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Citation for published version:

Sharp, GC, Saunders, PTK, Greene, SA, Morris, AD & Norman, JE 2014, 'Intergenerational transmission of postpartum hemorrhage risk: analysis of 2 Scottish birth cohorts', *American Journal of Obstetrics & Gynecology (AJOG)*, vol. 211, no. 1, pp. 51.e1-51.e7. <https://doi.org/10.1016/j.ajog.2014.01.012>

Digital Object Identifier (DOI):

[10.1016/j.ajog.2014.01.012](https://doi.org/10.1016/j.ajog.2014.01.012)

Link:

[Link to publication record in Edinburgh Research Explorer](#)

Document Version:

Peer reviewed version

Published In:

American Journal of Obstetrics & Gynecology (AJOG)

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Accepted Manuscript



Intergenerational transmission of postpartum haemorrhage risk – analysis of two Scottish birth cohorts

Gemma C. Sharp, MSc Philippa TK. Saunders, PhD Stephen A. Greene, MD Andrew D. Morris, MD Jane E. Norman, MD

PII: S0002-9378(14)00023-4

DOI: [10.1016/j.ajog.2014.01.012](https://doi.org/10.1016/j.ajog.2014.01.012)

Reference: YMOB 9633

To appear in: *American Journal of Obstetrics and Gynecology*

Received Date: 26 September 2013

Revised Date: 8 November 2013

Accepted Date: 7 January 2014

Please cite this article as: Sharp GC, Saunders PT, Greene SA, Morris AD, Norman JE, Intergenerational transmission of postpartum haemorrhage risk – analysis of two Scottish birth cohorts, *American Journal of Obstetrics and Gynecology* (2014), doi: 10.1016/j.ajog.2014.01.012.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

1 **Intergenerational transmission of postpartum haemorrhage risk – analysis of two Scottish birth**
2 **cohorts.**

3 Ms Gemma C SHARP MSc, Edinburgh, United Kingdom MRC Centre for Reproductive Health, The
4 University of Edinburgh

5 Prof Philippa TK SAUNDERS PhD, MRC Centre for Reproductive Health, The University of Edinburgh

6 Prof Stephen A GREENE MD, Tayside Children's Hospital, Maternal and Child Health Sciences
7 (MACHS) Building, Ninewells Hospital & Medical School, Dundee, University of Dundee

8 Prof Andrew D MORRIS MD, Centre for Molecular Medicine, Clinical Research Centre, Level 7,
9 Ninewells Hospital & Medical School, University of Dundee

10 Prof Jane E NORMAN MD, MRC Centre for Reproductive Health, The University of Edinburgh

11

12 **Conflicts of interest:** The authors GCS, PTKS, SAG and ADM have no conflict of interests to declare
13 regarding this submission. JEN has received research grants from charities and governmental bodies
14 for studies on understanding parturition and prevention of preterm parturition. On behalf of the
15 University of Edinburgh, JEN has done some consultancy work for a small drug company interested
16 in agents to prevent preterm parturition. Additionally JEN has received a lecture fee from an
17 overseas academic institution for a lecture on preterm birth.

18 **Financial support:** This work was supported by the University of Edinburgh Principal's Research Fund
19 (which co funded a PhD studentship for GCS), the Albert McKern Bequest, and Tommy's the baby
20 charity.

21 **Reprint requests:** Gemma C Sharp, University of Edinburgh MRC Centre for Reproductive Health,
22 Queen's Medical Research Institute, 47 Little France Crescent, Edinburgh, EH16 4TJ,
23 gemma.sharp@ed.ac.uk

24 **Correspondence related to the manuscript can be addressed to:** Gemma C Sharp, University of
25 Edinburgh MRC Centre for Reproductive Health, Queen's Medical Research Institute, 47 Little France
26 Crescent, Edinburgh, EH16 4TJ, gemma.sharp@ed.ac.uk, work telephone: +44 131 242 6602

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29

30 **Abstract word count: 245**

31 **Main text word count: 2766**

32 **One sentence condensation of paper:**

33 In two record-linked birth cohorts, the effects of family history of PPH are less than those conferred
34 by risk factors associated with the index pregnancy.

35 **Short title:**

36 Intergenerational transmission of postpartum haemorrhage

37

ACCEPTED MANUSCRIPT

38 **Abstract**

39 **Objective:** The purpose of this study was to determine risk factors for postpartum haemorrhage
40 (PPH) including intergenerational transmission of risk of postpartum haemorrhage.

41 **Study Design:** We linked birth records of women, their daughters and granddaughters in two
42 Scottish birth cohorts: the Walker cohort (collected from 1952 to 1966) and the Scottish Morbidity
43 Records cohort (collected from 1975 to present). We determined clinical risk factors for PPH. We
44 then quantified the risk of PPH in women whose mothers/grandmothers had postpartum
45 haemorrhage before and after adjustment for these risk factors.

46 **Results:** The risk of PPH in women whose mothers/grandmothers had PPH was no greater than in
47 those whose mothers/grandmothers did not have PPH. Our study had sufficient (80%) power to
48 detect an odds ratio (OR) of 1.3, should such an increase in odds associated with familial history
49 exist. In contrast, the adjusted ORs conferred by nulliparity, having a large baby, Caesarean section
50 and genital tract trauma were 1.47, 1.84, 8.20 and 9.61 respectively.

