variables

The main independent variables were a history of PPH in a previous delivery and the birthweight in the current delivery. To assess temporal changes in the occurrence of PPH, we divided the population into birth-year periods. Further, we investigated whether the occurrence and recurrence of PPH were influenced by maternal conditions such as pregestational and gestational diabetes mellitus, chronic hypertension, preeclampsia, operative vaginal delivery (forceps or vacuum), shoulder dystocia and uterine atony. The possible effect of offspring sex on the recurrence risk of PPH was also explored.

These analyses included the following possible confounding factors: maternal age (in 5-year categories), parity, inter-delivery interval, marital status, mother's country of birth (Norway or eight WHO regions) [11] and level of education (available until 2013). When analyzing recurrence, the period of birth was divided into five groups with approximately equal durations (1967–1977, 1978–1987, 1988–1997, 1998–2007 and 2008–2017). Supporting information (Statistical analysis) includes additional details.

Statistical analysis

We used multilevel logistic regression analyses to calculate odds ratios (ORs) with 95% confidence intervals (CIs) for PPH in the actual birth as the outcome, and a history of previous PPH was the main exposure variable.

Sensitivity analyses were performed to assess the impact of unmeasured confounders on the recurrence of PPH. We estimated the proportion of all cases of PPH in the Norwegian birth population attributable to previous PPH and current high birthweight (≥ 4000 g) [adjusted population attributable fractions (aPAFs)].

To assess likelihoods of a further delivery after PPH, we calculated further pregnancy rate [12], and used Cox proportional hazards regression of time from the first delivery. Supporting information (Statistical analyses) includes additional details.

The statistical analyses were performed using SPSS (version 25) and MLwiN (version 3.05).

Results

The study population included 2,790,090 singleton deliveries with a gestational age of at least 22 weeks from 1967 to 2017. PPH was registered in 10% of the deliveries ($n = 277{,}746$), and the rate of caesarean section was 11% ($n = 295{,}920$) (Supporting information Table S1). There was an increasing trend of the occurrence of PPH during the study period. Increasing occurrences were also observed in pregnancies with high maternal age, maternal medical conditions and pregnancy-related complications (preeclampsia, operative delivery and placental pathology) (Supporting information Table S1).

The risk of PPH for the total population was lower if the newborn was a boy (OR: 0.96, 95% CI 0.96–0.97). These results remained unchanged by adjustments for parity. After adjusting for birthweight this effect was stronger (aOR: 0.89, 95% CI 0.88–0.90).

While several maternal characteristics and conditions were associated with PPH (Supporting information Table S1), the ORs for the recurrence of PPH changed only marginally after adjusting for known possible confounders (Table 1). However, as an exception, the period of birth moderately decreased the effects on recurrence. When we included the assumption of a strong unknown confounder in addition to period of birth in our sensitivity analyses, the ORs of recurrence decreased by less than 5%. Therefore, in the final regression analyses we mainly adjusted for birth year period only.

Recurrence of bleeding

Mothers with PPH (> 500 ml) in their first delivery had a threefold higher risk of excessive bleeding in their second

Table 1 Recurrence of postpartum hemorrhage (PPH) (> 500 ml) according to year of delivery and change of father

		Total	PPH (*n*)	%	OR	95% CI		aOR	95% CI	
First delivery (PPH > 500 ml)		Second delivery								
	No	720 761	49 822	6.9	1	Reference		1	Reference	
	Yes	73 929	16 721	22.6	3.94	3.86	4.01	2.92	2.86	2.98
PPH	Year									
No	1967–1983	217 419	8973	4.1	1	Reference		1	Reference	
Yes		9589	1246	13.0	3.47	3.26	3.70	3.48	3.24	3.73
No	1983–1998	234 571	10 888	4.6	1	Reference		1	Reference	
Yes		14 793	1928	13.0	3.08	2.92	3.24	3.07	2.91	3.24
No	1999–2017	268 771	29 961	11.1	1	Reference		1	Reference	
Yes		49 547	13 547	27.3	3.00	2.93	3.07	2.94	2.87	3.01
PPH	Change of father[a]									
No	No	645 586	44 012	6.8	1	Reference		1	Reference	
Yes		67 547	15 401	22.8	4.04	3.96	4.12	2.98	2.92	3.05
No	Yes	64 097	4914	7.7	1	Reference		1	Reference	
Yes		5274	1059	20.1	3.03	2.81	3.26	2.49	2.31	2.69
First and second deliveries (PPH > 500 ml)		Third delivery								
First	Second									
No	No	247 823	13 876	5.6	1	Reference		1	Reference	
	Yes	14 666	2755	18.8	3.90	3.73	4.08	3.31	3.15	3.47
Yes	No	17 446	2382	13.7	2.67	2.55	2.79	2.10	2.00	2.20
	Yes	3772	1219	32.3	8.05	7.50	8.64	5.62	5.22	6.05

CI confidence interval, *OR* odds ratio, *aOR* OR adjusted for period (1967–1977, 1978–1987, 1988–1997, 1998–2007 and 2008–2017)

[a]Additionally adjusted for inter-delivery interval

delivery (Table 1). The probability of recurrence of bleeding decreased significantly during the study period (Table 1). The recurrence risk of PPH was highest if the father was the same in both pregnancies, also after adjustment for the inter-delivery interval. The risk of PPH and recurrent PPH was lower if the newborn was a boy. Stillbirth did not influence the risk of recurrent PPH, but was significantly associated with PPH in women without previous PPH. (Supporting information Table S2). Mothers with three deliveries had the highest recurrence risk of PPH in the third delivery if they had a history of PPH in the two preceding deliveries (Table 1). These effects were slightly stronger when we excluded cesarean deliveries (data not shown). Exclusion of induced deliveries had no effect on recurrence (data not shown). The region of birth of the mother did not affect recurrence (data not shown). From 1999 onwards, when data on severe PPH (> 1500 ml) were available, the risk of severe PPH in the second delivery was higher for mothers with severe PPH in the first delivery (aOR: 6.0, 95% CI 5.5–6.6), than for those with PPH of > 500 ml (aOR: 3.5, 95% CI 3.3–3.7).

Adjusting for factors other than birth year period had negligible effects on the ORs of PPH recurrence (Table 1). However, maternal medical conditions and pregnancy characteristics influenced the occurrence of PPH, but least in women with a history of PPH (Supporting information Table S2). Inter-delivery interval had almost no effect on the risk of PPH in the second birth (Supporting information Table S3).

Tracing men who fathered children with two different women, we found significantly increased risk of recurrent PPH (OR: 1.51, 95% CI 1.40–1.64), including after adjusting for period of birth and inter-delivery interval (aOR: 1.12, 95% CI 1.03–1.21). Adjusting for birthweight had negligible effect.

Subsequent delivery rate in the second delivery was lower in mothers who had experienced PPH in the first delivery, compared to those who had not (Fig. 1) (64.0 and 74.8%, respectively). Corresponding adjusted hazard ratios (with 95% CI) confirmed statistically significant differences (unadjusted and adjusted hazard ratio 0.97 (95% CI 0.96–0.97) and 0.98 (0.97–0.99). Exploring subsequent deliveries in women with three deliveries, we found that women with PPH in the first two deliveries had the lowest rate of third deliveries (30.9%), compared with no PPH in both deliveries (37.9%) (unadjusted and adjusted hazard ratios 0.86 (0.84–0.89) and 0.94 (0.91–0.97), respectively) (Fig. 1). The cumulative hazard ratio graphs began to diverge about five and three years after the first (Supporting information Figure S1) and second delivery (Supporting information Figure S2), respectively.

Combined effect of birthweight in actual pregnancy and PPH anamnesis

We explored the impact of birthweight on the risk of PPH according to the history of PPH (Table 2).

As an example of Table 2, if the mother experienced PPH in her previous delivery and gave birth to a newborn ≥ 5000 g in the current delivery, the risk of PPH was

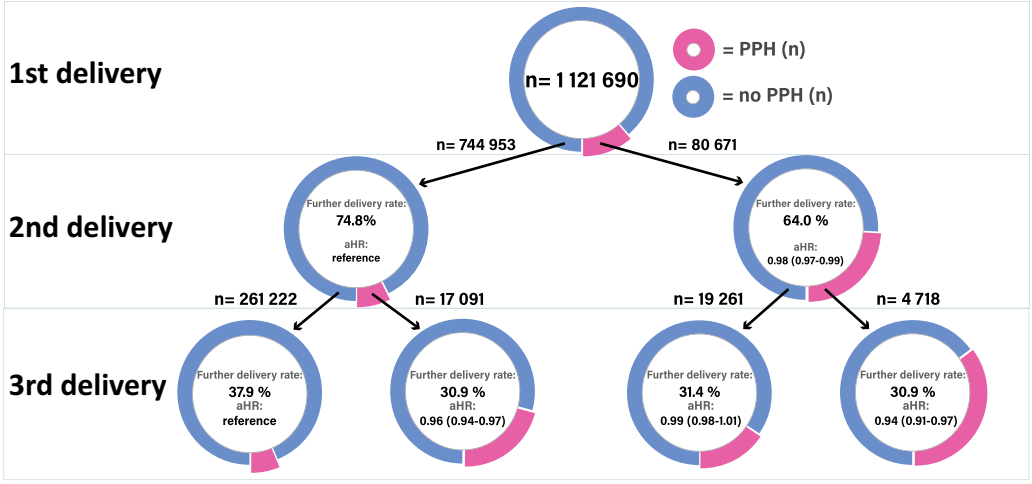

Fig. 1 Further delivery rate and adjusted Hazard ratios (aHR) in women with a history of postpartum hemorrhage (PPH) compared to women without

Table 2 Impacts of birthweight in the current delivery on the occurrence and recurrence of postpartum hemorrhage (PPH) (> 500 ml)

Recurrence in the same mother										
Birthweight in current delivery	PPH in mother's previous delivery	PPH in current delivery								
		Total	PPH (*n*)	%	OR	95% CI		aOR[a]	95% CI	
< 4000 g	No	885,286	49,911	5.6	1	Reference		1	Reference	
4000–4499 g	No	206,955	18,705	9.0	1.66	1.63	1.69	1.70	1.67	1.73
4500–4999 g	No	44,314	5667	12.8	2.46	2.38	2.53	2.58	2.50	2.66
≥ 5000 g	No	5762	943	16.4	3.28	3.05	3.52	3.63	3.37	3.90
< 4000 g	Yes	70,363	14,093	20.0	1	Reference		3.01	2.95	3.07
4000–4499 g	Yes	24,833	6471	26.1	1.40	1.36	1.45	4.56	4.42	4.70
4500–4999 g	Yes	6705	2097	31.3	1.81	1.71	1.92	6.24	5.91	6.59
≥ 5000 g	Yes	1026	367	35.8	2.21	1.94	2.53	8.06	7.06	9.21

[a]aOR, OR adjusted for marital status, period (1967–1977, 1978–1987, 1988–1997, 1998–2007 and 2008–2017), maternal age, parity and WHO region of maternal birth

eightfold higher compared with mothers who had no history of PPH giving birth to a newborn weighing less than 4000 g (Table 2).

The results in Table 2 indicate that the birthweight in the current delivery and a history of PPH had additive effects on subsequent PPH risk.

Similarly, the risk of PPH in primiparas ($n = 1{,}245{,}244$) was more than fourfold higher (aOR: 4.37, 95% CI 4.00–4.78) when the birthweight was ≥ 5000 g compared with a birthweight of < 4000 g.

Population attributable fractions

Among all deliveries with PPH in parous women, 14.4% (the value of aPAF, corresponding to 14,166 cases of PPH) was attributable to a history of PPH (with no previous PPH as the reference). Of all deliveries with PPH in parous females, 15.3% (15,015 cases) was attributable to any birthweight above 4000 g in the current delivery (< 4000 g (reference), 4000–4499 g, 4500–4999 g or ≥ 5000 g). Similarly, of all first pregnancies with PPH in the same population, 15.0% (15,486 cases) was attributable to any birthweight above 4000 g.

Discussion

This study confirmed and quantified that a history of PPH increased the risk of PPH in a mother's subsequent deliveries. The current birthweight was a strong modifier of recurrent PPH risk. Concomitantly with increasing absolute risks of PPH, the ORs of recurrence decreased slightly by birth year period. We found a weak paternal effect on PPH, and that the risk of PPH was lower if the offspring was a boy. The subsequent delivery rate was lowest in women with a delivery with PPH. A history of PPH and the current birthweight exerted strong effects at both the individual and population levels.

The main strengths of this study were its large size, essentially complete record linkage and the more than 50 years follow-up period, which made it possible to perform comprehensive sub-analyses. The population-based design and prospective collection of data reduced selection and recall biases. The sensitivity analyses indicated that unmeasured confounders did not reduce the reliability of the obtained results. Another strength is that many covariates and possible confounding factors were validated and found to be of adequate quality for utilization in epidemiological studies [13, 14].

When registrations of severe pregnancy complications between 2008 and 2013 were scrutinized, the variable of severe PPH was found to be of acceptable quality, with a sensitivity of 87.7% and a positive predictive value of 81.1% [15]. Keeping in mind that severe PPH is often misclassified as mild PPH [16], we consider the sensitivity of severe PPH in our study to be high.

We cannot rule out that the introduction of activity-based financing of the Norwegian health care system in 1997 and the use of a new notification form in 1999 might have resulted in increased registration (which may imply a higher proportion of false negatives before and/or increased rate of false positives after this introduction). However, it is likely that any such misclassification was non-differential, and thus did not affect the ORs of recurrence. ORs of recurrence decreased slightly during the study period, which was expected since mild PPH was likely to have been underreported during the previous period. Residual confounding caused by unmeasured confounding factors cannot be ruled out, but our sensitivity analyses indicated that this was not present.

The relatively ethnically homogeneous Norwegian birth population might limit the generalizability of our findings to other parts of the world. However, our finding that recurrence rates in immigrants from different regions were similar supports the generalizability of our results. The finding that the risk of PPH in the third delivery followed a dose response pattern to previous births with PPH, and that the recurrence risks were highest in severe PPH, strengthens the biological plausibility of our results.

Our findings for recurrence of PPH are consistent with the results of a Swedish study [17]. Concerning the paternal contribution to PPH, we found that the recurrence risk was significantly increased in deliveries where the father had changed partner which did not reach statistical significance in a Swedish study [9]. This inter-study difference is probably due to the larger sample in our study. However, the higher maternal recurrence risk when the father was the same in both pregnancies is consistent with the Swedish study [9]. Our finding that stillbirth was associated with PPH in women without previous PPH is consistent with earlier studies [18]. However, a new finding was the lack of association in women with previous PPH, which may represent index event bias [19]. However, it cannot be ruled out that stillbirth in women with and without previous PPH have different pathophysiological mechanisms.

Overall, we found the highest recurrence risk of PPH when the study population was restricted to include only vaginal deliveries, which corroborates the findings of the Swedish group [17]. However, we decided to include deliveries with spontaneous onset and induction of labour in order to make the findings more relevant to clinical practice. Because changing practices in induction of labor during the study period potentially influence recurrence risks, we excluded deliveries with induction of labor in a supplementary analysis, but this did not change the risk estimates.

A short inter-pregnancy interval has been associated with adverse perinatal outcomes in some studies [20–22] but not others [23]. We found that the inter-delivery interval had almost no effect on recurrence of PPH (Supporting information Table S3).

While fetal macrosomia has been associated with PPH [24], it has not previously been shown that birthweight influences the recurrence risk (Table 2), which may be explained by mechanisms such as atony caused by uterine distension, and a large uteroplacental wound surface.

Sex differences are present in birthweight, placental weight and umbilical cord properties [25–27], but it was an unexpected finding that delivering female neonates carried a higher risk of PPH, including after adjusting for birthweight. Fetal sex differences in occurrence of PPH have been reported in earlier studies with inconsistent results [28]. However, these studies had methodological weaknesses or were underpowered to answer this question. The finding is difficult to explain, but it is possible that the placentas of female fetuses have different vascular or invasive properties that increase the risk of PPH relative to placental weight and birthweight. One may also speculate if sex-specific preponderance differs between primary causes of PPH such as uterine atony and retained placenta. The effect of fetal sex on PPH risk is interesting from a biological, and possibly evolutionary perspective [29], and generates new research questions into sex differences in the placenta.

Acetylsalicylic acid has been offered to pregnant women at increased risk of developing preeclampsia in Norway since 1999 [30], but is a known risk factor for PPH [31], which may have contributed to the observed increased occurrence of PPH. To explore this further was beyond the scope of this study. During the study period, tranexamic acid to prevent PPH in women at risk was not routinely administered [32].

The recurrence of PPH may be caused by genetic and/or sustained environmental factors. We also found a paternal influence on recurrence, which was weaker than the maternal effect presumably due to paternal genes being limited to the fetus, placenta and decidua (through trophoblast invasion).

Further pregnancy rate after obstetric complications other than PPH has been studied [12]. The lower subsequent delivery rates in women who had experienced PPH were not evident before five and three years after the first and second delivery, respectively (Supporting information Figures S1 and S2). This may be due to a traumatic birth experience associated with PPH and could potentially influence recurrence risk estimates, but the latter is unlikely, since the divergence of the cumulative hazard ratio graphs was delayed.