51 **Conclusion:** Women whose mothers/grandmothers had PPH do not appear to be at increased risk
52 themselves. We confirmed an increased risk of PPH associated with nulliparity, delivering a large
53 baby, caesarean section and genital tract trauma. We were unable to demonstrate an effect of
54 intergenerational transmission of PPH, although our study was underpowered to detect an OR less
55 than 1.3. Thus we confirm that any risk conferred by familial history, should it exist, is less than that
56 conferred by factors in the index pregnancy itself.

57 **Keywords:**

58 Birth cohort, epidemiology, intergenerational transmission, postpartum haemorrhage, record
59 linkage.

60

61 Introduction

62 Postpartum haemorrhage (PPH) is widely defined as ≥ 500 ml blood loss from the genital tract in the
63 first 24 hours after childbirth. It is the leading cause of maternal death worldwide, occurring in
64 around 7-26% of all deliveries¹ and contributing to the deaths of an estimated 125,000 women each
65 year.² The annual incidence of PPH appears to be rising steadily, even in high resource countries.³
66 Known risk factors, causes and consequences of PPH are summarised in Figure 1, however the
67 aetiology is often unclear and PPH may occur in women with no identifiable risk factors. PPH can be
68 associated with a failure of the uterus to contract adequately after birth (atonic PPH; 90% of cases),
69 trauma to the genital tract (traumatic PPH; 7% of cases), or bleeding due to retention of placental
70 tissue or failure in the coagulation system (3% of cases).⁴

71 Previous PPH is a significant risk factor for subsequent PPH, with several studies finding women two
72 to three times more likely to have PPH in their second pregnancy if they had PPH in their first.⁵⁻⁸ If
73 individual women are at increased risk, it is possible that this predisposition could be heritable, but
74 to our knowledge no studies have previously addressed this. Understanding the biological and
75 potentially heritable basis to PPH could be useful in understanding the aetiology of this important
76 obstetric complication and developing better predictive and preventive tools. Additionally, it would
77 help in the counselling of pregnant women, who are often aware of their family history of pregnancy
78 related adverse events, including PPH.

79 We used Scottish population data in which quality and consistency has previously been confirmed,
80 and where database linkage is possible. This allowed patient-based analysis and analysis of
81 intergenerational transmission over three generations of women.

82 Methods

83 Record Linkage

84 Since the 1970's, people living in Scotland have been allocated a unique Community Health
85 Identification (CHI) number, which allows record linkage across clinical databases and generations.
86 We used the CHI number to record-link between the Walker Cohort and Scottish Morbidity Records
87 maternity admissions data (SMR02). Data were provided and by the Health Informatics Centre (HIC)
88 at the University of Dundee. The Information Services Division (ISD) Scotland provide SMR02 data to
89 HIC. All data were anonymised prior to analyses.

90 *The Walker Cohort*

91 The Walker cohort is a dataset of 48404 birth records that contains meticulously recorded details of
92 pregnancy, labour and care before discharge for births in hospital in Dundee, Scotland between 1952
93 and 1966. The details of the Walker cohort have been previously published and will not be repeated
94 here,⁹ but there is information about PPH stored as a dichotomous variable for Walker births
95 occurring between 1952-58. Information on later births was recorded on different cards that did not
96 include details of PPH. The criteria used to define PPH is not described for the Walker cohort, but we
97 have assumed it to be ≥ 500 ml blood loss in the first 24 hours following delivery, as diagnosed by the
98 doctor or midwife assessing the patient.

99 Maternities recorded in the Walker cohort account for 75% of all births in Dundee at this time.
100 34183 (73%) of these babies can be identified through their CHI number, and this presents the

101 opportunity to link this maternity or birth information with a large number of current health-
102 outcome datasets covering both primary and secondary care for Walker mothers and babies.

103 *Scottish Morbidity Records – SMR02*

104 The Scottish Morbidity Records 02 (SMR02) dataset contains detailed information on hospital
105 maternity admissions in Scotland collected from January 1975 to present. Outcomes are coded
106 according to the International Classification of Diseases (ICD9 and ICD10). Table 1 shows the codes
107 used to indicate PPH as an outcome. Again, we assume these codes were assigned based on
108 observation of blood loss ≥ 500 ml in the first 24 hours following delivery.

109 *The Generations*

110 We identified data on three generations of women, defined as follows:

- 111 • Generation 1 - Walker Mothers – Women who appear in the Walker cohort as mothers.
- 112 • Generation 2 - SMR02 Mothers – Women who appear in the Walker cohort as babies, and
113 the SMR02 cohort as mothers.
- 114 • Generation 3 - SMR02 Daughters – Women who appear in the SMR02 cohort as babies, and
115 also as mothers if they have had children themselves.

116 Data analysis

117 In SMR02, maternity admissions that were coded as not resulting in delivery of a child were
118 removed. Stillbirths of a baby >500 g were included.