The present study suggests that the combined history of PPH and anticipated fetal size may be useful in identifying women at risk of PPH. From an individual perspective a history of PPH and birthweight of ≥ 4000 g were the strongest exposure variables, warranting attention to fetal growth and preparedness and attention to exposed mothers during labor. From a public health perspective, a history of PPH and high birthweight in the current delivery have non-negligible impacts on the total number of PPH in the population. Investigating recurrence patterns between relatives and cause-specific PPH (e.g., PPH associated with uterine atony or retained placenta) is warranted.

Conclusion

This population-based study found that the recurrence risks of PPH was modulated by birthweight and had a modest paternal, and offspring sex influence. These effects were consistent throughout the 50-year study period despite the

trend of increasing occurrence. Our findings add to the understanding of recurrence of PPH and may be relevant for health care personnel who are counselling mothers with a history of PPH.

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Author contributions LEL prepared the analytic database under the supervision of SR. LEL also conducted the analyses and wrote the manuscript in collaboration with CE and SR. DM, JK, EB and MG contributed by discussing the intellectual content and revising the manuscript. LEL is the guarantor of the manuscript.

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Availability of data and materials Legal restrictions do not permit the authors to provide the data that constitute the basis of this study. The main data utilized are available from the data owner, the Norwegian Institute of Public Health (https://www.fhi.no/en/more/research--access-to-data/), after obtaining approval from The Regional Committee for Medical Research Ethics (https://rekportalen.no/), for researchers who meet the criteria for access to confidential data. Contact information: The Medical Birth Registry of Norway, University of Bergen, P.O. Box 7804, 5020 Bergen, Norway.

Code availability The data are confidential and cannot be shared.

Declarations

Conflict of interest The author(s) declare that they have no conflict of interest.

Ethics approval The study was approved by the Regional Committee for Medical and Health Research Ethics (2013/1484) and the registry owners (the Medical Birth Registry of Norway, the Norwegian Institute of Public Health, Statistics Norway and the Norwegian Tax Administration).

Consent to participate Not applicable.

Consent for publication Not applicable.

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Supplementary Table 1. Postpartum hemorrhage (PPH) (>500 ml) according to maternal and pregnancy characteristics of the study population[a]			
Characteristic	**Total (*n*)**	**PPH (*n*)**	**%**
Total population	**2 790 090**	**277 746**	**10.0**
Maternal age (Years)			
<20	137 679	8397	6.1
20–24	664 411	49 485	7.4
25–29	946 744	91 753	9.7
30–34	701 018	81 701	11.7
35–39	284 957	38 170	13.4
40–44	52 693	7779	14.8
45–49	2514	443	17.6
≥50	74	18	24.3
Parity			
0	1 161 540	135 430	11.7
1	978 573	90 718	9.3
2	447 693	36 037	8.0
3	135 235	10 241	7.6
≥4	67 049	5320	7.9
Year of delivery			
<1970	193 336	8736	4.5
1970–1979	553 307	22 875	4.1
1980–1989	481 392	22 966	4.8
1990–1999	535 289	35 732	6.7
2000–2010	561 738	84 281	15.0
>2010	465 028	103 156	22.2
Maternal height[b]			
<160 cm	45 610	10 745	23.6
160–169 cm	201 739	42 374	21.0
170–179 cm	121 785	25 442	20.9
≥180 cm	9135	2093	22.9
WHO region			
Norway	2 146 167	208 482	9.7
High-income countries	96 787	11 977	12.4
Central Europe, Eastern Europe and Central Asia	61 475	11 870	19.3
Sub-Saharan Africa	35 276	7260	20.6
North Africa and Middle East	41 934	6323	15.1
South Asia	25 942	3258	12.6
Southeast Asia, East Asia and Oceania	47 532	10 360	21.8
Latin America and Caribbean	8911	1961	22.0

Unknown or stateless	410	57	13.9
Education (years)[c]			
<8	15 284	1722	11.3
8–10	562 009	39 809	7.1
11–12	455 375	22 875	5.0
13–17	1 318 049	129 574	9.8
≥18	162 156	20 695	12.8
Not defined	40 781	5719	14.0
Marital status			
Married/ registered partner	1 818 200	153 432	8.4
Cohabitating	713 685	102 238	14.3
Not married/alone	219 502	18 313	8.3
Divorced / Separated / Widow	22 467	1641	7.3
Not defined	16 236	2122	13.1
Smoking at start of pregnancy[d]			
No	797 243	145 900	18.3
Occasionally	16 011	2526	15.8
Daily	112 604	15 305	13.6
Chronic hypertension	9446	1726	18.3
Anemia[e]	3068	500	16.3
Bleeding disorders[f]	10 191	1976	19.4
Pregestational diabetes mellitus	11 423	2310	20.2
Gestational diabetes mellitus	25 334	6207	24.5
Preeclampsia	80 321	11 886	14.8
HELLP syndrome[g]	1595	569	35.7
Onset of birth			
Spontaneous	2 249 026	191690	8.5
Induction	429 901	58 210	13.5
Cesarean section	111 131	27 846	25.1
Not recorded	32	0	0.0
Birthweight (grams)			
<4000 g	2 262 811	199 404	8.8
4000–4499 g	428 460	59 709	13.9
4500–4999 g	87 311	16 044	18.4
≥5000 g	11 508	2589	22.5
Newborn's sex			
Female	1 355 794	137 251	10.1
Male	1 434 080	140 477	9.8
Mode of delivery			
Cesarean section	295 920	69 428	23.5
Vaginal delivery	2 494 170	208 318	8.4
Shoulder dystocia	20 255	3866	19.1

Vacuum delivery	145 785	27 076	18.6
Forceps delivery	55 766	7061	12.7
Uterine curettage, retained placenta or placenta accreta	96 859	35 664	36.8
Uterine atony	72 484	72 484	100.0
Genital trauma, hematoma, tear or uterine inversion	121 691	28 673	23.6
Placental abruption	14 096	3598	25.5
Placenta previa	6918	2542	36.7
Dystocia	188 234	37 597	20.0

[a] Including singleton deliveries, gestational age ≥22 weeks from the last menstrual period or estimated by ultrasonography and specified maternal age, year of birth and birthweight
[b] Available from 2006–2017
[c] until 2013
[d] from 1998 onwards
[e] ICD-8 codes 280–285; ICD–10 codes D50–D53, D55, D58–D61, D63 and D64
[f] ICD-8 codes 286–289; ICD–10 codes D56, D57, D62, D65–D77, O460, O670 and O723
[g] HELLP; Hemolysis, Elevated Liver enzymes, Low Platelets

Supplementary Table 2. Risk of postpartum hemorrhage (PPH) (>500 ml) according to maternal and pregnancy characteristics										
Exposure variable		**Outcome: PPH >500 mL in current delivery**								
Complication	**Previous PPH >500 mL**	**Total**	***n***	**%**	OR	95% CI		**aOR**	95% CI	
Anemia[a]										
No	No	1 141 123	75 097	6.58	**1**			**1**		
Yes	No	1194	129	10.80	**1.72**	1.43	2.07	**1.22**	1.02	1.48
No	Yes	102 737	22 962	22.4	**1**			**1**		
Yes	Yes	190	66	34.7	**1.85**	1.36	2.51	**1.50**	1.10	2.05
Bleeding disorder[b]										
No	No	1 138 416	74 788	6.57	**1**			**1**		
Yes	No	3901	438	11.23	**1.80**	1.63	1.99	**1.07**	0.97	1.18
No	Yes	102 243	22 825	22.3	**1**			**1**		
Yes	Yes	684	203	29.7	**1.46**	1.24	1.73	**1.11**	0.94	1.32
Chronic hypertension										
No	No	1 138 690	74 793	6.57	**1**			**1**		
Yes	No	3627	433	11.94	**1.93**	1.74	2.13	**1.56**	1.40	1.72
No	Yes	102 440	22 876	22.3	**1**			**1**		
Yes	Yes	487	152	31.2	**1.58**	1.30	1.92	**1.34**	1.09	1.63
Pregestational diabetes mellitus										
No	No	1 138 800	74 783	6.6	**1**			**1**		
Yes	No	3517	443	12.6	**2.05**	1.86	2.27	**1.55**	1.40	1.72
No	Yes	102 404	22 858	22.3	**1**			**1**		
Yes	Yes	523	170	32.5	**1.67**	1.39	2.02	**1.39**	1.15	1.68
Gestational diabetes mellitus										
No	No	1 133 265	73 976	6.5	**1**			**1**		
Yes	No	9052	1250	13.8	**2.29**	2.16	2.44	**1.28**	1.20	1.36
No	Yes	100 947	22 352	22.1	**1**			**1**		
Yes	Yes	1980	676	34.1	**1.82**	1.65	2.00	**1.24**	1.12	1.37
Preeclampsia										
No	No	1 122 874	73 324	6.53	**1**			**1**		
Yes	No	19 443	1902	9.78	**1.55**	1.48	1.63	**1.56**	1.48	1.63
No	Yes	100 994	22 505	22.3	**1**			**1**		
Yes	Yes	1933	523	27.1	**1.30**	1.17	1.44	**1.29**	1.16	1.44
Preeclampsia, delivery before 37 weeks										
No	No	1 139 693	74 947	6.58	**1**			**1**		
Yes	No	2624	279	10.63	**1.69**	1.49	1.91	**1.66**	1.46	1.88
No	Yes	102 655	22 952	22.4	**1**			**1**		
Yes	Yes	272	76	27.9	**1.35**	1.03	1.77	**1.24**	0.94	1.63
Shoulder dystocia										

No	No	1 132 619	73 985	6.5	**1**			**1**		
Yes	No	9698	1241	12.8	**2.10**	1.97	2.23	**1.81**	1.70	1.93
No	Yes	101 637	22 583	22.2	**1**			**1**		
Yes	Yes	1290	445	34.5	**1.84**	1.63	2.07	**1.76**	1.56	1.99
Vacuum delivery										
No	No	1 121 044	72 477	6.5	**1**			**1**		
Yes	No	21 273	2749	12.9	**2.14**	2.06	2.23	**1.71**	1.64	1.78
No	Yes	99 506	21 946	22.1	**1**			**1**		
Yes	Yes	3421	1082	31.6	**1.64**	1.52	1.77	**1.35**	1.25	1.46
Forceps delivery										
No	No	1 135 180	74 516	6.6	**1**			**1**		
Yes	No	7137	710	9.9	**1.57**	1.45	1.70	**1.79**	1.65	1.94
No	Yes	102 238	22 818	22.3	**1**			**1**		
Yes	Yes	689	210	30.5	**1.53**	1.30	1.81	**1.57**	1.33	1.86
Retained placenta/membranes or invasive placenta										
No	No	1 107 247	64 220	5.80	**1**			**1**		
Yes	No	35 070	11 006	31.38	**7.42**	7.25	7.61	**6.85**	6.68	7.02
No	Yes	96 392	19 155	19.9	**1**			**1**		
Yes	Yes	6535	3873	59.3	**5.84**	5.54	6.16	**5.90**	5.59	6.23
Obstetric trauma or laceration										
No	No	1 112 020	69 542	6.25	**1**			**1**		
Yes	No	30 297	5684	18.76	**3.46**	3.35	3.56	**2.48**	2.40	2.56
No	Yes	97 441	21 010	21.6	**1**	Reference		**1.0**		
Yes	Yes	5486	2018	36.8	**2.12**	2.00	2.25	**1.74**	1.63	1.84
Placental abruption										
No	No	1 137 154	74 050	6.51	**1**	Reference		**1**		
Yes	No	5163	1176	22.78	**4.24**	3.96	4.53	**5.54**	5.18	5.93
No	Yes	102 509	22 842	22.3	**1**	Reference		**1**		
Yes	Yes	418	186	44.5	**2.79**	2.28	3.40	**3.51**	2.86	4.31
Placenta previa										
No	No	1 140 458	74 860	6.56	**1**	Reference		**1**		
Yes	No	1859	366	19.69	**3.49**	3.11	3.92	**4.53**	4.02	5.09
No	Yes	102 750	22 952	22.3	**1**	Reference		**1**		
Yes	Yes	177	76	42.9	**2.61**	1.92	3.54	**3.28**	2.40	4.49
Dystocia										
No	No	1 110 430	70 772	6.37	**1**			**1**		
Yes	No	31 887	4454	13.97	**2.38**	2.31	2.46	**2.40**	2.32	2.49
No	Yes	98 349	21 195	21.6	**1**			**1**		
Yes	Yes	4578	1833	40.0	**2.44**	2.29	2.60	**2.20**	2.06	2.35
Live or perinatal death										
Live	No	1 133 885	74 415	6.56	**1**			**1**		

Stillborn	No	5611	606	10.80	**1.73**	1.58	1.88	**2.13**	1.96	2.33
Early neonatal death	No	2821	205	7.27	**1.02**	0.97	1.07	**1.55**	1.35	1.80
Live	Yes	102 340	22 903	22.38	**1**			**1**		
Stillborn	Yes	435	91	20.92	**0.98**	0.94	1.02	**1.01**	0.97	1.05
Early neonatal death	Yes	152	34	22.37	**1.01**	0.94	1.08	**1.06**	0.99	1.13
Fetal sex in last pregnancy[c]										
Female	No	555 917	37 675	6.78	**1**			**1**		
Male	No	586 371	37 545	6.40	**0.94**	0.93	0.96	**0.87**	0.86	0.88
Female	Yes	49 962	11 420	22.86	**1**			**1**		
Male	Yes	52 964	11 608	21.92	**0.95**	0.92	0.98	**0.89**	0.86	0.91

CI, confidence interval; OR, odds ratio; aOR, OR adjusted for marital status, period (1967–1977, 1978–1987, 1988–1997, 1998–2007 and 2008–2017), maternal age, parity and WHO region of maternal birth

[a] ICD-8 (international classification of diseases) codes 280–285; ICD-10 codes D50–D53, D55, D58–D61, D63 and D64

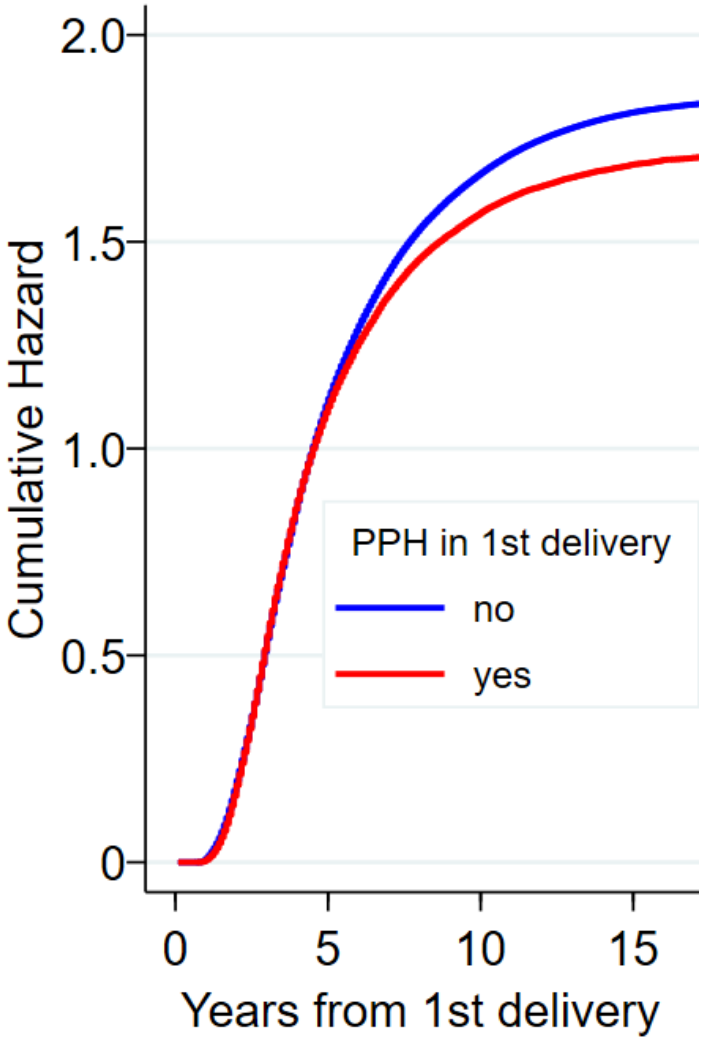
[b] ICD-8 codes 286–289; ICD-10 codes D56, D57, D62, D65–D77, O460, O670 and O723