119 We used IBM SPSS Statistics version 19 (IBM Corp., Armonk NY), to perform a univariate analysis of
120 the pooled (Walker and SMR02) data. We calculated unadjusted odds ratios to assess the effects of
121 each of: PPH in a previous pregnancy, multiple pregnancy, high birth weight (using the World Health
122 Organisation (WHO) definition of ≥ 4 kg), low birth weight (using the WHO definition of < 2.5 kg),
123 maternal age under 20-years-old (previously identified as a risk factor for PPH¹⁰), maternal age over
124 40-years-old (previously identified as a risk factor for PPH¹⁰), parity, preterm birth (using the WHO
125 definition of ≤ 37 weeks' gestation), post-term birth (using the WHO definition of ≥ 42 weeks'
126 gestation), delivery by caesarean section, instrumental delivery and smoking status on risk of PPH in
127 the index pregnancy. To calculate adjusted odds ratios, we built factors identified as significant in
128 the univariate analyses into a multivariate logistic regression model using function `glm()` in the R
129 package `lme4`¹¹ (R version 2.15.1¹²).

130 To assess intergenerational transmission of PPH, we used the CHI number to link records across
131 generations as follows:

- 132 • Generation 1 was linked to Generation 2
- 133 • Generation 2 was linked to Generation 3
- 134 • Generation 1 was linked to Generation 3
- 135 • Pooled mother-daughter analysis: mothers from Generations 1 and 2 were linked to
136 daughters in Generations 2 and 3.

137 To analyse intergenerational trends in PPH for each of these comparisons, we first calculated
138 unadjusted odds ratios using logistic regression model, again using `glm()` in R package `lme4`.¹¹ These
139 models assess the relationship between PPH in the younger generation (the dependent variable) and
140 PPH in the older generation (the independent variable) without taking into account any other
141 potential covariates. We then used function `glmer()` in R package `lme4`¹¹ to build generalised linear
142 mixed models (GLMMs) using a binomial distribution with a logit link. These models incorporated
143 any other covariates found to be significantly associated with PPH in the univariate analyses. The
144 models also adjust for the 'random effects' introduced through the appearance of the same women
145 in different mother-daughter/grandmother-granddaughter pairs (for example a woman could be a
146 mother in the comparison of generations 2 and 3, but a daughter in the comparison in generations 1
147 and 2. Additionally, one woman could be a mother to more than one daughter). It is important to
148 adjust for this non-independence, because it invalidates the assumptions of many statistical tests
149 and can introduce bias that can mask exposure effects. Where we suspected low power, we used
150 function `fe.mtdor()` in the R package `clinfun`¹³ to calculate the smallest effect size that our analyses
151 would have been able to detect at 80% power based on our actual sample sizes.

152 Results

153 Figure 2 outlines how records were linked in this study and the number of records used in the final
154 analysis.

155 The overall prevalence of PPH (1089/25322, 4.3%) was similar in both the Walker (176/3847, 4.6%)
156 and SMR02 (913/21475, 4.3%) cohorts. 82.3% (751) of cases of PPH in SMR02 deliveries were caused
157 by uterine atony. PPH was diagnosed as delayed or secondary in 8.9% (81) of SMR02 cases and
158 associated with retained placenta (third stage) in 8.4% (77). Coagulation defect was the least
159 common recorded cause of PPH (0.4%, 4 cases).

160 In univariate analyses of data pooled from Walker and SMR02 (Table 2), multiple pregnancy, baby
161 birth weight over 4kg, maternal age over 40-years, preterm gestation ≤ 37 weeks, caesarean delivery,
162 nulliparity, genital trauma/episiotomy and smoking during pregnancy were significant risk factors for
163 PPH (ORs ranging from 1.17 to 6.02). Delivery by forceps or ventouse was associated with a small but
164 significant lower risk of PPH. There were insufficient data on PPH in a previous pregnancy to
165 determine if this was a risk factor for PPH in a subsequent pregnancy.

166 A logistic regression model incorporating significant risk factors from the univariate analysis allowed
167 us to adjust for confounding and revealed that large birth weight, caesarean delivery, nulliparity and
168 genital trauma/episiotomy were significant independent risk factors for PPH (adjusted ORs ranging
169 from 1.47 to 9.61). After these adjustments (particularly for multiple pregnancy and Caesarean
170 section, which are significant confounders), delivery at ≤ 37 weeks was associated with a significant
171 decreased risk of PPH (OR 0.63 95% CI 0.55-0.97).

172 Table 3 shows that there is a small increased risk of PPH in women whose mothers and/or
173 grandmothers had PPH across generations 1-2 and 1-3, but this trend did not reach statistical
174 significance. Comparisons of generations 2 and 3 and pooling of mother and daughter comparisons
175 showed a reverse trend, i.e a trend to a protective effect of maternal PPH on the risk of PPH in the
176 daughter. GLMMs were used to adjust for non-independence between related mother-daughter
177 pairs and most risk factors identified as significant by the multivariate analysis (delivery by caesarean

178 section was excluded due to incomplete data). These analyses again confirmed no statistically
179 significant effect of maternal PPH on the risk of PPH in the daughter. These intergenerational
180 analyses had 80% power at an alpha of 0.05 to detect the following odds ratios: 2.1 for generation 1
181 linked to generation 2; 1.3 for generation 2 linked to generation 3; 2.1 for generation 1 linked to
182 generation 3; and 1.3 for the pooled mother to daughter analysis. Thus we can be reasonably
183 confident that any intergenerational effect of maternal PPH, should it exist, increases the odds of
184 PPH in the daughter by less than 1.3.

185 **Comment**

186 To our knowledge, this is the first attempt to investigate the intergenerational transmission of PPH.
187 Our analyses do not support a large increased risk of PPH for women whose mothers/grandmothers
188 had PPH. We identified caesarean delivery, genital trauma or episiotomy, high birth weight and
189 nulliparity as risk factors for PPH, thus confirming the results of previous studies.^{7,10,14-16} In particular,
190 the odds of PPH in nulliparous women (odds ratio 1.47) was very similar to that reported by Combs
191 et al. (odds ratio 1.45).⁷ In both the SMR02 and Walker cohorts, the prevalence of PPH (4.3% and
192 4.6%, respectively) was lower than that reported for other populations. In a meta-analysis of 104
193 datasets, Calvert et al.¹ showed that PPH prevalence shows high regional variation, ranging from
194 7.2% in Oceania to 25.7% in Africa. In Europe, they found a prevalence of 12.7%, which is similar to
195 the 13.2% incidence reported in the NHS maternity records for England and Wales in 2011-12.¹⁷
196 However, the authors also found that the prevalence depends strongly on the method of diagnosis
197 of PPH, with a subjective measurement of blood loss resulting in a lower prevalence compared to an
198 objective measurement. A subjective measure is likely to have been used for the SMR02 and Walker
199 cohorts, which may explain the relatively low prevalence of PPH in these datasets. Some authors
200 have argued that the traditional definition of PPH is of little clinical relevance and should be revised
201 so that PPH can be measured more easily and the diagnosis considers differences between individual
202 patients.^{18,19} For example, some authors have suggested PPH may be better defined by a fall in
203 haematocrit or percentage of total blood.²⁰ Similarly, some authors have argued that using a
204 definition of ≥ 500 ml blood loss overestimates the prevalence of PPH associated with any increased
205 risk of mortality or morbidity for the patient. Pritchard et al. found that 500ml is the average blood
206 loss for a vaginal delivery, with 7% of women losing ≥ 1000 ml of blood after vaginal delivery.¹⁹ They
207 identified the average blood loss for a caesarean delivery as ≥ 1000 ml. Therefore it could be argued
208 that using a definition of blood loss ≥ 500 ml for both vaginal and caesarean deliveries will result in
209 an overestimation of the number of cases of PPH, especially following caesarean deliveries.²¹ In
210 SMR02 and Walker, PPH was recorded as a dichotomous variable with no information on the volume
211 of blood loss postpartum, therefore we were unable to assess the clinical relevance of any of the
212 cases of PPH. However, we do not consider this to be a major limitation of our study because PPH
213 was diagnosed subjectively by trained doctors and midwives with experience of "clinically relevant"
214 cases. In our study there were too few cases to perform subgroup analyses on vaginal and
215 caesarean deliveries, although we did identify caesarean section as one of the strongest
216 independent risk factors for PPH and adjusted for caesarean section in our multivariate analyses,
217 where possible. In contrast to previous studies,²²⁻²⁵ we saw no significant change in the prevalence
218 of delivery by Caesarean section over time in either cohort. Therefore it is unlikely that between-
219 generation differences in the Caesarean prevalence is masking any real trends in our data.

220 For SMR02 only, data were available on the cause or type of PPH through ICD codes. The data quality
221 of SMR02 and Walker was not formally assessed for the purposes of this project, however previous
222 studies have validated these datasets, including confirmation of a low error rate in the recording of
223 ICD diagnostic codes in SMR02.^{9,26–28} Therefore, we believe that the ICD coding used to identify cases
224 of PPH is robust and any error in coding is not likely to introduce substantial bias. In line with
225 previous studies,^{10,29,30} the most frequent cause of PPH was uterine atony (82.3% of cases in SMR02),
226 which prevents constriction of blood vessels during placental separation. Unfortunately there were
227 insufficient data to analyse risk factors for different types of PPH individually. This is a limitation of
228 our study, as we recognise that the different aetiologies of PPH, particularly coagulation defects,
229 may be associated with different risk factors, including family history. We decided to include in our
230 analyses the 4 women from SMR02 with PPH associated with coagulation defects because similar
231 cases are likely to be included in the Walker cohort and it would have been impossible to identify
232 and exclude these cases in this dataset. No previous reports have investigated family history of PPH
233 as a risk factor for PPH. The historical Walker data linked to the more recent SMR02 data presented
234 a unique opportunity to do this. SMR02 data collection began in 1975, so we were able to make the
235 same comparison within this dataset. Special consideration was given to the appearance of the same
236 women in more than one mother-daughter/grandmother-granddaughter pair. This is further
237 complicated by the tendency for women to experience PPH in repeat pregnancies.^{5–8} This non-
238 independence invalidates the assumptions of many statistical tests and can lead to spurious
239 conclusions. One option for dealing with this “clustering” is to restrict analysis to one pregnancy per
240 woman (for example, the first pregnancy). However, this reduces statistical power and ignores a lot
241 of potentially important information. It also changes the definition of the study population from “all
242 births within the dataset” to “all first births within the dataset”, so it may not be possible to
243 generalise the results to “all births”.³¹ Another possible tactic is to include data on all pregnancies
244 and ignore the non-independence. We used this approach to calculate our “unadjusted odds ratios”
245 for intergenerational transmission of PPH. However, this will lead to incorrect standard errors and
246 potentially incorrect conclusions. Therefore, we used a mixed model in our final, multivariate
247 analysis to adjust for both covariates (fixed effects) and within-woman clustering (random effects).
248 This protects against bias and allows us to estimate the size of the effect introduced by this
249 clustering.³¹