[c] also adjusted for birthweight. Unspecified or unrecorded sex in 30 newborns

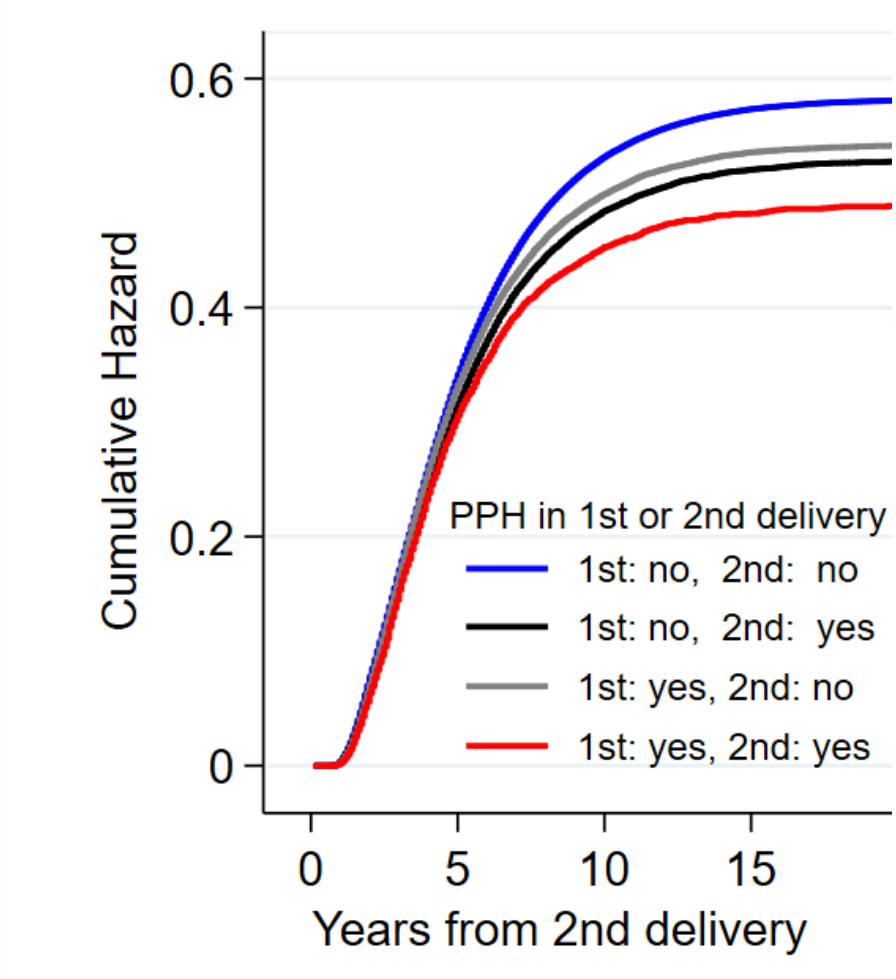
Supplementary Table 3. Inter-delivery interval and recurrence risk of postpartum hemorrhage (PPH, >500 ml)										
PPH in the previous delivery	**PPH in the current delivery**									
	Interval (years)	Total	PPH (*n*)	%	**OR**	95% CI		**aOR**	95% CI	
No	<1	5288	332	6.3	**0.95**	0.85	1.06	**1.15**	1.02	1.28
No	1 to <2	213 847	12 862	6.0	**0.91**	0.88	0.93	**0.95**	0.93	0.97
No	2 to <3	302 722	19 998	6.6	**1**			**1**		
No	3 to <4	221 581	14 750	6.7	**1.01**	0.98	1.03	**1.05**	1.03	1.08
No	4 to <5	135 529	8752	6.5	**0.98**	0.95	1.00	**1.06**	1.03	1.09
No	≥5	263 350	18 532	7.0	**1.07**	1.05	1.09	**1.12**	1.10	1.15
Yes	<1	365	86	23.6	**1.05**	0.83	1.34	**1.10**	0.85	1.41
Yes	1 to <2	20 522	4639	22.6	**1.00**	0.96	1.04	**0.99**	0.94	1.03
Yes	2 to <3	31 634	7165	22.6	**1**			**1**		
Yes	3 to <4	20 916	4836	23.1	**1.03**	0.99	1.07	**1.03**	0.99	1.08
Yes	4 to <5	11 044	2444	22.1	**0.97**	0.92	1.02	**0.97**	0.92	1.02
Yes	≥5	18 446	3858	20.9	**0.90**	0.86	0.94	**0.86**	0.82	0.90

aOR, OR adjusted for marital status, period (1967–1977, 1978–1987, 1988–1997, 1998–2007 and 2008–2017), maternal age, parity and WHO region of maternal birth

Supplementary file4 Figure S1: Cumulative Hazards of the second delivery according to postpartum hemorrhage in the first delivery, adjusted for period and maternal age.



Supplementary file5 Figure S2: Cumulative Hazards of the third delivery according to postpartum hemorrhage in the first or second delivery, adjusted for period and maternal age.



Supporting information Statistical analysis

Independent variables

The main independent variables were a history of PPH (postpartum hemorrhage) in a previous delivery and the birthweight in the current delivery. To assess temporal changes in the occurrence of PPH, we divided the population into birth-year periods. Further, we investigated whether the occurrence and recurrence of PPH were influenced by maternal conditions such as pregestational and gestational diabetes mellitus, chronic hypertension, preeclampsia, operative vaginal delivery (forceps or vacuum), shoulder dystocia and uterine atony. The possible effect of fetal sex on the recurrence risk of PPH was also explored.

These analyses included the following possible confounding factors: maternal age (<20 years, 20–24 years, 25–29 years, 30–34 years, 35–39 years or ≥40 years), parity (0, 1, 2, 3 or ≥4), inter-delivery interval (<1 year, 1 to <2 years, 2 to <3 years, 3 to <4 years, 4 to <5 years or ≥5 years), marital status (married/registered partner, cohabitating, not married/alone, divorced/separated/widow, not defined), mother's country of birth (Norway or eight WHO regions)(1) [(A) high-income countries, (B) Central Europe, Eastern Europe and Central Asia, (C) sub-Saharan Africa, (D) North Africa and Middle East, (E) South Asia, (F) Southeast Asia, East Asia and Oceania, (G) Latin America and Caribbean or (H) unknown or stateless] and level of education (available until 2013) (<8 years, 8–10 years, 11–12 years, 13–17 years, ≥18 years or no information). When analyzing recurrence, the period of birth was divided into five groups with approximately equal durations (1967–1977, 1978–1987, 1988–1997, 1998–2007 and 2008–2017).

Statistical analysis

We used logistic regression analyses to calculate odds ratios (ORs) with 95% confidence intervals (CIs) for PPH in the actual birth as the outcome, and a history of previous PPH as the main exposure variable. We accounted for the hierarchical nature of the family data by performing multilevel regression analyses in which the data were divided into different levels—in analyses including pairs of births of the same parent: current delivery (level 1) and parent (level 2). Possible confounding variables were included if they were associated with PPH in both the current and previous births of the same parent.

We used sensitivity analyses to assess the impact of unmeasured confounders on the recurrence of PPH between deliveries.(2) We performed a Markov Chain Monte Carlo simulation(3) with the prior assumption that adding an influential, unmeasured confounder to known confounder(s) would zero out the recurrence risk, which decreased the regression coefficient (β; standard deviation) for the main exposure variable of PPH to 0; 0.05, corresponding to an OR of 1 with a 95% CI of 0.9 to 1.1.

To estimate the proportion of all cases of PPH attributable to previous PPH and any category of birthweight ≥4000 g in the current delivery, adjusted population attributable fractions (aPAFs) were calculated:(4)

aPAF= $pd\frac{aRR-1}{aRR}$ and 1– $\sum_{i=0}^{k}\frac{pd_i}{aRR_i}$

for two or more exposure categories, respectively, where pd_i is the proportion of PPH cases in the i^{th} exposure category among all cases, and aRR_i is the adjusted relative risk in the i^{th} exposure category compared with the unexposed group (reference, i=0). We calculated aPAF for PPH in the same mother with a history of PPH or birthweight (<4000 g, 4000–4499 g, 4500–4999 g and ≥5000 g) in the current delivery as the exposure variable.

To assess likelihoods of a further delivery after PPH, we calculated further pregnancy rate, defined as the percentage of women who had å further delivery after the first,(5) and used Cox proportional hazards regression of time to a subsequent delivery, adjusting for possible confounding factors in the previous delivery. Logistic regression, adjusting for period of delivery, revealed no significant differences between women with and without PPH in maternal death (0.4 and 0.5%, respectively) or emigration (0.5 and 0.6%). Data on women who did not have a subsequent delivery were censored observations, with censored time equal to the last date of registration (31 December 2017).
The statistical analyses were performed using SPSS (version 25) and MLwiN (version 3.05).

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ORIGINAL RESEARCH ARTICLE

Recurrence of postpartum hemorrhage in relatives: A population-based cohort study

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Abstract

Introduction: Studies on the family aggregation of postpartum hemorrhage (PPH) are scarce and with inconsistent results, and to what extent current birthweight influences recurrence between relatives remains to be studied. Further, family aggregation of PPH has been studied from an individual, but not from a public heath perspective. We aimed to investigate family aggregation of PPH in Norway, how birthweight influences these effects, and to estimate the proportion of PPH cases attributable to a family history of PPH and current birthweight.

Material and methods: Using data from the Medical Birth Registry of Norway, Statistics Norway, and Central Population Registry of Norway we identified individuals as newborns, parents, grandparents, and full and half-siblings, and studied 1 002 687 mother–offspring, 841 164 father–offspring, and 761 011 both-parents–offspring pairs. We used multilevel logistic regression to calculate odds ratios (OR) with 95% CI.

Results: If the birth of the mother but not of the father involved PPH, then the OR of PPH (>500 mL) in the next generation was 1.44 (95% CI 1.39–1.49). If the birth of the father but not of the mother involved PPH, then OR was 1.12 (95% CI 1.08–1.16). These effects were stronger in severe PPH. Recurrence between siblings was highest between full sisters (OR 1.47, 95% CI 1.41–1.52), followed by maternal half-sisters, paternal half-sisters, and partners of full brothers. A family history of PPH or birthweight of 4000 g or more accounted for ≤5% and 15% of the total number of PPH cases, respectively.

Conclusions: A history of PPH in relatives influenced the recurrence risk of PPH in a dose–response pattern consistent with the anticipated proportion of shared genes. The recurrence was highest through the maternal line.

KEYWORDS
adjusted population attributable fraction, birthweight, cohort studies, fathers, mothers, postpartum hemorrhage, recurrence, siblings

Abbreviations: OR, odds ratio; PPH, postpartum hemorrhage.

1 | INTRODUCTION

Postpartum hemorrhage (PPH) is an increasingly common obstetric complication in developed countries despite preventive measures implemented in clinical guidelines,[1,2] and is the leading direct cause of maternal death worldwide.[3,4] Main causes and risk factors for PPH are identified, including a woman's own history of PPH,[5–7] but studies on the family aggregation of PPH are scarce with inconsistent results.[8–10] The potential of PPH in a woman's mother or other relatives to predict PPH, with relevance especially for nulliparous women, needs to be clarified.

The paternal contribution to PPH, which is mediated through the fetus and placenta, has not been explored in generational studies and necessitates large data sets. If studies of family aggregation of PPH suggest a dose–response relation reflecting the anticipated number of shared genes among family members, this could strengthen a hypothesis of a genetic component in the causal pathway of PPH and encourage further study on cause-specific recurrence of PPH. Among common specific causes of PPH, both uterine atony and obstetric trauma are associated with increased distention of the uterus by a large fetus and placenta.[11] Fetal macrosomia also has environmental and genetic causes. However, to what extent current birthweight influences recurrence of PPH between relatives remains to be studied. Further, familial aggregation of PPH has been studied from an individual, but not from a population perspective.

The aim of the present study was to explore the recurrence risk between generations, between full and half-siblings and cousins, and the maternal and paternal contributions to the risk of PPH. Additionally, we explored how current birthweight influences recurrence, and quantified the population proportions of PPH cases attributable to a family history of PPH and high birthweight in the current delivery.

Key message

The recurrence risk of postpartum hemorrhage is highest among relatives with a close genetic relationship, is strongest through the maternal line and is strongly modulated by current birthweight.

2 | MATERIAL AND METHODS

2.1 | Data sources

In this study we use data from The Medical Birth Registry of Norway; this is a mandatory registry for all deliveries from its inception in 1967. Information on maternal and paternal country of birth and education was provided by Statistics Norway and linked with the research database through the unique national identification number. Information on parents was provided by the Central Population Registry of Norway for individuals born after 1954,[12] which allowed us to construct a population-based pedigree for family aggregation.

We included singleton births with gestational age at birth of at least 22 weeks. As this study included pregnancies before the introduction of ultrasound (recorded from 1999), gestational age was based on menstrual dates and on ultrasonography if information on menstrual date was lacking. We primarily analyzed deliveries with spontaneous onset or induction of labor, including cesarean deliveries after onset of labor. Cesarean delivery may strongly influence the risk of PPH, so we performed additional analyses of the population with these selections: (a) including all deliveries or (b) excluding cesarean deliveries.

2.2 | Record linkage

During the total study period (1967–2017), 3 003 025 births were registered. We identified individuals as newborns, parents, or grandparents. This approach allowed us to trace full- and half-siblings among newborns and parents.

Generational information was revealed by identifying the individual both as a newborn and as a mother or father (Figures S1 and S2). We restricted the generational files to the first three births in the second generation, yielding 1 002 687 mother–offspring pairs, 841 164 father–offspring pairs and 761 011 both-parents–offspring pairs.

To study recurrence between siblings as parents, we aligned the generational information of siblings (Figure S3). In this way, each record included birth registry data for four births: (a) the birth of the parent, (b) the birth of its offspring, (c) the birth of the parent's sibling, and (d) the birth of the sibling's offspring (ie, the parent's niece/nephew). A parent and its sibling's offspring constituted an aunt/uncle–niece/nephew pair sharing on average 25% of their genes, whereas pairs of siblings and pairs of their offspring (cousin pairs) share 50% and 12.5% of their genes, respectively. If the parent had more than one sibling, we selected the niece/nephew born immediately before the birth of the parents' offspring. Hence, each record in the file included the chronology of the family history. We restricted the analyses to fewer than six records for each pair of siblings. This left 909 584 pairs of sibling–offspring units available to explore whether the recurrence of PPH between siblings and the intergenerational recurrence of PPH is influenced by a history of PPH in other family members, and whether recurrence is transmitted through the maternal or paternal line. Similarly, maternal and paternal half-sisters were identified.

2.3 | Outcome variables

The primary outcome variable was loss of more than 500 mL blood during labor, or within 24 h postpartum (hereafter referred to as PPH). From 1999, severe PPH—defined as blood loss of more than 1500 mL or the need for blood transfusion (regardless of blood volume)—was also recorded.[13]

TABLE 1 Recurrence of postpartum hemorrhage (>500 mL) between generations; singleton births ≥22 weeks of gestation and spontaneous onset or induction of labor

	Second generation						
First generation	**Period**	**Total**	**PPH (*n*)**	**%**	**OR**	**95% CI**	
PPH >500 mL	PPH >500 mL						
No	1967–2017	805 702	110 860	13.8	1	Reference	
Yes		37 977	7170	18.9	1.44	1.40	1.49
No	1967–2001	239 590	18 330	7.7	1	Reference	
Yes		10 601	1194	11.3	1.52	1.42	1.62
No	2002–2010	343 191	46 965	13.7	1	Reference	
Yes		15 856	3007	19.0	1.47	1.40	1.53
No	2011–2017	222 921	45 565	20.4	1	Reference	
Yes		11 520	2969	25.8	1.35	1.29	1.41
PPH >500 mL	PPH >1500 mL						
No	1999–2017	630 555	11 079	1.8	1	Reference	
Yes		30 304	831	2.7	1.58	1.46	1.70

Abbreviations: OR, odds ratio; PPH, postpartum hemorrhage.

2.4 | Independent variables

The main independent variables were a history of PPH in relatives and the birthweight in the current delivery (<4000 g [reference], 4000–4499 g, 4500–4999 g, ≥5000 g). We used birthweight less than 4000 g as reference, because proportions of PPH stabilized with birthweights decreasing below 4000g. The data were stratified according to birth-year periods.

Variables available in our database,[13] were considered as possible confounders if they were associated with PPH in the current as well as in previous births of the relative: maternal age, parity, inter-delivery interval, marital status, mother's country of birth or eight WHO regions,[14] maternal smoking status before pregnancy, maternal body mass index before pregnancy,[14] length of education (available until 2013), and birth-year period. When analyzing recurrence between relatives, the period was divided into groups with approximately equal numbers of records, with unequal durations because of longer follow-up time in earlier than later years to attain sufficient numbers of relatives (between generations: 1967–2001, 2002–2010, and 2011–2017; between pairs of siblings: 1967–2002, 2003–2007, 2008–2011, 2012–2014, and 2015–2017).

Appendix S1 includes additional details on statistical analysis.

2.5 | Statistical analyses

We carried out logistic regression analyses to calculate odds ratios (OR) with 95% CI for PPH in the actual birth as the outcome, and a history of PPH in relatives as the main exposure variable. We accounted for the hierarchical nature of the family data by performing multilevel regression analyses in which the data were divided into different levels in generational analyses and in analysis of pairs of siblings.

We performed sensitivity analyses to assess the impact of unmeasured confounders on the recurrence of PPH between generations and siblings.[15]

To estimate the proportion of cases of PPH attributable to a history of PPH in relatives or current high birthweight (<4000 g (reference), 4000–4499 g, 4500–4999 g, and ≥5000 g) we calculated the adjusted population-attributable fraction.[16]

The statistical analyses were performed using SPSS (version 25) and MLwiN (version 3.05). Appendix S1 includes additional details.

2.6 | Ethical approval

The study was approved by the Regional Committee for Medical and Health Research Ethics on 19 September 2013 (2013/1484) and the registry owners (the Medical Birth Registry of Norway, the Norwegian Institute of Public Health, Statistics Norway and the Norwegian Tax Administration).

3 | RESULTS

In the regression analyses, possible confounders for recurrence between relatives had negligible effects on inter-generational recurrence and only the year of birth had significant effect on recurrence between siblings. When including the assumption of a strong unknown confounder in our sensitivity analyses, the OR of recurrence between relatives decreased by less than 5%. Therefore, in the final analyses we generally presented unadjusted OR of inter-generational recurrence and in analyses of recurrence between siblings we only adjusted for period of birth.

After we had excluded cesarean sections from our analysis, the OR of recurrence between relatives were slightly stronger (data not shown). Recurrence rates were similar in women born in Norway and in immigrants from different regions.

3.1 | Transgenerational recurrence of PPH

The odds ratio of PPH was increased with about 40% for women who themselves had been born in a labor with PPH, and the effect was stronger, (almost 60% increased), in severe PPH (>1500 mL) in the second generation (Table 1, Figure S1). When stratifying the second generation by year of birth into three groups of equal numbers of cases, we found that this effect decreased slightly during the study period, whereas the absolute risks increased (Table 1).

Analyzing PPH in the mother's and father's own births as exposure variable revealed that the transgenerational OR of recurrence was higher through the maternal than the paternal line (Table 2, Figure S2). Adjusting for possible confounders (including period) had negligible effects on the results, and so they were not included in the final analyses. We observed that the associations in the second generation were strongest for severe PPH (>1500 mL) with OR 2.0 (95% CI 1.4–2.8) if both parents were born in labors with PPH.

3.2 | Recurrence of PPH between siblings

Table 3 and Figure S3 present OR of recurrence of PPH between pairs of siblings (full and half-sisters, and brothers' partners). The OR of PPH increased if the mother's sister or brother's partner had experienced PPH. The strongest effects were observed between full sisters (50% increased OR), followed by (in decreasing order) maternal half-sisters, paternal half-sisters, and partners of full brothers (20% increase).

3.3 | Combined effects of PPH in relatives

The risk of PPH generally increased with the number of relatives previously exposed (Table S1). Adjusting for possible confounders had negligible effects on the results, and so they were not adjusted in the final analyses.

3.4 | The combined effect of birthweight in actual pregnancy and history of PPH in relatives

We explored if transgenerational OR of recurrence of PPH between siblings was influenced by birthweight in the current delivery (Table 4A and B and Figure S4).

As an example, if the mother herself was born in a delivery with PPH and gave birth to a neonate weighing 5000 g or more, her risk of PPH was five-fold compared with mothers without a generational history of PPH and a birthweight of less than 4000 g (Table 4A). Further, if the mother herself was born in a delivery with PPH and gave birth to a newborn weighing less than 4000 g, her OR of PPH was increased by about 40% compared with mothers without a generational history of PPH and a birthweight of less than 4000 g (Table 4A).

The results presented in Table 4B indicate that the recurrence of PPH between sisters was similarly influenced by the birthweight of the neonate: if the mother gave birth to a neonate weighing 5000 g or more and her sister had experienced PPH, her OR of PPH was four-fold higher than if the neonate weighed less than 4000 g and her sister had not experienced PPH. If the mother had a neonate weighing less than 4000 g and her sister experienced PPH, then her OR of PPH was increased by about 40% compared with a birthweight of less than 4000 g and no experience of PPH in her sister (Table 4B).

These findings indicate that the birthweight in the current delivery and a history of PPH in a mother's relatives (her mother or sisters) had independent effects on subsequent PPH.

3.5 | Population attributable fractions

Among PPH in deliveries in the second generation 1.9% was attributable to PPH in the previous generation (corresponding to 2230 cases), whereas 14.2% (17 023 cases) were attributable to high birthweight in the current delivery (4000–4499 g, 4500–4999 g or ≥5000 g, reference: <4000g). The adjusted population-attributable fraction for pairs of sisters was 5.0% (1555 cases) for a history of PPH in the first sister and 14.6% (4520 cases) for the birthweight in the current delivery.

4 | DISCUSSION

Women with a family history of PPH had an increased risk of PPH in a dose–response pattern consistent with the anticipated proportion of shared genes in relatives. This risk was strongly modified by current birthweight. The OR of PPH recurrence were higher through

TABLE 2 Occurrence of postpartum hemorrhage (>500 mL) in the second generation according to postpartum hemorrhage status in parents' births; singleton births ≥22 weeks of gestation and spontaneous onset or induction of labor

First generation		Second generation					
Mother	Father	Total	PPH (*n*)	%	OR	95% CI	
No	No	583 015	85 231	14.6	1	Reference	
Yes	No	27 415	5466	19.9	1.44	1.39	1.49
No	Yes	24 506	3936	16.1	1.12	1.08	1.16
Yes	Yes	1345	273	20.3	1.49	1.29	1.72

Abbreviations: OR, odds ratio; PPH, postpartum hemorrhage.

TABLE 3 Recurrence risk of postpartum hemorrhage (>500 mL) between pairs of siblings; singleton births ≥22 weeks of gestation and spontaneous onset or induction of labor

Recurrence between siblings	PPH in first sibling	PPH in second sibling								
		Total	PPH (*n*)	%	OR	95% CI		aOR	95% CI	
Full sisters	No	174 792	24 392	14.0	1	Reference		1	Reference	
	Yes	23 579	4721	20.0	1.62	1.56	1.68	1.47	1.41	1.52
Partners of full brothers	No	138 025	21 924	15.9	1	Reference		1	Reference	
	Yes	21 367	3805	17.8	1.17	1.12	1.21	1.08	1.04	1.13
Maternal half-sisters	No	12 176	1961	16.1	1	Reference		1	Reference	
	Yes	1601	335	20.9	1.48	1.29	1.69	1.39	1.22	1.59
Paternal half-sisters	No	15 287	2412	15.8	1	Reference		1	Reference	
	Yes	1939	364	18.8	1.30	1.15	1.47	1.22	1.08	1.39

Abbreviations: aOR, adjusted odds ratio; OR, odds ratio; PPH, postpartum hemorrhage.

aOR, OR adjusted for period in groups of approximately equal number of deliveries 1967–2002, 2003–2007, 2008–2011, 2012–2014 and 2015–2017.

TABLE 4 Impacts of birthweight in the current pregnancy on the occurrence and recurrence of postpartum hemorrhage (>500 mL) between generations (A) and between pairs of sisters (B). Singleton births ≥22 weeks of gestation and spontaneous onset or induction of labor

A. Inter-generational recurrence

Birthweight in second generation	PPH in mother's delivery (first generation)	PPH in delivery in second generation								
		Total	PPH (*n*)	%	OR	95% CI		aOR*	95% CI	
<4000 g	No	641 138	77 169	12.0	1	Reference		1	Reference	
4000–4499 g	No	133 916	25 746	19.2	1.71	1.68	1.74	1.84	1.81	1.87
4500–4999 g	No	27 376	6876	25.1	2.39	2.32	2.46	2.68	2.60	2.76
≥5000 g	No	3272	1069	32.7	3.43	3.17	3.71	3.92	3.62	4.24
<4000 g	Yes	28 444	4655	16.4	1.42	1.37	1.47	1.41	1.36	1.46
4000–4499 g	Yes	7578	1855	24.5	2.31	2.18	2.44	2.47	2.34	2.62
4500–4999 g	Yes	1700	558	32.8	3.41	3.06	3.80	3.82	3.42	4.27
≥5000 g	Yes	255	102	40.0	4.65	3.56	6.08	5.34	4.08	7.00

B. Recurrence between sisters

Birthweight in second sister's delivery	PPH in first sister's delivery	PPH in second sister's delivery								
		Total	PPH (*n*)	%	OR	95% CI		aOR**	95% CI	
<4000 g	No	137 782	16 975	12.3	1	Reference		1	Reference	
4000–4499 g	No	30 035	5639	18.8	1.63	1.57	1.68	1.70	1.64	1.76
4500–4999 g	No	6228	1540	24.7	2.30	2.16	2.45	2.52	2.36	2.68
≥5000 g	No	743	240	32.3	3.32	2.82	3.91	3.85	3.26	4.54
<4000 g	Yes	17 956	3198	17.8	1.43	1.37	1.49	1.32	1.26	1.38
4000–4499 g	Yes	4469	1157	25.9	2.25	2.09	2.42	2.18	2.03	2.35
4500–4999 g	Yes	1012	310	30.6	2.83	2.45	3.27	2.93	2.53	3.39
≥5000 g	Yes	146	58	39.7	4.22	2.96	6.01	4.64	3.25	6.64

Abbreviations: aOR, adjusted odds ratio; OR, odds ratio; PPH, postpartum hemorrhage.

*aOR, OR adjusted for marital status, period (1967–2001, 2002–2010 and 2011–2017), maternal age, parity and WHO region of maternal birth.;
**aOR, OR adjusted for marital status, period (1967–2002, 2003–2007, 2008–2011, 2012–2014 and 2015–2017), maternal age, parity and WHO region of maternal birth.

the maternal than the paternal line. Through the half-century study period, OR of recurrence between relatives decreased slightly, whereas the absolute risk of PPH increased. On a population level, a history of PPH in relatives accounted for a low number of PPH cases, whereas the current birthweight accounted for a more significant number of PPH cases.

The population-based cohort design, its large size and almost complete record linkage between relatives are the main strengths of the study. The prospective collection of the data reduced potential selection and recall bias. The long follow-up time allowed study of recurrence between relatives, including generations. Linking different data sources made adjusting for several potential confounders possible. The sensitivity analysis indicated that the effects of unmeasured confounders were not significant. As possible confounders for recurrence are associated with PPH in both the current and previous births in relatives (the criterion most rarely met), the models were robust to confounding. The variable of severe PPH in our database (>1500 mL) was found to be of adequate quality for epidemiological research,[17] and several independent variables in the Medical Birth Registry have been validated with the result of adequate quality.[18,19]

It cannot be ruled out that the implementation of activity-based financing in the Norwegian health care system in 1997 and the use of the new notification form from 1999 may have resulted in an increased rate of false positives. However, if this increased registration in the later period represents misclassification, it is likely that it is non-differential and does not significantly influence OR of recurrence between relatives.

The generalizability of our results to other part of the world may be limited by the relatively ethnically homogeneous Norwegian birth population. However, the population-based design affords generalizability to Western birth populations. Our finding that recurrence rates in immigrants from different regions were similar supports the generalizability of our results. The OR of recurrence seemed to follow a dose–response pattern, in that the OR increased with the anticipated number of shared genes and the severity of bleeding, which strengthens the biological plausibility of our results. Further, our results are in accordance with polygenic theory including higher recurrence rates between relatives of a trait with a severe phenotype or involving more than one family member.[20]

Extra-pair paternity most likely does not bias OR of PPH through the paternal line because it is reported to be low (<2%),[21] and likely has non-differential proportions in male infants born with, compared to without, PPH.

We have previously reported on the familial aggregation of maternal perinatal complications, such as placental abruption, preeclampsia, and obstetric anal sphincter injuries, which is mainly transmitted through the maternal line.[22–24] Our findings for recurrence of PPH between siblings are consistent with the results of a Swedish study.[9] Concerning the paternal contribution to the development of PPH, our finding of paternal transgenerational recurrence (Table 2) is consistent with increased recurrence risk between succeeding deliveries, if the father had changed partner.[9] However, our findings of increased recurrence between first-degree relatives do not corroborate the results of another study in which no significant inter-generational recurrence was found.[10] The cause of this interstudy difference is not known, but one may speculate that the unclear definition of PPH in the latter study attenuated the effects.

Although fetal macrosomia has been associated with PPH,[5] it has not previously been shown how birthweight of the neonate influences the OR of recurrence of PPH between relatives (Table 4).

We found the highest OR of PPH recurrence between relatives when the study population was restricted to include only vaginal deliveries, which is consistent with a Swedish study.[8] However, to increase the relevance for acute obstetric scenarios, we also included deliveries with spontaneous onset and induction of labor, which could end with acute cesarean delivery.

The patterns of OR for recurrence of PPH between relatives in this study were consistent with the average anticipated proportions of shared genes, and suggest a genetic susceptibility, in part related to high birthweight. This is also supported by the small effects of adjusting for sustained risk factors and unknown confounders, although it cannot be ruled out that environmental factors influence recurrence between relatives. The results of our study suggest that a hereditary component is mainly transmitted through the maternal line. We also found a paternal influence on recurrence, which was weaker than the maternal effect, presumably because paternal genes are limited to the fetus, placenta, and decidua (through trophoblast invasion).

The present study indicates that in women with a family history of PPH, anticipated fetal size is a useful, powerful additional predictor of recurrent PPH. Our results add to the understanding of the recurrence of PPH in families. Women with a family history of PPH can be reassured by the moderate effect (about 50% increased risk compared with the reference) of a family history. From a public health perspective, a family history of PPH accounted for a small proportion of all PPH cases (≤5%), and current birthweight of 4000 g or more for 15% of all cases. We did not study cause-specific recurrence of PPH between relatives, eg PPH caused by uterine atony or retained placenta, because it would be of limited clinical value, as most women are probably unaware of the cause of previous PPH in their relatives.

5 | CONCLUSION

The OR of recurrence of PPH between relatives was higher among relatives with a closer genetic relationship, was modulated by birthweight and was stronger through the maternal than the paternal line of transmission. Our results suggest that the etiology of PPH includes a genetic component, which should be disentangled from environmental causes in future studies.

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A patient (Liv Kristin Heggheim) and a general practitioner (Stian Langeland Wesnes, MD, PhD) were involved from the planning stage of the project. The research group discussed the core research questions, outcome measures, design and results of the study with these two persons by correspondence and in meeting. We thank the user representatives for their effort and interest.

AUTHOR CONTRIBUTIONS

LEL prepared the analytic database under the supervision of SR. LEL also conducted the analyses and wrote the manuscript in

collaboration with CE and SR. DM, JK, EB and MG contributed by discussing the intellectual content and revising the manuscript. LEL is the guarantor of the manuscript.

CONFLICT OF INTEREST

None.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of the article at the publisher's website.

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Figure S1. Family pedigree with relations of interest explored in Table 1 highlighted

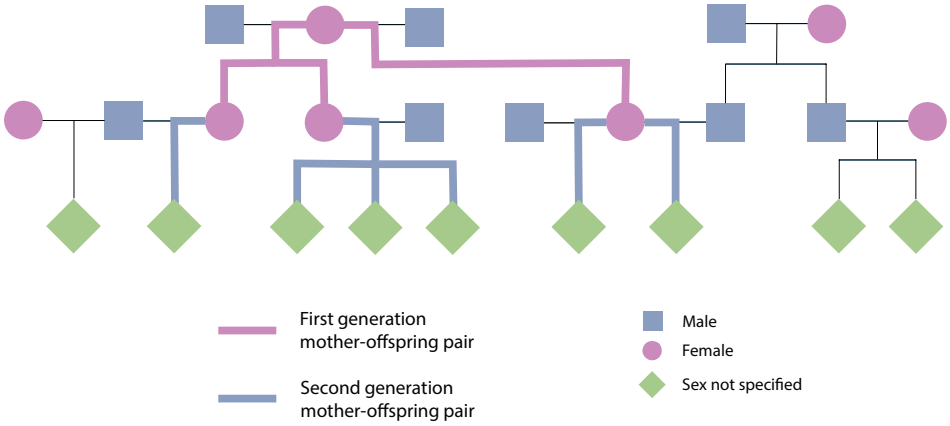

Figure S2. Family pedigree with relations of interest explored in Table 2 highlighted

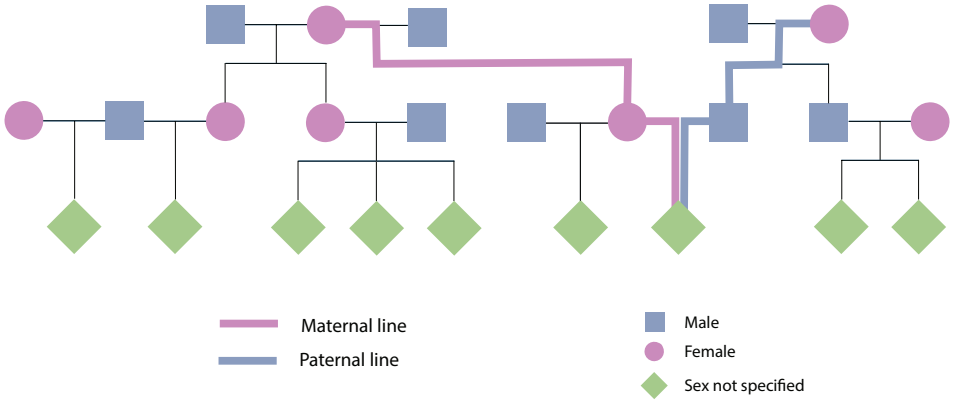

Figure S3. Family pedigree with relations of interest explored in Table 3 highlighted

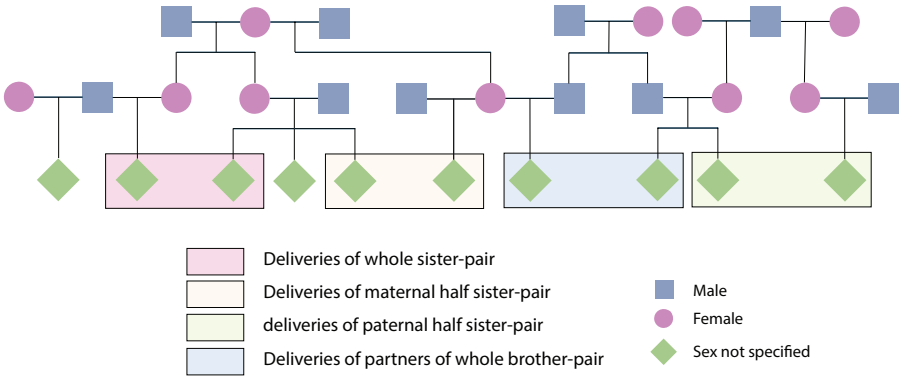

Figure S4. Family pedigree with relations of interest explored in Table 4 highlighted