250 We showed no significant association between PPH in the mother and the odds of PPH in daughters.
251 Our study had 80% power to detect an OR of 1.29 for maternal influence on PPH in the daughter.
252 This is a lower OR than conferred by birthweight > 4.0kg and nulliparity (1.87 and 1.47 respectively)
253 and very much lower than conferred by maternal Caesarean section and genital tract trauma (8.20
254 and 9.61 respectively). Thus any effect of the pregnant woman’s maternal history of PPH is (if it
255 exists) much less significant than those of the index pregnancy. These data contrast with the known
256 intergenerational transmission of pre-eclampsia and of preterm delivery.^{32,33} Pregnant women
257 whose mothers had PPH can be reassured that they are unlikely to be at any significantly increased
258 risk, compared to those whose mothers did not have PPH.

259 **Conclusion**

260 The results have confirmed several statistically significant risk factors for PPH. They also suggest that
261 women whose mothers/grandmothers had PPH are not at an increased risk themselves.

262 **Acknowledgments**

263 We acknowledge the support of the Health Informatics Centre, University of Dundee for managing
264 and supplying the anonymised data and NHS Tayside, the original data source. Special thanks go to
265 Professor Graham Horgan of Biostatistics Scotland for statistical advice and comments on the
266 manuscript. We are also grateful to Daniel Ayoubkhani of the Office for National Statistics for
267 statistical advice.

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346 **Tables****Table 1. International Classification of Diseases (ICD) 9 and 10 codes used to identify postpartum haemorrhage (PPH) in SMR02 birth records.**

Cause of PPH	ICD-9 code	ICD-10 code
Third stage (associated with retained, trapped or adherent placenta)	666.0	O72.0
Atonic (after placenta delivery)	666.1	O72.1
Delayed and secondary PPH (associated with retained portions of placenta)	666.2	O72.2
Coagulation defects	666.3	O72.3

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Table 2. Analysis of risk factors associated with postpartum haemorrhage.

Risk factor	(A)	(B)	(C)	Unadjusted odds ratio* (95% confidence interval)	Adjusted [†] odds ratio* (95% confidence interval)
	Number of births with information on PPH and risk factor	Number of births with PPH (% of column A)	Number of births with PPH where risk factor is present (% of column B)		
Multiple pregnancy	25322	1089 (4.3%)	58 (5.3%)	2.09 (1.59 to 2.76)	1.87 (0.77 to 4.53) <i>ns</i>
Low birth weight (<2.5kg)	24935	1059 (4.2%)	81 (7.6%)	1.11 (0.88 to 1.39) <i>ns</i>	n/a
High birth weight (≥4kg)	24935	1059 (4.2%)	199 (18.8%)	2.37 (2.02 to 2.78)	1.84 (1.27 to 2.67)

Maternal age \leq 20- years-old	20207	1015 (5.0%)	136 (13.4%)	1.34 (1.12 to 1.62)	1.13 (0.77 to 1.65) <i>ns</i>
Maternal age \geq 40- years-old	20207	1015 (5.0%)	44 (4.3%)	2.73 (1.98 to 3.77)	1.32 (0.73 to 2.38) <i>ns</i>
Nulliparity	25293	1085 (4.3%)	541 (49.9%)	1.17 (1.03 to 1.32)	1.47 (1.10 to 1.98)
Preterm birth (\leq 37 weeks' gestation)	23741	1003 (4.2%)	127 (12.7%)	1.33 (1.1 to 1.61)	0.63 (0.41 to 0.97) <i>ns</i>
Postterm birth (\geq 42 weeks' gestation)	23741	1003 (4.2%)	81 (8.1%)	0.79 (0.63 to 1.00) <i>ns</i>	n/a
Delivery by caesarean section [†]	3872	471 (12.2%)	283 (60.1%)	6.02 (4.92 to 7.38)	8.20 (6.19 to 10.86)
Instrumental delivery (forceps or ventouse)	3872	471 (12.2%)	21 (4.5%)	0.42 (0.27 to 0.66) <i>ns</i>	n/a
Genital trauma or episiotomy	18890	885 (4.7%)	25 (2.8%)	1.61 (1.07 to 2.44)	9.61 (2.15 to 43.02)
Mother smoked during pregnancy	8833	573 (6.5%)	140 (24.4%)	1.40 (1.15 to 1.71)	0.79 (0.57 to 1.08) <i>ns</i>

350 *ns*: non significant.