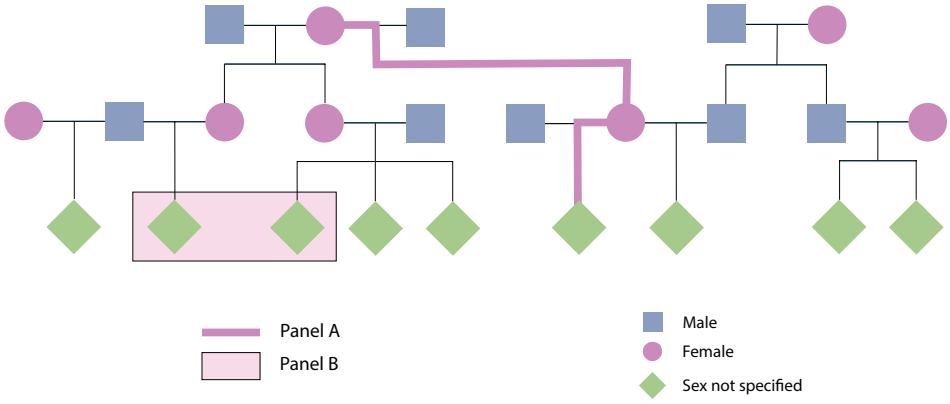

Figure S5. Family pedigree with relations of interest explored in Table S1 highlighted

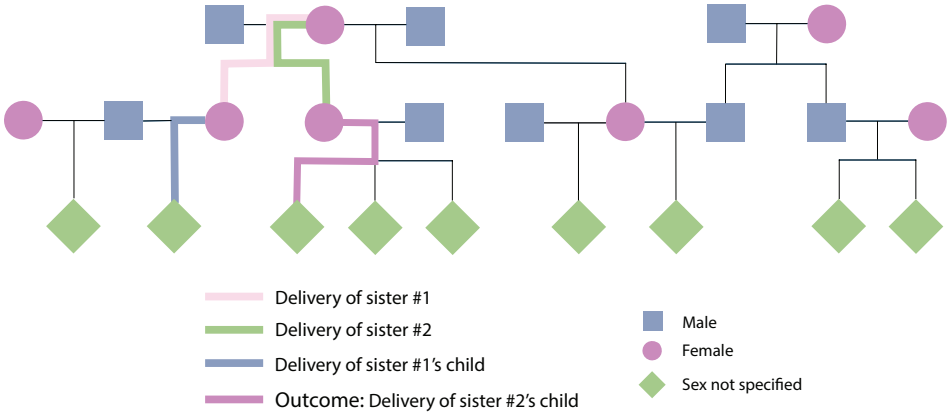

Table S1. Risk of postpartum hemorrhage (PPH) (>500 ml) in a sister (sister #2) according to family history of PPH (in their mother or sister #1). Singleton births ≥22 weeks of gestation and spontaneous onset or induction of labor.

PPH in delivery of sister		Sister #1 experienced PPH	Sister #2 experienced PPH					
Sister #1	Sister #2		Total	PPH (*n*)	%	OR	95% CI	
No	No	No	161 245	21 969	13.6	1	Reference	
Yes	No	No	6289	1039	16.5	1.26	1.17	1.35
No	Yes	No	6278	1163	18.5	1.44	1.34	1.55
Yes	Yes	No	976	223	22.8	1.89	1.60	2.22
No	No	Yes	21 088	4107	19.5	1.41	1.35	1.46
Yes	No	Yes	1200	262	21.8	1.61	1.39	1.87
No	Yes	Yes	1090	307	28.2	2.27	1.96	2.63
Yes	Yes	Yes	205	47	22.9	1.73	1.21	2.48

CI: confidence interval; OR: odds ratio

Combined effects of PPH in relatives

The risk of PPH generally increased with the number of relatives previously exposed. If two sisters (designated here as sister #1 and #2) were born with PPH, and sister #1´s child was also born in a delivery with PPH, then the risk of PPH was doubled for sister #2 compared with no family history of PPH. If only sister #2 was born with PPH and sister #1 did not experience PPH, the OR of PPH for sister #2 was 1.44 (isolated generational recurrence). As expected, the OR was similar (=1.41) if both sisters #1 and #2 were born without PPH, but sister #1 experienced PPH (isolated siblings' recurrence). These effects were additive when combined; if sister #1 was born without PPH but sister #2 was born with PPH, and sister #1 experienced PPH when she gave birth, the OR of PPH for sister #2 was 2.27 (combined generational/sibling recurrence). Adjusting for possible confounders had negligible effects on the results, and so they were not adjusted in the final analyses.

Appendix S1. Statistical analysis

Independent variables

The main independent variables were a history of postpartum hemorrhage (PPH) in relatives and the birthweight in the current delivery (<4000 g (reference), 4000–4499 g, 4500-4999 g, ≥5000 g). We used birthweight <4000 g as reference, because proportions of PPH stabilized with birthweights decreasing below 4000g. The data were stratified according to birth-year periods.

Variables available in our database,**(1)** were considered as possible confounders if they were associated with PPH in the current and as well in previous births of the relative: maternal age (<20 years, 20–24 years, 25–29 years, 30–34 years, 35–39 years, or ≥40 years), parity (0, 1, 2, 3, or ≥4), inter-delivery interval (<1 year, 1–<2 years, 2–<3 years, 3–<4 years, 4–<5 years, or ≥5 years), marital status (married/registered partner, cohabitating, not married/alone, divorced/separated/widow, not defined), mother's country of birth (Norway (88.7% of the total study population (2663806/3003025)) or eight WHO regions **(**11.3% of the total study population (339219/3003025)) [(A) high-income countries, (B) Central Europe, Eastern Europe and Central Asia, (C) sub-Saharan Africa, (D) North Africa and Middle East, (E) South Asia, (F) Southeast Asia, East Asia and Oceania, (G) Latin America and Caribbean or (H) unknown or stateless],**(2)** maternal smoking status before pregnancy (no, occasionally, daily, available from 1998 onwards), maternal BMI before pregnancy (<18.5 kg/m^2, underweight; 18.5–24.9 kg/m^2, normal weight; 25.0–29.9 kg/m^2, overweight; ≥30.0 kg/m^2, obese, available from 2006 onwards)**(2)**, length of education (available until 2013) (<8 years, 8–10 years, 11–12 years, 13–17 years, ≥18 years or no information), and birth-year period. When analyzing recurrence between relatives, the period was divided into groups with approximately equal numbers of record, with unequal durations because of longer follow-up time in earlier than later years to attain sufficient numbers of relatives (between generations: 1967–2001, 2002–2010 and 2011–2017; between pairs of siblings: 1967–2002, 2003–2007, 2008–2011, 2012–2014 and 2015–2017). There were differences in time period between the generational file and the sister file because in the generational file (Table 4 panel A) current births (in the second generation) were predominantly found in the later years of the study period (1967– 2017). In contrast, in the sister file (Table 4 panel B) current births (in sister 2) were more evenly distributed throughout the study period (1967–2017). Because of the relatively narrow timespan of current births in the second generation (Table 4 panel A) the

study period was divided into three categories, while a more even distribution throughout the study period in Table 4 panel B made division into more categories appropriate.

Statistical methods

We carried out logistic regression analyses to calculate odds ratios (ORs) with 95% confidence intervals (CIs) for PPH in the actual birth as the outcome, and a history of PPH in relatives as the main exposure variable. We accounted for the hierarchical nature of the family data by performing multilevel regression analyses in which the data were divided into different levels in generational analyses: current delivery (level 1), parent (level 2) and grandparent (level 3); and in analysis of pairs of siblings: current delivery (level 1), sibling pair (level 2) and sibship (level 3).

We performed sensitivity analyses to assess the impact of unmeasured confounders on the recurrence of PPH between generations and siblings.(3) We performed a Markov-chain Monte-Carlo simulation,(4) where we entered our regression models for recurrence and a prior assumption. The prior assumption was that adding an influential, unmeasured confounder to known confounder(s) would zero out the recurrence risk (null hypothesis), which decreased the regression coefficient (β_1; standard deviation) for the main exposure variable (PPH) to 0; 0.05, corresponding to an OR of 1 with a 95% CI of 0.9 to 1.1. We used a simple model (fixed effect: $\beta_0 + \beta_1$ PPH (0 or 1), where β_0 and β_1 are constants) to simulate confounding. (It is possible to extend the model adding covariates (which we did not), such as maternal age, thus simulating residual confounding (in addition to known confounding by maternal age)). We calculated ORs of PPH before and after including the prior assumption (OR_1 and OR_2, respectively). The percent difference between the ORs in our model ($100\% \times (OR_1\text{-}OR_2)/OR_1$), indicated robustness of the model to confounding. (A big difference, with OR_2 close to 1, would have indicated strong confounding.)

To estimate the proportion of cases of PPH attributable to a history of PPH in relatives or current high birthweight (<4000 g (reference), 4000–4499 g, 4500–4999 g and ≥5000 g) we calculated adjusted population attributable fraction (aPAF)(5)

aPAF= $pd\frac{aRR-1}{aRR}$ and 1– $\sum_{i=0}^{k}\frac{pd_i}{aRR_i}$

for two or more exposure categories, respectively, where pd_i is the proportion of PPH cases in the i^{th} exposure category among all cases, and aRR_i is the adjusted relative risk in the i^{th} exposure category compared with the unexposed group (reference, i=0).

The statistical analyses were performed using SPSS (version 25) and MLwiN (version 3.05).

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III

Risk factors and recurrence of cause-specific postpartum hemorrhage: A population-based study

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Abstract

Objective

To explore risk profiles of the different types of postpartum hemorrhage (PPH) and their recurrence risk in a subsequent delivery.

Methods

With data from The Medical Birth Registry of Norway and Statistics Norway we performed a populational-based cohort study including all singleton deliveries in Norway from 1967–2017. Multilevel logistic regression was used to calculate odds ratio (OR), with 95% confidence interval (CI), with different PPH types as outcomes (PPH >500ml or PPH >1500ml (severe PPH) combined with retained placenta, uterine atony, obstetric trauma, dystocia, or undefined cause).

Result

We identified 277 746 PPH cases of a total of 3 003 025 births (9.3%) from 1967 to 2017. Retained placenta and/or membranes was most often registered as severe PPH (29.3%). Maternal, fetal, and obstetric characteristics showed different associations with the PPH types. Male sex of the neonate was associated with reduced risk of PPH. This effect was strongest on PPH due to retained placenta (adjusted OR, (aOR): 0.80, 95% CI 0.78–0.82), atony (aOR 0.92, 95% CI: 0.90–0.93) and PPH with undefined cause (aOR 0.96, 95% CI: 0.95–0.97). Previous cesarean section showed a strong association with PPH due to dystocia (aOR of 13.2, 95% CI: 12.5–13.9). Recurrence risks were highest for the same type: PPH associated with dystocia (aOR: 6.8, 95% CI: 6.3–7.4), retained placenta and/or membranes (aOR: 5.9, 95% CI: 5.5–6.4), atony (aOR: 4.0, 95% CI: 3.8–4.2), obstetric trauma (aOR: 3.9, 95% CI: 3.5–4.3) and PPH of undefined cause (aOR: 2.2, 95% CI: 2.1–2.3).

Conclusion

Maternal, fetal and obstetric characteristics had differential effects on types of PPH. Recurrence differed considerably between PPH types. Retained placenta was most frequently registered with

severe PPH, and showed strongest effect of sex; delivery of a boy was associated with lower risk of PPH. Previous cesarean increased the risk of PPH due to dystocia.

Declarations

Conflicts of interest: None declared

Availability of data and material: Legal restrictions do not permit the authors to provide the data that constitute the basis of this study. The main data utilized are available from the data owner, the Norwegian Institute of Public Health (https://www.fhi.no/en/more/research--access-to-data/), after obtaining approval from The Regional Committee for Medical Research Ethics (https://rekportalen.no/), for researchers who meet the criteria for access to confidential data. Contact information: The Medical Birth Registry of Norway, University of Bergen, P.O. Box 7804, 5020 Bergen, Norway.

Code availability: The data are confidential and cannot be shared.

Authors' contributors: L.E.L. prepared the analytic database under the supervision of S.R.. L.E.L. also conducted the analyses and wrote the manuscript in collaboration with C.E. and S.R.. D.M., J.K., E.B. and M.G. contributed by discussing the intellectual content and revising the manuscript. L.E.L. is the guarantor of the manuscript.

Abbreviations

aOR: adjusted odds ratio

CI: confidence interval

MBRN: Medical Birth Registry of Norway

OR: odds ratio

PPH: postpartum hemorrhage

Introduction

Postpartum hemorrhage (PPH) is the leading direct cause of maternal mortality worldwide.[1] Main types of PPH described in literature are PPH associated with uterine atony and retention of the placenta.[2-4] It is important to disentangle the different types of PPH, in order to gain insight into the pathophysiological mechanisms, and to find potential clinical interventions that may reduce occurrence and severity of PPH.

In studies on risk factors of types of PPH, emphasis has usually been placed on two main causes of PPH; uterine atony [4-6] or retained placenta,[7] while important types, like PPH caused by obstetric trauma or dystocia, are widely ignored. Further, the considerable variation in estimated occurrence rates between populations,[2, 3, 8] exceeds what could be expected to be caused by environmental and genetic variations.

Studies have reported associations of PPH (in general) with demographic,[3, 9-13] and pregnancy-related factors,[3] obstetric history,[9] and complications related to the fetus, placenta, membranes and umbilical cord [14], while studies on risk factors of type specific PPH are scarce. Thus, we aimed to explore risk profiles of different PPH types through our specific objectives: to calculate the effects of demographic and pregnancy-related factors, obstetric history and complications related to the fetus, placenta, membranes and umbilical cord, and to investigate the recurrence risk of the different types of PPH in the Norwegian population.

Material and methods

Data sources

The Medical Birth Registry of Norway (MBRN), established in 1967, is a mandatory register containing information of all births in Norway.[15] We identified singleton births in the MBRN from 1967 to 2017 with gestational age at birth of ≥22 weeks and spontaneous onset or induction of labor. Gestational age was estimated from the last menstrual period and based on ultrasonography when data for the last menstrual period were lacking. Information on the parental education level

and country of birth was provided by Statistics Norway and linked with the birth registry using the unique national identification number of each parent.

Record linkage

During the period from 1967 to 2017, 3 003 025 births were registered. Using the national identification number, we linked the first two births in women who gave their first birth in 1967 or later, to assess the risk of PPH types according to pregnancy- and birth-related factors and obstetric history, including recurrence risk.

Ethics statement/approval

The study was approved by the Regional Committee for Medical and Health Research Ethics (2013/1484) and the registry owners (the Medical Birth Registry of Norway, the Norwegian Institute of Public Health, Statistics Norway and the Norwegian Tax Administration).
Consent to participate: Not applicable
Consent for publication: Not applicable

Outcome variables

The main outcome variables were PPH defined as the loss of more than 500ml of blood during labor or within 24 hours postpartum (hereafter referred to as PPH) in combination with one of seven predefined types of PPH described below. The PPH types were not mutually exclusive as more than one PPH type could be recorded in the same delivery.

In 1999, the notification form was upgraded with new, predominantly categorical, variables. From 1999, PPH of more than 1500ml or the need for blood transfusion (regardless of bleeding volume) were additionally recorded (hereafter referred to as severe PPH). PPH was notified in free text before 1999, and thereafter using check boxes.[15]

PPH types were defined as PPH combined with each of the following complications:

1 Retained placenta and/or membranes:

Defined as lack of expulsion of the placenta within 30 minutes of delivery,[16] or retention of membranes. This was notified to the MBRN by plain text before 1999 and by check box from 1999, or by plain text as manual removal of the placenta, uterine curettage or abnormally invasive placenta from 1967 to 2017.

2 Uterine atony:

Failure of the uterus to contract adequately following delivery,[17] notified in the MBRN by plain text before 1999 and by check box from 1999.

3 Obstetric trauma:

Notified in the MBRN as perineal laceration (1^{st} to 4^{th} degree) (by plain text before 1999 and by check boxes from 1999) or notified by plain text as other obstetric trauma (e.g., cervical or vaginal trauma) or inversio uteri from 1967.

4 Dystocia:

Duration of labor with spontaneous onset extends beyond the normal duration defined by the World Health Organization, (based on observational studies from 1973–2018).[18] First stage (time from five centimeters to full cervical dilatation) 12 and 10 hours in first and subsequent labors, respectively. Second stage (time from full cervical dilatation to birth) three and two hours in first and subsequent labors, respectively. Protracted labor or cephalopelvic disproportion has been notified in the MBRN by plain text before 1999 and from 1999 by check box.

5 Undefined PPH cause:

PPH without recorded cause.

6 Placental abruption:

Notified in the MBRN before 1999 by plain text, and from 1999 by check box.

7 Placenta previa:

Notified in the MBRN before 1999 by plain text, and from 1999 by check box.