351 * ratio of the odds of a birth being affected by PPH when the risk factor is present to the odds of a
352 birth being affected by PPH when the risk factor is absent.

353 [†]adjusted for all factors identified as significant in the univariate (anadjusted) analysis.

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Table 3. Analysis of intergenerational trends in postpartum haemorrhage.

Risk factor	(A) Number of linked births with information on PPH	(B) Number of linked births with PPH in younger generation (% of column A)	(C) Number of linked births with PPH in both generation s (% of column B)	Unadjust ed odds ratio (95% confidenc e interval)	Adjusted* odds ratio (95% confidence interval)
PPH in generation 1 as a risk factor for PPH in generation 2	2543	49 (1.9%)	3 (6.1%)	1.32 (0.41 to 4.32)	1.20 (4.83e-3 to 296.0)
PPH in generation 2 as a risk factor for PPH in generation 3	2464	290 (11.8%)	4 (1.4%)	0.68 (0.24 to 1.90)	0.58 (8.0e- 3 to 41.61)
PPH in generation 1 as a risk factor for PPH in generation 3	519	65 (12.5%)	6 (9.2%)	2.21 (0.85 to 5.72)	1.33 (9.43e-5 to 1.88e+4)
PPH in mothers as a risk factor for PPH in daughters (pooled analysis)	5007	339 (6.8%)	7 (2.1%)	0.59 (0.27 to 1.27)	0.69 (0.06 to 7.62)

361 *calculated using a generalised linear mixed model to adjust for the non-independence between
 362 linked births and risk factors identified as significant in the multivariate analysis (excluding delivery
 363 by caesarean section because of incomplete data).

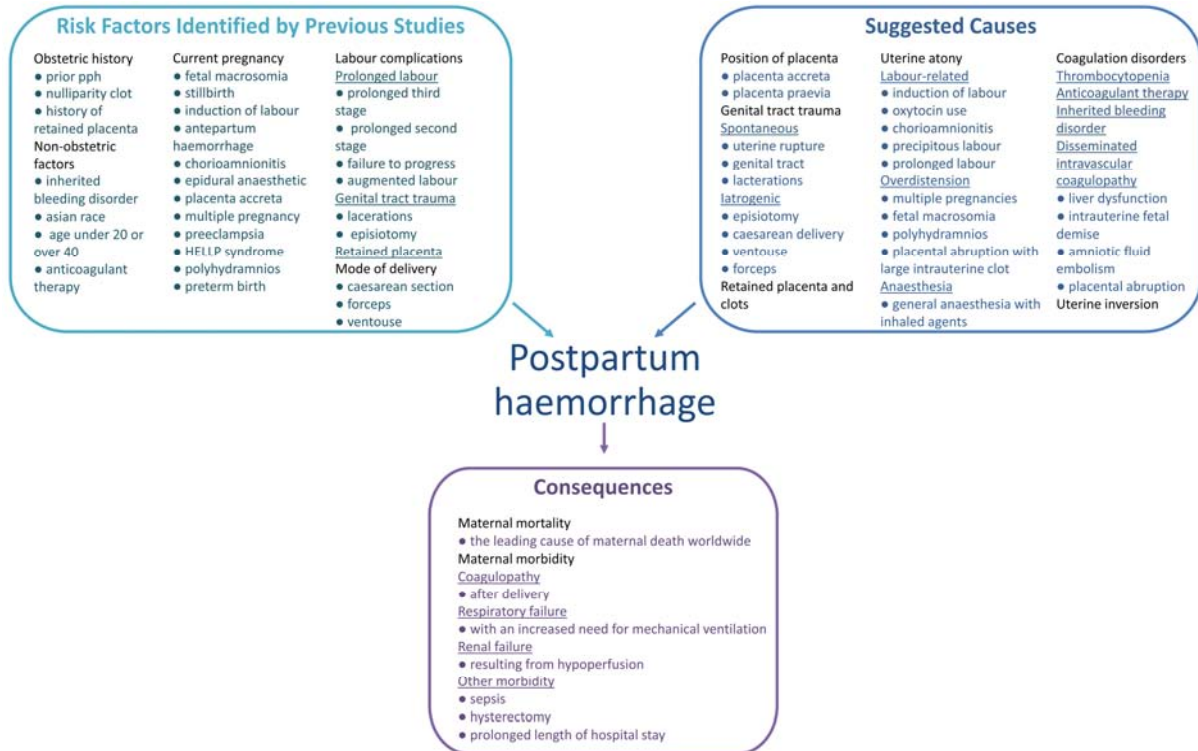
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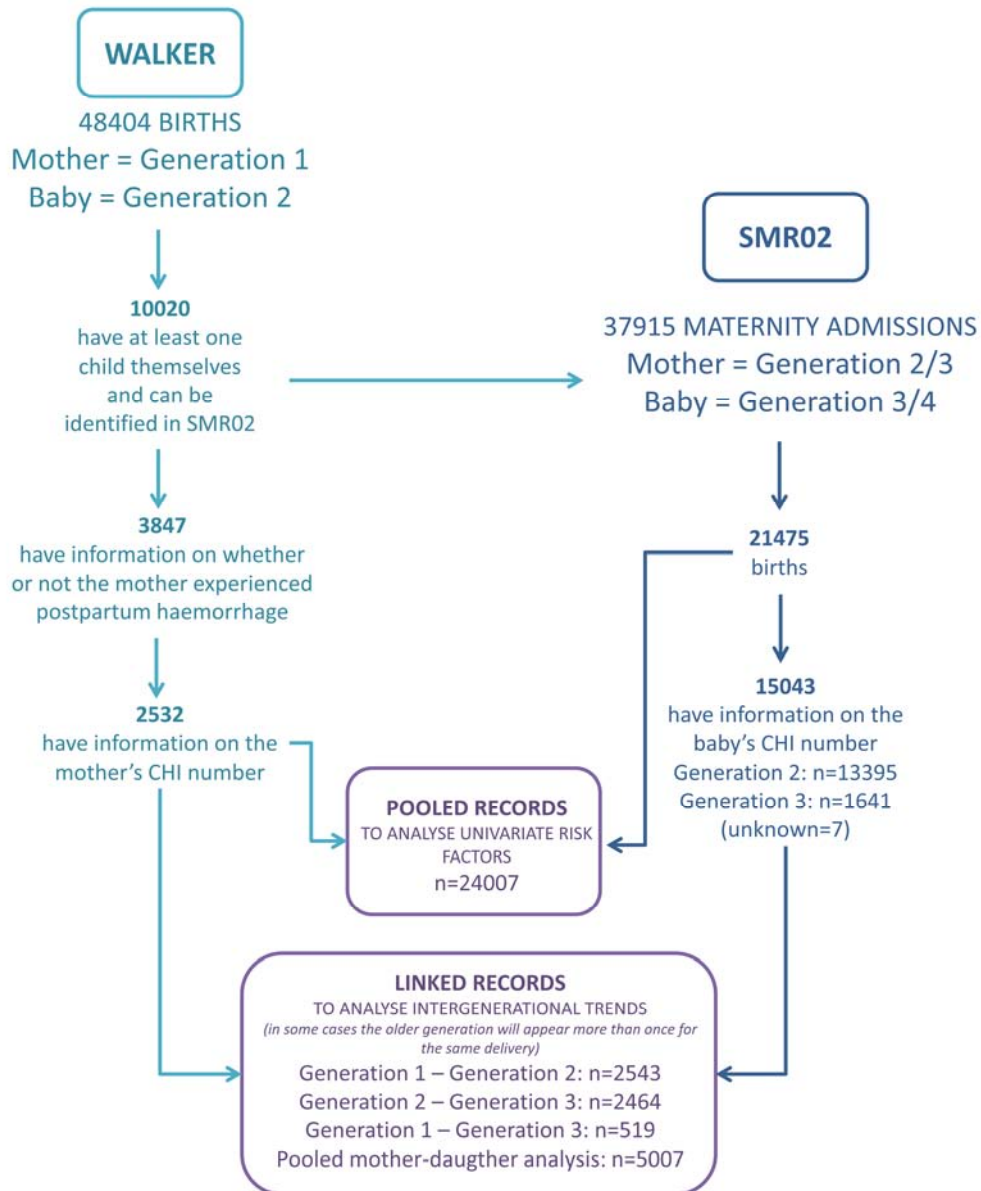
365 **Figure legends**