Independent variables

Independent variables were demographic characteristics (maternal age, country of origin, marital status, education), obstetric history, pregnancy and fetal complications, and characteristics of the placenta, membranes, or umbilical cord. Independent variables also included a history of PPH (including the type of PPH) in the first delivery, inter-delivery interval, change of father between pregnancies, and previous cesarean section. Our analyses included possible confounding factors: maternal age (in five categories), parity, marital status, inter-delivery interval, mother's country of birth, level of education, and the period of birth divided into five groups of approximately equal length (1967–1977, 1978–1987, 1988–1997, 1998–2007 and 2008–2017). Supporting information (S1 Statistical analysis) includes additional details.

Statistical analysis

We used multilevel logistic regression analyses to calculate odds ratios (ORs) with 95% confidence intervals (CIs) for PPH types as outcomes, and variables related to demographic characteristics, obstetric history, pregnancy, and fetal complications, and characteristics of the placenta, membranes, and umbilical cord as exposures. We also calculated ORs for PPH types in the actual birth as the outcomes and previous PPH types as exposure variables.

We used sensitivity analyses to assess if the associations studied persisted after adjusting for unmeasured confounders and to indicate potentially false positive associations by chance conducting multiple analyses. Supporting information (S1 Statistical analysis) includes additional details.

The statistical analyses were performed using SPSS (version 25) and MLwiN (version 3.05).

Results

Table 1. Occurrence of type specific postpartum hemorrhage (PPH); singleton births ≥22 weeks of gestation.

		All types			Retained placenta			Atony			Trauma or laceration			Placental abruption			Placenta previa			Dystocia			Undefined bleeding cause		
		(n)	%[a]	%[b]	(n)	%[a]	%[b]	(n)	%[a]	%[b]	(n)	%[a]	%[b]	(n)	%[a]	%[b]	(n)	%[a]	%[b]	(n)	%[a]	%[b]	(n)	%[a]	%[b]
All PPH (>500ml)	1967–2017	312528	100.0		35664	11.4		73284	23.4		28673	9.2		3598	1.2		2542	0.8		37597	12.0		131170	42.0	
Mild PPH (500–1500ml)	1999–2017	191730	100.0	87.2	17455	9.1	70.7	39048	20.4	84.3	16760	8.7	86.6	1785	0.9	77.9	1647	0.9	76.1	26644	13.9	87.0	88391	46.1	93.6
Severe PPH (>1500ml)	1999–2017	28149	100.0	12.8	7229	25.7	29.3	7276	25.8	15.7	2586	9.2	13.4	506	1.8	22.1	517	1.8	23.9	3980	14.1	13.0	6055	21.5	6.4

[a] Distribution between types in percent (row percent); [b] Proportions according to severity of PPH types (column percent) (since 1999, when severe PPH was specified)

Fig 1: Occurrence of type specific postpartum hemorrhage (>500ml) (1967-2017).

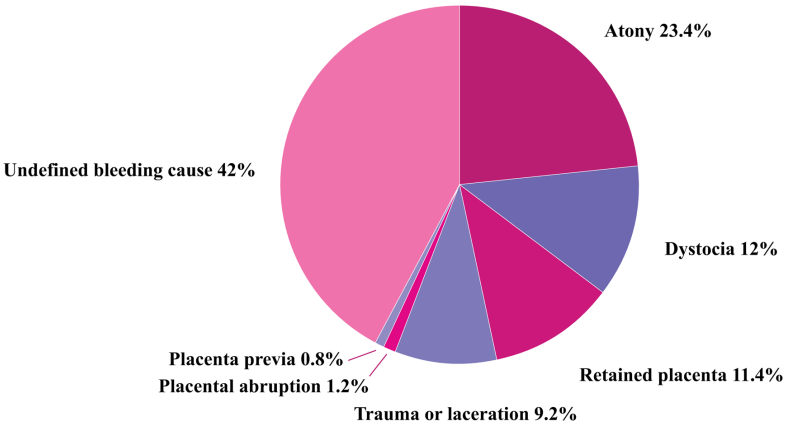

Table 1 and Figure 1 shows occurrence of type specific PPH among singleton pregnancies with gestational age at birth of ≥22 weeks of gestation. The distribution of PPH types, in decreasing order of group size, included 42.0% (n=131 170) without specified cause of PPH, 23.4% (n=73 284) due to atony, 12.0% (n=37 597) dystocia, 11.4% (n=35 664) retained placenta and/or membranes, and 9.2% (n=28 673) obstetric trauma. Placental abruption and placenta previa were registered as cause of PPH in 1.2% (n=3598) and 0.8% (n=2542), respectively. The total number of PPH registrations (n=312 528) exceeded the total number of births with PPH (n=277 746), since more than one PPH type could be recorded in the same birth.

Severe PPH (registered after 1999, 28 149 type specific cases) showed a different distribution with 25.8% (n=7276) caused by atony and 25.7% (n=7229) by retained placenta, followed in decreasing order: undefined bleeding cause 21.5% (n=6055), dystocia 14.1% (n=3980), obstetric trauma 9.2% (n=2586), placenta previa 1.8% (n=517) and placental abruption 1.8% (n=503) (Table 1).

Women who had PPH caused by retained placenta were more often registered with severe PPH (29.3%) compared with other categories of PPH (Table 1, Fig 2), while only 6.4% of those with undefined cause of PPH were severe PPH cases.

Fig 2: Occurrence of severe postpartum hemorrhage (>1500ml) within type specific postpartum hemorrhage (1999–2017).

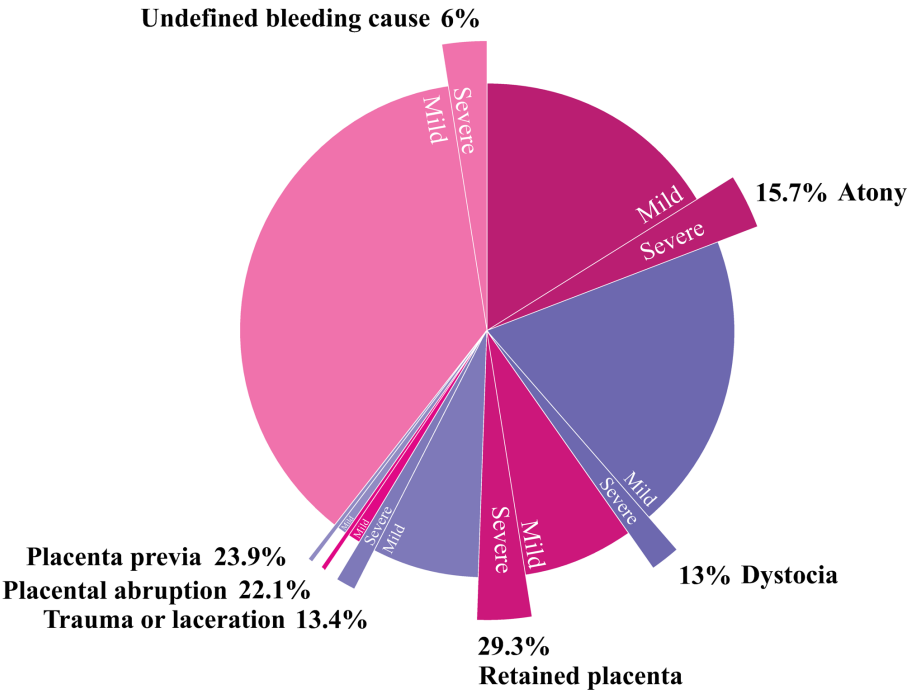

Table 2. Distribution of maternal, pregnancy and birth characteristics in types of postpartum hemorrhage (PPH >500ml); singleton births, ≥22 weeks of gestation.

		All types		Retained placenta		Atony		Trauma or laceration		Placental abruption		Placenta previa		Dystocia		Undefined bleeding cause	
		(n)	%	(n)	%	(n)	%	(n)	%	(n)	%	(n)	%	(n)	%	(n)	%
Maternal age (years)	<20	9332	3.0	863	2.4	2523	3.4	1054	3.7	106	2.9	13	0.5	801	2.1	3972	3.0
	20–24	55452	17.7	5711	16.0	14388	19.6	6045	21.1	576	16.0	136	5.4	5829	15.5	22767	17.4
	25–29	103710	33.2	11198	31.4	25115	34.3	10641	37.1	1098	30.5	513	20.2	13315	35.4	41830	31.9
	30–34	92251	29.5	11223	31.5	20744	28.3	7685	26.8	1086	30.2	922	36.4	11806	31.4	38785	29.6
	35–39	42678	13.7	5494	15.4	8802	12.0	2807	9.8	578	16.1	746	29.3	4914	13.1	19337	14.7
	40–44	8595	2.8	1112	3.1	1621	2.2	414	1.4	148	4.1	200	7.9	884	2.4	4216	3.2
	≥45	510	0.2	63	0.2	91	0.1	27	0.1	6	0.2	12	0.5	48	0.1	263	0.2
Parity	0	157617	50.4	16033	45.0	34849	47.6	18661	65.1	1290	35.9	739	29.1	28690	76.3	57355	43.7
	1	99371	31.8	12316	34.5	24554	33.5	7485	26.1	1217	33.8	1032	40.6	6838	18.2	45929	35.0
	2	38856	12.4	5204	14.6	9792	13.4	1931	6.7	668	18.6	469	18.5	1511	4.0	19281	14.7
	3	10994	3.5	1421	4.0	2731	3.7	416	1.5	240	6.7	203	8.0	372	1.0	5611	4.3
	4	3983	1.3	463	1.3	928	1.3	140	0.5	128	3.6	71	2.8	135	0.4	2118	1.6
	≥5	1707	0.5	227	0.6	430	0.6	40	0.1	55	1.5	28	1.1	51	0.1	876	0.7
Year of delivery	1967–1969	9042	2.9	779	2.2	2268	3.1	430	1.5	155	4.3	36	1.4	182	0.5	5192	4.0
	1970–1979	24384	7.8	2718	7.6	6836	9.3	1701	5.9	318	8.8	61	2.4	853	2.3	11897	9.1
	1980–1989	25760	8.2	3510	9.8	8007	10.9	3108	10.8	384	10.7	99	3.9	2157	5.7	8495	6.5
	1990–1999	40825	13.1	4990	14.0	11430	15.6	4559	15.9	543	15.1	230	9.0	4669	12.4	14404	11.0
	2000–2009	96120	30.8	12294	34.5	22990	31.4	7858	27.4	1179	32.8	1003	39.5	12572	33.4	38224	29.1
	2010–2017	116397	37.2	11373	31.9	21753	29.7	11017	38.4	1019	28.3	1113	43.8	17164	45.7	52958	40.4
Previous 1st trimester spontaneous abortion[a]	No	177174	80.4	19011	76.8	37367	80.5	16185	83.6	1759	76.5	1570	72.5	25314	82.5	75968	80.3
	Yes	43142	19.6	5737	23.2	9046	19.5	3181	16.4	539	23.5	597	27.5	5362	17.5	18680	19.7
1st trimester bleeding	**No**	303194	97.0	33940	95.2	71180	97.1	28130	98.1	3473	96.5	2386	93.9	36477	97.0	127608	97.3
	Yes	9334	3.0	1724	4.8	2104	2.9	543	1.9	125	3.5	156	6.1	1120	3.0	3562	2.7
Previous cesarean section	No	279188	89.3	32597	91.4	68194	93.1	25881	90.3	3119	86.7	2050	80.6	33216	88.3	114131	87.0
	Yes	33340	10.7	3067	8.6	5090	6.9	2792	9.7	479	13.3	492	19.4	4381	11.7	17039	13.0

Preeclampsia	No	299179	95.7	34182	95.8	70433	96.1	27615	96.3	3310	92.0	2502	98.4	35943	95.6	125194	95.4
	Yes	13349	4.3	1482	4.2	2851	3.9	1058	3.7	288	8.0	40	1.6	1654	4.4	5976	4.6
Smoking in start of pregnancy[a]	No	165227	89.1	18531	86.7	36750	89.6	15846	91.1	1491	79.1	158	43.3	23531	90.3	68920	89.2
	Occasionally	2880	1.6	333	1.6	604	1.5	258	1.5	52	2.8	28	7.7	405	1.6	1200	1.6
	Yes	17275	9.3	2509	11.7	3680	9.0	1288	7.4	341	18.1	179	49.0	2117	8.1	7161	9.3
Gestational or pregestational diabetes mellitus	No	302981	96.9	34768	97.5	71523	97.6	28001	97.7	3510	97.6	2459	96.7	36002	95.8	126718	96.6
	Yes	9547	3.1	896	2.5	1761	2.4	672	2.3	88	2.4	83	3.3	1595	4.2	4452	3.4
Start of delivery	Spontaneous	216838	69.4	26006	72.9	54963	75.0	22129	77.2	1946	54.1	624	24.5	26318	70.0	84852	64.7
	Induction	66721	21.3	7342	20.6	15513	21.2	6337	22.1	815	22.7	148	5.8	11279	30.0	25287	19.3
	Cesarean section	28969	9.3	2316	6.5	2808	3.8	207	0.7	837	23.3	1770	69.6	0	0.0	21031	16.0
Birthweight (grams)	<4000	222509	71.2	26665	74.8	49843	68.0	19593	68.3	3327	92.5	2404	94.6	23258	61.9	97419	74.3
	4000–4499	68414	21.9	6928	19.4	17788	24.3	6956	24.3	222	6.2	118	4.6	10539	28.0	25863	19.7
	4500–4999	18621	6.0	1803	5.1	4911	6.7	1851	6.5	41	1.1	18	0.7	3245	8.6	6752	5.1
	≥5000	2984	1.0	268	0.8	742	1.0	273	1.0	8	0.2	2	0.1	555	1.5	1136	0.9
Fetal sex[b]	Girl	154394	49.4	19241	54.0	37118	50.7	14021	48.9	1601	44.5	1184	46.6	16634	44.2	64595	49.2
	Boy	158114	50.6	16414	46.0	36163	49.3	14652	51.1	1997	55.5	1358	53.4	20962	55.8	66568	50.8
Cesarean section (irrespective of start)	No	237468	76.0	30622	85.9	65379	89.2	27751	96.8	1176	32.7	119	4.7	20995	55.8	91426	69.7
	Yes	75060	24.0	5042	14.1	7905	10.8	922	3.2	2422	67.3	2423	95.3	16602	44.2	39744	30.3
Vacuum delivery	No	275186	88.1	32333	90.7	66115	90.2	23458	81.8	3494	97.1	2537	99.8	22347	59.4	124902	95.2
	Yes	37342	11.9	3331	9.3	7169	9.8	5215	18.2	104	2.9	5	0.2	15250	40.6	6268	4.8
Forceps delivery	No	302559	96.8	34869	97.8	71598	97.7	26663	93.0	3547	98.6	2536	99.8	33700	89.6	129646	98.8
	Yes	9969	3.2	795	2.2	1686	2.3	2010	7.0	51	1.4	6	0.2	3897	10.4	1524	1.2
Shoulder dystocia	No	307711	98.5	35177	98.6	72058	98.3	27989	97.6	3586	99.7	2540	99.9	36558	97.2	129803	99.0
	Yes	4817	1.5	487	1.4	1226	1.7	684	2.4	12	0.3	2	0.1	1039	2.8	1367	1.0
Episiotomy[c]	No	171611	77.9	19634	79.3	35045	75.5	13164	68.0	2218	96.5	2149	99.2	19842	64.7	79559	84.1
	Yes	48705	22.1	5114	20.7	11368	24.5	6202	32.0	80	3.5	18	0.8	10834	35.3	15089	15.9

Epidural anasthesia	No	217383	69.6	26376	74.0	54188	73.9	19013	66.3	3101	86.2	2268	89.2	13166	35.0	99271	75.7
	Yes	95145	30.4	9288	26.0	19096	26.1	9660	33.7	497	13.8	274	10.8	24431	65.0	31899	24.3
Placenta defined as normal[c]	No	54383	24.7	18208	73.6	10490	22.6	3003	15.5	1050	45.7	714	32.9	6677	21.8	14241	15.0
	Yes	165933	75.3	6540	26.4	35923	77.4	16363	84.5	1248	54.3	1453	67.1	23999	78.2	80407	85.0
Velamentous umbilical cord incertion[c]	No	215432	97.8	23625	95.5	45476	98.0	19002	98.1	2205	96.0	2052	94.7	30159	98.3	92913	98.2
	Yes	4884	2.2	1123	4.5	937	2.0	364	1.9	93	4.0	115	5.3	517	1.7	1735	1.8
Marginal umbilical cord incertion[c]	No	206851	93.9	23027	93.0	43267	93.2	18090	93.4	2093	91.1	1949	89.9	28818	93.9	89607	94.7
	Yes	13465	6.1	1721	7.0	3146	6.8	1276	6.6	205	8.9	218	10.1	1858	6.1	5041	5.3

[a] 1999–2017, smoking status available in 163731 deliveries with PPH

[b] 18 newborns with unknown sex

[c] 1999–2017

Table 2 shows the distribution of maternal, pregnancy and birth characteristics in types of PPH. Young women were more often registered with PPH due to obstetric trauma, and women with PPH caused by dystocia and obstetric trauma were more often nulliparous.

Smoking was more common in PPH associated with placenta previa and placental abruption.

Diabetes mellitus was more common in PPH associated with dystocia (4.2%), while preeclampsia was more common in PPH associated with placental abruption (8.0%).