366 Figure 1. Causes, risk factors and consequences of postpartum haemorrhage, as identified
367 previously.

368 Figure 2. Method of record linkage and number of records analysed.

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Obstetrics

Intergenerational transmission of postpartum hemorrhage risk: analysis of 2 Scottish birth cohorts

Gemma C. Sharp, PhD; Philippa T. K. Saunders, PhD; Stephen A. Greene, MD; Andrew D. Morris, MD; Jane E. Norman, MD

From the MRC Center for Reproductive Health, University of Edinburgh, Edinburgh (Dr Sharp, Profs Saunders and Norman), and Tayside Children's Hospital (Prof Greene) and the Center for Molecular Medicine, Clinical Research Center (Prof Morris), Ninewells Hospital and Medical School, University of Dundee, Dundee, Scotland, UK.

J.E.N. has received research grants from charities and governmental bodies for studies on understanding parturition and prevention of preterm parturition. On behalf of the University of Edinburgh, she has done some consultancy work for a small drug company interested in agents to prevent preterm parturition. In addition, she has received a lecture fee from an overseas academic institution for a lecture on preterm birth. The other authors report no conflict of interest.

This work was supported by the University of Edinburgh Principal's Research Fund, which

cofunded a PhD studentship for G.C.S.; the Albert McKern Bequest; and Tommy's, the Baby Charity

Abstract will be inserted.

Background and Objective

Postpartum hemorrhage (PPH) is widely defined as ≥ 500 mL blood loss from the genital tract in the first 24 hours after childbirth. It is the leading cause of maternal death worldwide, occurring in around 7-26% of all deliveries and contributing to the death of an estimated 125,000 women each year.

Understanding the biological and potentially heritable basis of PPH could be useful in understanding the etiology of this important obstetric complication and developing better predictive and preventive tools. In addition, it would help in the counseling of pregnant women, who are often aware of their family history of pregnancy-related adverse events, including PPH.