High birthweight was commonly found in PPH caused by dystocia, atony and obstetric trauma. A history of first trimester bleeding was more common in women with PPH due to placenta previa (6.1%) and retained placenta (4.8%), while the opposite was the case for PPH caused by obstetric trauma (1.9%).

Women who experienced PPH due to retained placenta or atony were more likely delivering girls than boys, while those with PPH caused by dystocia, obstetric trauma and undefined bleeding cause were more often delivering boys.

Placenta was defined as “normal” (tic box) in most deliveries with PPH without defined cause, in PPH due to obstetric trauma, and due to dystocia (75–85%). The opposite was found for PPH caused by retained placenta, where 26% of the placentas were defined as normal.

Table 3. Risk of type specific postpartum hemorrhage (PPH >500ml) according to maternal, pregnancy and birth characteristics; singleton births, ≥22 weeks of gestation and spontaneous onset or induction of labor.

		Total	Retained placenta					Atony					Trauma or laceration					Dystocia					Undefined bleeding cause				
		(n)	(n)	%	aOR	95% CI		(n)	%	aOR	95% CI		(n)	%	aOR	95% CI		(n)	%	aOR	95% CI		(n)	%	aOR	95% CI	
Maternal age (Years)	<20	136032	841	0.6	0.55	0.51	0.59	2507	1.8	0.82	0.79	0.86	1049	0.8	0.55	0.51	0.59	801	0.6	0.33	0.31	0.36	3815	2.8	0.85	0.83	0.89
	20–24	652556	5540	0.8	0.74	0.72	0.77	14209	2.2	0.92	0.90	0.94	6035	0.9	0.73	0.70	0.75	5829	0.9	0.56	0.54	0.58	21328	3.3	0.93	0.91	0.94
	25–29	916125	10647	1.2	1	Ref		24536	2.7	1	Ref		10600	1.2	1	Ref		13315	1.5	1	Ref		36781	4.0	1	Ref	
	30–34	662257	10324	1.6	1.32	1.28	1.34	19722	3.0	1.03	1.01	1.05	7593	1.1	1.09	1.06	1.13	11806	1.8	1.42	1.38	1.46	31205	4.7	1.07	1.05	1.09
	35–39	260686	4932	1.9	1.62	1.56	1.68	8012	3.1	1.06	1.03	1.09	2751	1.1	1.16	1.10	1.22	4914	1.9	1.79	1.73	1.86	13969	5.4	1.17	1.14	1.20
	40–44	46563	929	2.0	1.75	1.62	1.89	1395	3.0	1.09	1.03	1.15	410	0.9	1.14	1.02	1.28	884	1.9	2.04	1.90	2.20	2819	6.1	1.34	1.29	1.40
	≥45	2198	43	2.0	1.97	1.43	2.70	76	3.5	1.40	1.11	1.76	26	1.2	1.80	1.18	2.74	48	2.2	2.50	1.83	3.41	164	7.5	1.79	1.53	2.09
Parity	0	1124388	15284	1.4	1	Ref		33966	3.0	1	Ref		18609	1.7	1	Ref		28690	2.6	1	Ref		50806	4.5	1	Ref	
	1	935991	11389	1.2	0.77	0.75	0.79	23415	2.5	0.78	0.77	0.79	7409	0.8	0.42	0.41	0.44	6838	0.7	0.22	0.22	0.23	37766	4.0	0.86	0.85	0.88
	2	423535	4700	1.1	0.64	0.62	0.67	9225	2.2	0.66	0.65	0.68	1872	0.4	0.22	0.21	0.24	1511	0.4	0.10	0.09	0.11	14758	3.5	0.74	0.73	0.76
	3	128264	1273	1.0	0.55	0.51	0.58	2564	2.0	0.59	0.57	0.62	407	0.3	0.16	0.15	0.18	372	0.3	0.08	0.07	0.09	4305	3.4	0.71	0.69	0.74
	4	46957	412	0.9	0.48	0.43	0.53	868	1.8	0.52	0.57	0.62	131	0.3	0.14	0.11	0.16	135	0.3	0.08	0.06	0.09	1721	3.7	0.77	0.73	0.81
	≥5	17282	198	1.1	0.56	0.48	0.66	419	2.4	0.66	0.59	0.73	36	0.2	0.09	0.06	0.13	51	0.3	0.07	0.05	0.09	725	4.2	0.82	0.75	0.89
Previous 1st trimester spontaneous abortion[a]	No	818952	17401	2.1	1	Ref		35221	4.3	1	Ref		16047	2.0	1	Ref		25314	3.1	1	Ref		60431	7.4	1	Ref	
	Yes	188824	5032	2.7	1.24	1.19	1.28	8437	4.5	1.09	1.07	1.12	3118	1.7	0.97	0.93	1.02	5362	2.8	1.07	1.04	1.11	13960	7.4	0.99	0.97	1.01
1st trimester bleeding	No	2628264	31692	1.2	1	Ref		68462	2.6	1	Ref		27927	1.1	1	Ref		36477	1.4	1	Ref		107109	4.1	1	Ref	
	Yes	48153	1564	3.2	2.10	1.99	2.22	1995	4.1	1.28	1.22	1.34	537	1.1	0.83	0.75	0.91	1120	2.3	1.10	1.03	1.17	2972	6.2	1.16	1.12	1.21
Previous cesarean section	No	2560531	31040	1.2	1	Ref		66385	2.6	1	Ref		25783	1.0	1	Ref		33216	1.3	1	Ref		101631	4.0	1	Ref	
	Yes	115886	2216	1.9	1.39	1.33	1.46	4072	3.5	1.27	1.22	1.31	2681	2.3	3.41	3.25	3.58	4381	3.8	6.08	5.82	6.35	8450	7.3	1.55	1.52	1.59
Start of labor	Spontaneous	2247799	25951	1.2	1	Ref		54953	2.4	1	Ref		22128	1.0	1	Ref		26318	1.2	1	Ref		84815	3.8	1	Ref	
	Induction	428618	7305	1.7	1.36	1.32	1.39	15504	3.6	1.41	1.38	1.43	6336	1.5	1.31	1.27	1.35	11279	2.6	1.87	1.82	1.91	25266	5.9	1.45	1.43	1.47
Birthweight (grams)	<2500	91074	1443	1.6	1.39	1.32	1.47	1073	1.2	0.42	0.39	0.45	245	0.3	0.22	0.19	0.25	191	0.2	0.12	0.11	0.14	3302	3.6	0.84	0.81	0.87
	2500–2999	271661	2829	1.0	0.85	0.82	0.89	3579	1.3	0.45	0.44	0.47	1343	0.5	0.38	0.36	0.41	1178	0.4	0.23	0.22	0.25	7915	2.9	0.64	0.63	0.66
	3000–3499	845937	8638	1.0	0.83	0.81	0.86	16106	1.9	0.66	0.65	0.68	6710	0.8	0.64	0.62	0.67	7351	0.9	0.50	0.49	0.52	27869	3.3	0.75	0.73	0.76
	3500–3999	957654	11706	1.2	1	Ref		26825	2.8	1	Ref		11114	1.2	1	Ref		14538	1.5	1	Ref		41202	4.3	1	Ref	

	4000–4499	415535	6669	1.6	1.32	1.28	1.36	17389	4.2	1.56	1.52	1.59	6934	1.7	1.69	1.63	1.75	10539	2.5	1.98	1.92	2.03	22974	5.5	1.32	1.29	1.34
	4500–4999	83839	1727	2.1	1.71	1.62	1.80	4784	5.7	2.22	2.15	2.29	1845	2.2	2.59	2.46	2.73	3245	3.9	3.61	3.46	3.76	5886	7.0	1.75	1.70	1.80
	≥5000	10717	244	2.3	1.93	1.70	2.20	701	6.5	2.73	2.53	2.94	273	2.5	3.43	3.03	3.89	555	5.2	5.78	5.26	6.35	933	8.7	2.29	2.14	2.45
Fetal sex[a]	Girl	1300887	18026	1.4	1	Ref		35733	2.7	1	Ref		13901	1.1	1	Ref		16634	1.3	1	Ref		54477	4.2	1	Ref	
	Boy	1375459	15225	1.1	0.80	0.78	0.82	34722	2.5	0.92	0.90	0.93	14563	1.1	0.99	0.97	1.01	20962	1.5	1.18	1.16	1.21	55601	4.0	0.96	0.95	0.97
Placental weight (grams)[b]	<500	92475	3759	4.1	2.03	1.95	2.11	2361	2.6	0.72	0.68	0.75	1223	1.3	0.74	0.80	0.75	1175	1.3	0.52	0.48	0.55	5623	6.1	0.89	0.87	0.92
	500–699	488935	9892	2.0	1	Ref		17118	3.5	1	Ref		8319	1.7	1	Ref		10732	2.2	1	Ref		31685	6.5	1	Ref	
	700–899	328966	6216	1.9	0.93	0.90	0.96	17552	5.3	1.55	1.51	1.59	7201	2.2	1.42	1.37	1.48	13355	4.1	2.07	2.02	2.12	27784	8.4	1.37	1.34	1.39
	900–1099	64314	1451	2.3	1.12	1.06	1.19	4995	7.8	2.32	2.24	2.40	1837	2.9	2.01	1.89	2.13	4175	6.5	3.74	3.60	3.89	6751	10.5	1.78	1.73	1.83
	≥1100	9934	270	2.7	1.37	1.21	1.54	933	9.4	2.85	2.65	3.06	336	3.4	2.59	2.28	2.94	746	7.5	4.62	4.26	5.00	1245	12.5	2.20	2.07	2.34
Velamentous cord insertion[c]	No	992869	21427	2.2	1	Ref		42830	4.3	1	Ref		18809	1.9	1	Ref		30159	3.0	1	Ref		73055	7.4	1	Ref	
	Yes	14907	1006	6.7	3.00	2.79	3.21	828	5.6	1.26	1.17	1.36	356	2.4	1.21	1.07	1.37	517	3.5	0.99	0.90	1.09	1336	9.0	1.24	1.17	1.31
Marginal umbilical cord insertion[c]	No	953165	20948	2.2	1	Ref		40821	4.3	1	Ref		17907	1.9	1	Ref		28818	3.0	1	Ref		70568	7.4	1	Ref	
	Yes	54611	1485	2.7	1.26	1.19	1.33	2837	5.2	1.24	1.19	1.29	1258	2.3	1.25	1.17	1.33	1858	3.4	1.12	1.06	1.18	3823	7.0	1.03	0.90	1.06

CI confidence interval, aOR: OR adjusted for maternal age, parity and period (1967–1977, 1978–1987, 1988–1997, 1998–2007 and 2008–2017)

[a] 71 newborns with unknown sex. The negative association with PPH due to trauma or laceration disappeared after adjusting for unmeasured confounder or stratification by preterm/term delivery

[b] 1999–2017, 23152 without placental weight

[c] 1999–2017

Table 3 shows risks of PPH types according to maternal, pregnancy and birth characteristics. We selected deliveries that were induced or had spontaneous onset, and found that PPH due to placental abruption and placenta previa represented a small proportion (2%) of all PPH registrations, and these were therefore not included in Tables 3–5. The risk of PPH increased with maternal age, and the association was strongest for PPH due to dystocia, followed by retained placenta, undefined bleeding cause and obstetric trauma. The effects were attenuated by adjustment for year of birth, while including parity in the model strengthened the associations. The risk of PPH was highest in primiparas, regardless of type, especially with PPH caused by dystocia and obstetric trauma. By including maternal age to the models these associations were strengthened.

First trimester bleeding was associated with a doubled risk of PPH due to retained placenta and had weaker association with PPH due to atony and without defined cause.

The risks of PPH types included in Table 3 increased with birthweight, especially PPH due to dystocia, obstetric trauma and atony. Including parity, maternal age and year of delivery in the models strengthened the associations, mainly for PPH due to dystocia and obstetric trauma. In term but not preterm deliveries, low birthweight (<2500g) was associated with PPH due to retained placenta and/or membranes.

Exploring the effect of fetal sex on the PPH types, we found that the risk of PPH was lower if the newborn was a boy. This association was strongest for PPH due to retained placenta (aOR: 0.80, 95% CI 0.78–0.82), followed by atony (aOR 0.92, 95% CI: 0.90–0.93) and undefined cause of PPH (aOR 0.96, 95% CI: 0.95–0.97). These associations were similar in strata of birthweight (<2500g, 2500–2999g, 3000–3499g, 3500–4000g, 4000–4499g, 4500–4999 g, ≥5000g). Adjusted OR for PPH due to obstetric trauma was also lower for deliveries of a boy, but this effect was only significant in weight groups between 3000 and 4499g. However, if the newborn was a boy, there was increased risk of PPH due to dystocia, but this association disappeared after stratification according to birthweight.

The association between placenta weight categories and the specific causes of PPH generally showed a pattern like that of birthweight.

Velamentous and marginal umbilical placental cord insertion were strongest associated with PPH due to retained placenta. This effect was significantly stronger for velamentous- (aOR: 3.1, 95% CI: 2.9–3.4) than marginal cord insertion (aOR: 1.3, 95% CI: 1.2–1.3).

Table 4. Risk of type specific postpartum hemorrhage (PPH>500ml) in the second delivery according to PPH types in the first delivery and pregnancy- and birth characteristic; singleton births, ≥22 weeks of gestation and spontaneous onset or induction of labor.

Type of PPH in first delivery and pregnancy/birth related exposures		Total	Type of PPH in second delivery																							
			Retained placenta					Atony					Trauma or laceration					Dystocia					Undefined bleeding cause				
		(n)	(n)	%	aOR	95% CI		(n)	%	aOR	95% CI		(n)	%	aOR	95% CI		(n)	%	aOR	95% CI		(n)	%	aOR	95% CI	
Retained placenta	No	785902	9107	1.2	1	Ref		19178	2.4	1	Ref		5795	0.7	1	Ref		4811	0.6	1	Ref		30674	3.9	1	Ref	
	Yes	8788	734	8.4	5.90	5.45	6.39	729	8.3	2.93	2.71	3.17	155	1.8	1.77	1.50	2.08	132	1.5	1.56	1.31	1.86	841	9.6	1.94	1.80	2.09
Atony	No	773349	8950	1.2	1	Ref		17745	2.3	1	Ref		5517	0.7	1	Ref		4612	0.6	1	Ref		29601	3.8	1	Ref	
	Yes	21341	891	4.2	2.91	2.71	3.13	2162	10.1	4.00	3.82	4.20	433	2.0	2.15	1.95	2.37	331	1.6	1.77	1.58	1.98	1914	9.0	1.90	1.81	1.99
Trauma or laceration	No	783198	9475	1.2	1	Ref		19031	2.4	1	Ref		5513	0.7	1	Ref		4855	0.6	1	Ref		30415	3.9	1	Ref	
	Yes	11492	366	3.2	2.01	1.81	2.24	876	7.6	2.65	2.47	2.85	437	3.8	3.86	3.49	4.27	88	0.8	0.77	0.63	0.96	1100	9.6	1.89	1.77	2.02
Dystocia	No	780869	9251	1.2	1	Ref		18800	2.4	1	Ref		5498	0.7	1	Ref		4080	0.5	1	Ref		29915	3.8	1	Ref	
	Yes	13821	590	4.3	2.44	2.24	2.66	1107	8.0	2.58	2.42	2.75	452	3.3	2.98	2.70	3.29	863	6.2	6.81	6.31	7.36	1600	11.6	2.09	1.98	2.21
Undefined bleeding cause	No	764798	9082	1.2	1	Ref		18281	2.4	1	Ref		5419	0.7	1	Ref		4501	0.6	1	Ref		28367	3.7	1	Ref	
	Yes	29892	759	2.5	1.64	1.52	1.77	1626	5.4	1.90	1.80	2.00	531	1.8	1.80	1.64	1.97	442	1.5	1.62	1.46	1.79	3148	10.5	2.21	2.12	2.30
Inter-delivery interval (year)	<1	3433	56	1.6	2.00	1.53	2.62	64	1.9	0.90	0.70	1.15	10	0.3	0.57	0.31	1.07	12	0.3	1.14	0.64	2.02	118	3.4	1.01	0.84	1.22
	1 to <2	151853	1815	1.2	1.08	1.01	1.14	3723	2.5	0.99	0.95	1.03	1001	0.7	0.92	0.86	1.00	809	0.5	1.00	0.91	1.09	5905	3.9	0.98	0.85	1.02
	2 to <3	239848	2924	1.2	1	Ref		6255	2.6	1	Ref		1906	0.8	1	Ref		1507	0.6	1	Ref		9898	4.1	1	Ref	
	3 to <4	166293	2118	1.3	1.08	1.02	1.15	4208	2.5	1.01	0.97	1.05	1319	0.8	1.05	0.98	1.12	968	0.6	0.98	0.91	1.07	6578	4.0	1.01	0.98	1.05
	4 to <5	88863	1046	1.2	1.02	0.95	1.10	2128	2.4	0.97	0.92	1.02	627	0.7	0.96	0.88	1.05	557	0.6	1.10	1.00	1.21	3364	3.8	1.01	0.97	1.05
	≥5	144400	1882	1.3	1.00	0.94	1.06	3529	2.4	0.93	0.89	0.97	1087	0.8	0.95	0.88	1.02	1090	0.8	1.10	1.02	1.19	5652	3.9	1.00	0.96	1.03
Change of father[a]	No	713133	8704	1.2	1	Ref		17912	2.5	1	Ref		5351	0.8	1	Ref		4303	0.6	1	Ref		28160	3.9	1	Ref	
	Yes	69371	981	1.4	1.00	0.94	1.07	1676	2.4	0.86	0.81	0.90	515	0.7	0.88	0.80	0.96	516	0.7	1.02	0.93	1.12	2808	4.0	0.93	0.90	0.97
Previous cesarean[b]	No	743587	8893	1.2	1	Ref		18127	2.4	1	Ref		4518	0.6	1	Ref		2270	0.3	1	Ref		27723	3.7	1	Ref	
	Yes	65619	1312	2.0	1.35	1.28	1.44	2368	3.6	1.28	1.23	1.34	1929	2.9	4.00	3.79	4.23	3368	5.1	13.16	12.46	13.89	5125	7.8	1.84	1.78	1.90

CI confidence interval, aOR OR adjusted for maternal age, parity and period (1967–1977, 1978–1987, 1988–1997, 1998–2007 and 2008–2017)

[a] 12186 births with unknown father in 1st or 2nd delivery

[b] First deliveries starting with cesarean section included

Table 4 shows the risk of PPH types in the second delivery (except for PPH caused by placental abruption and placenta previa) according to PPH types in the first delivery and pregnancy and birth related factors.

The risk of recurrent PPH was strongest for the same type. PPH associated with dystocia had highest risk of recurrence (aOR: 6.8, 95% CI: 6.3–7.4), followed by PPH due to retained placenta and/or membranes (aOR: 5.9, 95% CI: 5.5–6.4), atony (aOR: 4.0, 95% CI: 3.8–4.2) and obstetric trauma (aOR: 3.9, 95% CI: 3.5–4.3), while PPH of undefined cause had lowest risk of recurrence (aOR: 2.2, 95% CI: 2.1–2.3) (Table 4).

Exploring effects of pregnancy related factors on the PPH types in the second delivery, we found that inter-delivery interval had no significant effect on the risk in second delivery, except for PPH due to retained placenta where a short inter-delivery interval (less than one year) was associated with a doubled risk (aOR: 2.0, 95% CI: 1.5–2.6).

Change of father slightly decreased ORs of PPH due to obstetric trauma, atony and undefined bleeding cause. Additional adjustment for inter-delivery interval did not influence the associations.

A previous cesarean delivery was associated with a marked increased risk of PPH due to dystocia, (aOR of 13.2, 95% CI: 12.5–13.9), and a weaker association with PPH caused by obstetric trauma (aOR: 4.0, 95% CI: 3.8–4.2), undefined PPH, retained placenta and atony (aORs between 1.3 and 1.8). In additional analyses we compared risks of PPH associated with dystocia in three groups: second deliveries without previous cesarean section (reference), second deliveries with previous cesarean section, and first deliveries (Table 5). We found that the risk of PPH due to dystocia was higher in women with a previous cesarean (vaginal primiparas) than in primiparas.

Table 5. Risk of postpartum hemorrhage (PPH>500ml) due to dystocia in second deliveries without previous cesarean section (CS) (reference), second deliveries with previous CS, and first deliveries; singleton births, ≥22 weeks of gestation and spontaneous onset or induction of labor.

	Total	Dystocia related PPH				
Groups	**(n)**	**(n)**	**%**	**aOR**	**95% CI**	
2nd delivery without previous CS	864751	3146	0.4	1	Ref	
2nd delivery with previous CS	71240	3692	5.2	18.85	17.84	19.92
1st delivery	1124388	28690	2.6	9.10	8.72	9.48

CI confidence interval, aOR OR adjusted for maternal age and period (1967–1977, 1978–1987, 1988–1997, 1998–2007 and 2008–2017)

Our sensitivity analyses (S1 Statistical analysis) indicated that the associations described in Tables 3 and 4 persisted after adjusting for potential unmeasured confounders, and that false positive associations due to multiple testing were not present.

Discussion

Main findings

We found that maternal, fetal and obstetric characteristics had differential effects on the types of PPH. The risk of recurrence differed considerably between the PPH types; the strongest recurrence risks were found for PPH caused by dystocia, retained placenta and atony. PPH due to retained placenta was most prone to develop into severe PPH.

Strengths and limitations

A main strength of the study was the long study period with mandatory registration of all births in the country, and with almost complete record linkage, which made it possible to do comprehensive sub-analyses. We also consider it a strength that it has been possible to classify clinically relevant causes of PPH since the inception of the registry. The population-based design and prospective collection of data attenuate selection and recall bias. Ethically, this is the study design of choice as

we investigate a potentially life-threatening outcome.[19] Furthermore, the PPH-variable has been validated and found to be of adequate quality for epidemiological studies.[20] The robustness of our results for potentially unknown confounding variables, assessed in the sensitivity analyses, is reassuring.

The introduction of activity-based financing and update of the MBRN registration form in 1999 may have improved the registration and contributed to the increased occurrence of PPH without specified cause after 1999, representing 29.2 percent of all registered PPH cases in the total study period.

It is possible that misclassification between types of PPH occurs, for example between retained placenta and atony. We expect that such misclassification to be non-differential and would therefore not affect the ORs. Coexistence of more than one PPH type in a delivery, for example atony and obstetric trauma caused by macrosomia is plausible, and there was no upper limit for registration of types of PPH in each delivery.

Previous studies

International variation and demographic factors

In contrast to the situation worldwide, the maternal mortality rate of PPH in Norway is low,[1, 21] which may limit the generalizability of our results. However, in other settings we assume that proportions of severe bleeding in the different types of PPH may show similar pattern.

There are considerable differences in the reported proportions of PPH types in the literature, especially for PPH caused by atony and retained placenta. Bateman et al. [8] and Widmer et al. [2] reported that 79% and 62% of all registered PPH cases (>500ml and refractory PPH, respectively) were accounted for by atony, which is in contrast with our findings (23% PPH due to atony) (Table 1). Our result is more in line with the 41% due to atony in a Swedish study (>1000ml).[3] The proportion of PPH due to retained placenta in our study (11.4%) is in line with other studies.[8] Oberg et al. reported that 33.5% of PPH cases were due to retained placenta, which is comparable to our results in severe PPH (25.7% due to retained placenta).[2]

These inter-study variations may be caused by differences in code availability or definitions of excessive bleeding, although it cannot be ruled out that variations of population genetic and/or environmental properties, or medical culture, may also play a role.

Our results confirm that maternal age was associated with all types of PPH (with the strongest association for PPH caused by dystocia). The effect of maternal age on PPH caused by atony are in line with existing knowledge.[2, 4-6, 22] Studies on associations between maternal age and other types of PPH are scarce, but an association with retained placenta in general has been reported. [22] Parity had strongest effect on PPH due to dystocia; 76% of the cases were primiparas, which agrees with the higher risk of dystocia in nulliparas.[23]

As dystocia may result in uterine fatigue and atony, PPH due to dystocia may have been classified as atony in studies where dystocia is not recorded in the databases. This may, at least in part, explain the very high proportion of PPH due to atony found in some studies.[8]

Pregnancy-related factors

We found a slightly reduced risk of recurrent PPH (caused by obstetric trauma and atony and undefined bleeding cause) in mothers who had changed partner, also after adjusting for inter-delivery interval. This fits with our previous findings of a weak but significant paternal effect on recurrent PPH.[24] In the present study there was a significantly increased risk of PPH due to retained placenta when the inter-delivery interval was short (less than one year). This contrast findings regarding PPH in general, where inter-delivery interval had a negligible effect on recurrence.[24]

The association of first trimester bleeding and PPH caused by retained placenta is consistent with results from previous studies that retained placenta[25] and PPH in general[26] are associated with threatened abortion.

Obstetric history (including recurrence)

Recurrence risk of PPH due to retained placenta, [3, 7] atony and laceration,[3] and increased duration and pushing time of the second stage of labor have been associated with PPH, [27] which is in line with our results. However, we found that PPH caused by dystocia was the PPH type most prone to recur, which to our knowledge has not been reported before.

A history of cesarean section has been linked to risk of retained placenta in general [5, 9, 12] and atonic PPH,[8] but not consistently.[7, 28] In our population women with a previous cesarean carried increased risk of all causes of PPH, but the strongest association was found with dystocia PPH (Table 4).

Complications related to the fetus, placenta, membranes and umbilical cord

The finding that birthweight has a strong association to PPH (Table 3) is in line with previous findings.[24, 29, 30] However, a new finding was that the strength of associations markedly varied with type of PPH, and that birthweight had the strongest association with PPH due to dystocia.

Sex differences in properties of placenta, umbilical cord and birthweight are well known. [31-35] We found a strong effect of fetal sex on most types of PPH and especially for PPH caused by retained placenta. This was a new finding and is consistent with previous findings that delivery of girls carries higher risk of retained placenta in general [7, 9] and PPH due to atony. [36]

As expected, PPH without specific cause was dominated by mild cases. Its low risk of recurrence is in line with the concept that a mild phenotype of a polygenic trait or disease is generally less prone to recur than a severe phenotype. [37] This suggests that most of these cases were correctly assigned to the group.

Interpretation

Risk factors for dystocia, with and without PPH, have previously been reported,[27, 38-40] but the strong recurrence risk of PPH due to dystocia has to our knowledge not been studied before. As dystocia may be an indication for operative delivery, this may result in PPH due to trauma to the

birth canal. The recurrence risk of PPH due to dystocia may be caused by sustained or recurrent factors associated with PPH or indicative of operative delivery, such as tendency to deliver large babies and fetopelvic disproportion. Further, dystocia may lead to atonic PPH through exhausting workload on the uterus without adequate progression of labor.

It is reasonable to assume that the placenta accreta spectrum constitutes some of the cases of severe PPH in the retained placenta group. However, we do not have exact information on the occurrence of placenta accreta spectrum in our population, and this was beyond the scope of our study. Another possible explanation for the higher occurrence of severe PPH among women with PPH due to retained placenta is the lack of effective initial medical treatment, along with the need of surgical intervention which may be delayed. In contrast, atony often is sufficiently treated with medications.

A previous cesarean was strongly associated with PPH due to dystocia in the second delivery, and we also found associations with PPH due to obstetric trauma, retained placenta and atony. The risk of PPH due to dystocia was higher than in nulliparas. A possible explanation for the association of previous cesarean section with PPH due to dystocia may be ineffective labor contractions due to the uterine scar, and that no previous vaginal delivery may mimic a primipara, with increased risk of delayed progression in labor and exhaustion of uterine contractility. One may speculate that the association of previous cesarean section with PPH due to retained placenta is associated with an early stage of abnormal invasive placenta, consistent with the increased risk of abnormal invasive placenta in women with previous cesarean section.[41]

We found that birthweight was associated with all types of PPH, but especially PPH due to dystocia, birth canal lacerations and uterine atony. This was expected, as macrosomia is associated with PPH through distention of the uterus and large utero-placental wound surface.[2, 10, 24, 42] In addition, macrosomia may increase tension on maternal tissue during labor leading to increased risk of obstetric trauma.[43] Another explanatory mechanism is that fetal macrosomia, dystocia and atony may be indications for operative vaginal delivery and result in surgical bleeding.

A possible explanation for the reduced risk of PPH due to retained placenta if the newborn was a boy (Table 3) may be the more inadequate transformation of the uterine spiral arteries in pregnancies with male fetus.[44-46] This agrees with the fetal sex preponderance in complications of the placenta, like placental abruption[36] and preeclampsia,[47] although not consistently for the latter.[36]

To increase the relevance for clinical practice we analyzed deliveries with spontaneous onset or induction of labor, thus excluding cesarean sections before the onset of labor. Deliveries with PPH due to placenta previa or placental abruption are underrepresented in our material (only 2% of PPH cases) since they primarily are delivered by cesarean section before labor and were therefore not included in the main analyses.

The substantial variation of reported incidence of causes of PPH among populations call for initiatives to unite the international definitions and improve the understanding of PPH pathophysiological mechanism.

We have already addressed the need of alertness when a delivering woman or her relatives has experienced PPH. [24, 48] Based on our present results, we encourage special attention concerning PPH due to retention of placenta or membranes, as its recurrence risk is high, and that a retained placenta carried the highest risk of severe PPH.

PPH due to retention of placenta or membranes was related to velamentous and marginal umbilical cord insertion in a dose-response-pattern with strongest association to velamentous insertion. Both conditions are possible to diagnose by ultrasonography during pregnancy.[49] Thus, prenatal identification of an abnormal cord insertion may serve to alert clinicians and enhance their preparedness.

We found a strong association between previous cesarean section and PPH due to dystocia, and that it was likely to recur from the first to the second delivery. Dystocia is widely ignored as a cause of

PPH in the literature, but our study indicates that a history of PPH due to dystocia should be included in risk assessment for PPH.

Conclusions

In this large population-based study we found that maternal, fetal and obstetric characteristics had differential effects on types of PPH. Recurrence differed considerably between PPH types. Retained placenta was most frequently registered with severe PPH, and showed strongest effect of sex; delivery of a boy was associated with lower risk of PPH. Previous cesarean increased the risk of PPH due to dystocia.

Our research adds to the understanding of recurrence risk of PPH and suggests that PPH can be inherited. In future studies genetic influence on specific types of PPH needs to be disentangled from environmental influence.

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Table and Figure Captions

Table 1. Occurrence of type specific postpartum hemorrhage (PPH); singleton births ≥22 weeks of gestation.

Table 2. Distribution of maternal, pregnancy and birth characteristics in types of postpartum hemorrhage (PPH >500ml); singleton births, ≥22 weeks of gestation.

Table 3. Risk of type specific postpartum hemorrhage (PPH >500ml) according to maternal, pregnancy and birth characteristics; singleton births, ≥22 weeks of gestation and spontaneous onset or induction of labor.

Table 4. Risk of type specific postpartum hemorrhage (PPH>500ml) in the second delivery according to PPH types in the first delivery and pregnancy- and birth characteristic; singleton births, ≥22 weeks of gestation and spontaneous onset or induction of labor.

Table 5. Risk of postpartum hemorrhage (PPH>500ml) due to dystocia in second deliveries without previous cesarean section (CS) (reference), second deliveries with previous CS, and first deliveries; singleton births, ≥22 weeks of gestation and spontaneous onset or induction of labor.

Fig 1. Occurrence of type specific postpartum hemorrhage (>500ml) (1967– 2017).

Fig 2. Occurrence of severe postpartum hemorrhage (>1500ml) within type specific postpartum hemorrhage (1999–2017).

Supporting information. S1 statistical analysis

S1 Supporting information (Statistical analysis)

Independent variables

Independent variables were variables related to demographic characteristics, obstetric history, pregnancy and fetal complications, and placental/membranes/umbilical cord characteristics. Independent variables also included a history of previous postpartum hemorrhage (PPH) type in the first delivery, inter-delivery interval, change of father between pregnancies, first or second delivery bleeding before 13 weeks of gestation, and previous cesarean section.

These analyses included the following possible confounding factors: maternal age (<20 years, 20–24 years, 25–29 years, 30–34 years, 35–39 years or ≥40 years), parity (0, 1, 2, 3, 4 or ≥5), inter-delivery interval (<1 year, 1 to <2 years, 2 to <3 years, 3 to <4 years, 4 to <5 years or ≥5 years), marital status (married/registered partner, cohabitating, not married/alone, divorced/separated/widow, not defined), mother's country of birth (Norway or eight WHO regions) (1) (A) high-income countries, (B) Central Europe, Eastern Europe and Central Asia, (C) sub-Saharan Africa, (D) North Africa and Middle East, (E) South Asia, (F) Southeast Asia, East Asia and Oceania, (G) Latin America and Caribbean or (H) unknown or stateless], level of education (available until 2013) (<8 years, 8–10 years, 11–12 years, 13–17 years, ≥18 years or no information), and the period of birth divided into five groups with approximately equal durations (1967–1977, 1978–1987, 1988–1997, 1998–2007 and 2008–2017).

Statistical analysis

We used multilevel logistic regression analyses to calculate odds ratios (ORs) with 95% confidence intervals (CIs) for PPH types in the second delivery as outcomes, and variables related to demographic characteristics, obstetrical history, pregnancy and fetal complications, and placental/ membranes/ umbilical cord characteristics as exposures. We also calculated ORs for PPH types in the actual birth as outcomes and a history of PPH type as exposure variables.

We accounted for the hierarchical nature of the family data by performing multilevel regression analyses in which the data were sorted into different levels in analyses including one or more births of the same parent: current delivery (level 1) and parent (level 2). Possible confounding variables were included if they were associated with PPH in the current delivery and the exposure.

We performed sensitivity analyses to assess if the associations studied persisted after adjusting for unmeasured confounders (2) and to indicate potentially false positive associations caused by multiple testing (3). We implemented a Markov Chain Monte Carlo simulation (4) in which we entered the regression models and a prior assumption. The prior assumption was that adding an influential, unmeasured confounder to known confounder(s) would zero out the association (null hypothesis), decreasing the regression coefficient (β; standard deviation) for the main exposure variable (PPH) to 0; 0.05, corresponding to an OR of 1 with a 95% CI of 0.9–1.1. In order to simulate confounding, we entered a simple regression model (fixed effect: $\beta_0 + \beta_1$ PPH (0 or 1), where β_0 and β_1 are constants), and calculated the effects (ORs of PPH) before and after including the prior assumption. The statistical analyses were performed using SPSS (version 25) and MLwiN (version 3.05).

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