Materials and Methods

We used the CHI number to record-link between the Walker Cohort and Scottish Morbidity Records maternity admissions data (SMR02). The Walker cohort is a dataset of 48,404 birth records that contains meticulously recorded details of pregnancy, labor, and care before discharge for births in hospital in Dundee, Scotland, in 1952-1966.

Maternities recorded in the Walker cohort account for 75% of all births in Dundee at this time. Among these babies, 34,183 (73%) can be identified through their CHI number.

This presents the opportunity to link this maternity or birth information with a large number of current health outcome datasets covering both primary and secondary care for Walker mothers and babies.

The Scottish Morbidity Records 02 (SMR02) dataset contains detailed information on hospital maternity admissions in Scotland collected from January 1975 to the present. We identified data on 3 generations of women.

Results

The overall prevalence of PPH (1089/25,322, 4.3%) was similar in both the Walker (176/3847, 4.6%) and SMR02 (913/21,475, 4.3%) cohorts. Among cases of PPH in SMR02 deliveries, 82.3% (751) were caused by uterine atony. PPH was diagnosed as delayed or secondary in 8.9% (81) of SMR02 cases and associated with retained placenta (third stage) in 8.4% (77). Coagulation defect was the least common recorded cause of PPH (0.4%, 4 cases).

In univariate analyses of data pooled from Walker and SMR02, multiple pregnancy, baby birthweight over 4kg, maternal age over 40 years, preterm gestation ≤ 37 weeks, cesarean delivery, nulliparity, genital trauma/episiotomy, and smoking during pregnancy were significant risk factors for PPH (ORs ranging from 1.17 to 6.02). Delivery by forceps or ventouse was associated with a small but significant lower risk of PPH. There were insufficient data on PPH in a previous pregnancy to determine whether this was a risk factor for PPH in a subsequent pregnancy.

A logistic regression model incorporating significant risk factors from the univariate analysis allowed us to adjust for confounding and revealed that high birthweight, cesarean

delivery, nulliparity, and genital trauma/episiotomy were significant independent risk factors for PPH (adjusted ORs ranging from 1.47 to 9.61). After these adjustments (particularly for multiple pregnancy and cesarean section, which are significant confounders), delivery at ≤ 37 weeks was associated with a significant decreased risk of PPH (OR 0.63; 95% CI, 0.55-0.97).

Women whose mothers and/or grandmothers had PPH had a small increased risk of PPH across generations 1-2 and 1-3, but this trend did not reach statistical significance (Table). We can be reasonably confident that any intergenerational effect of maternal PPH, should it exist, increases the odds of PPH in the daughter by less than 1.3.

Comment

To our knowledge, this is the first attempt to investigate the intergenerational transmission of PPH. Our analyses do not support a large increased risk of PPH for women whose mothers/grandmothers had PPH. We identified cesarean delivery, genital trauma or episiotomy, high birthweight, and nulliparity as risk factors for PPH, thus confirming the results of previous studies.

Some authors have argued that the traditional definition of PPH is of little clinical relevance and should be revised so that PPH can be measured more easily and the diagnosis considers differences between individual patients. In SMR02 and Walker, PPH was recorded as a dichotomous variable with no information on the volume of blood loss postpartum; therefore, we were unable to assess the clinical relevance of any of the cases of PPH. However, we do not consider this to be a major limitation of our study because PPH was diagnosed subjectively by trained doctors and midwives with experience of “clinically

relevant” cases.

In line with previous studies, the most frequent cause of PPH was uterine atony (82.3% of cases in SMR02), which prevents constriction of blood vessels during placental separation. Unfortunately, data were insufficient to analyze risk factors for different types of PPH individually.

No previous reports have investigated family history of PPH as a risk factor for PPH. The historical Walker data linked to the more recent SMR02 data presented a unique opportunity to do this. Special consideration was given to the appearance of the same women in more than one mother-daughter/grandmother-granddaughter pair. This is further complicated by the tendency for women to experience PPH in repeat pregnancies. This nonindependence invalidates the assumptions of many statistical tests and can lead to spurious conclusions.

Therefore, we used a mixed model in our final, multivariate analysis to adjust for both covariates (fixed effects) and within-woman clustering (random effects). This protects against bias and allows us to estimate the size of the effect introduced by this clustering. We showed no significant association between PPH in the mother and the odds of PPH in daughters. Our study had 80% power to detect an OR of 1.29 for maternal influence on PPH in the daughter. This is a lower OR than conferred by birthweight >4.0 kg and nulliparity (1.87 and 1.47, respectively) and very much lower than conferred by maternal cesarean section and genital tract trauma (8.20 and 9.61, respectively). Thus any effect of the pregnant woman’s maternal history of PPH is (if it exists) much less significant than those of the index pregnancy.

CLINICAL IMPLICATIONS

- Pregnant women whose mothers experienced postpartum hemorrhage (PPH) can be reassured that they are unlikely to be at any significantly increased risk compared to those whose mothers did not experience PPH.

[Insert Table 3. Analysis of intergenerational trends in postpartum hemorrhage]